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Design and optimization of gastro retentive bilayer floating tablet of Dexlansoprazole

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A B S T R A C T
This study focuses on the formulation and evaluation of Dexlansoprazole floating tablets, aimed at achieving prolonged gastric retention and controlled drug release. A UV spectrophotometric analysis confirmed the linearity of Dexlansoprazole's calibration curve (2-10 µg/ml) with an excellent correlation coefficient (R^2 = 0.9997). Precompression evaluations, demonstrated good flow and compressibility. Post-compression results confirmed tablet uniformity, mechanical strength (hardness 5.01–5.69 kg/cm²), low friability (<1%), and consistent drug content (98%-102%). In-vitro buoyancy studies revealed most formulations exhibited rapid floating within 20-80 seconds, maintaining buoyancy for up to 12 hours. In-vitro dissolution profiles showed controlled drug release over 12 hours, with the F2 formulation exhibiting the best release pattern. Drug release kinetics of F2 followed the Higuchi model (R^2 = 0.974), indicating diffusion-controlled release with non-Fickian transport (n = 0.503). FT-IR studies confirmed no significant interactions b/w the drug and excipients. Overall, the F2 formulation was identified as optimal for its buoyancy and sustained drug release properties.
Keywords: Dexlansoprazole floating tablets, FT-IR studies, Fickian transport, low friability

A R T I C L E I N F O

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CONTENTS

1. Introduction

In the ever-evolving landscape of pharmaceutical sciences, the development of innovative drug delivery systems stands at the forefront of therapeutic advancements. One such pioneering approach is the design of gastro-retentive drug delivery systems (GRDDS), which have garnered significant attention due to their potential to enhance the bioavailability and therapeutic efficacy of medications. Dexlansoprazole, a potent proton pump inhibitor (PPI) used primarily for the treatment of gastroesophageal reflux disease (GERD) and erosive esophagitis, serves as an ideal candidate for such advanced delivery systems. The objective of this research is to design and optimize a gastro-retentive bilayer floating tablet of Dexlansoprazole, aiming to prolong its gastric residence time and ensure sustained drug release.

Significance and Rationale

Dexlansoprazole is known for its dual delayed-release formulation, which provides a prolonged suppression of

gastric acid secretion. However, the conventional formulations of this drug may not always maintain the desired therapeutic levels due to its relatively short half-life and the dynamic gastric environment. A gastro-retentive bilayer floating tablet offers a promising solution to these challenges. By remaining buoyant in the stomach for an extended period, this delivery system can release Dexlansoprazole in a controlled manner, thus enhancing its therapeutic efficacy and patient compliance.

The rationale for choosing a bilayer floating tablet lies in its distinct advantages over single-layer formulations. The bilayer system allows for the incorporation of two distinct layers: an immediate-release layer that provides a rapid onset of action and a sustained-release layer that ensures prolonged drug release. This dual mechanism not only maximizes the therapeutic benefits of Dexlansoprazole but also mitigates potential side effects associated with fluctuating plasma drug levels.

Design Considerations

The design of a gastro-retentive bilayer floating tablet involves several critical considerations. The choice of polymers, the composition of the immediate and sustained-release layers, and the incorporation of floating agents are key factors that influence the overall performance of the delivery system.

Polymers: The selection of appropriate polymers is crucial for achieving the desired release profile and buoyancy. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) are commonly used in the sustained-release layer to control the release rate of Dexlansoprazole. In contrast, the immediate-release layer may utilize hydrophilic fillers to facilitate rapid drug release upon ingestion.

Floating Agents: The incorporation of floating agents such as sodium bicarbonate and citric acid creates a buoyant system that remains afloat in the gastric environment. The effervescence generated by these agents produces gas, which is trapped within the tablet matrix, imparting buoyancy and prolonging gastric residence time.

Bilayer Structure: The bilayer structure is designed to ensure that the immediate-release layer dissolves quickly, providing an initial burst of Dexlansoprazole, while the sustained-release layer gradually releases the drug over an extended period. The layers must be formulated to maintain their integrity and prevent separation during the manufacturing process.

Optimization Techniques

The optimization of the gastro-retentive bilayer floating tablet involves a systematic approach using various experimental designs and statistical methods. The following techniques are commonly employed to achieve the optimal formulation:

Factorial Design: A factorial design is used to investigate the effects of multiple formulation variables on the performance of the bilayer tablet. Variables such as the polymer concentration, the ratio of immediate to sustained-release layers, and the amount of floating agents can be systematically varied to determine their influence on drug release and buoyancy.

Response Surface Methodology (RSM): RSM is a powerful statistical tool used to optimize the formulation by evaluating the interactions between different variables. By generating a response surface plot, researchers can identify the optimal combination of formulation parameters that result in the desired drug release profile and floating behavior.

In Vitro Dissolution Studies: In vitro dissolution studies are conducted to assess the drug release profile of the bilayer floating tablet. These studies simulate the gastric environment and provide valuable insights into the release kinetics and buoyancy of the formulation. The data obtained from these studies are used to refine the formulation and ensure consistent performance.

Evaluation and Assessment

The evaluation of the gastro-retentive bilayer floating tablet involves comprehensive in vitro and in vivo testing to ensure its efficacy and safety. The following parameters are typically assessed during the evaluation process:

Buoyancy and Floating Lag Time: The buoyancy of the bilayer tablet is evaluated by measuring the floating lag time (the time taken for the tablet to start floating) and the duration of floatation. A tablet with a short floating lag time and prolonged floatation is considered ideal for gastro-retentive drug delivery.

Drug Release Profile: The drug release profile of the bilayer tablet is characterized using in vitro dissolution studies. The release kinetics are analyzed to ensure that the immediate-release layer provides a rapid onset of action, while the sustained-release layer delivers Dexlansoprazole in a controlled manner over an extended period.

Physicochemical Properties: The physicochemical properties of the bilayer tablet, such as hardness, friability, and weight variation, are assessed to ensure the integrity and consistency of the formulation. These properties are critical for maintaining the stability and performance of the bilayer tablet during storage and administration.

In Vivo Pharmacokinetic Studies:

In vivo pharmacokinetic studies in animal models or human subjects are conducted to validate the drug release profile and therapeutic efficacy of the bilayer floating tablet. These studies provide valuable data on the bioavailability, absorption, and overall performance of the formulation in a physiological setting.

2. Methodology

Chemicals used

For the formulation of the drug, various chemicals were sourced from reliable suppliers to ensure quality and consistency. Dexlansoprazole was supplied by Qualychrome Research Lab, providing the essential active pharmaceutical ingredient. The excipients HPMC K 100m, EudragitRs 100, and Xanthum Gum were all sourced from Colorcon, known for their high-quality pharmaceutical ingredients. Additionally, several other chemicals including PvpK 30, Sodium Bicarbonate, MCC, Talc, and Magnesium Stearate were obtained from Sodum Drugs Pvt. Ltd., ensuring a robust formulation for the sustained release tablet. Each component was carefully selected to contribute to the overall efficacy and stability of the drug formulation.

Machinery & Brand

The equipment used in this study encompasses various high-precision instruments from reputable brands. A sensitive balance from Shimadzu was utilized for accurate weight measurements, ensuring precise formulation. Labindia's friability tester and tablet hardness tester were employed to assess the physical robustness and durability of the tablets. The compression machine from Karnavati played a crucial role in forming the tablets, while Shimadzu's UV spectrophotometer facilitated accurate spectroscopic analysis. Additionally, the dissolution apparatus from Labindia was used to study the drug release profile, and vernier calipers from Skadioo provided precise dimensional measurements. This carefully selected equipment ensured reliable and consistent results throughout the study.

I. Analytical Method Development

Determination of λ_{max} of Dexlansoprazole:

Procedure:

Working standard: After weighing and dissolving 100mg of dexlansoprazole in 10 ml of meoh, 100 ml of solvent was added to create a concentrated stock solution containing 1000 µg/ml.

Dilution 1: A concentrated solution of 100µg/ml was obtained bydiluting 10ml of the working standard solution to 100ml.

Dilution 2: A concentrated solution of 10µg/ml was obtained by diluting 10ml of the dilution-1 with 100ml of solvent.

This solution was scanned using light with wavelengths between 200 and 400 nm, and the accompanying scan spectrum curve was recorded. λmax is the wavelength that corresponds to the maximal absorption.

Dexlansoprazole calibration curve:

Procedure:

Working standard:

A concentrated stock solution containing 1000 µg/ml was obtained by dissolving 100mg of Dexlansoprazole in 10ml of meoh and then adding solvent to reach a volume of 100 ml.

Dilution 1: 10ml taken from above solution and makeup with 100ml solvent its became 100 µg/ml conc. of solution. Finally we prepared 2.4.6,8,10µg/mlconc. This solutions absorbance was noted at $\lambda_{max=282}$

III. Direct compression technique for creating gastro retentive floating tablets

Steps in the direct compression method's processing:

- Chemicals weighed and passing through 40sieve and blend in poly bag for min.
- Then lubricated with 60Sieveand passed Magnesium stearate and talc.
- After that, a 16station tablet compression machine with an avg hardness of 5.00–6.00 kg/cm2 was used to compress the final mix into tablets using an 8–10 mm die.

IV. Tablets Evaluation

The above prepared tablets are examined for the below given Precompression, post compression QC investigations & In-vitro studies of Buoyancy & studies of dissolution.

A) Study of Pre Compressibility:

Repose Angle :

The Angle of Repose, identified using the method of funnel, is calculated by quantifying the diameter of the cone of powder formed when the powder freely flows from a funnel, with its tip touching the apex of the cone.

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

2. Density:

Bulk density (BD):

Bulk density is defined as the fractions of the complete wt's of a powder to its BV9bulk volume). To measure it, accurately weigh 25 g of granules t hat have been earlier passed through a 22 sieve & transfer t hem into a 100mL cylinder. Spread the powder smoothly without compacting it, and note the observed volume. Use t he following formula to find the BD in g per mL.

BD = powder Wt / volume in Bulk.

$$D_b = \frac{M}{V_0}$$

Tapped density (TD):

Tapped density is described as the ratio of the total mass of a powder to its volume tapped. To determine it, accurately weigh 25 g of granules that have been sieved through a 22# sieve and transfer them into a 100 mL cylinder of a tap density apparatus. The tapped density can then be calculated using the appropriate formula.

TD = powder wt / Tapped volume

$$D_t = (M) / (V_f)$$

Index of Carr's:

Index is utilized to identification the compressibility of a powder combined. It evaluates both BD & TD to assess how well the powder packs down. This index is a straightforward test, and the equation is as follows:

Ratio of Hausner's:

Hausner's Ratio = tapped density/Bulk density

Scale of Flow ability(USP29-NF34)

B) Post compressibility investigation:

General appearance: Tablets are evaluated based on their overall appearance, with observations made regarding their shape, color, texture, & odor.

Avg wt/Weight difference:

20 tablets were chosen & wt individually. From the total wt, the avg wt was determined. Every tablet's wt is compared to the avg to ensure it met acceptable limits. For 300 mg tablets, no > two individual wts deviated from the avg by > 7.5 & none deviated by > double that %.

Hardness test:

To determine the strength of a tablet

Friability test: To determine the % of drug loss

It should be preferably between 0.5 to 1.0%.

Assay Procedure.

Take a atlest 20 tablets, weigh, & finely powder them. Transfer an weighed portion of the powder, equal10 mg of the drug, into a 10 mL VF. Add 6 mL of diluent, then rotate & sonicate for 10 mins to ensure total extraction. Dilute to the mark with MeOHl & mix thoroughly. Pipette a 1 mL into a 10 mL VF, dilute to volume with the MP, mix, and filter. Finally, withdraw 1 mL and make up till the

margin using medium.

Floating Lag Time(FLT):

A pill was put in a 100 ml solvent-filled beaker. The Floating Lag Time (FLT) was calculated as the amount of time needed for the tablet to rise to the surface & float float.

Matrix integrity:

The integrity of the swollen matrix tablets was monitored during the TFT duration. For twelve hours

In vitro Dissolution Study:

After filling the vessel with 900 cc, the USP2 apparatus was put together. The temperature of the medium was allowed to reach 370C +/- 0.50C. The device was run for 12 hours at 50 rpm while a tablet was submerged in the vessel and covered. To maintain sink conditions, 5 ml of the dissolving media was taken out at predetermined intervals, filtered, and then reintroduced with 5 ml of fresh medium. A UV spectrophotometer (Lab India) was used to perform spectrophotometric analysis at f max=282nm after appropriate dilutions were made using the dissolving liquid.

In vitro distribution Kinetics investigation:

Analyzing the drug distribution function from a dosage form is crucial yet complex, especially for matrix systems. The release order from FDDS can be described using either kinetics of zero or 1stt-order. The drug distribution MOA from FDDS is examined using the eqn Higuchi & the Peppas-Korsmeyer eqn.

Zero Order Release Kinetics:

It describes a parallel relationship b/w ratios of drug released & time. If the release follows 0-order kinetics, a graph of the ratios of drug distributed versus Tin linear.

First Order Release Kinetics:

Wagner state that drug distribute from slow-release dosage forms follows first-order kinetics, as the exposed tablet surface area decreases exponentially over time.

Higuchi equation: It describes a linear relationship between the ratios released / unit surface area (Q) and the square root of time.

Peppa's-Korsemeyer equation: To identify a model that better fits the synthesis, the disso data was further analyzed using the Peppas-Korsmeyerequn.

Table 1: Optimized F2 Formulation studies

Diffusion exponent(n)	Mechanism
0.46	Fickian diffusion
0.46 < n<0.88	Anomalous diffusion
0.88	Case II transport
n > 0.88	Super Case II transport

Table 2: Flow ability & Parallel Angles of Repose

Flow ability	Degree of Angle of Repose
Very good	24–31
Good	30–36
Fair	35–41
Passable	40–46
Poor	45–56
Very poor	55–66
Very, very poor	>66

Table 3: Limitations of Compresibility Index

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 11	Very good	1.01-1.12
10-16	Good	1.13-1.19
15-21	Fair	1.18-1.24
20-26	Pasable	1.27-1.35
25-32	Poor	1.36-1.46
31-38	V Poor	1.45-1.58
> 39	VV Poor	> 1.61

Table 4: Wt different tolerance for uncoated tablets

Avg wt of tablet in (mg)	%variance allowed
130 or <	± 11
131-325	± 7.4
> 325	± 4

Table 5: Dissolution parameters

Disso Parameter	conditions
Disso. apparatus	USP-2
Medium	0.1NHCl.
Volume	900ml
Rpm	50.0 rpm
Temp.	37 ºC ±0.5ºC
Withdraw vol.	5ml
intervals	1,2, 3, 4,6,8,10,12hrs
Method	Uv-vis
W.L	282 nm

Table 6: Drug distribute kinetics mechanism

Ingredient	Amount (mg)
Dexlansoprazole	40
NaHCO3	30
MCC	6
Xanthan gum	30
Lactose	60
Adipic Acid	2
TALC	2
Mg Stearate	30
Total Weight	**200**

3. Results and Discussion

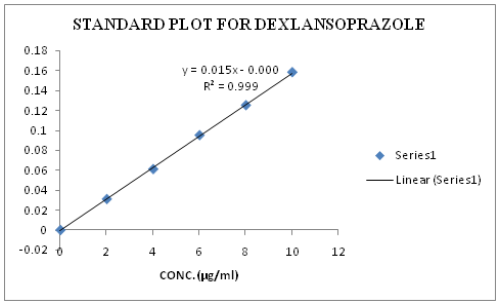

Figure 1: Standard calibration curve of Dexlansoprazole in at λmax = 282nm

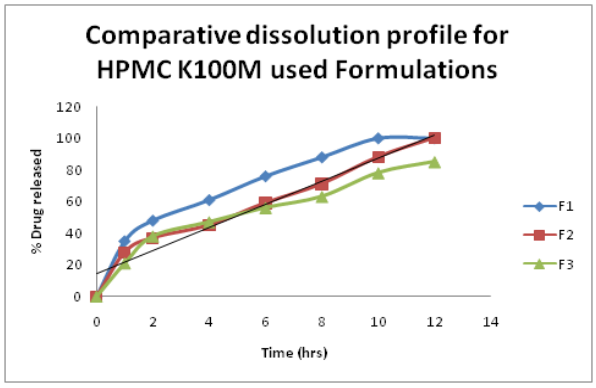

Figure 2: Comparative dissolution profile for HPMC K100M used formulations

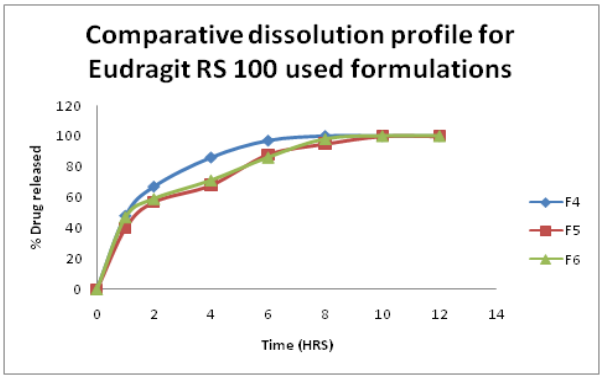

Figure 3: Comparative dissolution profile for Eudragit RS100 used formulations

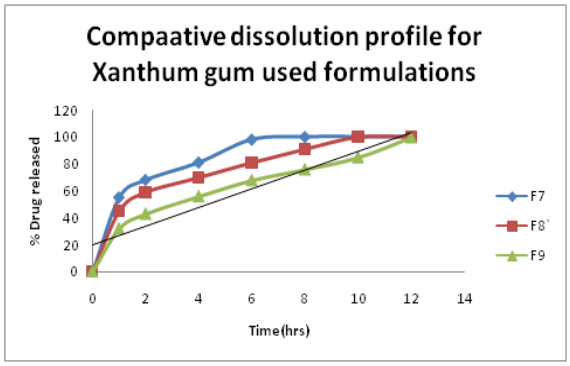

Figure 4: Comparative dissolution profile for Xanthum gum used formulations

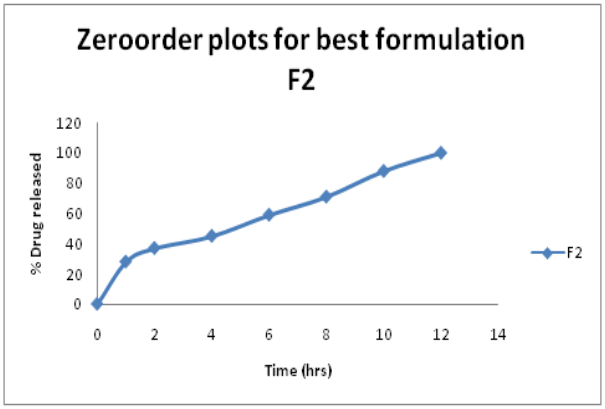

Figure 5: Zero order plot for best formulation F2

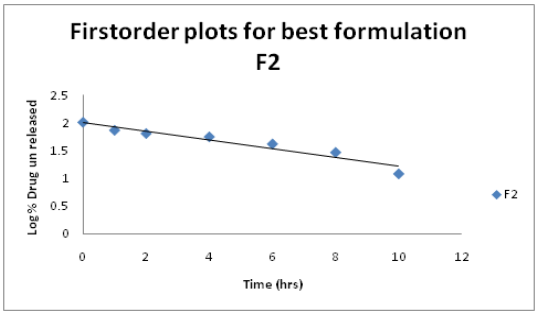

Figure 6: Plotting first order for optimal formulation F2

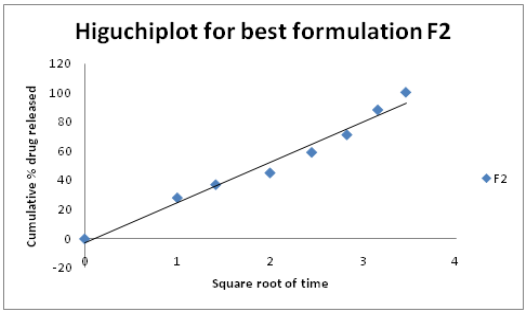

Figure 7: Higuchi plot for best formulation F2

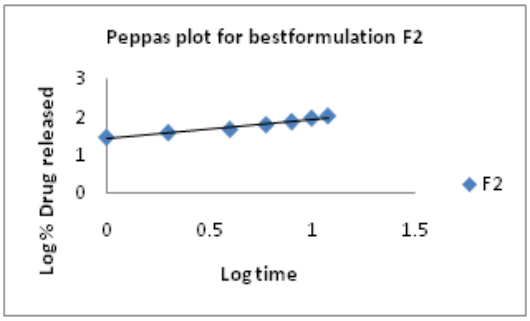

Figure 8: Korsmayerspepas plot for best formulation F2

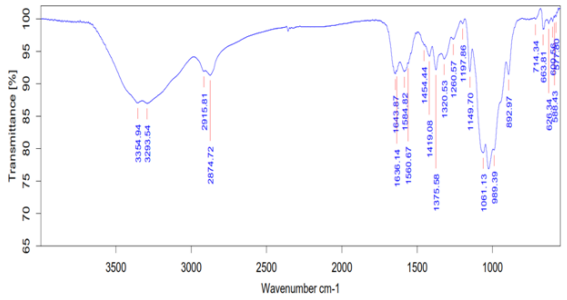

Figure 9: FT-IR of Dexlansprozole

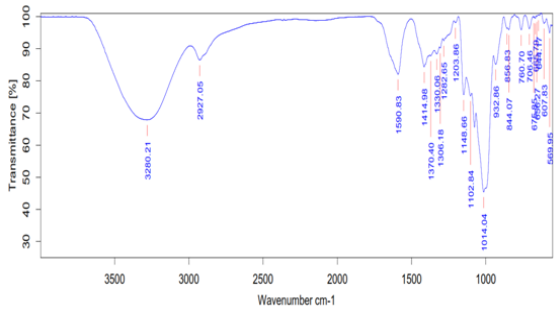

Figure 10: FT-IR of $NAHCO_3$

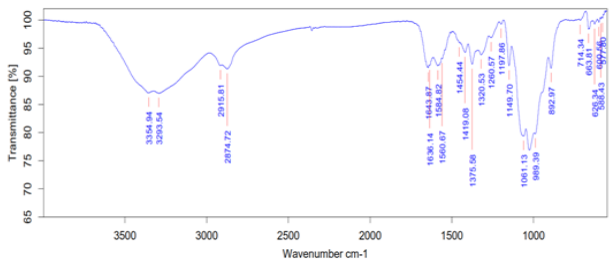

Figure 11: FT-IR of Chitosan

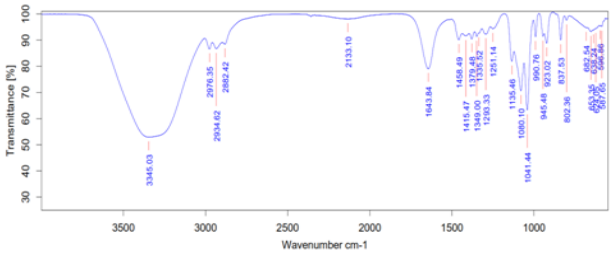

Figure 12: Optimized Formulation

Table 7: Precompression studies of Dexlansoprazole

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Carsindex	Hausners ratio	Angle of repose(˚)
F1	0.43	0.46	15.7	1.4	12.31
F2	0.45	0.52	12.8	1.4	11.35
F3	0.52	0.56	14.2	1.8	12.10
F4	0.41	0.44	16.1	1.42	11.89
F5	0.36	0.43	9.52	1.22	11.53
F6	0.48	0.50	16.9	1.32	10.98
F7	0.41	0.52	11.8	1.21	10.04
F8	0.38	0.39	9.1	1.09	10.97
F9	0.29	0.47	17.42	1.18	12.05

Table 8: Dexlansoprazole floating tablet post-compression investigations

Formulation Code	%weight variation	Thickness (mm)	%Friability	%Drug Content	Hardness (Kg/cm^2)
F-1	P	5.05±0.10	0.145	101.0 ±1.0	5.51 ±0.052
F-2	P	5.05±0.14	0.153	102.5 ±1.2	5.04 ±0.109
F-3	P	5.02±0.055	0.60	100.5 ±1.0	5.04 ±0.12
F-4	P	5.08±0.12	0.149	100.2 ±1.2	5.61 ±0.06
F-5	P	5.02±0.04	0.140	99.2±1.1	5.59 ±0.02
F-6	P	5.02±0.12	0.139	98.1 ±2.5	5.49 ±0.05
F-7	p	4.95±0.06	0.114	99.9.± 1.2	5.65 ±0.12
F8	pass	4.8±0.12	0.133	100.5± 1.4	5.53 ±0.04
F9	pass	4.9±0.1	0.14	99.0±1.0	5.55 ±0.06

Table 9: In-vitro Buoyancy studies of Dexlansoprazole floating tablets

Formulation Code	Floating Lag time(sec) n=3	Total floating time n=3	MatrixIntegrity upto12 hrs. n=3
F-1	20±0.53	Upto 12	+
F-2	40±0.22	Upto 12	+
F-3	80±0.62	Upto 12	+
F-4	20±0.72	Upto 10	-
F-5	30±0.83	Upto 12	+
F-6	35±0.52	Upto 12	+
F-7	24±0.32	Upto 10	-
F-8	20±0.82	Upto 12	+
F-9	36±0.72	Up to 12	+

Table 10: Results of in-vitro dissolution for formulation trials

Time(hrs)	%Drug released								
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8`**	**F-9**
0	0.0	**0. 0**	0. 0	0. 0	0. 0	0. 0	0. 0	0. 0	0. 0
1	35	**28**	21	48	40	47	55	45	32
2	48	**37**	38	67	57	59	68	59	43
4	61	**45**	47	86	68	71	81	70	56
6	76	**59**	56	97	88	86	98	81	68

8	88	**71**	63	100	95	98	100	91	76
10	100	**88**	78	100	100	100	100	100	85
12	100	**100**	85	100	100	100	100	100	100

Table 11: R^2value &"n" result table

Formulation code	R2 value				"n" value
	Zero Order	First Order	.Higuchi	.Peppas	
F2	0.957	0.923	0.974	0.962	0.503

4. Conclusion

Dexlansoprazole Floating Tablets are designed to lengthen the duration of stomach residency, which enhances the medication's therapeutic effectiveness. Better sustained medication release of dexlansoprazole was shown by HPMC K100M. The release rate falls as the concentration of the drug polymer rises. This is because the diffusion route length increases as the concentration of the polymer increases. In-vitro drug release were among the post-compression assessment criteria for which the prepared tablets showed good results. Compared to the other formulations, Formulation F2 provided superior regulated drug release and floating qualities. The Korsmeyer-Peppas, Higuchi, and first-order models best matched the release pattern of the F2 formulations. Non-Fickian or anomalous diffusion was the most likely cause for the drug release pattern from the prepared formulation.

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