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Formulation and Evaluation of Bilayer Tablets of Lovastatin and Oleanolic acid

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ABSTRACT:
The present research work was envisaged to develop bilayer tablets to improve therapeutic efficacy of antilipidemic drugs for the treatment of high cholesterol and triglyceride levels in the blood. The combination of two antilipidemic drugs i.e. lovastatin and oleanolic acid were used for the preparation of bilayer tablets. The formulations comprise of lovastatin as immediate release layer formulated using different superdisintegrants and oleanolic acid as extended release layer containing HPMC K100M. Evaluation of bilayer tablets were performed for the immediate release lovastatin layer and sustain release oleanolic acid layer with optimization of excipients. The immediate release layer of lovastatin showed complete release within 60 min and oleanolic acid release was extended up to 12 h. Among the various formulations BLV9 for immediate release containing sodium starch glycolate (12 mg): Croscarmellose sodium (12 mg) and BOA1 for sustained release containing HPMC K100M (10 mg): Ethyl Cellulose (10 mg)) were optimized based on the better drug release within 30 min and 12 h respectively. Stability studies revealed that the optimized formulation was intact without any deterioration for 6 months. The present study revealed that lovastatin and oleanolic acid bilayer tablets were successfully developed to reduce the level of bad cholesterol and increase the level of good cholesterol in the blood.
Key words: Bilayer tablet, Oleanolic acid, Lovastatin, HPMC K100, Croscarmellose sodium.

Introduction:

Cholesterol is nothing but the organic molecule which plays an important role in membrane structure. In human body cholesterol is responsible for formation of steroid hormones, bile salts and vitamin D (Tabas & Tabas, 2002). Cholesterol is present in the human body from two sources, liver produces almost 75% of cholesterol and remaining 25% of cholesterol comes from diet. Body regulates synthesis and use of cholesterol which prevents high levels of cholesterol in the body (Sumathy T et al., 2023). Increase in the levels of cholesterol increases abnormal deposition of cholesterol in the coronary artery and leads to atherosclerosis and various heart diseases. The cholesterol produced in liver is through mevalonate path way. The rate limiting stage of mevalonate pathway is 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase (Simonen et al., 2023). Statins are responsible for inhibiting HMG-CoA reductase enzyme. So, statin therapy is

effective in lowering blood cholesterol level. It reduces low density lipoprotein and triglyceride level and increases the high density lipoprotein level (Morofuji et al., 2022). Maintain the cholesterol levels in the body it is also necessary to regulate the cholesterol which comes from the diet. Intestinal acyl-CoA:cholesterolacyl transferase (ACAT), is intracellular enzyme which involved in the cholesterol absorption process from the small intestine and converts into cholesteryl esters. Due to accumulation of cholesteryl ester in macrophages leads to formation of foamy cells and this is nothing but the hallmark of initial stage of atherosclerosis (Chang et al., 2009). In order to get dual actions i.e. control of cholesterol by liver synthesis and from absorption from diet it is ideal to prepare bilayer tablets by using combination of two drugs. From this combination one drug is instant release and one drug is sustained release. Bilayer tablet is most acceptable method of controlled release of drug with pre-defined release profiles. Due to physical separation of active pharmaceutical ingredient one should avoid chemical compatibilities between the API and it is possible to formulate various drug release profile i.e. instant release with sustained release. Bilayer tablet is nothing but the drug delivery system which consists of immediate release drug as well as sustained release drug. The bilayer tablet can be used for formation of repeat action tablet in which immediate release layer rapidly disintegrates and gives the initial dose of drug while the sustained release layer releases afterward. To avoid the release of drug from the two layers at the same time, sustained release layer is coated with various polymers which will give extended release of drug in intestine while the immediate release, releases immediately in the stomach (Kottala et al., 2012; Momin et al., 2015; Siva et al., 2015).

MATERIAL AND METHODS

MATERIALS

Pharmaceutically pure gift sample of Lovastatin was provided by Lupin Pharmaceutical Ltd, Mumbai and Oleanolic acid was procured from Shri Samartha Enterprises, Pune. All other chemicals and solvents were used of analytical and HPLC grade.

METHODS

Preformulation studies

To ensure that the drug and polymer are compatible under the experimental conditions, it is essential to verify that no reaction occurs between them. This confirmation was achieved using Fourier Transform Infrared (FTIR) spectroscopy (Maniyar & Kokare, 2019). The spectra of the samples were recorded using a Shimadzu FTIR spectrometer. Approximately 2-3 mg of each sample was blended with an equal weight of dried potassium bromide (KBr) and compressed into a disc. The samples were then scanned across a wavenumber range of 400 to 4000 cm^{-1}.

Development of Oleanolic acid sustained release (SR) tablets

Factor combination for optimization of SR tablets containing oleanolic acid. The independent factors i.e. HPMC and ethyl cellulose were optimized in SR tablets as quantity of both will also be responsible for the drug release which is the dependent factor in this process. A two factor 3 level full factorial design was employed to optimize the quantities of HPMC and Ethyl cellulose (Shirsat et al., 2014).

Sustained release tablet of oleanolic acid was prepared by direct compression technique by adding required quantities of drug and other ingredients like HPMC K100, Ethyl Cellulose, Micro crystalline cellulose and Lactose. Weigh accurately all the excipients and drugs and pass through sieve no. 100. Later magnesium stearate and talc were added (Makwana et al., 2015; Swetanshu & Sharma, 2019). The above mixture was compressed into Rimek tablet compression machine (Make

Karnavati) B tooling using 8 mm concave punch. The BOA1 to BOA9 batches of SR tablets of oleanolic acid were prepared using various compositions given in Table 1.
This mixture was subsequently evaluated for various pre-compression parameters, including bulk density, tapped density, angle of repose, Hausner's ratio, and Carr's index.

Table 1- Composition of oleanolic acid SR tablets

Batch No.	Ingredients (mg)							
	Oleanolic Acid	HPMC K100	Ethyl Cellulose	Magnesium Stearate	Talc	Lactose	Micro Crystalline Cellulose	Total Weight
BOA1	50	10	10	2	3	12.5	12.5	100
BOA2	50	10	15	2	3	10	10	100
BOA3	50	10	20	2	3	7.5	7.5	100
BOA4	50	15	10	2	3	10	10	100
BOA5	50	15	15	2	3	7.5	7.5	100
BOA6	50	15	20	2	3	5	5	100
BOA7	50	20	10	2	3	7.5	7.5	100
BOA8	50	20	15	2	3	5	5	100
BOA9	50	20	20	2	3	2.5	2.5	100

Development of Lovastatin immediate release (IR) tablets

Factor combination for optimization of IR tablets containing Lovastatin. The independent factors i.e. Sodium Starch Glycolate and Croscarmellose sodium were optimized in IR tablets as quantity of both will also be responsible for the drug release which is the dependent factor in this process. A two factor 3 level full factorial design was employed to optimize the quantities of Sodium Starch Glycolate and Croscarmellose sodium.
Immediate release tablet of lovastatin was prepared by adding required quantities of drug and other ingredients like Sodium Starch Glycolate, Croscarmellose sodium, Micro crystalline cellulose and Lactose. Weigh accurately all the excipients and drugs and pass through sieve no. 100. Later magnesium stearate and talc were added (Girish S. Sonar et al., 2007). The IR tablet of lovastatin was prepared by direct compression using Rimek tablet compression machine (Make Karnavati) B tooling (8 mm concave punch). The BLV1 to BLV9 batches of IR tablets of lovastatin were designed as per table 2.

Table 2- Composition of Lovastatin IR tablets

Batch No.	Ingredients (mg)							
	Lovastatin	Sodium Starch Glycolate	Croscarmellose sodium	Magnesium Stearate	Talc	Lactose	Micro Crystalline Cellulose	Total Weight
BLV1	10	4	4	4	6	86	86	200
BLV2	10	4	8	4	6	84	84	200
BLV3	10	4	12	4	6	82	82	200
BLV4	10	8	4	4	6	84	84	200
BLV5	10	8	8	4	6	82	82	200
BLV6	10	8	12	4	6	80	80	200
BLV7	10	12	4	4	6	82	82	200
BLV8	10	12	8	4	6	80	80	200
BLV9	10	12	12	4	6	78	78	200

Table 3- Preformulation study of Oleanolic acid powder mixture

Batch No	Bulk Volume (mL)	Tapped volume (mL)	Bulk density (gm/mL)	Tapped density (gm/mL)	Hausner ratio	Carr index (%)	Angle of Repose
BOA1	11.9	11	0.58	0.64	1.10	9.38	18.40
BOA2	10.1	9.5	0.60	0.63	1.05	4.76	18.60
BOA3	10.9	9.7	0.59	0.67	1.14	11.94	22.60
BOA4	9.9	8	0.50	0.63	1.26	20.63	14.50
BOA5	9.5	8.5	0.53	0.59	1.11	10.17	19.20
BOA6	9.8	9	0.56	0.61	1.09	8.20	24.30
BOA7	10.3	8.5	0.50	0.59	1.18	15.25	28.40
BOA8	11.8	9.5	0.47	0.58	1.23	18.97	29.40
BOA9	10.2	8.5	0.49	0.59	1.20	16.95	27.60

Table 4- Preformulation study of Lovastatin powder mixture

Batch No	Bulk Volume (mL)	Tapped volume (mL)	Bulk density (gm/mL)	Tapped density (gm/mL)	Hausner ratio	Carr index (%)	Angle of Repose
BLV1	10.41	8.06	0.48	0.62	1.29	22.58	19.60
BLV2	7.93	6.94	0.63	0.72	1.14	12.50	24.30
BLV3	8.47	7.04	0.59	0.71	1.20	16.90	21.20
BLV4	10.41	8.20	0.48	0.61	1.27	21.31	21.30
BLV5	9.80	8.20	0.51	0.61	1.20	16.39	18.80
BLV6	9.60	8.20	0.52	0.61	1.17	14.75	23.80
BLV7	10.64	8.06	0.47	0.62	1.32	24.19	24.50
BLV8	11.11	8.93	0.45	0.56	1.24	19.64	23.40
BLV9	8.20	7.35	0.61	0.68	1.11	10.29	23.40

Table 5- Evaluation parameters of SR tablets

Sr. No.	Batch No	Hardness (Kg/cm^2)	Friability (%)
1	BOA1	5.40	0.24
2	BOA2	4.54	0.21
3	BOA3	5.08	0.26
4	BOA4	5.18	0.23
5	BOA5	5.42	0.21
6	BOA6	4.52	0.22
7	BOA7	4.76	0.20
8	BOA8	5.18	0.23
9	BOA9	5.19	0.25

Table 6- Evaluation parameters of IR tablets

Batch No	Hardness Kg/cm²	Friability %	Disintegration time (sec)
BLV1	4.74	0.28	98
BLV2	4.80	0.16	75
BLV3	5.24	0.17	72
BLV4	5.53	0.16	78
BLV5	5.08	0.14	72
BLV6	4.84	0.18	56
BLV7	5.16	0.14	62
BLV8	5.52	0.15	36
BLV9	5.70	0.14	24

Table 7: Release of Lovastatin from IR tablets

Batch	Time (min)							
	10	20	30	60	90	120	150	180
BLV1	18.25± 0.498	35.55± 0.346	52.85± 0.625	72.2± 0.69	91.65± 0.483	99.1± 0.348	101± 0.756	99.8± 0.345
BLV2	23.5± 0.483	45.3± 0.698	67.23± 0.756	90.55± 0.364	98.6± 0.486	100.2± 0.684	99.8± 0.348	101.1± 0.598
BLV3	25.35± 0.648	50.55± 0.486	73.5± 0.985	95.2± 0.745	99.85± 0.358	99.9± 0.648	100.8± 0.368	99.9± 0.483
BLV4	22.66± 0.483	46.8± 0.681	65.13± 0.318	86.2± 0.478	96.65± 0.684	99.42± 0.792	100.25± 0.348	99.95± 0.982
BLV5	23.55± 0.483	47.33± 0.698	67.89± 0.348	91.35± 0.483	98.85± 0.467	100.1± 0.467	99.9± 0.843	101.35± 0.958
BLV6	24.65± 0.489	48.2± 0.364	72.56± 0.589	96.2± 0.317	99.85± 0.613	100.25± 0.314	99.15± 0.248	100.54± 0.347
BLV7	25.6± 0.483	50.65± 0.624	74.62± 0.792	99.44± 0.678	100.36± 0.468	99.85± 0.391	100.25± 0.34	99.98± 0.463
BLV8	30.9± 0.483	55.65± 0.324	84.28± 0.486	98.65± 0.308	100.65± 0.468	99.8± 0.716	101.25± 0.368	100.55± 0.409
BLV9	35.5± 0.483	65.7± 0.373	95.23± 0.943	99.68± 0.686	100.24± 0.761	100.6± 0.491	99.75± 0.678	100.85± 0.348

Table 8: Drug release models for optimized batch of Lovastatin

REGRESSION COEFFICIENT				
Optimized Batch	Zero order (R^2)	First order (R^2)	Higuchi model (R^2)	Krosmeyer-Peppas Model (R^2)
BLV9	0.6959	0.6369	0.7987	0.8590

Table 9- Release of oleanolic acid from SR tablets

Batch	Time (h)							
	1	2	3	4	6	8	10	12
BOA1	18.1± 0.483	20.65± 0.632	33.81± 0.486	51.95± 0.694	84.1± 0.348	90.95± 0.476	96.25± 0.347	98.18± 0.647
BOA2	14.3± 0.742	30.56± 0.34	35.15± 0.684	40.25± 0.69	74.36± 0.971	81.6± 0.617	90.12± 0.435	92.92± 0.483
BOA3	15.68± 0.473	23.25± 0.483	28.4± 0.243	44.62± 0.476	74.9± 0.314	83.1± 0.462	84.65± 0.846	86.34± 0.586
BOA4	18.6± 0.476	26.2± 0.852	38.85± 0.671	47.95± 0.317	78.2± 0.913	83.25± 0.648	84.48± 0.347	86.17± 0.436
BOA5	21.15± 0.713	28.85± 0.348	31.98± 0.674	43.5± 0.846	79.24± 0.694	81.2± 0.423	83.65± 0.348	85.32± 0.942
BOA6	16.35± 0.48	19.36± 0.348	31.65± 0.761	41.94± 0.348	77.45± 0.762	82.3± 0.348	84.38± 0.942	86.07± 0.348
BOA7	14.1± 0.743	18.4± 0.648	36.25± 0.348	45.2± 0.493	79.1± 0.347	81.25± 0.614	83.3± 0.431	85.97± 0.348
BOA8	18.64± 0.473	24.3± 0.672	34.68± 0.482	44.15± 0.347	75.8± 0.62	82.6± 0.347	88.18± 0.954	89.94± 0.672
BOA9	20.64 ± 0.469	33.65± 0.469	40.36± 0.647	44.85± 0.598	76.96± 0.347	79.4± 0.435	81.69± 0.397	84.32± 0.498

Table 10: Drug release model for optimized batch of oleanolic acid

REGRESSION COEFFICIENT				
Optimized Batch	Zero order (R^2)	First order (R^2)	Higuchi model (R^2)	Krosmeyer-Peppas Model (R^2)
BOA1	0.9809	0.9440	0.9589	0.9580

Table 11: Release of oleanolic acid from bilayer tablet

Time (h)	Cum % drug release of Oleanolic acid				Std Dev.
	I	II	III	Avg	
1	15.31	16.49	17.46	16.42	0.879128
2	21.17	20.24	19.28	20.23	0.771622
3	29.29	28.18	27.94	28.47	0.588048
4	39.21	41.33	40.24	40.26	0.865602
6	64.91	63.57	65.89	64.79	0.950929
8	85.4	87.94	87.12	86.82	1.058427
10	95.14	94.43	93.57	94.38	0.641924
12	99.11	98.41	97.5	98.34	0.659141

Table 12: Release of Lovastatin from bilayer tablet

Time (min)	Cum % drug release of Lovastatin				Std Dev.
	I	II	III	Avg	
10	32.13	34.51	33.8	33.48	0.997631
20	63.66	62.4	61.2	62.42	1.00439
30	92.95	93.54	94.34	93.61	0.56962
60	96.12	97.24	97.49	96.95	0.595707
90	97.4	99.09	98.29	98.26	0.690266
120	98.37	100.71	100.38	99.82	1.034118
150	101.14	100.36	99.16	100.22	0.814371
180	99.97	101.11	102.19	101.09	0.906422

Table 13: Physical Parameters and Stability study of bilayer tablets

Time	Physical appearance	Weight Variation	Hardness (kg/cm²)	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

Evaluation of tablets

The developed Oleanolic acid IR and Lovastatin SR tablets were studied for post compression parameters viz., friability, hardness, drug content, weight variation as per standard procedures and conditions (M.Toma & I.Khalil, 2017).

In vitro drug release studies

The dissolution test of Oleanolic acid IR tablets and Lovastatin SR tablets were performed on Dissolution testing apparatus (Electrolab, USP Type II- Paddle Type) using 900 mL volume of 0.1% SLS solution in water as dissolution media at 37 ± 0.5˚C and 100 rpm speed. At specific time points, 10 ml of dissolution medium was withdrawn and replaced with a fresh dissolution medium. Withdrawn aliquots were filtered through 0.45 µm filter paper and analyzed at 210 nm with a High performance liquid chromatography (HPLC). All measurements were carried out in triplicate (Parashar & Singh, 2018).

Drug release kinetic model

To describe the kinetics of drug release from the optimized oleanolic acid SR tablets (BOA1) and lovastatin IR tablets (BLV9), mathematical models zero-order, first order, Higuchi, Korsmeyer-Peppas were used. Several equations are reported in the literature to identify the mechanism of drug release from tablets (Rao et al., 2021). Drug release data of SR and IR tablets were evaluated according to the following equations,

i) Zero order release model

Zero-order equation is followed when the drug dissolution from tablet is without disaggregate of the polymer and drug is released slowly in controlled manner. The following equation is adopted:

$Q = Q_0 + k_0t$

Where Q represents the amount of drug dissolved in time t, Q_0 is the initial amount of the drug in the solution and k_0 is the zero-order release constant expressed in units of concentration/time. Zero-order data is plotted as cumulative percentage drug released versus time.

ii) First order release model

First-order equation is followed for the release of the drug from the matric and can be expressed by the first order release kinetics equation:

$Log\ C = Log\ C_0 - K_t\ /2.303$

where C_0 is the initial concentration of the drug, K is the first-order rate constant, and t is the time. First order is obtained by plotting log cumulative percentage drug released versus time.

iii) Higuchi model

Higuchi equation is followed when matrix is swelling and drug release is affected by change in the surface area and can be expressed by the Higuchi model equation:

$Q = k_Ht^{1/2}$

Where Q is the amount of drug release at time t and k_H is the Higuchi release constant. As per Higuchi model data is plotted as cumulative percentage drug released versus the square root of time.

iv) Korsmeyer-Peppas model

It is used to describe a simple relationship which explains drug release from a polymeric system equation. The model is useful when the release mechanism is unknown or when more than one type of drug release phenomenon is involved.

$Q_t/Q_\infty = K_kt^n$

Where, Q_t/Q_∞ is a fraction of drug released at time t, K_k is the release rate constant and n is the release exponent. To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time.

Formulation of bilayer tablets

Bilayer tablets were developed with Oleanolic acid as the sustained release (SR) layer and Lovastatin as the immediate release (IR) layer. The optimized formulations, specifically the Oleanolic acid SR tablets (BOA1) and Lovastatin IR tablets (BLV9), were chosen for the bilayer tablet formulation. Initially, the immediate release blend of Lovastatin (200 mg) was lightly compressed using a Rimek tablet compression machine (Make Karnavati) with B tooling and an 8 mm concave punch. Subsequently, the sustained release layer containing Oleanolic acid (100 mg) was manually added on top of the compressed layer. The combined layers were then compressed to achieve a tablet hardness ranging from 5 to 6 kg/cm², resulting in the formation of the bilayer tablet (Atram et al., 2009; Value et al., 2012).

In-vitro drug release studies of bilayer tablets

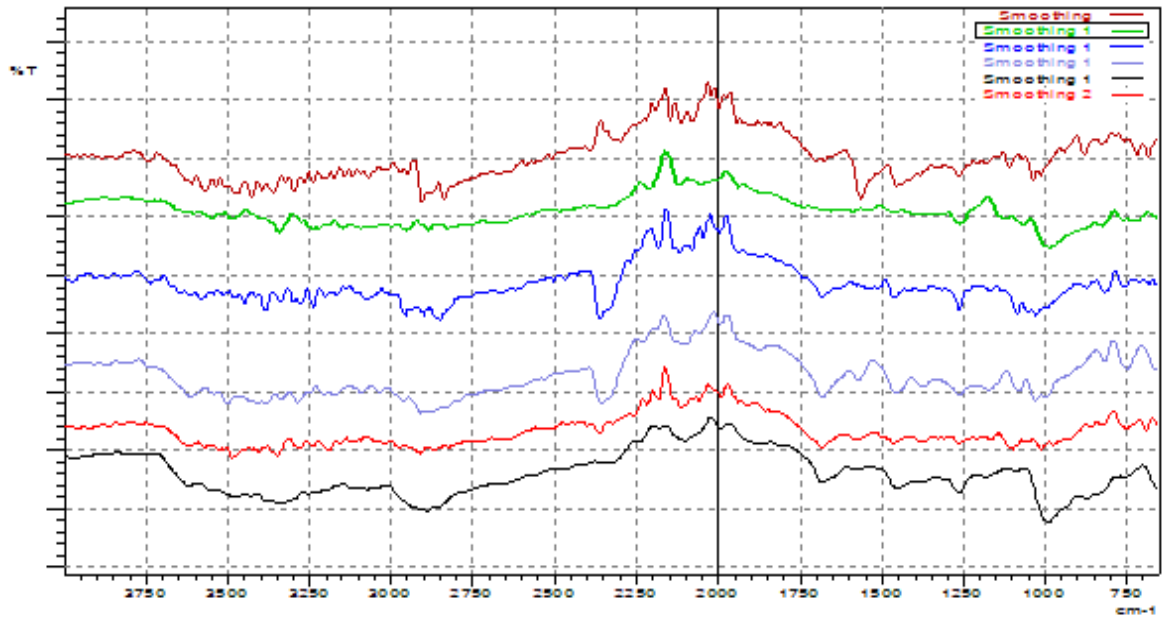
In-vitro dissolution studies of oleanolic acid and lovastatin bilayer tablets were carried out separately as per the above described procedure. The withdrawn samples were analyzed simultaneously by HPLC at λmax 210 nm (Ryakala et al., 2015).

Stability studies

Stability testing was carried out to provide evidence of how the quality of the manufactured tablets may change with time under the influence of environmental factors such as temperature, humidity and storage. They were important and necessary for observing drug's degradation in the process of time. The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use (e.g., reconstitution or dilution as recommended in the labelling). The recommended accelerated and long-term storage conditions and minimum times are Long-term testing (25°C±2°C/60% RH ± 5 % 12 months; Accelerated Testing 40°C±2°C/75% RH±5% for 6 months. Assurance that long-term testing will continue to cover the expected shelf life should be provided. [ICH Q1A] The accelerated stability testing of formulations was carried out at 40°C±2°C/75% RH±5% for 6 months (Maddiboyina et al., 2020; Unnisa et al., 2018; Botre & Maniyar, 2020). The tablets were analyzed as per assay procedure given for content analysis.

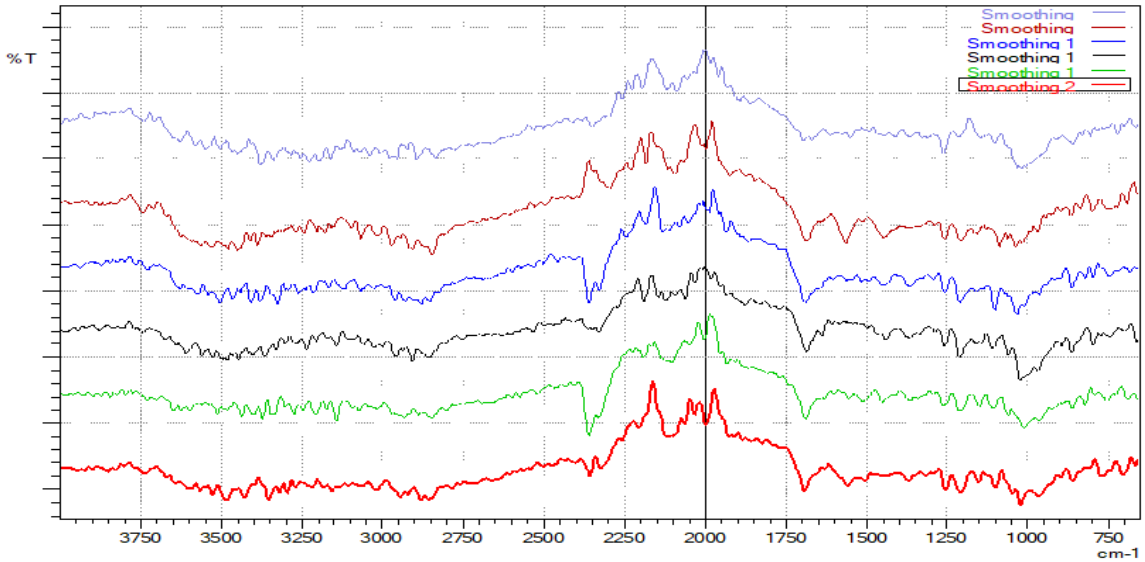
RESULTS

To assess compatibility and determine potential interactions between the drugs and the excipients, FT-IR spectroscopic analysis was conducted on both the physical mixture of the drug and the drug combined with excipients. The FT-IR spectra for Lovastatin and oleanolic acid displayed distinctive peaks corresponding to their molecular structures. (Figure 1 and 2). Characteristic peaks of Lovastatin appeared 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) and 1379.1 cm^{-1} (C-H bending), 2963.2 cm^{-1} (C-H stretching) were observed. Characteristic peaks of oleanolic acid 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) were observed.



1) OA + Magnesium Stearate (Brown) 2) OA + HPMC (Green) 3) OA + Lactose (Navy Blue)
4) OA + Microcrystalline Cellulose (Sky Blue) 5) OA + Talc (Red) 6) OA + Ethyl Cellulose (Black)

Figure 1: Drug excipient study of Oleanolic acid (OA)



1) LV + Microcrystalline Cellulose (Sky Blue) 2) LV + Magnesium Stearate (Brown) 3) LV + Lactose (Navy Blue) 4) LV + Talc (Black) 5) LV + Sodium Starch Glycolate (Green) 6) LV + Croscarmellose Sodium (Red)

Figure 2: Drug excipient study of Lovastatin (LV)

The powder formulations of oleanolic acid and lovastatin were assessed for their physical properties, including angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio (Table 3 and 4). The bulk density and tapped density of the oleanolic acid powder mixtures ranged from 0.47 to 0.60 g/ml and 0.58 to 0.67 g/ml, respectively. For the lovastatin powder mixtures, these values ranged from 0.47 to 0.63 g/ml for bulk density and 0.56 to 0.72 g/ml for tapped density. The angle of repose varied from 14.5 to 29.4 for oleanolic acid and 18.80 to 24.30 for lovastatin, indicating good flow properties. The Hausner ratio for the oleanolic acid powder mixtures ranged from 1.09 to 1.23, and for the lovastatin powder mixtures, it ranged from 1.11 to 1.32. The compressibility index ranged from 4.76 to 20.63 for the oleanolic acid mixtures and from 10.29 to 24.19 for the lovastatin mixtures. These results suggest that the powder mixtures from all formulation batches exhibited good flow properties.

The drug content was consistently above 95% across different batches of oleanolic acid and lovastatin tablets. The compressed tablets were assessed for hardness, friability, and disintegration time (specifically for Lovastatin IR tablets) as shown in Table 5 and 6. The hardness of both sustained-release (SR) and immediate-release (IR) tablets ranged from 4.52 to 5.70 kg/cm^2. The lovastatin IR tablets had a disintegration time of less than 1 minute, significantly below the USP limit of 15 minutes for uncoated IR tablets. Notably, batch BLV9 disintegrated faster than other batches, with a disintegration time of 24 seconds due to the inclusion of 12 mg each of Sodium Starch Glycolate and Croscarmellose sodium. Drug release studies comparing various batches (BLV1-BLV9) with different ratios of these disintegrants showed that BLV9 had the best drug release profile, achieving 95.23±0.943% release within 30 minutes (Table 7). Therefore, the BLV9 formulation was deemed optimal and was selected for further development of bilayer tablets. The regression coefficient (R^2) values of release data of BLV9 formulations obtained by the curve fitting method for zero-order, first-order, Higuchi model and Krosmeyer-Peppas are reported in Table 8. For the optimized formulation, the R^2 value of Krosmeyer-Peppas Model is 0.8590 is the most probable model comparing to other models which indicates that the drug release is determined by the log % drug release of the log time.

The dissolution study data for oleanolic acid SR tablets indicated that higher concentrations of HPMC K100 resulted in a decreased release rate of oleanolic acid. The presence of ethyl cellulose contributed to the formation of a more rigid complex with the hydrophilic polymer HPMC K100,

effectively retaining the drug within the matrix and preventing rapid diffusion. Based on these findings, batch BOA1 emerged as the most suitable for the SR layer in bilayer tablets, achieving the highest drug release of 98.18±0.647% at 12 hours compared to other formulation batches (Table 9). Consequently, the BOA1 formulation was selected as the optimized batch for further development of bilayer tablets. For the optimized formulation, the R^2 value of zero order release is 0.9809 is the most probable model comparing to other models which indicates that the drug release is determined by the % drug release of the time (Table 10).

Bilayer tablets comprising lovastatin (IR) and oleanolic acid (SR) were formulated using the optimized batches BLV9 and BOA1. Upon evaluation, all the physical parameters of the tablets were within the acceptable range. The lovastatin IR layer of the bilayer tablets, derived from the BLV9 blend, demonstrated a disintegration time of 24 seconds. In-vitro dissolution studies were conducted using an Electrolab Dissolution Testing Apparatus, Type II- Paddle Type, and drug release was simultaneously quantified using HPLC as detailed in Table 11 and 12. Accelerated stability studies over six months indicated no significant changes in the drug release profile. Other physical parameters also remained stable throughout the six-month period (Table 13).

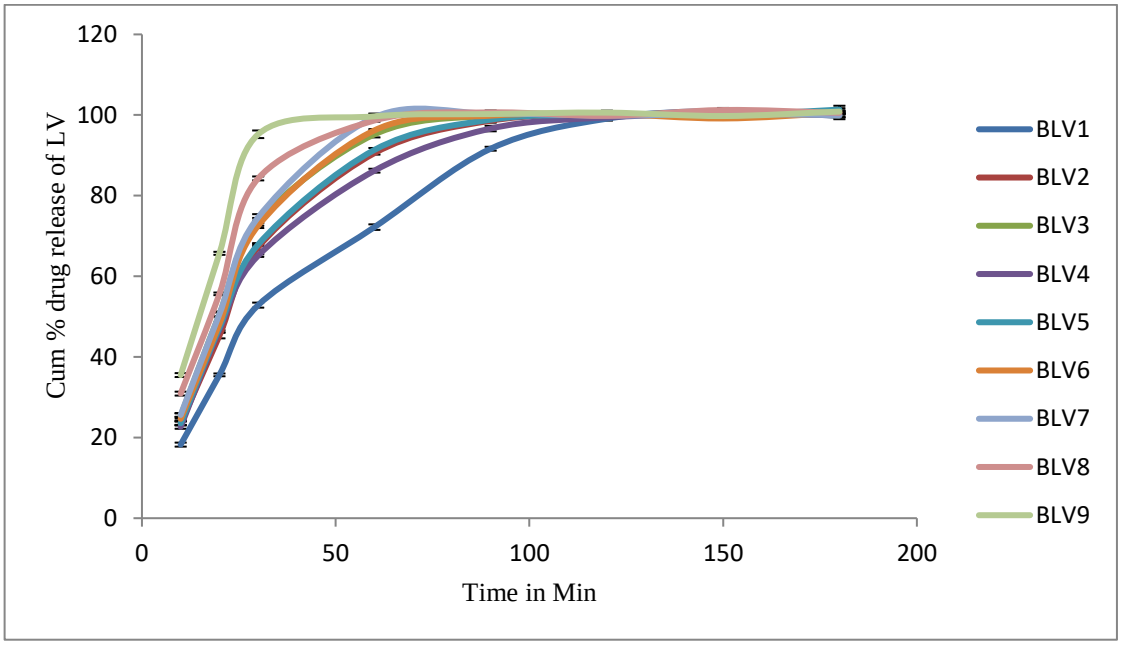


Figure 3: Drug release profile of Lovastatin IR tablets

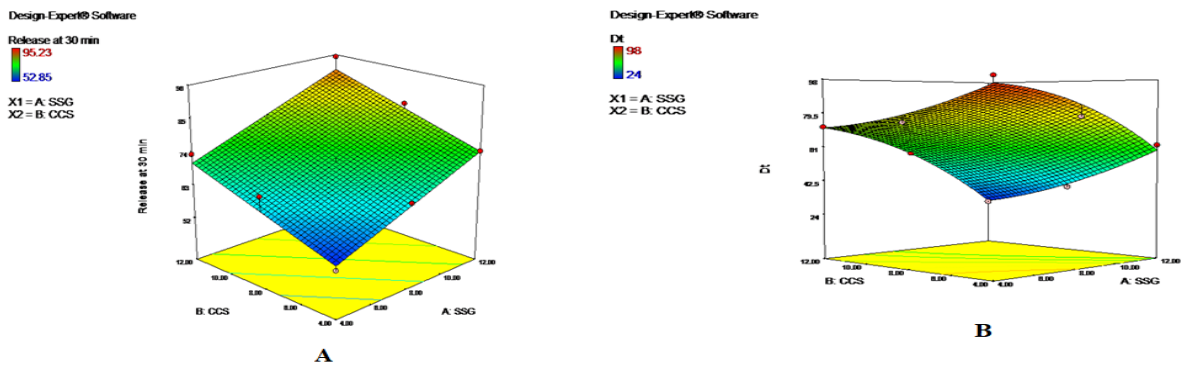


Figure 4: Surface response plot of immediate release LV layer at A) 30 min. B) Disintegration Time

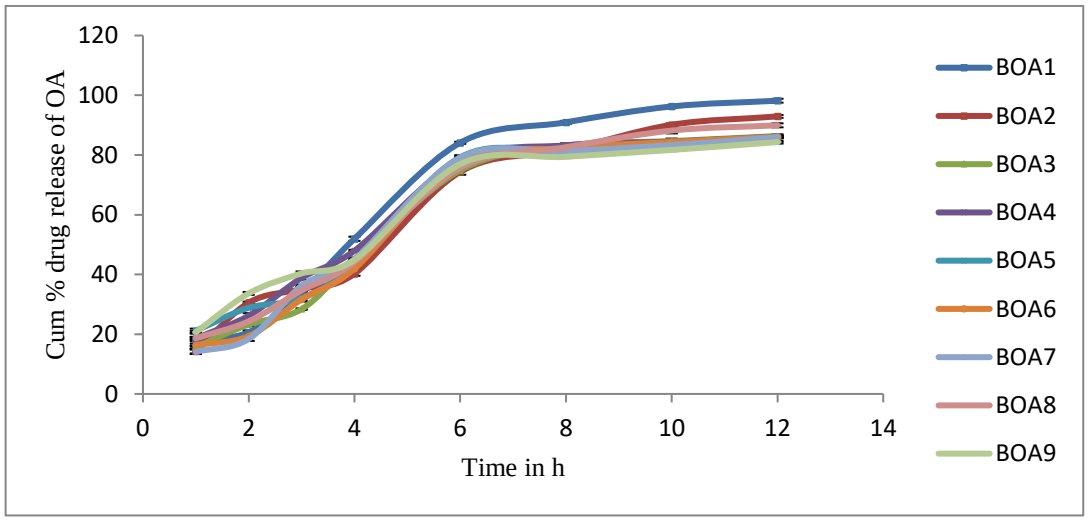


Figure 5- Drug release profile of oleanolic acid SR tablets

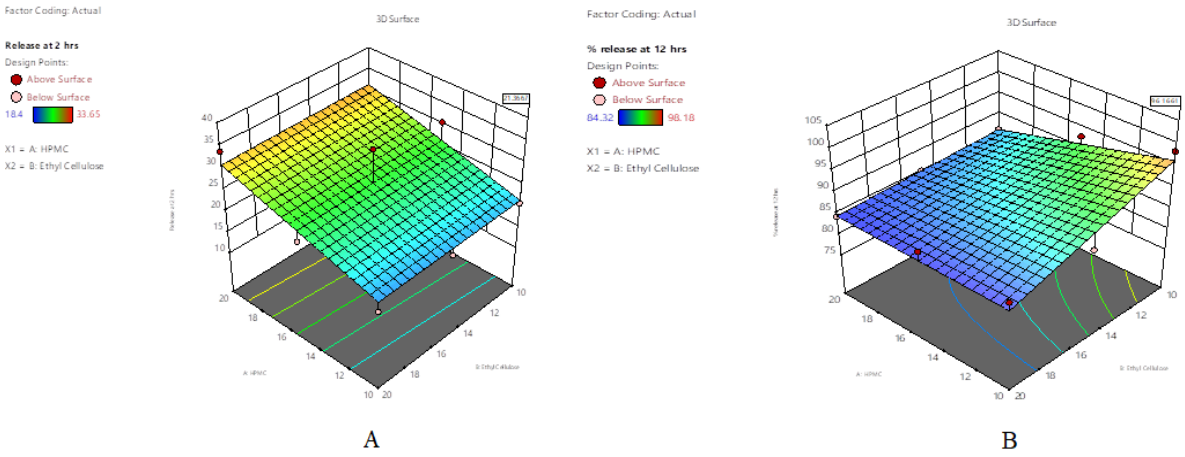


Figure 6: Surface response plot of Oleanolic acid SR layer at A) 2 h B) 12 h

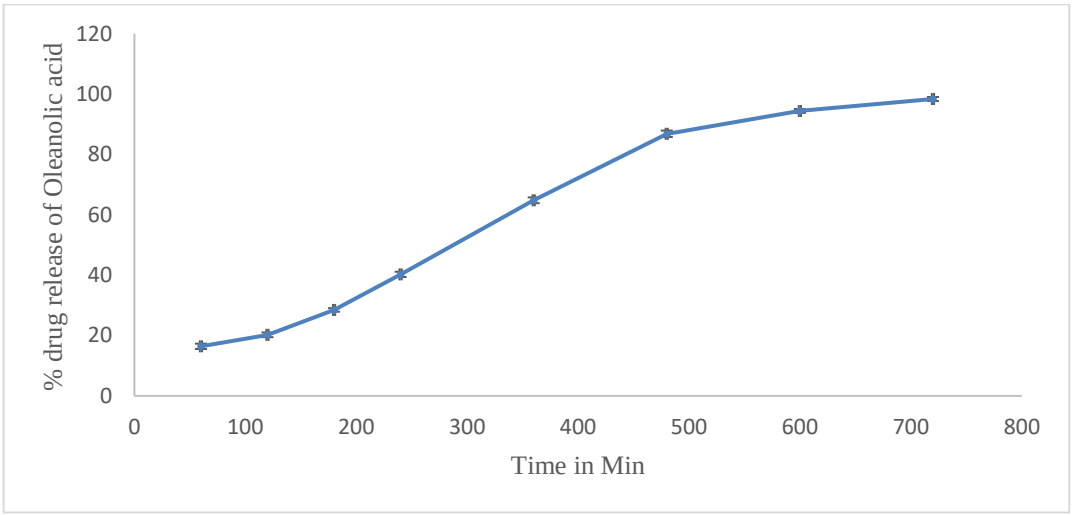


Figure 7: Drug release of OA from optimized batch

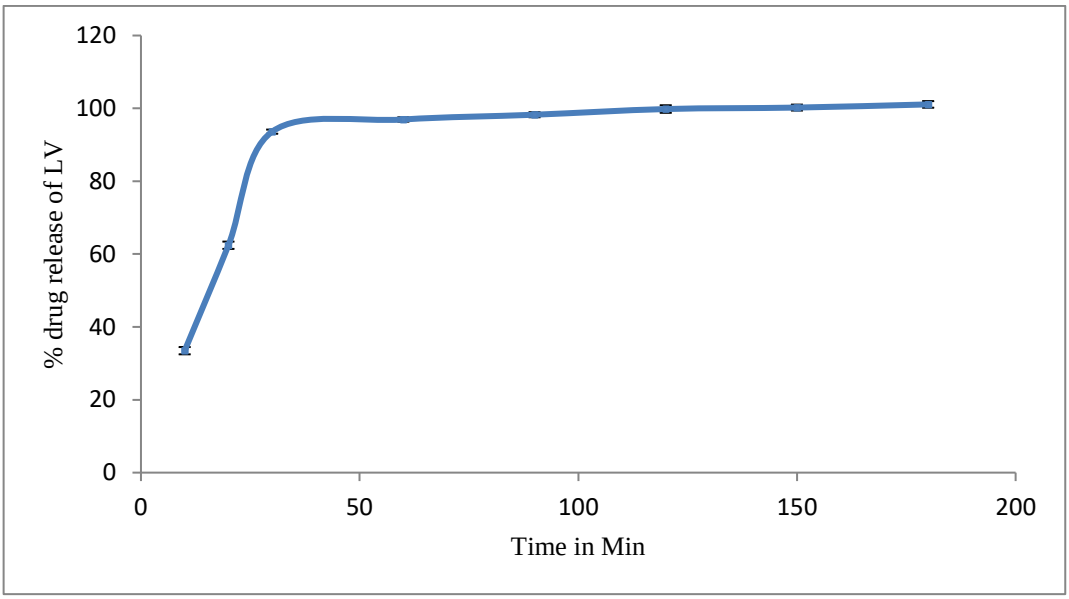


Figure 8: Drug release of LV from optimized batch

DISCUSSION

The FT-IR spectrum confirmed that there were no interactions between the drugs themselves or between the drugs and the excipients, such as disintegrants, microcrystalline cellulose, and HPMC K100, used in the formulations. The angle of repose values indicated satisfactory flow behavior. Disintegration is considered the initial step in the dissolution process of immediate release tablets. Analysis of friability, disintegration time, and dissolution rate parameters showed that an increase in friability did not significantly affect the disintegration time, likely due to the presence of superdisintegrants. The Korsmeyer-Peppas model was identified as the best fit for the drug release kinetics of the BLV9 batch, suggesting that the release mechanism is either complex or involves multiple phenomena. Dissolution studies demonstrated that the immediate release layer of lovastatin released over 90% of the drug within 30 minutes, meeting the desired criteria. The sustained release layer of oleanolic acid achieved a 98.94% release at 12 hours. Physical parameter evaluations after six months of accelerated stability studies showed no significant changes. The drug content of the bilayer tablets was within USP specifications, and there were no significant differences in drug release profiles between batches. This indicates that the bilayer tablets remained stable under the tested conditions and period. The combination of lovastatin and oleanolic acid offers a dual mode of action: lovastatin controls cholesterol production in the body by inhibiting HMG-CoA reductase, while oleanolic acid reduces dietary cholesterol absorption by inhibiting intestinal acylCoA:cholesterol acyltransferase (ACAT). This release profile is advantageous as it allows for immediate lovastatin release for rapid action and sustained oleanolic acid release to maintain steady drug levels in the blood. Formulating lovastatin as an immediate release and oleanolic acid as a sustained release layer in a bilayer tablet reduces both the frequency of administration and the required drug dosage, thereby potentially decreasing adverse effects. A successful bilayer tablet formulation of lovastatin and oleanolic acid was developed for once-daily administration to regulate cholesterol levels in the body.

CONCLUSION

Based on the results, it can be concluded that bilayer tablets containing 10 mg of lovastatin as an immediate release component and 50 mg of oleanolic acid as a sustained release component were successfully developed. The bilayer tablets demonstrated stability under accelerated stability

conditions, indicating that a stable dosage form was achieved. The lovastatin and oleanolic acid bilayer tablet shows promising potential as an alternative to conventional dosage forms. Given that no similar delivery systems are currently available in the market, this new dosage form also holds significant commercial potential.

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