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DEVELOPMENT AND IN-VITRO CHARACTERIZATION OF NOVEL GASTRORETENTIVE FLOATING FILM

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ABSTRACT

This research delves into the innovative realm of gastroretentive floating film drug delivery systems, focusing specifically on the formulation and evaluation of Vildagliptin-loaded films for diabetes management. Through a meticulous 3^2 full factorial design, the study explores the influence of Hydroxypropyl Methylcellulose (HPMC) K4M and HPMC E4M concentrations on film properties and drug release kinetics. Comprehensive evaluations, including physical characterization, in vitro dissolution studies, and Fourier Transform Infrared Spectroscopy (FTIR) analysis, illuminate the performance of each formulation. Results highlight Batch FB8 as an optimized formulation, showcasing superior swelling index and extended drug release over 12 hours. This research signifies a pivotal step forward in advancing gastroretentive drug delivery technologies, promising enhanced therapeutic efficacy and patient compliance in diabetes therapy.

Keywords: Gastroretentive drug delivery system (GRDDS); Floating Film; Solvent Casting Method; Controlled Release; Diabetes; Vildagliptin; Floating Film Drug Delivery System.

INTRODUCTION

The goal of drug delivery systems is to deliver therapeutic doses effectively while minimizing side effects. The oral route is favored for its convenience, formulation flexibility, and cost-effectiveness. Gastroretentive drug delivery systems (GRDDS) enhance drug absorption and stability in the gastrointestinal (GI) tract, crucial for drugs with narrow absorption windows or stability issues. Traditional dosage forms often require frequent dosing due to lack of precise control over drug release. GRDDS offer advantages such as prolonged gastric residence time, controlled drug release, and enhanced bioavailability with predictable absorption [1]. They employ mechanisms like buoyancy, bioadhesion, and swelling to extend gastric retention and can be tailored to patient needs,

improving compliance and therapeutic outcomes. Strategies for enhancing gastroretention include physiological, pharmacological, and pharmaceutical approaches.

Floating film drug delivery systems represent an innovative approach in pharmaceutical research, leveraging thin films capable of floating on gastric fluid for extended durations to ensure controlled, sustained drug release and enhanced bioavailability. Despite extensive research on floating dosage forms like tablets and capsules, the potential of floating films remains relatively unexplored, presenting significant opportunities for advancement. Floating films, categorized as effervescent dosage forms, utilize CO2 microbubbles within the film matrix to maintain buoyancy, distinguishing them from other forms. These systems offer a contemporary alternative to traditional dosage forms by encapsulating drug-loaded thin film strips within capsules [2]. Their advantages include ease of preparation, cost-effectiveness, reduced cross-contamination risk, and improved handling compared to microspheres. The manufacturing process typically involves solvent casting, where the drug-polymer mixture is dissolved, combined with additional ingredients, and cast into a thin, uniform film layer conducive to effective drug delivery. Integrating floating and expandability concepts with biodegradable polymers presents a novel strategy for prolonging gastric retention. This approach involves encapsulating a folded, swelling film within a dissolvable capsule, which expands upon contact with gastric fluid, thereby extending drug release time. Despite these advantages, challenges persist in designing polymeric films to precisely control drug release rates and selecting suitable polymers with desired characteristics[3-6].

floating film drug delivery systems hold tremendous promise in pharmaceutical research, offering unique advantages in terms of controlled drug release, enhanced bioavailability, and patient convenience. Addressing current research gaps and overcoming formulation challenges are essential for realizing the full therapeutic potential of these innovative dosage forms. The optimized formulation developed in this study demonstrates significant potential for improving therapeutic efficacy and patient compliance in oral drug delivery systems[7-9].

Diabetes mellitus (DM) poses a significant global health challenge, with Type 2 DM driving the current epidemic. The surge in Type 2 DM cases, particularly in regions like Asia, underscores the urgency to explore innovative treatment modalities. As traditional approaches struggle to meet the demands of effective DM management, emerging technologies offer promising solutions. Floating film drug delivery systems, with their unique ability to provide controlled release, prolonged gastric retention, and enhanced bioavailability, present an attractive option for optimizing drug delivery in diabetes therapy. By leveraging these systems, healthcare providers can potentially improve patient

outcomes by addressing the complexities of DM treatment and enhancing patient adherence to therapy.

Vildagliptin's characteristics, including its three-hour half-life, rapid absorption, and favorable pharmacokinetic profile, position it as an ideal candidate for floating film drug delivery systems. Its mechanism of action, which enhances insulin secretion and reduces glucagon secretion, aligns well with the goals of diabetes management. Additionally, its low risk of hypoglycemia and potential for extended dosing intervals contribute to its suitability for sustained-release formulations aimed at optimizing therapeutic outcomes in diabetes patients.

MATERIALS AND METHODS

MATERIALS

Vildagliptin Was Gifted by Natco Pharma Hyderabad, HPMC E4M Was Gifted by Colorcon, Goa, India. HPMC K4M Was Supplied by S.D. FINE. Other Chemicals Such as Isopropyl Alcohol, Polyethylene Glycol 400, Sodium Bicarbonate Were Supplied by S. D. Fine Chemicals, Mumbai.

Factorial Design

A factorial design is an experimental strategy used to evaluate multiple factors simultaneously, where each factor is a categorical variable with two or more levels. This method is more efficient than one-factor-at-a-time experiments and allows for the detection of interactions between factors. In intervention studies, when two or more categorical explanatory variables are used to predict numerical outcome variables, the design is referred to as a factorial design[10].

In this research, utilized a 3^2 full factorial design (FFD) to explore the effects of two factors: the concentrations of Hydroxypropyl Methylcellulose (HPMC) K4M and HPMC E4M. The concentration as the level for both factors, based on preliminary studies conducted prior to the main experimental design. All other formulation and processing variables were kept constant throughout the study to ensure the reliability of the results.

Table No.1: Amount of Variables In 3^2 Factorial Design Batches

Coded Value	Actual Value (mg)	
	X1(HPMCK4M)	X2(HPMCE4M)
-1	30	30
0	40	40
+1	50	50

Table No. 3: Composition of Floating Film as Per 3^2 Factorial Design

Sr. No.	Batch Code	X1	X2
1	**FB1**	-1	-1
2	**FB2**	0	-1
3	**FB3**	+1	-1
4	**FB4**	-1	0
5	**FB5**	0	0
6	**FB6**	+1	0
7	**FB7**	-1	+1
8	**FB8**	0	+1
9	**FB9**	+1	+1

Method of Preparation of Floating Film of Vildagliptin.

Floating films of vildagliptin were prepared by solvent casting technique using HPMC K4M and HPMC E4M in combinations. Ratio of all the ingredients including drug, polymers and excipients were weighed accurately according to the batch formula (Table 3). Initially, the required amounts of Vildagliptin and polymers, as mentioned in table, were weighed. Subsequently, the drug was dissolved in a Water to form a homogeneous solution, while the polymers are dissolved separately in another part of Water. These two solutions are then combined and thoroughly mixed to achieve a uniform drug-polymer mixture. Then sodium bicarbonate was dissolved in isopropyl alcohol, was added to the above mixture followed by the addition of PEG 400 with constant stirring. The resulting mixture is spread onto a clean petri dish, in a controlled environment to ensure consistency. The solvent from the solution is allowed to evaporate, with the drying process carefully managed to achieve a uniform film thickness. Finally, after drying, the films are carefully removed from the petri dish using a sharp blade [11].

Table No. 3: Formulations For Preparation Floating Films of Vildagliptin

Name of Ingredients	FB1	FB2	FB3	FB4	FB5	FB6	FB7	FB8	FB9
Vildagliptin (mg)	100	100	100	100	100	100	100	100	100
HPMC K4M (mg)	30	40	50	30	40	50	30	40	50
HPMC E4M (mg)	30	30	30	40	40	40	50	50	50
PEG 400 (ml)	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Sodium Bicarbonate (mg)	25	25	25	25	25	25	25	25	25
Water (ml)	3	3	3	3	3	3	3	3	3
Iso Propyl Alcohol (ml)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

EVALUATION OF FORMULATIONS [12-14]

1. **Thickness Measurement:** To ensure uniformity and consistent quality, the thickness of polymeric films was meticulously measured at various locations using a Vernier caliper. This step was crucial in verifying the film's mechanical integrity and its ability to provide consistent drug delivery.
2. **Weight Uniformity:** The weight uniformity of the films was assessed by randomly selecting three samples from each batch and individually weighing them using a digital balance. Calculations of mean weight and standard deviation were performed to ascertain uniformity across the batch, ensuring reliable dosage delivery.
3. **Folding Endurance:** The mechanical toughness of the films was evaluated through a folding endurance test. A strip of predetermined area was repetitively folded at a consistent location until it fractured. This test provided valuable insights into the film's ability to withstand stress and deformation during handling and administration.
4. **Swelling Index:** Understanding the film's swelling behavior in different environments is crucial for its performance. Films were immersed in a 0.1N HCl solution at 37 ± 1°C, and the change

in weight over time was measured. The swelling index, calculated as the percentage increase in weight, indicated the film's capacity to absorb fluids and swell appropriately.

The swelling index was then calculated using the formula:

Swelling index (%) = ((W2 - W1) / W1) x 100

5. **In-vitro Unfolding Study:** To simulate real-world conditions, films underwent folding in both rolling and zigzag patterns before being encapsulated within gelatin capsules. Using a USP dissolution apparatus II, the unfolding behavior of the films was observed under simulated gastric conditions. This study provided insights into the films' ability to unfold and release the drug payload effectively.
6. **In-vitro Buoyancy Studies:** The buoyancy characteristics of the films were evaluated by placing gelatin capsules containing the films in a 0.1N HCl solution and stirring at a constant speed. Observations were made regarding the duration of floating and any observed expansion, providing valuable insights into the films' ability to float and remain buoyant under gastric conditions.
7. **Floating Lag Time:** The floating lag time, indicating the onset of buoyancy, was determined by recording the time taken for a dosage form to begin floating on the surface of a dissolution medium after introduction. This parameter is essential for assessing the potential for sustained drug release and prolonged gastric retention.
8. **Drug Content:** Accurate determination of the drug content in the films is critical for dosage accuracy and efficacy. Film pieces were thoroughly extracted in 0.1N HCl solution, and the drug content was determined spectrophotometrically at 210 nm after appropriate dilution. This ensured precise quantification of the drug content in the films.
9. **In vitro Dissolution Studies:** The drug release study utilized a USP paddle apparatus, paired with a double beam UV spectrophotometer (Jasco V-530, Shimadzu Corporation, Japan). The experiment was conducted at 37±0.5°C with a rotation speed of 50 rpm, employing 900 mL of acidic buffer (pH 1.2) as the dissolution medium. Capsules containing the folded film were placed into the dissolution vessel. Samples of 5 mL were withdrawn at specified time intervals, appropriately diluted, and their absorbance measured at 210 nm using the UV spectrophotometer. Fresh dissolution medium was promptly added to replace the withdrawn samples. The percentage of drug dissolved was calculated, facilitating the determination of the in vitro release profile [15-16].

Fourier Transform Infrared Spectroscopic Study (FTIR)

The interaction between the drug and polymers was studied using IR spectroscopy. The IR spectra of Vildagliptin, a physical mixture of Vildagliptin with polymers, and the film were obtained using the KBr disk method (FTIR-8400S, Shimadzu Corporation, Japan). The scanning range was 400 to 4000 cm^{-1}, with a resolution of 1 cm^{-1}.

RESULTS AND DISCUSSION

To assess the compatibility of Vildagliptin with the selected polymers, Fourier Transform Infrared (FTIR) spectroscopy was employed. The functional groups present in the drug was identified based on their frequencies, as detailed in Table No. 4. The FTIR spectra, illustrated in Graph No. 1, were carefully analysed. Notably, the observed peaks in the spectra aligned with the principal peak region associated with the functional groups. This observation suggests that there is no interaction between Vildagliptin and the polymers, indicating their compatibility for potential pharmaceutical applications.

The weight variation of the prepared floating films was evaluated, and the average weight for each formulation is provided in Table No. 5. Low standard deviation values suggest uniform weight distribution across the films, with variations in average weight attributed to changes in polymer concentration. The thickness of all floating films, measured using a Vernier caliper, was within an acceptable range. Folding endurance tests indicated good flexibility, although an increase in polymer concentration resulted in decreased folding endurance, with formulation FB1 exhibiting the highest and FB9 the lowest endurance.

The swelling index of the floating films ranged from 27.48±1.74 to 37.52±2.01, with batch FB8 showing the highest index, followed by batch FB9. The unfolding properties were assessed, showing that the films unfolded within 13-17 minutes after the gelatin capsule disintegrated in the stomach. Floating lag time for all formulations was within 51 to 54 seconds. The total floating time ranged from 9 to 12 hours, increasing with higher polymer concentrations. The percentage of drug content in formulations FB1 to FB9 ranged from 96.07±0.45 to 99.36±0.12, all within acceptable limits. Overall, the prepared floating films demonstrated satisfactory performance across all evaluated parameters**.**

From in-vitro drug dissolution study (Table No 7), The maximum cumulative percentage of drug release, observed over 12 hours, was found to be 99.39±0.4% for **batch FB8**. An interesting trend emerged as the concentration of polymers increased, resulting in a retardation of the drug release

from the formulation. Specifically, from batch FB1 to FB8, an increase in polymer concentration correlated with an extended drug release time. Notably, among these formulations, **batch FB8** exhibited an optimized drug release profile, demonstrating its potential as a promising formulation for controlled drug delivery applications.

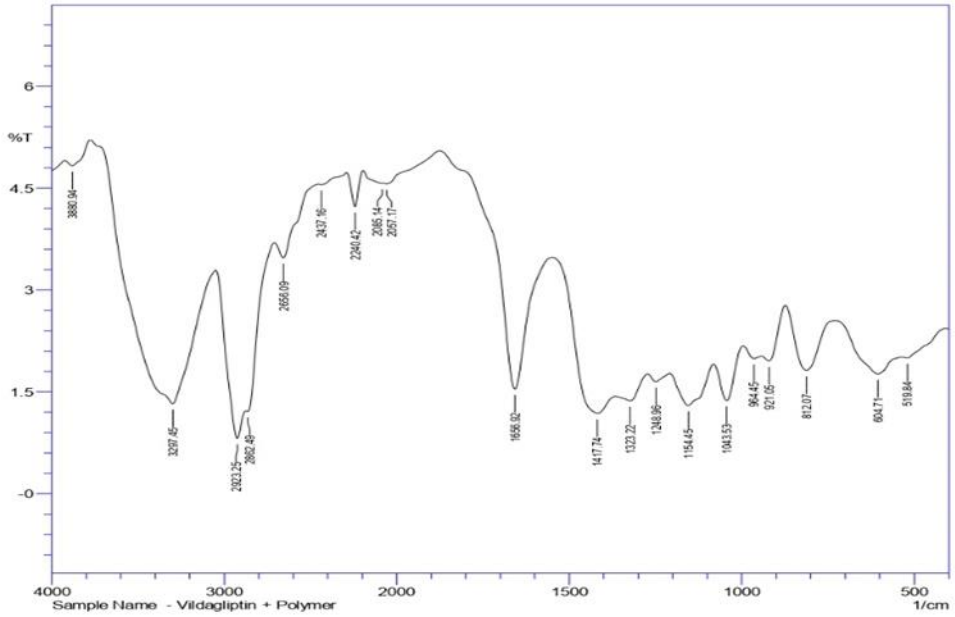


Figure.1: FTIR Spectrum of Drug & Polymer

Table No. 4: Interpretation of IR Spectrum of Vildagliptin and Polymer

Sr. No.	Functional Groups	Peak Values	Observed Peak Values
1	-N-H	3200-3500	3297.45
2	-CH	2800-2960	2923.25
3	-CN	2240-2280	2240.42
4	-C=O	1650-1690	1656.92
5	C-N	1000-1250	1154.45
6	-O-H	1395-1440	1417.74

Table No. 5: Results of Evaluation of Factorial Batches

Batch No.	Weight uniformity (mg)	Thickness of Film (mm)	Folding Endurance	% Swelling Index
FB1	140.2±0.61	0.81±0.005	239±3.6	27.48±1.74
FB2	151.4±0.96	0.81±0.007	236±5.5	29.52±1.57
FB3	162.2±0.65	0.93±0.006	232±5	32.87±2.47
FB4	151.1±0.72	0.82±0.020	238±6.5	30.25±1.95
FB5	160.7±0.96	0.92±0.022	234±4	31.79±1.27
FB6	172.5±0.70	0.84±0.038	224±4	35.88±2.12
FB7	160.3±0.55	0.93±0.011	235±5	34.87±2.28
FB8	171.2±0.60	0.94±0.032	226±4	37.52±2.01
FB9	181.5±0.91	0.95±0.030	220±5	36.58±2.01

All values are expressed as Mean ± Standard Deviation, n=3

Table No.6: Results of Evaluation of Factorial Batches

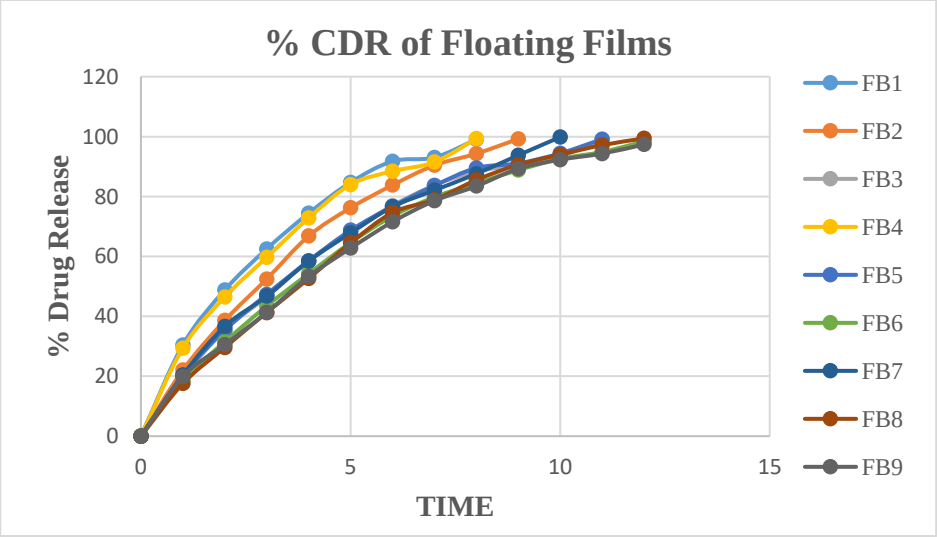
Batch No.	Unfolding Study (min)	Floating Lag Time (sec)	Floating Time (hour)	% Drug Content
FB1	17±2	54±2.64	9±0.5	96.07±0.45
FB2	16±4	54±2.64	11±0.2	97.88±0.74
FB3	13±1	52±2.64	12±0.75	98.68±0.62
FB4	17±3	53±4	10±0.81	97.33±0.58
FB5	14±4	52±3	12±0.92	97.52±0.38
FB6	13±3	52±4.35	12±0.40	98.06±0.4
FB7	15±3	53±2	12±0.70	97.22±0.5
FB8	13±1	51±2.64	12±0.40	99.11±0.54
FB9	14±4	52±2	12±0.85	99.36±0.12

All values are expressed as Mean ± Standard Deviation, n=3

Table No.7: *In-Vitro* Dissolution Study of Factorial Batches of Floating Film

TIME	% Drug Release								
	FB1	**FB2**	**FB3**	**FB4**	**FB5**	**FB6**	**FB7**	**FB8**	**FB9**
0	0	0	0	0	0	0	0	0	0
1	30.44± 0.85	22.05± 0.84	19.49± 1.6	29.38± 0.83	20.38± 0.8	18.66± 0.8	20.38± 0.8	17.55± 1.2	19.88± 0.8
2	48.77± 0.84	38.61± 0.88	35.49± 0.85	46.44± 1.0	35.33± 0.59	31.49± 1.3	36.61± 1.2	29.59± 1.01	30.49± 0.8
3	62.49± 0.85	52.44± 0.86	46.52± 0.76	59.69± 1.3	47.3± 0.8	43.44± 1.2	46.7± 1.3	41.25± 0.9	41.27± 0.9
4	74.39± 0.85	66.79± 1.68	58.44± 0.93	72.8± 0.8	58.51± 1.0	54.23± 0.85	58.4± 1.6	52.59± 0.8	53.3± 1.0
5	84.69± 0.90	76.21± 0.87	68.37± 1.2	83.98± 1.6	68.72± 1.6	64.59± 0.88	67.78± 0.8	64.49± 0.8	62.74± 0.8
6	91.76± 0.93	83.79± 0.65	76.92± 0.63	88.44± 1.2	76.65± 0.8	73.44± 0.5	76.53± 0.8	74.62± 0.9	71.53± 0.8
7	93.04± 0.78	90.42± 0.88	83.73± 0.87	91.49± 1.1	83.63± 0.8	79.79± 1.1	82.07± 0.8	78.92± 0.5	78.56± 0.8
8	99.1± 0.32	94.3± 0.87	88.41± 1.2	99.34± 0.82	89.52± 1.1	84.44± 1.1	87.57± 0.8	85.52± 0.8	83.46± 1.2
9		99.92± 0.54	90.44± 1.08		91.06± 0.8	88.79± 1.1	93.77± 1.05	90.6± 1.2	89.3± 0.8
10			93.38± 1.1		94.4± 0.5	92.6± 0.98	99.83± 1.0	93.97± 0.8	92.28± 0.5
11			99.01± 0.56		99.14± 0.7	94.88± 0.5		97.15± 0.8	94.33± 1.0
12						98.34± 0.5		99.39± 0.4	97.34± 1.1

All values are expressed as Mean ± Standard Deviation, n=3



Graph No. 2 Time Vs. % CDR Of Floating Films of Vildagliptin

CONCLUSION

In conclusion, our research journey has illuminated the paramount importance of meticulous formulation design in optimizing gastroretentive floating films. Through systematic exploration of polymer concentrations in factorial batches, we have unearthed critical insights into film properties and drug release kinetics, paving the way for advancements in gastroretentive drug delivery systems. Among the array of formulations scrutinized, Batch FB8 has emerged as a beacon of excellence, showcasing unparalleled performance with the highest swelling index and maximum cumulative drug release over 12 hours. This optimized formulation represents the culmination of our efforts, signaling a promising avenue for further refinement and development in gastroretentive drug delivery.

The identification of Batch FB8 as the optimized formulation heralds a significant milestone in our research endeavor. It not only underscores our commitment to excellence but also lays the foundation for improved therapeutic efficacy and enhanced patient compliance in gastroretentive drug delivery.As we move forward, our focus remains steadfast on leveraging these findings to drive positive impacts in pharmaceutical sciences. By prioritizing meticulous formulation design, we aim to elevate patient outcomes through optimized therapeutic efficacy and enhanced patient compliance, thus shaping the future landscape of drug delivery technologies.

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