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Original Article

Enhanced Bioavailability of Valsartan through Mucoadhesive Pellets Fabricated via Fluidized Bed Processor: A Novel Drug Delivery Approach

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ABSTRACT

Background: Novel delivery strategies are being explored since low bioavailability presents a challenge for medications like valsartan. Mucoadhesive drug delivery systems present a viable alternative by enhancing drug absorption and retention. **Aim:** This study aimed to develop mucoadhesive drug delivery systems to enhance the bioavailability of valsartan, leveraging a novel mucoadhesive polymer isolated from *Samanea saman* seeds. **Materials and Methods:** The study involved formulating oral mucoadhesive pellets by layering valsartan on starch pellets, followed by coatings of release-retardant polymer HPMC K15M and the novel *Samanea saman* gum. Optimization was achieved through response surface methodology, with assessments including mucoadhesive strength, drug release kinetics, compatibility studies, and pharmacokinetics evaluation. **Results and Discussion:** The optimized formulation, featuring 10% w/w HPMC K15M and 40% w/w *Samanea saman* gum coating, exhibited robust mucoadhesive strength and sustained drug release for 14 hr. Increasing *Samanea saman* gum concentration enhanced mucoadhesive strength and drug release retardation. Compatibility assessments confirmed the suitability of excipients, while microscopy and radiography revealed pellet integrity. **Conclusion:** The developed mucoadhesive drug delivery system effectively enhanced the bioavailability of valsartan, as evidenced by *in vitro* dissolution studies and *in vivo* pharmacokinetic studies in rats. This comprehensive approach offers a promising strategy for improving the therapeutic efficacy of valsartan through enhanced mucoadhesion and sustained release.

Keywords: Mucoadhesive drug delivery systems, Valsartan bioavailability, *Samanea saman* gum, Sustained drug release, Pharmacokinetic studies.

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INTRODUCTION

For potential medical uses, researchers are looking intently at naturally occurring biopolymers from fungus, plants, and animals. These biopolymers consist of polysaccharides like chitosan and pectin as well as proteins like albumin and zein.[1] They offer advantages like biocompatibility, enzymatic degradation, low toxicity, and controlled drug release capabilities, making them versatile candidates for medical purposes.[2] Chemical modifications are feasible, enhancing their adaptability for various medical objectives. In the realm of healthcare materials, there is a burgeoning interest in biopolymer-based solutions. These encompass numerous innovative drug delivery systems in which mucoadhesive drug delivery systems are very common.[3] Mucoadhesive biopolymers offer the potential to enhance drug delivery via diverse routes, including the gastrointestinal, nasal, ocular, buccal, vaginal, and rectal pathways.[4] The mucoadhesive property of these polymers makes them invaluable in drug delivery systems, enabling prolonged contact with the mucosa, thus enhancing drug absorption and therapeutic efficacy. Mucoadhesive polymers can be synthetic or natural, offering a versatile range of options for formulating pharmaceutical and biomedical products. They operate through various mechanisms, including electrostatic, hydrophobic, and covalent interactions, ensuring secure adhesion to mucosal tissues. As a result, they have gained increasing attention in the development of mucoadhesive drug delivery systems for controlled release and improved patient compliance.[5] The present investigation set out to separate gum from *Samanea saman* seeds, evaluate the gum's preclinical safety via a single dosage toxicity analysis, and explore its possibilities as a mucoadhesive excipient.

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MATERIALS AND METHODS

Materials

Legumes of *Samanea saman* were gathered from Nasik, Maharashtra. Indoco Remedies Ltd, Navi Mumbai, provided a gift sample of valsartan. Instamodel 41 polymer was acquired from Ideal Cures, Mumbai. A herbarium of *Samanea saman* was prepared and authenticated by the Botanical Survey of India, Pune.

Procurement of legumes of *Samanea saman*

Early in the morning, legumes from *Samanea saman* were collected from Ashok nagar, Satpur, Nasik, Maharashtra, India. Subsequently, they underwent washing with distilled water two to three times, followed by sun drying for two days.

Isolation and purification of gum from seeds

The gum extraction process from *Samanea saman* pod seeds involved stirring seed powder in water using a mechanical stirrer at 60°C for 4 hr, followed by overnight soaking. The resulting solution underwent filtration, and the filtrate was subjected to ethanol treatment to precipitate the gum. To ensure that any remaining ethanol was removed, the dried gum was further dried in an oven at 40°C for three to 4 hr after being ground into a powder using a mortar and pestle.[6,7]

Physicochemical evaluation of *Samanea saman* gum[8-10]

The macroscopic studies were carried out for organoleptic properties like color, odor and taste of the *Samanea saman* gum. Gum was evaluated for solubility, loss on drying for moisture content evaluation, total ash and acid insoluble ash determination, pH determination, swelling index and viscosity. The dried purified gum was used for the identification of different phytoconstituents like alkaloids, phenolic, flavonoids, proteins, amino acids, saponins, and carbohydrates by using different qualitative chemical tests.

Characterization of Samanea saman gum

Novel polymer used *Samanea saman* gum was evaluated for swelling study, mucoadhesive strength, viscosity and shear stress measurement.[11,12]

Swelling study

For the swelling study placebo tablets were formulated by using different concentrations of pure individual polymers like 10%, 30%, 50%, 70%, and 90%. The swelling study determined by dissolution apparatus I. The following formula was used to calculate the Swelling Index (S.I.).

$$\text{Swelling Index (\%)} = \frac{Wt - W0}{W0} \text{ X } 100$$

In the above formula, Wo is considered as the weight of the tablet before swelling, and Wt is considered as the weight of the swelled tablet at each time interval.

Measurement of mucoadhesive strength

Mucoadhesive strength was determined for different concentrations of *Samanea saman* polymers by the following method.

Mucoadhesion force strength

Bioadhesive performance was evaluated using tensile strength to measure the force needed to detach a tablet from mucosal surfaces. The laboratory setup featured a two-arm balance, with a mobile platform on the left arm securing a model mucosal membrane. Goat intestine mucosa was excised, equilibrated at 37°C for 30 min in pH 6.8 phosphate buffer, and used for bioadhesion force determination. A polymeric tablet was placed beneath the left-hand pan, and after hydrating with pH 6.8 phosphate buffer, contact was established with the goat intestine mucosa. Incremental weight in the right-hand pan, starting with a 20 g preload, was applied until tablet detachment and the recorded weight represented the bioadhesion force. The formula for bioadhesion force is as follows:

$$F = \frac{W \text{ X } g}{A}$$

In the above equation, F refers to the bioadhesion force (dyne. cm^{-2}), W refers to the weight required for the detachment of the tablet (g), and A considered as the surface area of the tablet (cm^2).

Shear stress measurement

The sliding glass slab model determined the shear stress of *Samanea saman* polymers. The weight just sufficient to pull the upper slab is the shear stress which shows the adhesion strength of the polymer.

Viscosity

Aqueous solutions of 1% w/v polymer were prepared for each polymer and the viscosity was measured by spindle number 6 at 10 rpm and room temperature by using a Brookfield viscometer.

Single dose toxicity study of Samanea saman gum in rat

In a single-dose toxicity study, three male Albino Rats were utilized. Weekly records were maintained for both feed intake and body weight throughout the experimental period. After six days of acclimatization to laboratory conditions, the animals were orally administered the test item on the first day of the experiment.[13,14] The animals were closely monitored for signs of toxicity twice daily over 14 days, including observations of pre-terminal death, food intake, and body weight. Clinical symptoms, especially lethality, were carefully assessed. On the 15th day, euthanasia was

performed on all animals, and necropsy and histopathological studies were conducted to further evaluate the study's findings.

Preliminary formulation of valsartan mucoadhesive pellet

Valsartan and PVP 30 K were separately dispersed in IPA with talc as an anti-tacking agent, each stirred for 30 min. Subsequently, the two solutions were combined, and PEG 400 was introduced as a plasticizer. Additional IPA was added to reach the desired volume. The valsartan dispersion was then sprayed over starch using a fluidized bed processor until the desired drug loading was achieved. Table 1 lists the composition of drug layering, while Table 2 outlines the other processing parameters utilized.[15,16]

Preparation of HPMC K5M, and K15M non-aqueous barrier film coating system

To control drug release, valsartan layered pellets underwent coating with HPMC K5M (P1, P2, and P3) and HPMC K15M (Q1, Q2, and Q3) using a fluidized bed processor (FBP). A 1% coating suspension was prepared, and weight gain was incrementally adjusted to 5%, 10%, and 15% w/w through three trials. HPMC polymers were mixed in IPA with agitation and solubilized using dichloromethane. Instacoat universal was added, volume adjusted with dichloromethane, followed by fluidization and drying (50°C, 30 min) to form pellets. Coating composition and processing parameters are listed in Tables 3 and 4 respectively.

Evaluation of micromeritic properties, *in vitro* dissolution testing, and drug content was conducted on HPMC K5M and HPMC K15M non-aqueous coated pellets. Finally depending upon the *in vitro* drug release (90%) study of each weight gain pellets polymer and the final coating weight gain was selected for further study.[17,18]

Outer functional coat of mucoadhesive polymer

To achieve mucoadhesion pellets were coated with mucoadhesive polymer *Samanea saman* gum. This method of mucoadhesion continues to be a simple and practical means for achieving mucosal sustained delivery drug throughout GIT.[19] The schematic diagram for the coating of pellets by polymers is shown in Figure 1. To prepare a 1% *Samanea saman* gum coating solution, a specified amount of gum was added to a mixture of IPA and purified water, and mixed until a clear solution formed. As a plasticizer, triethyl citrate was introduced. This dispersion was applied for coating drug and polymer-coated pellets. The coating was performed to achieve 10%, 20%, 30%, 40%, and 50% w/w coating weight gains in batches R1 to R5. Processing parameters are listed in Table 5.

Statistical optimization by using 3^2 factorial design[20,21]

Results obtained from the *in vitro* release study for preliminary batches, the batch which showed 90% drug release within 12 hr and mucoadhesion time was selected to optimize the effects of variables on the formulation. A 3^2 full factorial design was implemented, where the extent of *Samanea saman* coating (X1) and HPMC K15M coating (X2) served as the two independent variables. The dependent variables were mucoadhesion time (Y1) and the time required to release 90% of the drug (Y2). The independent and dependent variables utilized are detailed in Table 6. The Design Expert® tool (Design Expert trial version 12.0.12.0, State-Ease Inc., Minneapolis, MN, USA) was employed to generate a mathematical model, using a conventional linear regression technique, to study the impacts of independent factors on the dependent variables.

Evaluation of valsartan layered pellets[22]

Formulated pellets were evaluated for particle size, encapsulation efficiency; percent yield value, friability test, micromeritic study like the angle of repose, tapped and bulk density, Hausner's ratio, and compressibility index.

Pellet shape

Optimized pellet formulations were assessed for shape using optical microscopic image analysis. A motic microscope and digitalized software were employed to analyze images, measuring maximum (dmax) and minimum (dmin) diameters, circumferences, and areas of ten pellets for each formulation.[23] The following formulae were used to calculate the two parameters, aspect ratio and pellet circularity.

$$\text{Aspect Ratio} = \frac{\text{dmax}}{\text{dmin}}$$

$$\text{Pellet Circularity} = 4\pi a/P^2$$

Where P is the perimeter of the pellet and A is the projected area as seen through the microscope.

Ex vivo mucoadhesion strength

The mucoadhesive qualities can be determined *in vitro* using a wash-off test and falling liquid film tests. A minimum of 25 pellets of each formulation were tested.

In vitro wash-off test

Small intestinal and stomach tissues, obtained from a slaughterhouse, were maintained in Tyrodes solution. Affixed on a plastic slide, each tissue was covered with 25 pellets. These slides were attached to a USP tablet disintegrating apparatus, moving steadily in test fluids (0.1 N HCl and pH 6.8 phosphate buffer) at 37°C. After a set time, the remaining adhered pellets were quantified to calculate the percent bioadhesion.[24]

Falling liquid film method

A goat's small intestine piece spread on a glass slide had about 100 pellets evenly distributed on its mucosal layer. Hydration with phosphate buffer (pH 6.8) was followed by a 50° tilt, and mucosa

washing at 15±2 mL/min for 45 min. Bioadhesion was measured at 2 cm from the application site, with detached pellets collected in a receiver. The experiment, conducted in triplicate, was limited to 2 hr due to changes in tissue surface characteristics.

In vitro drug release study

Valsartan pellets with a 51 mg equivalent dose were encapsulated in a hard gelatin capsule. *In vitro* drug dissolution was conducted using a USP dissolution basket apparatus at 100 rpm in 900 mL dissolution media. The temperature was maintained at 37.5± 0.1°C throughout the study. The initial 2 hr utilized 0.1N HCl (pH 1.2), followed by pH 6.8 phosphate buffer for an additional 10 hr. Dissolution samples were analyzed at 252 nm using a UV spectrophotometer.[25,26]

Kinetic analysis of dissolution data

Drug release kinetics were assessed using different release kinetic models like the zero-order, first-order, Higuchi, and Korsmeyer-Peppas models.[27]

Surface topography

The surface characterization studies by scanning electron microscopy were conducted on the batch of pellets that had been optimized.[28]

Compatibility study of drug and polymer

Formulation stability relies on drug-excipient compatibility, crucial for detecting potential interactions that may impact bioavailability and stability.[29] Several techniques can be used to determine drug-excipient interaction in the optimized formulation of gum such as XR-D and FTIR.

X-ray image study of pellets for mucoadhesion[30]

An X-ray image study on mucoadhesive pellets in NZW rabbits, approved by IAEC (registration CRY/2021/037), aimed to assess pellets mucoadhesive capacity through oral administration. Four fasted Albino male rabbits (1.5-2.0 Kg) underwent an *in vivo* study with gastrointestinal X-ray radiographs at various time points. Pellets, coated with barium sulfate, were monitored using 40 KV and 5 mA radiation. Fixed intervals of 1, 2, 4, 6, 8, 10, and 12 hr captured abdominal radiographs, revealing pellet attachment locations and durations in the GIT.

In vivo pharmacokinetic study of optimized valsartan mucoadhesive pellets[31,32]

In vivo tests on male Wistar rats (200-220 g) involved pure valsartan and an optimized mucoadhesive pellets formulation. Animals were housed in a controlled environment, fasted overnight, and given water ad libitum. The study, approved by IAEC (registration IAEC/2020-21/68-5), followed ethical guidelines (CPCSEA). Three groups, each with twelve animals, received pure valsartan, optimized mucoadhesive pellets (10 mg/kg orally), and a marketed valsartan formulation. Blood samples were collected at various intervals post-dose, centrifuged, and stored at -20°C. Valsartan concentrations in plasma were determined using HPLC with a calibration curve.

Stability study of optimized pellets[33]

Stability studies were performed on the final dosage form of three distinct batches of an optimized formulation following ICH guidelines over three months. The study assessed filled capsules containing pellets under two temperature conditions 30°C±2°C, 65±5% RH, and 40°C±2°C, 75±5% RH. Sampling occurred monthly, with evaluations conducted on UV spectra, drug content, and percentage drug release.

RESULTS AND DISCUSSION

Authentication of Samanea saman gum[34]

The herbarium specimen of Samanea saman underwent authentication at the Botanical Survey of India, Pune, and was assigned registration number BSI/WRC/IDEN.CER/2017/H3-17/334.

Physicochemical evaluation of Samanea saman gum

The macroscopic examination of *Samanea saman* gum is presented in Table 7. The isolated *Samanea saman* gum, obtained as a pale white powder with a distinctive odor and mucilaginous taste, displayed a rough and irregular texture, yielding 6% w/w following purification. With water solubility and resistance to alcohol, chloroform, acetone, and ether, the gum exhibited low moisture content (3.2% w/w), ensuring stability in formulations. Ash values, including total ash and acid-insoluble ash, suggested effective purification and the absence of contaminants. A notable

Table 1: Composition of Valsartan Layering Solution.

Sl. No.	Ingredient	Quantity
1	Valsartan IP	0.5 g
2	PVP K30 IP	1 g
3	PEG 400 IP	0.5 mL
4	Talc IP	0.1 g
5	Isopropyl alcohol IP	100 mL

Table 2: Parameters for Valsartan Layering over Celpheres.

Sl. No.	Process Parameters	Drug layering
1	Pellets bed size (g)	100
2	Spray rate (g/min)	1-1.5
3	Air flow (bar)	0.6-1.2
4	Atomizing pressure (bar)	0.8-1.8
5	Nozzle diameter (mm)	0.5
6	Inlet temperature (°C)	50-60
7	Product temperature (°C)	36-40

Table 3: Composition of HPMC K5M and K15M Non-Aqueous Coating Solution.

Sl. No.	Ingredients	Quantity (%)
Coating Solution P		
1	HPMC K5M	1
2	Instacoat universal	0.5
3	PEG 400 IP	0.5 mL
4	Isopropyl alcohol	45
5	Dichloro methane	qs.
Coating Solution Q		
1	HPMC K15M	1
2	Instacoat universal	0.5
3	PEG 400 IP	0.5 mL
4	Isopropyl alcohol	50
5	Dichloro methane	qs.

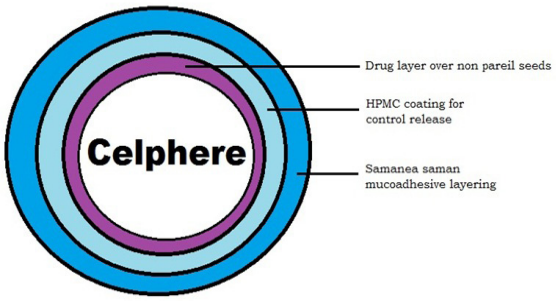

Figure 1: Schematic Presentation of Steps Involved in Drug Layering and HPMC K5M/K15M and Outer *Samanea saman* Coating.

Table 4: Coating Parameters for HPMC K5M and K15M over Drug Layered Pellets.

Sl. No.	Process Parameters	Coating Solution P	Coating Solution Q
1	Drug layered pellets (g)	50	50
2	Spray rate (g/min)	1.5-2	1.5-2.5
3	Air flow (bar)	1.8-2.2	2.0-2.5
4	Atomizing pressure (bar)	1.5-2.0	1.5-2.0
5	Nozzle diameter (mm)	0.5	0.5
6	Inlet temperature (°C)	45-50	45-50
7	Product temperature (°C)	35-40	35-40
8	Final drying in oven	50°C, 1 hr	50°C, 1 hr

Table 5: Process Parameters for Coating of *Samanea saman* Solution.

Sl. No.	Process Parameters	Conditions
1	Pellets bed size (g)	50
2	Spray rate (g/min)	0.6-2.5
3	Air flow (bar)	0.8-1.5
4	Atomizing pressure (bar)	1.0-1.8
5	Nozzle diameter (mm)	0.5
6	Inlet temperature (°C)	35-45
7	Product temperature (°C)	30-35
8	Final drying in oven	50°C, 2 hr

Table 6: Experimental Design: Independent and Dependent Variables and the Levels Used for Factorial Design.

Factors (independent variables)	Levels used			Levels used
	-1	0	1	
X1=Extent of *Samanea saman* coating weight gain (% w/w)	30	40	50	Y1= mucoadhesion time
X2= Extent of HPMC K15M coating weight gain (% w/w)	8	10	12	Y2= t_{90} (Time required to release 90% drug)

Table 7: Physicochemical Characterization of Gum.

Sl. No.	Properties evaluated	Observation
1	Color	Pale white
2	Odor	Characteristic
3	Taste	Mucilaginous
4	Nature	Crystalline
5	Solubility	Forms colloidal solution in water and insoluble in Ethanol, chloroform.
6	Loss on Drying	3.2% w/w
7	Percentage Yield	6% w/w
8	Total ash value	7.5% w/w
9	Acid insoluble ash value	1.4% w/w
10	Viscosity (1% solution)	16.451 Pas
11	Swelling Index	7.5
12	pH (By Digital pH Meter)	7.1

Table 8: Micromeritic Study of HPMC K5M and K15M Coated Valsartan Pellet.

Trial Batch code	Bulk density * (gm/mL)	Tapped density * (gm/mL)	Angle of repose * (°)	Hausner ratio *	Friability * (%)	%Drug Content *
P1	0.864±0.53	0.902±1.05	18.31±2.01	1.043±0.47	0.061±1.56	82.22±0.29
P2	0.851±1.3	0.898±1.4	18.52±1.99	1.055±1.1	0.056±1.4	84.38±1.26
P3	0.830±0.21	0.846±0.4	14.34±1.24	1.019±1.33	0.033±1.67	85.42±0.34
Q1	0.788±0.84	0.824±1.24	19.22±1.47	1.045±0.24	0.048±0.27	84.87±0.77
Q2	0.802±0.41	0.892±1.03	16.24±1.69	1.112±0.36	0.052±0.09	86.4±1.09
Q3	0.814±1.42	0.915±1.22	12.42±1.12	1.124±0.65	0.028±1.29	87.74±2.14

*=mean±SD; *n*=3.

Table 9: Micromeritic Study of *Samanea saman* Coated Valsartan Pellets.

Trial Batch code	Bulk density g/mL)	Tapped density g/mL)	Angle of repose (°)	Hausner ratio	Friability (%)
R1	0.818±1.09	0.888±0.78	17.17±1.3	1.08	0.087±0.26
R2	0.825±0.04	0.908±1.23	19.54±0.7	1.10	0.064±1.087
R3	0.860±2.1	0.892±1.57	16.63±0.09	1.03	0.070±1.44
R4	0.849±3.02	0.904±2.03	21.94±1.7	1.06	0.043±0.65
R5	0.797±0.8	0.832±0.09	19.78±1.2	1.04	0.048±2.14

*Mean±S.D., *n*=3.

swelling index of 7.5 indicated significant water absorption, leading to the formation of a mucilaginous gummy gel conducive to mucoadhesion. The gum's neutral pH (7.1) is relevant for applications where pH considerations are crucial. Phytochemical tests, such as Molisch's, Benedict's, and Barfoed's, confirmed the presence of carbohydrates, affirming the purity of the isolated gum.

Single-dose toxicity study of *Samanea saman* gum in rat

The rat single-dose toxicity study on *Samanea saman* gum revealed no pre-terminal deaths and normal food intake and body weight patterns were observed. Comprehensive clinical assessments showed no significant changes in various parameters, including skin, fur, eyes, mucous membranes, respiratory

Table 10: Mucoadhesive study of *Samanea saman* Coated Valsartan Pellets.

Trial Batch code	Goat Tissue part	Method	Adhesion Number*
R1	Stomach	I	70.66±4.98
	Intestine	I	45.33±3.77
	Intestine	II	50.66±6.79
R2	Stomach	I	74.66±4.98
	Intestine	I	54.66±6.79
	Intestine	II	52±8.64
R3	Stomach	I	72±6.53
	Intestine	I	68±5.65
	Intestine	II	49.33±6.79
R4	Stomach	I	89.33±4.98
	Intestine	I	70.66±8.21
	Intestine	II	72.33±6.76
R5	Stomach	I	92±3.26
	Intestine	I	74.66±4.98
	Intestine	II	72±3.26

function, salivation, diarrhea, and behavior. Evaluation of the autonomic and central nervous systems detected no tremors, convulsions, or coma. Necroscopy studies found no significant gross organ changes, and histopathological examination of liver and kidney specimens revealed no adverse effects. Overall, the study supports the safety of *Samanea saman* gum for further development and use.[35]

Evaluation of Polymer-coated pellets

The drug layering process exhibited notable efficiency, yielding consistent drug-layered pellets within the range of 90-95% w/w. The suspension layering efficiency, spanning from 90-98% w/w, signifies the adept integration of process and formulation parameters. These findings substantiate the efficacy of the devised Valsartan layering methodology, emphasizing its suitability for pharmaceutical applications.[36]

Micromeritic study of HPMC K5M and K15M coated valsartan pellets

Pellets (P1-P3 and Q1-Q3) exhibited excellent flow properties with angle of repose values ranging from 12.42 to 19.22. The Hausner ratio, indicative of packing ability, was close to 1, signifying good flow properties. Friability test results demonstrated robustness, with all formulations achieving values below 1%. The results are shown in Table 8.

Microscopic swelling study of HPMC K5M and K15M coated valsartan pellets

Utilizing optical microscopy, temporal variations in pellet dimensions were examined, revealing an incremental surface area at distinct time intervals. Figure 2 depicts the swelling kinetics of HPMC pellets on pre- and post-introduction of a water droplet. The observations validated that following water incorporation, the pellet exhibited an enlarged surface area, culminating in the formation of a compact gel-like structure on the pellet surface after a 2 hr interval. This empirical evidence implies the efficacious entrapment of the drug within the gel matrix, indicative of a potential mechanism for sustained drug release.[37]

In vitro drug release study of HPMC K5M and K15M coated pellets

In the *in vitro* drug release study using phosphate buffer pH 6.8, six batches of coated pellets were examined, focusing on the time required for more than 90% drug release. (Figure 3) The findings revealed that elevating the concentration of HPMC polymer resulted in a delayed drug release. The interaction of HPMC with the dissolution media led to the formation of a polymeric gel network. The increased viscosity of the gel, attributed to higher concentrations of HPMC K5M and K15M (P1 to P3 and Q1 to Q3), extended the drug diffusion path, consequently retarding the drug release.[38]

Outer functional mucoadhesive coating of *Samanea saman* gum over valsartan pellets

Based on % drug release, HPMC K15M was chosen to control sustained drug release for up to 12 hr. Consequently, the Q2 batch, featuring HPMC K15M at 10%, was selected for further coating. Subsequent to HPMC coating, *Samanea saman* coating, a mucoadhesive polymer, was chosen to facilitate adhesion in the Gastrointestinal Tract (GIT) and achieve sustained drug release. Post-coating, pellet analysis for weight gain indicated the efficacy of the process parameters and solution composition in facilitating

Table 11: Micromeritic Study of Valsartan Optimization Batches S1-S9.

Batch Code	Bulk density (g/mL)*	Tapped density (g/mL) *	Angle of repose *	Hausner's ratio *	% Drug Content *
S1	0.854±0.21	0.935±0.16	29.01±0.39	1.09	84.11±0.01
S2	0.846±0.12	0.938±0.20	27.85±0.42	1.10	86.23±0.5
S3	0.814±0.10	0.945±0.14	24.38±0.45	1.16	87.23±0.62
S4	0.827±0.14	0.908±0.15	30.03±0.84	1.08	85.66±1.42
S5	0.841±0.15	0.904±0.18	28.94±0.73	1.07	78.36±1.89
S6	0.850±0.18	0.936±0.13	27.04±0.74	1.10	81.47±1.2
S7	0.816±0.10	0.854±0.15	25.38±0.63	1.04	80.69±0.67
S8	0.848±0.17	0.899±0.12	26.57±0.50	1.06	85.63±0.94
S9	0.896±0.13	0.943±0.10	29.08±0.37	1.05	84.36±1.42

*Mean±SD; *n*=3.

Table 12: Results of Mucoadhesion Testing of Optimized Formulation Batches (S1-S9) At 08 Hr.

Batch Code	Mucoadhesion Number		
	Method I		Method II
	Stomach	Intestine	Intestine
S1	74.66±4.98	56.44±6.79	45.33±3.77
S2	85.33±4.38	60±5.65	52.86±8.64
S3	90.66±4.98	63.22±4.61	59.33±6.79
S4	84.67±10.06	58.50±4.65	60.20±6.53
S5	90.08±6.65	69.60±3.26	66.66±4.98
S6	92.74±3.26	73.33±5.69	70.66±4.98
S7	78.70±6.11	61.23±6.79	63.80±6.76
S8	89.33±4.98	70.66±8.21	72±6.53
S9	94±3.26	72.33±6.76	74.66±4.98

*Mean±SD; *n*=3.

the desired coating efficiency. Pellets were again evaluated for micromeritic characteristics (Table 9).

In vitro drug release study of valsartan experimental trial batches

The obtained data of % drug release batch R4 and R5 showed close to similar results of mucoadhesion and cumulative percent drug release. Hence it was concluded that valsartan layered and 10% HPMC K15M coated pellets with outer *Samanea saman* coat with about 40% weight gain (R4) showed good mucoadhesive strength which indicates that *Samanea saman* is a suitable mucoadhesive polymer and above 90% of drug release in 14 hr. The results of % drug release are shown in Figure 4.

Ex vivo mucoadhesion testing

Among formulations R1-R5, batches R1 and R2 exhibited no surface cracking during the entire test duration. As shown in Table 10 batches R4 and R5 demonstrated comparable and robust mucoadhesion in both mucoadhesion testing methods. Consequently, R4 was selected for further statistical optimization. In the production and *ex vivo* mucoadhesion testing of study formulations, insights from preliminary trials will be considered. Notably, intestinal pH exhibited superior mucoadhesion strength, as indicated by a higher percentage adhesion number that resisted wash-off compared to gastric pH. The hydration and mucoadhesive strength of the polymers were found to be significantly influenced by the pH of the medium. Wash-off test results underscored the pellets commendable mucoadhesive properties under gastric conditions.[39]

Statistical optimization of valsartan formulation using 3^2 factorial design

The R4 formulation, featuring a 40% weight gain in the *Samanea saman* coat and a 10% weight gain in the HPMC K15M coat, was selected for optimization based on successful experimental

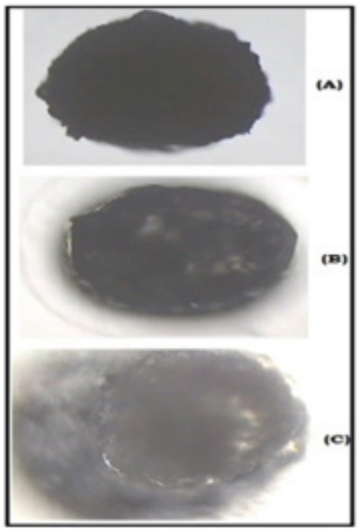

Figure 2: Microscopic Swelling Study of HPMC K15M Coated Valsartan Pellet (A) Pellet Before Addition of Water Droplet, (B) Pellet After Addition of Water Droplet (2 Hrs.)(C) Pellet after Addition of Water Droplet (6 Hrs.) at 40x Magnification.

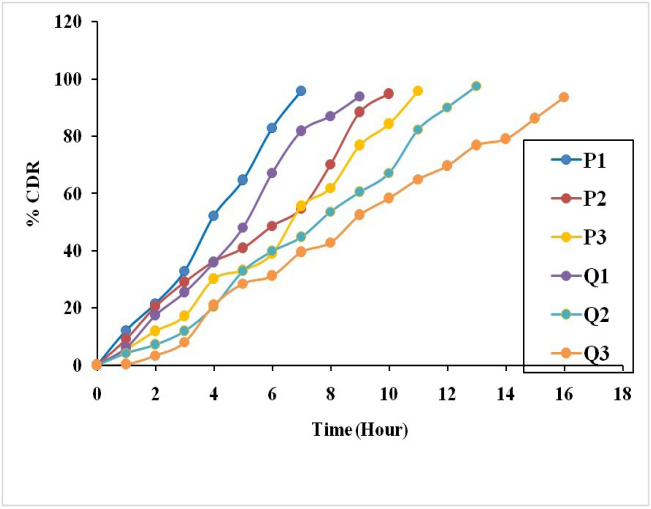

Figure 3: % Drug Release from HPMC K5M (P1-P3) and HPMC K15M (Q1-Q3) Coated Valsartan Pellets.

trial batches. This formulation demonstrated sustained release and desirable mucoadhesion. Using a 3^2 general factorial design, the investigation explored varying coating weight gains (30-50% w/w for *Samanea saman* and 8-12% w/w for HPMC K15M), generating nine formulations (S1 to S9). This systematic approach allows for the refinement of coating weight gain combinations, optimizing sustained release and mucoadhesion properties in the pharmaceutical development process.

Evaluation of valsartan optimization batches

Micromeritic study of valsartan optimization batches

The micromeritic properties of pellets S1-S9, derived from optimized formulation batches, were systematically assessed. The angles of repose for all optimization batches were observed

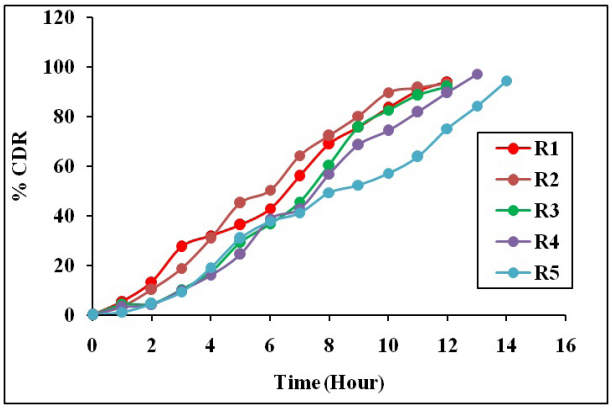

Figure 4: % Drug Release from the *Samanea saman* Coated Valsartan Pellets (R1-R5).

to range between 24 and 28º, indicating favorable flow characteristics of the pellets. The Hausner's ratio, being proximate to 1, signifies commendable packing and flow capacity. These findings contribute valuable insights into the particle behavior and pharmaceutical characteristics of the optimized pellet formulations. The results of the micromeritic study are shown in Table 11.

Ex vivo mucoadhesion testing

The wash-off test results demonstrated superior mucoadhesive properties of the pellets in gastric conditions compared to intestinal conditions. The mucoadhesive strength in the stomach ranged from 74.66±4.98 to 94±3.26, indicating excellent bioadhesion to goat stomach tissue across all formulations (Table 12). Notably, formulations S6 and S9 exhibited the highest bioadhesion in the stomach, highlighting maximal affinity and attachment to the gastric mucosa Figure 5. These findings affirm the efficacy of the developed pellet formulations for achieving sustained drug release and robust mucoadhesion, particularly in gastric environments.[40]

The findings from the *in vitro* drug release study indicate that the hydrophilic properties inherent in HPMC K15 instigate gel formation, leading to an elevation in the viscosity of the dissolution medium. Simultaneously, this phenomenon contributes to an increase in pore tortuosity within the polymeric matrix. These combined effects act synergistically to impede the diffusion process of the drug, causing a discernible deceleration in the release kinetics. Consequently, the observed trend suggests that with an incremental rise in the concentration of HPMC K15, there is a corresponding retardation in the drug release profile from the valsartan mucoadhesive pellets Figure 6.

In vitro drug release kinetics

The drug release patterns from the formulations adhere to the zero-order release kinetic model, implying a uniform and concentration-independent release mechanism. Across

Table 13: ***In vivo*** **Pharmacokinetics Parameters for Pure Valsartan drug, Valsartan Pellets and Marketed Tablet.**

Parameter	Valsartan Pure Drug*	Optimized formulation*	Marketed formulation*
C_{max} (µg/mL)	8.7±0.38	8.6±0.43	9.5±0.83
T max (hr)	4±0.18	8±0.46	8±0.58
K_{el} (hr)	0.403±0.01	0.310±0.01	0.2418±0.01
CL (mL/hr/Kg)	122.521±14.55	65.371±5.90	53.363±6.87
$t_{1/2}$ (hr)	1.72±0.02	2.236±0.03	2.872±0.04
MRT (hr)	8±0.23	11.4±0.72	12.4±1.26
$AUC_{0\to t}$ (µg· hr/mL)	81±5.88	274.4±2.88	177.5±1612
$AUMC_{0\to t}$ (µg.hr*hr/mL)	629±48.36	1738.7±153.89	2316.7±144.26

*mean±S.D, *n*=3.

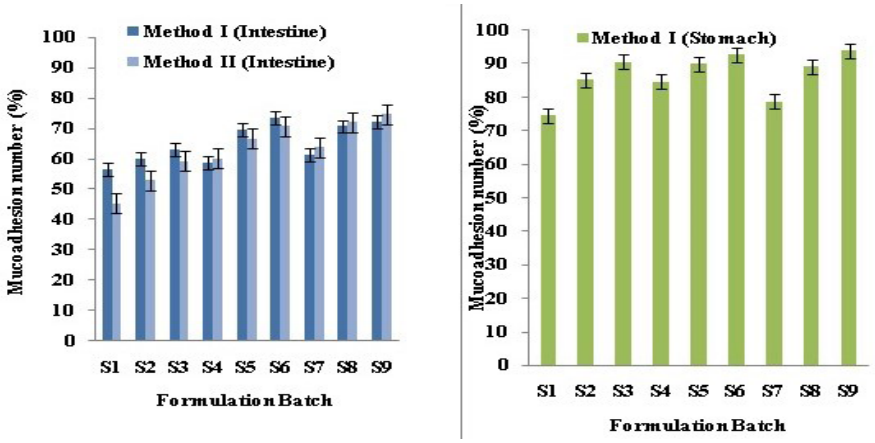

Figure 5: Mucoadhesion Strength Testing of Optimized Formulation Batches. *In vitro* Drug Release Study of Optimization Batches S1-S9.

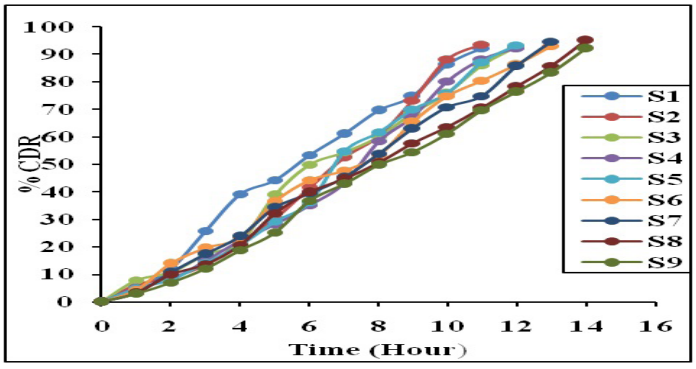

Figure 6: % Drug Release Profile of Valsartan Optimization Batches (S1-S9).

formulations S1 to S9, except S6, the release exponent values (n) fall within the range of 0.57 to 0.88. This range is indicative of a non-Fickian diffusion mechanism governing the drug release from the pellets. However, formulation S6 exhibits a super case II transport mechanism.

Optimization data analysis

Response surface methodology was employed to optimize variables. The *ex vivo* mucoadhesive number and t90% values from all nine batches were analyzed and fitted to different models using Design Expert® software. Based on the P values and a low

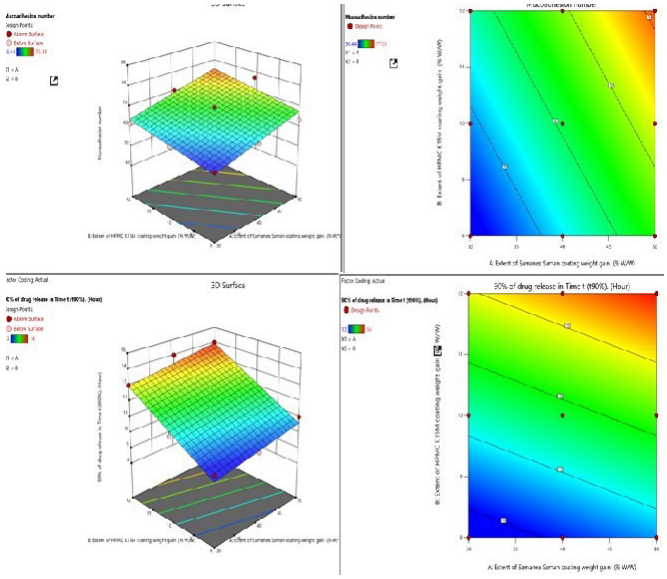

Figure 7: Response Surface Graph and Contour Plot for Showing the Effect of Both Variables on Mucoadhesive Strength and t90% of Pellets

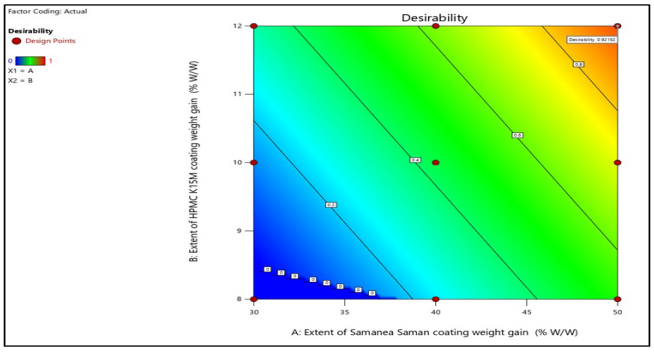

Figure 8: Desirability Plot for Mucoadhesive Pellets.

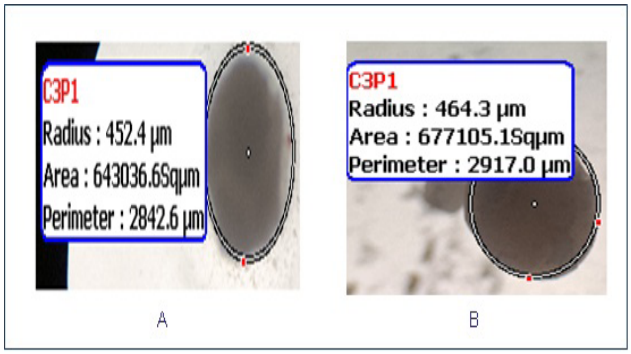

Figure 9: A) Microscopic Image of Valsartan Pellet after HPMC Coating. B) Microscopic Image of Valsartan Pellet after *Samanea saman* Coating.

PRESS value, indicating sufficient model fitting, a quadratic model was chosen for both responses.[22]

The linear model was selected for both the responses based on the P values and low PRESS value indicating adequate fitting of the model. The final equation in terms of actual factors of the mucoadhesive strength of pellets is as per the following

Mucoadhesive strength of pellets =+20.53889+0.611833(A)+2.04667(B)

A=Extent of *Samanea saman* coating weight gain.

B=Extent of HPMC K15M coating weight gain.

The positive sign of polynomial terms for individual effects shows a synergetic effect. As the *Samanea saman* gum concentration

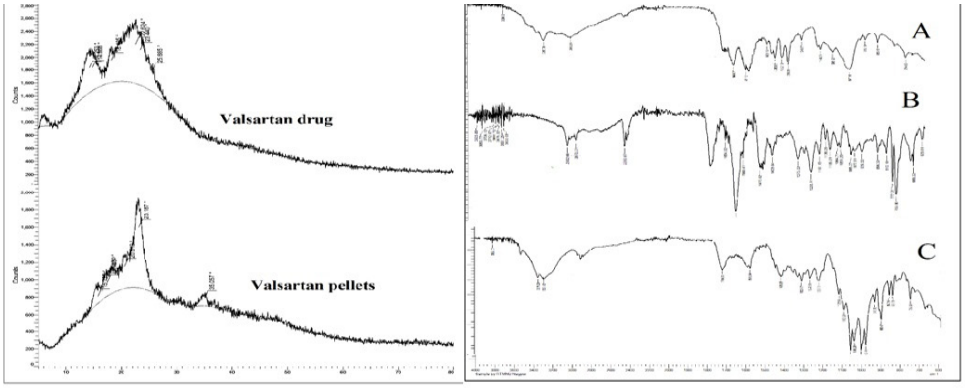

Figure 10: Compatibility study of Optimized Valsartan pellets by X-RD and FTIR.

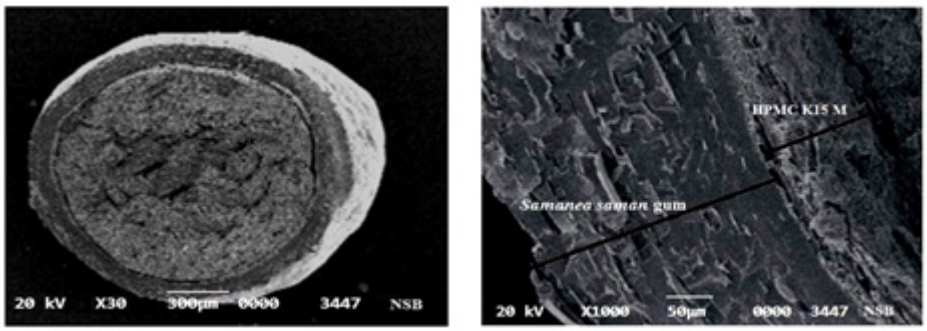

Figure 11: SEM for Cross Section of *Samanea saman* coated Valsartan Pellet at x30 and at x1000 Magnification.

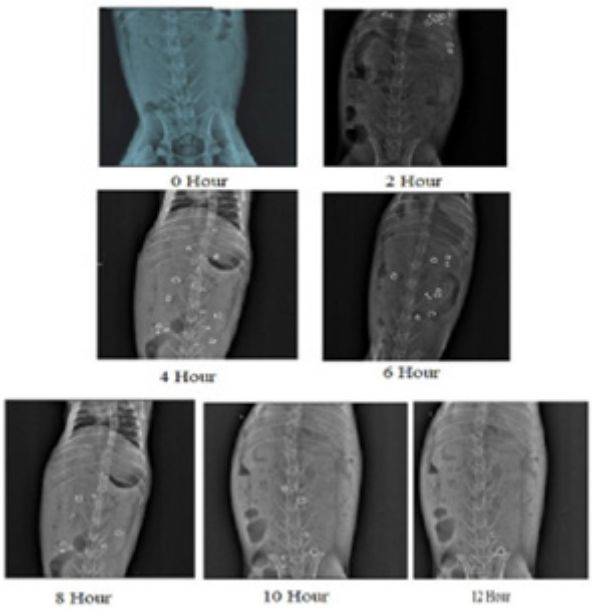

Figure 12: Abdominal X-ray of Rabbit with 40Kv and 5mA's from 0 Hr to 12 Hr.

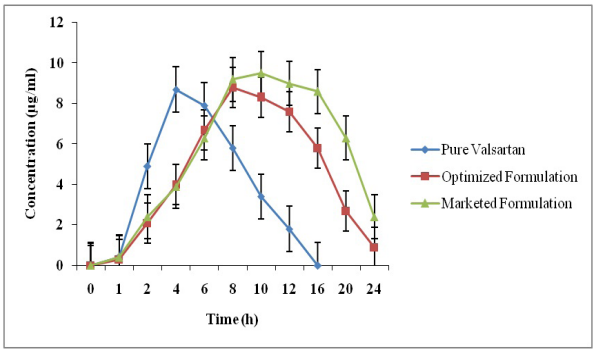

Figure 13: Pharmacokinetic % Drug Absorption of Valsartan Pure Drug, Optimized and Marketed Formulation.

present in the coating of pellets increases mucoadhesive strength of pellets is also increased. The Model F-value of 10.88 suggests the model is significant. P Values of 0.0101 less than 0.0500 indicate model terms are significant. The final equation represents the time needed for 90% of drug release is represented below

Time required to release 90% drug (t90%)=+11.78+0.5000 (A) 1.67 (B)

Contour plot and response surface analysis

Three-dimensional response surface plots (Figure 7) demonstrated a linear correlation between *Samanea saman* gum concentration and mucoadhesive strength. Simultaneously, drug release studies indicated that an elevation in HPMC K15M concentration resulted in a retardation effect on drug release. The optimization

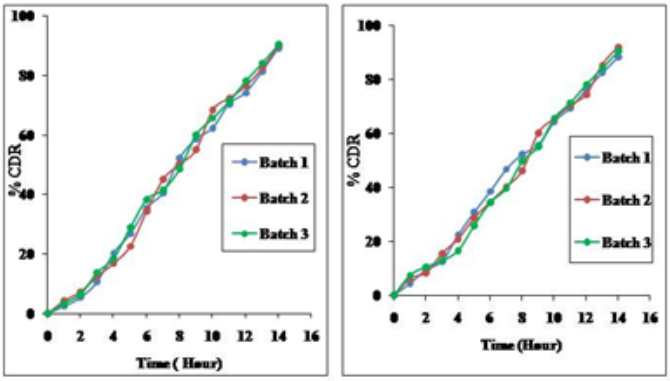

Figure 14: *In vitro* Comparative Dissolution Data of Valsartan Mucoadhesive Pellets for Three Batches at 30ºC±2ºC, 65±5%RH and 40ºC±2ºC, 75±5%RH.

process identified batch S9 as the optimal formulation, with a desirability Value of 0.922 Figure 8. The validation results demonstrated a percent prediction error within±10% for both mucoadhesive strength (3.135%) and the time required to achieve 90% drug release (0.307%). These findings affirm the accuracy and reliability of the optimization process and highlight the efficacy of the optimized batch (S9) in achieving the desired pharmaceutical characteristics.[41]

Shape of HPMC and *Samanea saman coated optimized* valsartan pellets

Utilizing Motic microscopy, *Samanea saman*-coated pellets were examined, determining an average aspect ratio of 1.08 and pellet circularity of 0.94. Both metrics, closer to 1 than 0 indicate a shift towards a more spherical form post-coating Figure 9. This suggests the efficacy of *Samanea saman* in influencing pellet morphology, essential for applications requiring precise shapes.[37]

Compatibility study of optimized valsartan pellets

The compatibility study of valsartan with excipients in pellets formulation was done by X-RD and FTIR.

By X-ray diffractometry

The X-ray diffraction analysis revealed characteristic crystalline peaks of valsartan at 2θ angles of 14.253º, 14.868º, 18.485º, 22.624º, 23.440º, and 25.685º (Figure 10), confirming the presence of crystalline valsartan. In the optimized pellet formulation, these peaks were still discernible but with reduced intensity, indicating a potential alteration in the crystallinity of the pure drug during the layering process with the polymer.[42]

By FTIR

In the optimized pellet formulation (depicted in Figure 10), the distinctive peaks of valsartan at 3417.6 cm^{-1} (N-H stretching) and 1734.01 cm-1 (C=O stretching) displayed slight shifts, suggesting alterations possibly due to solubilization or bond formation with the polymer. Additionally, the emergence of a peak at 1741.41 cm^{-1} in the pellet's FTIR spectrum indicated potential hydrogen bond formation involving the carbonyl group of the pure drug.[17,43]

SEM of *Samanea saman* coated pellet

Following the drug layering process and subsequent coating with HPMC and *Samanea saman*, the resulting pellets exhibited a spherical morphology. The SEM analysis, conducted at magnifications of x30, x500, x1000, x3000, and x6000, revealed well-defined surfaces of the Samanea saman coated pellets without any observable cracks or porous structures. (Figure 11) This microscopy study provides detailed insights into the morphology and surface characteristics of the coated pellets, confirming their overall integrity and uniformity.[44]

X-ray image study of microspheres for mucoadhesion

The structural integrity and shape retention of optimized coated pellets loaded with barium sulfate in the stomach and small intestine were validated by rabbit abdominal radiography. At 1, 2, 4, 6, 8, 10, and 12 hr, there were distinct signs of pellet adhesion to the gut; by the 12 hr point, the number had significantly decreased. The complete disappearance of all pellets occurred after the 12 hr time point. (Figure 12).

In vivo pharmacokinetic results in rats

The data were generated using the first-order absorption and one-compartment model with first-order elimination. Plasma concentration versus time plots facilitated the direct calculation of the maximal peak concentration (C_{max}) and the corresponding time (T_{max}). The elimination rate constant (Ke) was derived from the terminal phase of the log plasma concentration versus time profile using least squares regression analysis. Utilizing the trapezoidal rule, areas under the plasma concentration-time curve (AUC0→t), area under the first moment curve (AUMC0→t), and Mean Residence Time (MRT) were determined.[45] (Table 13). In an *in vivo* pharmacokinetic study in rats, C_{max} was found to be 8.6±0.43 µg/mL, with a T_{max} of 8 hr and a bioavailability of 64.68% Figure 13. Analysis of pharmacokinetic data indicated a twofold increase in the bioavailability of valsartan after coating with HPMC K15M and mucoadhesive *Samanea saman* gum.

Stability study

For the optimized pellets stability study was conducted as per ICH guidelines. Evaluation results (Figure 14) indicate the absence of significant degradation in drug quantity, thereby affirming the stability and robustness of the formulated pellets under the specified storage conditions.

CONCLUSION

Novel mucoadhesive drug delivery systems, utilizing a unique polymer derived from *Samanea saman* seeds, significantly enhance valsartan's bioavailability. Optimized formulations

exhibit robust mucoadhesive strength and sustained drug release over 14 hr. Response surface methodology highlights the positive correlation between *Samanea saman* gum concentration and both mucoadhesive properties and drug release retardation. *In vivo* studies demonstrate substantial improvements in pharmacokinetic parameters, showcasing the potential of this approach to enhance valsartan's therapeutic efficacy. Overall, these findings offer a promising strategy for improving valsartan's bioavailability and therapeutic effectiveness through advanced mucoadhesive delivery systems.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

HPMC: Hydroxy Propyl Methyl Cellulose, **PVP:** Poly vinyl pyrolidone, **PEG:** Poly ethylene glycol, **IPA:** Isopropyl alcohol, **SEM:** Scanning Electron Microscopy, **X-RD:** X-ray diffractometry, **FTIR:** Fourier-transform infrared spectroscopy.

SUMMARY

Mucoadhesive drug delivery systems utilizing *Samanea saman* gum were developed to enhance valsartan bioavailability. With an optimized formulation, there was a 14 hour continuous release and strong mucoadhesive strength. Increasing gum concentration improved both adhesion and drug release retardation. Excipient suitability was validated by compatibility experiments, and pellet integrity was confirmed by radiography and microscopy. In vitro dissolution studies and *in vivo* pharmacokinetic in rats demonstrated improved therapeutic efficacy of valsartan, suggesting a promising drug delivery method.

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