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Research Article

FORMULATION OF SUSTAINED RELEASE CORE AND COAT TABLETS OF LOVASTATIN AND OLEANOLIC ACID: AN *IN VITRO* AND *IN VIVO* ANALYSIS

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ABSTRACT

Objectives: This research aimed to develop core and coat tablets to enhance the therapeutic efficacy of antilipidemic drugs for treating high cholesterol and triglyceride levels in the blood.

Methods: The core and coat tablets were formulated using a combination of two antilipidemic drugs: Lovastatin (LV) and oleanolic acid (OA). LV was incorporated into an immediate-release (IR) layer with various superdisintegrants, while OA formulated into extended-release layer with hydroxypropyl methylcellulose K100.

Results: The core and coat tablets were evaluated for the release profiles of both layers, and excipients were optimized. The IR layer of LV achieved complete release within 60 min, while the release of OA was sustained for up to 12 h. Among the formulations tested, LV9 (95.23%) for immediate release, and OA1 (97.13%) for sustained release, were found to be most suitable when scaled at the desired drug release up to 30 min and 12 h, respectively. Stability studies demonstrated that the optimized formulation remained stable without any degradation for 6 months. Pharmacokinetic and pharmacodynamic studies conducted in rabbit models examined the effects of LV/OA tablets on lipid profiles and body weight. Obesity was induced in the rabbits through a high-fat diet.

Conclusion: The core and coat LV/OA tablets demonstrated significant efficacy in reducing lipid levels and mitigating weight gain compared to the control group.

Keywords: Core and coat, Oleanolic acid, Lovastatin, Hydroxypropyl methylcellulose, Croscarmellose sodium.

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INTRODUCTION

Lovastatin (LV) is a cholesterol-lowering medication that was initially extracted from the fungus *Aspergillus terreus* [1]. It is approved by the Food and Drug Administration (FDA) for treating and preventing conditions such as coronary heart disease (CHD), hypercholesterolemia, and for adolescents with heterozygous familial hypercholesterolemia. While not FDA-approved, it is sometimes used to reduce cardiac risks associated with noncardiac surgery and to manage noncardioembolic strokes [2]. LV is converted to the active form of beta-hydroxy acid, which works by competitively diminishing the effect of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase [3]. This enzyme is vital for cholesterol production. Additionally, HMG-CoA inhibitors can lower high-sensitivity C-reactive protein levels, enhance endothelial function, reduce inflammation, and inhibit platelet aggregation with anticoagulant properties. Furthermore, a reduction in serum cholesterol levels can lead to increased expression of low-density lipoprotein (LDL) receptors in liver cells, promoting the breakdown of LDL cholesterol [4].

Oleanolic acid (OA) is a biologically active pentacyclic triterpenoid found in nearly 200 different plant species [5]. Research has demonstrated that OA possesses a range of pharmacological properties, including hepatoprotective, antioxidant, lipid-regulating, anticancer, and anti-inflammatory effects. Chemically, OA is defined as (4aS,6aS,6bR,8aR,10S,12aR,12bR,14bS)-10-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl 1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-4a-carboxylic acid [6]. OA specifically inhibits intestinal acyl-CoAacyltransferase (ACAT), an enzyme involved in the metabolism of cholesterol, where it converts cholesterol into cholesteryl esters for transfer to the liver. The accumulation of cholesteryl esters in macrophages can lead to the formation of foamy cells, a key indicator of early atherosclerosis [7]. By reducing cholesterol absorption in the small intestine, OA helps lower plasma cholesterol and triglyceride levels, decreases hepatic production of very-low-density lipoprotein synthesis, and minimizes lipid deposition in blood vessels, lowering chances of cardiac arrest [8]. Elevated cholesterol and triglyceride levels are indicative of CHD, and cardiac infarction [9]. Through its action as an ACAT inhibitor, OA serves as a safe and effective option for managing lipid-related disorders. Co-administering LV and OA can further lower cholesterol levels derived from both hepatic synthesis and dietary absorption [10].

The core and coat tablet is a widely accepted method for achieving controlled drug release with predefined release profiles. This drug delivery system consists of both an immediate and sustained-release layer. In a core and coat tablet, the outer coat layer disintegrates rapidly to provide an initial dose, while the inner core layer delivers the drug gradually over time [11,12]. To prevent both layers from releasing the drug simultaneously, the sustained-release core layer is coated with various polymers that allow for extended-release in the intestine, while the immediate-release (IR) layer dissolves quickly in the stomach. This design can also be applied to create repeat-action tablets [13].

MATERIALS AND METHODS

Materials

A pharmaceutically pure sample of LV was generously supplied by Lupin Pharmaceutical Ltd., Mumbai, while OA was obtained from

Shri Samartha Enterprises in Pune. All other chemicals" and solvents utilized were of analytical and HPLC grade.

Experimental animals

Healthy NewZeland white rabbits of either sex having a weight range of 2–3 kg were divided into various groups, animals were housed individually in stainless steel cages throughout the study and maintained standard laboratory conditions, fed with a normal diet or high-fat diet and water ad libitum. Animals were kept under fasting conditions before the start of the experiment for approximately 18–24 h. Protocol was approved by the Institutional Animal Ethics Committee (IAEC) of AISSMS College of Pharmacy, Pune constituted under the Committee for the Control and Supervision and Experiments on Animals (CPCSEA). Approval No. CPCSEA/IAEC/PT-25/02-2K23.

Methods

Preformulation studies

To confirm the compatibility of the drug and polymer under experimental conditions and ensure no reactions between them, FOURIER transform infrared (FT-IR) spectroscopy was employed. The spectra of samples were obtained using a Shimadzu IRSpirit-X FT-IR spectrometer. About 3 mg of each test sample was mixed with an equal amount of dried KBr and compressed into a disc [14]. The samples were then scanned at 400 cm^{-1}–4000 cm^{-1}.

Development of core layer

The core tablets were formulated to achieve the desired release profile and ensure stability. Each core tablet contained 50 mg of OA along with hydroxypropyl methylcellulose (HPMC K100), ethyl cellulose, magnesium stearate, talc, lactose, and microcrystalline cellulose (MCC) [15]. The formulation process involved precise weighing and thorough mixing of the ingredients using a mortar and pestle to create a good blend. It was then granulated using the wet granulation method and compressed into core tablets with a Cadmac CMD3 tablet punching machine [16]. Batches OA1 to OA9 of the core layer containing OA were formulated using different compositions as outlined in Table 1.

Development of coat layer

All ingredients were carefully weighed in the specified amounts. LV, sodium starch glycolate, croscarmellose sodium, magnesium stearate, talc, and MCC were then combined, and thoroughly grinded with mortar-pestle to create a uniform blend. This blending process is crucial for ensuring even distribution of the ingredients, which is important for the consistent performance of the coating. The uniform powder blend was transferred to a tablet punching machine. The machine was calibrated to compress the blend into tablets, ensuring each tablet had a consistent weight and shape [17,18]. The compression process was closely monitored to maintain consistent tablet quality. Batches LV1 to LV9 of the LV coat layer were formulated according to the compositions listed in Table 2.

In vitro drug release studies

A dissolution study was performed to assess the release profile of OA from the core tablets and LV from the coated tablets. Electrolab, Type II- paddle dissolution apparatus was used with a dissolution medium consisting of 900 mL of 0.1% sodium lauryl sulfate (SLS) solution, maintained at 37±0.5°C, and paddles were rotated at 100 rpm. Sample to be tested is kept in each vessel of the Electrolab Type II paddle apparatus [19]. At specified time intervals, 10 mL aliquots were taken out and sink conditions were maintained with fresh 0.1% SLS solution. The collected samples were analyzed using HPLC to measure concentrations of OA and LV released at each time point [20].

Formulation of core and coat tablets

Core and coat tablets were formulated using OA as the core layer and LV as the coat layer. The optimized formulations, specifically the OA core (OA1) and the IR LV blend (LV9), were selected for this development. The LV blend was divided into two portions, with one half placed in the die to form a powder bed. The optimized core tablet (OA1) was then centered on this bed, and the remaining LV blend was added to cover the core [21,22]. The entire contents were compressed to create the final core and coat tablets.

Table 1: Composition of oleanolic acid core layer tablets

Batch No.	Ingredients (mg)							
	Oleanolic acid	HPMC K100	Ethyl cellulose	Magnesium stearate	Talc	Lactose	Micro crystalline cellulose	Total weight (mg)
OA1	50	10	10	2	3	12.5	12.5	100
OA2	50	10	15	2	3	10	10	100
OA3	50	10	20	2	3	7.5	7.5	100
OA4	50	15	10	2	3	10	10	100
OA5	50	15	15	2	3	7.5	7.5	100
OA6	50	15	20	2	3	5	5	100
OA7	50	20	10	2	3	7.5	7.5	100
OA8	50	20	15	2	3	5	5	100
OA9	50	20	20	2	3	2.5	2.5	100

Table 2: Composition of lovastatin coat layer tablets

Batch No.	Ingredients (mg)							
	Lovastatin	Sodium starch glycolate	Croscarmellose sodium	Magnesium stearate	Talc	Lactose	Micro crystalline cellulose	Total weight (mg)
LV1	10	4	4	4	6	86	86	200
LV2	10	4	8	4	6	84	84	200
LV3	10	4	12	4	6	82	82	200
LV4	10	8	4	4	6	84	84	200
LV5	10	8	8	4	6	82	82	200
LV6	10	8	12	4	6	80	80	200
LV7	10	12	4	4	6	82	82	200
LV8	10	12	8	4	6	80	80	200
LV9	10	12	12	4	6	78	78	200

In vitro drug release studies of core and coat tablets

This study was conducted individually, following the previously outlined procedure [23]. The collected samples were analyzed using HPLC at a wavelength of 210 nm.

Stability studies

Stability testing is crucial to ensure that the quality of manufactured tablets remains consistent over time under varying environmental conditions. This involves evaluating the effects of temperature, humidity, and storage conditions on both physico-chemical characteristics of the tablets [24]. The recommended storage conditions and minimum durations for such tests include long-term testing at 25°C±2°C with 60% RH±5% for 12 months and accelerated testing at 40°C±2°C with 75% RH±5% for 6 months. It is important to confirm that long-term testing will continue to cover the tablet's expected shelf life, as per International Council for Harmonization Q1A guidelines. Accelerated stability tests were conducted for formulations at 40°C±2°C with 75% RH±5% for 6 months [25].

Experimental design

The rabbits were randomly assigned to four groups: Group I (normal control, n=6) was fed a standard diet; Group II (high-fat diet control, n=6) received a high-fat diet containing 1% cholesterol for 4 weeks; Group III (n=6) was given a high-fat diet for 2 weeks, followed by oral administration of LV (0.52 mg/kg body weight) with a standard diet for the next 2 weeks; and Group IV (n=6) was given a high-fat diet for 2 weeks, followed by oral administration of a core-and-coat tablet containing OA in the core (2.65 mg/kg body weight, sustained release) and LV in the coat (0.52 mg/kg body weight, immediate release) with a standard diet for another 2 weeks [26]. The tablets were placed at the pharyngeal site to ensure immediate swallowing by the rabbits. The statistical analysis of the grouped data was conducted using a one-way analysis of variance (ANOVA), followed by a Bonferroni *post hoc* test for multiple comparisons. The results for each group are presented as mean±standard deviation. A statistically significant result was defined as $p<0.05$.

Body weight was recorded throughout the study. Blood samples (0.3 mL) were collected in heparin-treated microtubes (15 µL heparin in 1.5 mL microtubes) via marginal ear vein or jugular vein cannulation at the following time points: 0 (prior to drug administration), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 10, 16, 24, and 48 h post-dose. The samples were centrifuged at 1500 rpm for 15 min to separate plasma, which was then frozen at −70°C until analysis. Before testing, the samples were thawed to room temperature and analyzed using an API 2000 LC/MS/MS system equipped with a pump (Shimadzu LC 2OADvp) [27].

RESULTS

FT-IR spectroscopy characterizations

To evaluate the compatibility and identify potential interactions between the drugs and excipients, FT-IR spectroscopy was done on both "the physical mixture of the drug" sample and combination with excipients. A FT-IR spectra for LV and OA showed distinct peaks corresponding to their molecular structures. In the case of LV, key peaks were observed at 3015.4 cm-1 (C=C stretching), 3537.2 cm^{-1} (O-H stretching), 1215.1 cm^{-1} (C-O-C stretching), 1054.8 cm^{-1} (C-O stretching), 1379.1 cm^{-1} (C-H bending), and 2963.2 cm^{-1} (C-H stretching). For OA, the characteristic peaks appeared at 1427.37 cm^{-1} (C=C stretching), 3495.13 cm^{-1} (O-H stretching), 1597.11 cm^{-1} (C-O stretching), and 3117.07 cm^{-1} (C-H stretching). The characteristic peak of drug and excipients are shown in Figs. 1 and 2.

Pre-compression characterization of tablets

The granules of LV and OA formulations were assessed for various flow properties, including bulk density (BD) tapped density (TD), angle of repose, Carr's index, and Hausner ratio (HR), with results summarized in Tables 3 and 4.

The BD for OA formulation was ranged between 0.44 and 0.53 g/mL, while the TD ranged from 0.41 to 0.51 g/mL. For the LV formulation, the BD ranged from 0.48 to 0.61 g/mL, and the TD ranged between 0.53 and 0.71 g/mL. The angle of repose values for OA ranged from 16 to 28.40, and for LV, from 18.20 to 26.30, indicating good flowability. The HR for OA formulations ranged between 1.09 and 1.42, while for LV formulations, it was between 1.05 and 1.18. The compressibility index values ranged from 9 to 28.94 for OA formulations and from 6.67 to 18.33 for LV formulations, suggesting that all batches exhibited favorable flow characteristics.

Characterization of the prepared tablets

The core and coat layers of the formulation were tested on the parameters like hardness, friability, and disintegration time (for the coat layer), with results presented in Tables 5 and 6. Hardness for both layers ranged between 3.8 and 5.5 kg/cm^2, while the value for friability was found between 0.1% to 0.24%.

***In vitro* drug release studies**

The disintegration time for the LV coat layer was under 98 s, which is well below the USP limit of 15 min for uncoated IR tablets. Batch LV9

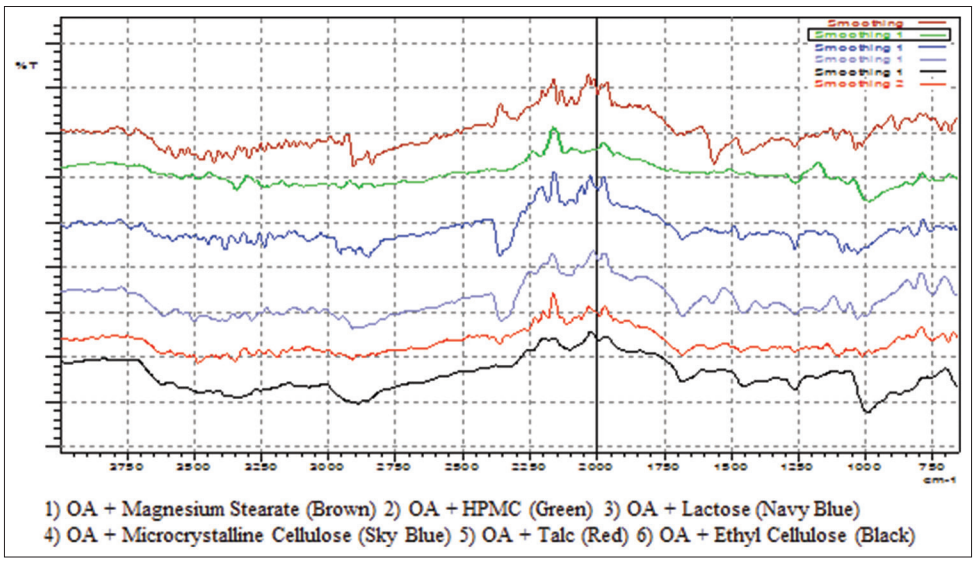

Fig. 1: Drug excipient study of oleanolic acid

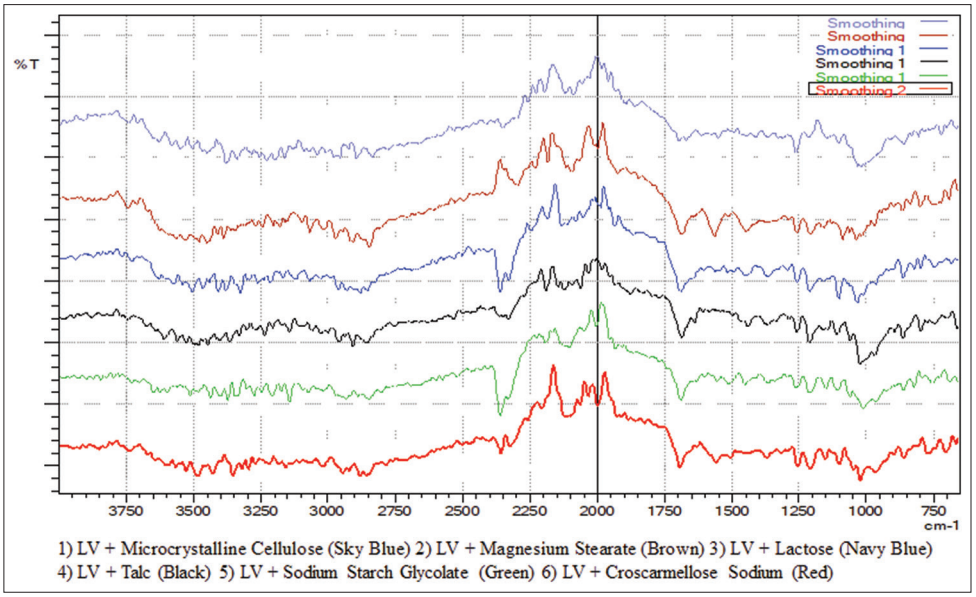

Fig. 2: Drug excipient study of lovastatin

Table 3: Preformulation study of lovastatin coat tablet formulation

Batch No.	BD (g/mL)	TD (g/mL)	HR	CI (%)	Angle of repose (degrees)
LV 1	0.49	0.53	1.15	15.22	21.2
LV 2	0.61	0.71	1.18	18.33	26.3
LV 3	0.57	0.59	1.07	7.27	20.0
LV 4	0.51	0.68	1.13	13.33	21.3
LV 5	0.53	0.64	1.07	6.67	18.2
LV 6	0.54	0.67	1.12	11.67	24.7
LV 7	0.50	0.67	1.12	11.67	24.7
LV 8	0.48	0.54	1.08	8.00	21.4
LV 9	0.59	0.62	1.05	5.08	19.6

BD: Bulk density (g/mL), TD: Tapped density (g/mL), HR: Hausner ratio and CI: Carr's index (%)

Table 4: Preformulation study of oleanolic acid core tablet formulation

Batch no.	BD (g/mL)	TD (g/mL)	HR	CI (%)	Angle of repose (degrees)
OA1	0.53	0.45	1.09	9	16
OA2	0.53	0.45	1.11	11	18
OA3	0.52	0.42	1.13	13	20
OA4	0.49	0.43	1.11	11	17.50
OA5	0.48	0.41	1.11	11	18
OA6	0.52	0.47	1.21	21.50	29
OA7	0.45	0.51	1.42	13.33	21
OA8	0.44	0.49	1.39	22.50	28.40
OA9	0.46	0.49	1.39	28.94	32

BD: Bulk density (g/mL), TD: Tapped density (g/mL), HR: Hausner ratio and CI: Carr's index (%)

demonstrated the fastest disintegration time of 24 s, attributed to the highest concentration of super disintegrants. Drug release studies across various batches (LV1-LV9) with varying ratios of disintegrants revealed that LV9 exhibited the best release profile (Fig. 3), with 95.23% release within 30 min (Table 7). As a result, the LV9 formulation was selected for further development of core and coat tablets.

In the dissolution study for OA core tablets, it was observed that at higher concentrations of HPMC K100 OA release was reduced

Table 5: Evaluation of oleanolic acid core tablets

Batch No.	Hardness (kg/cm^2)	Friability (%)
OA1	3.8	0.23
OA2	4.2	0.18
OA3	4.8	0.24
OA4	4.7	0.21
OA5	5.0	0.19
OA6	4.2	0.20
OA7	4.5	0.18
OA8	4.8	0.21
OA9	4.8	0.23

Table 6: Evaluation of lovastatin coat tablets

Batch No.	Hardness (kg/cm^2)	Friability (%)	DT of coat (sec)
LV1	4.2	0.2	98
LV2	4.6	0.12	75
LV3	5.1	0.16	72
LV4	5.3	0.14	78
LV5	4.8	0.16	72
LV6	4.5	0.15	56
LV7	4.9	0.132	62
LV8	5.3	0.145	36
LV9	5.5	0.1	24

(Fig. 4). The addition of ethyl cellulose formed a more rigid structure in combination with the hydrophilic polymer HPMC K100, effectively retaining the drug within the matrix and slowing diffusion. Among the formulations, batch OA1 demonstrated the highest drug release rate, with 97.13% released over 12 h (Table 8). Based on these findings, OA1 was identified as the optimal formulation for further development of the core and coat tablet system.

Core and coat tablets containing LV in the coat layer and OA in the core layer were formulated using the optimized batches LV9 and OA1. Upon evaluation, all physical parameters were found within acceptable limits. The LV coat layer, formulated from the LV9 batch, had a disintegration time of 24 s. *In vitro* dissolution studies were done with drug release quantified using HPLC. The average percentage of drug release from the core and coat tablets was 96.34% for OA at 12 h and 100.17% for LV at 3 h (Tables 9 and 10).

Table 7: % Release of lovastatin from coat tablets

Batch No.	10 Min	20 Min	30 Min	60 Min	90 Min	120 Min	150 Min	180 Min
LV1	15.25±0.633	32.4±0.560	52.85±0.831	70.2±0.873	90.88±0.758	98.1±0.327	100.3±0.609	99.9±0.530
LV2	21.1±0.509	42.65±0.600	67.23±0.484	88.2±0.892	96.33±0.520	100.65±0.344	101.15±0.714	99.96±0.372
LV3	22.2±0.746	47.95±0.568	73.5±0.735	94.2±0.497	99.15±0.679	100.36±0.702	99.8±0.821	100.25±0.508
LV4	21.66±0.572	44.8±0.615	65.13±0.555	95.65±0.790	98.9±0.556	100.1±0.892	100.55±0.805	101.1±0.494
LV5	20.55±0.321	49.53±0.494	67.89±0.687	94.3±0.937	99.1±0.890	100.25±0.404	100.65±0.834	100.1±0.906
LV6	22.7±0.490	46.1±0.450	72.56±0.640	95.2±0.494	99.25±0.703	99.98±0.375	101.25±0.487	100.9±0.737
LV7	23.5±0.589	51.25±0.478	74.62±0.553	96.23±0.498	99.5±0.633	100.46±0.625	101.1±0.365	100.8±0.636
LV8	28.9±0.592	52.75±0.704	84.28±0.475	97.23±0.420	99.9±0.484	100.15±0.485	99.9±0.749	100.45±0.594
LV9	32.4±0.425	63.7±0.429	95.23±0.393	96.23±0.943	98.99±0.638	100.8±0.869	101.15±0.360	100.5±0.778

Values are in mean±SD (%); (n=6)

Table 8: Drug release profile of oleanolic acid formulations

Time (Hr)	OA1 (%)	OA2 (%)	OA3 (%)	OA4 (%)	OA5 (%)	OA6 (%)	OA7 (%)	OA8 (%)	OA9 (%)
1	16.54±0.701	12.94±0.821	13.73±0.830	22.66±0.591	19.78±0.849	14.12±0.636	21.54±0.630	18.96±0.584	25.82±0.904
2	22.54±0.649	18.23±1.036	19.72±0.581	28.32±0.575	23.43±0.944	21.64±0.802	27.32±0.520	26.22±0.380	32.23±0.597
3	31.10±0.492	25.85±0.564	26.70±0.655	36.55±0.764	30.60±0.564	29.25±0.698	34.95±0.558	32.96±0.995	38.25±0.750
4	49.50±0.910	38.30±0.792	42.44±0.792	45.90±0.610	41.63±0.787	39.84±0.434	43.55±0.670	42.23±0.422	42.44±0.901
6	82.75±0.807	72.66±0.738	73.32±0.957	79.34±0.842	77.96±0.556	75.55±0.659	80.22±0.609	73.88±0.667	75.83±0.299
8	91.65±0.869	79.42±0.422	81.55±0.616	87.64±0.808	86.35±0.732	81.60±0.581	85.25±0.875	80.33±0.936	79.23±0.397
10	95.23±0.946	83.47±0.877	84.32±0.666	88.41±0.391	87.52±0.563	82.62±0.602	85.32±0.564	81.27±0.567	80.23±0.781
12	97.13±0.961	85.14±1.087	86.01±0.823	90.18±0.528	89.27±0.394	84.27±0.821	87.03±0.559	83.96±0.505	82.83±0.395

Values are in mean±SD (%); (n=6)

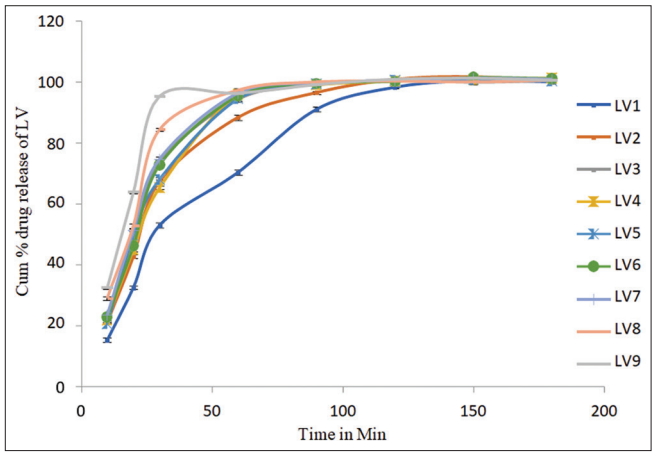

Fig. 3: *In vitro* dissolution studies of lovastatin coat tablets

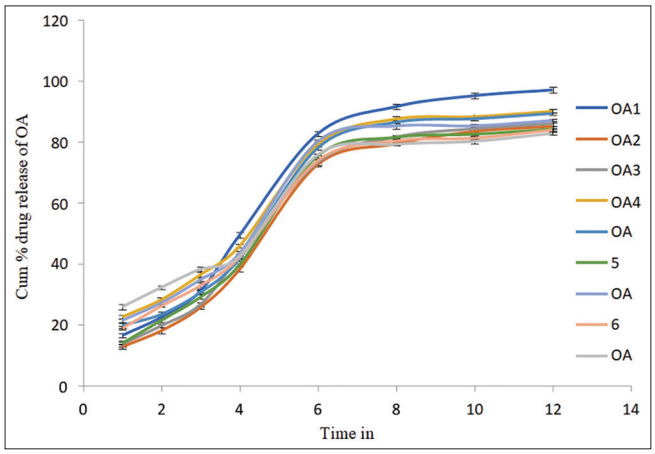

Fig. 4: *In vitro* dissolution studies of oleanolic acid core tablets

Stability studies

Accelerated stability studies conducted over 6 months showed no significant changes in the drug release profile or in other physical parameters, which remained stable throughout the study period as shown in Table 11.

***In vivo* study**

Pharmacodynamic study

Rabbits are widely used as a model to investigate hypercholesterolemia as their lipoprotein profile is comparable to humans. As shown in Table 12, the plasma levels of total cholesterol (TC), LDL, and triglycerides (TG) were increased significantly ($p<0.05$) in rabbits of group II (n=6) after 4 weeks of nutrition with the dietary cholesterol as compared with group I, which was fed with a normal diet. The high-density lipoprotein (HDL) decreased significantly ($p<0.05$) in group II compared to group I after week 4.

After administration of LV API in group III for 2 weeks, the level of TC was decreased as compared to group IV ($p<0.0001$). In group IV after administration of core and coat tablet for 2 weeks, the levels of TG and LDL were decreased ($p<0.0001$). Furthermore, the level of HDL was increased in group IV after 4 weeks compared to the other groups ($p<0.001$). The body weight was increased in group II from the beginning of the experiment till week 4, but in the treated group till week 2, in comparison to the normal control group as presented in Table 13.

Pharmacokinetic study

The plasma concentrations of LV and OA at various time points following the administration of the optimized core and coat tablet are shown in Fig. 5.

Statistical comparisons of the parameters were performed using one-way ANOVA, with a significance level set at $p<0.05$. The pharmacokinetic parameters were calculated based on the plasma concentration-time profiles of both the drugs and the results are summarized in Table 14.

The average peak plasma concentrations (C_{max}) for LV and OA were 9.246±0.319 ng/mL and 482.635±20.173 ng/mL, respectively. The time to reach the maximum plasma concentration (t_{max}) was 30 min for LV and 6 h for OA. The areas under the concentration-time curve (AUC) from 0 to 48 h (AUC_{0-48}) and from 48 h to infinity ($AUC_{t48-\infty}$) for the optimized core and coat tablet were found to be 12666.596 ng h/mL and 3983.503 ng h/mL, respectively. The pharmacokinetic data analysis of the core and coat tablet indicated no significant pharmacokinetic interaction between LV and OA. The combination of these two drugs suggests a potential synergistic effect in lowering lipid levels, which may be beneficial for patients with hypertension and hyperlipidemia.

Table 9: Dissolution study of OA1 of core and coat tablets

Time (min)	Cum. % drug release of oleanolic acid				Standard deviation
	I	II	II	Avg	
60	13.48	16.67	15.39	15.18	1.310
120	18.78	20.95	19.79	19.84	0.886
180	27.33	29.64	28.38	28.45	0.944
240	38.87	40.51	39.84	39.74	0.673
360	64.23	66.39	65.61	65.41	0.893
480	83.1	85.55	84.31	84.32	1.001
600	91.66	93.78	93.32	92.82	0.911
720	97.18	96.12	95.72	96.34	0.616

Table 10: Dissolution study of LV9 of core and coat tablets

Time (Min)	I	II	III	Average	Standard deviation
10	30.53	31.61	33.14	31.76	1.070
20	60.11	61.37	62.21	61.23	0.863
30	90.07	92.31	91.34	91.24	0.917
60	96.17	97.22	98.09	97.16	0.784
90	97.61	99.89	99.08	98.86	0.943
120	101.11	99.91	99.40	100.14	0.716
150	101.73	99.95	100.87	100.85	0.726
180	99.10	101.35	100.06	100.17	0.921

DISCUSSION

The FT-IR spectrum confirmed the absence of interactions between the drugs themselves and between the drugs and excipients, including disintegrants, MCC, and HPMC K100, used in the formulations. The angle of repose values indicated satisfactory flow properties. Disintegration considered the first step in the dissolution process of coated tablets, was analyzed alongside friability and dissolution rate parameters. It was observed that an increase in friability did not significantly impact disintegration time, likely due to the inclusion of super disintegrants. Dissolution studies revealed that the outer coat layer of LV released over 90% of the drug within 30 min, meeting the desired criteria, while the core layer of OA achieved a 97.13% release over 12 h. After 6 months of accelerated stability testing, the physical parameters remained unchanged, and the drug content in the core and coat tablets was within USP specifications. No significant differences were noted in drug release profiles between batches, indicating that the tablets maintained stability throughout the testing period. The combination of LV and OA provides a dual mechanism of action: LV reduces cholesterol production by inhibiting HMG-CoA reductase, while OA decreases dietary cholesterol absorption by inhibiting intestinal ACAT. This release profile is advantageous as it enables rapid LV release from the coat layer for quick action, and sustained OA release from the core layer to maintain steady drug levels in the bloodstream. Formulating LV into IR layer while OA as a SR layer in a core and coat tablet can lower the administration of number of doses and the required API dosage, potentially lowering the risk of adverse effects. The *in vivo* results demonstrate that treatment with LV API effectively reduced TC levels, whereas the administration of the core and coat tablet further decreased TG and LDL levels and improved HDL levels, highlighting its potential therapeutic benefit. Additionally, body

Table 11: Stability study of optimized batch of core and coat tablets

Time	Physical appearance	Weight variation[a]	Hardness (kg/cm^2)[b]	Drug content (%)		Friability (%)
				OA	LV	
Initial	White	305.400±1.586	5.440±0.049	99.511	100.208	0.091
1st Month	White	305.500±1.558	5.380±0.075	99.631	100.059	0.091
3rd Month	White	305.450±1.527	5.500±0.110	99.394	99.800	0.115
6th Month	White	305.300±1.384	5.360±0.080	99.454	99.963	0.124

[a]Values are in mean±SD (mg); (n=6): [b]Values are in mean±SD (kg/cm^2)

Table 12: Changes in lipid profile in rabbits in all groups

Groups	TC	TG	HDL	LDL
Group I (Normal control)	58.67±9.33	50.5±2.93	34.2±4.30	50.17±4.0
Group II (Disease control)	594.7±21.33	214±18.43	13.5±2.64	608.2±57.54
Group III (lovastatin (API)	111.67±19.91	126.17±27.13	19.03±6.30	207.8±44.19
Group IV (core-and-coat tablet)	182.17±42.7	116.63±13.16	31.5±5.01	125.8±23.64

Values are in mean±SD (µg/mL); (n=6); a=p < 0.0001 versus Group III, b=p < 0.0001 versus Group IV; Statistics used: Repeated measures analysis of variance followed by Bonferroni multiple comparison *post hoc* test. TC: Total cholesterol, TG: Triglycerides, LDL: Low-density lipoprotein cholesterol and HDL: High-density lipoprotein cholesterol

Table 13: Changes in body weight (n=6) in rabbits in all groups

Groups	Body weight (gm)			
	1st week	2nd week	2rd week	4th week
Group I (normal control)	2.66±0.13	2.83±0.15	3.03±0.15	3.26±0.19
Group II (disease control)	2.77±0.14	3.16±0.18	3.69±0.12	4.00±0.11
Group III (lovastatin (API)	2.77±0.13	2.86±0.14	2.90±0.19	2.93±0.25
Group IV (core-and-coat tablet)	2.18±0.15	2.95±0.18	3.02±0.25	2.90±0.17

Values are in mean±SD (gm); (n=6)

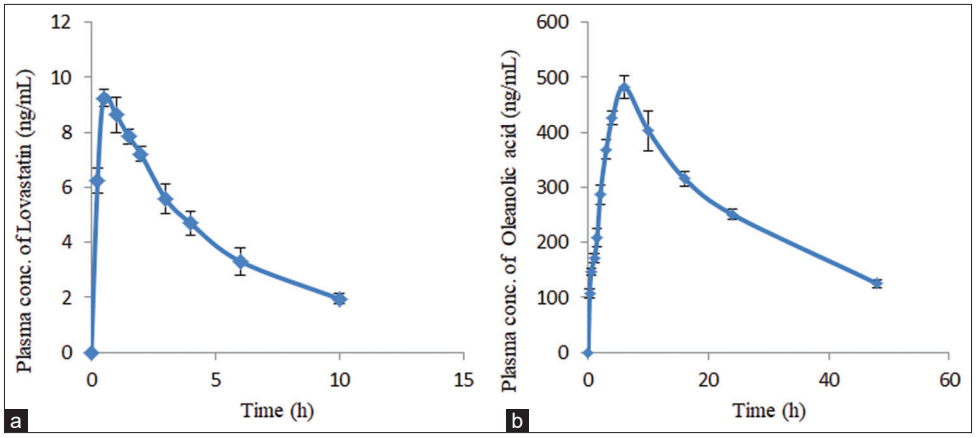

Fig. 5: Mean plasma concentration versus time (mean±SD) profile of optimized core and coat tablet of (a) lovastatin (b) oleanolic acid

Table 14: Pharmacokinetic parameters for lovastatin and oleanolic acid of core and coat tablet

PK parameter[a]	Unit	Optimized core and coat tablet	
		Lovastatin	Oleanolic acid
T_{max}	h	0.5	6
C_{max}	ng/ml	9.246	482.635
$AUC_{(t48-\infty)}$	ng/ml×h	11.478	3983.503
$AUC_{(0-48)}$		44.714	12666.596
K_{el}	h^{-1}	0.1692	0.0314

[a]T_{max}: Time to reach maximum concentration, (C_{max}): Maximum plasma concentration, AUC: Area under plasma concentration-time curve, Kel: Elimination rate constant

weight trends showed an increase in untreated hypercholesterolemic rabbits, whereas the treated groups exhibited moderated weight gain, suggesting a favourable impact of the treatments on metabolic parameters. The pharmacokinetic study of the core and coat tablet formulation revealed improved absorption and bioavailability of LV, along with prolonged therapeutic levels of OA, ensuring a more effective and sustained treatment. These findings support the efficacy of the tested formulations in managing hypercholesterolemia and its associated complications.

CONCLUSION

The combination of immediate and sustained release allows for a dual mode of action, where LV controls cholesterol synthesis and OA inhibits dietary cholesterol absorption. This approach reduces both the frequency of administration and the overall drug dosage, potentially minimizing side effects and improving patient compliance. The *in vivo* study concludes that the core and coat tablet formulation demonstrated significant potential in managing hypercholesterolemia by effectively reducing TC, TG, and LDL levels while increasing HDL levels and moderating body weight in treated rabbits. These findings highlight its therapeutic efficacy compared to LV API and provide a promising approach for cholesterol management. Thus, the core and coat tablet system provides an effective and stable formulation for the combined delivery of LV and OA. The pharmacokinetic study highlighted the rapid absorption of LV, improved oral bioavailability of LV, and sustained therapeutic levels of OA in the bloodstream, which were facilitated by the core and coat tablet formulation approach.

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AUTHOR'S CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing as well as editing, and approved the final draft for publication.

CONFLICTS OF INTEREST

No conflict of interest was declared by the authors.

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