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DEVELOPMENT OF ESOMEPRAZOLE MUCOADHESIVE TABLETS USING *MANILKARA ZAPOTA* SEED MUCILAGE: A NOVEL APPROACH FOR IMPROVED BIOAVAILABILITY

Pharmaceutical Science

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ABSTRACT

Objectives: Develop Esomeprazole (ESR) Mucoadhesive Tablets using natural and synthetic polymers to achieve prolonged drug release, preventing gastric degradation and enhancing oral bioavailability. **Methods:** Tablets were formulated using *Manikara Zapota* Mucilage, Guar gum, HPMC15K, and HPMC4K via wet granulation. **Results:** Evaluation of pre- and post-compression parameters showed promising results, and ESM3 had superior mucoadhesive strength (30.58±1.15g & 2.99±0.042N), longest *in-vitro* mucoadhesion time (8.1±0.37hrs), significant swelling index (78.05%), and highest percentage in drug release with favorable kinetics. Optimized ESM3 & ESMH15K showed strong mucoadhesive properties. **Conclusions:** Mucoadhesive ESR tablets offer promise for gastroesophageal reflux disease and gastric ulcer and patient compliance.

KEYWORDS

Esomeprazole, Mucoadhesive tablets, Manikara Zapota, Bioavailability

INTRODUCTION

Oral drug administration, while convenient, faces challenges like low bioavailability, short action duration, and reduced compliance. Controlled Drug Delivery Systems (CDDS) [1], offer extended release but are hindered by gastric emptying and absorption issues. Mucoadhesive systems, using water-soluble polymers, improve drug retention in the gastrointestinal (GI) tract, beneficial for ulcer patients[2]. Esomeprazole (ESP), treating GERD and ulcers, degrades rapidly in acidic environments[3]. *Manilkara Zapota* Linn. (*M.zapota*) gum, extracted from its seeds, is biocompatible, stable, and cost-effective[4-6]. This study develops ESP mucoadhesive tablets with *M. zapota* seed mucilage to enhance bioavailability, prolong GI residence, reduce dosing frequency, minimize side effects and improve patient adherence.

MATERIALS AND METHODS

Esomeprazole was obtained as a Gift sample from Aurobindo Pharma Pvt ltd, Hyderabad, Andra Pradesh, India. HPMC15K, HPMC4K, Magnesium Stearate were obtained as Gift samples from Qualikems Fine Chem. Pvt Ltd, Vadodara, Gujarat. All other chemicals and solvents used were of analytical grade.

Preformulation studies

Compatibility studies - Fourier transforms infrared spectroscopy (FTIR)

Preformulation were performed for compatibility studies**.** FTIR spectrum was recorded using Schimadzu instrument. Drug alone and combination with polymers (1:1) was taken and subjected to studies[7]**.**

Preparation of mucoadhesive tablets

Mucoadhesive Esomeprazole (ESR) tablets (**Table-01**) were formulated by wet granulation method[8]. ESR, *Manilkara Zapota* Mucilage, HPMC, Guar gum, and Avicel pH 102 were combined, wetted with 15% starch paste, dried and compressed. Magnesium stearate and talc were added before compression. Tablets (180 mg each, containing 40 mg ESR) were produced using a rotary tablet compression machine and stored for analysis.

Table - 01: Composition of mucoadhesive tablet

Ingredients* (Equivalent to mg)	Formulations Code					
	ESM1	ESM 2	ESM 3	ESGG	ESH1 5K	ESH 4K
Esomeprazole (ESR)	40	40	40	40	40	40
M. Zapota mucilage	25	50	60	_	_	_
Guar Gum	_	_	_	25	_	_
HPMC 15K	_	_	_	_	25	_
HPMC 4K	_	_	_	_	_	25
Avicel PH102	45	30	25	45	45	45
Starch Paste	q.s	q.s	q.s	q.s	q.s	q.s
Talc	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5

Pre-compression parameters of granules

ESR granules were evaluated [9-11] using Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose.

Evaluation of Mucoadhesive Tablets (Post-compression parameters)

Tablet thickness, Hardness, weight variation and friability was conducted as per standard procedure [12]. The experiment was performed in triplicate, and the average value was determined.

Drug content uniformity

Three tablets from each formulation weighed, powdered and dissolved in phosphate buffer (pH 6.8). Solutions were filtered and 1ml taken for UV spectrophotometric analysis at 310 nm. Average drug content[13] calculated from results.

Ex-vivo mucoadhesive strength

The mucoadhesive strength of tablets was assessed using Modified Physical Balance method[14-15] with detachment approach. Fresh sheep intestine membrane served as the model mucosal surface, prepared by washing and securing to a block moistened with phosphate buffer. Tablets attached to the membrane, and detachment force was measured.

Force of adhesion (N) = (Mucoadhesive strength × 9.81) ÷100

In-vitro mucoadhesive time

The mucoadhesive properties of the tablets were evaluated using the wash-off method[16]. Intestinal mucosa pieces mounted on glass slides, tablet affixed to each slide. The slides were suspended in a USP tablet disintegration apparatus in pH 6.8 at 37°C. The time taken for tablet detachment was recorded.

Swelling index (Water uptake capacity)

Tablet initially weighed (Wo), placed in petri dish containing 5 ml phosphate buffer (pH 6.8) for 8 hours. At specified intervals, tablets removed, excess water removed and reweighed (Wt) after removed excess water using filter paper [17].

Swelling index (SI) = (Wt-Wo)/Wo×100, Wt = Weight after time (t); Wo = Initial weight.

In–vitro drug release studies

In-vitro drug release of tablets was investigated using a USP dissolution apparatus type II[18]. The dissolution medium comprised 900ml acidic buffer (pH 1.2) for 2 hours, followed by phosphate buffer (pH 6.8) for 12 hours. Tablets were placed in the basket, and the temperature was maintained at 37±0.5°C with stirring at 100 rpm. Samples withdrawn, UV spectrophotometric analysis performed. Release profiles plotted as mean values over time, drug release kinetics and mechanism examined[19].

Mucoadhesive strength test

Mucoadhesive strength was tested using a Stable Microsystems Texture Analyzer (Model TAXT plus) with mucoadhesive rig[20]. Tablets attached to probe point, immersed in phosphate buffer at room temperature. Goat intestine piece placed in rig, tablets allowed contact for 60, 120 and 180 seconds at force <10 g. Testing conducted at 25 mm distance.

Tablets crushing strength

The tablets breaking force [21] was measured using a Stable Microsystems Texture Analyzer (Model TAXT plus) with a 1/4-dimension spherical stainless-steel probe. The probe moved downward at appropriate rate, data acquisition started at trigger force level. Compression force to break tablets recorded. Analysis involved testing at least 3 tablets, data processed with Texture Expert® software.

Enteric coating of tablets

Best formulations were coated with enteric coating polymer solution using dipping method[22]. Coated tablets immersed for desired weight gain. Coated tablets assessed for drug content, *in-vitro* mucoadhesion strength, mucoadhesion time, swelling index and *in-vitro* drug release.

Stability studies

Tablets were subjected to stability test for three months per ICH guidelines[23]. Tablets stored at 40°C and 75% relative humidity. Samples collected at 1, 2 & 3 months and the formulations primarily assessed for drug content at these intervals.

RESULTS AND DISCUSSION

Compatibility studies - Fourier transforms infrared spectroscopy (FTIR)

Compatibility studies were determined by IR spectroscopy using KBr method. FT-IR spectra of prepared sample were taken in the wavelength region was 600-3800cm^{-1} at ambient temperature and resolution was 4cm^{-1}. Spectra of pure samples and ESR physical admixtures with suitable polymers were analyzed (**Figure-01 to Figure-03**), with interpretations of the spectra highlighting functional groups of both pure drugs and physical admixtures.

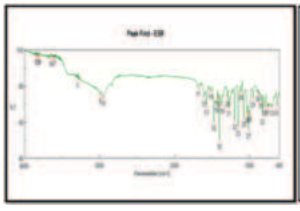


Figure-01: IR spectra of Esomeprazole

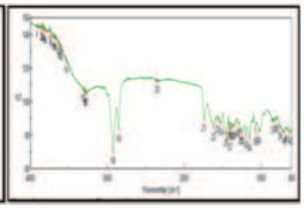


Figure-02: IR spectra of *manikara zapota* mucilage

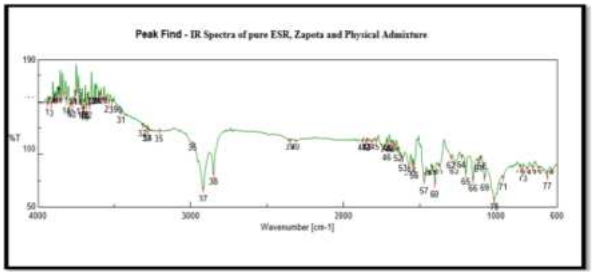


Figure-03: IR spectra of pure drug, mucilage and physical admixtures

Essential functional groups of pure drug (C-H stretching, N-H bending, aromatic C=C stretching, C-F stretching, C-N bending) remained unchanged in ESR physical admixtures. This suggests no modification or chemical interaction between the drug and polymers, as main peaks in functional group and fingerprint regions were identical. The absence of significant differences between the IR spectra of the pure drug and physical admixtures confirms the drug's intactness in the admixtures, with no alterations in peak shape or shift. Drug deemed compatible with polymers, indicating stability in the physical admixtures.

Pre-compression parameters of granules

Bulk Density & Tapped Density

The bulk density and tapped density values were less than 1.2 g/cm3, indicate good packing properties. Bulk density ranged from 0.431±0.002 to 0.512±0.221 g/cm3, showing excellent packing for all granules.

Carr's Index, Hausner's Ratio and Angle of repose

Carr's index (5.85±0.93 to 14.58±0.18) and Hausner's ratio (1.062±0.24 to 1.170±0.21) indicate excellent flowability. Hausner's ratios less than 1.25 show good flow properties. Angle of repose (25.31±0.18 to 29.16±0.41) indicates free-flowing properties of granules (**Table-02**).

Table - 02: Precompression analysis of ESR granules

Formulations code	Bulk density (g/cm3)	Tapped density (g/cm3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
ESM1	0.442±0.012	0.489±0.002	9.61±0.13	1.106±0.14	29.16±0.41
ESM2	0.482±0.014	0.512±0.018	5.85±0.93	1.062±0.24	27.58±0.33
ESM3	0.512±0.221	0.564±0.058	9.21±0.15	1.101±0.04	26.52±0.14
ESGG	0.465±0.174	0.542±0.048	14.20±0.17	1.165±0.15	26.12±0.04
ESH15K	0.445±0.001	0.521±0.014	14.58±0.18	1.170±0.21	25.31±0.18
ESH4K	0.431±0.002	0.498±0.004	13.45±0.64	1.155±0.12	26.18±0.05

Results are mean S.D of three trials (n=3)

Preparation of mucoadhesive tablets

The ESR granules were compressed into the mucoadhesive tablets, as shown in **Photomicrographs-1**,

Photomicrograph-1: Esomeprazole Mucoadhesive Tablets

Post-compression parameters

ESR mucoadhesive tablets were evaluated for their thickness, hardness, average weight, friability and drug content. The results were shown in the **Table-03**.

Table - 03: Post-compression analysis of ESR tablets

Formulations Code	Thickness (mm)	Hardness (Kg/cm2)	Average Weight (mg)	Friability (%)	Drug Content (%)
ESM1	3.12±.036	4.67 ±0.05	160± 0.145	0.41 ± 0.05	95.41± 0.32
ESM2	3.73± 0.024	4.83 ± 0.13	158± 0.128	0.31 ± 0.03	93.42± 0.59
ESM3	3.63± 0.031	4.97 ± 0.01	161± 0.178	0.32 ± 0.01	98.43± 0.42
ESGG	3.52± 0.042	4.58 ± 0.05	159± 0.668	0.43 ± 0.04	91.48± 0.21
ESH15K	3.52± 0.041	4.61 ± 0.10	162± 0.412	0.33 ± 0.01	96.21± 0.24
ESH4K	3.16± 0.046	4.68 ± 0.03	161± 0.547	0.35 ± 0.03	94.54± 0.12

Results are mean S.D of three trials (n=3)

The thickness of tablets ranged from 3.12±0.036 to 3.73±0.024 mm, with tablet hardness varied from 4.67±0.05 to 4.97±0.01 kg/cm2, showing increasing with polymer proportions. Average weight ranged from 158 mg to 161 mg, with no significant variation. Friability less than 1%, meeting IP standards for good mechanical resistance[24]. Drug content ranged from 91.48±0.21% to 98.43±0.42%, indicating uniform drug distribution across tablets.

Ex-vivo mucoadhesive strength

Mucoadhesive strength of tablets influenced by polymer nature and concentration. ESM1 to ESM3 exhibited ranging from 22.47±1.47g to 30.58±1.15g, with mucoadhesion force from 2.20±0.043N to 2.99±0.042N. Formulations ESGG to ESH4K demonstrated mucoadhesive strengths from 26.65±1.14g to 27.52±1.25g, with forces ranging from 2.61±0.017N to 2.69±0.013N. ESM3 showed superior mucoadhesive strength and higher mucoadhesion force (**Figure-04**) [25].

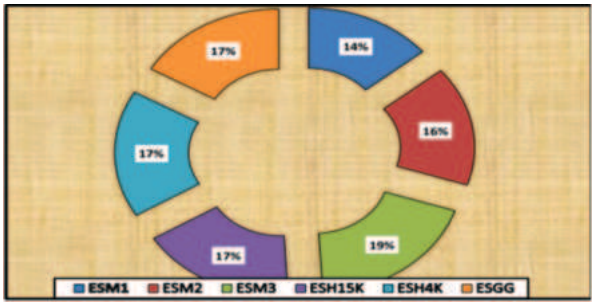
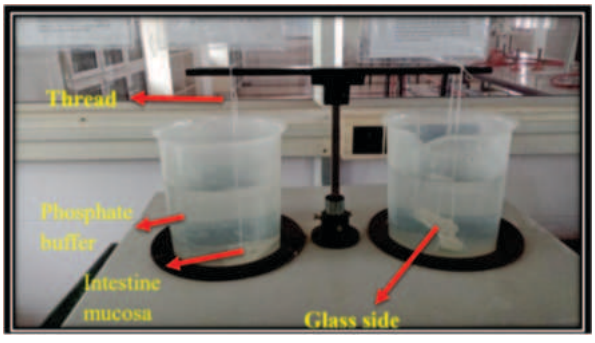


Figure-04: *Ex-vivo* mucoadhesive force of esomeprazole tablets

In-vitro mucoadhesive time

The mucoadhesive properties of the tablets were evaluated using the wash-off method (**Photomicrographs-2**).The mucoadhesive formulations demonstrated mucoadhesive times ranging from 6.5±0.51 to 8.1±0.37 hours (**Table-04**), indicating fairly good mucoadhesive properties in PBS (pH 6.8).



Photomicrograph -2: *In-vitro* wash-off test of mucoadhesive tablet

Table - 04: *In-vitro* mucoadhesive time of esomeprazole tablets

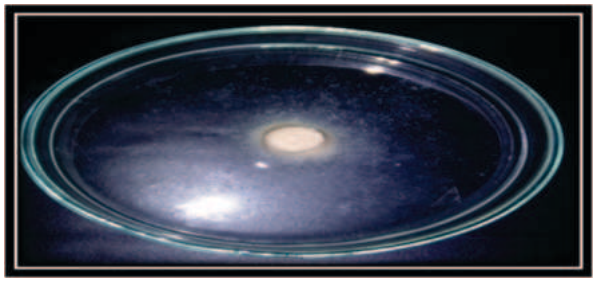
Formulations Code	Mucoadhesive time (hrs)
ESM1	6.5 ± 0.51
ESM2	7.2 ± 0.69
ESM3	8.1 ± 0.37
ESGG	6.9 ± 0.91
EH15K	7.7 ± 0.77
ESH4K	7.5 ± 0.56

Results are mean S.D of three trials (n=3)

Swelling index

Swelling studies were conducted by hydrating 12 tablets with PBS (pH 6.8) for up to 8 hours. Water content variations significantly influenced mechanical properties, with swelling indices ranging from 61.15% to 78.05% at 8 hours. Swelling order was: ESM3 > ESH15K > ESM2 > ESM1 > ESH4K5 > ESGG. ESM3 showed highest swelling index due to mucilage, highlighting polymers' hydrophilic nature.

Photomicrographs-3 depicts the swelling behavior of ESM3.



Photomicrograph-3: Swelling behaviour of ESM3 tablet at eight hours

In-vitro drug release studies

In-vitro release profiles of tablets were assessed using HCl (pH 1.2) for the initial 2 hours, followed by phosphate buffer (pH 6.8) for the remaining time. ESM1, ESM2, ESM3 with *Manikara Zapota* mucilage exhibited 94.60%, 87.83%, and 79.78% drug release, respectively. For ESGG, ESH15K, and ESH4K, drug release were 97.91%, 85.77%, and 91.55%, respectively. ESM3 demonstrated best release (79.78%) over 12 hours due to increased mucilage concentration, similarly to ESH15K found the drug release of 85.77%. Higher mucilage concentrations sustained drug release, likely by increasing diffusion distance. This suggests that, zapota mucilage shown sustained drug release up to 12 hours, acting as a mucoadhesive polymer. Comparative drug release curves are depicted. **Figure - 05 & Figure - 06**

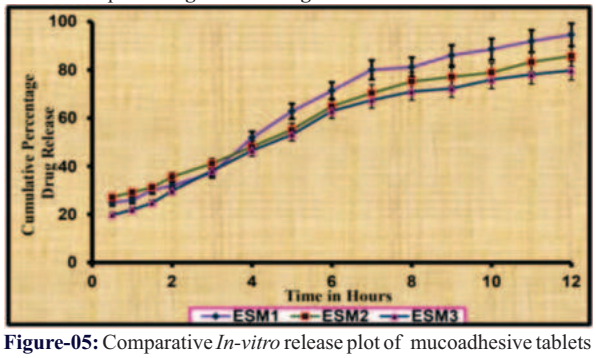


Figure-05: Comparative *In-vitro* release plot of mucoadhesive tablets (ESM1 to ESM 3)

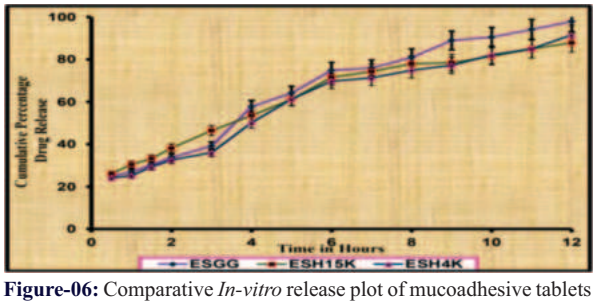


Figure-06: Comparative *In-vitro* release plot of mucoadhesive tablets (ESGG to ESH4K)

Kinetic analysis of *in-vitro* drug release studies

The *in-vitro* drug release study was analysed using Zero order, first order, Higuchi matrix, and Korsmeyer & Peppas equations. The results, including coefficient of correlation (r) values, are presented in **Table-05**.

Table - 05: Kinetics analysis of *in-vitro* drug release of mucoadhesive tablets

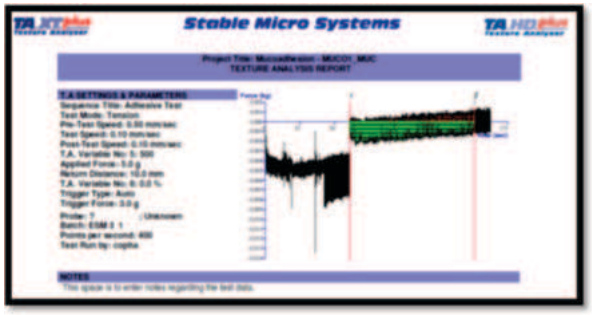
Formulations Code	Release model							
	Zero order		First Order		Higuchi's		Korsmeyer and peppa's	
	R	S	R	S	R	S	R	S
ESM1	0.934	6.75	0.973	-0.076	0.970	26.48	0.976	0.783
ESM2	0.921	5. 50	0.988	-0.065	0.986	24.49	0.982	0.728
ESM3	0.925	5.64	0.987	-0.057	0.982	24.41	0.988	0.798
ESGG	0.932	6.84	0.936	-0.011	0.977	29.25	0.977	0.807
ESH15K	0.896	5.52	0.982	-0.070	0.984	25.11	0.987	0.737
ESH4K	0.930	6.12	0.987	-0.098	0.974	28.76	0.973	0.806

Correlation coefficient ®, Slope(s)

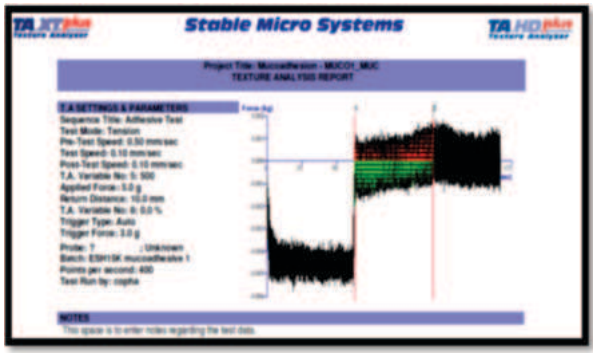
Formulations showed linear relationship, with higher r2 values for the first-order model, indicating first-order controlled release. Correlation coefficient (r) values for ESM1 to ESM3 were 0.973, 0.988 and 0.987, while for ESGG to ESH4K, they were 0.936, 0.982, and 0.987 respectively. Higuchi's model also exhibited linearity with r2 values from 0.970 to 0.986, suggesting diffusion mechanism. Korsmeyer-Peppas model revealed diffusion exponent (n) values between 0.728 to 0.807, with correlation coefficient values ranging from 0.973 to 0.988, indicating Non-Fickian diffusion mechanism. Overall, *in-vitro* drug release demonstrated sustained release patterns over a sufficient duration.

Mucoadhesive strength test

Best formulations (ESM3 & ESH15K) were selected based on *in-vitro* drug release performance. Mucoadhesive tablet analysis conducted using microsystems texture analyzer. **Photomicrographs-4 &5** show similar mucoadhesive properties for ESM3 and ESH15K tablets with minimal variation in adhesive force reported at 60-second contact time.



Photomicrograph -4: Mucoadhesive strength of tablet (ESM 3**)**



Photomicrograph -5: Mucoadhesive strength of tablet (ESH15K)

Enteric coating (EC) of tablets

The best formulation (ESM3) was selected for enteric coating and the results of tablets as shown in **Table-06**.

Table - 06: Evaluation of enteric coated mucoadhesive tablet

Enteric coated tablet	Evaluated Parameters			
	Drug content (%)*	Mucoadhesive strength (g)*	Mucoadhesive time (hrs)*	Swelling index (%) (at end of 8h)
EESM3	99.51±0.38	42.12±0.54	9.1±0.21	82.24%

*Results are mean S.D of three trials (n=3)

EESM3 demonstrated satisfactory drug content (99.51±0.38%) and promising mucoadhesion strength (42.12±0.54g). The *in-vitro* mucoadhesion time yielded 9.1 hours using USP disintegration apparatus.

Swelling index behavior of coated tablets showed good swelling index (82.24%) in PBS (pH 6.8) up to required intervals. Overall, optimized enteric-coated formulations showed superior strength and value compared to plain tablets.

***In-vitro* drug release of EC tablets**

Results showed that, drug release of the coated tablet (EESM3) was 69.57% at end of appropriate hours, indicating minimal release in acidic pH and stability in alkaline conditions (**Figure-07**). Comparative studies showed EC formulation (EESM3) had superior strength and sustained effects. So an *in-vitro* release of EESM3 was delayed by barrier coating, ensuring drug release in intestinal environment, beneficial for ulcer patients.

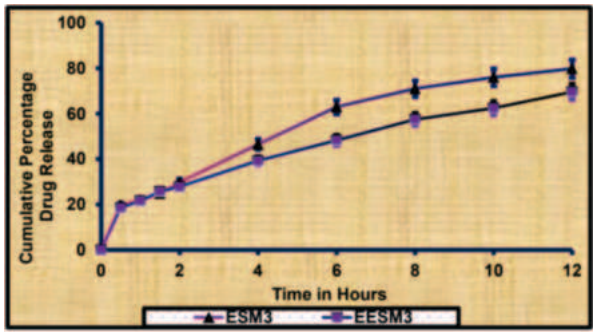


Figure-07: *In-vitro* release plot of plain and enteric coated mucoadhesive tablets

Stability studies

Stability studies were conducted on coated ESM3 formulations as per ICH guidelines and the results indicated no significant difference in drug content, as demonstrated in **Table-07**.

Table - 07: Stability study of enteric coated mucoadhesive tablets

Formulations Code	At end of 1 month	At end of 2 months	At end of 3 months
ESM3	99.48%	99.35%	99.31%

CONCLUSION

ESR mucoadhesive tablets developed using Zapota mucilage, HPMC4K, HPMC15K, and Guar gum via wet granulation. Tablets showed favorable mechanical properties and uniform drug content. ESM3 formulation had superior mucoadhesive strength, swelling index and prolonged drug release. Tablet crushing strength analysis favored ESM3 for enteric coating, leading to EESM3 formulation. Overall, ESM3 displayed optimal mucoadhesive properties and sustained release, making it a promising candidate for improving the bioavailability and patient compliance.

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