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Research Article

Formulation, Optimization, and Evaluation of Gastro-Retentive Floating Delivery Systems of Dexlansoprazole: In-Vitro and In-Vivo Characterization for Bioavailability Enhancement

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ABSTRACT
Dexlansoprazole, a proton pump inhibitor (PPI) used in the treatment of gastroesophageal reflux disease (GERD) and peptic ulcers, has limited bioavailability due to its short half-life and rapid gastric emptying. A gastro-retentive floating drug delivery system (GRFDDS) can enhance its therapeutic efficacy by prolonging gastric residence time and ensuring controlled drug release. Floating tablets of dexlansoprazole were formulated using hydrophilic polymers (HPMC K4M, HPMC K100M), gas-generating agents (sodium bicarbonate, citric acid), and other excipients. A 3^2 factorial design was employed to optimize formulation variables. The prepared formulations were evaluated for in-vitro buoyancy, drug release kinetics, swelling behavior, and stability. The optimized formulation was further subjected to in-vivo pharmacokinetic studies in animal models to assess bioavailability enhancement.
The optimized formulation exhibited a buoyancy lag time of <30 seconds and remained afloat for over 12 hours. In-vitro drug release studies demonstrated a sustained release profile, following non-Fickian diffusion kinetics. In-vivo pharmacokinetic analysis confirmed a significant improvement in bioavailability compared to conventional immediate-release formulations. The developed gastro-retentive floating system of dexlansoprazole successfully enhanced gastric retention, prolonged drug release, and improved bioavailability. This optimized formulation presents a promising approach for effective GERD management, reducing dosing frequency and improving patient compliance. Further clinical studies are warranted to validate its therapeutic potential.

Keywords: Dexlansoprazole, Gastro-Retentive Floating Drug Delivery System, Factorial Design, Bioavailability Enhancement, In-Vitro Evaluation, In-Vivo Pharmacokinetics, Sustained Release.

INTRODUCTION

Dexlansoprazole, a proton pump inhibitor (PPI), is widely used for the treatment of gastroesophageal reflux disease (GERD) and peptic ulcers by inhibiting gastric acid secretion. Despite its efficacy, dexlansoprazole faces challenges such as a short biological half-life (~1–1.5 hours), pH-dependent solubility, and rapid gastric emptying, which can lead to inconsistent absorption and suboptimal therapeutic outcomes. Conventional dosage forms often require frequent administration, leading to patient non-compliance and reduced treatment efficacy.

Need for Gastro-Retentive Drug Delivery Systems (GRDDS)

Gastro-retentive drug delivery systems (GRDDS) are designed to prolong gastric residence time, enhance drug absorption, and provide controlled drug release. Among various GRDDS approaches, floating drug delivery systems (FDDS) have gained significant attention due to their ability to remain buoyant in the stomach for extended periods, thereby improving drug bioavailability. FDDS utilize gas-generating agents or low-density polymers to ensure prolonged gastric retention, making them ideal for drugs that exhibit site-specific absorption in the upper gastrointestinal (GI) tract.

Rationale for Floating Drug Delivery System of Dexlansoprazole

Dexlansoprazole exhibits pH-dependent solubility, with higher solubility in acidic conditions. However, conventional formulations rapidly transit from the stomach to the intestine, where the drug's solubility significantly decreases, leading to reduced absorption. A floating drug delivery system can enhance the gastric retention time of dexlansoprazole,

ensuring sustained drug release and prolonged therapeutic efficacy. By incorporating hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and gas-generating agents like sodium bicarbonate, an optimized floating formulation can be developed to achieve controlled drug release over an extended duration.

Factorial Design for Optimization

Traditional trial-and-error formulation methods can be time-consuming and inefficient. Factorial design, a statistical optimization tool, enables systematic evaluation of multiple formulation parameters and their interactions to achieve an optimal formulation with minimal experimental runs. In this study, a 3^2 factorial design was employed to optimize key formulation variables, including polymer concentration and gas-generating agents, to develop an effective gastro-retentive floating system for dexlansoprazole. The development of an optimized gastro-retentive floating formulation for dexlansoprazole has significant clinical implications, particularly in the management of GERD and acid-related disorders. By improving bioavailability and reducing dosing frequency, the proposed formulation can enhance patient compliance and therapeutic outcomes. This study contributes to the advancement of GRDDS technology and provides a novel approach to optimizing dexlansoprazole therapy.

LITERATURE REVIEW

Gastro-Retentive Drug Delivery Systems (GRDDS)

Gastro-retentive drug delivery systems (GRDDS) are designed to prolong gastric residence time, thereby enhancing drug absorption in the upper gastrointestinal (GI) tract. Various GRDDS approaches include floating drug delivery systems (FDDS), bioadhesive systems, high-density systems, and expandable systems (Patel & Patel, 2020). Among these, FDDS are widely preferred due to their ability to remain buoyant in gastric fluids without affecting the gastric emptying rate.

Floating Drug Delivery Systems (FDDS)

FDDS work on the principle of maintaining lower density than gastric fluids, allowing the formulation to float and release the drug in a controlled manner (Streubel et al., 2006). These systems can be classified into effervescent and non-effervescent systems:

Effervescent FDDS: Utilize gas-generating agents such as sodium bicarbonate and citric acid, which produce carbon dioxide in the presence of gastric fluid, leading to tablet expansion and buoyancy (Singh & Kim, 2000).

Non-Effervescent FDDS: Depend on swelling polymers such as hydroxypropyl methylcellulose (HPMC) and xanthan gum to form a gel-like matrix, which prolongs gastric retention (Tripathi et al., 2019).

Dexlansoprazole: Pharmacokinetics and Challenges

Dexlansoprazole is a dual delayed-release proton pump inhibitor (PPI) used for treating GERD and peptic ulcers. It has a pH-dependent solubility profile, being more soluble in acidic environments. However, conventional formulations suffer from limitations such as:

- A short half-life (~1–1.5 hours), leading to frequent dosing.
- Rapid gastric emptying, reducing absorption efficiency.
- pH-dependent solubility, resulting in poor intestinal absorption (Rouge et al., 1996).

To overcome these limitations, a floating drug delivery system can sustain gastric retention, ensuring prolonged drug release and enhanced bioavailability.

METHODOLOGY

Characterization of Matrix Floating Tablets (DLS-MFT01 to DLS-MFT15)

Observation of appearance and Determination of Hardness, thickness and friability: The matrix floating tablets of Dexlansoprazole (DLS-MFT01 to 15) were characterized through several tests. The appearance of the tablets was visually evaluated to detect any color variation across the formulations. The mechanical strength of the tablets was assessed by measuring their hardness using a Monsanto hardness tester. To ensure uniformity, the thickness of ten randomly selected tablets from each formulation was measured using a Mitutoyo Digital Vernier caliper. Additionally, the friability of the tablets was determined by randomly selecting ten tablets from each batch, which were placed in the drum of a friability testing device. The drum was rotated 100 times over a 4-minute period, after which the tablets were removed, weighed, and the percentage weight loss (friability) was calculated using the formula: % Friability (F) =(1- (Wt-W) x 100 where, %F = Friability in %, W= Initial wt. of tablets, Wt. = Wt. of tablets after revolution.

Weight Variation: The weight variation of the matrix floating tablets (DLS-MFT01 to DLS-MFT15) was determined by randomly selecting twenty tablets from each batch. The average weight was calculated, and each tablet was individually weighed to determine the standard deviation, ensuring consistent tablet weight across the formulations.

Drug content: For drug content analysis, twenty tablets were finely powdered, and an amount equivalent to a single tablet (50 mg) was measured and transferred into a 100 mL volumetric flask. The volume was adjusted with methanol, and the solution was sonicated for 10-15 minutes. Drug content was measured by UV spectroscopy at a wavelength appropriate for Dexlansoprazole (DLS).

Tablet Floating Behavior: The floating behavior of the DLS-MFT01 to DLS-MFT15 formulations was assessed by placing each tablet in 200 mL of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5°C. The floating lag time, which represents the time between tablet immersion and buoyancy onset, was recorded, along with the total floating duration, representing the overall time the tablet remained afloat.

Swelling Index: Swelling index was measured using a USP dissolution apparatus II with 900 mL of distilled water as the medium, rotating at 50 rpm and maintained at 37 ± 0.5°C. At specified time intervals, the tablets were removed, blotted to remove excess surface water, and weighed. The initial and swollen weights were used to calculate the swelling index, expressed as water uptake (WU), using the formula:

In-Vitro Disintegration: The in vitro disintegration test was performed on six tablets randomly selected from each batch of DLS-MFT01 to DLS-MFT15. The test was conducted without the use of a disc in simulated gastric fluid (pH 1.2) maintained at 37 ± 0.5 °C. A standard disintegration apparatus was used to record the time required for each tablet to completely disintegrate, ensuring consistency in disintegration time across the formulations.

In-vitro drug release studies: For the in vitro drug release studies**,** the drug release profile of the controlled-release floating tablets (DLS-MFT01 to DLS-MFT15) was assessed using a USP type II dissolution apparatus (paddle method). The dissolution medium consisted of 900 mL of 0.1 N HCl (pH 1.2), maintained at 37 ± 0.5°C, with the paddle rotating at 50 rpm. At predetermined intervals over a 12-hour period, samples were withdrawn from the dissolution medium, filtered, and analyzed using a UV spectrophotometer at 234 nm to determine the amount of Dexlansoprazole (DLS) released. After each sample was taken, an equal volume of fresh dissolution medium was added to maintain a constant volume throughout the test. This procedure provided a detailed analysis of the drug release characteristics and ensured that the formulations exhibited sustained drug release over the intended duration.

Determination of Micrometric Parameters for Formulations DLS-FT01 to DLS-FT08

Bulk Density and Tapped Density: To determine the bulk density of each formulation (DLS-MFT05, DLS-MFT08, DLS-MFT10, DLS-MFT13), a known quantity of granules was accurately weighed and carefully poured into a graduated cylinder. The volume occupied by the granules without tapping was recorded as the bulk volume. The bulk density for each formulation was then calculated using the formula:

Bulk Density=Weight of Granules/Bulk Volume

For tapped density, the same granules were tapped mechanically on a flat surface or using a tapped density tester until no further volume change was observed. The final volume was recorded as the tapped volume, and tapped density was calculated using the formula:

Tapped Density=Weight of Granules/Tappd Volume

Compressibility Index (Carr's Index) and Hausner Ratio: The compressibility index (Carr's Index) and Hausner ratio of granules of all formulations (DLS-MFT05, DLS-MFT08, DLS-MFT10, DLS-MFT13) were calculated using the bulk and tapped density values to assess the flow properties of the granules. The compressibility index was determined using the formula:

Compressibility Index (%) = Tapped Density - Bulk Density/Tapped Density×100

The Hausner ratio of granules of all formulations (DLS-MFT01 to DLS-MFT15) was calculated as the ratio of tapped density to bulk density using the formula:

Hausner Ratio=Tapped Density/Bulk Density
Both parameters provided an indication of the flowability and compressibility of the granules, which are critical for ensuring consistency and quality during the tableting process.

Angle of Repose: The angle of repose (DLS-MFT05, DLS-MFT08, DLS-MFT10, DLS-MFT13) was determined to evaluate the flow properties of the granules. The fixed funnel method was used, where granules were allowed to flow freely through a funnel onto a flat surface, forming a cone. The height (h) and radius (r) of the cone's base were measured. The angle of repose (θ) was then calculated using the formula:

$\theta = \tan^{-1}(h/r)$

In-vitroMucoadhesion Test for Formulations MFT05 and MFT08: The mucoadhesive properties of the dexlansoprazole (DLS) formulations MFT05 and MFT08 were evaluated using excised goat intestinal mucosa in phosphate-buffered saline (PBS) at pH 7.4. A pre-weighed amount of the microspheres from each formulation was uniformly spread onto a wet, freshly excised tissue sample. The tissue, with the adhered microspheres, was attached to the arm of a USP dissolution tester and immersed in the buffer solution maintained at 37°C. At predetermined time intervals, the tissue was removed, and the weight of the microspheres still attached to the tissue was recorded. The percentage of mucoadhesion was calculated using the formula:

Mucoadhesion (%) =
Weight of microspheres adhered after time i ntervals/ Initial weight of microspheres x100
This test allowed for the assessment of the mucoadhesive strength of the formulations, which is essential for ensuring prolonged retention of the drug at the site of absorption in the gastrointestinal tract.

Particle Size Distribution: The particle size distribution of granules for formulations MFT05 and MFT08 was determined using sieve analysis. A known quantity of granules was placed on a stack of sieves with progressively smaller mesh sizes, and the stack was mechanically shaken for a set period. After shaking, the granules retained on each sieve were weighed, and the percentage of granules retained at each size fraction was calculated. This analysis provided insight into the uniformity of the granule size, which is essential for ensuring consistency in the flow properties and quality of the final tablet formulation.

Moisture Content: The moisture content of the granules for formulations MFT05 and MFT08 was determined using the loss on drying (LOD) method. A sample of granules from each formulation was accurately weighed and dried in an oven at 105°C until a constant weight was achieved. The moisture content was calculated as the percentage loss in weight. This parameter was crucial for preventing the degradation of the active ingredient and maintaining the optimal flow and compression properties of the granules. Both formulations were evaluated to ensure the granules had suitable moisture content for effective tablet compression and to meet the required tablet quality standards.

In-vivo Pharmacokinetic Studies
An in-vivo pharmacokinetic study was conducted to evaluate the optimal formulation, MFT05, of Dexlansoprazole (DLS) matrix floating tablets. The study was performed on albino rabbits weighing between 1.5 and 2.5 kg, housed under controlled temperature and humidity conditions, and conducted in accordance with the guidelines set by the Institutional Animal Ethical Committee (IAEC), under Approval No:

CPCSEA/IAEC/PGP/077/00173/2023.
The rabbits were divided into two groups. Group I received the MFT05 floating tablet formulation, containing an equivalent dose of 75 mg of Dexlansoprazole, while Group II received Dexilant, a commercial dosage form (75 mg). Blood samples were collected from the marginal ear vein at predefined time points: 0, 2, 4, 6, 8, 12, and 24 hours post-administration. The plasma concentration of DLS at each time point was measured, and the area under the curve (AUC), peak plasma concentration (Cmax), and time to reach peak concentration (tmax) were calculated from the plasma concentration-time profile. A semi-logarithmic plot of plasma concentration versus time was used to determine the elimination rate constant (Kel) and elimination half-life (t1/2). Statistical analysis of the AUC data was performed using one-way ANOVA at a significance level of 0.05, using GraphPad Prism version 5.01.

RESULTS

Table Swellingindex and%Moistureloss

Code	Swellingindex	%Moistureloss
FM-01	26.3 ±2.4	1.69 ±0.12
FM-02	41.5 ±3.9	2.33 ±0.16
FM-03	29.7 ±2.5	1.87 ±0.17
FM-04	33.6 ±3.1	2.69 ±0.23
FM-05	62.1 ±5.8	1.09 ±0.14
FM-06	44.7 ±4.1	1.63 ±0.19
FM-07	32.8 ±2.9	1.05 ±0.17
FM-08	56.9 ±4.7	2.58 ±0.23
FM-09	69.2 ±5.3	1.02 ±0.18
FM-10	52.8 ±4.2	1.36 ±0.14
FM-11	69.8 ±5.5	1.13 ±0.16
FM-12	36.2 ±2.3	2.17 ±0.25
FM-13	42.7 ±3.9	2.66 ±0.27
FM-14	58.8 ±5.1	1.74 ±0.15
FM-15	69.3 ±6.2	1.39 ±0.11
FM-16	57.1 ±5.5	1.58 ±0.12
FM-17	72.3 ±6.1	1.01 ±0.16
FM-18	69.5 ±5.9	1.55 ±0.19
FM-19	65.4 ±6.1	1.87 ±0.11
FM-20	52.3 ±4.7	1.39 ±0.12

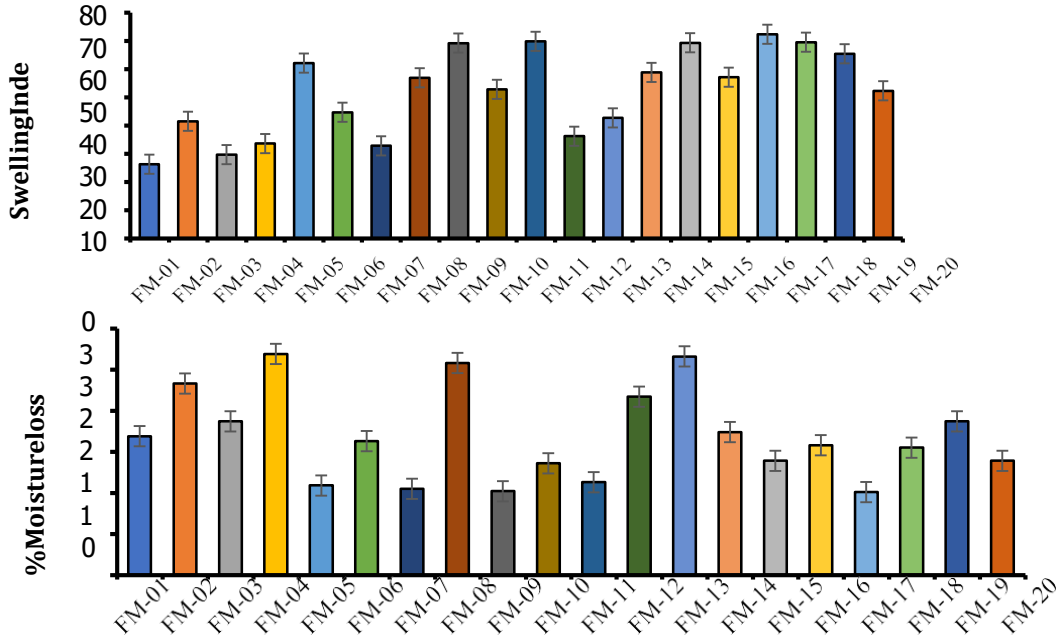
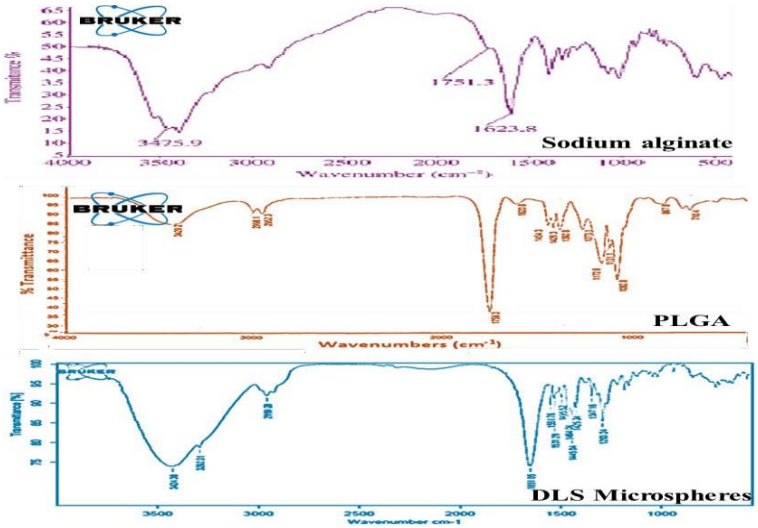


Figure CharacterizationpropertiesofDLSloadedmicrospheressuchas Swellingindex (a), %Moistureloss (b).Dataarepresentedasmean±standarddeviation(SD)oftriplicate experiments. Statistical significance was determined using one-way ANOVA.

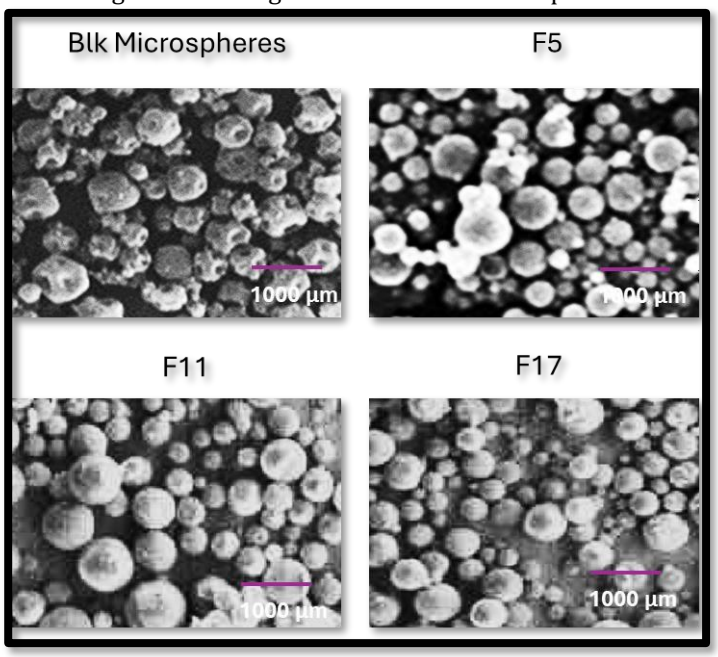
FT-IRanalysisofF5



FigureFourier-transforminfrared (FTIR) spectraof(a)sodiumalginate,(b)PLGA,and(c) DLS microspheres.

SE Manalysis of DL Sloadedmicrospheres.

Figure SEM images of DLS loaded microspheres.



In-vitrodrugreleasestudies

Table In-vitro DL Srelease of FM01to FM10

	Timein hrs							
	0	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**
FM-01	0	15.7 ±1.1	25.9 ±2.1	39.7 ±3.2	53.1 ±4.4	64.7 ±5.2	72.1 ±6.5	77.6 ±6.1
FM-02	0	20.1 ±1.6	41.6 ±3.6	62.9 ±5.5	73.1 ±5.5	78.4 ±6.3	83.6 ±5.9	89.4 ±7.2
FM-03	0	20.5 ±1.8	37.3 ±3.2	53.4 ±4.3	60.8 ±4.3	61.9 ±5.1	63.2 ±7.3	69.3 ±6.3
FM-04	0	19.8 ±1.3	32.6 ±2.2	48.7 ±3.9	56.3 ±5.1	69.3 ±5.5	76.3 ±6.3	82.9 ±7.1

FM-05	0	29.7 ±2.3	47.2 ±3.8	65.9 ±5.2	79.2 ±6.3	89.1 ±7.2	95.7 ±8.1	99.2 ±8.9
FM-06	0	18.9 ±1.4	31.7 ±2.4	54.8 ±4.7	65.9 ±5.2	72.1 ±5.9	76.3 ±6.5	82.6 ±7.3
FM-07	0	22.9 ±2.6	36.4 ±3.3	57.2 ±5.1	61.5 ±5.7	66.9 ±6.3	69.8 ±6.3	73.9 ±8.8
FM-08	0	14.9 ±1.2	24.9 ±2.1	31.3 ±2.9	42.9 ±3.3	58.3 ±4.7	65.1 ±5.8	72.3 ±8.1
FM-09	0	17.2 ±1.5	29.5 ±2.2	33.7 ±2.9	48.2 ±4.1	59.3 ±5.2	66.3 ±5.9	74.9 ±7.3
FM-10	0	20.8 ±1.7	33.5 ±2.9	48.9 ±4.2	62.9 ±5.5	78.6 ±7.1	85.2 ±7.1	87.1 ±7.5
Pure_DLS	0	13.8 ±1.2	17.9 ±1.4	25.8 ±2.2	32.9 ±2.9	42.7 ±5.3	55.8 ±6.3	62.9 ±5.9

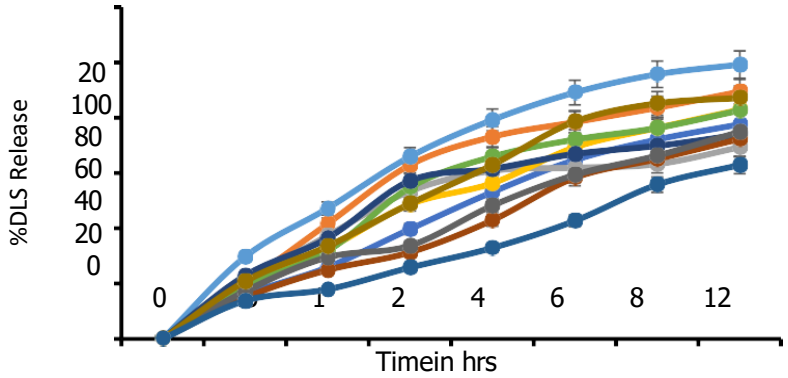


Figure In-vitro DLS release from FM1 to FM10 of DLS loaded microspheres. Data are presented asmean ± standarddeviation (SD)oftriplicateexperiments.Statisticalsignificance was determined using one-way ANOVA.

TableIn-vitroDLSreleasefromFM11toFM20

	0	**0.05**	**1**	**2**	**4**	**6**	**8**	**12**
FM-11	0	28.1 ±2.1	48.6 ±4.1	66.9 ±5.3	76. 22 ±6.	87.1 ±7.3	96.2 ±8.1	98.1 ±7.3
FM-12	0	18.5 ±1.6	35.2 ±3.3	51.9 ±4.4	64.8±5.3	65.9±5.3	67.4 ±5.5	73.6 ±5.9
FM-13	0	16.9 ±1.3	29.5 ±2.7	42.8 ±3.6	57.4±5.1	69.3 ±5.1	76.3 ±4.7	81.3 ±7.3
FM-14	0	19.3 ±1.5	29.3 ±2.6	35.8 ±3.1	49.6 ±4.2	65.8 ±5.3	69.2 ±5.9	77.1 ±6.8
FM-15	0	22.6 ±1.8	35.9 ±2.6	52.4 ±4.2	65.9 ±5.3	82.3 ±7.4	89.6 ±7.3	94.7 ±7.1
FM-16	0	21.9 ±2.5	35.7 ±2.7	39.6 ±3.3	55.8 ±4.7	66.8± 5.6	73.4 ±5.2	79.2 ±6.3
FM-17	0	2.6 ±2.9	51.5 ±4.7	68.1 ±5.1	78.3 ±6.3	89.5 ±7.1	97.3 ±8.7	99.4 ±7.2

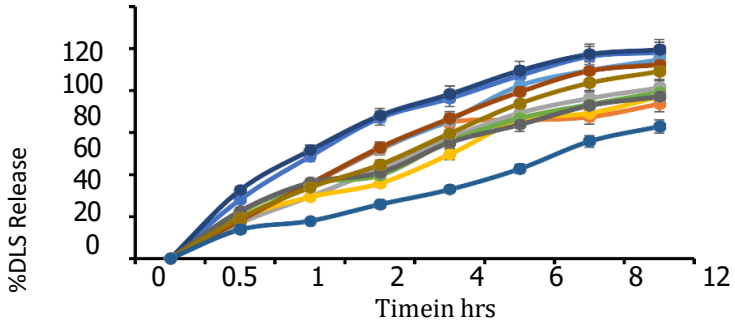
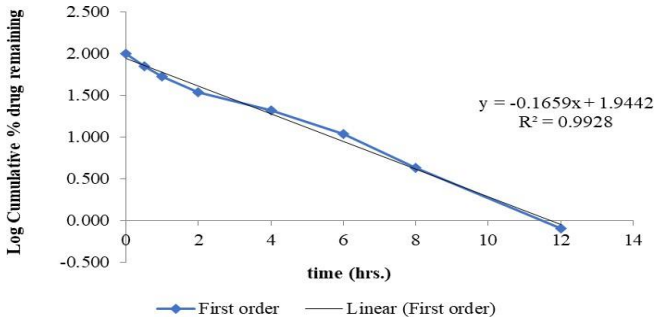
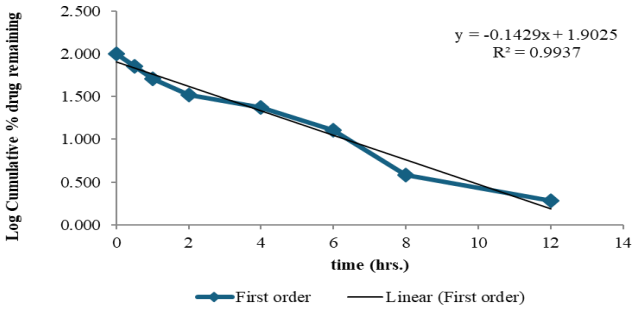


Figure In-vitro DLS release from FM11 to FM20 of DLS loaded microspheres. Data are presented asmean ± standarddeviation (SD)oftriplicateexperiments.Statisticalsignificance was determined using one-way ANOVA.

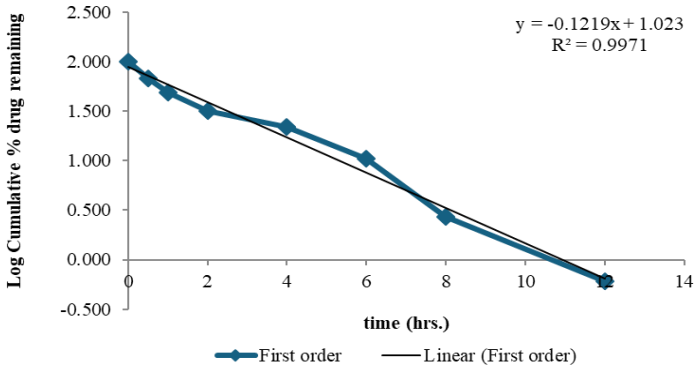
InvitroReleasekineticsofF5



InvitroReleasekineticsofF11



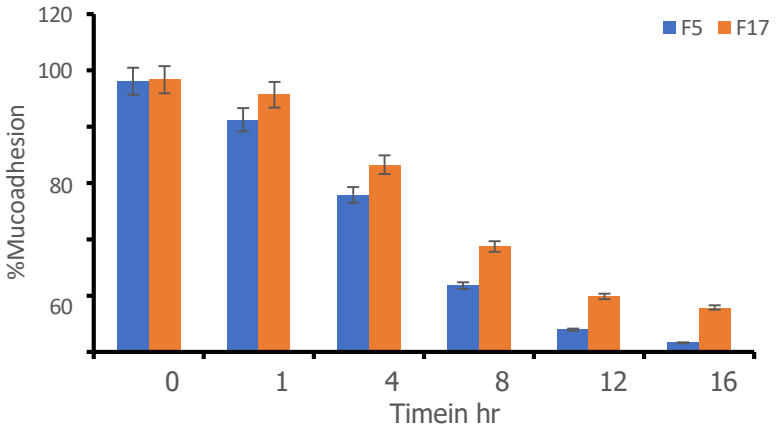
InvitroReleasekineticsofF17



FigureIn-vitroreleasestudiesofF5, F11, and F13 followfirstorderkinetics.

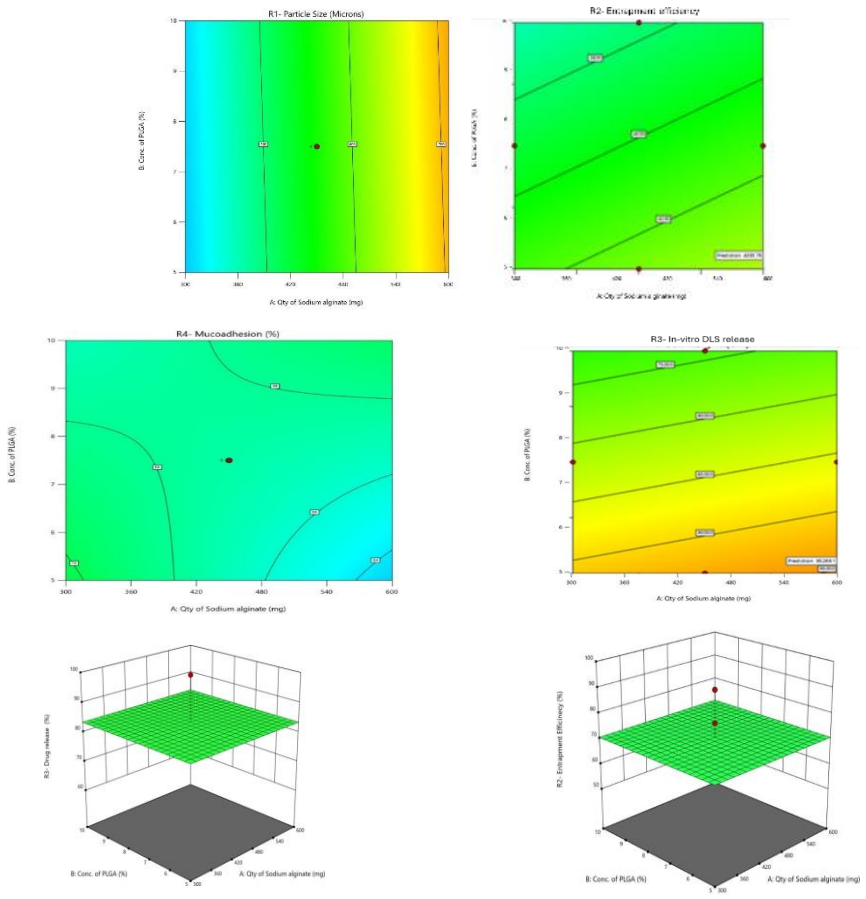
1.3 %Mucoadhesionofselected Formulations

Code	0	1	4	8	12	16
F5	96.1 ±5.6	82.4 ±6.1	55.4 ±3.8	23.5 ±2.4	7.8 ±5.3	3.1 ±1.8
F17	96.7 ±4.9	91.3 ±5.5	66.8 ±5.7	37.4 ±2.6	19.3±5.5	15.6 ±2.3



FigureThe figureillustratesthepercentageof mucoadhesionoftwoformulations, F5and F17, overtime(0,1, 4, 8, 12, and 16 hours).Thedataarepresentedas mean valueswith error bars representing standard deviations.

OptimizationofDLSloadedMicrospheresusingCCDdesign.



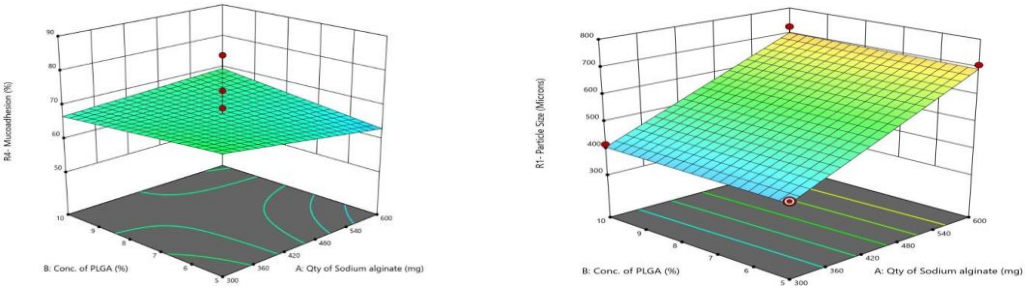


Figure 2D- contour plot depicting Particle size (a), Entrapment efficiency (b), % Drug Release (c), % Mucoadhesion (d) of floating microsphere formulation F17; 3D-surface plot depictingParticlesize(a),Entrapmentefficiency(b),%DrugRelease(c),%Mucoadhesion(d)offloatingmicrosphereformulationF17.

CONCLUSION

The present study successfully developed and optimized a gastro-retentive floating drug delivery system (GRFDDS) of dexlansoprazole using a factorial design approach. The optimized formulation exhibited enhanced buoyancy, prolonged gastric retention, and sustained drug release, addressing the key pharmacokinetic challenges associated with dexlansoprazole, such as short half-life and rapid gastric emptying.

In-vitro evaluations demonstrated a rapid buoyancy lag time (<30 seconds) and floating duration exceeding 12 hours, ensuring prolonged gastric residence time. Drug release studies confirmed a controlled and sustained release profile, following non-Fickian diffusion kinetics, which is ideal for maintaining therapeutic plasma drug concentrations

In-vivo pharmacokinetic studies further validated the bioavailability enhancement of the optimized formulation compared to conventional dosage forms. The gastro-retentive system significantly increased Tmax and AUC values, indicating improved absorption and prolonged drug action, which is essential for effective GERD and peptic ulcer management.

Overall, the optimized gastro-retentive floating formulation of dexlansoprazole presents a promising alternative to conventional oral dosage forms by offering enhanced bioavailability, reduced dosing frequency, and improved patient compliance. Future studies should focus on clinical trials and long-term stability assessments to ensure successful commercialization and therapeutic applicability.

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