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Design and Formulation of Modified-Release Bilayer Tablets of Rosuvastatin and Ezetimibe

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Abstract

Cardiovascular disease (CVD) causes a significant number of morbidity and mortality worldwide, primarily driven by dyslipidemia and abnormal lipid levels. Effective management of hyperlipidemia and CVD typically involves using various pharmacological agents, including statins (like atorvastatin and rosuvastatin), cholesterol absorption inhibitors (like ezetimibe) and fibrates. The combined use of these agents has been shown to decrease cardiovascular events effectively over a long duration. This study formulated and designed a bilayer tablet containing sustained-release formulations of rosuvastatin and immediate-release formulations of ezetimibe. The compatibility of drugs within themselves and with the release modifiers was confirmed using FTIR and DSC. The effectiveness of the formulations was evaluated by *in-vitro* dissolution studies and release kinetics. The release of the ezetimibe was 90% within 60 minutes, whereas rosuvastatin was released 90% from its sustained release formulation within 6 hours. The release rates were evaluated with the Higuchi model, Korsmeyer-Pappas model and first-order kinetics, revealing the best ezetimibe formulation containing cross-povidone and the best rosuvastatin formulation containing methocel K4M. The combined use of the two formulations would ensure a rapid onset of action and an effective release profile over a long duration.

Key words: Cardiovascular diseases, bilayer tablets, modified release, rosuvastatin, ezetimibe.

Introduction

Cardiovascular disease (CVD) is one of the leading causes of mortality and morbidity in Bangladesh, responsible for approximately 17% of the country's deaths (Islam *et al.*, 2016; Zhao, 2021). The increasing prevalence of CVD underscores the urgent need for improved therapeutic strategies, particularly for managing lipid abnormalities such as hypercholesterolemia, which is a significant risk factor for these diseases. Enhancing the efficacy of current treatment options through developing novel dosage forms is crucial.

Abnormal lipid levels, including elevated low-density lipoprotein cholesterol (LDL-C), are central to the pathogenesis of various cardiovascular conditions such as stroke, coronary artery disease and peripheral arterial disease (Poels *et al*., 2020; Kosmas *et al.*, 2020). Current therapeutic strategies include statins, fibrates and cholesterol absorption inhibitors, prescribed based on individual lipid profiles and the severity of the patient's condition (Fazio and Linton, 2004; Reith *et al*., 2022). Statins, particularly HMG-CoA reductase inhibitors, are the first-line drugs for managing hypercholesterolemia and are well-established in the treatment of CVD (Stroes, 2020;

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Bellosta and Corsini, 2012; Stancu and Sima, 2001). On the other hand, cholesterol absorption inhibitors like ezetimibe (EZT) have been shown to effectively lower LDL-C levels by inhibiting intestinal cholesterol absorption (Miettinen, 2001). Recent clinical evidence supports the combination of statins with cholesterol absorption inhibitors for an enhanced reduction in LDL-C levels, especially in patients with high cardiovascular risk who require aggressive lipid-lowering therapy (Marrone *et al*., 2012; Mubeen *et al*., 2022).

Clinical trials have demonstrated that the combination therapy of ezetimibe and statins offers better clinical outcomes compared to statin monotherapy, particularly in patients who are statin-resistant or experience adverse effects at high doses of statins (Yang *et al*., 2017; Robinson *et al*., 2006). Furthermore, the combination of rosuvastatin and ezetimibe has shown superior efficacy in reducing LDL-C levels compared to monotherapy with rosuvastatin alone (Lee *et al*., 2020; Kim *et al*., 2016).

Although combinations of ezetimibe with various statins like simvastatin, atorvastatin, and rosuvastatin are already approved and marketed globally (Grigore *et al*., 2008; Gorniak *et al*., 2022; Gardouh *et al*., 2020), the combination of rosuvastatin and ezetimibe in a bilayer tablet dosage form is not yet available. This creates a necessity for developing an industrially feasible, fixed-dose combination bilayer tablet that could provide an effective solution for long-duration treatment of hypercholesterolemic patients in Bangladesh. The proposed bilayer tablet formulation will be designed to deliver rosuvastatin and ezetimibe in a controlled manner, optimizing the reduction of LDL-C and improving the management of hyperlipidemia in patients at high cardiovascular risk.

This study aims to design and evaluate a combination bilayer tablet of rosuvastatin and ezetimibe that could effectively manage hypercholesterolemia in high cardiovascular-risk patients. The study focuses on developing a simple, feasible, cost-effective formulation and comprehensive *in vitro* evaluation, including physicochemical characterization, stability analysis, and dissolution testing. Addressing the current gap in available therapies, the proposed bilayer tablet formulation could significantly improve LDL-C management in CVD patients, particularly those not adequately controlled with monotherapy.

Materials and Methods

The bilayer tablets were prepared by compressing sustained-release rosuvastatin and immediate-release ezetimibe formulations. The sustained-release formulations of rosuvastatin contained rosuvastatin, magnesium stearate, microcrystalline cellulose, talc, eudragit L-100, methocel K100, and methocel K4M. The immediate-release formulations of ezetimibe contained ezetimibe, sodium starch glycolate, cross-povidone, starch, PVP K-30 (Polyvinyl pyrrolidone K-30), magnesium stearate, microcrystalline cellulose, molloidal anhydrous silica (Aerosil) and lactose monohydrate.

Formulation: Rosuvastatin sustained release granules were prepared by blending powdered rosuvastatin, microcrystalline cellulose and a release retardant in 12% water (Table 1). The mixture was then dried for 30 minutes at 50 °C to give it a dough-like consistency (Kumar *et al*., 2016). After drying, the mixture was sieved through a 20-mesh screen to guarantee consistent particle size. Talc and magnesium stearate were then added in the proper amounts. Lastly, concave-faced punches were used to compress the mixture into 200 mg tablets. The same procedure was followed for other formulations, using methocel 100 M and methocel K4 M. A total of 9 formulations were prepared using different release retardant concentrations.

A mixture of ezetimibe powder, lactose monohydrate as a filler and sodium starch glycolate as super-disintegrants was mixed thoroughly. Then, the other ingredients, PVP K-30, MCC and sodium lauryl sulfate were mixed. A combination of isopropyl alcohol and water was added to it. After getting the expected dough-like structure, the mixture

was dried in a heater at 60 °C for 30 minutes (Karim *et al.*, 2015). After drying, the mixture was passed through a 30 mesh to ensure particle size uniformity. Then, magnesium stearate was added as a lubricant, and aerosil was added as a glidant. Finally, the mixture was punched into 100 mg tablets with concave-faced punches. The same procedure was followed using cross-povidone and starch for other formulations. A total of 6 formulations were prepared by using different concentrations of super-disintegrants (Table 2).

Table 1. Sustained release formulations of rosuvastatin.

Ingredients	Justification	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rosuvastatin	API	20	20	20	20	20	20	20	20	20
Methocel k100	Release retardant	20	40	60	-	-	-		-	-
Eudragit L-100	Release retardant	-	-	-	20	40	60	-	-	-
Methocel K4 M	Release retardant	-	-	-	-	-	-	20	40	60
MCC	Diluent	154	134	114	154	134	114	154	134	114
Talc	Glidant	4	4	4	4	4	4	4	4	4
Magnesium stearate	Lubricant	3	3	3	3	3	3	3	3	3
Total weight (mg)		200	200	200	200	200	200	200	200	200

Table 2. Immediate release formulations of ezetimibe.

Ingredients	Justification	F1	F2	F3	F4	F5	F6
Ezetimibe	API	10	10	10	10	10	10
Sodium starch glycolate	Disintegrating agent	4	3	-	-	-	-
Cross-povidone		-	-	3	4	-	-
Starch		-	-	-	-	5	4
Lactose monohydrate	Filler	71	72	72	71	70	71
Colloidal anhydrous silica (Aerosil)	Glidant	2	2	2	2	2	2
MCC	Diluent	5	5	5	5	5	5
PVP K-30	Binder	3	3	3	3	3	3
Magnesium stearate	Lubricant	2	2	2	2	2	2
Sodium lauryl sulfate	Emulsifying agent	3	3	3	3	3	3
Total weight		100	100	100	100	100	100

After performing the pre- and post-compression test, F3 and F4 from the ezetimibe immediate-release formulations were combined with F3 and F4 from the rosuvastatin sustained-release to formulate bilayer tablets.

Determination of moisture content: Moisture content was determined by measuring the loss on drying (LOD). LOD was calculated by measuring the weight of the samples before and after drying. It was maintained below 5% for better compression.

Angle of repose (θ): The angle of repose is the maximum angle that can be formed between a powder pile and the horizontal plane. It assists in quantifying the frictional forces present in granules or loose powder. It was calculated using the formula: $\tan(\theta) = h/r$, where 'h' represents the pile's height, 'r' is its radius, and θ is the angle of repose (Jayaswal *et al*., 2014).

Carr's compressibility index: Carr's compressibility index is calculated as a percentage using the

following formula to determine the compressibility of granules (Jayaswal *et al*., 2014).

Compressibility index=100 (Bulk density -tapped density)/bulk density

Hausner Ratio: It is the ratio of bulk density to tapped density, an indicator of powders' flow property. A Hausner ratio of 1.6 or greater indicates poor flow property and a ratio between 1.00-1.11 indicates excellent flow property (Jayaswal *et al*., 2014).

HR= (Bulk density)/(Tapped density)

Fourier transform infrared (FTIR) spectroscopy: Approximately 300 mg of potassium bromide (KBr) was weighed and ground into a fine powder. About 2-3 mg of the pure drug or a drug-excipient mixture was added and the combination was thoroughly ground to ensure uniform mixing. The resulting KBr mixture was then compressed using an 8-ton infrared (IR) press to form a pellet. Fourier-transform infrared (FTIR) analysis was conducted using the IRSpirit Infrared Spectrophotometer (Shimadzu Corporation, Japan) within the 4000 – 600 cm^{-1} range.

Differential scanning calorimetry (DSC): DSC was performed in DSC250 (TA instruments, USA) equipped with a Tzero aluminum pan, an autosampler, and an RCS90 Refrigerated Cooling System. The samples were heated from 25 °C to 300 °C at 10 °C/min.

Thickness and diameter: We used slide calipers to measure the thickness and diameter of the tablets.

Hardness: Tablets were positioned longitudinally in the tester to measure the hardness. Five tablets were tested and their average hardness was calculated. Oral pills have a hardness of 4 to 10 kg, while formulations for sustained release were approximately 6-9 kg, according to USP (Mubeen *et al*., 2022).

Friability: To check friability, the total weight of 10 tablets was measured. Then, the tablets were placed in the friabilator running at 25 rpm for 4 minutes. Then, the weight of the tablets was measured again. Friability was calculated using the following formula (Mubeen *et al*., 2022):

Friability=100×(Initial weight - final weight)/Initial weight.

Weight Variation: The weight of 10 tablets was measured and the average weight was calculated. Weight variation is calculated by following the formula.

Weight variation=100×(Average weight – individual weight)/Average weight

According to USP, tablets having an average weight of more than 130 mg or less, the acceptable range of variation is within ±10%. If the average weight is more than 130 mg through 324 mg, the acceptable difference is ± 7.5%, and in the case of weight more than 324 mg, the variation acceptance is ±5% (Mubeen *et al*., 2022).

Disintegration time: The disintegration of the prepared tablets was studied by an Electrolab ED-2L disintegration tester. According to USP guidelines, the disintegration time was measured in 900 ml purified water at 37 ± 0.5 °C. The average disintegration of 12 individual tablets was recorded (Momin *et al.*, 2015).

In-vitro dissolution study: The *in-vitro* dissolution was performed in USFDA-recommended media in 900 ml PH 6.8 phosphate buffer at 37 ± 0.5 °C and 50 rpm. Samples were withdrawn at 10, 20, 30, 45, 60, 90, 120, 180 and 360 minutes respectively and then diluted as required. These samples were analyzed in a UV-Vis spectrophotometer at a maximum wavelength of 244 nm (Momin *et al.*, 2015).

Results and Discussion

Bilayer tablets were formed by compressing formulations of sustained-release rosuvastatin and immediate-release ezetimibe. Precompression tests were carried out to assess the physical and mechanical properties of the granules or powders used to form the tablets.

Bulk and tapped density: The bulk and tapped density of rosuvastatin formulations were found in the 0.437-0.684 g/cc and 0.470-0.782g/cc range, respectively (Table 3). Ezetimibe formulations' bulk and tapped density were found in the range of 0.316-

0.648 g/cc and 0.368-0.734g/cc, respectively (Table 4).

Carr's compressibility index: The range of good compressibility is 15%. The formulations of rosuvastatin of F3-F9 showed good compressibility. All but F5 of ezetimibe have compressibility within the limit (Tables 3 and 4).

Hausner ratio: The Hausner ratio is a parameter used to assess the cohesiveness and flowability of a powder or granular material. Hausner's ratio of 1.0 to 1.10 indicates high compressibility of blends (Baratam, 2018). It is obtained by using the tapped and bulk density. The F3-F5 and F9 formulations of the rosuvastatin granules had Hausner ration within the specified ranges. The F1, F2, F4 and F6 formulations of ezetimibe showed a Hausner ratio, indicating excellent compressibility (Tables 3 and 4).

Angle of repose: The angle of repose of F1, F3, F4, F7 and F8 formulations of rosuvastatin was suitable (Table 3). The F1, F3 and F4 formulations of ezetimibe also showed a good angle of repose within the required range (Table 4). The specified range of angle of repose is 35° (Baratam, 2018).

Table 3. Precompression parameters of sustained-release formulations of rosuvastatin.

Formulations	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility	Hausner ratio	Angle of repose
F1	0.626	0.782	19.94%	1.25	33.02°
F2	0.496	0.617	19.6%	1.24	35.89°
F3	0.562	0.665	14.45%	1.08	32.61°
F4	0.491	0.525	6.475%	1.07	31.23°
F5	0.437	0.470	7%	1.08	39.65°
F6	0.515	0.561	8.1%	1.09	41.5°
F7	0.596	0.640	7.3%	1.07	32.61°
F8	0.614	0.702	12.5%	1.14	31.53°
F9	0.684	0.722	11.6%	1.13	38.75°

Table 4. Precompression parameters of immediate-release formulations of ezetimibe.

Formulations	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility	Hausner ratio	Angle of repose
F1	0.449	0.526	14.63%	1.07	33.02°
F2	0.476	0.494	10.73%	1.02	36.89°
F3	0.316	0.368	14.13%	1.16	32.61°
F4	0.584	0.657	11.11%	1.02	31.23°
F5	0.525	0.636	17.45%	1.21	39.75°
F6	0.648	0.734	11.72%	1.03	41.5°

Fourier transform infrared spectroscopy (FTIR): FTIR assays were carried out to confirm that the rosuvastatin and ezetimibe are compatible with the investigated excipients. FTIR spectra were recorded in transmittance mode with a spectral resolution of 4 cm^{-1} from a frequency region of 4000 cm^{-1} to 400 cm^{-1}. (Rani and Muzib, 2020). The FTIR peaks of OH group at 3319 cm^{-1}, CN group at 1545 cm^{-1} and SO stretching at 1150 cm^{-1} are consistent with literature data for rosuvastatin (Sadhana *et al.* 2023, Parimoo 2007). We also observed C-OH stretching at 3460 cm^{-1} and CO stretching at 1602 cm^{-1} for ezetimibe, which matched the literature values (Prajapati *et al.* 2016, Parimoo 2007). For the prepared formulations,

the physical mixing of the API and the release-modifying polymers did not exhibit significant changes in the major peaks at higher frequencies (Figure 1). The results indicate the compatibility among the drugs and the excipients.

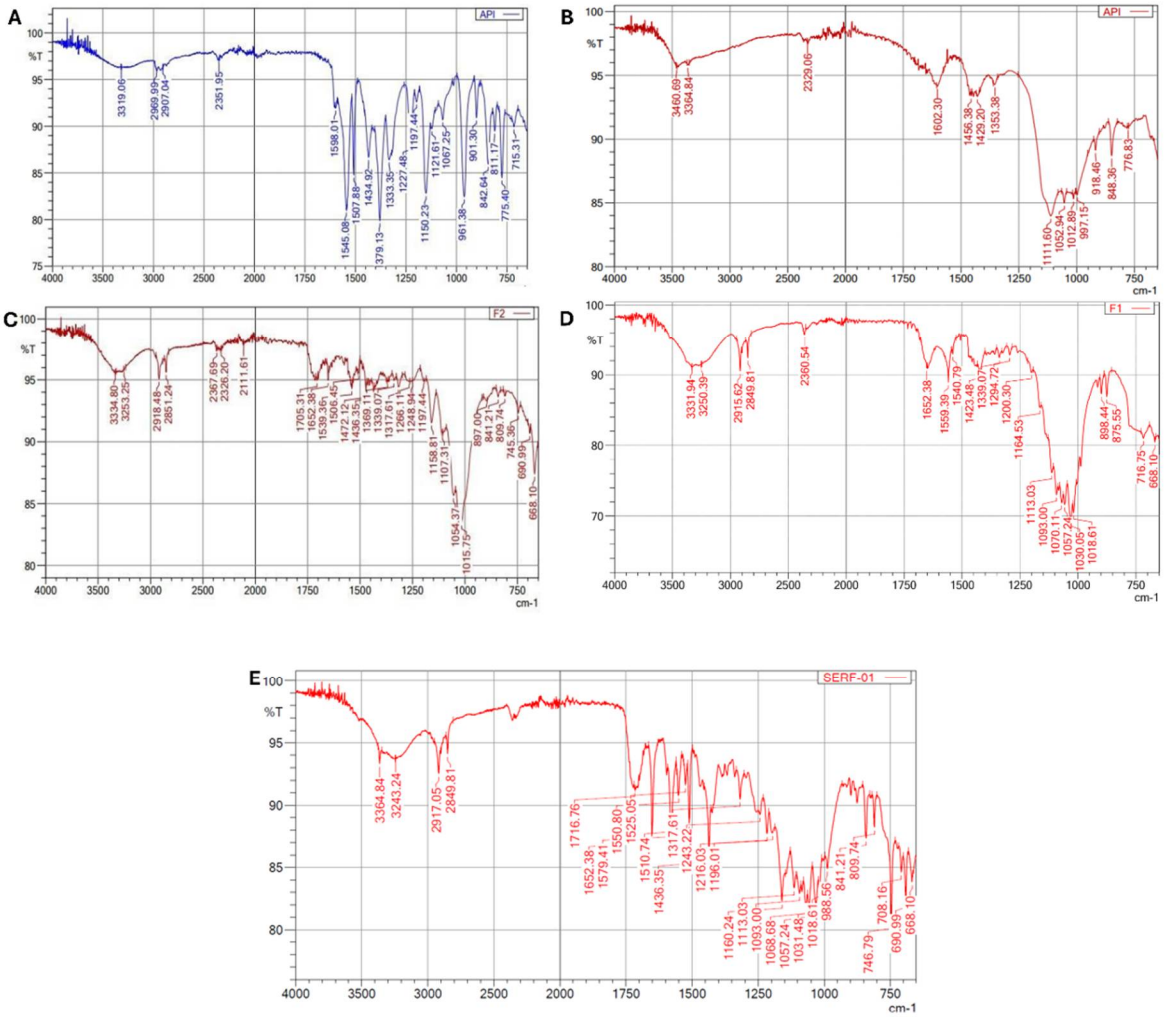

Figure 1. FTIR spectra of A) pure rosuvastatin, B) pure ezetimibe, C) rosuvastatin with excipients, D) ezetimibe with excipients and E) combined rosuvastatin and ezetimibe with excipients for bilayer tablets.

Differential scanning calorimetry (DSC): DSC is an efficient and precise technique for evaluating drug-excipient compatibility, offering valuable insights into possible interactions. Interactions are identified in DSC when existing endothermic peaks disappear and new peaks emerge. The process of grinding and drying can change the form of the drug in the dosage form (Parimoo, 2007). So, we used the DSC to study whether the drug form remains stable during the processing. Rosuvastatin showed an endothermic peak at 140-156 °C, consistent with the previously published data (González *et al.* 2022). The drug behavior remains similar in the presence of excipients (Figure 2). Pure ezetimbe showed an endothermic peak at 93-136 °C, indicating its melting temperature. After mixing with excipients, we observed the endothermic peak at 142-163 °C, which is the melting point of an isomer (S,R,S) of ezetimibe (Filip *et al.* 2011). The DSC thermographs did not show significant changes in the drugs' stability in the presence of the excipients.

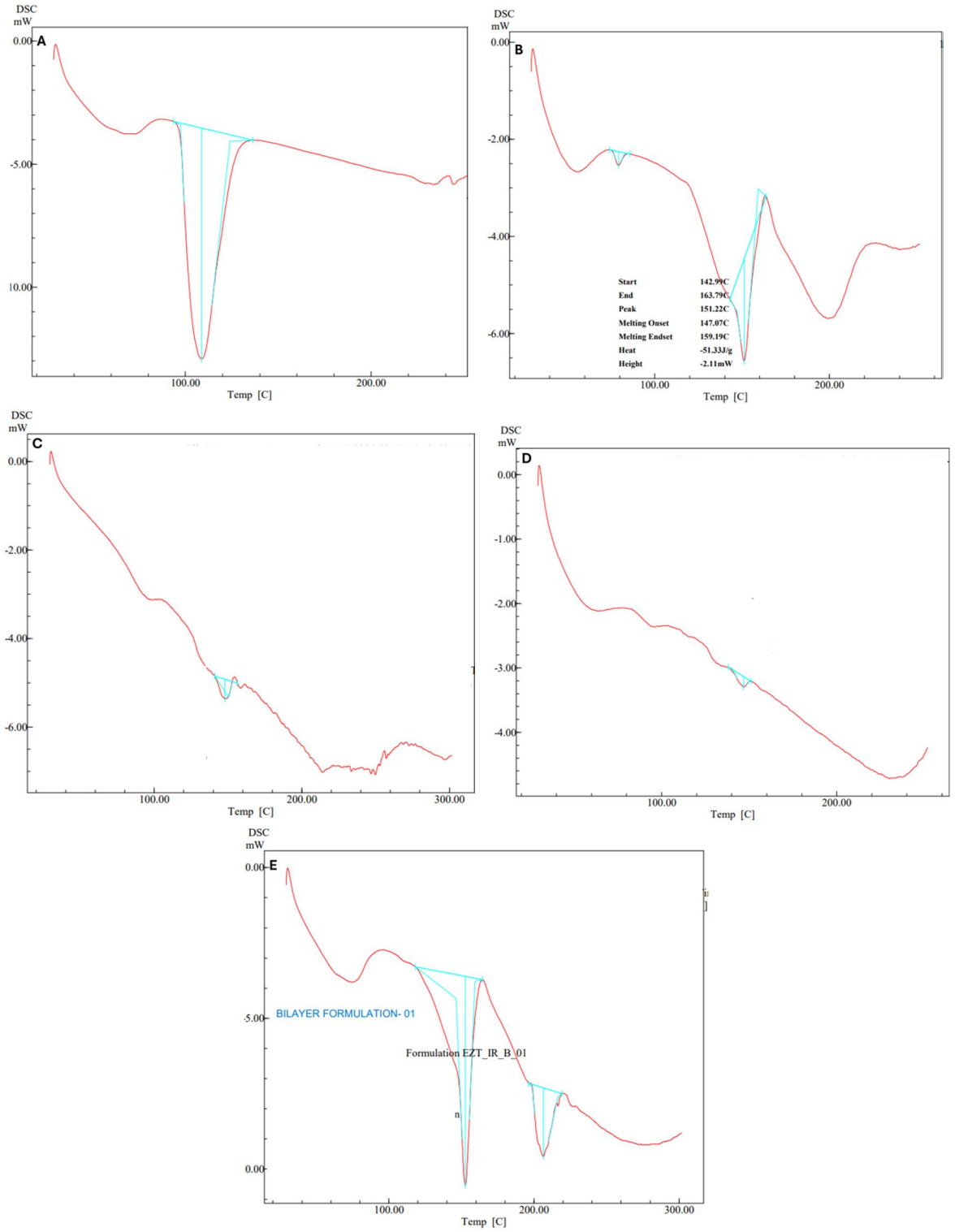

Figure 2. DSC thermographs of A) pure ezetimibe, B) ezetimibe with excipients, C) pure rosuvastatin, D) rosuvastatin with excipients and E) combined rosuvastatin and ezetimibe with excipients for bilayer tablets.

Weight variation test: The weights of the sustained-release rosuvastatin tablets and immediate-release ezetimibe tablets were observed within the specified range. The weight of the bilayer tablets was also in the expected range (Table 5). The weight variation was within 1.12% for the bilayer tablets. According to USP, tablets having an average weight of 130 or less, the acceptable range of variation is within ±10%. Again, according to Indian pharmacopeia, the variation limit for tablets weighing 85-250 mg should be ±7.5% (Thakur and Sharma, 2019). So, all the tablets followed the required specifications.

Thickness and diameter: The tablets' thickness and diameter measurements, which is essential for ensuring the consistency and quality of tablet production table 5 (Yadav *et al*., 2014). The diameter and thickness of the rosuvastatin and ezetimibe are found in the specific range by the USP guidelines.

Hardness test: The tablets' hardness were evaluated using the YD-1A Hardness Tester device. (Table 5) Maintaining a hardness range of 6–9 kg is necessary to decrease friability and optimize the disintegration period. F1-F6 formulations of rosuvastatin are within the required range. All of the ezetimibe formulations had hardness between 4.958 and 6.134. The value of RSD for each formulation is less than 3%. Usually, immediate-release formulations should have a 3-9 kg hardness. So, all the formulations have sufficient hardness for better disintegration with suitable rigidity.

Friability test: Tablets of all the formulations had friability within 1%, within the limit and the standard deviation was less than 1% (Table 5). The friability of the bilayer tablets was about 0.32%.

Table 5. Post-compression parameters of the sustained-release formulations of rosuvastatin.

Formulations	Average weight ± SD, mg	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	203 ±1.4	7.02 ± 0.01	3.74 ± 0.01	6.4 ± 0.14	0.71 ± 0.15
F2	205.5 ± 0.7	7.04 ± 0.01	3.78 ± 0.01	6.15 ± 0.21	0.63 ± 0.32
F3	198.5 ± 0.7	7.03 ± 0.04	3.82 ± 0.04	5.9 ± 0.14	0.64 ± 0.18
F4	191 ± 1.4	6.95 ± 0.07	3.79 ± 0.01	7.9 ± 0.14	0.65 ± 0.17
F5	198 ± 1.4	7.03± 0.03	3.81 ± 0.01	8.35 ± 0.21	0.77 ± 0.05
F6	200.5 ± 0.7	7.06 ± 0.02	3.82 ± 0.01	8.0 ± 1.41	0.58 ± 0.12
F7	204.5 ± 2.1	7.01 ± 0.01	3.76 ± 0.02	3.75 ± 1.06	0.71 ± 0.22
F8	196.5 ± 0.7	7.03 ± 0.01	3.74 ± 0.01	4.4 ± 0.14	0.69 ± 0.21
F9	203.5 ± 0.7	7.03 ± 0.01	3.76 ± 0.01	5.4 ± 0.84	0.72 ± 0.25

Table 6. Post-compression parameters of the immediate-release formulations of ezetimibe.

Formulations	Average weight ± SD, mg	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	105.1 ± 1.9	6.46 ± 0.42	3.16 ± 0.83	5.1 ± 0.14	0.67 ± 0.16
F2	106.5 ± 2.1	6.46 ± 0.77	3.17± 0.66	4.9 ± 0.13	0.71 ± 0.5
F3	107 ± 2.2	6.45 ± 0.58	3.18 ± 0.63	5.6 ± 0.12	0.63 ± 0.32
F4	108 ± 0.6	6.44 ± 0.29	3.18 ± 0.44	5.1 ± 0.12	0.61 ± 0.13
F5	109 ± 0.7	6.43 ± 0.31	3.13 ± 0.53	6.3 ± 0.16	0.49 ± 0.23
F6	104 ± 1.4	6.42 ± 0.44	3.16 ± 0.75	5.8 ± 0.19	0.53 ± 0.22

Disintegration time: The four prepared tablets of each formulation were timed to disintegrate and the results were recorded (Table 7). The disintegration time is a crucial parameter to evaluate how quickly the tablets break down in a physiological environment, impacting their effectiveness and bioavailability. The sustained release tablet of rosuvastatin showed disintegration time within 10-30 min. The disintegration time of the immediate-release tablets should be within 2.5-10 minutes (Sharma and Sonawane, 2017). All the formulations of ezetimibe have favorable disintegration times between 4.023 and 7.112 and a standard deviation between 0.75-1.073. So, all of the formulations had proper disintegration time for better release.

In vitro dissolution study: Using a UV-vis spectrophotometer (Shimadzu 1700, Shimadzu Corp, Kyoto, Japan) in comparison to a blank PH 6.8 phosphate buffer, the absorbance of the rosuvastatin and ezetimibe dissolution samples were analyzed at different time points (Yadav et al., 2014). The dissolution study was performed for 6 hours for rosuvastatin sustained-release formulations and 1 hour for ezetimibe immediate-release formulations. The study was conducted for 6 hours for the bilayer tablets.

Table 7. Disintegration time of the tablets.

Rosuvastatin		Ezetimibe	
Formulation	Time (min)	Formulation	Time (min)
F1	22.85 ± 0.64	F1	5.412±0.763
F2	18.5 ± 0.14	F2	4.543±0.642
F3	18.93 ± 0.53	F3	4.812±0.512
F4	20.95 ± 0.78	F4	4.023 ± 0.386
F5	30.53 ± 0.11	F5	7.112 ± 1.073
F6	11.61 ± 0.71	F6	5.512 ± 0.755
F7	16.62 ± 0.54		
F8	21.57 ± 0.61		
F9	12.97 ± 0.38		

Avg ± SD, n = 4

Table 8. The dissolution study of rosuvastatin. The study of nine formulations is shown in two fragments below.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	25.0 ± 0.62	26.71±1.50	26.87±0.15	18.31±0.47	23.45±1.56	18.32±1.73	22.87±0.75	17.72±0.20	25.70±1.20
20	31.93±0.86	31.76±2.67	31.00±0.62	19.27±0.56	30.55±0.95	25.06±0.82	30.99±0.81	19.99±0.77	31.0±0.34
30	32.71±1.19	48.13±0.72	31.82±1.17	22.06±0.55	31.6±1.62	26.650±.93	31.39±1.05	21.26±0.40	46.68±1.32
45	35.26±0.55	51.22±1.63	35.44±0.60	25.87±1.56	32.99±0.61	32.38±2.92	34.54±0.79	25.05±0.70	50.95±1.14
60	44.81±1.18	56.78±1.38	42.66±1.55	31.55±1.4	41.59±1.32	37.38±1.54	42.26±0.11	31.50±1.33	55.20±0.78
90	47.82±1.19	57.83±0.07	46.30±0.67	34.38±0.84	47.59±0.33	42.62±1.61	45.95±1.17	33.35±0.68	58.12±0.32
120	56.15±0.24	66.66±1.42	57.28±0.82	42.1±2.05	56.13±0.38	49.06±1.01	55.04±0.26	43.37±2.12	66.33±0.63
180	71.03±0.23	77.91±1.19	71.39±1.85	53.01±0.63	71.92±1.7	63.01±0.75	72.31±0.90	51.94±0.70	76.32±1.88
360	89.77±3.12	90.43±1.11	89.34±0.94	68.21±0.48	86.94±2.58	69.9±0.62	88.75±2.08	68.69±1.21	89.27±1.48

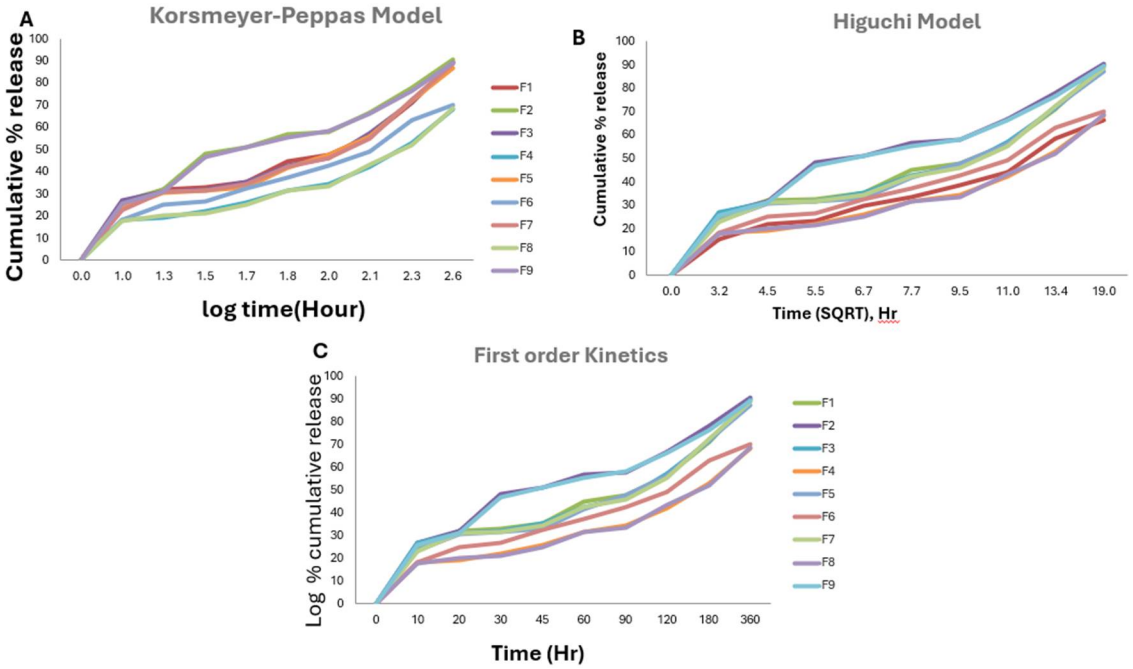

Figure 3. Mathematical release model of rosuvastatin, A) Korsmeyer-Peppas model, B) Higuchi model and C) First order kinetics model.

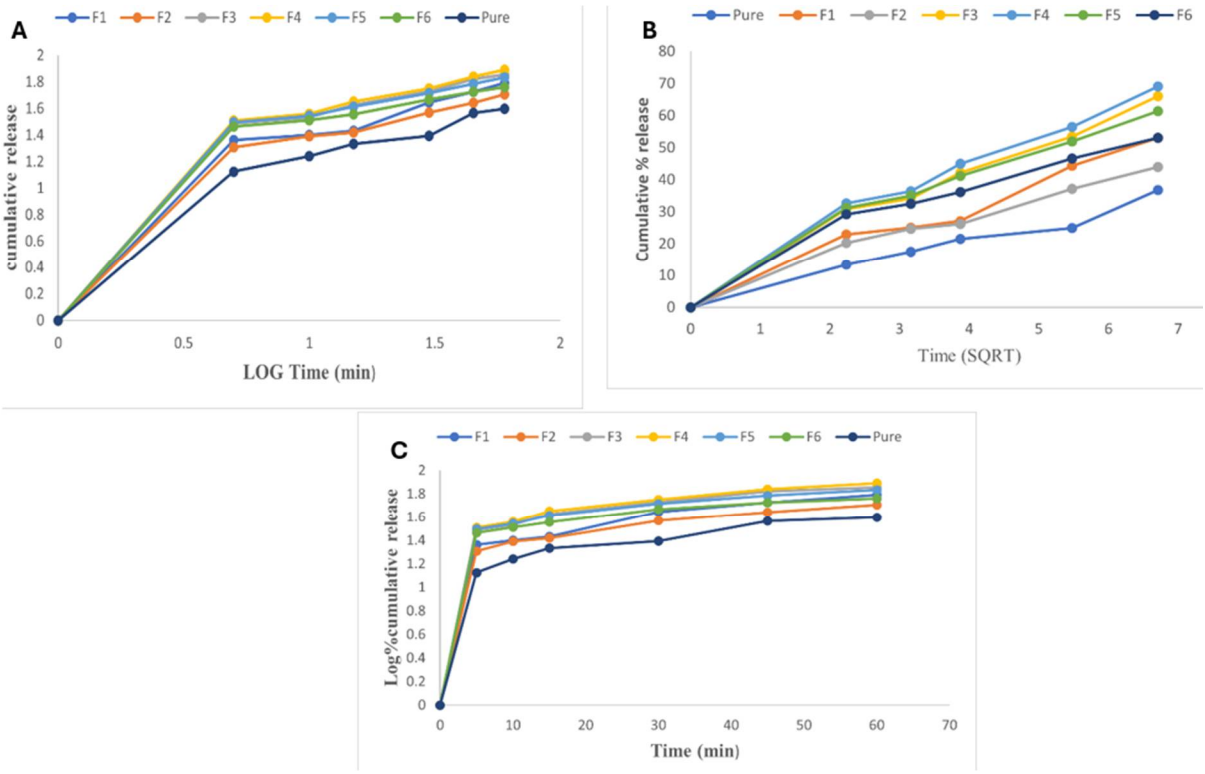

Figure 4: Mathematical release model of ezetimibe, A) Korsmeyer-Peppas model, B) Higuchi model and C) First order kinetics model.

Table 9. Dissolution study of ezetimibe immediate release tablets.

Time(min)	F1	F2	F3	F4	F5	F6
5	22.97±0.12	20.28±0.32	30.81±0.54	32.40±0.12	31.25±0.63	29.24±0.04
10	25.11±0.69	24.65±0.65	34.14±0.73	36.44±0.01	35.01±0.13	32.54±0.03
15	27.14±0.87	26.24±0.87	42.24±0.89	44.98±0.21	41.22±0.45	36.14±0.42
30	44.39±0.02	37.22±0.11	53.37±0.46	56.46±0.13	51.88±0.53	46.68±0.52
45	53.11±0.09	44.00±0.39	66.04±0.21	69.02±0.05	61.32±0.05	53.00±0.82
60	62.23±0.38	50.97±0.52	71.69±0.35	78.02±0.02	68.09±0.17	57.74±0.63

The F4, F6 and F8 formulations of rosuvastatin sustained-release formulations showed about 70% release within 6 hours, whereas other formulations showed a release of 80-90% of release (Table 8; Figure 3).

Among the ezetimibe immediate-release formulations, F3 and F4 showed a good release profile of 70% within 1 hour (Table 9; Figure 4). These results indicate that cross-povidone was most effective in accelerating the release of ezetimibe.

Based on the dissolution data, the release rates were studied with different mathematical models, i.e., Higuchi, Korsmeyer-Peppas and first-order kinetics models. The best R^2 was observed with F4 of ezetimibe and F2 of rosuvastatin.

The solubility of ezetimibe was improved by using different super disintegrants in the immediate-release formulations. We observed the most promising results with the F4 formulation of ezetimibe having cross-povidone. The order of release rate was observed to be F4 > F3 > F1 > F5 > F2 > F6. Our results are consistent with studies by Rajesh *et al.*, 2010; Karim *et al.*, 2015; Rani and Muzib, 2020. The formulation F2 of rosuvastatin containing methocel K100M (20 mg) demonstrated a drug release of 90.484% within 6 hours. This significant release profile underscores the formulation's efficacy in achieving sustained drug release. Additionally, other formulations, including F1, F3, F7 and F9, also exhibited drug release rates exceeding 80%, further confirming the effectiveness of these sustained release formulations in providing controlled and prolonged drug release. Comparative analysis of the dissolution profiles of these formulations against the pure drug dissolution revealed substantial enhancements in drug solubility and release rates. These improvements were notably influenced by incorporating varying polymer ratios (1:1, 1:2 and 1:3 drug-to-polymer ratios) in the formulations, particularly in F1, F2, F3, F7, F8 and F9. The modulation of polymer ratios highlights the potential to fine-tune drug release profiles, allowing for the development of customized drug delivery systems that offer more effective and controlled release. Incorporation of the best formulation of immediate-release ezetimibe and sustained-release rosuvastatin ensures a rapid onset of anti-hypercholesterolemic action for prolonged duration.

Conclusion

In conclusion, the formulation of bilayer tablets combining rosuvastatin and ezetimibe presents a promising strategy for effectively managing hypercholesterolemia and hyperlipidemia, critical risk factors for cardiovascular disease. By leveraging the distinct mechanisms of action of these two medications, this approach aims to optimize lipid profiles and enhance patient adherence through a convenient dosing regimen. The anticipated reduction in LDL-C levels and subsequent decrease in cardiovascular events underscores the potential clinical significance of this formulation. Future studies will be essential to validate the efficacy and safety of this combined therapy, paving the way for improved therapeutic options in the fight against cardiovascular disease.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

Baratam, S.R. and Ratnam, B.V. 2018. Formulation and optimization of sustained release tablets of rosuvastatin using HPMC K4M, HPMC K100M and carrageenan. *Int. J. ChemTech Res.* **11,** 376-386.

Bellosta, S. and Corsini, A. 2012. Statin drug interactions and related adverse reactions. *Expert Opin. Drug Saf.* **11**, 933-946.

Fazio, S. and Linton, M.F. 2004. The role of fibrates in managing hyperlipidemia: mechanisms of action and clinical efficacy. *Curr. Atheroscler. Rep.* **6**, 148-157.

Filip, K., Bańkowski, K., Sidoryk, K., Zagrodzka, J., Łaszcz, M., Trzcińska, K. and Maruszak, W. 2011. Physicochemical characterization of ezetimibe and its impurities. *J. Mol. Struct*. **991,** 162–170.

Gardouh, A.R., Nasef, A.M., Mostafa, Y. and Gadet, S. 2020. Design and evaluation of combined atorvastatin and ezetimibe optimized self-nano emulsifying drug delivery system. *J. Drug Delivery Sci. Technol.* **60,** 102093.

Górniak, A., Złocińska, A., Trojan, M., Pęcak, A. and Karolewicz, B. 2022. Preformulation studies of ezetimibe-simvastatin solid dispersions in the development of fixed-dose combinations. *Pharmaceutics* **14**, 912.

González, R., Peña, M.Á., Torres, N.S., and Torrado, G. 2022. Design, development, and characterization of amorphous rosuvastatin calcium tablets. *PLoS One* **17,** e0265263.

Grigore, L., Norata, G.D. and Catapano, A.L. 2008. Combination therapy in cholesterol reduction: focus on ezetimibe and statins. *Vasc. Health Risk Manage.* **4**, 267-278.

Islam, A.M., Mohibullah, A. and Paul, T. 2016. Cardiovascular disease in Bangladesh: a review. *Bangladesh Heart J*. **31**, 80-99.

Karim, S., Bhuiyan, M.A., and Rana, M.S. 2015. Formulation and *in vitro* evaluation of glimepiride sustained release tablets: comparison with immediate release tablets. *Bangladesh Pharm. J.* 18, 157-162.

Kim, K.J., Kim S.H., Yoon Y.W., Rha S.W., Hong S.J., Kwak C.H., Kim W., Nam C.W., Rhee M.Y., Park T.H., Hong T.J., Park S., Ahn Y., Lee N., Jeon H.K., Jeon D.W., Han K.R., Moon K.W., Chae I.H. and Kim H.S. 2016. Effect of fixed-dose combinations of ezetimibe plus rosuvastatin in patients with primary hypercholesterolemia: MRS-ROZE (Multicenter Randomized Study of ROsuvastatin and eZEtimibe). *Cardiovasc. Ther*. **34**, 371-382.

Kosmas, C.E., Estrella, A.M., Skavdis, A., Genao, E.P., Martinez, I. and Guzmanet, E. 2020. Inclisiran for the treatment of cardiovascular disease: a short review on the emerging data and therapeutic potential. *Ther. Clin. Risk Manage*. **16**, 1031-1037.

Kumar, P.T., Mishra, J. and Podder, A. 2016. Design, fabrication and evaluation of rosuvastatin pharmacosome – a novel sustained release drug delivery system. *Eur. J. Pharm. Med. Res*. **3,** 332-350.

Lee, J., Hwang Y.C., Lee W.J., Won J.C., Song K.H., Park C.Y., Ahn K.J. and Park J.Y. 2020. Comparison of the efficacy and safety of rosuvastatin/ezetimibe combination therapy and rosuvastatin monotherapy on lipoprotein in patients with type 2 diabetes: multicenter randomized controlled study. *Diabetes Ther*. **11**, 859-871.

Miettinen, T.A. 2001. Cholesterol absorption inhibition: a strategy for cholesterol-lowering therapy. *Int. J. Clin. Pract*. **55**, 710-716.

Momin, M.M., Kane, S. and Abhang, P. 2015. Formulation and evaluation of bilayer tablet for bimodal release of venlafaxine hydrochloride. *Front. Pharmacol*. **6,** 144.

Morrone, D., Weintraub, W.S., Toth, P.P., Hanson, M.E., Lowe, R.S., Lin, J., Shah, A.K. and Tershakovec A.M. 2012. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. *Atherosclerosis* **223**, 251-261.

Mubeen, I., Zaman, M., Farooq, M., Mehmood, A., Azeez, F.K., Rehman, W., Akhtar, S., Chaudhry, M.A., Butt, M.H., Shamim, Q., Adnan, S., Khan, M.R. and Rehmanet, A. 2022. Formulation of modified-release bilayer tablets of atorvastatin and ezetimibe: an *in-vitro* and *in-vivo* analysis. *Polymers* **14**, 3770.

Parimoo, P. 2007. *Pharmaceutical Analysis*. CBS Publishers and Distributors., New Delhi, p. 335.

Poels, K., van Leent, M.M.T., Reiche, M.E., Kusters, P.J.H., Huveneers, S., de Winther, M.P.J., Mulder, W.J.M., Lutgens, E. and Seijkenset, T.T.P. 2020. Antibody-mediated inhibition of CTLA4 aggravates atherosclerotic plaque inflammation and progression in hyperlipidemic mice. *Cells* **9**, 1987.

Prajapati, P., Pandey, J., Shimpi, M.R., Srivastava, A., Tandon, P., Velaga, S.P. and Sinha, K. 2016. Combined spectroscopic and quantum chemical studies of ezetimibe. *J. Mol. Struct.* **1125,** 193-203.

Rajesh, Y.V., Rekha, N.B. and Newton, A.M.J. 2010. Role of type and concentration of superdisintegrants on immediate release tablets of ezetimibe starch tartrate as novel superdisintegrant in formulation and evaluation of fast disintegrating telmisartan tablets. *Int. J. Adv. Pharm. Sci.* **1,** 264-280.

Rani, T.N. and Muzib, Y.I. 2020. Formulation and *in vitro* evaluation of ezetimibe rapid melts. *Asian J. Pharm. Clin. Res*. **13,** 97-103.

Reith, C., Baigent, C., Blackwell, L., Emberson, J., Spata, E., Davies, K., Halls, H., Holland, L., Wilson, K., Armitage, J., Harper, C., Preiss, D., Roddick, A., Keech, A., Simes, J. and Collins R. 2022. Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomised, double-blind trials. *Lancet* **400**, 832-845.

Robinson, J.G. and Davidson, M.H. 2006. Combination therapy with ezetimibe and simvastatin to achieve aggressive LDL reduction. *Expert Rev. Cardiovasc. Ther*. **4**, 461-476.

Sadhana, N., Praveen, B.V.S, Jyothi, G. and Vishnu, P. 2023. Design and evaluation of nanostructured formulations of rosuvastatin. *Mater. Today: Proc*. **72,** 465-470.

Sharma, S. N. and Sonawane, R. S. 2017. Role of superdisintegrants in immediate release tablets: a review. *J. Pharm. BioSci*. **5,** 1-5.

Stancu, C. and Sima, A. 2001. Statins: mechanism of action and effects. *J. Cell. Mol. Med*. **5**, 378-387.

Stroes, E. 2005. Statins and LDL-cholesterol lowering: an overview. *Curr. Med. Res. Opin.* **21**, S9-S16.

Thakur, D. and Sharma, R. 2019. Solid dispersion a novel approach for enhancement of solubility and dissolution rate: a review. *Indian J. Pharm. Biol. Res*. **7,** 05–11.

Yadav, G., Chand, T. and June, A. 2014. Formulation and optimization evaluation of floating tablet of ofloxacin. *Res. J. Pharm., Biol. Chem. Sci*. **4,** 590–597.

Yang, Y.J., Lee, S.H., Kim, B.S, Cho, Y.K., Cho, H.J., Cho, K.I., Kim, S.Y., Ryu, J.K., Cho, J.M., Park, J.I., Park, J.S., Park, C.J., Chun, W.J., Kim, M., Jin, D.L., Lee, N., Kim, B.J., Koh, K.K., Suh, J., Lee, S.H., Lee, B.K., Oh, S.J., Jin, H.Y., Ahn, Y., Lee, S.G., Bae, J.H., Park, W.J., Lee, S.C., Lee, H.C., Lee, J., Park, C., Lee, B. and Jang, Y. 2017. Combination therapy of rosuvastatin and ezetimibe in patients with high cardiovascular risk. *Clin. Ther.* **39**, 107-117.

Zhao, D. 2021. Epidemiological features of cardiovascular disease in Asia. *JACC: Asia* **1**, 1-13.