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A PHARMACEUTICAL FORMULATION AND EVALUATION OF A CARDIOVASCULAR DRUG FOR IMPROVING PULMONARY ARTERIAL HYPERTENSION

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ABSTRACT

The present investigation concerns the development of sustained release matrix tablets of Selexipag, which after oral administration are designed to prolong the duration up to 12 h and thereby increase patient compliance, reduced frequency of administration and increase therapeutic efficacy. Nine batches of tablets were fabricated containing Selexipag, polymers HPMC K5M, ethyl cellulose, sodium CMC and other excipients. All the batches were formulated by direct compression. The evaluation was done on the granules which include compressibility and flow property. The tablets were evaluated for appearance, thickness, hardness, assay, weight variation, friability, and in vitro release studies in three different media mimicking physiological pH of GIT. The results obtained were satisfactory and complies with the Pharmacopoeial specifications. The formulation containing 1:1 ratio of HPMC K5M and ethyl cellulose (F**5**) showed slower release as compared to other formulations. The in-vitro release data were also treated with mathematical equations and were found to be following zero order with diffusion mechanism when investigated in pH 6.8 Phosphate Buffer. Thus the combination of HPMC K5M and ethyl cellulose (1:1) shows satisfactory retarding release of Selexipag from matrix upto 12 hrs.

Keywords: Selexipag, sustained release, release retarding agent, pulmonary arterial hypertension, kinetics

1. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a hemodynamic and pathophysiological condition affecting the pulmonary arterioles and characterized by progressive increases in pulmonary vascular resistance and pulmonary artery pressure, ultimately leading to right heart failure and premature death [1, 2]. Recent therapeutic options have significantly improved the long-term outcome of patients with PAH, but PAH remains a disease with a poor prognosis [3–5].

Reduced expression of prostacyclin synthases in the lung and reduced levels of prostacyclin are key features of PAH [6–8]. Prostacyclin is produced by endothelial cells from prostaglandin H2 (PGH2) by the enzyme prostacyclin synthase [6]. Prostacyclin is a potent vasodilator and also has anti-proliferative, antithrombotic, and anti-inflammatory effects [8, 9]. As PAH is associated with vasoconstriction, proliferation, and thrombosis, there is a strong rationale for using prostacyclin treatment [1,2,10]. Restoration of IP receptor signaling using prostacyclin receptor (IP receptor) agonists is an effective strategy in the treatment of the disease.

Selexipag is a novel, orally available, long-acting (half-life of 6.2–13.5 h), highly selective IP receptor agonist that targets the prostacyclin pathway [11-14]. Selexipag is a diphenylpyrazine derivative with a chemical structure (Figure 1) unrelated to prostacyclin and its analogues (e.g. it lacks the typical cyclopentane ring of prostacyclin analogues). It has a molecular formula of $C_{26}H_{32}N_4O_4S$ and a molecular weight of 496.62 dalton.

Selexipag is a pale yellow crystalline powder that is practically insoluble in water. In the solid state selexipag is very stable, is not hygroscopic, and is not light sensitive [15].

As a consequence, its pharmacokinetics and molecular pharmacology are favourably differentiated from those of prostacyclin and its analogues, thus allowing for twice-daily oral dosing and highly selective activation of the target IP receptor without the potential for tachyphylaxis (Figure. 2) [16- 20].

It is the only drug directed towards the prostacyclin pathway that is recommended for sequential double and triple combination therapy in patients in WHO FC II and III (i.e. selexipag in addition to an ERA and/or PDE-5i) [15, 21]. It has a narrow therapeutic range and undergoes enzyme-catalyzed hydrolysis to ACT-333976, which is 37-fold more potent than selexipag itself. [22].

The objective in designing a sustained release system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time.

2. MATERIALS AND METHODS

2.1 Materials

Selexipag (SPG) was kindly supplied from Hetro Drugs Limited, Hyderabad, India. Microcrystalline cellulose (MCC, Avicel PH 102) was obtained from FMC Bio polymers, Mumbai. Sodium carboxymethylcellulose (Sodium CMC; Cekol 2000P) was obtained from C P Cekol, Mumbai. Hydroxypropyl methyl cellulose (HPMC K 5M) and Ethylcellulose (EC; Ethocel Std 4 Premium) were obtained from Dow Chemical Company, Mumbai. Magnesium stearate was obtained from Ferro, Mumbai. Double distilled water was used throughout the study. All other reagents and solvents used were of analytical grades.

2.2 Preparation of Matrix tablets (Direct Compression)

Components of formula are shown in Table 1. Selexipag, MCC (Avicel PH 102) and respective drug release retarding agents (Sodium CMC, EC and HPMC K 5M) were co-sifted through #30 ASTM, loaded in a double cone blender (Bectochem Lodgie, Ankleshwar, India) and mixed for another 15 minutes at 10 rpm. Magnesium stearate was sifted through #60 ASTM and was added to above blend and was mixed for another 5 minutes at 10 rpm.

The blend was compressed into tablet using a flat-faced 7 mm punch in a ten-station rotary tablet machine (EP200, Eliza Parle Tools, Sanand, Ahmedabad). The tablet hardness was kept within the range of 4-5 kg/cm^2 and tablet weight of 100 mg. Each tablet contained 1.6 mg of SPG.

2.3. Pre-compression studies

2.3.1. Flow properties

A flow property of pre-compression blend was evaluated by measuring angle of repose. Bulk density, tapped density, Carr's index (compressibility index) and Hausner's ratio of blends were measured using tap density apparatus (TD 1025, Labindia Analytical Instruments, Pvt. Ltd, Mumbai, India).

2.3.1.1. Angle of repose: It was determined using the fixed height method [23, 24]. The granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2 cm above hard surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Each powder formulation was

allowed to flow freely from a funnel at a fixed height onto a horizontal surface to form a cone. The base of the cone was marked and the height of the orifice of the funnel from the horizontal surface was measured. The height of the cone was measured and the angle of repose was calculated from the height of the cone (h) and the radius (r) of its base using the equation, $\theta = \tan^{-1} h/r$.

Where, θ = angle of repose, h = height of heap, r = radius of base of heap circle.

2.3.1.2. Bulk density: Bulk density (D_b) is determined through measuring the volume (V_b) of known weighed quantity (W) of granules using bulk density apparatus [23-25].

$$D_b = W/V_b$$

2.3.1.3. Tapped density: Tapped density (D_t) is calculated by measuring the volume (V_t) of known weighed quantity (W) of granules using bulk density apparatus and using the formula [23-25].

$$D_t = W/V_t$$

After the determination of D_b, the cylinder is allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 s intervals. The tapping is continued until no further change in volume is observed.

2.3.1.4. Hausner's index: The Hausner's index or Hausner's ratio (*HR*) is calculated by dividing the tapped density by the bulk density of the granules [23-26].

$$\text{Hausner's index} = D_t/D_b$$

Where, D_t= tapped density and D_b = bulk density

2.3.1.5. Carr's index: The Carr's index or compressibility index (*CI*) that determines % of compressibility of the granules can be measured from the difference between the tapped and bulk densities divided by the tapped density and the ratio expressed as a percentage [23,24,27].

$$\text{Carr's Index (\%)} = (D_t - D_b)/D_t \times 100$$

Where, D_t= tapped density and D_b = bulk density

The determination of micromeritics of all the formulations were carried out in triplicate, the consolidated results (mean ± SD) have been reported in Table 2.

2.4. Evaluation of compressed tablets

2.4.1. Physical parameters

2.4.1.1. Shape of tablet and general appearance: It was checked by magnifying lens after compression.

2.4.1.2. Physical appearance: The tablets were visually observed for capping, chipping, lamination and changes in colour.

2.4.1.3. Tablet Weight Uniformity: The uniformity of weight of 20 tablets was determined according to the USP method

[27]. An electronic balance (ME204, Mettler Toledo, Switzerland) was used to accurately weigh 20 tablets of each formulation which were randomly selected and the results (mean ± SD) were reported.

2.4.1.4. Weight variation: Twenty tablets are selected randomly and weighed individually to check for weight variation [24, 27].

2.4.1.5. Tablet thickness: The thicknesses of the tablets were determined by using Vernier calliper (Origin, Mitutoyo, Japan). Average values of 10 tablets were calculated. Variation in tablet may cause problems in counting and packaging. Tablet thickness should be controlled within a ±5% of a standard value [24, 28].

Similarly the diameter of the tablet can be used as initial controlled parameter. Ten tablets are required, and average values are calculated. Tablet diameter should be controlled within a ± 5% of a standard value.

2.4.1.6. Hardness: This test determines the ability of the tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined by using Monsanto hardness tester (EBT-2PL, Electrolab, Mumbai, India). It is expressed in kg/cm^2. Twenty tablets were randomly picked and hardness of the tablets was determined and reported [24].

2.4.1.7. Friability: The friability of the tablets was determined with Friabilator (EF2, Electrolab, Mumbai, India) according to the procedure for the USP [27]. Twenty tablets were selected randomly and weighed. The friability of tablets is determined by using Roche Friabilator for 100 revolutions. The friabilator is operated at 25 rpm for 4 min. The tablets are subject to combine effect of abrasion and shock in a plastic chamber and dropping a tablet at height of 6 in. in each revolution. The tablets were removed, de-dusted and weighed again. It is expressed in percentage (%). Friability of tablets less than 1% is considered acceptable. The % friability was then calculated by following formula [24, 28].

% Friability = (Initial Weight - Final Weight) / Initial Weight x 100

2.4.3. Drug content

Ten tablets (1.6 mg Tablets) were weighed and powdered in a glass mortar. A quantity of the powder equivalent to about 10 mg SPG was transferred into a 10-ml volumetric flask and volume was made upto the mark with diluent (Acetonitrile: O-Phosphoric acid; 70:30 %v/v). The stoppered flask was sonicated for 3 h in an Ultrasonicator bath (UCB-30, Spectralab, Mumbai, India). The resultant mixture was filtered through 0.45 µ membrane filter (Millipore Merck, Mumbai, India) and an

aliquot of 3 ml was taken in a 10-ml volumetric flask and volume was made up to 10 ml using diluent. Following suitably diluted aliquot and filtered through 0.22µ filter (Millipore Merck, Mumbai, India) was analyzed by HPLC at 270 nm using a UV detector spectrophotometer (Agilent 1260, USA) for SPG content. The HPLC apparatus consisted of Agilent 1260 HPLC pump (Agilent, USA), equipped with a UV detector, a Chromeleon Software (version 6.8) integrator software and a Inertsil ODS (4.6 mm x 250 mm) column. The mobile phase consisted of a mixture of acetonitrile and 0.1% O-phosphoric acid, pH 3 adjusted with Sodium hydroxide (70:30 % v/v) at a flow rate of 1.0 ml/min that led to retention time of 2.16 min when detection was carried out at 270 nm by injecting 10µl sample.

2.4.4. In vitro drug release study

Drug release studies were carried out on the matrix tablets of SPG using USP type II (Paddle) apparatus (EDT-08Lx, Electrolab, Mumbai, India) at 37°C ± 0.5°C and at 50 rpm. The dissolution studies were performed separately in three different media having distinct simulated physiological GIT pH and sampling time intervals. The dissolution study was performed in 900 ml of 0.1N HCl for two hours, and samples were withdrawn at 15, 20, 45, 60, 120 min. Second selected dissolution medium was pH 4.5 Acetate Buffer and samples were withdrawn at 0.5, 1,2,3,4 h. The third and most important dissolution medium selected was pH 6.8 Phosphate buffer and samples were withdrawn at 1,2,3,4,5,6,7,8,9,10,11,12 h. Sample (5 ml) was collected for analysis. Aliquot was withdrawn at different times and replenished immediately with the same volume of fresh dissolution medium. The withdrawn samples were filtered through whattman filter paper, suitably diluted and were analyzed by HPLC. The cumulative percentage of drug released was determined as a function of time.

The amount of SPG in matrix tablets was determined using regression data ($y= 1793.8x + 55364$, $R^2 = 0.9998$) obtained from calibration plot of SPG in pH 6.8 Phosphate. From this, plots of percentage drug released from the tablet formulations (mean ± S.D., n =6) versus time were established.

2.4.4.1. Kinetics of drug release

The kinetics of drug release from the matrix tablets was determined by fitting the appropriate drug release data to zero order [29], first order [30, 31], Higuchi equation [32] and the Korsmeyer-Peppas model [33, 34].

$Q = Q_0 + k_0 t$ (Zero Order)

$\ln Q = \ln Q_0 + k_1 t$ (First Order)

$Q = k_H t^{1/2}$ (Higuchi model)

$Q/Q_T = k_{kp} t^n$ (Korsmeyer-Peppas mode

where Q is amount of drug release at time t, Q_0 is the initial amount of drug, Q_R is the amount of drug remaining at time t, and Q_T is the total amount of drug release. k_0, k_1, k_H and k_{kp} are the kinetic constants for zero order, first order, Higuchi and Korsmeyer-Peppas models, respectively, and *n* is the release exponent.

The consolidated release kinetics of SPG matrix tablets has been tabulated.

2.4.4.1.1. Zero order kinetics

$$C = K_0 t$$

It describes the system in which the drug release rate is independent of its concentration [35]. *C* represents the cumulative amount of drug released in time *t* and K_0 is zero order release constant.

2.4.4.1.2. First order kinetics

$$LogC_t = logC_0 - K_1 t/2.303$$

It describes the drug release from the systems in which the release rate is concentration dependent [35]. Whereby, C_t is the amount of drug released in time *t*, C_0 is the initial concentration of drug and K_1 is the first order release constant.

2.4.4.1.3. Higuchi kinetics

$$W = K_2 t^{1/2}$$

It describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion [35]. *W* represents the cumulative amount of drug released in time *t* and K_2 is the Higuchi dissolution constant.

2.4.4.1.4. Korsmeyer Peppas equation

$$M_t/M_\infty = K_4 t^n$$

It describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation. Where K_4 is release constant, *n* is release exponent, indicative of the drug release mechanism and *F* represents the cumulative amount of drug dissolved in time *t*. For matrix tablets, if the release exponent $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion [36]. An exponent value of 0.89 is indicative of Case-II Transport or typical zero order release.

2.5. Accelerated stability studies

Accelerated stability studies for 3 months were carried out according to International Conference on Harmonization (ICH) guidelines [37] to study the quality of the finished optimized formulation F5 under a variety of conditions (time, humidity, and

temperature). Tablets were packed and sealed in a HDPE Bottle with child-resistant-closure of 60 tablets count. These sealed HDPE bottles were kept in a humidity chamber (KCS-1000 S/G, Kesar Control System, Ahmedabad, India) maintained at 45°C and 75% RH. At the end of every month the, samples were withdrawn and evaluated for drug content and % drug dissolved.

3. RESULTS AND DISCUSSION

In the present study, matrix tablets were formulated by direct compression method as described in materials and methods. Matrix tablet formulation needs an efficient release retarding materials which play a critical role in regulating drug release from matrix tablets. The objective of the study is to design Selexipag sustained release tablets employing a combination of retarding polymers for better controlled release.

The SPG sustained release tablets were prepared by direct compression method using 7 mm punch and each tablet contains 1.6 mg of SPG. In order to obtain sustained release dosage form, the release retardants like HPMC K5M, Sodium CMC and EC were exploited in the present study. The magnesium stearate was used as a lubricant to overcome sticking problem that may occur during the process of compression. MCC is used as an insoluble diluent.

All the formulations were evaluated for angle of repose, Carr's index and Hausner's ratio which provide the insight of flow property. Angle of repose was found in the range between 27° to 38°. Carr's index was found in the range of 9.49 % to 19.07 % and Hausner's ratio was found between 1.10 - 1.23. All these results as shown in Table 2 indicated that, the powder blend possesses good to excellent flow-ability and compressibility properties [27].

All the batches were produced under similar conditions to avoid processing variables and the hydrophilic matrix tablets from each batch were analyzed according to Pharmacopoeial methods for average mass, mass uniformity, crushing resistance and friability.

The prepared tablets were evaluated for their various physico-chemical properties. The tablets were white, circular in shape and were found to be uniform with respect to thickness (3.01 – 3.05 mm) and hardness (4.08 – 4.14 Kg/cm^2). The weight variation (0.4 – 0.7 %) and friability (0.11 – 0.56%) of different batch of tablets were found within the acceptable limits. Drug content (99.02 – 101.21%) was found uniform within the batches of different tablets. The results of physico-chemical evaluation of tablets are given in Table 3.

All the formulated sustained release tablets of SPG were prepared using three different

retarding polymers namely HPMC K5M, Sodium CMC and EC either as singular or in various combinations of two polymers at a time in different ratios (see Table 1). Following successful compression into tablets all formulated tablets were subjected for drug release. Results of percent cumulative drug released values are shown in (Figure 2-4).

The formulation with 1.6 % w/w of sodium CMC (F2) alone showed maximum release of SPG from 1.6 mg sustained release tablet (38.14%) within 2 hours in 0.1N HCl. The least release (14.41%) was observed with 1.6% EC (F3) as a single retarding agent. A similar release pattern was observed in pH 4.5 Acetate Buffer (Figure 3). The true sustained release characteristics of the developed formulations were revealed in pH 6.8 Phosphate Buffer. A complete drug release was observed with a single retarding agent, Sodium CMC (1.6%) in F2. Formulation F1, F4, F8 and F9 showed complete release of SPG within 9 hours (see Figure. 4). F1 consisted of sodium CMC 1.6%, F8 comprised of 0.4% HPMC K5M, 0.4% EC and Sodium CMC 0.8%. The composition of F9 is 0.8% HPMC K5M, 0.4% of each Sodium CMC and EC (see Table 1). Ratios of 1:1 of either of retarding agents were able to sustain the release of SPG for upto 9 hours in F4 and more than 11 hours in F5 and F6 at pH 6.8 (see Table 1 and Figure 4). At pH 6.8, F5 with 1:1 ratio of HPMC K5M and EC showed best sustained action for 12 hours. From the curves, it was also observed that EC alone at 1.6% (F3) was nearly similar to combination of 1:1 ratio (F5) of HPMC K5M and EC. The results of release pattern and kinetics showed that batch F3 and F5 having 1.6% sodium CMC and equal proportion of HPMC K5M and EC making 1.6% total or retarding agents, respectively gave better drug release in a controlled manner for 12 hours. Therefore, formulation F3 and F5 were considered as best formulations among all formulated batches.

Mean cumulative % release of SPG at different time intervals in pH 6.8 Phosphate Buffer are shown in Figure 4.

To describe the kinetics of drug release from matrix tablets, release data were analyzed according to different kinetic equations (zero order, first order, Higuchi model and Korsmeyer's-Peppas model). The data were analyzed by the regression coefficient method and regression coefficient values (r^2) of all batches in pH 6.8 Phosphate Buffer are shown in Table 4. On analyzing regression coefficient values of all batches, it was found that formulation F3 and F5 tablets exhibited almost zero-order kinetics. The *in vitro* release profiles of drug from all these formulations could

be best expressed by Higuchi's equation as the plots showed highest linearity (r^2 =0.98 to 0.99), except F3, F6 and F7 (r^2 = 0.97). To confirm the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation. The formulations showed good linearity (r^2 =0.97 to 0.99) with slope (*n*) between 0.54-0.75, which appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous non-Fickian diffusion. All formulations with slope (n) between 0.54 to 0.75, showed that they followed non-fickian diffusion.

This indicates drug release mechanisms involving combination of both diffusion and chain relaxation mechanisms. Therefore, the release of SPG from the prepared tablets is controlled by swelling of the polymers like HPMC K5M and Sodium CMC followed by drug diffusion through the swelled polymer and slow erosion of the tablet. Hydrophilic matrix tablets swell upon ingestion and a gel layer forms on the tablet surface. This gel layer retards further ingress of fluid and subsequent drug release. It has been shown that in case of hydrophilic matrices, swelling and erosion of the polymer occurs simultaneously and both of them contribute to the overall drug-release rate [38]. It is well documented that the drug release from hydrophilic matrices shows a typical time-dependent profiles (i.e. decreased drug release with time because of increased diffusion path length [34,39] this inherent limitations leads to zero-order release kinetics.

The stability study of selected formulations F3 (data not shown) and F5 were carried out and the results are as shown in Table 5. The results showed no significant changes in the physical parameters and % drug content. The dissolution studies were also carried out for both formulation F3 and F5 in pH 6.8 Phosphate Buffer and it was found that the % drug release pattern in 12 h were nearly similar to that of the initial zero month release behaviour (Figure 5) when stored at 40° C and 75% RH for 3 months. So it was considered that formulations having good stability.

Table 1: Composition of Selexipag Matrix Tablets

Component	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Selexipag	1.60	1.60	1.60	1.60	1.60	1.60	1.60	1.60	1.60
HPMC K 5M	1.60	0.00	0.00	0.80	0.80	0.00	0.40	0.40	0.80
Sodium CMC	0.00	1.60	0.00	0.80	0.00	0.80	0.40	0.80	0.40
Ethylcellulose	0.00	0.00	1.60	0.00	0.80	0.80	0.80	0.40	0.40
Microcrystalline cellulose (Avicel PH 101)	93.40	93.40	93.40	93.40	93.40	93.40	93.40	93.40	93.40
Magnesium Stearate	3.40	3.40	3.40	3.40	3.40	3.40	3.40	3.40	3.40
Total weight (mg)	100	100	100	100	100	100	100	100	100

Table 2: Pre-compressional parameters of granules

Formula Code	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index	Hausner's Ratio	Angle of Repose (°)
F1	0.54	0.60	10.7143	1.12	31
F2	0.65	0.81	19.0726	1.2356	38
F3	0.69	0.83	17.1461	1.2069	37
F4	0.59	0.69	14.1716	1.1651	34
F5	0.63	0.76	17.4603	1.2115	37
F6	0.59	0.68	13.095	1.1506	32
F7	0.66	0.73	9.4922	1.1048	27
F8	0.65	0.72	9.7826	1.1084	27
F9	0.57	0.64	10.5769	1.1182	30

Table 3: Post-compressional parameters of Tablets

Formula Code	Weight (mg ± SD) (*n*=20)	Thickness (mm ± SD) (*n*=10)	Hardness (Kg/cm^2) (*n*=10)	Friability (%)	Assay (%)
F1	100.50 ± 0.685	3.04 ± 0.06	4.13 ± 0.10	0.17	99.83
F2	100.69 ± 0.867	3.03 ±0.03	4.13 ± 0.08	0.56	100.05
F3	100.68 ± 0.892	3.03 ± 0.02	4.14 ± 0.11	0.27	100.01
F4	100.72 ± 0.846	3.03 ± 0.03	4.14 ± 0.13	0.30	99.02
F5	100.92 ± 0.840	3.04 ± 0.03	4.12 ± 0.11	0.20	100.02
F6	100.62 ± 1.083	3.05 ± 0.03	4.13 ± 0.11	0.14	100.24
F7	99.73 ± 0.486	3.01 ± 0.02	4.10 ± 0.11	0.11	99.45
F8	100.02 ± 0.024	3.02 ± 0.01	4.08 ± 0.09	0.55	101.21
F9	100.01 ± 0.067	3.01 ± 0.01	4.08 ± 0.10	0.50	101.00

Table 4: Release Kinetics of SPG Matrix Tablets in pH 6.8 Phosphate Buffer

Formula Code	Zero Order		First Order		Higuchi		Korsmeyer Peppas	
	r^2	K_0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_H ($h^{-1/2}$)	r^2	*n*
F1	0.922	18.240	0.864	2.232	0.990	5.730	0.991	0.564
F2	0.938	15.110	0.945	2.084	0.995	7.306	0.993	0.548
F3	0.995	5.821	0.909	2.132	0.976	27.850	0.987	0.759
F4	0.951	16.570	0.844	2.151	0.983	7.397	0.979	0.527
F5	0.979	12.040	0.873	2.180	0.980	17.980	0.981	0.628
F6	0.977	11.910	0.864	2.160	0.973	17.150	0.977	0.613
F7	0.964	13.120	0.937	2.081	0.978	4.980	0.974	0.615
F8	0.955	15.580	0.889	2.109	0.984	8.827	0.981	0.542
F9	0.922	18.600	0.936	2.099	0.991	5.601	0.991	0.562

Table 5: Physico-chemical parameters of Matrix Tablets after 3 months storage at 40°C/75% RH

Formula Code	Weight (mg ± SD) (*n*=20)	Thickness (mm ± SD) (*n*=10)	Hardness (Kg/cm2) (*n*=10)	Friability (%)	Assay (%)
F1	100.43 ± 0.672	3.01 ± 0.03	4.21 ± 0.11	0.20	98.81
F2	100.58 ± 0.789	3.03 ± 0.04	4.18 ± 0.09	0.50	99.92
F3	100.72 ± 0.825	3.02 ± 0.03	4.20 ± 0.13	0.34	99.78
F4	100.65 ± 0.892	3.01 ± 0.05	4.19 ± 0.15	0.38	98.02
F5	100.81 ± 0.798	3.04 ± 0.04	4.21 ± 0.11	0.29	99.05
F6	100.59 ± 1.028	3.04 ± 0.03	4.13 ± 0.12	0.25	99.62
F7	99.81 ± 0.525	3.02 ± 0.03	4.14 ± 0.11	0.21	98.85
F8	100.05 ± 0.152	3.01 ± 0.01	4.15 ± 0.09	0.57	100.37
F9	100.00 ± 0.089	3.01 ± 0.01	4.13 ± 0.10	0.58	100.00

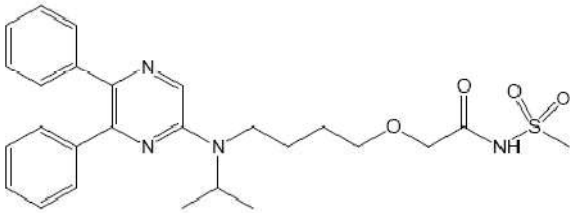

Figure 1: Structure of Selexipag

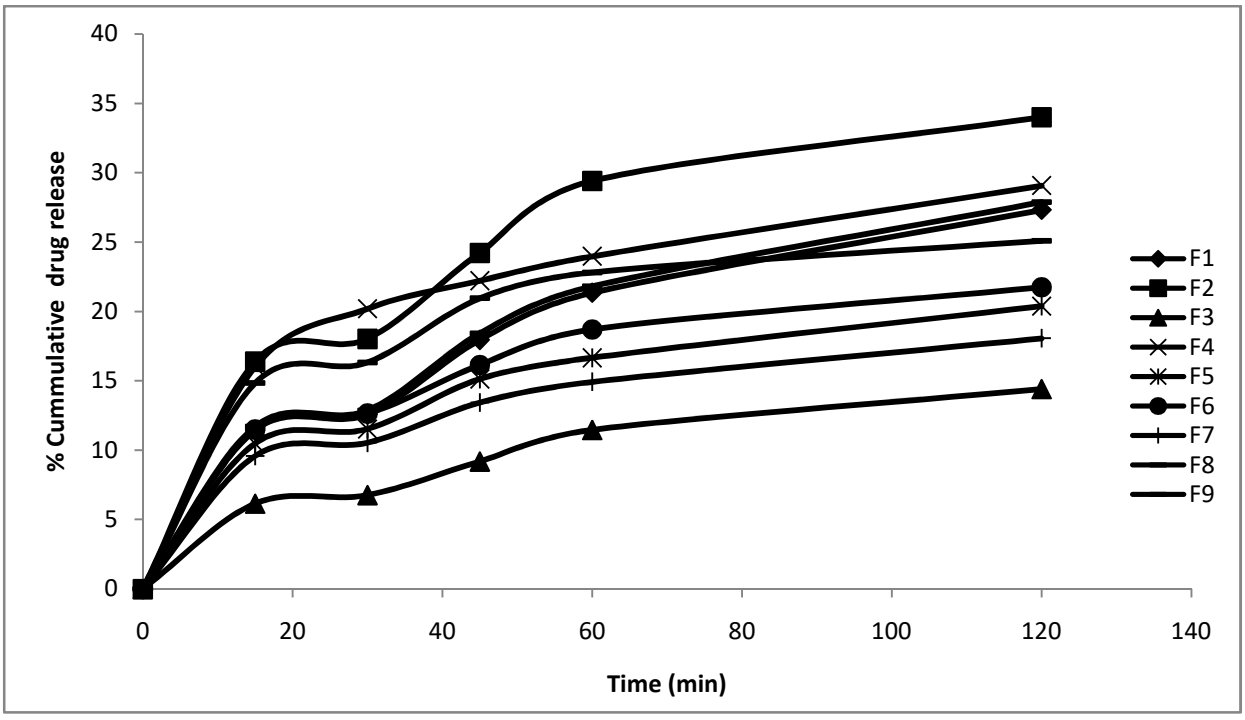

Figure 2: Drug release profile of SPG Matrix tablets in 0.1N HCl

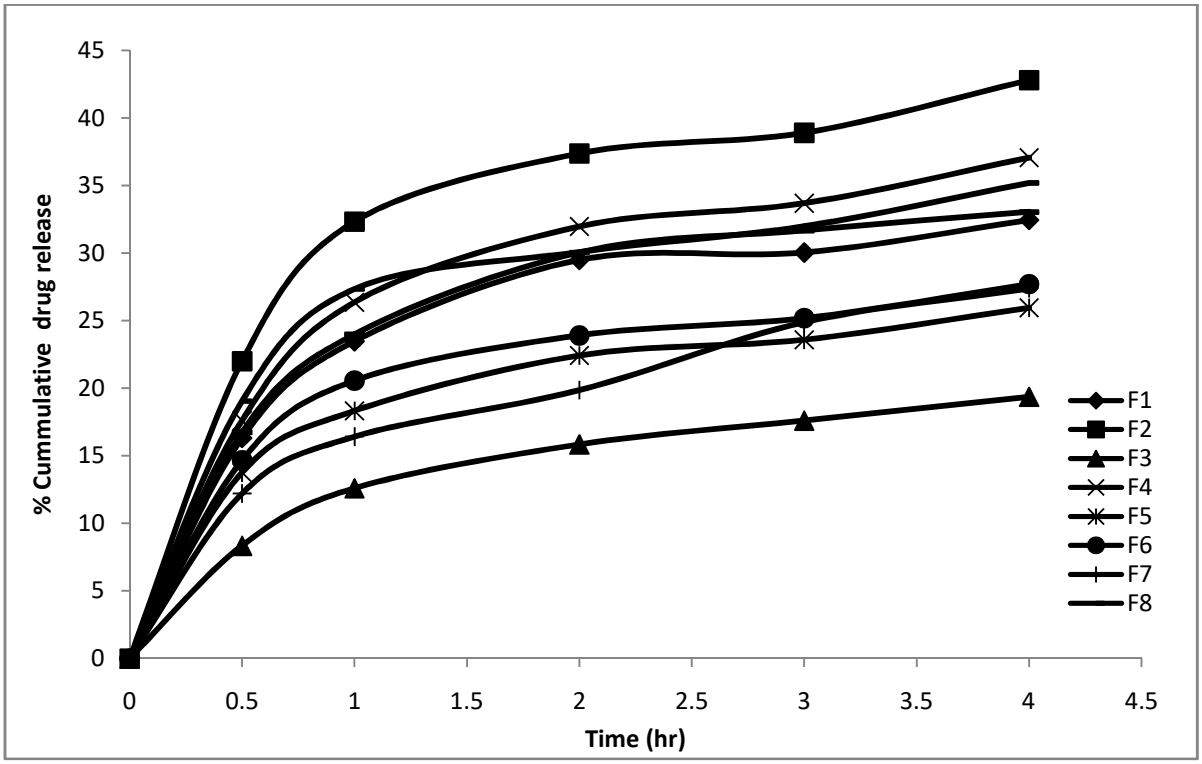

Figure 3: Drug release profile of SPG Matrix tablets in pH 4.5 Acetate Buffer

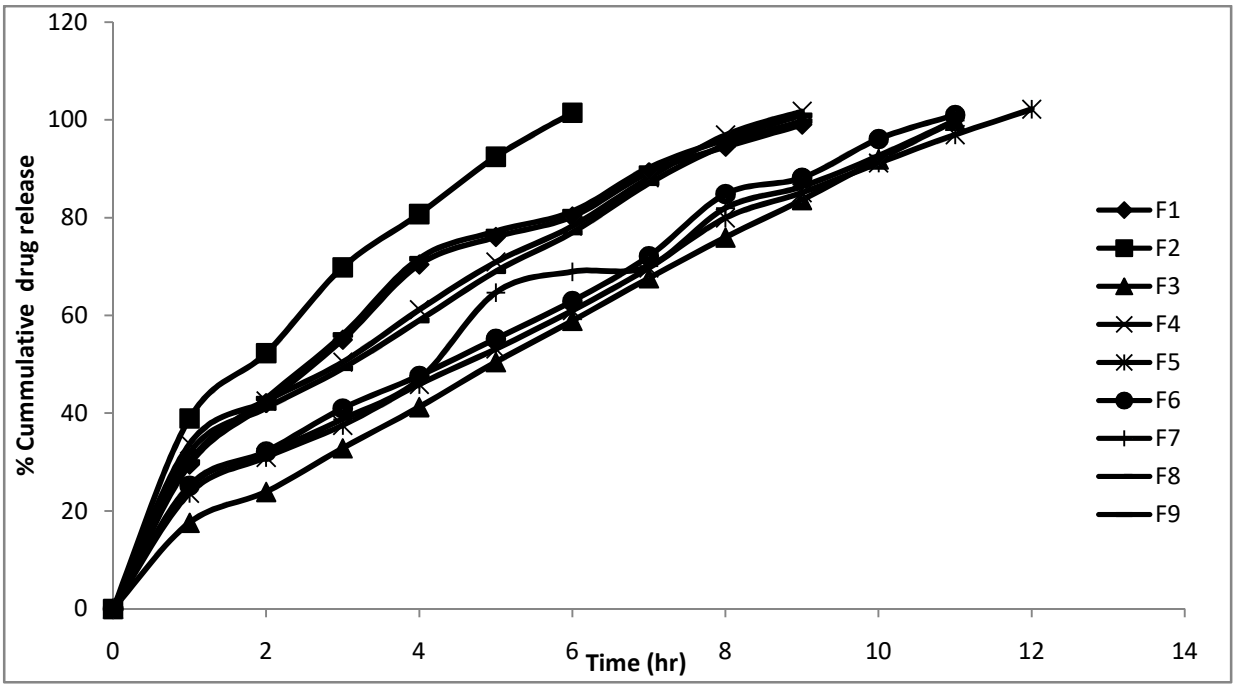

Figure 4: Drug release profile of SPG Matrix tablets in pH 6.8 Phosphate Buffer

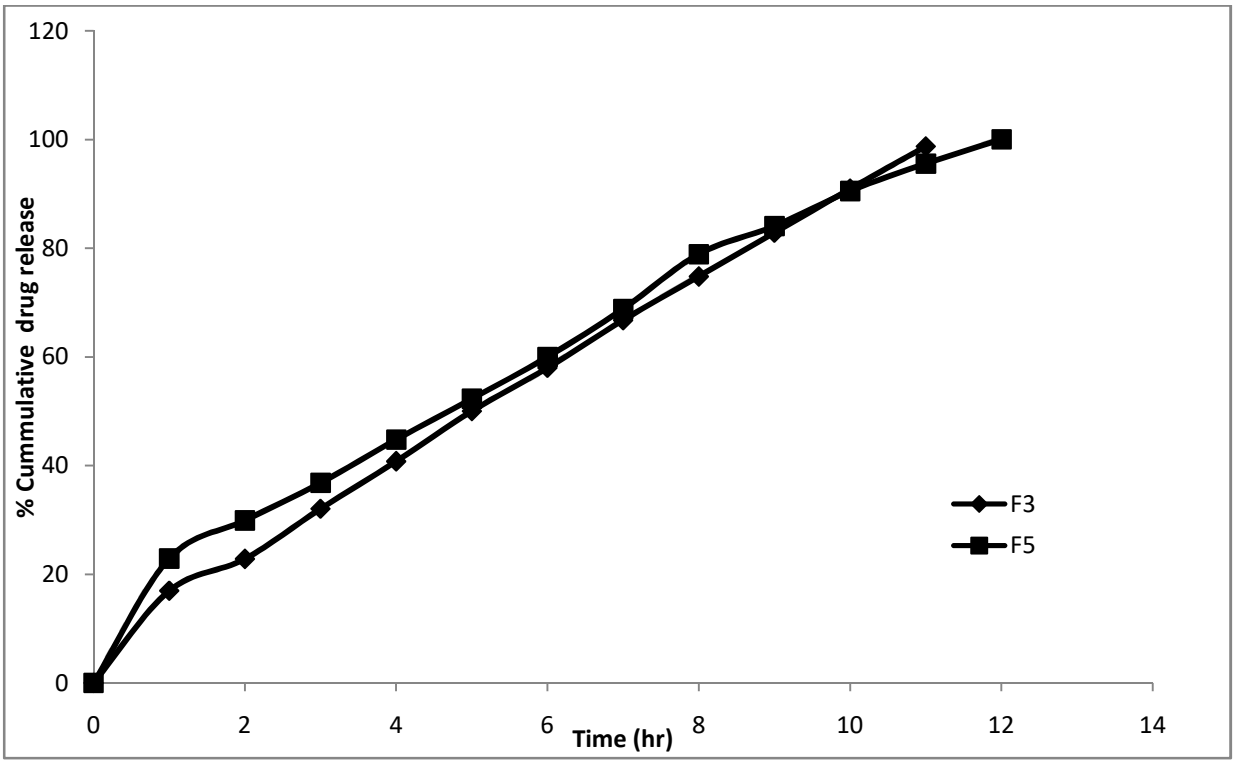

Figure 5: Drug release profile of SPG Matrix tablets in pH 6.8 Phosphate Buffer after 3 months (40°C/75% RH)

4. CONCLUSIONS

Sustained release matrix tablets of Selexipag were prepared using different ratios of hydroxypropylmethylcellulose, sodium carboxymethylcellulose and ethylcellulose. Direct compression method was employed to prepare the tablets. The comparative release studies revealed that the release rate was dependent on the relative amounts of polymers. The drug release for all the prepared tablets has shown mechanisms involving a combination of both diffusion and chain relaxation of polymers. It is thus possible to choose either single polymer ethylcellulose or combination of hydroxypropylmethylcellulose with ethylcellulose to formulate a sustained release tablet for controlled delivery of Selexipag for better management of pulmonary arterial hypertension. Future studies can be conducted to evaluate these matrix tablets *in vivo* in the case of developing a sustained release dosage form of the drug for better therapy and more patient compliance.

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