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Compatability study of selexipag and ezetimibe with selected excipients in formulation of bilayer tablet

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***Abstract*---**Present study was carried out to study compatibility of Selexipag and Ezetimibe with selected generally regarded as safe excipients and to prepare bilayer tablet. Isothermal stress testing was performed in binary a mixture which was subjected to 50°C for 4 weeks. Isothermal stressed samples were evaluated with RP-HPLC method and FTIR analysis. A trial was conducted with single disintegrants and diluent with direct compression technique and in-vitro dissolution was carried out. To improve the release profile of Immediate Release layer of Selexipag, multiple disintegrants were used namely croscarmellose sodium (CCS), sodium starch glycolate (SSG) and Crospovidone (CP). Similarly, extended release layer of Ezetimibe was prepared by wet granulation technique. Intra and extra granulation was done with mixtures of disintegrants. Extended release layer of Ezetimibe was formulated using polymers and gums like HPMC, MCC, PVP, Talc, Gaur gum, and Xanthan gum, Magnesium stearate. The results show that Selexipag and Ezetimibe were compatible with the all the polymers used in the study. The polymers used in the present study and the formulations developed using the compatible excipients were found to be stable.

***Keywords*---**ezetimibe, selexipag, compatibility, isothermal stress testing, bilayer tablet.

Introduction

The safety, efficacy, quality and stability of a formulation are the cornerstones of any new drug development process. In order to consistently maintain these attributes in a finished dosage form, it is important to have a comprehensive

understanding of the Physico-chemical characteristics of the active pharmaceutical ingredient (API), as well as all other components (e.g. excipients, manufacturing aids, packaging materials) of the drug product[1] .The preformulation stage involves characterization of several aspects of the API including solubility, dissolution, permeability, polymorph/salt screening, stability, ionization properties, particle size distribution, API-excipient compatibilities etc [2]. Due to the intimate contact of the API with one or more excipients in a formulation, there exists a likelihood of physical and/or chemical interactions between them. Any such interactions may result in a negative impact on the physical, stability or performance attributes of the drug product. The choice of excipients is of crucial importance to avoid these negative effects, and to facilitate the development of a robust and an effective formulation. Thus, for a rational selection of excipients, screening of excipient-API compatibility is recognized as an important aspect of formulation [3].

The present study was to develop bilayer tablets. The co-administration of antilipidemic and antihypertensive drug pose significant incompatibility. So in order to administer these drugs there is need to design a novel drug delivery system to overcome incompatibility. Additionally we intent to modify drug release pattern of both drugs using suitable excipients which will enhance the release of drug from delivery system. Antihyperlipidemic and Antihypertensive for the treatment of hypertension and hypercholesterolemia together through oral administration of single bilayer tablet [4].

Material and Method

Materials

The Selexipag and Ezetimibe is a gift sample from Thermosil Fine Chem Pvt. Ltd. (Pune, India), croscarmellose sodium, sodium starch glycolate, Crospovidone, Hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate, , PVP, Talc was also supplied by Thermosil Fine Chem Pvt. Ltd. (Pune, India)

Preformulation Studies[5]

To check the drug-drug and drug-excipient interactions, preformulation studies were performed. In the preformulation studies check the organoleptic properties of drugs like color, taste and odor. Melting point of drugs by using capillary method and Drug-Excipient Compatibility Studies by FT-IR and in the physical characteristics check loss on drying of both drugs.

Compatibility studies of Selexipag and Ezetimibe
Micro-environmental pH testing

To 20 ml vial, 300 mg of Selexipag and 300 mg of different excipients as mentioned were taken. This mixture was blended under vortex mixer for 4 minutes followed by addition of 60 µl of purified water using a micropipette to achieve water concentration of 20% w/w. This mixture was further mixed for 4 minutes in a vortex mixer in order to achieve consistent mixing. Vials were sealed properly and were stored in an oven set at 50°C for 4 weeks period. Drug-

excipient blends, without addition of water, stored in refrigerator were taken as controls. The micro environmental pH of drug-excipient blend was estimated by adding 3 ml of previously boiled and cooled purified water to 600 mg blend in the vial, mixing the suspension with a vortex mixer and then recording the pH with a pH meter. Micro environmental pH at zero time was also checked. Similarly micro environmental pH of Ezetimibe with different excipients was observed[6].

Isothermal stress testing

100 mg of each of Selexipag and selected excipients (Crospovidone, Croscarmellose sodium, Sodium starch glycolate, Microcrystalline cellulose, Magnesium Stearate) in the ratio of 1:1 as mentioned excipients were accurately weighed into 10.0 ml borosilicate glass vial (n=3) with screw capped vial followed by mixing in a vortex mixer for 4 minutes and to this mixture 20 µl of purified water was added using a micropipette to achieve water concentration of 10% w/w. This mixture was mixed for 4 minutes in a vortex mixer in order to achieve consistent mixing. The mixture blend is further mixed using a glass capillary (both the ends of which were heat sealed). To prevent any loss of material, the capillary was broken and left inside the vial. Vials were sealed properly and were stored in an oven set at 50°C for 4 weeks period. These vials were identified as 'stability samples'. Drug- excipient blends, without addition of water, stored in refrigerator, served as controls. Similarly Ezetimibe and excipients (HPMC, Guar gum, Xanthum gum, microcrystalline cellulose, Polyvinyl pyrollidine, Magnesium Stearate, talc) in the ratio 1:1 as mentioned excipients were treated. The drug excipient blends were periodically examined for any unusual color change. After completion of 4 weeks samples were analyzed as follows[7].

Relative Potency=Dose Standard sample / Dose Test sample when the 2 doses produce the same effect.
Mathematically this is the same as
Log (Relative Potency)= Log(Dose std) – Log(Dose test)

HPLC analysis

The control sample and samples were analyzed in HPLC as mentioned in method.

Drug-Excipient compatibility studies by Fourier transform infrared of Selexipag and Ezetimibe [8]

The compatibility of drugs with their respective excipients was studied by FT-IR spectroscopy. The scanning was performed 20 times at scanning speed 2mm/sec with resolution of 4 cm^{-1} over the region 4000–400cm^{-1}. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks, and appearance of new peaks due to polymer interaction.

Construction of Calibration Curve of Selexipag

Standard dilutions were prepared in the range of 5–40 µg/mL for Selexipag and absorbance was determined at (270nm) in UV spectrophotometer (UV-1700,

Shimadzu, India).From the values obtained, standard graph can be plotted between concentration and absorbance values.

Construction of Calibration Curve of Ezetimibe

Standard dilutions were prepared in the range of 0-30 µg/mL for Ezetimibe and absorbance was determined at (232 nm) in UV spectrophotometer from the values obtained, standard graph can be plotted between concentration and absorbance values.

Preparation of Immediate Release Selexipag Tablet

Direct compression method is used to prepare Selexipag Immediate release tablet and other excipients were accurately weighed and sifted through sieve #40 and mixed in a polybag and these formulations are given in Table No.1. The sifted powders were thoroughly mixed for approximately 5 min and again passed through sieve #40 to get uniform particle size. Magnesium stearate was added into the powder mixture for lubrication after passing through sieve #40[9].

Table 1
Composition of Selexipag immediate release tablets (100mg)

Batch	SL-1	SL-2	SL-3	SL-4	SL-5	SL-6
Selexipag	1	1	1	1	1	1
Crospovidone	8	16				
Croscarmellose sodium			8	16		
Sodium starch glycolate					8	16
Microcrystalline cellulose	89	81	89	81	89	81
Magnesium Stearate	2	2	2	2	2	2

Ezetimibe extended release tablets
Preparation of Extended Release Ezetimibe Tablets

Wet granulation technique was used to prepare extended release layer of Ezetimibe by adding PVP K 30 dissolved in isopropyl alcohol as a binding agent and these formulations are represented in the Table 2. Required quantities of Ezetimibe and other excipients like HPMC E_{15}, Guar gum, Xanthan gum and microcrystalline cellulose were weighed accurately and were sifted through sieve 40 and were mixed thoroughly and a sufficient volume of binding agent was added slowly to get cohesive mass. Then mass was passed through sieve #20 to obtain the granules. Next the granules were dried at 50°C in a hot air oven until dry the dried granules were lubricated uniformly with magnesium stearate; then talc was added and mixed properly. The above granules were compressed into tablets by 10-station tablet compression machine using 9 mm punch. [10]

Table 2
Composition of Ezetimibe Extended release tablets (200mg)

Batch	EZ-1	EZ-2	EZ-3	EZ-4	EZ-5	EZ-6
Ezetimibe	10	10	10	10	10	10

HPMC	30	50				
Guar gum			30	50		
Xanthum gum					30	50
Microcrystalline cellulose	135	115	135	115	135	115
Polyvinyl pyrollidine	10	10	10	10	10	10
Magnesium Stearate	7.5	7.5	7.5	7.5	7.5	7.5
Talc	7.5	7.5	7.5	7.5	7.5	7.5

Preparation of Bilayer Tablets

On the basis of dissolution test of both immediate release and extended release layer bilayer tablet was prepared. Based on dissolution behavior, formulations SL-6 and EZ-5 were selected for bilayer tablet. First, Ezetimibe extended release layer was placed in the die cavity and punched with low compression force. Then the Selexipag immediate release layer was placed in the die cavity and allowed for punching with optimum hardness of 6–8 kg/cm^2 to form bilayer tablets. Compression was made by using 10 mm punches. The total weight of each bilayer tablet was adjusted to 300 mg. Prepared bilayer tablets were evaluated for various post compression parameters and in vitro dissolution studies.[11]

Results and Discussion

Preformulation Studies Organoleptic Properties

Table 3
Organoleptic Properties for Ezetimibe

Test	Specification	Observations
Colour	White crystalline powder	White crystalline powder
Taste	Bitter	Bitter
Odor	Strong Pungent odor	Strong Pungent odor

Table 4
Organoleptic Properties for Selexipag

Test	Specification	Observations
Colour	Pale yellow crystalline powder	Pale yellow crystalline powder
Taste	Bitter	Bitter
Odor	Strong odor	Strong odor

Melting Point

Table 5
Melting Point of Ezetimibe and Selexipag

Sr.No.	Name of Drug	Specification melting point	Melting Point
1	Ezetimibe	163°C [12]	162 °C
2	Selexipag	134-138°C [13]	136 °C

Physical Characteristics
Loss on Drying

Table 6
Loss on Drying

Test	Drug	Specification	Observations
Loss on drying	Selexipag	Not more than 0.2 %	0.1%
Loss on drying	Ezetimibe	Not more than 0.2 %	0.2%

Compatibility studies of Selexipag and Ezetimibe
Micro-environmental pH testing

In the micro environmental pH study of binary mixture of drugs and their stability samples and control samples, the blend mixtures impart pH in the range of pH 3.6 to 9.8 at zero time. The stability samples and control samples also showed the pH in the range of pH 3.6 to 9.8. The results indicate that the micro environmental pH did not affect the compatibility of drugs and excipients.

Isothermal stress testing

On periodic observation of samples and control samples, there was no any physical change in the color. There was no significant change in the potency of control samples and samples. In addition, no any additional peaks were appeared in the chromatographs of control samples and samples. Effect of combination of Selexipag and Ezetimibe was also studied with and without addition of 10% w/w moisture. The chromatograms of samples revealed no significant degradation was seen.

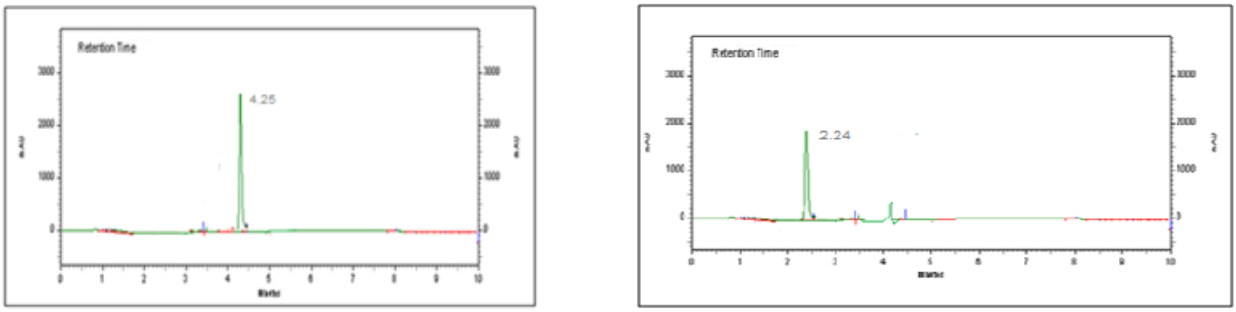

Figure 1. Chromatograms of samples

Drug-Excipient Compatibility Studies by Fourier Transform Infrared of Selexipag and Ezetimibe

The compatibility of drugs with their respective excipients was studied by FT-IR spectroscopy. The scanning was performed 20 times at scanning speed 2 mm/sec with resolution of 4 cm^{-1} over the region 4000–400 cm^{-1}. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks, and appearance of new peaks due to polymer interaction.

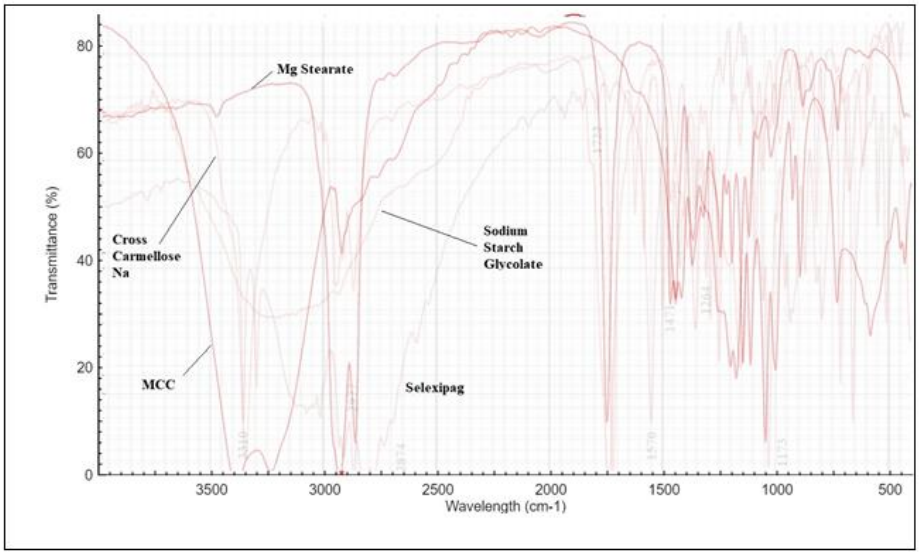

Figure 2. FTIR Spectra of Selexipag with excipients

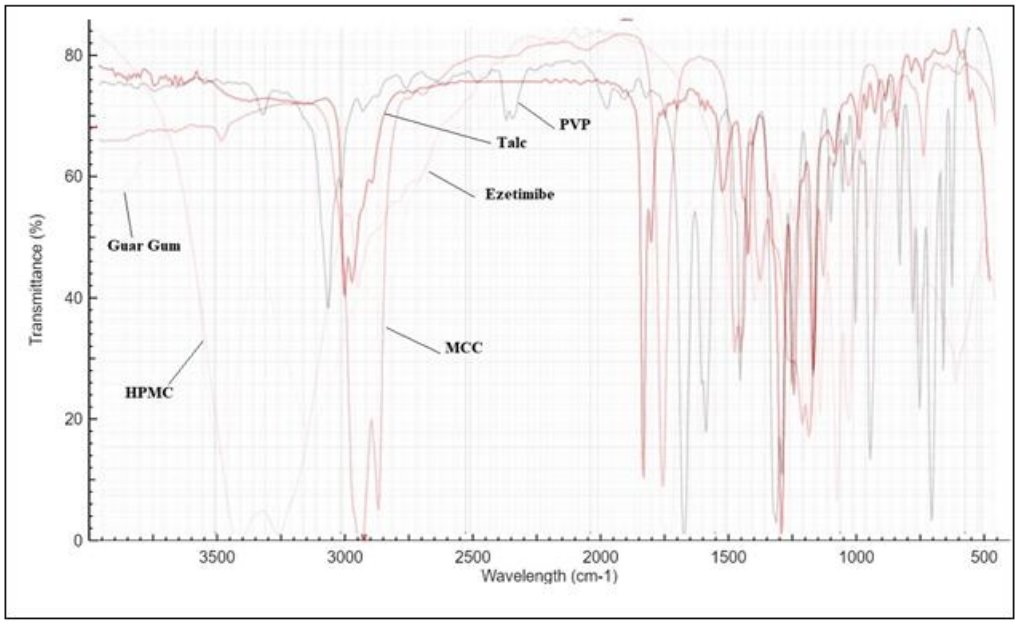

Figure 3. FTIR Spectra of Ezetimibe with excipients

Construction of Calibration Curve of Selexipag

Calibration curves were plotted for Selexipag based on the data obtained in UV spectrophotometer and these curves showed regression coefficient of 0.9904.

Table 7
Calibration curve of Selexipag

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.314
3	10	0.526
4	15	0.756
5	20	0.830
6	25	0.985
7	30	1.150
8	35	1.312
9	40	1.534

Calibration curve of Selexipag

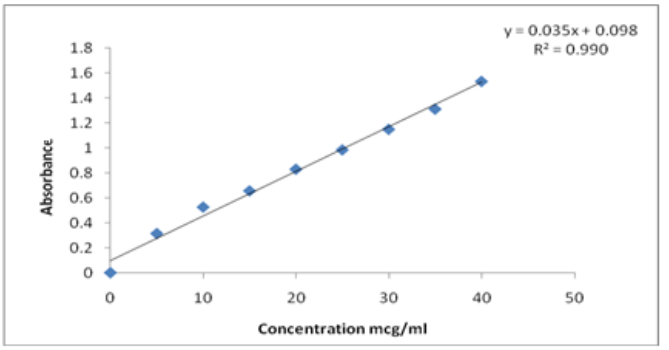

Figure 4. Calibration curve of Selexipag

Construction of Calibration Curve of Ezetimibe

Calibration curves were plotted for Ezetimibe based on the data obtained in UV spectrophotometer and these curves showed regression coefficient of 0.9904.

Table 8
Calibration curve of Ezetimibe

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.213
3	10	0.432
4	15	0.654
5	20	0.798
6	25	0.912
7	30	1.123

Calibration curve of Ezetimibe

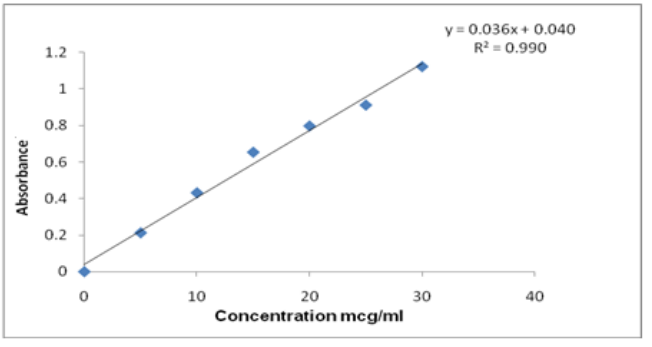

Figure 5. Calibration curve of Ezetimibe

Evaluation of Bilayer Tablets

Bilayer tablets were prepared successfully after selecting the optimized formulations of immediate release layer (SL 6) and sustain release layer (EZ5) using 10 mm punches, The prepared bilayer tablets were evaluated for post compression parameters and results were found to be within the limits mentioned in the above section and were shown in Table 8. In vitro drug release studies of bilayer tablets were carried out using USP dissolution apparatus type II in 900 mL of 0.1 N HCl for first 30 minutes and in 900 mL of 6.8 phosphate buffer solution up to 12 hours. From the results, drug release of Selexipag immediate release layer was found to be 97.43% in 30 minutes and that of the Ezetimibe extended release layer was 97.22% at the end of 12 hours drug release of bilayer tablet and values are represented in the Table 9. and Figure 4.

Table 9
Evaluation parameter of bilayer tablet

Batch code	Weight variation (%)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
Bilayer tablet	0.53	6.4	5.29	0.56

Table 10
In vitro drug release data of from bilayer tablet

	Selexipag(SL-6)	Ezetimibe(Ez-5)
Time (min)	% drug release	
Phosphate buffer 6.8 solution		
0	0	0
5	28 ± 3.58	1.5 ± 1.01
10	42 ± 3.34	2.3 ± 1.23
15	58 ± 3.60	3.2 ± 1.34
20	74 ± 5.31	3.7 ± 1.32
25	89± 2.78	4.2 ± 1.48
30	97 ± 3.74	4.8 ± 1.36
Time (hrs)		
1		9± 3.89
2		15 ± 4.68
3		25 ± 3.62
4		31 ± 4.50
5		43 ± 4.63
6		49 ± 3.56
7		55 ± 3.47
8		63 ± 2.27
9		79 ± 4.54
10		83 ± 3.64
11		94 ± 3.58
12		96 ± 3.32

Cumulative % drug release of bilayer tablet

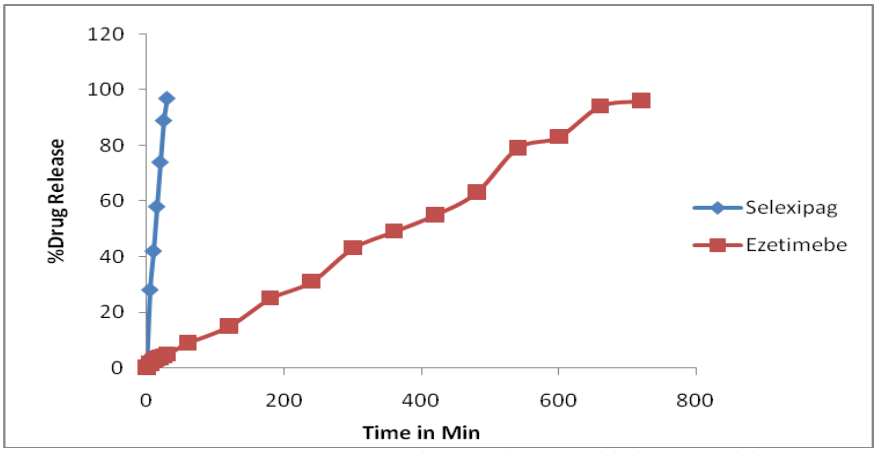

Figure 6. Cumulative % drug release of bilayer tablet

Conclusion

Compatibility studies of Selexipag and Ezetimibe was conducted with selected excipients and found to be compatible as per the result of micro environmental pH and FTIR analysis of Isothermal Stress Testing samples. The micro environmental pH study indicates that Selexipag and Ezetimibe did not undergo pH sensitive degradation. There was no significant change in potency remained in samples and control samples which indicates that Selexipag and Ezetimibe did not undergo degradation. The results of FTIR analysis also favored the compatibility as there was no significant change in principal peaks in IR spectra of binary mixtures of samples when compared with corresponding control samples of binary mixtures. In order to enhance the release of drugs multiple disintegrants were used with intra and extra granulation. Similarly in case of bilayer tablet, it was found that as concentration of SSG, CP and CCS increases, the release of drug also increases. When multiple disintegrants were used in the combination, better release was obtained. The bilayer tablet was evaluated for hardness; friability and in-vitro dissolution. According to the in vitro dissolution profile date one formulation of each layer were selected for bi-layered tablet. SL-6 from immediate release formulations as they showed 97.43 % drug releases within 30 minute. EZ-5 from extended release formulation they showed 97.22 % drug release within 12 hours. The bilayer tablets were prepared using the selected immediate and extended release layer. The percentage drug content was uniform in all the formulations of prepared bi-layered tablets. Selecting appropriate formulation excipients and manufacturing technology is the design feature of any dosage form. Screening of incompatible excipient and selection of compatible excipient helps to reduce instability problem. The present study shows that Selexipag and Ezetimibe are compatible with selected excipients. Bilayer tablet prepared by using optimize formulation of each layer, showed better release profile of both drug contents.

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