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Research Article

FORMULATION AND IN VITRO EVALUATION OF SELEXIPAG CONTROLLED RELEASE TABLETS

[1]Surisetty Sridevi, [2]N. Venkata Sai Nikitha, [3]Dr. M. Sudhakar.

[1]M.Pharmacy, Department of Pharmaceutics, Faculty of Pharmaceutics, Malla Reddy College Of Pharmacy, Hyderabad, Telangana, India
[2]Department of Pharmaceutics, MALLA REDDY COLLEGE OF PHARMACY, Hyderabad, Telangana, India
[3]HOD and Professor, Malla Reddy College Of Pharmacy, Hyderabad, Telangana, India.

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ABSTRACT:
Selexipag has a short biological half-life of 0.8-2.5 hours and having less bioavailability which necessitates multiple daily dosing. Hence the present study was aimed to develop a controlled release formulation of Selexipag to reduce the dose related side effects and to reduce the dosage regimen. The present research project aimed to develop a Control release oral formulation of hypertension drug Selexipag, the present research comprising Selexipag used for the symptomatic relief of pulmonary arterial hypertension. Polymers like HPMC K15 M, Carbopol 940, Pectin and Gellan Gum were used for controlling the drug release, and the polymers are mixed in a predetermined ratio. Totally 12 formulations were prepared and evaluated for pre-compression and post-compression parameters, and all the results were found to be within the limits. From the drug and excipients compatibility studies (FT-IR) it was confirmed that the drug and excipients used weren't have any interactions. The in vitro dissolution studies revealed that the F9 formulation containing 6mg of Pectin controls the drug release up to 12 hours. So Pectin containing F9 formulation was considered to be suitable for the formulation of Selexipag controlled release tablet and the drug release kinetics revealed that the F9 formulation shows zero order kinetics with super case- II transport mechanism.
Keywords: Selexipag, Pectin, Pulmonary Arterial Hypertension, FT-IR.

INTRODUCTION

Selexipag is an oral, selective IP prostacyclin receptor agonist approved for the long-term treatment of PAH in adults with World Health Organization functional class II/III symptoms. Selexipag was developed to avoid off-target prostanoid effects in the treatment of PAH, especially of the gastrointestinal system. In a post-hoc analysis of the GRIPHON study in PAH, 334 patients were identified with PAH related to underlying CTD, the majority of whom were patients with SSc (n=170). Selexipag reduced the risk of composite morbidity/mortality events in patients with PAH-CTD by 41% (HR 0.59; 95% CI, 0.41–0.85) and the treatment effect was consistent irrespective of baseline PAH therapy or CTD subtype [1]. Selexipag was well-tolerated among PAH-CTD patients, including those with PAH-SSc. To determine the effects of an 8-week course of selexipag on the frequency of attacks of Raynaud's phenomenon in SSc, a multicenter, double-blind, randomized, placebo-controlled, parallel-group, phase II study was conducted in 74 SSc patients [2]

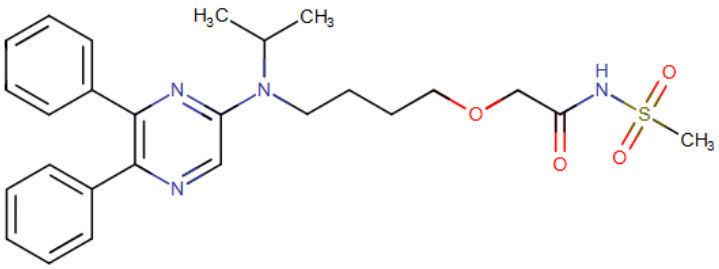

Figure No.1 Structure of Selexipag

The oral route of drug administration is the most acceptable and frequently used route because of the convenience of self-administration, ease of manufacturing, and high-degree of dose accuracy.[3] Dosage forms are designed by exploiting the unique features of the gastro-intestinal tract (GIT) as the drug has to pass from the walls of GIT before getting access to the systemic circulation.[4] The

Address for Correspondence: Surisetty Sridevi**,** M. Pharmacy, Department of Pharmaceutics, Faculty of Pharmaceutics, Malla Reddy College Of Pharmacy, Hyderabad, Telangana, India, **Mail ID:** venkatanikitha9862@gmail.com.

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pharmaceutical industry is focusing on the establishment of novel drug delivery systems rather than investigating and developing new drug entities due to the increased investigational cost of new drugs.[5] Over the past several decades, controlled-release technology has rapidly emerged as a drug delivery system that offers novel approaches for the delivery of bioactive compounds into systemic circulation at a predetermined rate, which significantly improves drug bioavailability and clinical outcomes with decreased toxicity. Sustained-release (SR) dose forms are designed in such a way that the rate of drug release from the tablet matrix occurs in a controlled manner over an extended period of time maintaining a constant plasma drug level thus improving patient compliance and effective clinical outcomes.[6] A constant therapeutic drug level is maintained throughout the dosing intervals, which often prolongs the onset of pharmacologic action.[7] The development of sustained drug delivery systems is a challenging task in terms of providing a constant drug release profile retaining the dosage form in the stomach or upper small intestine until all the drug is completely released in the desired time.[8] An ideal oral drug delivery system will steadily release a measurable and reproducible amount of drug over an extended period of time.[9] Several mechanisms are involved in the release of drugs from controlled-release formulations such as dissolution- controlled release systems and diffusion-controlled release systems. In dissolution- controlled systems, dissolution is the rate-controlling step. The drug is embedded in slowly dissolving or erodible matrix or by coating it with slowly dissolving substances, whereas in diffusion-controlled release systems, the release rate of drug is dependent on its diffusion through an inert water insoluble membrane barrier. In matrix-diffusion controlled devices, the therapeutic agent is dispersed in an insoluble matrix of rigid non-swellable hydrophobic materials or a swellable (soluble) hydrophilic substance. Among different strategies to prolong the drug action, matrix tablet formulations have gained immense popularity because they have the advantage of simple processing and low-cost fabrication.[10] Matrix tablets are cost effective, easy to prepare, and exhibit predictable release behavior.

MATERIALS & METHODS USED: Selexipag API was procured from A. R. Life Sciences, Hyderabad and HPMC K15 M, Carbopol 940 were procured from Strides arcolab, Bangalore., Gellan Gum, MCC Lactose, PVP K 30, Magnesium Stearate, Talc were procured from Loba chemie pvt.ltd, Mumbai and Pectin were procured from Himedia laboratory. Mumbai.

Table.1: Tablet composition of different formulations of Selexipag Controlled Release tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Selexipag	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
MCC	30.8	28.8	26.8	30.8	28.8	26.8	30.8	28.8	26.8	30.8	28.8	26.8
HPMC K15 M	2	4	6	_-	-	-	-	-	-	-	-	-
Carbopol 940	-	-	-	2	4	6	-	-	-	-	-	-
Pectin	-	-	-	-	-	-	2	4	6	-	-	-
Gellan Gum	-	-	-	-	-	-	-	-	-	2	4	6
Lactose	5	5	5	5	5	5	5	5	5	5	5	5
PVP K30	10	10	10	10	10	10	10	10	10	10	10	10
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Mg. stearate	1	1	1	1	1	1	1	1	1	1	1	1
Total (mg)	50	50	50	50	50	50	50	50	50	50	50	50

Preparation of Selexipag Controlled Release Tablets: [11-16]

Controlled release tablets of Selexipag were prepared by Direct compression method using variable concentrations of different polymers like Xanthan Gum, Carbopol 940, and Guar Gum. Direct compression method is widely employed method for production of compressed tablets.

Direct Compression:

In this process, the tablets are compressed directly from powder blends of active ingredient and suitable excipients, which will flow uniformly in to the die cavity and forms a firm compact.

Brief manufacturing procedure for the preparation of tablets:

- Step 1- Weighed all the ingredients separately.
- Step 2- The l drug and the other excipients were passed through 40# sieve together and blended for 10 minutes.
- Step 3- The magnesium stearate was passed through 60# sieve and added to the blend of step2 and blended for 5 minutes.
- Step 4- Compressed the blend of step 3 in to tablets by using 8.5mm, round punches.

Evaluation Parameters [17-20]

Pre Compression Parameters

A. Bulk density (D_b)

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

$$D_b = M / V_o$$

B. Tapped density (D_t)

Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

$$D_t = M / V_t$$

C. Compressibility index:

The compressibility of the powder was determined by the Carr's compressibility index.

$$\mathrm{CI} = \frac{\rho_{\mathrm{tap}} - \rho_{\mathrm{bulk}}}{\rho_{\mathrm{tap}}} \times 100$$

D. Hausner ratio:

Hausner ratio = tapped density/ bulk density

E. Angle of repose (θ)

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Post Compression Parameters[21]

A. Thickness and diameter

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

B. Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm2.

C. Friability (F)

Tablet strength was tested by Friabilator USP EF-2. Pre weighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The % friability was then calculated by,

$$\mathrm{F} = \frac{(\mathrm{W}_{\mathrm{initial}}) - (\mathrm{W}_{\mathrm{final}})}{(\mathrm{W}_{\mathrm{intial}})} \times 100$$

D. Weight variation test

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation

E. Uniformity of drug content.

Five tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in different buffers, the drug content was determined using a UV/Visible Spectrophotometer (Single beam spectrophotometer).

F. In-vitro release study:

Table.2 Dissolution details

Apparatus	USP XXIV dissolution testing apparatus II (Paddle method)
Dissolution medium	0.1N HCL, 6.8 pH phosphate buffer,
Temperature	37± 0.5^0 C
RPM	50
Vol. withdrawn and replaced	5ml every 1 hour
λ max	270 nm in pH 1.2 buffer and 270 nm in pH 6.8
Blank solution	Buffers used
Duration of study	12 hours
Volume of dissolution media	900ml

Procedure:

The release rate of Selexipag from tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of pH 1.2, for first 2 hours and followed by phosphate buffer (pH 6.8; 900 mL) for remaining hours at 37.5±0.5^0C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with respected dissolution medium. Absorbance of these solutions was measured using a UV-Visible Spectrophotometer (Single beam spectrophotometer). Cumulative percentage of drug release was calculated.

G. Kinetic Analysis of In-Vitro Release Rates of Controlled Release Tablets

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

RESULTS AND DISCUSSIONS

Determination of melting point

The melting point of Selexipag was found to be 136ºC which compiled with BP standards, indicating purity of the drug sample. which was determined by capillary method

Solubility studies:

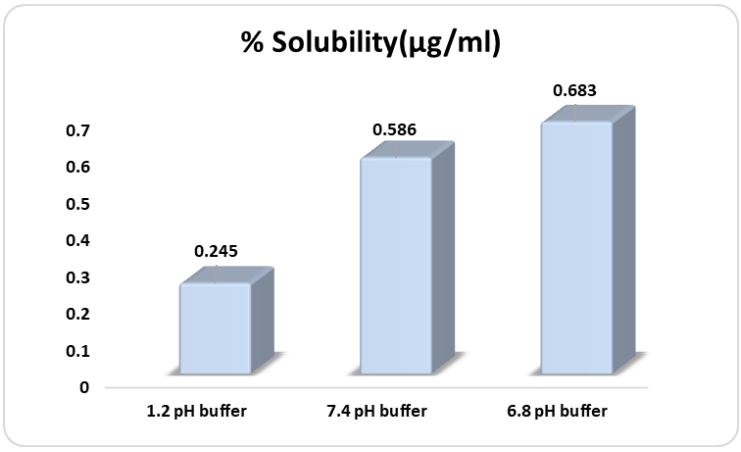

Figure No.2 Solubility studies of Selexipag

Discussion: From the above solubility studies, it was observed that among that 3 buffer solutions (0.1N HCL i.e pH 1.2, 7.4 pH Phosphate buffer and 6.8 pH phosphate buffer) the drug was soluble freely in 6.8 pH buffer.

FTIR studies:

Drug-Excipient compatibility studies:

The IR spectrum of pure drug was found to be similar to the standard spectrum of Selexipag. From the spectra of Selexipag, combination of Selexipag with polymers, it was observed that all characteristic peaks of Selexipag were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and polymers. FTIR spectra of Selexipag, and Optimized formulation are shown in Figure respectively.

FTIR Spectra of Pure drug:

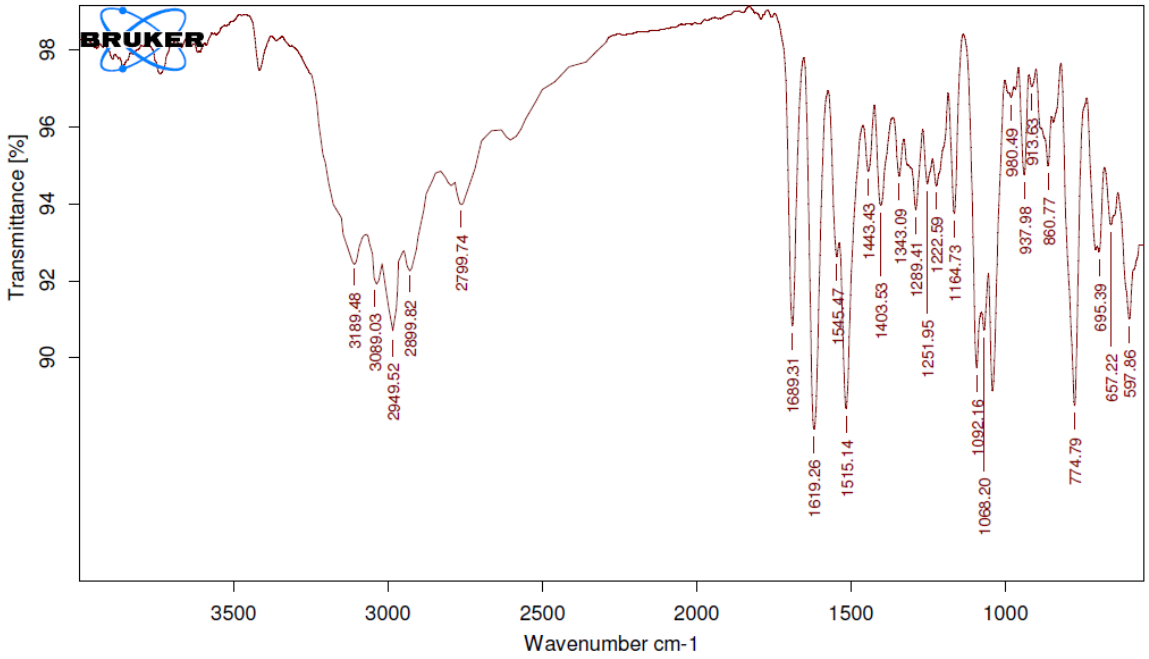

Figure No.3 FTIR Spectra of Pure drug

FTIR Spectra of Drug and Excipients:

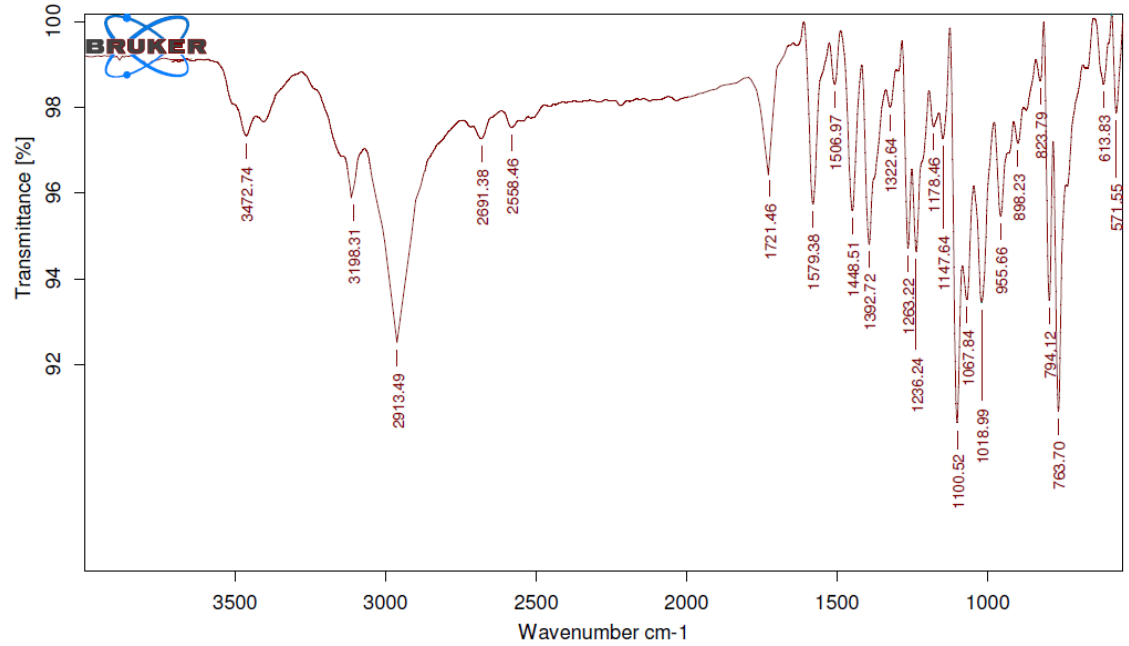

Figure No.4 FTIR Spectra of Drug and Excipients

Discussion: From the drug excipients compatibility studies we observe that there are no interactions between the pure drug and (drug+ excipients) which indicates there are no physical changes.

UV Determination:

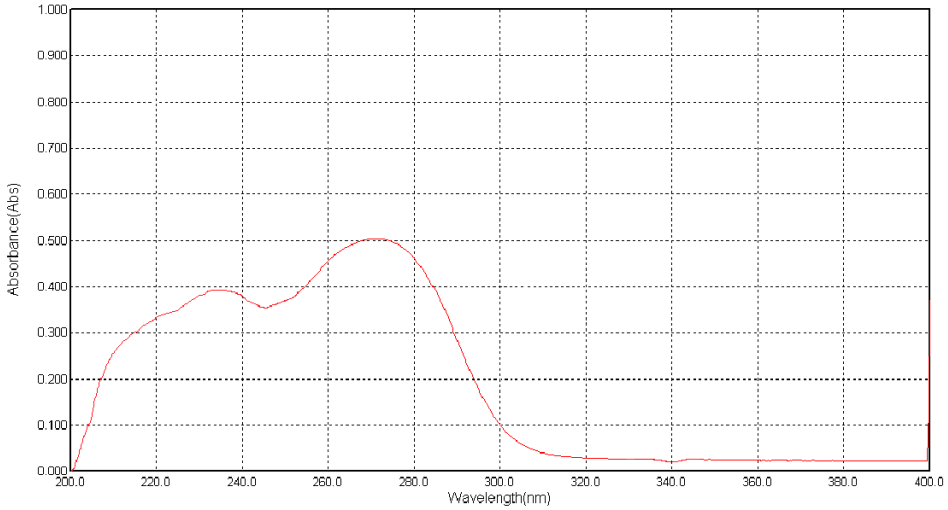

Figure No.5 UV spectrum of Selexipag

Discussion: A solution of Selexipag containing the conc. 8µg/ ml was prepared in 6.8pH buffer and UV spectrum was taken using Single Beam Spectrophotometer (YIS-294). The solution was scanned in the range of 200 – 400 nm. The maximum absorbance was found to be at 270 nm.

Standard Calibration Curve of Selexipag in pH 1.2 Buffer:

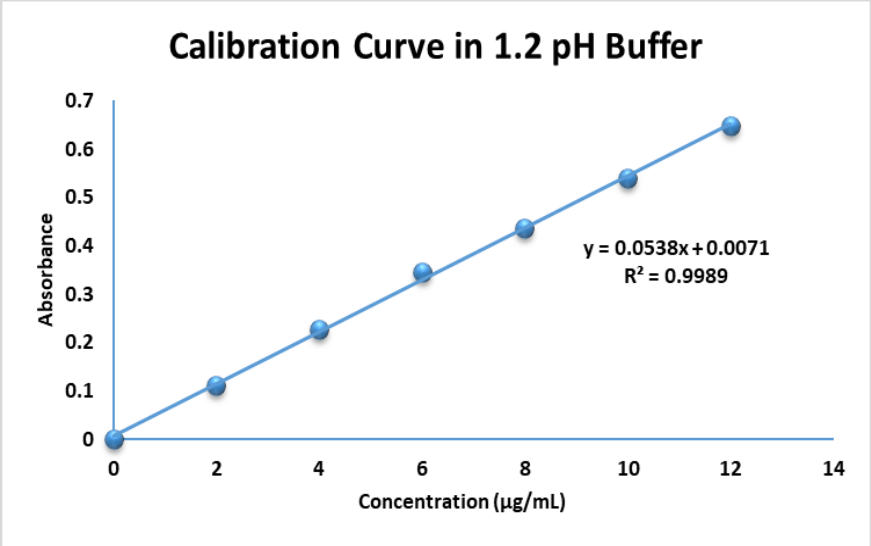

Figure No.6 Standard calibration curve of Selexipag in pH 1.2

Discussion:

The standard calibration curve shown 0.998, through that the drug obeys Beers and Lamberts law in the concentration range of 0 to 12 µg/mL. A standard graph was plotted by keeping the known concentration on X – axis and obtained absorbance on Y – axis.

Standard Calibration Curve of Selexipag in pH 6.8:

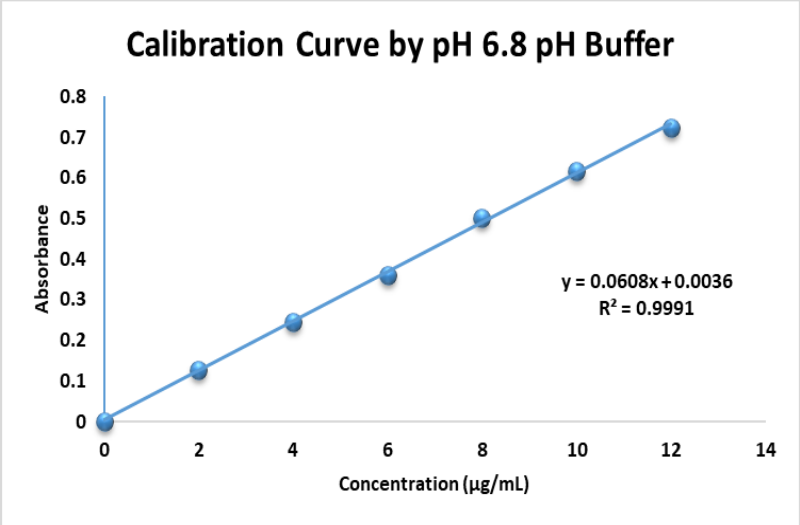

Figure No.7 standard calibration curve Selexipag in pH 6.8 Phosphate Buffer

Discussion:

The standard calibration curve shown R^2 value 0.999 which ie near to 1 shows the linearity, through that the drug obeys Beers and Lamberts law in the concentration range of 0 to 12 µg/mL. A standard graph was plotted by keeping the known concentration on X – axis and obtained absorbance on Y – axis.

Evaluation of Selexipag controlled release matrix Tablets

Table.3 Pre Compression Parameters of Selexipag controlled release Tablets

FC	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of Repose
F1	0.127±0.007	0.210±0.004	19.59±1.72	1.17±0.02	29.25±0.45
F2	0.142±0.005	0.235±0.003	17.37±1.20	1.16±0.01	27.48±0.45
F3	0.152±0.003	0.248±0.005	16.15±1.37	1.15±0.03	26.26±0.12
F4	0.135±0.005	0.226±0.006	18.37±1.23	1.19±0.02	27.16±0.37
F5	0.159±0.008	0.245±0.003	17.45±1.19	1.17±0.01	26.48±0.45
F6	0.165±0.002	0.254±0.005	16.201.15	1.15±0.02	25.02±0.26
F7	0.142±0.005	0.235±0.006	15.67±1.28	1.16±0.04	25.39±0.18
F8	0.158±0.004	0.241±0.007	14.45±1.24	1.15±0.03	24.12±0.45
F9	0.179±0.006	0.275±0.002	12.13±1.16	1.11±0.02	23.48±0.20
F10	0.152±0.004	0.234±0.003	16.46±1.12	1.17±0.01	28.58±0.46
F11	0.158±0.003	0.259±0.004	14.37±1.24	1.16±0.02	27.74±0.38
F12	0.171±0.005	0.264±0.005	13.24±1.18	1.14±0.03	26.03±0.42

Discussions: The angle of repose of different formulations (F1-F12) was found to be in the range of 29.25±0.45 to 23.48±0.20. But the formulation F9 having the excellent flow property with 23.48±0.20. So, it was confirmed that the flow property of blends was free flowing. The bulk density of blend was found between 0.127±0.007 to 0.179±0.006. The Tapped density was found between 0.210±0.004 to 0.264±0.005. These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 19.59±1.72 to 12.13±1.16 and Hausner's ratio from 1.17±0.02 to 1.11±0.02, which reveals that the blends have good flow character.

Post Compression Parameters of Selexipag controlled release tablets:

Table.4 Physical properties of tablet formulation (F1 to F12)

FC	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug Content (%)
F1	2.16±1.66	4.27±0.04	0.78±0.08	50.04±1.37	94.43±0.42
F2	2.37±0.78	4.36±0.02	0.65±0.02	51.02±0.45	95.25±0.26
F3	2.58±0.88	4.49±0.05	0.51±0.06	49.56±0.21	96.63±0.39
F4	2.27±0.74	4.42±0.06	0.67±0.08	48.28±0.54	94.18±0.25
F5	2.54±0.82	4.59±0.08	0.58±0.05	50.02±0.76	96.25±0.26
F6	2.69±0.79	4.67±0.04	0.46±0.04	51.51±0.51	97.43±0.38
F7	2.45±072	4.53±0.07	0.68±0.02	48.24±0.29	95.67±0.45
F8	2.63±0.36	4.68±0.02	0.55±0.08	51.47±0.63	97.35±0.26
F9	2.78±0.84	4.75±0.09	0.37±0.05	50.12±0.45	99.74±0.38
F10	2.32±0.29	4.37±0.04	0.75±0.03	52.14±0.72	96.47±0.84
F11	2.49±0.46	4.46±0.09	0.65±0.09	48.15±0.51	97.47±0.84
F12	2.65±0.85	4.59±0.07	0.43±0.05	49.52±0.36	98.68±0.84

Discussion: Thickness of the Selexipag tablets were found to be in the range of 2.16±1.66 mm to 2.78±0.84 mm. Hardness of the Selexipag tablets were found to be in the range of 4.27±0.04 to 4.75±0.09 kg/cm2. Friability of the Selexipag tablets were found to be in the range of 0.37±0.05 to 0.78±0.08%. The Weight Variation of the Selexipag tablets were found to be in the range of 48.15±0.51 to 52.14±0.72 mg. Drug content of the Selexipag tablets were found to be in the range of 94.43±0.42 to 99.74±0.38%.

In-vitro drug release studies:

In-vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Lab India DS 8000) at 50 rpm. The dissolution medium consisted of 900 ml of buffer, maintained at 37+0.50C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (PG Instruments). The study was performed in triplicate

Table.5 In vitro dissolution studies with formulation F1 to F6

Time (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	31.82±1.13	24.48±1.14	28.24±1.47	29.82±1.48	22.86±1.14	13.58±0.14
2	47.26±1.22	33.78±1.26	37.48±1.54	35.26±1.27	31.78±1.26	26.47±1.24
3	59.24±1.38	42.14±1.42	45.24±1.29	48.24±1.34	39.14±1.42	34.45±1.21
4	66.84±1.42	54.81±1.19	56.34±1.61	55.84±1.54	47.81±1.19	48.19±1.25
5	75.86±1.19	66.46±1.04	63.48±1.24	68.88±1.42	56.46±1.04	53.48±1.17
6	83.92±1.58	75.98±1.54	70.19±1.37	75.95±1.14	65.98±1.54	64.15±1.28
7	91.64±1.22	81.89±1.12	79.18±1.45	87.47±1.25	78.89±1.12	72.41±1.15
8	98.86±1.04	89.21±1.36	85.29±1.36	98.24±1.15	84.21±1.36	79.16±1.42
9		93.15±1.28	91.42±1.28		91.15±1.45	84.45±1.21
10		98.26±1.36	95.43±1.28		97.26±1.26	89.68±1.10
11			98.41±1.25			96.14±1.48
12						98.58±1.44

Table.6 In vitro dissolution studies with formulation F7 to F12

Time(hrs)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	25.47±1.48	29.47±1.45	17.47±1.24	23.87±1.46	25.47±1.24	16.72±1.21
2	34.47±1.19	43.77±1.22	26.45±1.21	38.82±1.22	38.18±1.54	28.42±1.67
3	48.47±1.45	55.42±1.16	34.19±1.25	51.46±1.14	44.14±0.25	31.46±1.22
4	59.87±1.47	67.41±1.01	45.48±1.17	66.84±1.22	53.48±0.15	39.58±1.44
5	74.58±1.65	75.92±1.24	57.15±1.28	74.48±1.54	65.47±0.15	48.82±1.51
6	88.47±1.25	83.72±1.36	66.41±1.15	86.25±1.28	78.21±0.19	57.77±1.13
7	96.48±1.62	89.35±1.87	72.16±1.42	95.36±1.26	86.15±0.18	68.21±1.27
8		92.08±1.11	81.45±1.21		93.24±0.11	76.48±1.25
9		98.47±1.24	88.68±1.10		98.18±1.06	82.46±1.57
10			93.14±1.48			91.49±1.64
11			95.58±1.44			94.16±1.95

12			99.21±1.37			98.24±1.47

In Vitro Drug Release Studies:

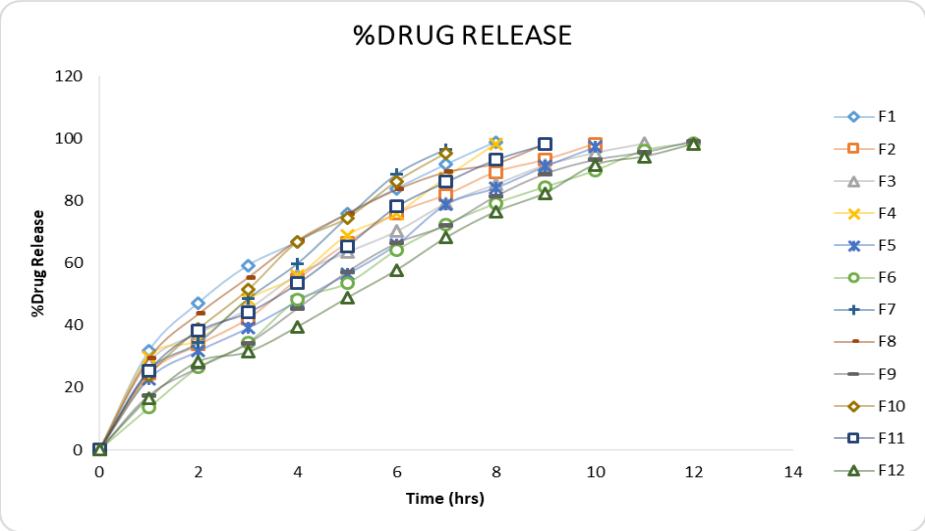

Figure No.8 In Vitro Drug Release Studies of F1-F12 Formulations

SUMMARY AND CONCLUSION

From the in vitro drug release studies of Selexipag controlled release tablets using HPMC K15 M, Carbopol 940, Pectin and Gellan Gum in three different polymer ratios using lactose as a diluent, MCC as a binder and PVP K30 as filler. From Formulations, the F1-F3 were formulated using HPMC K15 M in three different ratios like 2mg, 4mg, and 6mg, the drug release of F1 was 98.86±1.04% at the end of 8th hour, F2 was 98.26±1.36% at the end of 10th hour and F3 was 98.41±1.25at the end of 11th hour. So, when the polymer concentration increases the drug release time was increased but F3 showing the highest release at the end of 11th hour only. So further dissolution was takes on the polymer Carbopol 940. The formulation F4-F6 were formulated by using Carbopol 940 in three different ratios like 2mg, 4mg, and 6mg, the drug release of F4 was 98.24±1.15% at the end of 8th hour, F5 was 97.26±1.26% at the end of 10th hour and F6 was 98.58±1.44% at the end of 12th hour.
So further studies were done with Pectin. The formulations from F7-F9 were formulated by using Carbopol 940 in three different ratios like 100mg, 150mg, and 200mg, so the drug release of F7 was 96.48±1.62% at the end of 7th hour, F8 was 98.47±1.24% at the end of 9th hour and F9 was 99.21±1.37% at the end of 12th hour. In this turn, with the polymer Pectin the formulation F9 shows the better results up to 12th hour. Next the formulations from F10 to F12 with Gellan Gum shows the release of F10 was 95.36±1.26% at the end of 8th hour, F11 was 98.18±1.06% at the end of 10th hour and F12 was 98.24±1.47% at the end of 12th hour. So in this dissolution studies with ethyl cellulose also shows good results at the end of 12th hour. But when comparted to all the formulations the Formulation of drug with the polymer Pectin in the concentration of 6mg shows the highest drug release at the end of 12th with 99.21±1.37% which results in the drug was released in controlled manner up to 12 hour. Hence, the formulation F9 was identified as the Optimized formulation. So further Release kinetics was done to this formulation.

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