International Journal of Enhanced Research in Medicines & Dental Care
(IJERMDC), ISSN: 2349-1590, Vol. 12 Issue 3, March 2025

Formulation and In-Vitro Evaluation of Alogliptine Gastroretentive Floating Pellets

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ABSTRACT

Metabolic syndrome (MS) is a cluster of conditions including obesity, insulin resistance, dyslipidemia, and hypertension, posing significant global health challenges. Alogliptin, a dipeptidyl peptidase-4 (DPP4) inhibitor, is effective in managing type 2 diabetes mellitus (T2DM) and associated metabolic disorders. However, its oral bioavailability is limited due to P-glycoprotein (P-gp)-mediated efflux. This study aimed to design and optimize gastroretentive floating pellets of alogliptin to enhance bioavailability. A 3-level, 3-factor Box-Behnken design was employed to optimize formulations, varying Eudragit RS 100 (release retardant), sodium bicarbonate (effervescent agent), and Eudragit RL 100 (gas-entrapped polymer). The optimized formulation exhibited a floating lag time of 3.4 min and sustained drug release (86.54% in 10 h). Pharmacokinetic studies in Wistar rats demonstrated a 2.51-fold increase in bioavailability compared to plain alogliptin. The developed system offers a promising approach for improving alogliptin delivery in MS management.

INTRODUCTION

Metabolic syndrome (MS) is a multifactorial disorder characterized by insulin resistance, obesity, dyslipidemia, and hypertension, increasing the risk of cardiovascular diseases (CVD) and T2DM. Current treatment strategies involve multiple drugs, leading to poor patient compliance and drug-drug interactions. Alogliptin, a DPP4 inhibitor, enhances incretin hormone activity, improving glycemic control and lipid metabolism. However, its oral bioavailability is hindered by P-gp efflux in the intestine.

Gastroretentive floating drug delivery systems (GRDDS) prolong gastric residence time, enhancing drug absorption in the upper gastrointestinal tract (GIT). Multiparticulate pellets offer advantages such as reduced inter-subject variability, flexible release kinetics, and minimized dose dumping. This study focused on developing alogliptin-loaded floating pellets using an effervescent technique to overcome P-gp efflux and improve bioavailability.

MATERIALS AND METHODS

Materials

Alogliptin (Wockhardt Ltd.), Eudragit RS 100 and RL 100 (Evonik Pharma), sodium bicarbonate (Himedia), hydroxypropyl methylcellulose (HPMC E5 LV), and microcrystalline cellulose were used.

Preparation of Floating Pellets

Core Pellets: Prepared by extrusion-spheronization using alogliptin (40% w/w) and microcrystalline cellulose (60% w/w) with PVP K30 binder.

Coating:
Layer 1: Eudragit RS 100 (0.5–1.5% w/w) as a release retardant.
Layer 2: Effervescent layer ($NaHCO_3$:HPMC, 1:2 to 2:1).
Layer 3: Eudragit RL 100 (5–15% w/w) as a gas-entrapped polymer.

Experimental Design

A Box-Behnken design (3 factors, 3 levels, 13 runs) was used to optimize:

Independent Variables:
Characterization

FTIR & XRD: Confirmed drug-excipient compatibility.
Particle Size & Sphericity: Sieve analysis and aspect ratio measurement.
Floating Behavior: Lag time and % floating pellets at 10 h.
In Vitro Release: USP Type II dissolution apparatus (0.1 N HCl, 50 rpm).

Evaluation of alogliptine gastroretentive floating pellets

Spectrophotometric Studies

Fig. : λ max of alogliptine in 0.1 N HCl

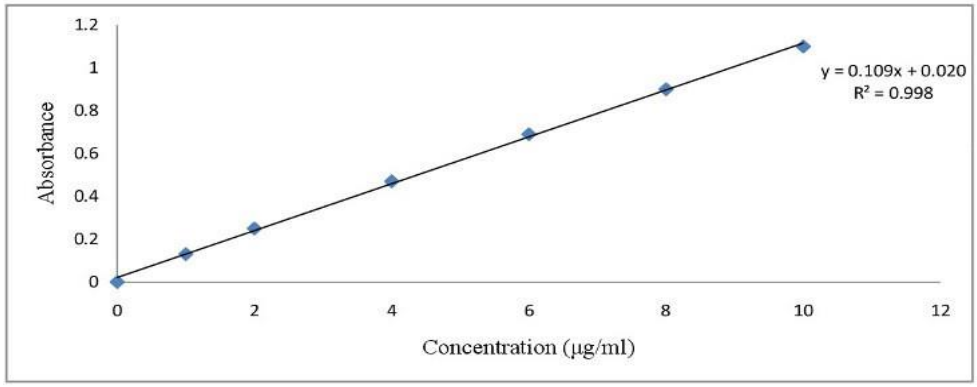

Fig. a: Calibration curve of alogliptine in 0.1 N HCl

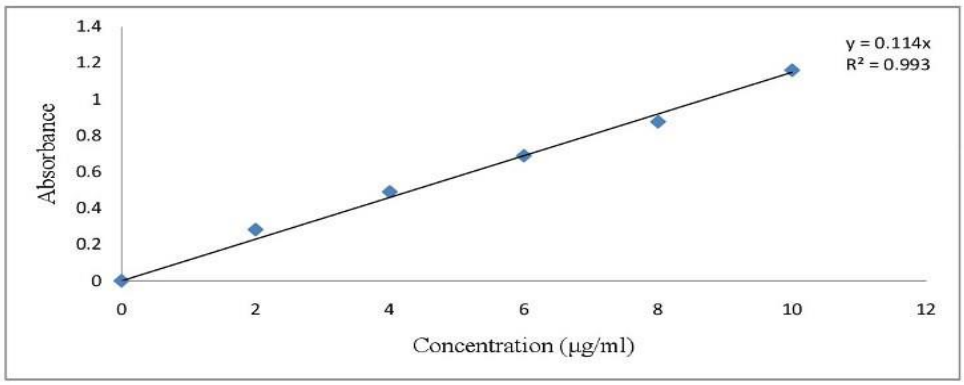

Fig. b: Calibration of alogliptin in distilled water

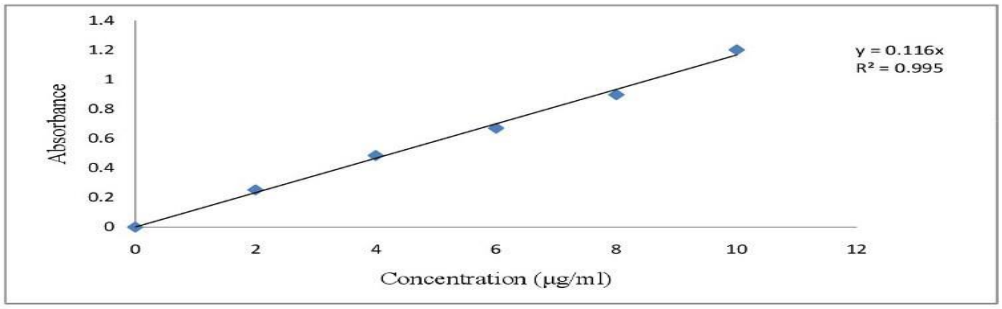

Fig.: Calibration curve of alogliptine in methanol

- **Fourier Transform Infra-Red (FTIR) spectrum and X-ray diffraction (XRD)**

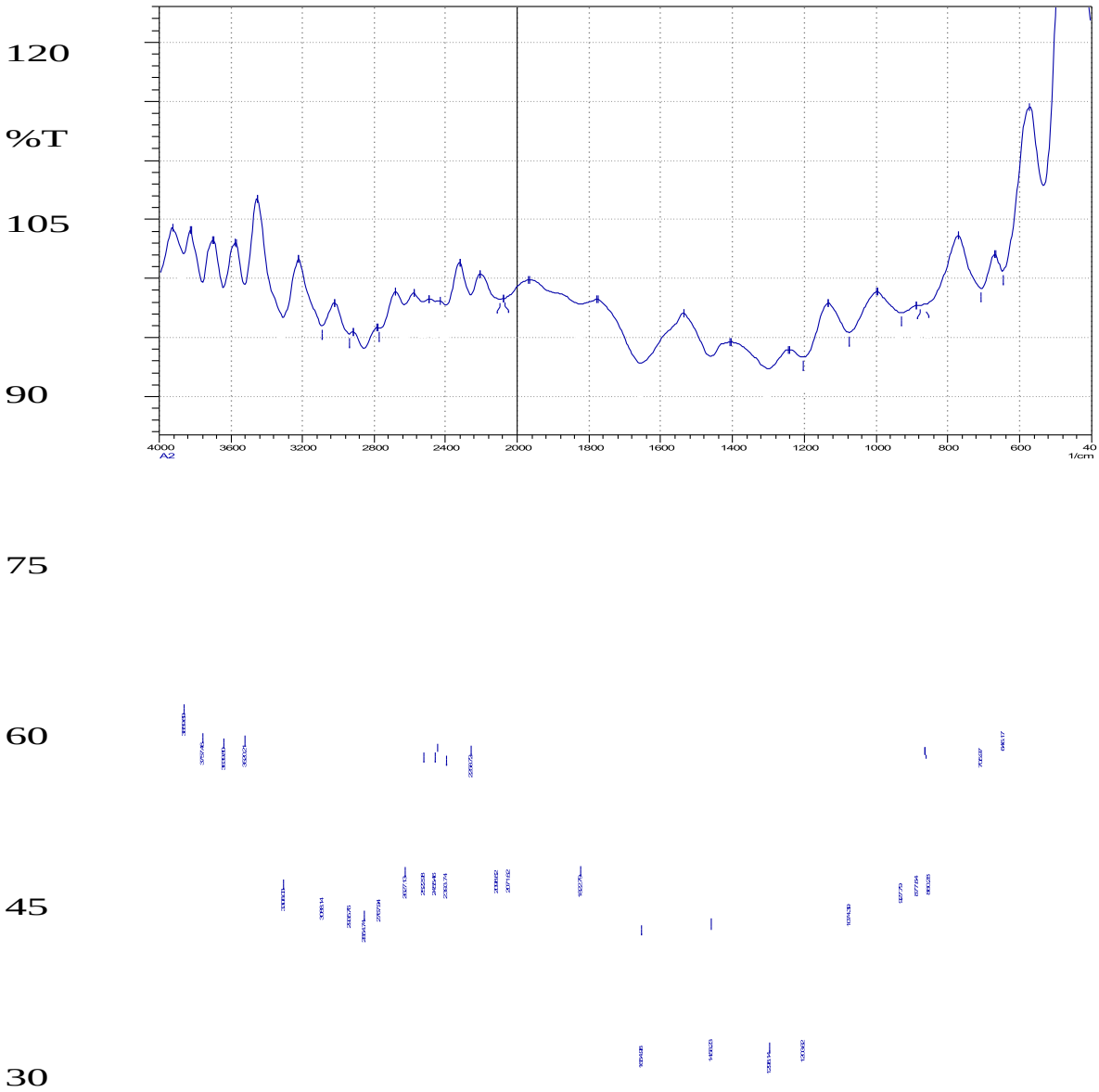

Fig. a: FTIR scan of Alogliptine

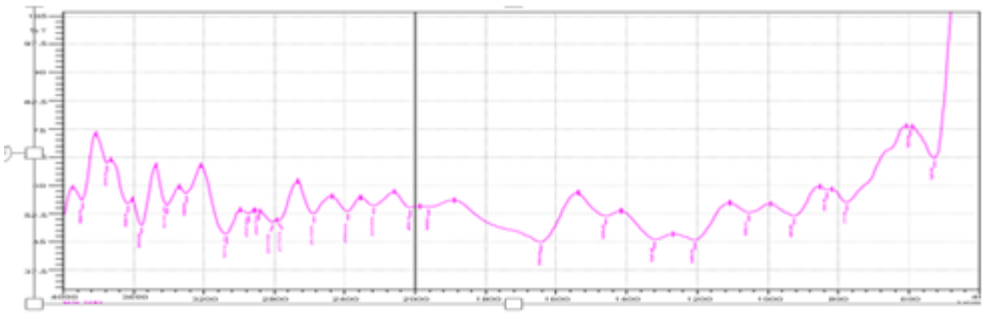

Fig. b: FTIR scan of Eudragit RS 100

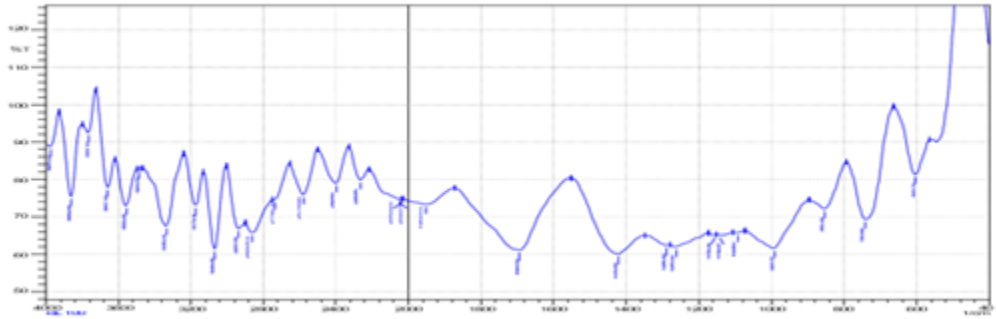

Fig. c: FTIR scan of Eudragit RL 100

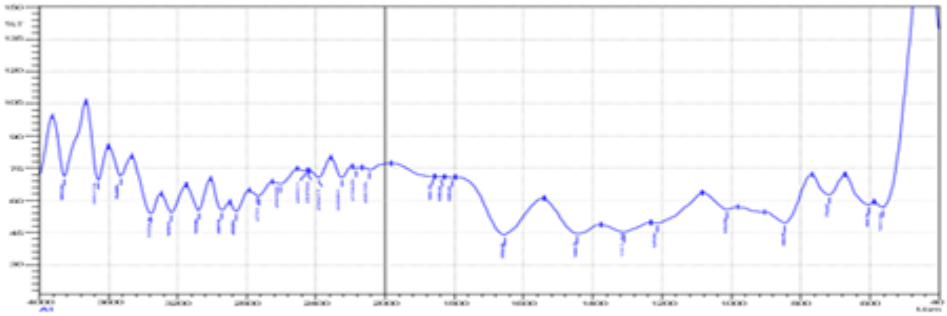

Fig. d: FTIR scan of Physical mixture (Anagliptin & Eudragit)

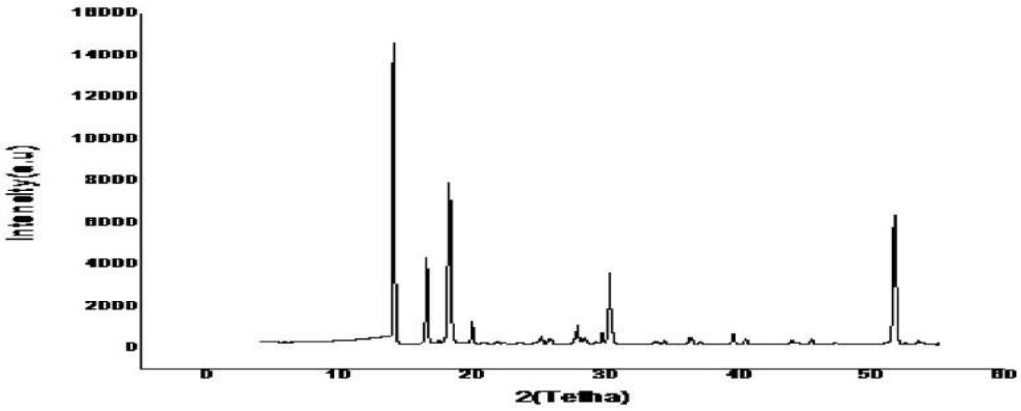

Fig. e: X-ray diffraction of Alogliptine

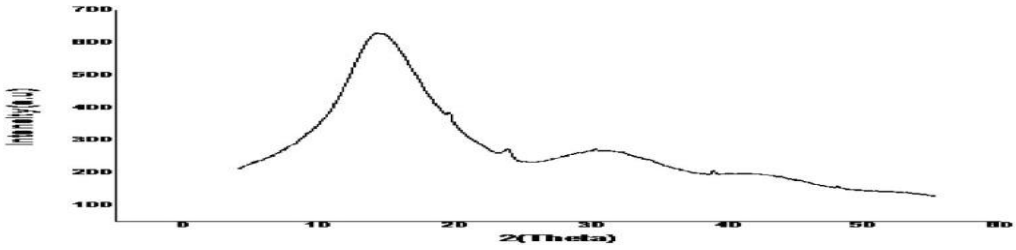

Fig. f: X-ray diffraction of Eudragit RS 100

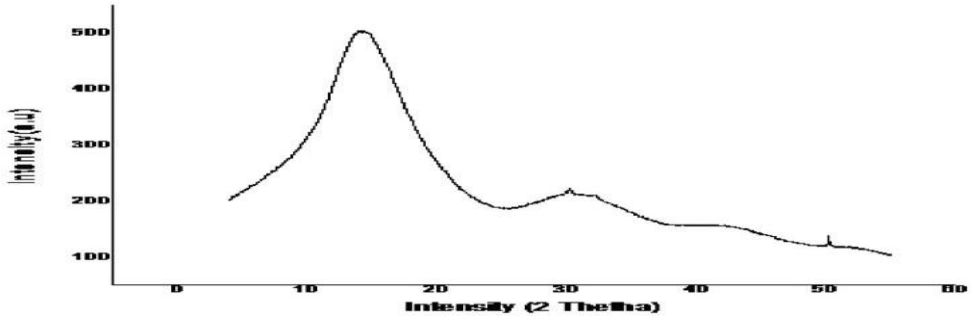

Fig. g: X-ray diffraction of Eudragit RL 100

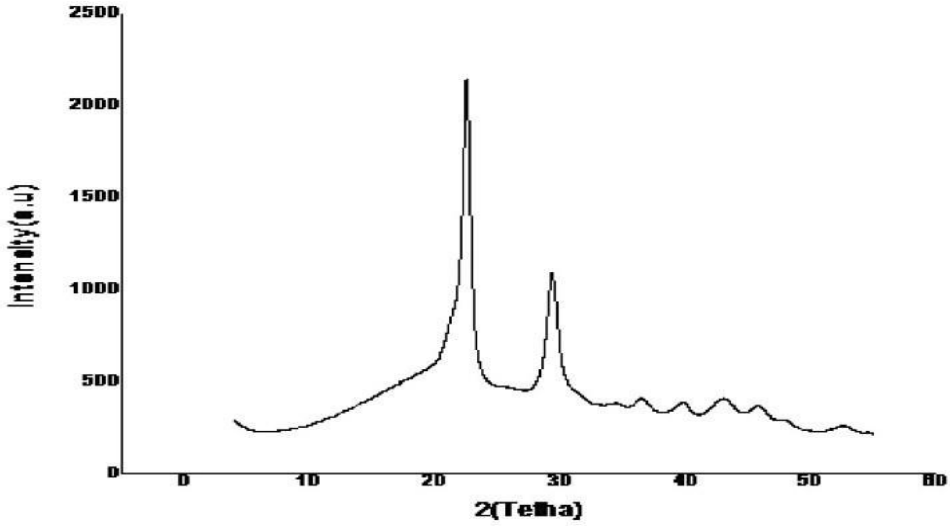

Fig. h: X-ray diffraction of Alogliptine Formulation

2. Physical characterization

3. Particle size distribution analysis

Table : Mean size and weight retained of floating pellet formulation (F 1 – F 14)

Mean Size	Weight Retained (g)													
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12	F 13	F 14
1550	1.5	2.5	1.8	1.52	2.36	1.1	0.33	2.84	2.65	2.46	1.46	0.76	1.3	1.52
1200	8.2	7	7.5	7.58	6.54	8.5	9.1	6.52	7.1	5.74	6.5	7.84	5.89	7.5
855	0.3	0.5	0.7	0.9	1.1	0.4	0.57	0.64	0.25	1.8	2.04	1.4	2.81	0.98
655	0	0	0	0	0	0	0	0	0	0	0	0	0	0

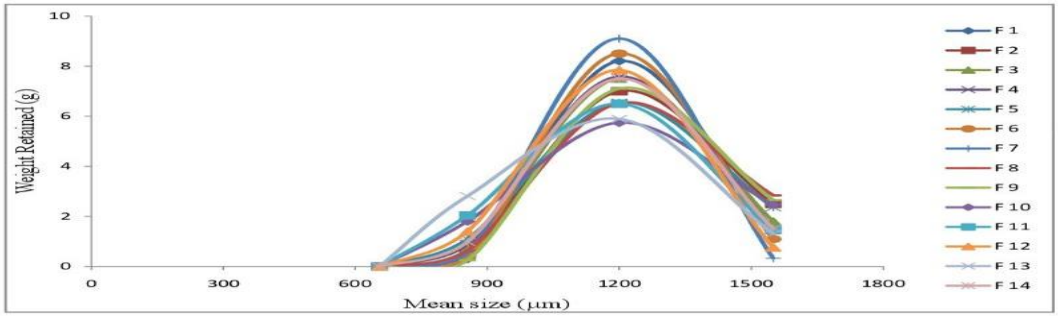

Fig : Plot of pellet mean size vs. weight retained of floating pellet formulation (F 1 – F 14)

Scanning electron microscopy (SEM)

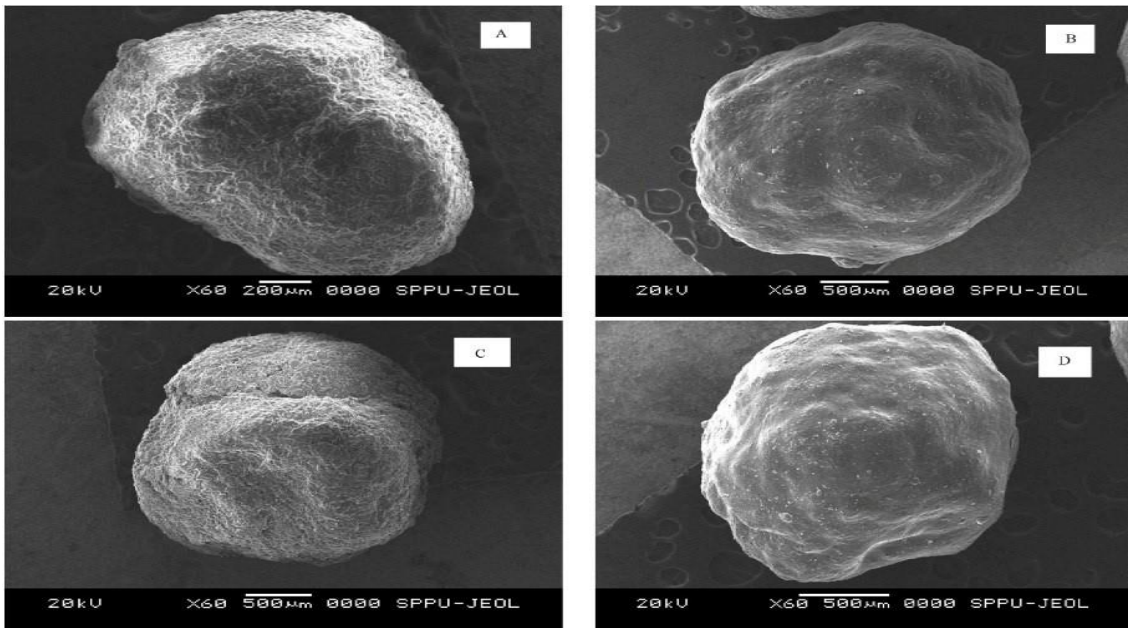

Fig. : Scanning electron microphotographs of (A) Drug loaded uncoated pellets, (B) Pellets coated

Swelling studies

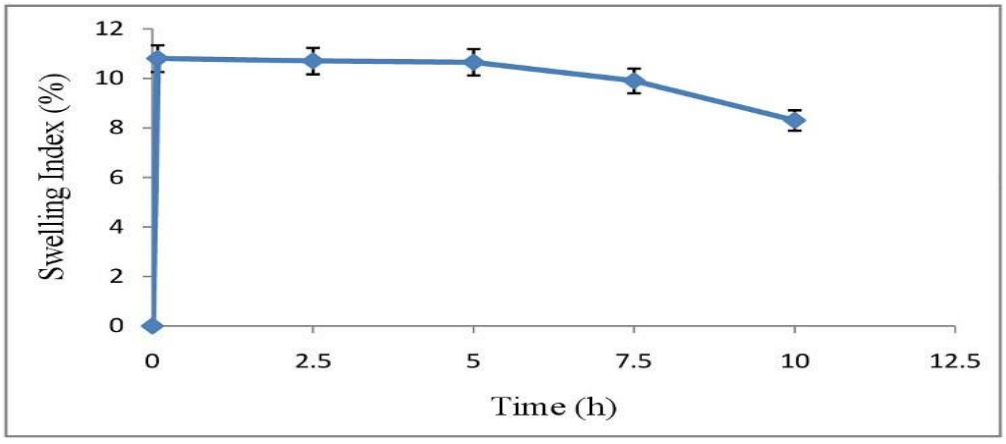

Fig.. Percentage swelling index batch (F 14)

Floating studies

Table : Floating studies of batches F1-F14, Mean ± S.D.; n = 3

Batch No.	Percentage floating (10 h)	Floating lag time (min) - Y_1
F1	92.45 ± 2.7	9.8 ± 1.7
F 2	85.23 ± 3.8	17.9 ± 2.1
F 3	90.99 ± 2.9	21.2 ± 2.4
F 4	74.36 ± 2.1	13.4 ± 1.3
F 5	70.79 ± 3.4	25.6 ± 2.5
F 6	88.85 ± 1.7	6.4 ± 1.9
F 7	81.95 ± 4.1	29.2 ± 1.5
F 8	81.92 ± 3.1	29.4 ± 3.2
F 9	91.11 ± 2.6	20.9 ± 2.8
F 10	78.11 ± 1.1	3.6 ± 1.2
F 11	89.55 ± 2.8	6.2 ± 1.4
F 12	82.11 ± 1.6	33.6 ± 2.5
F 13	75.43 ± 3.3	13.2 ± 1.6
F 14	*79.24*± 2.5	*3.4 ± 1.5*

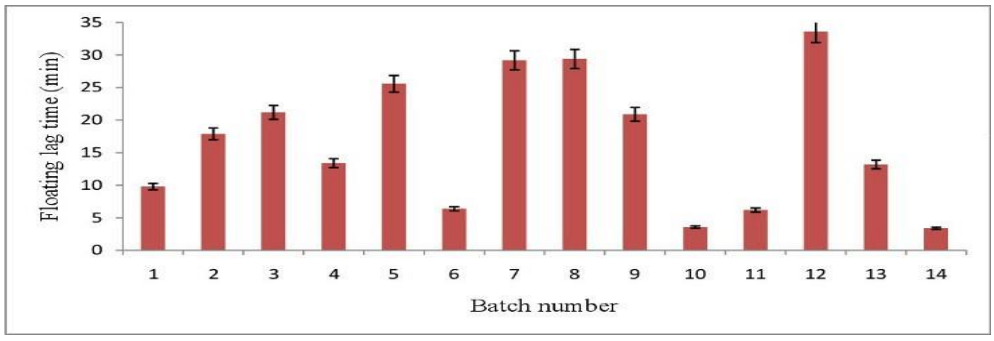

Fig. : Floating lag time of batches F 1 to F 14

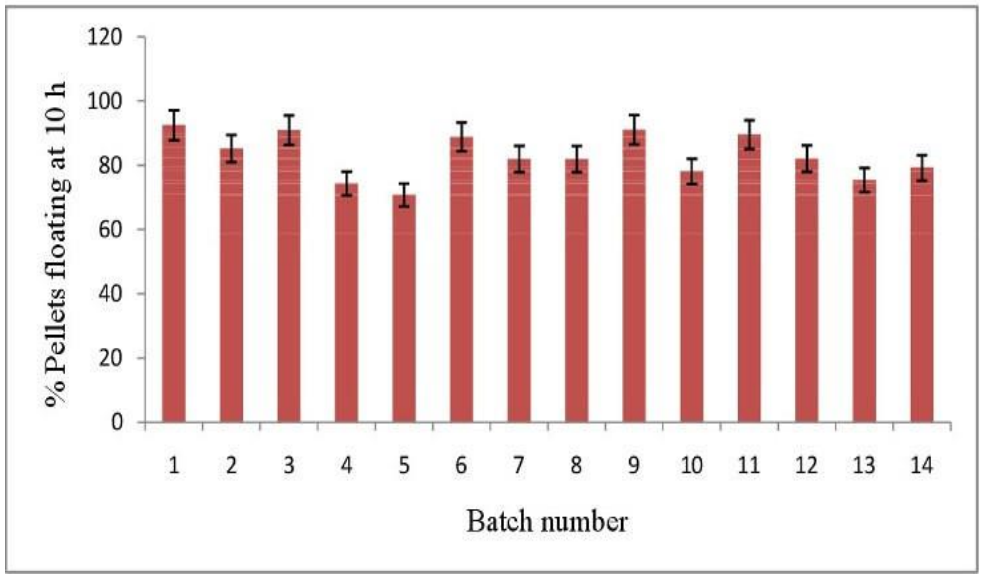

Fig. : Percentage pellets floating at 10 h of batches F 1 to F 14

In vitro drug release study

Table : Avg. Drug Release in 10 h of batches F1-F14

Batch No.	Avg. Drug Release (%) Y_2
F1	64.79 ± 0.21
F 2	68.58 ± 0.15
F 3	75.86 ± 0.29
F 4	84.88 ± 0.34
F 5	73.78 ± 0.41
F 6	79.85 ± 0.23
F 7	80.19 ± 0.26
F 8	56.24 ± 0.33
F 9	52.23 ± 0.37
F 10	73.29 ± 0.22
F 11	55.79 ± 0.23
F 12	65.57 ± 0.24
F 13	59.71± 0.43
F 14	*86.54 ± 0.35*

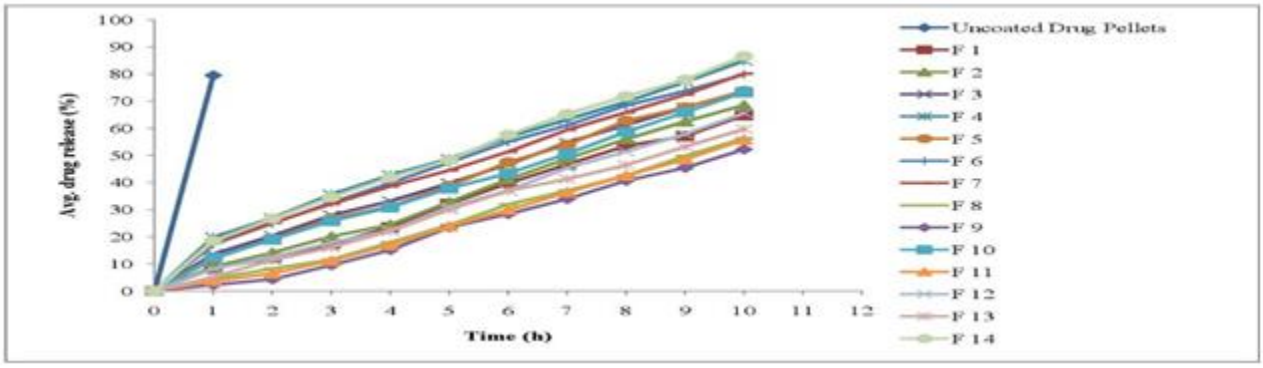

Fig. : In vitro dissolution study of uncoated and floating pellet formulations (batch F 1 – F 14)

Table : Regression coefficients of various mathematical models

Batch No.	Zero order	First order	Higuchi release	Korsmeyer-Peppas (n)
F 14	0.9977	0.9811	0.9906	0.63

Statistical data analysis and Optimization

Table : Summary of ANOVA results for response surface quadratic model

Parameter	Sum of squares	Degrees of freedom	Mean square	F value	P value Prob > F	Remark
Floating lag time						
Model	1167.04	9	129.67	2951.87	< 0.0001	significant
Residual	0.31	7	0.044			

Lack of Fit	0.25	3	0.083	5.50	0.0666	not-significant
Pure Error	0.060	4	0.015			
Drug Release in 10 h						
Model	1314.87	9	146.10	1131.47	< 0.0001	significant
Residual	0.90	7	0.13			
Lack of Fit	0.11	3	0.037	0.19	0.8986	not-significant
Pure Error	0.79	4	0.20			

Table : Summary of statistical parameters for the responses

Parameter	Floating lag time	Drug Release in 10 h
Mean	17.82	68.49
SD	0.21	0.36
CV	1.18	0.52
R^2	0.9997	0.9993
Adjusted R^2	0.9994	0.9984
Predicted R^2	0.9965	0.9977
Adeq Precision	188.959	117.944

SD: Standard deviation; CV: Coefficient of variation

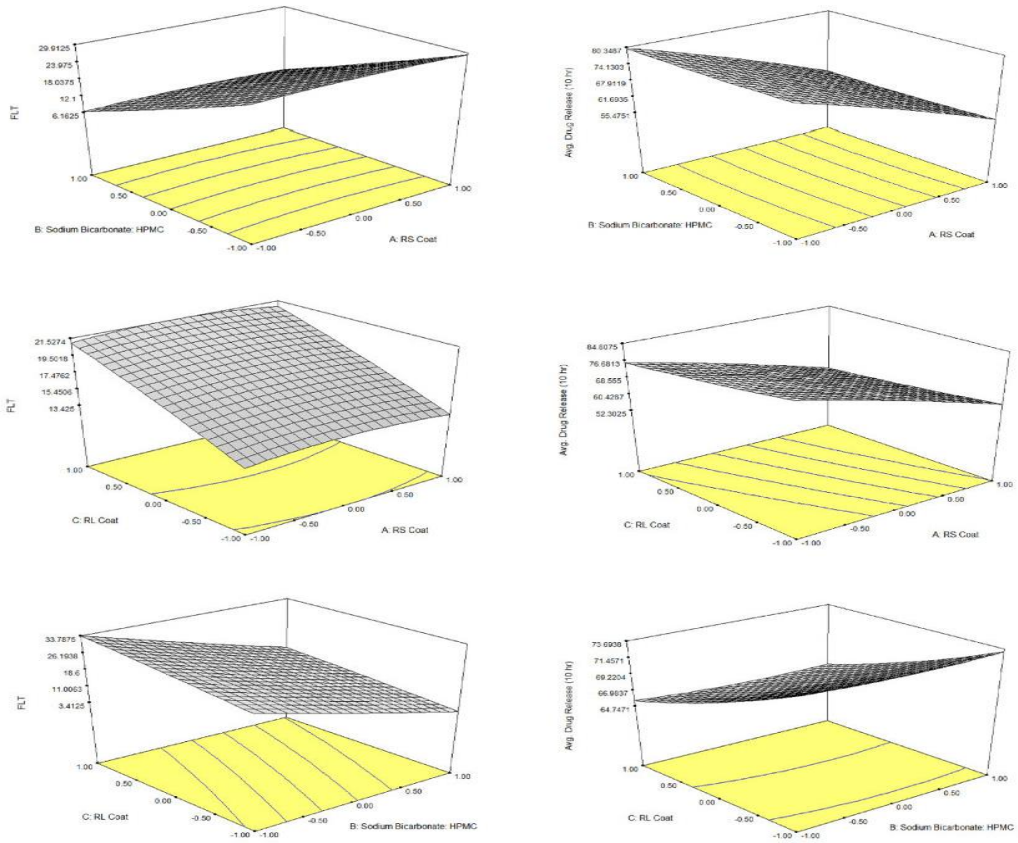

Fig. : Response surface plot of floating lag time and average drug release in10 h

Regression equations of the fiited quadratic model:

Y_1 – Floating lag time = $18.10 – 0.063A - 11.48B + 3.71C – 0.64A^2 + 0.34B^2 – 0.29C^2 – 0.01AB - 0.025AC – 0.45BC$

Y_2 - Avg. drug release (10 h) = $68.43 - 12.10A - 0.26B – 4.15C – 0.80A^2 + 0.39B^2 + 0.54C^2 – 0.028AB + 0.38AC – 0.072BC$

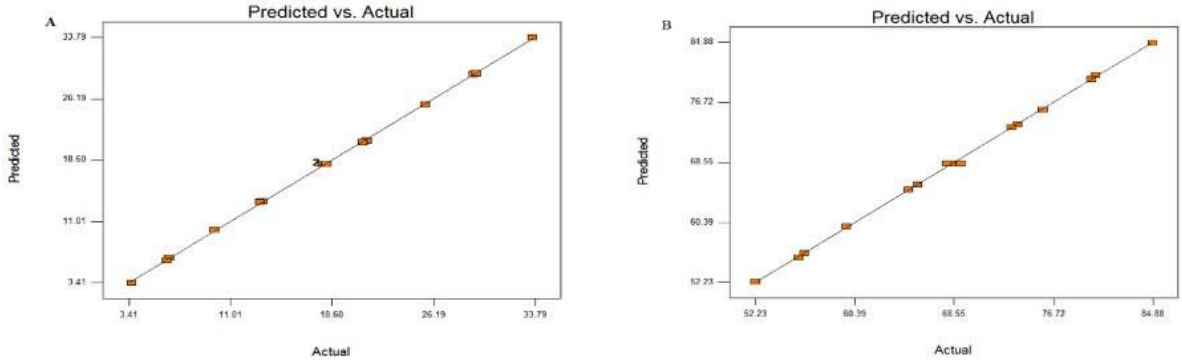

Fig. : Correlation between actual and predicted values for (A) Floating lag time and (B) Drug release in 10 h

Table : Summary of numerical optimization

Parameters	Goal	Solution	Desirability	Remark
Independent Variables				
Eudragit RS 100	in range	-1 (0.5%)		
$NaHCO_3$: HPMC	in range	+1 (2:1)		
Eudragit RL 100	in range	-1 (5%)		
Dependent Variables				
Floating lag time	minimum	3.1 min		
Percent drug release in 10 h	maximum	84.94 %	1	Selected

Stability studies

Table : Accelerated Stability study results for formulation (batch F 14)

Month	Appearance	Drug Content (%)	Drug release at 10 h (%)
0	White	98.75 ± 0.41	86.54 ± 0.35
1	White	98.24 ± 1.01	85.49 ± 0.98
3	White	97.52 ± 0.95	85.11± 1.12
6	White	96.16 ± 1.29	84.04 ± 1.67

CONCLUSION

The developed gastroretentive floating pellets of alogliptin demonstrated rapid floating, sustained release, and enhanced bioavailability. The optimized formulation (F14) effectively overcame P-gp efflux, making it a promising therapeutic strategy for metabolic syndrome. Future studies could explore clinical translation and combination therapies for improved MS management.

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