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Research Article

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Optimization and Evaluation of Immediate Release Tablet in combination of Ezetimibe and Simvastatin drugs

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Abstract

Hypercholesterolemia disease treatment with HMG-CoA reductase inhibitors has been very successful. The purpose of this study was to assess the efficacy and safety of ezetimibe administered with simvastatin in patients with primary hypercholesterolemia. This paper will examine two of the more popular secondary agents, ezetimibe and Simvastatin and describe their research data and potential for usefulness in further reducing hypercholesterolemia. This study was performed with the intention of finding the effect of preparation methods on the solubility and dissolution of Simvastatin by using the surfactant. The complexes were prepared by wet granulationation and Spray drying techniques. The formulations were evaluated for phase solubility and in-vitro release study. The formulations were also subjected for physicochemical characterizations

Key words: Ezetimibe, Simvastatin, Propyl gallate, Butylated Hydroxy Anisole, Polysorbate 80, Sodium Laurvl sulphate.

Introduction

Intoduction to Immediate Release Formulation

Many formulations are formulated to release the drug as quickly as possible after tacking dosage form. This formulation is use when quick onset of action is necessary for therapeutic response. IR allows the active ingredient to dissolve in the GI contents, with no of delaying the dissolution or absorption of the drug.

1.3.1 Definition

The term “immediate release” is P’ceutical preparation includes any preparation in which the release rate of API from the formulation and the absorption of API, is never reduce by galenic manipulations[1]. Immediate release delivery systems give a quick onset of action and to produce therapeutic activity the drug should be in solution, so

disintegration of the formulation and dissolution of the drug may have to occur first depending on the dosage form. IRsystems usually release the drug in a single action following a first order kinetics profile. The action of the drug is limited to the time that the concentration of the drug is above the MEC.

1.3.2 Desired Criteria for Immediate Release Drug Delivery System

Immediate release solid dosage forms have following criteria.

1. Ii should dissolve or disintegrate in short time in stomach.
2. It should not remain in the mouth after oral administration.
3. Having less sensitivity to atmospherelike humidity and temperature.
4. Preparedby use of ordinary process and packaging equipment at low cost.
5. It should have quick dissolution and absorption of active ingredient, which produce quick action.

Immediate release is indicating that the release of the active ingredient is faster than the release from a sustained release formulation. Drug has a less solubility in an acidic medium having a pH of from 1 to 3 i.e. pH relating to the stomach pH. The traditional formulations are lead for giving proper drug disintegration but not required that provide proper dissolution of drug under acidic condition means that plain tablet having the ability for proper disintegration in media but the drug is not dissolve in media due to property of itself. The absorption ability of drug i.e. entry of drug in to the circulating system which depend on the dissolved drug because only dissolved drug or substance are able to pass through mucous membrane in GIT. So it is necessary that the dissolution of drug is fast also in acidic media due to this fast absorption becomes possible so real immediate therapeutic response produce.

1.3.3 Immediate Release Tablets: [2,3,4]

Immediate release tablets are designed or developed to disintegrate and release of drug with no special rate controlling property, such as special coating and any other method.

Now a day's immediate release tablet become most popular and acceptable drug delivery system, because of easy administration, having rapid onset of action, economical for manufacturing and having better patient compliance.

Ideal candidates for Immediate Release Dosage Form:

1. Disintegrates and dissolves within a few minutes.
2. Has sufficient strength to withstand the rigors of the manufacturing process and Post-manufacturing handling.
3. Allow high drug loading.
4. Insensitive to environmental conditions such as humidity and temperature.
5. Adaptable and amenable to existing processing and packaging machineries.

Advantages

- Economical and cost effective.
- Quick on set of action.
- Suitable for industrial production.
- Improved stability and bioavailability.

Disadvantages

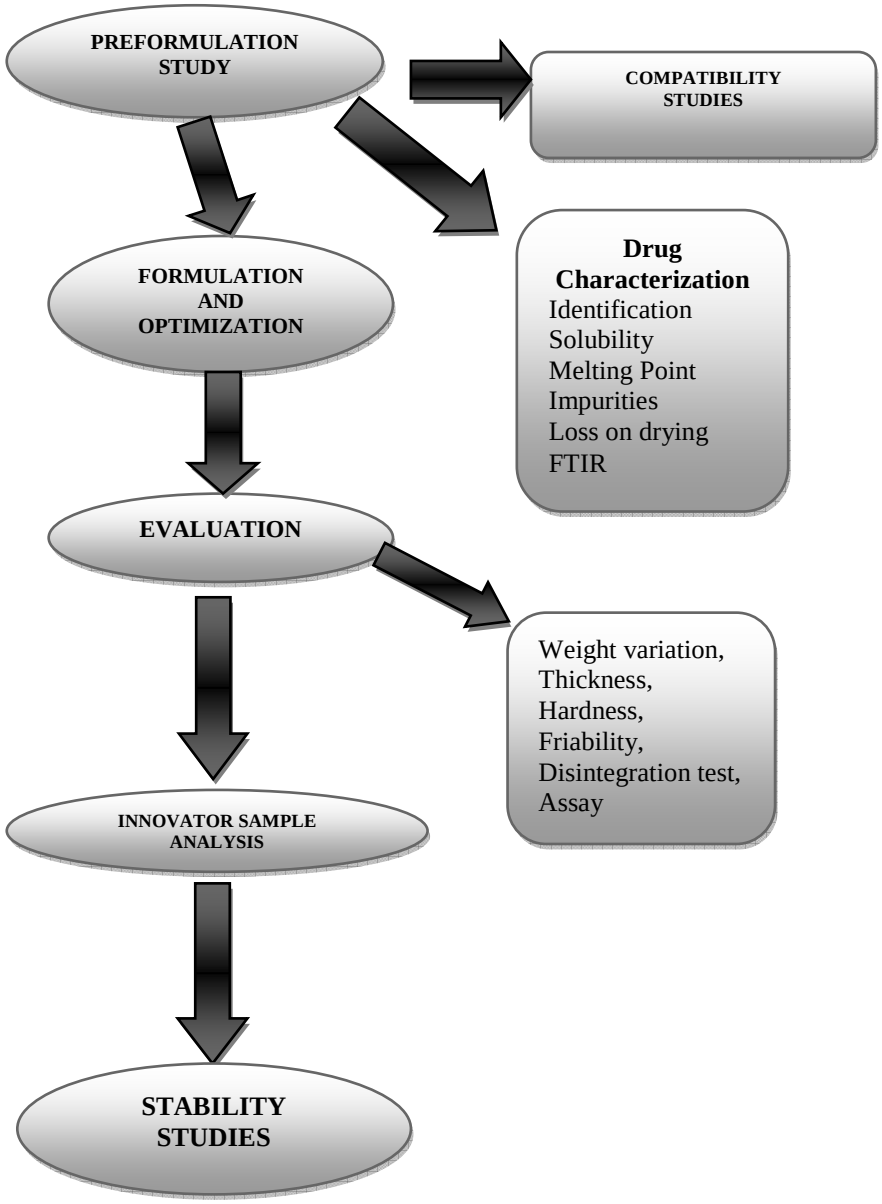
- Sometime may require more frequency of administration.
- Dose dumping may occur.
- Decrease the potential for accurate dose adjustment.

Material and Methods

Materials for component selection:

Ezetimibe and Simvastatin drug was a gift sample from Torrent pharmaceutical limited, Ahmadabad (Gujarat, India). Lactose monohydrate, Pregelatinized starch, Croscarmellose sodium, Butylated hydroxyl anisole,Propyl gallate,Ethanol,Citric acid monohydrate was gift sample from Leon chemicals, Bangalore, India and HPMC 3 CPS, Polysorbate 80,Microcrystalline cellulose (pH 102),Sodium lauryl sulfate were gift samples from S.D. Fine Chem. Ltd, Mumbai, India. All other chemicals were of analytical grade.

3. Methodology



Preformulation Studies

Assay (By HPLC)

Assay of both drugs was done by HPLC method.

Chromatography system:

1. High performance liquid chromatograph equipped with variable wavelength detector and integrator.
2. COLUMN: Zorbax Eclipse plus C18 (50 X 4.6mm) 5µ
3. FLOW RATE: 1.2 mL/minute
4. WAVE LENGTH: 230nm
5. INJECTION VOLUME : 20µL
6. COLUMN TEMPERATURE: 25°C

Buffer: Dissolve about 6.8 g of potassium dihydrogen phosphate into a 950 mL of water. Adjust a pH 3.00 with phosphoric acid and dilute to volume up to 1000 mL with water and filter through 0.45 µ Nylon filter.

Mobile phase: Prepare a mixture of 400 volume of buffer and 600 volume of Acetonitrile.

Diluent: Prepare a mixture of 250 mL of Water and 750 volume of Acetonitrile.

Drug Ezetimibe standard preparation:

Transfer about 50.0 mg of Ezetimibe in to 50 mL volumetric flask. Add about 25 mL of diluent, dissolve and dilute to volume with diluent and mix well. Dilute 5 mL with 100 mL diluent in volumetric flask and mix well.

DrugEzetimibesample preparation:

Transfer about 50.0 mg of Drug Ezetimibe in to 50 mL volumetric flask. Add about 25 mL of diluent, dissolve and dilute to volume with diluent and mix well. Dilute 5 mL with 100 mL diluent in volumetric flask and mix well.

Drug Simvastatin standard stock preparation:

Dissolve accurately weight quantity of Drug Simvastatin in diluent to obtain a solution having a known concentration of about 1.5mg per mL.

DrugSimvastatin sample stock preparation:

Transfer about 75.0 mg of Drug simvastatin in to 50 mL volumetric flask. Add about 25 mL of diluent, dissolve and dilute to volume with diluent and mix well.

Procedure: Separately inject duplicate injection of sample preparation in to liquid chromatography and record chromatograms.

Calculate the assay of Drug Ezetimibe and Drug Simvastatin in percentage of label claim using following formula.

For Drug Ezetimibe

$$\frac{Au}{As} \times \frac{W_1}{50} \times \frac{5}{100} \times \frac{50}{W_2} \times \frac{100}{5} \times \frac{P}{100} \times 100$$

Where,

Au = Mean peak area due to Drug Ezetimibe obtained with assay preparation

As = Mean peak area due to Drug Ezetimibe obtained with standard preparation

W_1 = Weight of Drug Ezetimibe working standard taken in mg

W_2 = Weight of sample taken in mg

P = Potency of Drug Ezetimibe working standard in percentage

For Drug Simvastatin

$$\frac{Au}{As} \times C \times \frac{50}{W_2} \times \frac{P}{100} \times 100$$

Where,

Au = Mean peak area due to Drug Simvastatin obtained with assay preparation

As = Mean peak area due to Drug Simvastatin obtained with standard preparation

C = concentration of Drug Simvastatin in mg per mL in standard prepartion

W_2 = Weight of sample taken in mg in test prepartion

P = Potency of Drug Ezetimibe working standard in percentage

1.2. Potency calculation

Potency calculation was done. To calculate the exact amount of drug, this should be taken during dispensing for making tablet. Potency can be calculated as per equation:

POTENCY = DOSE×100×100 / ASSAY (100−LOD)

Precompression Parameters of developed formulation

Characterization of drugs

1. From powder characteristics like Hausner‘s ratio (1.56) and Carr‘s index (36.0%), Drug Ezetimibe was found to have very poorly compressibility and flow properties.
2. So for the preparation of the tablet wet granulation method was opted for better compression and good flow property. After the step of the granulation, the powder characteristics of the prepared granules would be evaluated.

Table.1 Results of Characterization of Drug Ezetimibe

Sr. No.	Study	Parameter	Results	
1.	Physical nature	State	white Powder	
2.		Color	White	
3.		Odor	Odorless	
4.		Taste	Tasteless	
5.		Melting point	About 163°C	
6.	Chemical nature	LOD	0.11%	
7.		Assay	99.6% (98.0% - 102.0%)	
8.		Potency	10.05%	
9.	Micromeritics	Bulk density	0.200g/ml	
10		Tapped density	0.312g/ml	
11.		Carr's index	36.0%	Very poor flow
12.		Hausner's ratio	1.56	

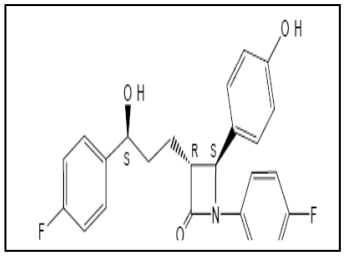
Table.2: Results of Characterization of Drug Simvastatin

Sr. No.	Study	Parameter	Results	
1.	Physical nature	State	Crystalline Powder	
2.		Color	White	
3.		Odor	Odorless	
4.		Taste	Tasteless	
5.		Melting point	135- 138°C	
6.	Chemical nature	LOD	0.10%	
7.		Assay	99.6% (97.0% - 102.0%)	
8.		Potency	80.40	
9.	Micromeritics	Bulk density	0.180g/ml	
10		Tapped density	0.310g/ml	
11.		Carr's index	42.0%	Very poor flow
12.		Hausner's ratio	1.722	

1. From powder characteristics like Hausner's ratio (1.722) and Carr's index (42.0%), Drug simvastatin was found to have very poorly compressibility and flow properties.
2. So for the preparation of the tablet wet granulation method was opted for better compression and good flow property. After the step of the granulation, the powder characteristics of the prepared granules would be evaluated.

1.2: Identification of drugs

1.2.1: FT-IR Spectra of Ezetimibe



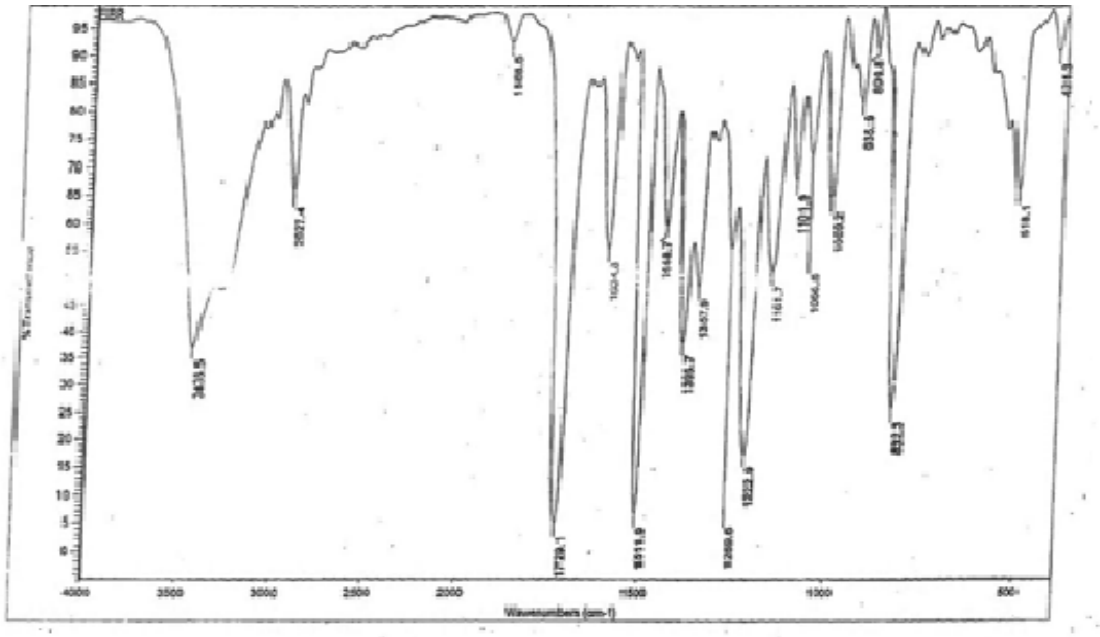
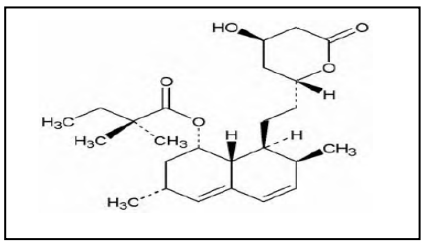


Figure.1 IR Spectra of Pure drug (Ezetimibe)

Table.3: Characteristic Peaks Found in IR Spectra of Ezetimibe

Wave number (cm^{-1})	Assignment	Mode of Vibration
3435.5	O-H	Stretching
2927.4	Aromatic C-H	Stretching
1729.1	-C=O	Stretching
1511.9	Aromatic C=C	Stretching
1222.9	C-O	Stretching
1101.9	C-F	Stretching
832.3	Aromatic C-H	Bending
1357.9	C-N	Stretching

1.2.2: FT-IR Spectra of Simvastatin



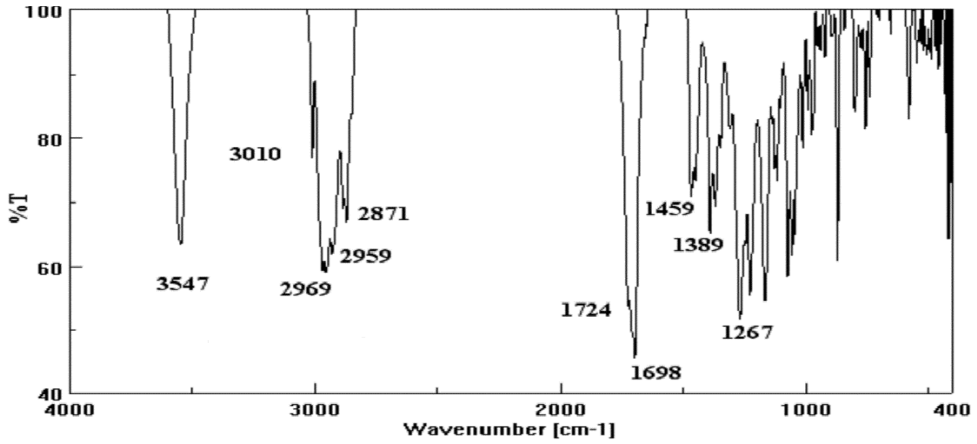


Figure 13.2: IR Spectra of Pure drug (Simvastatin)

Table 4: Characteristic Peaks Found in IR Spectra of Simvastatin

Wave number (cm^{-1})	Assignment	Mode of Vibration
3547	O-H	Stretching
2969	C-H	Stretching
2959	C-H	Stretching
2871	Aromatic C-H	Stretching
1724	C=O	Stretching
1698	Aromatic C=C	Stretching
1459	C-H	Bending
1389	C-H	Bending
1267	-O-	Stretching

1.3: pH Solubility Profile

Table 5: pH Solubility profile of Ezetimibe

Sr.No.	Medium	Solubility mg/ml	Sink conditions
1	0.1N HCl	0.0000	No
2	0.1N HCl+0.45%SLS	0.0380	YES
3	Glycine buffer pH 3.0	0.0000	No
4	Glycine buffer pH 3.0+0.45%SLS	0.0550	YES
5	Acetate buffer pH 4.5	0.0000	No
6	0.05M Acetate buffer pH 4.5	0.0000	No
7	0.25%SLS in 0.05M Acetate buffer pH 4.5	0.0280	No
8	0.45%SLS in 0.05M Acetate buffer pH 4.5	0.0390	YES
9	Phosphate buffer pH 7.0	0.0000	No
10	Phosphate buffer pH 7.0+0.5%SLS	0.0450	YES

Sink condition are achived if solubility is above 0.033mg/ml.

Conclusion: Both the drugs are insoluble in all media. So, SLS is required to achieve to solubility and sink condition.

Drug-Excipients Compatibility Study

Physical observation study

There was no physical changes occurs in any blend of drug and excipients and also no changes occurs in assay of drugs, therefore it could be concluded that there was no interaction occurs between drug and any excipients and would be used for preparation of immediate release tablet.

Table.7: Results of drug excipient compatibility study for Drug Ezetimibe

DRUG:EXCIPIENT	PARAMETERS	INITIAL	1 MONTH
Drug Ezetimibe	Appearance	White powder	NC
	% Assay of drug	99.86	99.78
(simvastatin + Ezetimibe)(A)	Appearance	White powder	NC
	% Assay of drug	99.86	99.89
A + Lactose monohydrate	Appearance	White powder	NC
	% Assay of drug	99.88	99.84
A + Starch 1500	Appearance	White powder	NC
	% Assay of drug	99.83	99.89
A + Butylated hydroxyl Anisole	Appearance	White powder	NC
	% Assay of drug	99.78	98.02
A + Ascorbic acid	Appearance	White powder	NC
	% Assay of drug	99.90	99.87
A + citric acid	Appearance	White powder	NC
	% Assay of drug	99.89	97.46
A + Croscarmellose sodium	Appearance	White powder	NC
	% Assay of drug	99.86	99.85
A + MCC PH 102	Appearance	White powder	NC
	% Assay of drug	99.88	99.85
A + Magnesium Stearate	Appearance	White powder	NC
	% Assay of drug	99.87	99.89
A + Tween 80	Appearance	White powder	NC
	% Assay of drug	98.92	93.95
A + SLS	Appearance	White powder	NC
	% Assay of drug	99.88	99.89

Table: 8: Results of drug excipient compatibility study for Drug Simvastatin

DRUG:EXCIPIENT	PARAMETERS	INITIAL	1 MONTH
Simvastatin	Appearance	White crystalline powder	NC
	% Assay of drug	98.92	98.94
(Simvastatin + Ezetimibe)(A)	Appearance	White crystalline powder	NC
	% Assay of drug	98.92	98.94
A + Lactose monohydrate	Appearance	White crystalline powder	NC
	% Assay of drug	98.92	98.84
A + Starch 1500	Appearance	White crystalline powder	NC
	% Assay of drug	98.95	98.94
A + Butylated hydroxyl Anisole	Appearance	White crystalline powder	NC
	% Assay of drug	98.23	98.62

A + Ascorbic acid	Appearance	White crystalline powder	NC
	% Assay of drug	98.91	98.94
A + citric acid	Appearance	White crystalline powder	NC
	% Assay of drug	98.95	98.46
A + Croscarmellose sodium	Appearance	White crystalline powder	NC
	% Assay of drug	98.92	98.94
A + MCC PH 102	Appearance	White crystalline powder	NC
	% Assay of drug	98.91	98.92
A + Magnesium Stearate	Appearance	White crystalline powder	NC
	% Assay of drug	98.92	98.93
A + Tween 80	Appearance	White crystalline powder	NC
	% Assay of drug	98.91	98.64
A + SLS	Appearance	White crystalline powder	NC
	% Assay of drug	98.92	98.92

***Conclusion:-**From the Analytical Assay,it can be concluded that Ezetimibe and Simvastatin are compatible with studied Excipients when stored at 40^0C/75%RH in open condition for 30 days. No significant change is observed.

13.1.5: Hygroscopicity studies

This study was done to check the hygroscopic nature of drug.

Table.13.9 Result for hygroscopicity of Drug Ezetimibe

Exposure	**LOD (%w/w) at 105°C Storage condition (40°C/75%RH)**	**LOD (%w/w) at 105°C Storage condition (25°C/65%RH)**
Initial	0.77%	0.77%
1 hr	3.61%	2.42%
2 hr	4.13%	3.20%
4 hr	4.36%	3.52%
8 hr	4.46%	4.07%
24 hr	4.86%	4.25%

Table. Result for hygroscopicity of Drug Simvastatin

Exposure	**LOD (%w/w) at 105°C Storage condition (40°C/75%RH)**	**LOD (%w/w) at 105°C Storage condition (25°C/65%RH)**
Initial	0.64%	0.64%
1 hr	0.68%	0.62%
2 hr	0.68%	0.68%
4 hr	0.70%	0.70%
8 hr	0.71%	0.72%
24 hr	0.70%	0.72%

Conclusion: From above data it can be concluded that Simvastatin did not exhibit any hygroscopic characteristics but Ezetimibe appears to be highly hygroscopic material.

Formulation Development
Precompression Evaluation of Granules
Evaluation of granules ready for compression
(n=3, mean ± S.D.)

Trial No.	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Compressibility index (%)
3-B	0.56 ± 0.02	0.70 ± 0.03	1.25 ± 0.02	19.57 ± 1.00
3-C	0.59 ± 0.02	0.74 ± 0.03	1.26 ± 0.01	20.90 ± 1.20
4.	0.57 ± 0.01	0.71 ± 0.01	1.24 ± 0.02	19.43 ± 1.15
5.	0.58 ± 0.01	0.73 ± 0.02	1.26 ± 0.01	20.52 ± 0.85
6.	0.56 ± 0.02	0.70 ± 0.03	1.25 ± 0.02	19.57 ± 1.00
7.	0.59 ± 0.01	0.74 ± 0.01	1.25 ± 0.02	20.24 ± 1.10
8.	0.57 ± 0.01	0.71 ± 0.01	1.25 ± 0.01	20.14 ± 0.45
9.	0.57 ± 0.02	0.70 ± 0.02	1.24 ± 0.02	19.43 ± 1.15
10.	0.59 ± 0.02	0.74 ± 0.03	1.26 ± 0.01	20.90 ± 1.20
11.	0.59 ± 0.01	0.75 ± 0.02	1.26 ± 0.02	20.63 ± 1.45
12.	0.61 ± 0.02	0.75 ± 0.02	1.24 ± 0.02	19.57 ±1 .75
13.	0.62 ± 0.01	0.76 ± 0.01	1.23 ± 0.01	18.70 ± 0.55

2.2: Post Compression Evaluation of Tablet
2.2.1 Physical characterization of tablets
2.2.1.1 Appearance
Visual examination of tablet from each batch showed white to off white capsule shaped biconvex uncoated tablet debossed with ES4 on one side and plain on other side.
2.2.1.2 Thickness
The mean tablet thickness (n=6) were uniform in all batches with values ranging between 5.60 – 5.85 mm. These values thus indicate uniformity within batch and batch to batch.
2.2.1.3 Weight variation
The average weight of tablet formulations was within the range of 817.19- 822.03 mg. So, all tablets passed weight variation test as the % weight variation was within the Indian Pharmacopoeial limits of 5% of the weight.
2.2.1.4 Hardness
The measured hardness of tablets of each batch ranged between 129 – 168 N. This ensures good handling characteristics of all batches.
2.2.1.5 Friability
The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.
2.2.1.6 Assay
The assay of tablet formulations was within the range of 99.2 – 100.2 %. Therefore, all the batches fall within assay limit 95-105%.

Table:12: Post compression evaluation of tablets

Trial No.	Avg. tablet wt. (mg)	Hardness (N)	Thickness (mm)	Friability (%)
3-B	820.16±1.19	150±8	5.77±0.04	0.034
3-C	819.20±2.16	145±7	5.69±0.07	0.040
4.	819.19 ± 2.64	153 ± 3	5.68 ± 0.05	0.039
5.	817.19 ± 2.64	130 ± 10	5.83 ± 0.09	0.053

6.	820.85 ± 2.28	129 ± 10	5.85 ± 0.07	0.067
7.	819.68 ± 4.41	136 ± 6	5.78 ± 0.06	0.050
8.	821.37 ± 2.32	138 ± 8	5.79 ± 0.09	0.049
9.	821.46 ± 3.28	168 ± 8	5.60 ± 0.10	0.034
10.	819.09 ± 2.97	140 ± 6	5.71 ± 0.05	0.060
11.	820.89 ± 2.25	152 ± 7	5.70 ± 0.06	0.038
12.	822.03 ± 2.82	154 ± 8	5.67 ± 0.08	0.046
13.	820.57 ± 2.60	149 ± 6	5.73 ± 0.07	0.056

Table.13: Mean of Assay

Sr. No.	**% Assay**										**Limit**
Trial No.	4	5	6	7	8	9	10	11	12	13	NLT 95% & NMT 105%
1	99.7	98.3	100.3	99.5	100.5	98.5	100.9	100.7	98.7	100.3	
2	98.9	99.5	99.4	97.9	99.9	99.2	100.2	98.5	100.5	100.6	
3	100.2	99.7	97.9	100.9	98.4	99.7	99.4	100.1	99.9	99.3	
Mean	99.6	99.2	99.2	99.4	99.6	99.1	100.2	99.8	99.7	100.1	
Mini-mum	98.9	98.3	97.9	97.9	98.4	98.5	99.4	98.5	98.7	99.3	
Maxi-mum	100.2	99.7	100.3	100.9	100.5	99.7	100.9	100.7	100.5	100.6	
SD	0.66	0.76	1.21	1.50	1.08	0.60	0.75	1.14	0.92	0.68	
%RSD	0.66	0.76	1.22	1.51	1.09	0.61	0.75	1.14	0.92	0.68	

2.2.5 In vitro drug release study (In vitro dissolution)
All the formulations were evaluated for *in-vitro* drug release study.
The data and curves obtained from *in vitro* release test were as shown in table no.6.9-6.19 and figure no. 6.1-6.10.

Dissolution profile of Ezetimibe Simvastatin tablets 10/80 mg
The critical dissolution medium for routine testing was considered as per OGD recommendation i.e;
Medium: Phosphate Buffer pH + 0.5% SLS
Volume: 900 ml
Apparatus: type II (Paddle type)
RPM: 50 rpm

Cumulative % drug release data of TRIAL 12

Sr. No.	**Time (min)**	**% cumulative drug release**	
		Drug Ezetimibe	**Drug Simvastatin**
1.	5	55	53
2.	10	77	75
3.	15	87	84
4.	20	90	88
5.	30	94	92
6.	45	95	93
7.	60	96	96

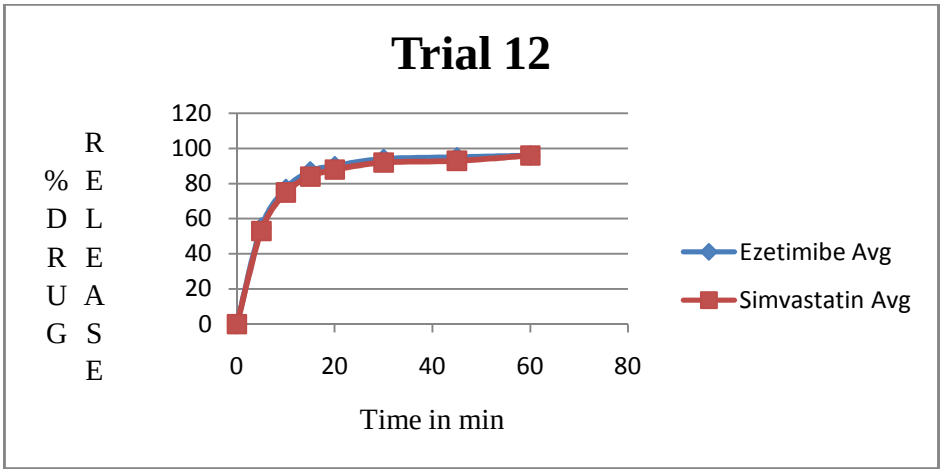


Figure 13.13: Cumulative % drug release profile of trial 12

4.0: Stability Study of Ezetimibe Simvastatin Tablets 10/80 mg

Stability study of Ezetimibe Simvastatin Tablets 10/80 mg was performed in Alu-Alu Blister for 3 month at 40°C / 75% RH.

Table.29: Stability Data of Ezetimibe Simvastatin Tablets 10/80 mg

Tests	**Limit**	**Initial**	**40°C / 75 % RH 3 month**
			Alu-Alu Blister
Description	White to off white capsule shaped biconvex uncoated tablet debossed with ES4 on one side and plain on other side	White to off white capsule shaped biconvex uncoated tablet debossed with ES4 on one side and plain on other side	White to off white capsule shaped biconvex uncoated tablet debossed with ES4 on one side and plain on other side
Assay Ezetimibe Simvastatin	 95.0-105.0 % 95.0-105.0 %	 86.6% 100.3%	 99.4% 99.2%
Dissolution Ezetimibe Simvastatin	 NLT 75% in 45 minutes	 86% 97%	 89% 92%
BHA Content	NLT 30%	116.4%	101.9%
Propyl gallate Content	NLT 50%	89.1%	91.2%
Citric acid Content	NLT 50%	91.5%	78.7%

Conclusion: From the result of stability data, it can be concluded that the developed formulation of Ezetimibe Simvastatin tablets 10/80 mg is stable in Alu-Alu Blister for 3 month at 40°C/75% RH.

Summary and Conclusion

When co-administered with simvastatin, ezetimibe provided significant incremental reductions in LDL-C and TG, as well as increases in HDL-C. Co-administration of ezetimibe with simvastatin was well tolerated and comparable to statin alone. Coadministration of ezetimibe 10 mg plus simvastatin 10 mg as with simvastatin 80 mg alone. Reductions in the plasma concentrations of TC, TG, and apolipoprotein B and increases in the plasma concentrations of HDL-C were all significantly enhanced by the coadministration of ezetimibe plus simvastatin. The coadministration of ezetimibe plus simvastatin was well tolerated and had an overall safety profile similar to that of simvastatin alone and to placebo. Coadministration of ezetimibe and simvastatin offers a highly efficacious new treatment strategy for lipid-regulating therapy in patients with hypercholesterolemia.

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