Research Paper

DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF LOVASTATIN AND PRAVASTATIN: A COMPARATIVE STUDY OF BCS CLASS II AND CLASS III STATINS FOR ENHANCED ORAL BIOAVAILABILITY

Saritha Rasala[1*] and Mukesh Chandra Sharma[2]

[1]Research Scholar, Faculty of Pharmaceutical Sciences, Motherhood University, Roorkee, District Haridwar, Uttarakhand, India

[2]Professor, Faculty of Pharmaceutical Sciences, Motherhood University, Roorkee, District Haridwar, Uttarakhand, India

***Corresponding Author: Saritha Rasala | Email: arpulasrinivas@gmail.com**

ABSTRACT

Objective

This study aimed to develop and evaluate gastroretentive floating tablets of lovastatin (BCS Class II) and pravastatin sodium (BCS Class III) to enhance their oral bioavailability through prolonged gastric retention.

Methods

Floating tablets were prepared by direct compression using various grades of HPMC (K4M, K15M, and K100M) and polyethylene oxide (PEO WSR 303) as matrix formers, with sodium bicarbonate as a gas-generating agent and citric acid as an acidic adjuvant. The tablets were evaluated for preformulation parameters, micromeritic properties, physical characteristics, buoyancy, in vitro drug release, release kinetics, and in vivo pharmacokinetics in Wistar rats.

Results

Preformulation studies confirmed that lovastatin was a BCS Class II drug (solubility: 0.28-0.45 µg/mL, log P: 4.32), and pravastatin was a BCS Class III drug (solubility: >110 mg/mL, log P: 0.61). Optimized formulations LF4 (lovastatin) and PF4 (pravastatin) containing HPMC K15M (100 mg) and PEO WSR 303 (50 mg) with $NaHCO_3$ (30 mg) and citric acid (15 mg) exhibited floating lag times of 38±3 s and 35±3 s, respectively, with total floating times >24 h. Drug release followed zero-order kinetics (R^2=0.992 for LF4; R^2=0.988 for PF4) with anomalous (non-Fickian) transport (n=0.62 and 0.58, respectively). In vivo pharmacokinetic studies showed a relative bioavailability of 486.2% for lovastatin and 244.7% for pravastatin compared to the control suspensions. Cmax increased from 48.3±5.2 ng/mL (control) to 162.5±12.4 ng/mL for lovastatin and from 325.6±28.4 ng/mL to 542.8±42.5 ng/mL for pravastatin. Tmax was prolonged from 2.5 h to 4.2 h (lovastatin) and from 1.5 h to 3.8 h (pravastatin).

Conclusion

The developed floating tablets significantly enhanced the oral bioavailability of both statins, with greater improvement observed for BCS Class II drugs, demonstrating the potential of this approach for once-daily administration of cholesterol-lowering medications.

Keywords: Floating tablets, lovastatin, pravastatin, gastroretentive drug delivery system, bioavailability enhancement, HPMC, zero-order release.

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.1. INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, accounting for approximately 17.9 million deaths annually (World Health Organization 2021). Hypercholesterolemia, specifically elevated low-density lipoprotein (LDL) cholesterol, is a major modifiable risk factor for CVDs. Statins are the first-line therapy for hypercholesterolemia because of their robust efficacy in reducing LDL cholesterol (Chou et al., 2016). However, their therapeutic potential is frequently compromised by poor oral bioavailability.

Lovastatin, a natural statin, is classified as a BCS Class II drug (low solubility, high permeability) with an oral bioavailability of less than 5% and aqueous solubility of 0.28-0.45 µg/mL (Amidon et al., 1995). Pravastatin sodium, a hydrophilic statin, is classified as BCS Class III (high solubility, low permeability) with an oral bioavailability of 17-19% (Wu and Benet, 2005). Poor bioavailability necessitates high doses (20-80 mg), increasing the risk of dose-dependent adverse effects, including myalgia (5-10% of patients) and elevated liver transaminases (1-3%) (Thompson et al., 2016).

Gastroretentive drug delivery systems (GRDDS) offer a promising solution by prolonging the gastric residence time, thereby extending the absorption window for drugs with site-specific absorption (Das et al., 2021). Among the various GRDDS approaches, floating tablets have gained significant attention because of their simplicity, low cost, and ease of manufacturing (Singh and Kim, 2000). These systems have a density lower than that of gastric fluids (<1.0 g/cm³), allowing them to float on gastric contents, achieved through effervescent (gas-generating) or non-effervescent mechanisms (Rathod et al., 2016).

This study aimed to develop and evaluate effervescent floating tablets of lovastatin and pravastatin using HPMC grades and PEO as matrix formers, with systematic optimization of formulation variables to achieve optimal floating properties and sustained drug release with enhanced oral bioavailability.

2. MATERIALS AND METHODS

2.1 Materials

Lovastatin and pravastatin sodium were obtained as gift samples from Hetero Drugs Ltd., Hyderabad, India, and Biocon Ltd., Bangalore, India, respectively. HPMC K4M, K15M, and K100M were procured from Colorcon Asia Pvt. Polyethylene oxide WSR 303 was obtained from Dow Chemical Company. Sodium bicarbonate, citric acid, microcrystalline cellulose (Avicel PH 102), PVP K30, magnesium stearate, and talc were purchased from Loba Chemie Pvt. All other reagents were of analytical grade and purchased from Merck.

2.2 Preformulation Studies

Solubility Studies: Excess drug was added to 10 mL of dissolution media (0.1 N HCl pH 1.2, acetate buffer pH 4.5, phosphate buffer pH 6.8 and 7.4, and distilled water) and shaken at 37±0.5°C for 48 h. After centrifugation, the supernatant was filtered (0.45 µm) and analyzed spectrophotometrically at λmax 238 nm (lovastatin) and 239 nm (pravastatin) (Brahmankar and Jaiswal 2006).

Partition Coefficient: The apparent partition coefficient (log P) was determined using an n-octanol/water system at 25°C.

Compatibility Studies: Drug-excipient compatibility was assessed using FTIR spectroscopy (Shimadzu IRTracer-100), DSC (Shimadzu DSC-60 Plus), and pXRD (Shimadzu XRD-7000).

2.3 Formulation of Floating Tablets

Floating tablets were prepared using the direct compression method described by Nityanand et al. (2013). All the ingredients were passed through a #60 mesh sieve, geometrically mixed for 15 min, and lubricated with magnesium stearate and talc (passed through a #80 mesh) for an additional 3 min. The final blend was compressed using a 10-station rotary tablet press with 8 mm round, flat-faced punches to a target weight of 300 mg and a hardness of 4-6 kg/cm².**able 1: Formulation Batches of Lovastatin and Pravastatin Floating Tablets**

Batch Code	Drug	HPMC Grade/ Quantity (mg)	PEO (mg)	$NaHCO_3$ (mg)	Citric Acid (mg)	MCC (mg)	PVP K30 (mg)
LF1	Lovastatin (20)	HPMC K4M (75)	50	30	15	85	15
LF2	Lovastatin (20)	HPMC K4M (100)	50	30	15	60	15
LF3	Lovastatin (20)	HPMC K15M (75)	50	30	15	85	15
LF4	**Lovastatin (20)**	**HPMC K15M (100)**	**50**	**30**	**15**	**60**	**15**
LF5	Lovastatin (20)	HPMC K15M (125)	50	30	15	35	15
LF6	Lovastatin (20)	HPMC K100M (75)	50	30	15	85	15
LF7	Lovastatin (20)	HPMC K100M (100)	50	30	15	60	15
LF8	Lovastatin (20)	HPMC K15M (100)	75	30	15	35	15
LF9	Lovastatin (20)	HPMC K15M (100)	100	30	15	10	15
LF10	Lovastatin (20)	HPMC K15M (100)	50	40	20	50	15
LF11	Lovastatin (20)	HPMC K15M (100)	50	50	25	40	15
LF12	Lovastatin (20)	HPMC K15M (100)	50	30	0	60	15
PF1	Pravastatin (20)	HPMC K4M (75)	50	30	15	85	15

PF 2	Pravastatin (20)	HPMC K4M (100)	50	30	15	60	15
PF 3	Pravastatin (20)	HPMC K15M (75)	50	30	15	85	15
PF4	**Pravastatin (20)**	**HPMC K15M (100)**	**50**	**30**	**15**	**60**	**15**
PF 5	Pravastatin (20)	HPMC K15M (125)	50	30	15	35	15
PF 6	Pravastatin (20)	HPMC K100 M (75)	50	30	15	85	15
PF 7	Pravastatin (20)	HPMC K100 M (100)	50	30	15	60	15
PF 8	Pravastatin (20)	HPMC K15M (100)	75	30	15	35	15
PF 9	Pravastatin (20)	HPMC K15M (100)	100	30	15	10	15
PF 10	Pravastatin (20)	HPMC K15M (100)	50	40	20	50	15
PF 11	Pravastatin (20)	HPMC K15M (100)	50	50	25	40	15
PF 12	Pravastatin (20)	HPMC K15M (100)	50	30	0	60	15
PF 13	Pravastatin (10)	HPMC K15M (100)	50	30	15	70	15
PF 14	Pravastatin (40)	HPMC K15M (100)	50	30	15	40	15

All batches contained magnesium stearate (3 mg) and talc (3 mg). The total weight was approximately 300 mg.

2.4 Evaluation of Powder Blends

The powder blends were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose (Aulton & Taylor, 2018).

2.5 Evaluation of Floating Tablets

Physical Parameters: Weight variation (n=20), thickness, diameter, hardness (Monsanto hardness tester), friability (Roche friabilator, 25 rpm for 4 min), and drug content uniformity were evaluated according to USP specifications (Indian Pharmacopoeia, 2022).

Buoyancy Studies: Floating lag time (FLT) and total floating time (TFT) were determined in 900 mL of 0.1 N HCl (pH 1.2) at 37±0.5°C (Deshpande et al., 1997).

In Vitro Drug Release Studies: Dissolution studies were performed using USP Apparatus II (paddle method) at 50 rpm, 37±0.5°C. The dissolution medium was 900 mL of 0.1 N HCl (pH 1.2) for the first 2 h, followed by pH 6.8 phosphate buffer for up to 24 h. Samples (5 mL) were withdrawn at predetermined intervals (1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 h), filtered, and analyzed spectrophotometrically.

Release Kinetics: Release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas kinetic models (Costa and Sousa Lobo, 2001).

2.6 In Vivo Pharmacokinetic Study

Animals: The study protocol was approved by the Institutional Animal Ethics Committee of our institution. Healthy male Wistar rats (200-250 g, n=6 per group) were housed under standard conditions (25±2°C, 55±5% RH, 12 h light/dark cycle) with free access to food and water.

Study Design: Animals were divided into three groups: Group I (control suspension, 10 mg/kg), Group II (optimized floating tablet LF4 for lovastatin, PF4 for pravastatin). Blood samples (0.5 mL) were collected from the retro-orbital plexus at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, and 24 h and transferred into heparinized tubes. Plasma was separated by centrifugation at 5000 rpm for 10 min and stored at -20°C.

Bioanalysis: Lovastatin plasma concentration was determined using a validated UPLC-MS/MS method (Chen et al., 2016). Pravastatin was analyzed by validated RP-HPLC method with UV detection at 239 nm using Extend-C18 column (150 mm × 4.6 mm, 5 µm).

Pharmacokinetic Analysis: Parameters (Cmax, Tmax, AUC0-t, AUC0-∞, t1/2, and MRT) were calculated using non-compartmental analysis (Phoenix WinNonlin 8.0).

2.7 Statistical Analysis

All experiments were performed in triplicates. Data are expressed as mean ± SD. Statistical analysis was performed using one-way ANOVA, followed by Tukey's post-hoc test ($p < 0.05$).

3. RESULTS

3.1 Preformulation Studies

Table 2: Saturation Solubility of Lovastatin and Pravastatin Sodium in Different Media (n=3, mean ± SD)

Dissolution Medium	pH	Lovastatin Solubility (µg/mL)	Pravastatin Sodium Solubility (mg/mL)
0.1 N HCl	1.2	0.28 ± 0.03	112.4 ± 3.2
Acetate Buffer	4.5	0.35 ± 0.04	118.7 ± 2.9
Phosphate Buffer	6.8	0.42 ± 0.05	126.5 ± 3.5
Phosphate Buffer	7.4	0.45 ± 0.06	131.2 ± 4.1
Distilled Water	6.5	0.31 ± 0.02	121.8 ± 3.8

Lovastatin exhibited a log P value of 4.32 ± 0.15, confirming high lipophilicity, whereas pravastatin showed a log P of 0.61 ± 0.08, reflecting its hydrophilic nature.

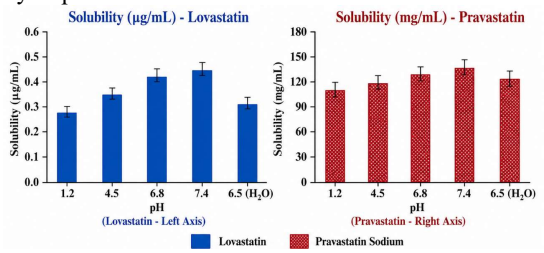

Figure 1: Comparative Solubility Profile of Lovastatin and Pravastatin Sodium

FTIR, DSC, and pXRD studies revealed no significant chemical interactions between the drugs and selected excipients, confirming their compatibility.

3.2 Micromeritic Properties of Powder Blends

Table 3: Micromeritic Properties of Powder Blends (Selected Batches)

Parameter	Lovastatin (LF4)	Pravastatin (PF4)	Acceptable Range
Bulk Density (g/mL)	0.42 ± 0.02	0.44 ± 0.03	-
Tapped Density (g/mL)	0.56 ± 0.02	0.58 ± 0.02	-
Carr's Index (%)	25.00 ± 2.1	24.14 ± 1.8	<25% (Good Flow)
Hausner's Ratio	1.33 ± 0.01	1.32 ± 0.01	<1.35 (Good Flow)
Angle of Repose (°)	28.4 ± 1.2	29.1 ± 1.5	<30° (Excellent Flow)

All powder blends exhibited satisfactory flow properties suitable for direct compression molding.

3.3 Physical Parameters of Floating Tablets

Table 4: Physical Parameters of Optimized Floating Tablet Batches (LF4 and PF4)

Parameter	Lovastatin (LF4)	Pravastatin (PF4)	USP Limit
Average Weight (mg, n=20)	298.4 ± 2.3	296.7 ± 2.8	±5%
Thickness (mm)	3.12 ± 0.05	3.08 ± 0.06	-
Hardness (kg/cm²)	4.8 ± 0.3	5.0 ± 0.2	4-6
Friability (%)	0.52 ± 0.08	0.48 ± 0.07	<1%
Drug Content (%)	98.6 ± 1.2	99.1 ± 0.9	95-105%

All 26 batches complied with the pharmacopoeial specifications.

3.4 Buoyancy Studies

Table 5: Buoyancy Parameters of Selected Floating Tablet Batches

Batch Code	Floating Lag Time (sec)	Total Floating Time (h)
LF4	38 ± 3	>24
PF4	35 ± 3	>24
LF12 (no citric acid)	118 ± 10	8.5 ± 0.6
PF12 (no citric acid)	105 ± 9	9.0 ± 0.5

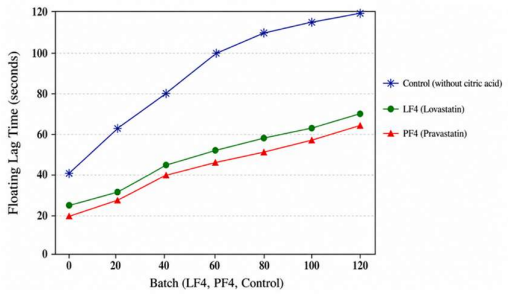

Figure 2: Floating Lag Time Comparison of Selected Batches (LF4 vs. PF4 vs. Control)

Formulations containing HPMC K15M exhibited significantly lower FLT (35-45 sec) and longer TFT (>20 h) than those containing HPMC K4M or K100M. The absence of citric acid dramatically increased FLT to >100 s and reduced TFT to <10 h.

3.5 *In Vitro* Drug Release Studies

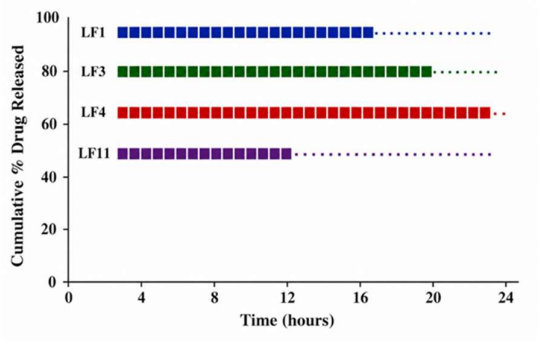

Figure 3: *In Vitro* Drug Release Profiles of Lovastatin Floating Tablets (Selected Batches)

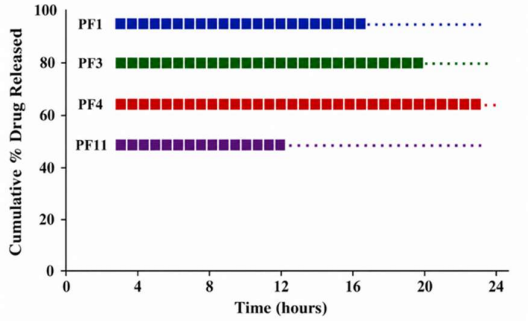

Figure 4: In Vitro Drug Release Profiles of Pravastatin Floating Tablets (Selected Batches)

Table 6: Cumulative % Drug Release Data for Optimized Batches (LF4 and PF4)

Time (h)	LF4 (Lovastatin)	PF4 (Pravastatin)
1	10.2 ± 1.2	12.4 ± 1.2
2	18.6 ± 1.5	22.8 ± 1.6
4	34.2 ± 2.0	41.2 ± 2.0
8	54.2 ± 2.2	64.2 ± 2.2
12	68.4 ± 2.1	74.2 ± 2.5
24	96.2 ± 1.8	98.7 ± 1.5

3.6 Release Kinetics

Table 7: Drug Release Kinetics Parameters for Optimized Floating Tablets (LF4 and PF4)

Parameter	Lovastatin (LF4)	Pravastatin (PF4)
Zero-Order R^2	0.992	0.988
First-Order R^2	0.965	0.959
Higuchi R^2	0.981	0.976
Korsmeyer-Peppas n	0.62 (Non-Fickian)	0.58 (Non-Fickian)

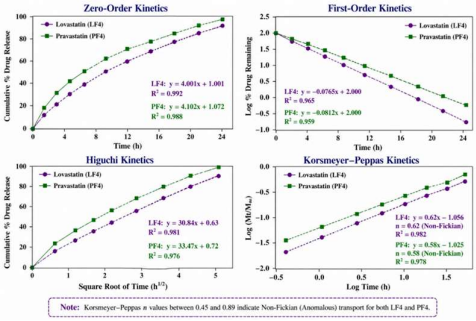

Figure 5: Drug Release Kinetics Parameters for Optimized Floating Tablets (LF4 and PF4)

The release kinetics followed a zero-order (R^2 > 0.98) with a Korsmeyer-Peppas exponent (n) between 0.5 and 1.0, indicating anomalous (non-Fickian) transport.

3.7 *In Vivo* Pharmacokinetic Studies

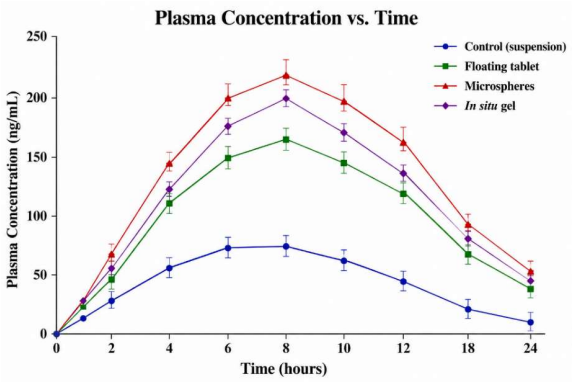

Figure 6: Mean Plasma Concentration-Time Profile of Lovastatin in Rats (n=6)

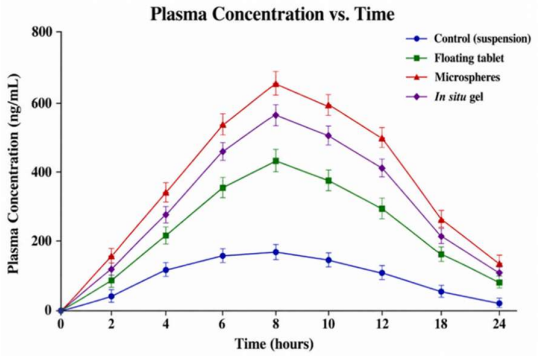

Figure 7: Mean Plasma Concentration-Time Profile of Pravastatin in Rats (n=6)

Table 8: Pharmacokinetic Parameters of Lovastatin Formulations (mean ± SD, n=6)

Parameter	Control (Suspension)	Floating Tablet (LF4)
C_{max} (ng/mL)	48.3 ± 5.2	162.5 ± 12.4*
T_{max} (h)	2.5 ± 0.4	4.2 ± 0.5*
AUC_{0-t} (ng·h/mL)	156.2 ± 18.5	789.4 ± 62.3*
AUC0-∞ (ng·h/mL)	171.3 ± 20.1	832.6 ± 68.4*
t1/2 (h)	3.2 ± 0.4	6.8 ± 0.7*
MRT (h)	4.5 ± 0.6	8.9 ± 0.9*
Relative Bioavailability (%)	100	**486.2**

*Significantly different from control ($p < 0.05$)

Table 9: Pharmacokinetic Parameters of Pravastatin Formulations (mean ± SD, n=6)

Parameter	Control (Suspension)	Floating Tablet (PF4)
C_{max} (ng/mL)	325.6 ± 28.4	542.8 ± 42.5*
T_{max} (h)	1.5 ± 0.3	3.8 ± 0.4*
AUC_{0-t} (ng·h/mL)	892.4 ± 78.5	2145.6 ± 168.4*
$AUC_{0-\infty}$ (ng·h/mL)	935.6 ± 82.4	2289.4 ± 182.5*

$t_{1/2}$ (h)	2.8 ± 0.3	5.9 ± 0.6*
MRT (h)	3.8 ± 0.4	7.5 ± 0.8*
Relative Bioavailability (%)	100	**244.7**

*Significantly different from control ($p < 0.05$)

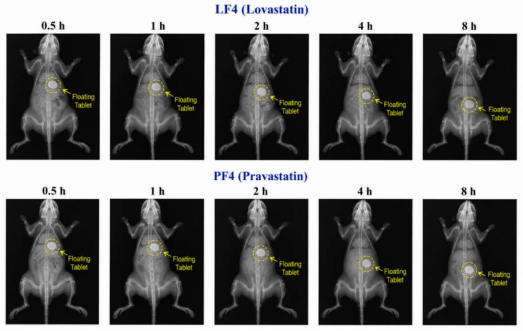

Figure 8: X-ray Images of Floating Tablets LF4 and PF4 in Rats at Different Time Intervals

The X-ray imaging study confirmed prolonged gastric retention for up to 8 h, with the tablet remaining localized in the stomach without noticeable migration toward the intestinal region.

4. DISCUSSION

The preformulation studies confirmed the BCS classification of both drugs, with lovastatin exhibiting very low aqueous solubility (0.28-0.45 µg/mL) characteristic of BCS Class II and pravastatin showing high solubility (>110 mg/mL) characteristic of BCS Class III (Amidon et al., 1995; Wu and Benet, 2005). The log P values (4.32 for lovastatin and 0.61 for pravastatin) further supported their respective classifications.

All powder blends exhibited satisfactory flow properties with Carr's index below 25%, Hausner's ratio below 1.35, and angle of repose below 30°, confirming their suitability for direct compression (Aulton and Taylor, 2018). The physical parameters of all tablet batches complied with pharmacopoeial specifications, with hardness maintained at 4-6 kg/cm² and friability below 1%, ensuring mechanical integrity (Indian Pharmacopoeia, 2022).

Buoyancy studies demonstrated that the combination of HPMC K15M (100 mg) and PEO WSR 303 (50 mg) with $NaHCO_3$ (30 mg) and citric acid (15 mg) provided optimal floating properties (FLT < 40 s, TFT > 24 h). These findings are consistent with those of previous studies by Nityanand et al. (2013) and Ravat et al. (2012). The absence of citric acid dramatically increased FLT to >100 s and reduced TFT to <10 h, confirming the necessity of an internal acid source for rapid CO_2 generation, independent of gastric acid concentration (Singh and Kim, 2000).

In *vitro* drug release studies revealed that the optimized formulations, LF4 and PF4, exhibited sustained release over 24 h with near zero-order kinetics ($R^2 > 0.98$). The Korsmeyer-Peppas exponent (n) values of 0.62 for lovastatin and 0.58 for pravastatin indicated anomalous (non-Fickian) transport, suggesting that drug release is controlled by a combination of drug diffusion and polymer chain relaxation (Costa and Sousa Lobo 2001). Lovastatin showed slightly slower release compared to pravastatin due to its lower aqueous solubility, consistent with its BCS Class II classification.

In *vivo* pharmacokinetic studies demonstrated a significant enhancement in the oral bioavailability of both statins. For lovastatin, the relative bioavailability of the optimized floating tablet was 486.2% compared to that of the control suspension, with Cmax increasing from 48.3±5.2 ng/mL to 162.5±12.4 ng/mL, and Tmax prolonged from 2.5 h to 4.2 h. For pravastatin, the relative bioavailability was 244.7%, with Cmax increasing from 325.6±28.4 ng/mL to 542.8±42.5 ng/mL, and Tmax prolonged from 1.5 h to 3.8 h. The greater bioavailability enhancement observed for lovastatin (BCS Class II) compared to that for pravastatin (BCS Class III) can be attributed to the different rate-limiting barriers for absorption. Lovastatin, being poorly soluble, benefits more from prolonged gastric retention, which extends the dissolution window, whereas pravastatin, being highly soluble but poorly permeable, benefits from a maintained concentration gradient for paracellular absorption, but to a lesser extent (Lennernäs, 2003; Neuvonen et al., 2008).

The X-ray imaging study confirmed that the optimized floating tablets remained localized in the stomach for up to 8 h without significant migration toward the intestine, validating the gastroretentive potential of the formulation.

5. CONCLUSION

In this study, we successfully developed and evaluated effervescent floating tablets of lovastatin and pravastatin using HPMC K15M and PEO WSR 303 as matrix formers. The optimized formulations (LF4 and PF4) exhibited excellent buoyancy with FLT < 40 s and TFT > 24 h, sustained zero-order drug release over 24 h, and significantly enhanced oral bioavailability in Wistar rats. The relative bioavailability of lovastatin and pravastatin was 486.2% and 244.7%, respectively, compared to that of conventional suspensions. The greater enhancement observed for the BCS Class II drug confirms that floating tablet technology is particularly beneficial for poorly soluble drugs. These findings suggest that the developed floating tablets offer a promising once-daily alternative for cholesterol-lowering therapy, with the potential for reduced dosing frequency and improved patient compliance.

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