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DEVELOPMENT AND CHARACTERIZATION OF GASTRORETENTIVE FLOATING FILMS OF VILDAGLIPTIN FOR ENHANCED DIABETES MANAGEMENT

Ankit G. Bhopaye[1], Nishant N. Bobade[2], Yukta K. Mhaskey[3], Aditi V. Tikait[4]

[1,2,3,4]Department of pharmaceutics, Vidyabharati College of Pharmacy, Amravati – 444 602, India

For Correspondence: Ankit G. Bhopaye

Mail id: ankitbhopaye01@gmail.com

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ABSTRACT

This study developed gastroretentive floating films of Vildagliptin using various polymers (HPMC K4M, HPMC E4M, HPMC E5LV, and Hydroxyethyl cellulose) via solvent casting to enhance drug delivery for diabetes management. The formulations were extensively characterized for weight uniformity, thickness, folding endurance, swelling behavior, buoyancy, drug content, and in vitro dissolution profiles. Results demonstrated uniform weight distribution and adequate thickness across all formulations, ensuring consistent dosing. Films exhibited good flexibility and mechanical strength, with formulations containing HPMC K4M and HPMC E4M showing superior swelling indices, effective gastric retention, and controlled drug release. In vitro studies confirmed quick unfolding and prolonged floating times (8-11 hours), with formulations P8 and P2 achieving over 99% drug release in 9 hours. Fourier Transform Infrared Spectroscopy indicated polymer-drug compatibility, supporting their pharmaceutical viability. Overall, Vildagliptin-loaded floating films hold promise for improving diabetes therapy by enhancing drug delivery efficiency, extending gastric retention, and potentially improving patient adherence, suggesting future avenues for optimizing these formulations in clinical settings.

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

1. INTRODUCTION

Diabetes mellitus (DM) continues to pose a significant global health challenge, particularly with the increasing prevalence of Type 2 DM in Asia, necessitating innovative treatment strategies. Conventional therapeutic approaches often encounter limitations in effectively managing DM, prompting exploration into advanced drug delivery technologies such as gastroretentive drug delivery systems (GRDDS) and floating film drug delivery systems (DDS). These systems offer promising avenues to optimize diabetes therapy by addressing the intricate nuances of disease management and improving patient adherence.

GRDDS are specifically designed to extend gastric residence time and enhance drug absorption in the gastrointestinal tract. They achieve this through various mechanisms, including buoyancy, bioadhesion, and swelling, which collectively facilitate sustained drug release and consistent absorption. By prolonging drug exposure within the stomach, GRDDS can overcome challenges posed by variable gastric emptying times and ensure targeted delivery to absorption sites in the upper gastrointestinal tract.

In parallel, floating film DDS represent a novel advancement in pharmaceutical technology. These systems utilize thin films that float on gastric fluids, leveraging their effervescent properties to generate CO2 microbubbles and maintain buoyancy. Compared to traditional oral dosage forms such as tablets and capsules, floating films offer several advantages, including enhanced bioavailability, prolonged drug release, and reduced dosing frequency. They are composed of active pharmaceutical ingredients, polymers, plasticizers, and solvents, typically manufactured through solvent casting to form uniform film layers. Vildagliptin, chosen for its favorable pharmacokinetic profile and therapeutic efficacy, stands out as a promising candidate for floating film DDS in diabetes management. With a short half-life of approximately three hours, Vildagliptin facilitates rapid absorption and exerts favorable effects on insulin and glucagon secretion, aligning with therapeutic goals in DM treatment. Its low propensity for hypoglycemia and potential for extended dosing intervals make it well-suited for sustained-release formulations, potentially improving treatment outcomes and patient compliance. The decision to focus on diabetes mellitus and Vildagliptin within the context of floating film DDS and GRDDS underscores the urgent need for innovative solutions to address the complex dynamics of diabetes management globally. Leveraging the distinctive advantages of Vildagliptin and these advanced drug delivery systems holds promise for achieving prolonged therapeutic effects, optimizing drug delivery efficiency, and enhancing patient adherence in diabetes treatment regimens.

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2. MATERIALS AND METHODS

MATERIALS

Vildagliptin Was Gifted by Natco Pharma Hyderabad; HPMC E4M Was Gifted by Colorcon, Goa, India. HPMC K4M and HPMC E5LV Was Supplied by S.D. FINE. Hydroxyethyl cellulose was obtained from JMG Enterprises. Other Chemicals Such as Isopropyl Alcohol, Polyethylene Glycol 400, Sodium Bicarbonate Were Supplied by S. D. Fine Chemicals, Mumbai.

Method of Preparation of Floating Film of Vildagliptin

Gastroretentive floating films were prepared by employing solvent casting method following different concentration of polymers (HPMC K4M, HPMC E5LV, Hydroxy Ethyl Cellulose, HPMC E4M) as per mention in **Table No. 1.**

Initially, the required amounts of Vildagliptin and polymer, as mentioned in table, were weighed. Subsequently, the drug is dissolved in a Water to form a homogeneous solution, while the polymer is 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 dissolve into 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.

Table No. 1: Formulation Floating Films Using Different Concentration of Polymers

Name of Ingredients	P1	P2	P3	P4	P5	P6	P7	P8
Vildagliptin (mg)	100	100	100	100	100	100	100	100
HPMC K4M (mg)	80	90						
HPMC E5LV (mg)			80	90				
Hydroxy Ethyl Cellulose (mg)					80	90		
HPMC E4M (mg)							80	90
PEG 400 (ml)	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
Water (ml)	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

3. EVALUATION OF FORMULATIONS

1. Thickness: The thickness of the polymeric films was measured using a Vernier caliper at various points to ensure uniformity.

2. Weight Uniformity: Three films randomly selected from each batch were individually weighed using a digital balance to determine mean weight and standard deviation, ensuring consistent dosage delivery.

3. Folding Endurance: A strip of specified area was repeatedly folded at the same point until it broke, with the number of folds indicating the film's toughness and resistance to breakage.

4. Swelling Index: The initial weight of each film (W1) was recorded, followed by immersion in 0.1N HCl solution at 37 ± 1°C for 360 minutes. The final weight (W2) was then measured to calculate the swelling index using the formula: Swelling index (%) = ((W2 - W1) / W1) x 100.

5. In vitro Unfolding Study: Films were folded in either a rolling or zigzag manner and encapsulated in gelatin capsules. Using a USP dissolution apparatus II with a paddle, unfolding behavior was observed in 900 ml of 0.1 N HCl solution at 37 ± 0.5°C and 50 rpm, assessing their ability to unfold upon capsule disintegration in simulated gastric conditions.

6. In vitro Buoyancy Studies: Gelatin capsules containing films were placed in a beaker with 250 ml of 0.1N HCl solution and stirred at 50 rpm. Floating duration and expansion were visually observed to determine the films' buoyancy characteristics under simulated gastric conditions.

7. Floating Lag Time: The time taken for the film to start floating on the surface of the dissolution medium after immersion was recorded, indicating the onset of buoyancy critical for gastroretentive drug delivery systems.

8. Drug Content: Film pieces were extracted in 100 ml of 0.1N HCl solution, stirred continuously, and analyzed spectrophotometrically at 210 nm after dilution with 0.1N HCl to determine drug content accurately.

9. In vitro Dissolution Studies: Dissolution profiles were evaluated using a USP paddle apparatus and double beam UV spectrophotometer at 37±0.5°C and 50 rpm in pH 1.2 acidic buffer. Samples were withdrawn at intervals, diluted, and absorbance measured at 210 nm to calculate the percentage of drug released, providing insights into release kinetics and performance under simulated physiological conditions.

Fourier Transform Infrared Spectroscopic Study (FTIR)

Fourier Transform Infrared Spectroscopy (FTIR) was employed to investigate the interaction between Vildagliptin and polymers. The IR spectra were obtained using the KBr disk method with a Shimadzu FTIR-8400S spectrometer, scanning from 400 to 4000 cm-1 at a resolution of 1 cm-1. This method allowed for the characterization of Vildagliptin alone, the physical mixture of Vildagliptin with polymers, and the resultant film. Analysis of these spectra provided insights into the chemical interactions and compatibility between the drug and polymers used in the formulation, crucial for understanding the structural stability and performance of the floating films in drug delivery applications.

4. RESULTS AND DISCUSSION

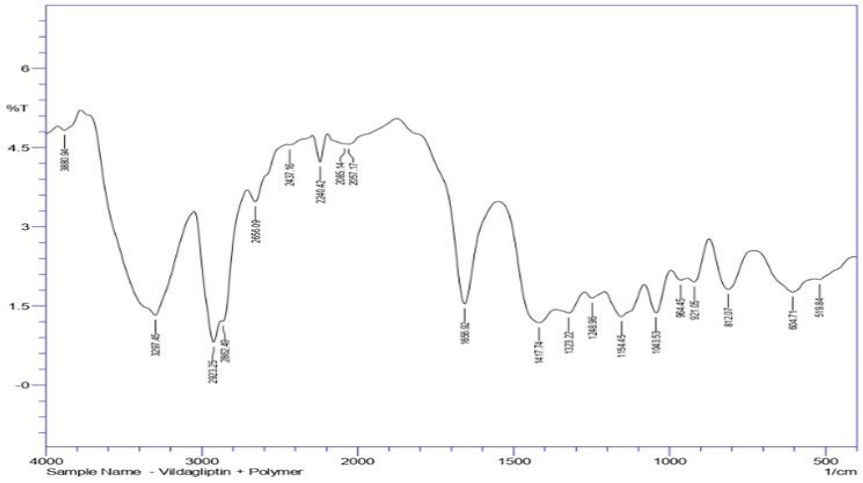
To evaluate the compatibility of Vildagliptin with the selected polymers, Fourier Transform Infrared (FTIR) spectroscopy was utilized. The functional groups present in the drug were identified based on their characteristic frequencies, as detailed in Table 2. Analysis of the FTIR spectra, depicted in Graph 1, revealed that the observed peaks corresponded well with the primary peak regions associated with the functional groups. This alignment indicates no significant interaction between Vildagliptin and the polymers, suggesting their suitability for pharmaceutical applications.

The evaluation of floating films formulated with various polymers demonstrates consistent performance across critical parameters. Low standard deviations indicate uniform weight distribution among formulations, while acceptable thickness ranges confirm the films' structural integrity, despite increased polymer concentrations leading to thicker films. Folding endurance tests revealed good flexibility across all films, with slightly reduced endurance at higher polymer concentrations, while formulations P1 and P7 exhibited the highest endurance.

The swelling index, crucial for assessing film buoyancy and drug release kinetics, highlighted batches P1, P2, P7, and P8 as superior performers. Films incorporating HPMC K4M (P1 and P2) and HPMC E4M (P7 and P8) showed notably higher swelling indices, facilitating prolonged floating and controlled drug release. Evaluations of unfolding properties demonstrated that films, particularly those with HPMC K4M and HPMC E4M, unfolded within 14-17 minutes in simulated gastric conditions.

Floating lag times were consistently within 53 to 61 seconds for all formulations, indicating rapid onset of buoyancy upon contact with dissolution media. The total floating times ranged from 8 to 11 hours, with formulations containing HPMC K4M and HPMC E4M exhibiting the longest durations. Drug content analyses confirmed that formulations P1 to P9 met acceptable limits, ranging from 96.42±0.52% to 98.85±0.33%.

Moreover, maximum cumulative drug release percentages for 9 hours were observed in batches P8 (99.22±0.54%) and P2 (99.30±0.86%). These batches, containing HPMC E4M and HPMC K4M respectively, demonstrated superior drug release profiles. Batch P8, in particular, stood out with its excellent drug release and prolonged floating time of 10 to 11 hours, highlighting its optimized performance among the formulations tested. Overall, these findings underscore the promising potential of these floating film formulations in achieving prolonged gastric retention, enhanced drug release, and consistent drug content uniformity, crucial for optimizing therapeutic efficacy in pharmaceutical applications.



Graph No.1: FTIR Spectrum of Drug & Polymer

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Table No. 2: 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. 3: Results of Evaluation of Floating Flms

Batch No.	Weight Variation (mg)	Thickness of Film (mm)	Folding Endurance	% Swelling Index
P1	160.2±0.56	0.84±0.004	236±2	33.58±2.01
P2	171.4±0.56	0.97±0.005	233±3	36.31±2.7
P3	157.6± 0.81	0.74±0.007	211±5	18.89±3.69
P4	168.3±0.45	0.81±0.006	208±4	21.29±1.38
P5	158.5±0.6	0.79±0.005	214±4	26.59±1.63
P6	169.4± 0.56	0.82±0.003	210±8.7	28.38±2.96
P7	159.2±0.30	0.83±0.008	239±9.16	31.87±2.28
P8	170.5 ±0.68	0.95±0.005	236±3.6	35.52±2.01

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

Table No: 4 Results of Evaluation of Floating Flms

Batch No.	Unfolding Study (min)	Floating LagTime (sec)	Floating Time (hour)	% Drug Content
P1	14min	53±4.58	10±0.25	97.71±0.33
P2	15min	55±6.24	11±0.5	98.85±0.33
P3	25min	59±8.54	8±0.38	96.42±0.52
P4	27min	61±5.29	8±0.38	97.17±0.58
P5	19min	61±4.16	8±0.52	96.57±0.66
P6	23min	60±5.56	9±0.25	96.94±0.33
P7	16min	54±4.58	10±0.25	97.8±0.59
P8	17min	56±4	10±0.38	98.26±0.44

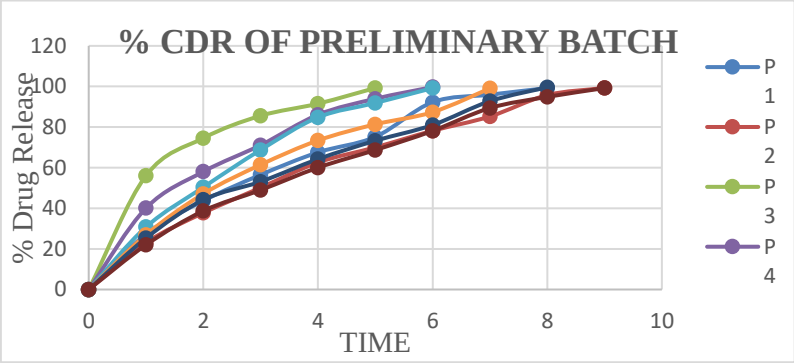
All values are expressed as Mean ± Standard Deviation, n=3

Table No. 5: In-Vitro Dissolution Study of Floating Flms

TIME	% Drug Release							
	P1	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**
0	0	0	0	0	0	0	0	0
1	27.27± 0.5	23.1± 0.42	56.16± 1.67	40.10± 0.91	30.77± 1.13	26.94± 0.84	25.33± 0.83	21.99± 0.83
2	43.68± 0.85	37.74± 0.84	74.58± 0.84	58.05± 0.88	50.38± 0.9	47.14± 0.83	44.19± 0.64	38.73± 0.84
3	56.5± 0.67	50.17± 0.44	85.58± 0.84	71.11± 0.96	68.76± 0.84	61.46± 0.85	53.13± 1.67	49± 0.84
4	67.56± 0.85	62.56± 0.84	91.54± 0.36	86.09± 0.6	84.81± 0.85	73.41± 0.45	64.23± 0.85	60.04± 0.76

5	75.19± 0.6	70.02± 0.68	99.27± 0.89	93.96± 0.85	91.88± 0.52	81.37± 0.87	73.28± 1.09	68.71± 1.10
6	92.26± 0.77	78.19± 0.68		99.7± 0.94	99.2± 0.86	87.37± 0.55	81.04± 0.94	78.14± 0.9
7	95.97± 0.42	85.24± 0.87				99.07± 0.62	92.76± 1.48	89.38± 1.04
8	99.2± 0.23	95.75± 0.86					99.60± 0.94	94.87± 0.32
9		99.3± 0.86						99.22± 0.54

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



Graph No. 2 Time vs. % CDR of Floating Films of Vildagliptin

5. CONCLUSION

In conclusion, this study focused on formulating and characterizing gastroretentive floating films of Vildagliptin, aiming to optimize drug delivery for diabetes management. Using various polymers such as HPMC K4M, HPMC E4M, HPMC E5LV and Hydroxyethyl cellulose, formulations exhibited uniform weight and maintained structural integrity with acceptable thickness ranges. Despite a slight reduction in folding endurance with increased polymer concentrations, formulations P1 and P7 demonstrated the highest flexibility and mechanical strength. The films, particularly batches P1 (HPMC K4M) and P8 (HPMC E4M), showed superior swelling indices, enabling prolonged gastric retention and controlled drug release. They also displayed rapid unfolding and short floating lag times, with total floating times ranging from 8 to 11 hours. In-vitro dissolution studies highlighted formulations P8 and P2 for their maximum drug release percentages over 9 hours (99.22% and 99.30%, respectively), emphasizing the optimized performance of batch P8 containing HPMC E4M. Fourier Transform Infrared Spectroscopy confirmed the compatibility of Vildagliptin with the polymers used. Overall, these findings underscore the potential of Vildagliptin-loaded floating films to enhance diabetes therapy through improved drug delivery efficiency and patient compliance.

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