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Research Article

Optimization of Selexipag Cocrystal Encapsulated Formulation to Improve Drug Release

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ABSTRACT

Selexipag, a prostacyclin receptor agonist for pulmonary arterial hypertension (PAH), exhibits poor aqueous solubility and limited oral bioavailability. This study aimed to enhance its solubility and dissolution by forming pharmaceutical cocrystals with Nicotinamide and Benzoic acid using the solvent evaporation method in molar ratios of 1:1, 1:1.5, and 1:2. Characterization through FTIR, DSC, and PXRD confirmed new crystalline phases, while SEM revealed morphological changes supporting improved solubility. Among all, F6 (Selexipag: Benzoic acid, 1:2) showed the highest solubility (0.016 mg/mL) and 97.10% drug release at 60 minutes, followed by F3 (Selexipag: Nicotinamide, 1:2) with 93.98%. Capsule formulations of F3 and F6 achieved over 94% release within 30 minutes, outperforming the pure drug (38.75%). All formulations exhibited excellent micromeritic properties and complied with USP standards. Thus, co-crystallization proved an effective approach to improve Selexipag solubility and therapeutic potential in PAH treatment.

INTRODUCTION

Poor aqueous solubility remains one of the major challenges in pharmaceutical formulation and drug development. A large proportion of newly discovered drug molecules fall under Biopharmaceutical Classification System (BCS) Class II and IV, which exhibit low solubility and variable bioavailability. Insufficient solubility leads to slow dissolution in gastrointestinal fluids, resulting in reduced absorption and therapeutic efficacy. To achieve desired pharmacological action, a drug must first dissolve in the biological medium before it can be absorbed into systemic circulation. Therefore, improving the solubility and dissolution rate of poorly water-soluble drugs is crucial for enhancing bioavailability and therapeutic performance.

Various strategies have been explored to overcome solubility-related challenges, including

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micronization, salt formation, solid dispersion, and use of surfactants. However, these methods often have limitations depending on the physicochemical nature of the drug. In recent years, pharmaceutical cocrystallization has emerged as an effective and versatile approach for modifying the physicochemical properties of active pharmaceutical ingredients (APIs) without altering their pharmacological activity. Cocrystals are formed by the interaction of the drug with a pharmaceutically acceptable co-former through non-covalent hydrogen bonding. This approach enhances solubility, dissolution rate, and stability, making it a promising technique for improving the oral bioavailability of poorly soluble drugs such as Selexipag.

PRE-FORMULATION STUDIES:[1]

1) Organoleptic properties:

The colour, odour, and taste of the drug were characterized and recorded and the results of this are shown in table no 4.

2) Solubility studies:

It determined by dissolving drug substance in water, phosphate buffer pH6.8, methanol, ethanol, DMSO, the solubility study was conducted taking excess amount of the drug in 10ml of solution. Then the samples were kept in the water bath shaker and agitated for 24hrs at 37±0.5ºC. the samples were filtered and suitably diluted. The samples were analysed spectrophotometrically at λ max. the concentration of drug was determined using respective standard graph and shown in table no 4.

3) Melting Point:

Melting point of Selexipag was determined by open capillary method. Fine powder of Selexipag was filled in a glass capillary tube (sealed at one end). Capillary tube was tied to thermometer and was placed in the Thieles tube was further placed on flame. The temperature at which the powder starts melting was noted and reported in table no 4.

SPECTROSCOPIC STUDIES; [2]

Determination of λ max:

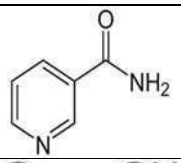
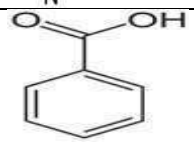
Most of the drugs absorbs light in UV wavelength region (200-400) nm hence λmax was determined by using UV spectrophotometer. beers range for Selexipag was found to be (10 µg/ml -30 µg/ml). The solution containing 10µg/ml concentration prepared and scanned over the range of 200-400nm phosphate buffer pH 6.8 as blank using double beam UV spectrometer. The maximum wavelength obtained in the graph at Fig No.8 was consider as λmax of the pure drug

PREPARATION OF STANDARD STOCK SOLUTION AND STANDARD CALIBRATION CURVE OF SELEXIPAG

A standard stock solution of Selexipag (1000 µg/mL) was prepared in phosphate buffer (pH 6.8). An intermediate stock (100 µg/mL) was obtained by dilution, followed by serial dilutions (0–30 µg/mL). Absorbance was measured at λmax, and a calibration curve was constructed for analysis.

Screening of Co-formers[3]

Table.No.01 The data of co-formers considered for the study

Sr. No.	Co-former	Structure	Molecular formula	Molecular weight (g/mol)	Melting point (°C)	HB Donors	HB Acceptors
1	Nicotinamide		$C_6H_6N_2O$	122.12g/mol.	128–131°C	2	2
2	Benzoic acid		$C_7H_6O_2$	122.12g/mol.	122–123°C	1	1

Selection of co-formers[4]

Co-formers were selected based on Hansen solubility parameter and ΔpKa.

Hansen solubility parameter

It divides cohesive energy into dispersion, polar, and hydrogen-bonding components to predict miscibility and compatibility of pharmaceutical materials. Theoretical HSP values of Selexipag and its co-formers were calculated using group contribution methods to evaluate their miscibility and potential for co-crystal formation.

Group contribution method:

The solubility parameter was estimated using Van Krevelen's, Fedor's, and Hoy's group contribution methods. These theoretical approaches aid in selecting co-formers compatible with the drug. Partial solubility parameters were calculated by combining molecular force and molar volume contributions from all structural fragments.

- **Fedor's substituent constant =**

$$CED = \frac{\Sigma \Delta U}{\Sigma \Delta V} \quad \text{....(1)}$$

- **Hoy's substituent constant =**

$$\square MA \div \square\square V \quad \text{....(2)}$$

- **Krevelen =**

$$\sqrt{\delta F_d^2 + \delta F_p^2 + \delta U_h^2} \quad \text{....(3)}$$

Based on ΔpK_a Values:

The ΔpK_a value ($\Delta pK_a = pK_a$ drug - pK_a co-former) is widely accepted as the key to predict the formation of a salt or co-crystal. It is generally considered that if $\Delta pK_a > 3$, the resulting compound will be a salt. A co-crystal may result, if ΔpK_a is < 0. For ΔpK_a between 0 to 3, the outcome can be either a salt or a co-crystal or a complex with partial proton transfer. The pK_a values were collected from the literature, ΔpK_a values were calculated, and summarized.

METHOD FOR PREPARATION OF CO-CRYSTAL OF SELEXIPAG

Table No.2. Preparation of Selexipag Co-crystals

Formulation Code	API (mg)	Co-former (mg)
F1 (1:1 NIC)	1.6	1.6
F2 (1:1.5 NIC)	1.6	2.4
F3 (1:2 NIC)	1.6	3.2
F4 (1:1 BNZ)	1.6	1.6
F5 (1:1.5 BNZ)	1.6	2.4
F6 (1:2 BNZ)	1.6	3.2

SYNTHESIS VIA SOLVENT EVAPORATION METHOD

Cocrystals of Selexipag with Nicotinamide and Benzoic acid were prepared by the solvent evaporation method in 1:1, 1:1.5, and 1:2 molar ratios. The drug was dissolved in methanol and the co-former in water, then mixed with stirring and

ultrasonication. The co-former solution was added dropwise to the drug solution under constant stirring until solvent evaporation. The resulting cocrystals were dried overnight in a desiccator.

CHARACTERIZATION OF SELEXIPAG CO-CRYSTALS

Melting point: The melting point of the Selexipag co-crystals were determined using open capillary tubes.

Drug content: Accurately weighed 10 mg of co-crystals were dissolved in methanol and the volume made up to 10 mL. From this, 1 mL was diluted to 10 mL with phosphate buffer (pH 6.8), and absorbance was measured. The percentage drug content was then calculated and recorded.

Aqueous solubility studies: The solubility of pure Selexipag and its co-crystals was evaluated in distilled water. Excess samples were shaken at 25 °C and 75 rpm for 24 hours to reach equilibrium. The equilibrated solutions were filtered, diluted with phosphate buffer (pH 6.8), and analyzed at 298 nm.

***In vitro* dissolution studies:** Dissolution studies were performed in phosphate buffer (pH 6.8) using a USP Type II (paddle) apparatus for 60 minutes. Capsules containing pure Selexipag or co-crystals equivalent to 25 mg of drug were tested in 900 mL of medium at 37 ± 0.5 °C and 50 rpm. Samples were withdrawn at 5, 10, 20, 30, 45, 50, and 60 minutes. Each sample was filtered through a 0.45 µm membrane and suitably diluted. The absorbance was measured at 298 nm using phosphate buffer (pH 6.8) as blank.

FTIR: FTIR spectrum of Selexipag co-crystals were obtained and compared with the pure drug to determine the possibility of co-crystal formation.

Differential Scanning Calorimetry: DSC studies were performed for co-crystals in the manner explained earlier. The DSC thermogram of the co-crystals were compared with that of the pure drug.

X-Ray diffraction studies: PXRD (Powder X-ray Diffraction) was used to study the crystal structure and identify crystalline phases of Selexipag co-crystals

SEM: Surface morphology of cocrystals was examines by Scanning Electron Microscopy (SEM)

FORMULATION DESIGN FOR DRUG LOADED CAPSULES.

Table No.3. Formulations design for capsule containing Selexipag co-crystals.

Formulation code	Selexipag cocrystals (mg)	Microcrystalline cellulose (mg)	Crospovidone (mg)	Magnesium stearate (mg)
F1 (1:1) NIC	1.994	89.150	4.920	3.936
F2(1:1.5) NIC	2.191	88.953	4.920	3.936
F3 (1:2) NIC	2.388	88.756	4.920	3.936
F4(1:1) BNZ	1.994	89.150	4.920	3.936
F5(1:1.5) BNZ	2.191	88.953	4.920	3.936
F6(1:2) BNZ	2.388	88.756	4.920	3.936

MICRO MERITIC STUDY:

i. Angle of repose: [6]

The angle of repose (θ) was determined by the fixed funnel method to assess the flowability of Selexipag cocrystals. The funnel height was

adjusted so that its tip just touched the pile surface. Accurately weighed cocrystals were allowed to freely pass through the funnel to form a heap.

ii. Determination of Bulk density :[7]

Bulk density is the ratio of the weight of the powder and the volume it occupies; it is expressed in gms/ml. Bulk density is imparted in determining the size of the container needed for handling and processing. A weighed quantity of the cocrystals (W) was carefully taken into a graduated measuring cylinder and the volume occupied by it (V_0) was measured. The bulk density was calculated using the formula

$$\text{Bulk density} = \frac{\text{weight of the cocrystal(w)}}{\text{Initial volume occupied by the cocrystals}}$$

iii. Tapped density:

Tapped density is the ratio of the powder weight to the volume after compaction, expressed in g/ml. It was determined by tapping a graduated cylinder containing a known weight of cocrystals until the volume became constant. The procedure was performed using a bulk density apparatus set for 100 tapings. The initial (V_0) and final (Vf) volumes were recorded to calculate tapped density.

$$\text{Tapped density} = \frac{\text{Weight of the cocrystal(w)}}{\text{Final volume occupied by the cocrystal}}$$

iv. Determination of Hausner's ratio:

It is another parameter for measuring flow ability of the microsphers.it is calculated using the formula.

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

v. Determination of compressibility index:

It is indirect measurement of bulk density, size, and shape, surface moisture content and cohesiveness of materials since all that can influence the consolidation index. It is also called as compressibility index. It is denoted by Ci and is calculated using the formula below.

$$Ci = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

CHARACTERIZATION OF CAPSULE CONTAINING CO-CRYSTALS OF SELEXIPAG.

Percentage weight variation

The test was carried out by weighing 6 capsules individually using analytical balance, then calculating the average weight, and comparing the individual capsule weights to the average. The percentage of weight variation is calculated by using the following formula.

$$\textbf{\% weight variation} = \frac{\text{Individual weight}}{\text{Average weight}} \text{ X } 100$$

Disintegration test.[9]

The disintegration apparatus, described in IP was used for the study. It contains two basket rack assembly. Each basket rack assembly consists of six glass tubes that are the 3 inches long, open at the top and held against the 10-mesh screen at the bottom. Each capsule was placed in each tube, and containing distilled water as medium. 37±2º C temperature was maintained throughout the study. Time required for the complete disintegration of capsule was noted.

***In-vitro* drug release study:** [8]

In-vitro dissolution studies were performed using a USP Type-I apparatus with 900 ml of 6.8 pH phosphate buffer at 37 ± 0.5 °C and 50 rpm for 1 hour. Samples (5 ml) were withdrawn at 5–60 min

intervals and replaced with fresh medium. Drug concentration was analyzed using a UV spectrophotometer at 298 nm. Comparative dissolution studies were conducted for pure Selexipag and formulation F6 under identical conditions.

RESULTS AND DISCUSSIONS

PREFORMULATION STUDIES OF SELEXIPAG

Table.No.4. Preformulation studies of Selexipag

Properties	Reported	Observed
Appearance	White powder	Complies
Taste	Slightly bitter in taste	Complies
Odour	Odourless	Complies
Melting point	134ºC - 139ºC	139ºC
Solubility	Poorly soluble in water	0.01mg/mL
	Soluble in ethanol	19mg/mL

Preformulation studies confirmed that Selexipag meets pharmacopeial standards. It is a white, odourless powder with a slightly bitter taste. The melting point was 139 °C, indicating purity and crystalline nature. UV spectroscopy showed a λmax at 299 nm, confirming the drug's identity and suitability for formulation development.

Determination of λ max

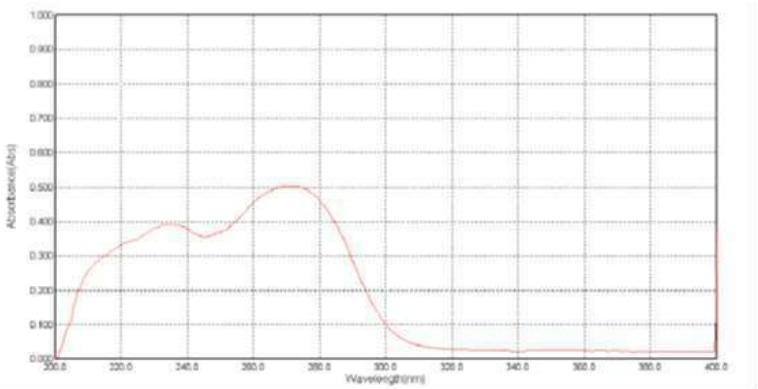


Fig No.1: λ max of Selexipag in phosphate buffer pH 6.8.

This was performed by using UV spectrophotometer by using pH 6.8 phosphate buffer as medium. The spectrum of Selexipag (10µg/ml) in pH 6.8 showed the peak at 298nm. The absorption maximum (λ max) of 298 was selected for the study.

Calibration curve of Selexipag:

Table No.5: Spectrometric data for standard cure of Selexipag in Ph 6.8 Phosphate buffer

Sr. No	Concentration (µg/mL)	Absorbance (AU)
1	0	0.0013
2	5	0.1263
3	10	0.2512
4	15	0.3761
5	20	0.5011
6	25	0.6260
7	30	0.7509

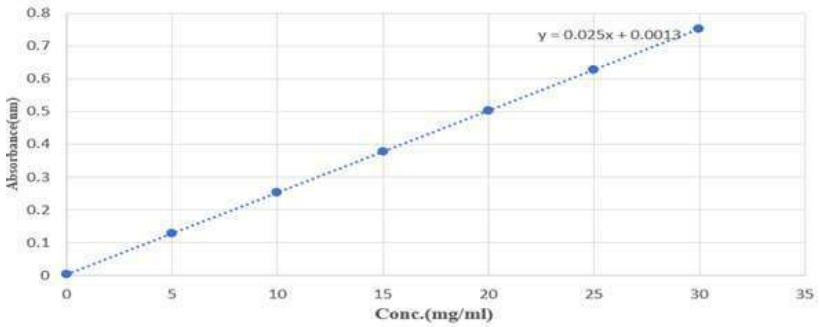


Fig No.2. Standard plot of Selexipag in phosphate buffer 6.8

The calibration curve of Selexipag in pH 6.8 phosphate buffer exhibited excellent linearity within the concentration range of 0–30 µg/mL. The absorbance values increased proportionally with concentration, following the equation Absorbance = 0.02499 × Concentration + 0.00130, with a correlation coefficient (R^2) of 0.9999, indicating high precision and accuracy of the method. The lowest absorbance recorded was 0.0013 at 0 µg/mL, while the highest was 0.7509 at 30 µg/mL. This strong linear relationship confirms the suitability of this method for the quantitative estimation of Selexipag.

Authentication of Selexipag

Melting point: Melting point of Selexipag was found to be 138 °C which agreed to the value 134-139 °C in the literature.

FTIR spectrum: IR spectrum of Selexipag is shown in Figure 3. The spectra showed peaks at 3360.60cm^{-1} corresponding to N-H stretch, 1240.23cm^{-1} corresponding to C-N stretching, 1724 cm^{-1} and 1558 cm^{-1} corresponding to carbonyl group and C stretching respectively.

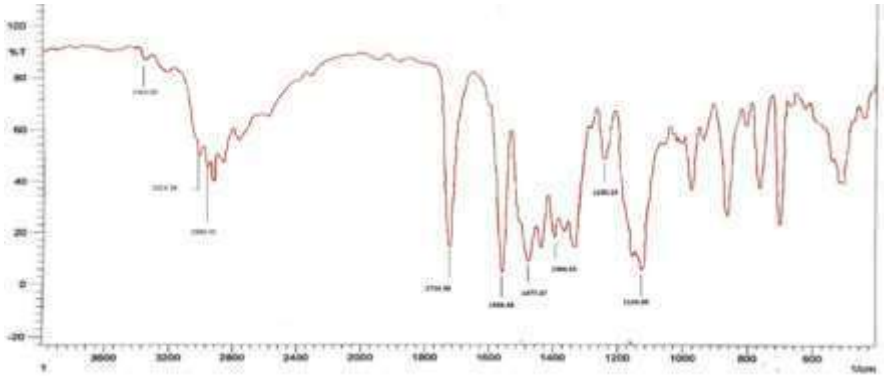


Fig.No.3. FTIR spectrum of pure Selexipag

DSC

Thermogram obtained from DSC study is shown in figure 4.

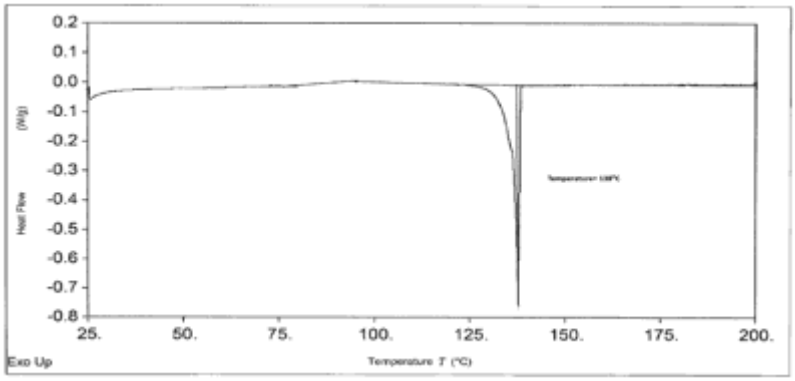


Fig.No.4. DSC of pure Selexipag

Selection of Co-formers

Hansen solubility parameter: The HSPs of the co-formers and drug were calculated using group contribution methods and the values are tabulated in Table 6,7,8

Table.No.6 Calculation of solubility parameter of Selexipag based on Fedor's substituent constants

Structural group	ΔU (cal/mol)	Count	Total ΔU (cal/mol)	ΔV (cm^3/mol)	Total ΔV (cm^3/mol)
-CH3	1125	2	2250	33.5	67.0
-CH2-	1125	4	4500	16.1	64.4
Aromatic CH (-C-H)	1180	10	11800	16.1	161.0
Aromatic C (quaternary)	1000	2	2000	14.0	28.0
>C< (quaternary sp3)	1090	1	1090	-5.5	-5.5
-C=O (amide)	4150	1	4150	10.8	10.8
-SO2- (sulfonyl)	3380	1	3380	12.0	12.0
-NH- (amide NH)	1000	1	1000	-9.0	-9.0
-O- (ether)	1700	1	1700	3.8	3.8
Aromatic N (pyrimidine)	500	2	1000	2.0	4.0
TOTAL			31120		336.5

Solubility parameter of Selexipag based Hoy's Molar attraction constants

Table. No.7 Calculation based Hoy's Molar attraction constants

Fragment (atom/group)	Number of groups	Molar attraction for each (F) [(cal·cm^3) ^1/2·mol^{-1}]	Total molar attraction (count × F) [(cal·cm^3) ^1/2·mol^{-1}]	ΔV for each fragment (cm^3/mol)	Total ΔV (count × ΔV) (cm^3/mol)
Aliphatic CH_3 (methyl)	3	147.30	441.90	33.5	100.5
Aliphatic CH_2 (methylene)	5	131.50	657.50	16.1	80.5
>CH (aliphatic, methine)	1	85.99	85.99	10.8	10.8
Aromatic CH (Ar–CH)	10	117.12	1,171.20	16.4	164.0
Aromatic C (quaternary, Ar–C)	2	98.12	196.24	14.8	29.6
Ether oxygen (–O–, ether link)	1	114.98	114.98	6.0	6.0

Amide carbonyl (>C=O)	1	262.96	262.96	10.8	10.8
Tertiary aliphatic N (–N–)	1	125.00	125.00	2.3	2.3
Aromatic N (pyrazine/pyridine-type N)	2	121.50	243.00	2.3	4.6
Sulfone (–SO_2–) + S–CH_3 (estimated)	1	**300.00** (estimated)	300.00	**46.0** (estimated)	46.0
Totals (sum)	—	—	**3,598.77**	—	**455.10**

Calculation of solubility parameter of Selexipag based on partial solubility parameter or Van Krevelen method

Table No.8. Calculation of solubility parameter of Selexipag based on partial solubility parameter or Van Krevelen method

Structural group	No. groups	Fd (per) (cm^3/mol)	Total Fd (cm^3/mol)	Fp (per) (units)	Total Fp (units)	Fp^2 (per)	Uh (per)	Total Uh
Aliphatic CH_3 (methyl)	3	33.50	100.50	0.00	0.00	0.000	0.00	0.00
Aliphatic CH_2 (methylene)	5	16.10	80.50	0.00	0.00	0.000	0.00	0.00
Aliphatic >CH (methine)	1	10.80	10.80	0.00	0.00	0.000	0.00	0.00
Aromatic CH (Ar–CH)	10	16.40	164.00	0.00	0.00	0.000	0.00	0.00
Aromatic C (quaternary Ar–C)	2	14.80	29.60	0.00	0.00	0.000	0.00	0.00
Ether O (–O–, ether link)	1	6.00	6.00	0.80	0.80	0.64	0.50	0.50
Amide carbonyl (>C=O, amide)	1	10.80	10.80	3.20	3.20	10.24	8.00	8.00
Amide –NH (amide H-donor)	1	0.00	0.00	1.50	1.50	2.25	6.00	6.00
Tertiary aliphatic N (–N–)	1	2.30	2.30	1.20	1.20	1.44	0.30	0.30
Aromatic N (pyridine/pyrimidine type)	2	2.30	4.60	1.50	3.00	2.25	0.20	0.40
Sulfone –SO_2– (incl. S–CH_3) (est.)	1	46.00	46.00	2.50	2.50	6.25	10.00	10.00
Totals (sum)	—	—	**455.10**	—	**12.20**	**23.02**	—	**25.20**

In a similar manner, HSP values were calculated for 2 co-formers selected based on the literature and availability in laboratory and are shown in the Table No.9. The differences in the solubility parameter values of Selexipag and co-formers were calculated. These values indicated the possibility of co-crystal formation.

HSP values of co-formers by different methods

Table No.9. Calculated HSP values of co-formers by different methods

Sr. No.	Co-former	Solubility parameter ($MPa^{1/2}$)		
		Fedors	Hoy's	Van Krevelen's
1	Selexipag (drug)	19.68	16.16	16.0
2	Nicotinamide	22.9	23.0	23.1
3	Benzoic acid	22.0	22.2	22.4

Table No.10. Differences in the solubility parameter values of drug & co-former and possibility of co-crystal formation.

Sl. No.	Co-former	Fedors	Hoy's	Van Krevlen's	Inference
1	Nicotinamide	-3.3	-6.84	-7.1	Co-crystal
2	Benzoic acid	-2.4	-6.1	-6.4	Co-crystal

Based on ΔpK_a Values: The pK_a values were collected from the literature, ΔpK_a values were calculated, and summarized as shown in Table.No.11

Table No.11. The data of pK_a of co-formers and ΔpK_a values

Sr. No.	Drug	pK_a	ΔpKa	Inference
1	Selexipag (API)	5.6	-	-
	Co-formers			
2	Nicotinamide	3.35	2.25	Co-crystal
3	Benzoic acid	4.20	1.4	Co-crystal

Comparing all formulation to Hansen solubility parameter

Table No.12 Interpretation of Hansen solubility parameters

Formulation	Coformer Ratio	δD ($MPa^{1/2}$)	δP ($MPa^{1/2}$)	δH ($MPa^{1/2}$)	δ_total ($MPa^{1/2}$)	Ra vs Selexipag
F1	1:1(NIC)	16.4	5.9	8.8	20.0	10.1
F2	1:1.5(NIC)	16.9	6.9	9.6	20.9	9.9
F3	1:2(NIC)	17.3	7.7	10.5	21.7	9.7
F4	1:1 (BNZ)	16.5	4.1	9.0	19.5	9.2
F5	1:1.5 (BNZ)	17.1	4.7	10.0	20.5	9.0
F6	1:2 (BNZ)	17.6	5.1	10.5	21.2	8.6

Comparing pKa values helps predict cocrystal or salt formation. Selexipag has a weakly acidic group (pKa 4.8). Nicotinamide (pKa 3.3) and Benzoic acid (pKa 4.2) show $\Delta pKa < 3$, indicating a tendency toward cocrystal formation rather than salt. This supports selecting these coformers for screening.

Co-crystals were prepared by solvent evaporation method. Nicotinamide and Benzoic acid were selected hence; the co-crystals were successfully obtained with these co-formers. The prepared co-crystals were further subjected to evaluation and characterization.

Preparation of Selexipag co-crystal

Fig No.5. Selexipag Cocrystal

Characterization of Selexipag co-crystals

a. Melting point

Table No.13. Melting point of Selexipag co-crystals

Formulation Code	Observed Melting Point (°C)
Pure Selexipag	139.0
F1 (1:1 NIC)	136.8
F2 (1:1.5 NIC)	134.6
F3 (1:2 NIC)	134.1
F4 (1:1 BNZ)	137.5
F5 (1:1.5 BNZ)	135.2
F6 (1:2 BNZ)	133.9

The melting point of pure Selexipag was 139°C. All cocrystal formulations showed a decrease in melting point, with F3 and F6 exhibiting the greatest reduction, confirming stable co-crystal formation and improved solubility.

Drug content determination:

Table No.14. Drug content determination

Sr. No.	Formulation code	Drug content (mg)
1	F1	89.24±0.48
2	F2	78.03±0.74
3	F3	75.00±0.52
4	F4	89.24±0.48
5	F5	78.03±0.74
6	F6	75.00±0.52

All the value represents are mean of 3 readings (n-3)

The drug content results show uniformity among formulations, indicating consistent mixing and encapsulation. F1 and F4 have the highest drug content (89.24 mg), followed by F2 and F5 (78.03 mg), while F3 and F6 have slightly lower content (75.00 mg). All values are within acceptable limits, confirming formulation accuracy and reproducibility.

b. Solubility studies

Table No.15. Solubility profile of Selexipag cocrystals

Formulation	Solubility in Water (mg/mL)
F1 (NIC)	0.0085
F2 (NIC)	0.0120
F3 (NIC)	0.0155
F4 (BNZ)	0.0090
F5 (BNZ)	0.0125
F6 (BNZ)	0.0160

The aqueous solubility of Selexipag cocrystals increased with higher co-former ratios for both Nicotinamide (F1–F3) and Benzoic acid (F4–F6). F6 (1:2 BNZ) exhibited the highest solubility (0.016 mg/mL), while lower-ratio formulations showed moderate solubility.

c. *In vitro* dissolution studies:

The *in vitro* drug release in 6.8 pH phosphate buffer from the prepared cocrystals

Table.No.16. Dissolution data of Selexipag co-crystals

Time (min)	F1 (1:1NIC)	F2 (1:1.5NIC)	F3 (1:2NIC)	F4 (1:1BNZ)	F5 (1:1.5BNZ)	F6 (1:2BNZ)
5	5.86	28.74	34.96	6.54	30.92	38.42
10	11.24	51.85	55.72	12.68	52.98	59.84
15	17.43	69.25	73.85	19.86	71.84	76.25
20	24.68	83.12	87.24	28.42	85.12	90.12
30	32.41	92.46	94.86	38.52	92.82	95.12

45	39.84	94.12	94.92	46.84	94.35	96.01
60	44.92	93.75	93.98	50.92	92.95	97.10

Dissolution study of Selexipag- Nicotinamide Co-crystals

Table.No.17. Dissolution data of Selexipag Nicotinamide co-crystals

Time (min)	F1 (1:1NIC)	F2 (1:1.5NIC)	F3 (1:2NIC)
5	5.86	28.74	34.96
10	11.24	51.85	55.72
15	17.43	69.25	73.85
20	24.68	83.12	87.24
30	32.41	92.46	94.86
45	39.84	94.12	94.92
60	44.92	93.75	93.98

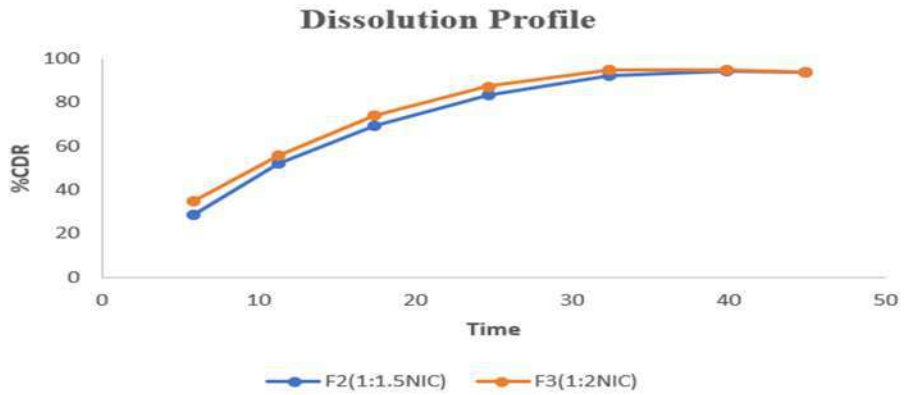


Fig No.6. Dissolution profile of F1, F2 and F3

The dissolution study revealed that F2 (1:1.5 NIC) and F3 (1:2 NIC) showed significantly enhanced drug release compared to F1 (1:1 NIC). F2 achieved 91.36% release at 30 minutes, while F3 showed a slightly higher initial release (93.02% at 30 minutes) but declined slightly afterward. In contrast, F1 exhibited a slower and lower release (42.86% at 60 minutes). This indicates that increasing Nicotinamide concentration improves dissolution, with F2 providing optimal performance.

Dissolution study of Selexipag- Benzoic acid Co-crystals

Table No.18. Dissolution data of Selexipag-Benzoic acid co-crystals

Time(min)	F4(1:1BNZ)	F5(1:1.5 BNZ)	F6 (1:2 BNZ)
5	6.54	30.92	38.42
10	12.68	52.98	59.84
15	19.86	71.84	76.25
20	28.42	85.12	90.12
30	38.52	92.82	95.12
45	46.84	94.35	96.01
60	50.92	92.95	97.10

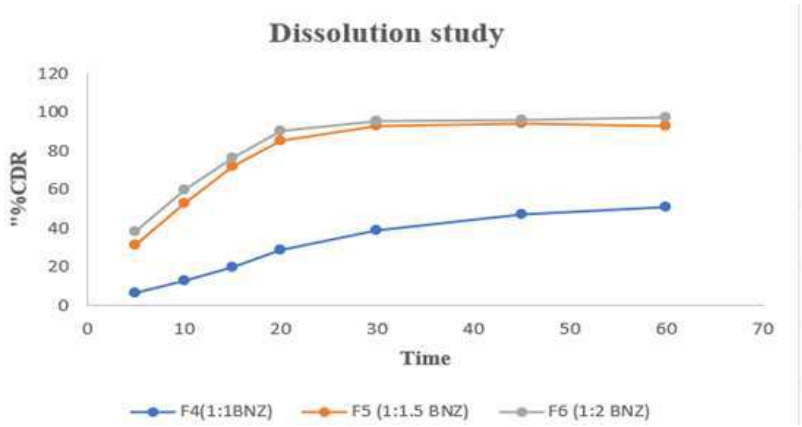


Figure 07: Dissolution profile of F4, F5 and F6

The dissolution profile of Benzoic Acid cocrystals showed that F6 (1:2 BNZ) had the highest drug release, reaching 94.32% at 30 minutes and maintaining 95.24% at 60 minutes. F5 (1:1.5 BNZ) demonstrated slightly lower but comparable release (91.75% at 30 minutes), while F4 (1:1 BNZ) exhibited slower and incomplete release (48.12% at 60 minutes).

Table. No.19. Comparing drug release of F3 and F6

Time (min)	F3 (1:2NIC)	F6 (1:2BNZ)
5	34.96	38.42
10	55.72	59.84
15	73.85	76.25
20	87.24	90.12
30	94.86	95.12
45	94.92	96.01
60	93.98	97.10

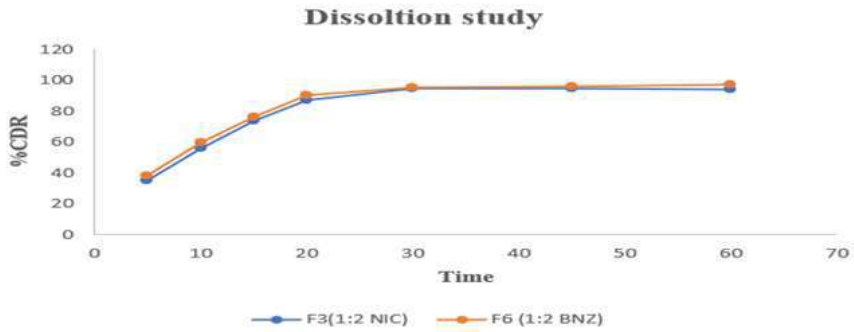


Figure 08: Dissolution profile of F3 and F6

The dissolution data show that both F3 (1:2 NIC) and F6 (1:2 BNZ) exhibit significantly improved drug release compared to the pure drug. F6 demonstrates slightly higher release, reaching 97.10% at 60 minutes, while F3 achieves 93.98%. Rapid release is observed within the first 20 minutes, with over 87% for F3 and 90% for F6. This enhancement indicates that cocrystallization with benzoic acid and nicotinamide improves solubility and dissolution, with F6 showing superior performance.

d. FT- IR Analysis

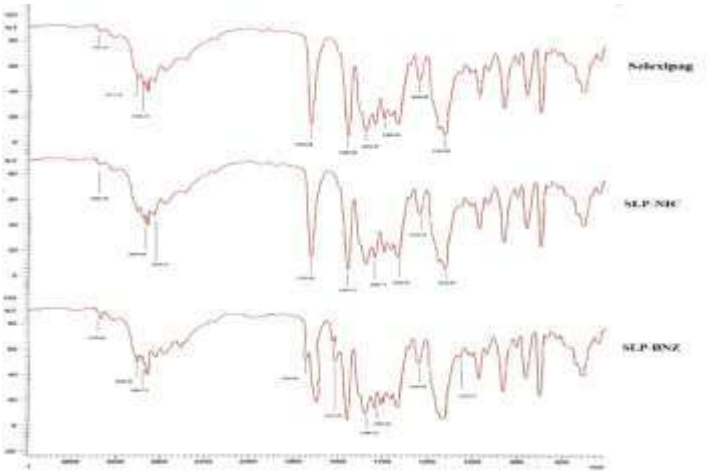


Fig No 09 a) Pure drug, b) Selexipag-Nicotinamide c) Selexipag- Benzoic acid

Table No.20. Interpretation of IR data

Sr. No	Types of vibrations	Drug (Selexipag)	SLP-NIC Co-crystal F3	SLP-BNZ Cocrystal F6
1	O–H / N–H stretching	3360.60	3365.70	3370.92
2	Aromatic C-H stretching	3024.38	3030.94	3035.66
3	Aliphatic C-H stretching	2988.45	2995.51	2999.72
4	C=O stretching	1724.36	1729.16	1735.93
5	C=C ring stretch	1558.48	1265.72	1670.56
6	C=N stretching	1477.47	1485.71	1490.12
7	SO2 stretching	1385.60	1390.401	1400.18
8	C-N stretching	1240.23	1245.20	1250.85
9	C-O-C stretching	1124.50	1130.23	1135.27

The FTIR spectrum clearly demonstrates the formation of Selexipag cocrystals with Nicotinamide (F3) and Benzoic acid (F6) through noticeable peak shifts. Pure Selexipag shows a distinct O–H/N–H stretching band at 3360.60 cm^{-1}, which shifts to 3365.70 cm^{-1} in F3 and 3370.92 cm^{-1} in F6, indicating hydrogen bonding interactions. Similarly, the C=O stretching peak of the pure drug at 1724.36 cm^{-1} shifts slightly to 1729.16 cm^{-1} (F3) and 1735.93 cm^{-1} (F6), confirming molecular interaction with the co-formers. A significant change is observed in the C=C ring stretch, where the pure drug peak at 1558.48 cm^{-1} shifts drastically to 1265.72 cm^{-1} in F3 and 1670.56 cm^{-1} in F6, providing strong evidence of cocrystal formation. These spectral variations confirm the successful interaction of Selexipag with Nicotinamide.

e. Differential Scanning Calorimetry

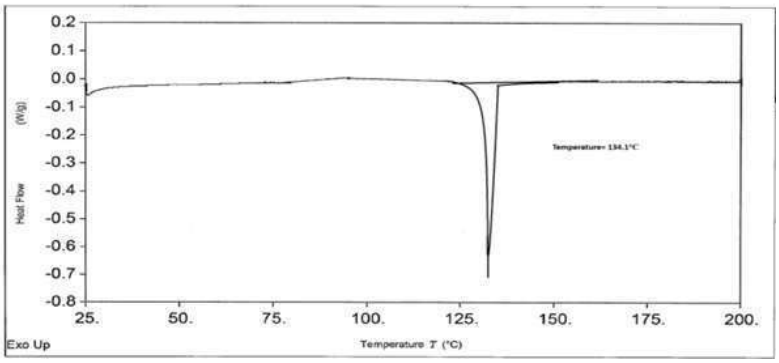


Fig No.10. DSC curves for SLP-NIC cocrystal

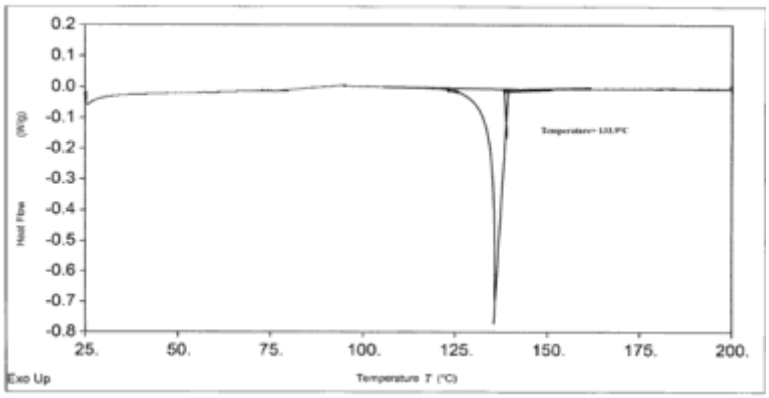


Fig No.11. DSC curves for SLP-BNZ cocrystal

DSC thermograms showed endothermic peaks for Selexipag, Nicotinamide, and Benzoic acid at 139.0, 134.1, and 133.9 °C, respectively. Co-crystals (F3 and F6) exhibited different melting points from the pure drug, indicating co-crystal formation. Absence of co-former peaks confirmed the formation of true co-crystals rather than physical mixtures. The thermal variations provided clear evidence of successful co-crystallization.

f. Powder X-RAY diffractometry

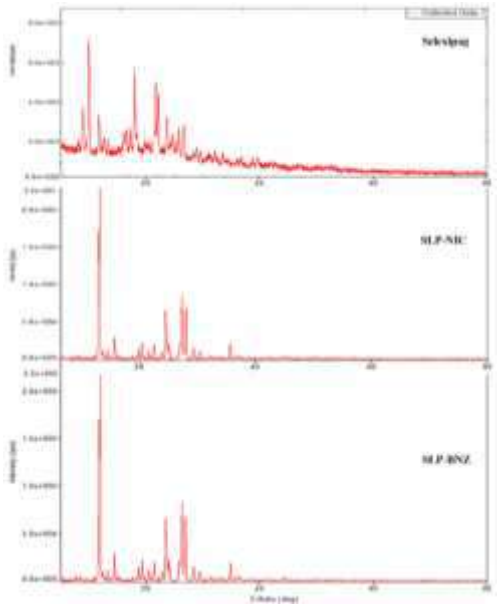


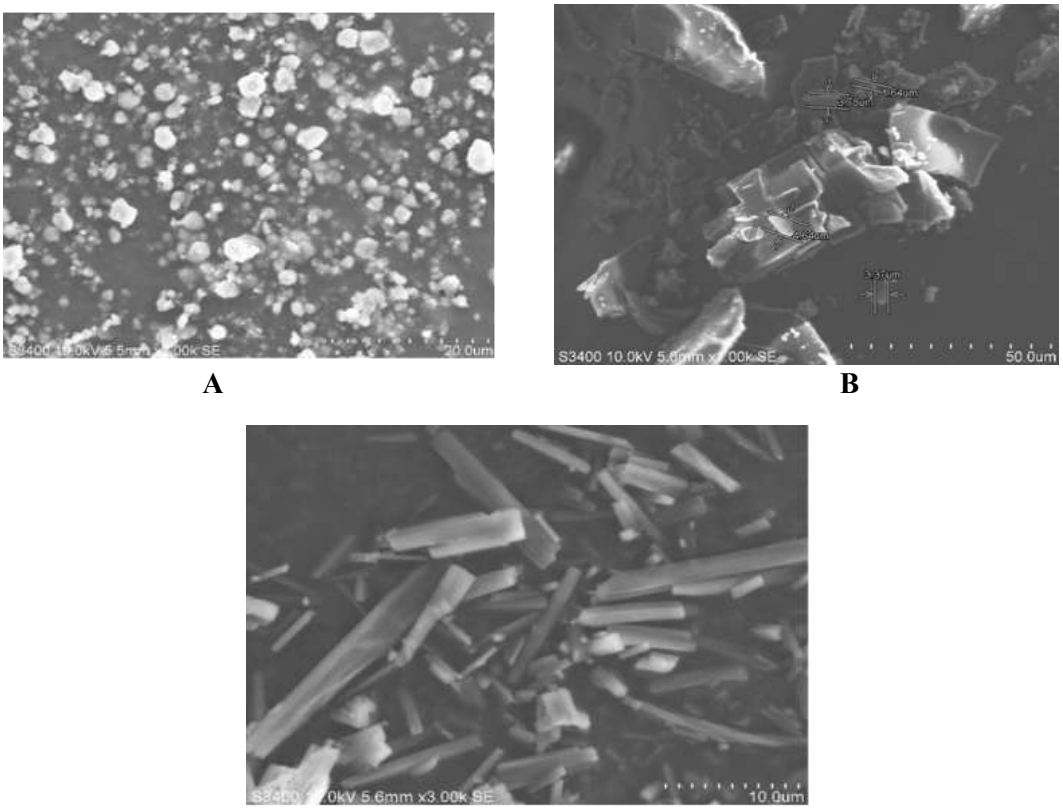
Fig No.12: a)Powder X-RAY Diffractometry of Selexipag, b) SLP-NIC c) SLP-BNZ

Table No .21: XRD spectrum of Selexipag-NIC, BNZ co-crystal

Sr. No	Co-crystal	Peak 2θ values	Intensity	Inference
1	Selexipag	13.021 13.668 14.63 16.29 17.10	7.41 43.43 100 30.55 15.91	-
2	SLP-NIC	6.81 6.9 7.28 7.95 8.57	34 10 9 61 141	Formation of co-crystal
3	SLP- BNZ	6.60 8.56 9.189 9.318 12.334	135 78 105 157 30	Formation of co-crystal

The PXRD diffractogram of Selexipag showed characteristic peaks at 2θ values of 13.021, 13.668, 14.63, 16.29, and 17.10°, confirming its crystalline nature. Nicotinamide (F3) and Benzoic acid (F6) exhibited peaks at 11.1, 26.5, 27.1° and 7.14, 12.60, 14.40°, respectively. The co-crystals showed additional peaks at 2θ values absent in the pure components, indicating the formation of a new crystalline phase. This confirms successful co-crystal formation.

g. SEM



A **B**

C

Figure 13: a) SEM images of Selexipag b) SLP-NIC c) SLP-BNZ

The images of co-crystals exhibited change in the particle size and shape when compared with the pure drug. This indicates that there is a change in the particle size and shape.

Micromeritic Study:

Table No.22. Micromeritic properties of Selexipag cocrystals

Formulation	Angle of Repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner Ratio
F1	30.18 ± 0.012	0.42 ± 0.012	0.50 ± 0.016	16.0	1.19
F2	27.12 ± 0.015	0.40 ± 0.014	0.48 ± 0.018	16.7	1.20
F3	32.11 ± 0.013	0.38 ± 0.015	0.46 ± 0.016	17.4	1.21
F4	31.13 ± 0.014	0.44 ± 0.017	0.52 ± 0.015	15.4	1.18
F5	32.14 ± 0.015	0.41 ± 0.017	0.49 ± 0.017	16.3	1.20
F6	29.17 ± 0.017	0.39 ± 0.014	0.47 ± 0.015	17.0	1.21

*All the Values represents are mean of 6 readings (n=6)

a. Angle of Repose:

The value of angle of repose of co-crystals of Selexipag was found to be in the range of 27.12±0.015- 32.11 ± 0.013 which indicates the good flow property. An obtained value of angle of repose was depicted in Table No.22.

b. Bulk density & Tapped density:

The bulk density and tapped density values ranged from 0.38 ± 0.015 to 0.44 ± 0.017g/ml for bulk density and 0.46 ± 0.016to 0.52 ± 0.015g/ml for tapped density respectively So, it shows that all formulations having good flow properties and packability and which were within the limit as per IP specifications.

c. Carr's index:

The Carr's index values for Selexipag were found to be in the range 16.0%-17.4% which lies between the normal values indicating good flow property. An obtained value of Carr's index was depicted in Table No.22.

d. Hausner's ratio:

The Hausner's ratio values for Selexipag cocrystals were found to be in the range 1.18 to 1.21. These values are within the range of 1.25 which indicated that the powder mixture exhibited good flow property. An obtained value of Hausner's ratio was depicted in Table No.22.

CHARACTERIZATION OF CAPSULE CONTAINING CO-CRYSTALS OF SELEXIPAG

%Weight variation and Disintegration time

Table No.23. Weight variation and Disintegration time

% Weight variation (RSD)	Disintegration time (min ± SD)
1.19%	6.8 ± 0.4
1.00%	5.2 ± 0.3
0.90%	4.1 ± 0.3
1.30%	7.0 ± 0.5
1.10%	5.5 ± 0.3
0.80%	3.9 ± 0.2

All six formulations demonstrated excellent uniformity, with mean weights ranging from 99.6 to 100.6 mg and %RSD values between 0.8% and 1.3%, which are well within the acceptable. Disintegration times varied according to coformer ratio. Formulations with higher coformer content, such as F3 (1:2 NIC) and F6 (1:2 BNZ), exhibited the fastest disintegration, around 4 minutes, due to improved wettability and porosity. In contrast, F1 (1:1 NIC) and F4 (1:1 BNZ) showed slightly

longer disintegration times, approximately 6–7 minutes.

Fig No.14: Capsule formulation loaded with Selexipag cocrystals

In-vitro drug release of capsule containing Selexipag

Table No.24. *In-vitro* drug release of pure drug, F3 and F6 encapsulated Selexipag

Time (min)	Pure drug	After Encapsulation (% Release) F3	After Encapsulation (% Release) F6
5	4.82	34.96	35.92
10	9.46	55.72	57.45
15	14.38	73.85	74.32
20	18.92	87.24	88.64
30	25.64	94.86	94.32
45	32.17	94.92	94.86
60	38.75	93.98	95.24

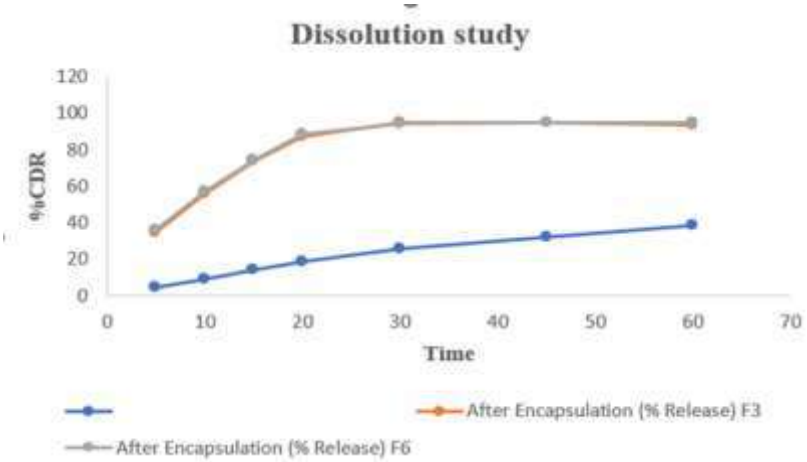


Fig No.15: Dissolution profile of cocrystal loaded capsule

The dissolution profile shows that pure Selexipag has a slow release, with only 38.75% drug release at 60 minutes. In contrast, F3 and F6 formulations exhibit significantly enhanced release, achieving over 87% within 20 minutes and more than 94% by 30 minutes. This improvement indicates that cocrystallization followed by encapsulation effectively increases solubility and dissolution rate. Both F3 and F6 show similar performance, demonstrating the efficiency of encapsulated cocrystals in improving drug release compared to the pure drug.

CONCLUSION

The present study focused on enhancing the solubility and dissolution rate of Selexipag through crystal engineering. Co-formers were selected based on Hansen Solubility Parameters (HSP) and ΔpKa values, and co-crystals were successfully developed using the solvent evaporation technique. Characterization by FTIR, DSC, XRD, and SEM confirmed co-crystal formation with changes in melting point and crystal morphology. The co-crystals exhibited significantly improved solubility and dissolution, following the order SLP-BNZ (1:2) > SLP-NIC (1:2) > others > pure drug. Capsule formulations of SLP-BNZ (1:2) and SLP-NIC (1:2) further

enhanced drug release, with F6 > F3 > pure drug. Hence, co-crystallization proved to be an efficient solubility enhancement approach.

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