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RESEARCH ARTICLE

SOLUBILITY ENHANCEMENT OF SELEXIPAG BY β-CYCLODEXTRIN INCLUSION COMPLEXES

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Abstract

Background: Selexipag is an oral, non-prostanoid IP receptor agonist used in treating pulmonary arterial hypertension (PAH). Selexipag has poor aqueous solubility, especially in acidic solution medium. Hence, for the purposes of overcoming solubility limitations associated with selexipag, various techniques such as complexation with appropriate complexing agents have been considered. Cyclodextrins are unique molecules that are cyclic carbohydrates that have been shown to be suitable for the purpose of inclusion complex formation. This is because they form inclusion complexes when combined with insoluble drugs.
Method: The inclusion complex between Selexipag and β-cyclodextrin was prepared using kneading method.
Result: The ability of β-cyclodextrin to increase the solubility of Selexipag has been shown from the results indicating that β-cyclodextrin improves significantly both the solubility and dissolution of selexipag which is a poorly soluble drug. The formation of the inclusion complex was further confirmed using UV-visible spectrophotometry and Fourier transform infrared spectroscopy. In addition, dissolution studies indicated improved dissolution behavior of the complexed drug.
Conclusion: From the results obtained above, β-cyclodextrin appears to be very efficient carrier agent for poorly soluble drugs such as Selexipag which belong to BCS class II.
Keywords: Cyclodextrins, inclusion complexes, kneading, pulmonary arterial hypertension, solubility enhancement.

INTRODUCTION

Solubility is an important physicochemical property which plays a critical role in influencing the quality, stability and efficacy of formulated medicines. The solubility of a substance is defined as the largest possible quantity that will dissolve in a definite quantity of solvent at a particular set of conditions of temperature and pressure forming a saturated solution[1]. On a quantitative basis, solubility is described as the concentration of solute in the saturated solution while qualitatively, solubility is defined as a spontaneous mixing of molecules of the solute and molecules of a solvent leading to homogenized mixture. Solubility may be expressed in different ways for example in terms of grams of solute per litre, molarity, molality, mole fraction and grams of solute per 100ml of solvent[2]. In the context of pharmaceutical sciences, solubility is one of the most significant determinants of dissolution, absorption and ultimately bioavailability of the formulations administered orally. Most of the available drugs are normally administered orally due to the convenience of administering the drug[3]. The bioavailability of drugs is dependent on the rate at which drugs dissolve in the gastrointestinal tract fluids before being absorbed across the biological membrane. Poor aqueous solubility is one of the most critical challenges facing pharmaceutical industry currently. This is because it has been estimated that up to 40% of compounds synthesized are poorly soluble in water, therefore unable to achieve proper bioavailability due to slow dissolution rates[4]. More than 90% of newly marketed drugs since mid 1990's are poorly soluble in water. The process of estimating the rate of absorption of drugs is done by Biopharmaceutics Classification System (BCS). All drugs are classified by BCS into four different groups. The BCS II classes of drugs consist of poorly soluble but highly permeable drugs whose absorption rates are limited by their dissolution rates. Therefore, it is important to enhance their aqueous solubility[5]. Different techniques and mechanisms have been developed to improve the solubility of poorly water-soluble drugs. These include physical methods like reducing particle size, nanosuspensions, and solid dispersions, as well as chemical methods such as salt formation, adjusting pH,

and cocrystals[6]. Other than the discussed methods above, complexation has also been considered to enhance the physicochemical behavior of poorly soluble drugs without changing the drug structure[7]. Complexation involves associating more than one molecule through intermolecular bonds which include hydrogen bond, Van der Waals forces, and hydrophobic interactions. Inclusion complexation is another advanced type of complexation where one molecule called guest molecule becomes enclosed within another molecule known as host molecule[8]. This leads to improving the aqueous solubility, dissolution rate, and stability of the guest molecule[9].

The use of different host molecules in inclusion complexation process has increased the complexity of producing inclusion complexes. Among the host molecules used in inclusion complexation, cyclodextrins have gained much popularity due to their physicochemical and molecular characteristics. They are cyclic molecules consisting of glucopyranose units connected together by α-(1,4) glycosidic bonds forming a truncated cone-like shape[10]. The molecular geometry makes cyclodextrins have their outer surfaces being hydrophilic and inner surface being hydrophobic. The common natural cyclodextrins used are alpha-, beta-, and gamma-cyclodextrins that vary in their sizes because they contain six, seven, and eight glucopyranose units, respectively[11]. Beta-cyclodextrins are used in pharmaceutical preparations due to their ability to form inclusion complexes with hydrophobic molecules and have proper cavity sizes, availability, low cost, and stability[12]. Cyclodextrins increase the aqueous solubility, dissolution rate, and chemical stability as well as bioavailability of drugs. Several techniques are involved in the preparation of inclusion complexes of cyclodextrins such as kneading, co-precipitation, spray drying, microwave irradiation, freeze-drying, and grinding[12]. Among those, kneading technique is most commonly used since it is simple, repeatable, affordable and does not require any special equipment. In kneading technique, cyclodextrins are first mixed with a small quantity of solvent to yield a homogeneous paste, then the drugs are added to the mixture through kneading technique[13]. Various drug formulations are used in treatment of Pulmonary Arterial Hypertension (PAH). It is characterized by high pressure in pulmonary arteries. Among them, one type of such drug formulations is the use of selective IP receptors agonists such as selexipag. Mode of action of selexipag is by causing dilation of pulmonary arteries thus reducing resistance in pulmonary blood vessels as well as enhancing cardiac output. Despite the important role played by the drug formulation in the treatment of patients with PAH, selexipag drug belongs to Class II of BCS drugs, meaning that it has low aqueous solubility while permeability remains high. This means that its solubility in intestinal fluids is low. Therefore, a mechanism must be designed through which aqueous solubility of selexipag can be improved[14]. This study therefore focuses on how aqueous solubility of selexipag can be enhanced. Among various ways of doing so, one way is through inclusion complex formation technique. Beta cyclodextrins have ability to form inclusion complexes with drug molecules due to their unique properties. This research aims at evaluating the efficiency of kneading technique in forming selexipag inclusion complexes.

MATERIALS AND METHODS

The drug selexipag was collected as a gift sample and employed as the model drug for solubility enhancement studies. Beta-cyclodextrin (β-CD) was sourced from Chemdye Corporation, Rajkot, India and used as the complexing agent. PVP K-30 and PEG-400 were employed as binding agents. Microcrystalline cellulose (MCC) was used as the diluent, CCS as the super disintegrator, magnesium stearate as the lubricant, and colloidal silicon dioxide as the glidant. All reagents and excipients employed were of pharmaceutical quality.

Preparation of selexipag beta-cyclodextrin inclusion complexes

The inclusion complexes of selexipag and β-cyclodextrin were prepared using the kneading method in order to improve the aqueous solubility of selexipag. In the first step, PVP K-30 was dissolved in distilled water (1-2 mL). Subsequently, PEG-400 was dissolved to form a uniform binder solution. A uniform binder solution was formed. Selexipag along with β-cyclodextrin was mixed together in different ratios (1:1, 1:2, 1:3, 1:4, 1:5) in the mortar and pestle to prepare the dry inclusion complexes. Excipients such as MCC, CCS, and colloidal silicon dioxide were homogenized in another mortar. Subsequently, dry inclusion complex was mixed with excipients' mixture to prepare drug excipients uniform mixture. Binder solution was then gradually mixed with powders along with kneading to prepare cohesive wet mass. The wet mass was passed through the sieve number 10 to prepare wet granules. Wet granules were dried in hot air oven heated up to 40-50°C. After that, the dried granules were passed through the sieve number 44 to form uniform granules.

Table 1: Composition of the tablets.

S. N.	Ingredients	F1	F2	F3	F4	F5
1	Selexipag (mg)	80	80	80	80	80
2	Beta cyclodextrin (mg)	80	160	240	320	400
3	MCC (mg)	356	276	196	116	36
4	CCS (mg)	40	40	40	40	40
5	Colloidal silicon dioxide (mg)	8	8	8	8	8
6	PVP K-30 (mg)	8	8	8	8	8
7	PEG- 400 (mg)	20	20	20	20	20
8	Magnesium stearate (mg)	8	8	8	8	8

Magnesium stearate was mixed with sieved granules and compressed using automatic tablet compression machine to form tablets. Five different formulations were prepared in which β-cyclodextrin[15].

Selexipag β-cyclodextrin inclusion complex powder evaluation

The prepared inclusion complex powder blends were characterized for pre-compression parameters to establish the flow properties and ability to be compressed to tablet form.

Compressibility Index (Carr's Index)

Compressibility index was established by taking into consideration the compressibility features of the powder, and this was done through the use of the following formula.

$$\text{Carr's Index } (\%) = \frac{Pt - Pb}{Pt} x100$$

Where; Pt = Tapped density, Pb = Bulk density

Bulk density was established through the weighing of a certain quantity of powder and putting it in a calibration cylinder[16]. Tapped density was determined through the tapping of the measuring cylinder containing the powder mixture 500 times through the use of the tapped density apparatus.

Hausner's ratio

Hausner's ratio was determined in order to establish the flowability of the powder through the following formula.

$$\text{Hausner's Ratio} = \frac{Pt}{Pb} x100$$

Angle of repose

Angle of repose was established by use of the fixed funnel method. Powder mixture was poured down the funnel to form a cone-shaped heap[17]. Angle of repose was then calculated using the following formula-

$$\theta = \tan^{-1} \frac{h}{r}$$

Where; h = height of cone; r = radius of base.

Compressed tablet evaluation

Compression technique was employed to produce selexipag β-cyclodextrin tablets. Some post-compression tests were performed to determine certain characteristics of the manufactured tablets.

Weight variation

In determining the weight variation, fifteen tablets were weighed using an analytical balance. The mean weight was computed as well as the percentage variation of the weights from the mean weight[18].

Hardness testing

The hardness of the tablets was measured by placing them on a tablet hardness tester whereby pressure was applied on both sides of the tablet until it broke. This was recorded in kilogram-force (kgf)[20].

Friability

The friability test involved ten tablets that were tested using the friabilator at 25 revolutions per minute for four minutes (100 turns). The tablets were removed from the friabilator where dusting was performed before weighing[18]. The percentage friability was obtained using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} x100$$

Thickness testing

The thickness testing of the developed tablets was determined through the use of Vernier calipers. The thickness was obtained through averaging the values of different batches of formulations[18].

Disintegration time

Disintegration testing of the produced tablets was conducted by employing USP disintegration tester where the tablet samples were placed inside 0.1 N hydrochloric acid solution held at 37±2 °C while noting the time taken before disintegration occurred[19].

Drug excipients interaction study (FT-IR)

To conduct the study, FT-IR spectroscopy technique was applied. Equal ratios of the drug and excipients were mixed and subjected to an accelerated condition (40±2°C and 75% RH) for different time intervals. After each period, samples were analyzed for any chemical interaction using the FT-IR. The sample was compared to the pure drug[20,21].

Content uniformity

UV-Visible spectrophotometer was used for the content uniformity determination. Firstly, tablet samples were crushed and weighed 2 mg then dissolved in methanol to obtain stock solution. Then the calibration curve of selexipag was developed. Drug concentration was found from the graph[22].

***In-vitro* dissolution test**

For *in-vitro* dissolution test, the tablets were dissolved using USP type II (paddle type) dissolution tester where the dissolution medium was prepared by adding 900 mL of 0.1 N hydrochloric acid maintained at 37±0.5°C while keeping the paddle speed to 50 rpm. Five mL samples were collected and replaced at specific intervals with a new medium. Finally, the filtrate was analyzed using UV-Visible spectrophotometer at 258 nm wavelength[22].

RESULTS AND DISCUSSION

This research has been conducted for optimization of solubility and dissolution behavior through the development of β-cyclodextrin inclusion complexes of selexipag. All the powder blends used showed good flow and compressibility characteristics that made them suitable for tablet compression. On the basis of calculations, it was found that the prepared blends were well packed, as shown by the calculated values of bulk density and tapped density[23]. The acceptable range of values of Carr's index and Hausner's ratio provided indication that the blends could be compressed into tablet form, while Hausner's ratio close to one implied good flowability of blends[24]. Out of all blends, the highest flowability was achieved by blend F2 because of low values of Carr's index and Hausner's ratio, suggesting negligible interparticulate friction (Table 2)[25]. Despite having the highest density in comparison with other formulations, formulation F5 showed poor flowability due to high values of Carr's index and Hausner's ratio owing to its high cyclodextrin concentration[26]. Hence, it could be said that the use of moderate quantities of cyclodextrin led to good flow characteristics, but larger quantity led to poor compressibility characteristics because of hygro-

scopicity and bulkiness[27]. The study results of compressed tablets proved that they met quality requirements as stated in the pharmacopeia. Hardness values were high enough to withstand compression and handling pressures. The highest hardness value was obtained in formulation F1, followed by the lowest friability value among others, implying high strength. Most of the formulation showed acceptable friability values, indicating satisfactory mechanical strength of compressed tablets. The formulation F5 showed higher friability value as a consequence of high cyclodextrin content affecting tablet strength during compression[28].

Table 2: Pre-compression results.

Batch code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose
F1	0.48	0.54	11.11	1.125	42.4±4.05
F2	0.32	0.34	5.88	1.06	37.6±0.59
F3	0.30	0.33	9.1	1.1	36.7±0.63
F4	0.46	0.52	11.5	1.13	35.9±0.16
F5	0.54	0.63	14.3	1.17	34.6±5.84

All formulations met acceptable thickness and weight variation values, indicating their consistency in size. The results of disintegration time were within the acceptable limit for all formulations, implying effective disintegration time because of the use of super-disintegrant such as the effects of binders and cyclodextrin that caused compaction (Table 3)[29,30]. All formulations of inclusion complexes were found to have drug in uniform concentrations and acceptable pharmacopeia limits. The maximum amount of drug content was obtained in 1:1 ratio of drug: β-cyclodextrin, implying that drug was uniformly dispersed in the formulation.

Table 3: Results of post-compression parameters.

Batch code	Hardness (kgf)	Thicknes (mm)	Friability (%)	Weight variation	Disintegration time (min)
F1	3.36	3.20±0.05	0.38	0.385±0.7	12
F2	2.76	3.18±0.04	0.68	0.390±0.5	14
F3	2.31	3.22±0.03	0.65	0.396±0.3	10
F4	2.55	3.15±0.02	0.63	0.386±0.5	10
F5	2.4	3.30±0.06	3.43	0.38±0.6	13

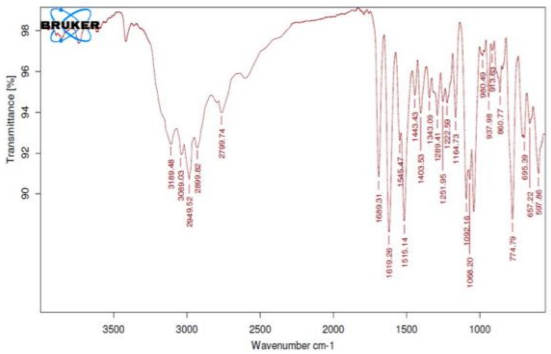

Figure 1: FT-IR result of pure SLX drug.

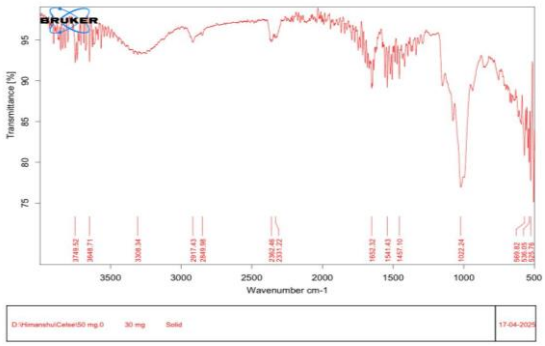

Figure 2: FT-IR result of 1:1, SLX:BCD inclusion complex.

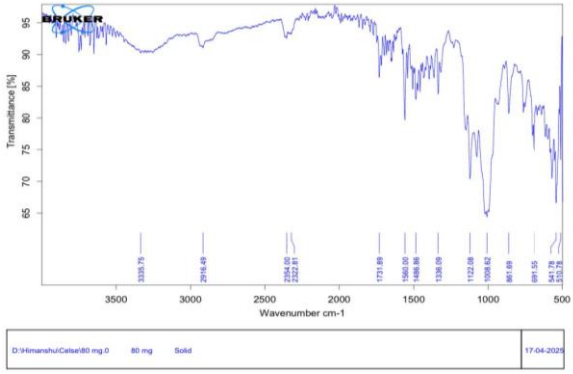

Figure 3: FT-IR result of 1:2, SLX:BCD inclusion complex.

There was a gradual decrease in the drug concentration when ratios increased to 1:3 and 1:5 because of the dilution effect in the case of excess cyclodextrin (Table 4)[29]. The results of the *in vitro* dissolution test revealed that there was a significant increase in the drug release profile of all formulations with respect to dissolution profiles of poorly soluble drugs. Progressions in drug release rate were also obtained in all formulations, showing that selexipag was uniformly dispersed in the cyclodextrin matrix. In the case of F2 formulation, drug release rate was the fastest as indicated by 99 percent drug release within 60 minutes of time (Table 5)[31]. This result showed that there was an improvement in dissolution profile of selexipag because of the formation of optimal inclusion complexes, improving wettability of drugs. This was because of 1:2 ratio of drug to cyclodextrin[32].

Table 4: Drug content estimation of selexipag β-cyclodextrin inclusion complexes.

S. N.	Drug β-CD ration	Complex code	Amount of drug present (mg) in 2 mg powder	% drug content	Status
1	1:1	BK1	2.004	102.2	Pass
2	1:2	BK2	1.988	99.4	Pass
3	1:3	BK3	1.965	98.25	Pass
4	1:4	BK4	1.948	97.4	Pass
5	1:5	BK5	1.930	96.5	Pass

Table 5: *In-vitro* dissolution data.

Batch code	% CDR at different Time (mins) intervals												
	0	5	10	15	20	25	30	35	40	45	50	55	60
F1	0.0	12.0	19.8	26.4	33.0	39.6	46.2	52.8	59.4	66.0	72.6	85.8	94.0
F2	0.0	18.7	20.6	26.1	32.7	37.7	44.8	46.7	54.6	60.3	70.4	83.5	99.0
F3	0.0	10.5	17.2	24.7	31.8	38.1	45.0	51.3	58.7	65.5	72.3	88.1	95.0
F4	0.0	13.0	19.8	26.4	33.0	39.6	46.2	52.8	59.4	66.0	72.6	85.8	96.0
F5	0.0	18.6	20.7	26.5	32.7	37.7	44.8	46.7	54.6	60.3	70.4	83.6	97.0

To verify the formation of inclusion complexes of selexipag and β-cyclodextrin, Fourier Transform Infrared (FT-IR) Spectral Analysis was carried out. Significant changes in the form of peak shifting and broadening were observed in O-H/N-H stretching and carbonyl (C=O) bands, suggesting hydrogen bonding interaction between selexipag and hydroxyl group of β-cyclodextrin[33]. Some minor changes in C-H stretching band were observed due to hydrophobic interactions of selexipag in the non-polar region of hydrophobic cavity of β-cyclodextrin. Changes in fingerprint area confirmed the formation of inclusion complexes. It could also be noticed that 1:2 ratio of selexipag and β-cyclodextrin produced more peak shifting in comparison with 1:1 ratio[34]. Thus, the success of formation of inclusion complexes of selexipag and β-cyclodextrin was confirmed. All blends showed improved dissolution behavior[35]. Therefore, it was concluded that F2 formulation had optimum pharmaceutical and dissolution characteristics because of its improved wettability and stability of inclusion complexes[36].

Limitation of the study:

The study is limited by relieance on *in vitro* results without *in vivo* validation, which may not reflect the actual clinical perfomance of selexipag.

CONCLUSION

This study successfully formulated selexipag tablets with improved solubility using β-cyclodextrin via the kneading method. Among the five formulations, F2 (1:2 drug: β-CD ratio) demonstrated optimal pre-compression flow properties, acceptable post-compression mechanical characteristics, and superior *in-vitro* drug release, achieving 99% cumulative drug release within 60 minutes. The study concludes that complexation with β-cyclodextrin significantly enhances the solubility and dissolution rate of selexipag.

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AUTHOR'S CONTRIBUTIONS

Kwitonda C: writing the original draft, methodology, investigation. **Choki S:** conceptualization, literature survey, data processing. **Diadone KG:** editing, data curation. Final manuscript was checked and approved by all authors.

DATA AVAILABILITY

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST

None to declare.

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