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Inclusion Complex of Iloperidone with Sulfobutyl ether beta-cyclodextrin: Characterization and Dissolution Dtudies

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Abstract: Iloperidone (ILO) is a second-generation antipsychotic drug, is the first-line treatment, and approved by USFDA in May 2009. Iloperidone belongs to Biopharmaceutical Classification Systems (BCS) class II; thus, it is poorly water-soluble, highly permeable, and has pH-dependent solubility. Cyclodextrins and its derivatives have a wide range of applications in different formulations due to their complexation ability, which improves the solubility, stability, safety, and bioavailability of a drug. We have tried the complexation of iloperidone with sulfobutyl ether-β-cyclodextrin (SEβCD) to improve its solubility and dissolution. Complexation was done by the kneading method. Characterization of SEβCD complexes with Iloperidone was done by FTIR, DSC, saturation solubility, etc. Multimedia dissolution of the complex was carried out and compared with the plain drug. Significant improvement in drug release was found from SEβCD complexes in all media when compared with drug alone.

Keywords: β-cyclodextrin; binary complex; antipsychotic drug; dissolution studies

1. Introduction

Drug solubility is a crucial element for safe and efficacious formulation as the absorption and bioavailability depend on its solubility. Furthermore, to display its efficacy, a drug molecule desires water solubility and permeability, which may be absorbed in the site of action. More than 90% of new chemical molecules have low water solubility [1]. Several techniques can be used to boost the solubility like chemical and physical techniques. Cyclodextrin is widely used to enhance drug solubility by altering the physicochemical properties of the drugs. [2]. Cyclodextrin forms the inclusion complex with guest molecules by fitting in their cavity, which satisfies structural specifications and forces required to form a complex [3,4]. Inclusion complexes showed improved drug absorption, rapid drug release, and decreased side effects [5]. Cyclodextrin-based inclusion complex with the lipophilic drug has raised a position in the pharmaceutical field as it can alter the physicochemical properties of drugs [6]. These amendments have an imperious part in drug delivery.

Iloperidone (ILO) is an atypical antipsychotic drug used to treat schizophrenia approved by USFDA in May 2009 [7]. Schizophrenia is a chronic and severe mental disorder affecting more than 20milion individuals globally. ILO is a potent drug as it shows better activity in comparatively less amount of dose (12-16mg) and acts as a dopaminergic and serotonergic antagonist. Tablets of ILO are existing in several strengths ranging from 1mg to 12mg. Also, it has less affection for the histamine and its receptor, the lowest sedation-related complications, and substantial progress in extrapyramidal symptoms [8-10]. ILO belongs to Biopharmaceutical Classification Systems (BCS) class II drug with low solubility and high permeability.

This work aimed to prepare complex with sulfobutyl ether-β-cyclodextrin (SEβCD) to improve solubility and dissolution, consequently enhancing bioavailability. The inclusion complex was characterized by saturation solubility, FTIR, DSC, and multimedia dissolution.

2. Experiments

2.1. Materials

ILO and SEβCD were a kind gift from Symed Labs, Hyderabad, and Cyclolab. Purified water, analytical grade reagents, and chemicals were used to prepare the solution.

2.2. Method

2.2.1. Phase Solubility studies

Higuchi and Connors defined method was used to perform phase solubility studies for ILO with SEβCD. A UV spectrophotometer analyzed the samples at 229nm. Complexation efficiency (CE) is the solubility of guest molecules by cyclodextrin (equation 1). The effect of cyclodextrin on solubility was analyzed from the solubility graph. The stability constant (Kc) was calculated from the ILO solubility graph in water (equation 2).

2.2.2. Formulation of solid inclusion complex

The kneading method was used to prepare the inclusion complex, which provides maximum solubility [11]. The Drug and SEβCD were calculated precisely in a ratio of 1:1. A uniform paste of SEβCD was formulated in the mortar by adding an adequate portion of methanol: water (1:1) followed by the addition of ILO, with continuous kneading for 45mins. The suitable paste consistency was maintained by adding a sufficient quantity of methanol: water (1:1). The complex was dried using a preheated hot air oven at 55°C for 6 hours. The dried complex was crushed and pass through sieve No.44, and keep in a sealed container [12].

2.3. Characterization of solid inclusion complex

2.3.1. Saturation solubility

The solid inclusion complex's saturation solubility was analyzed by adding an extra quantity of inclusion complex to achieve steady-state in a conical flask containing 10ml phosphate buffer (pH 6.8), acetate buffer (pH 4.5), and 0.1N HCl buffer. The conical flasks containing various solvents were kept in an orbital shaker, 24 hours at 100rpm at ambient temperature. After reaching the steady-state, the sample was filtered through a 0.45µm syringe filter and analyzed spectrophotometrically at 229nm[11].

2.3.2. Drug content

The 10mg equivalent solid inclusion complex was weighed accurately and dispersed in methanol. Subsequently, subject to orbital shaker for an hour to confirm the complete extraction of ILO. It was then filtered and estimated spectrophotometrically at 229nm.

2.3.3. Attenuated total reflection- Fourier-transform infrared spectroscopy (ATR-FTIR)

FT-IR of ILO, SEβCD, and inclusion complex was analyzed using the ATR-FTIR spectrometer (Perkin Elmer) at a broad range of 4000-400cm^{-1}. The sample was kept at the diamond substrate, and the pressure was applied with a compression bar. The software converts the ATR to absorbance. The characteristics peaks were analyzed compared with ILO and SEβCD to check the interaction between them.

2.3.4. Thermal analysis

Thermal analysis of ILO, SEβCD, and inclusion complex was studied using Mettler Toledo's Differential scanning calorimetry *(DSC)*. An empty aluminum plate was used as a reference. Around 5mg of each test sample were pursed in an aluminum plate, and thermograms were found under a nitrogen gas flow of 10ml/min. Thermal analysis was conducted at a heating rate of 10°C/min from 30°C-300°C.

2.3.5. Multimedia dissolution study

In-vitro analysis of ILO and inclusion complex (in capsule shell) was carried out using Dissolution apparatus USP Type II (Paddle type) (Electrolab, India), respectively. Phosphate buffer (pH 6.8), acetate buffer (pH 4.5), and 0.1 N HCl buffer (500ml) were used as dissolution media at 37±0.5°C at 50rpm. 10ml aliquot of dissolution media was taken at pre-determined time intervals. The drug release profile of ILO and inclusion complex were studied and compared to check the release of drug in multimedia.

3. Results and discussion

3.1. Experimentals

3.1.1. Phase solubility studies

The phase solubility studies are a crucial parameter during the development of the inclusion complex with the drug. The drug (ILO) solubility curve in aqueous SEβCD was carried out, which depicted ILO solubility linearly improved with an increase in the concentration of SEβCD. ILO showed an A_L-type of a graph, demonstrating the first-order dependency of interaction with SEβCD. The linear A_L-type of the solubility curve suggests a 1:1 ratio for the complexation of ILO and SEβCD (Figure 1, Table 1). The higher value of CE and K_C specifies the stable formation of the complex by interacting with SEβCD. Kim et al. showed an enhanced intrinsic solubility, resulting in an improved CE in the presence of SEβCD by forming salt [13].

3.1.2. Saturation solubility and drug content

The saturation solubility of ILO and inclusion complex in phosphate buffer (pH 6.8), acetate buffer (pH 4.5), and HCl buffer is represented in Figure 2. The improved solubility of ILO in multimedia compared with plain ILO resulted from the inclusion complex of ILO and SEβCD. The percent drug content was found to be 99.23± 0.49, which complies with specifications.

3.1.3. ATR-FTIR

ATR-FTIR is a convenient method to evaluate drug (guest) and SEβCD (host) solid-state interaction. In IR spectra, detected peaks describe distinct functional groups that may change or modify the intensity of contacting host molecules by forming an inclusion complex, signifying effective complexation [14]. The ATR-FTIR spectra displayed C-F stretch at 1262cm^{-1}, N-O stretching at 1352 cm^{-1}, C=O stretching at 1668 $cm^{-1,}$ and 2949 cm^{-1} due to C-H stretching vibration. The spectrum of SEβCD is mainly characterized at ~1644 cm^{-1} reflects H-O-H stretching of water molecules, whereas the peaks at ~1153 cm^{-1} and ~1032 cm^{-1} are attributed to C-H and C-O stretching vibrations. The IR spectra of the inclusion complex depicted a decrease in intensity, alter, and disappearance of some distinctive IR bands of ILO. The interaction of ILO with SEβCD was confirmed by a significant shift of some distinctive bands of ILO. (Figure 3).

3.1.4. Thermal analysis

Thermal analysis delivers additional suggestions for forming the inclusion complex due to the melting or decay of drugs that may shift to different temperatures or disappear when formulated

with SEβCD [15]. The thermogram of ILO, SEβCD, and inclusion complex is shown in figure 4. DSC of ILO displayed a sharp and well-defined endothermic peak at 120°C, conforming to the drug (ILO) melt point. In the endotherm of SEβCD, a broad peak was detected at 86°C. The endotherm of ILO was utterly disappeared into the stable inclusion complex. The amorphization of the drug describes an enhancement in the dissolution profile of ILO.

3.1.5. Multimedia dissolution study

The dissolution study was analyzed to examine the enhanced solubility of ILO from the inclusion complex. Multimedia dissolution of inclusion complex was done to identify the behavior of complex over a wide range of pH. The inclusion complex and ILO's dissolution was done in Phosphate buffer (pH 6.8), acetate buffer (pH 4.5), and 0.1 N HCl buffer, shown in Figure 4. More than 80% of drug release was found in 0.1 N HCl and buffered pH 4.5, which depicts the significant difference between the drug ($p \leq 0.05$). In phosphate buffer (pH 6.8), no significant difference was observed between the drug. In multimedia, the inclusion complex showed no significant difference when compared with HPβCD based inclusion complex [16]. The multimedia dissolution data depict that as the buffer's pH decreased from 6.8 to 4.5 and 1.2, the dissolution rate was significantly enhanced.

3.2. Figures, Tables and Schemes

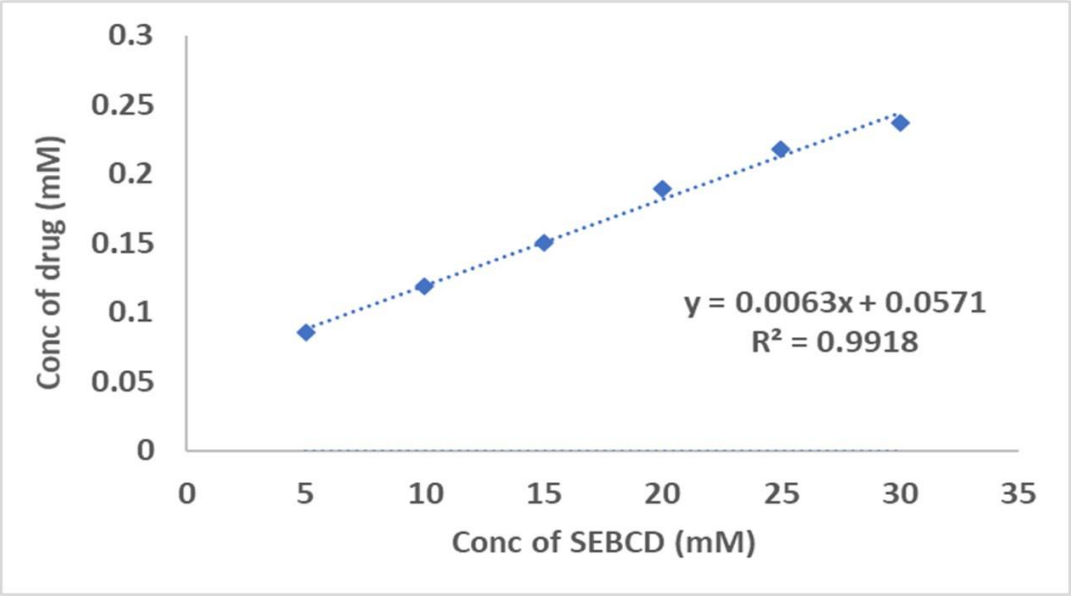

Figure 1. Solubility curve of ILO: SEβCD in water (Mean±SD).

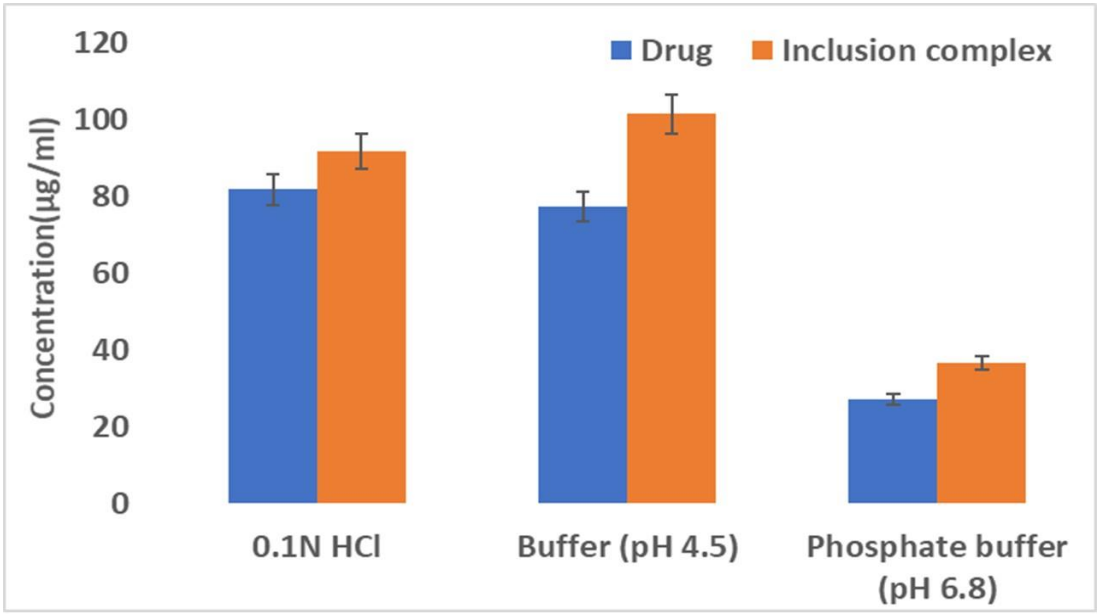

Figure 2. Multimedia saturation solubility of drug and inclusion complex (Mean±SD, n=3).

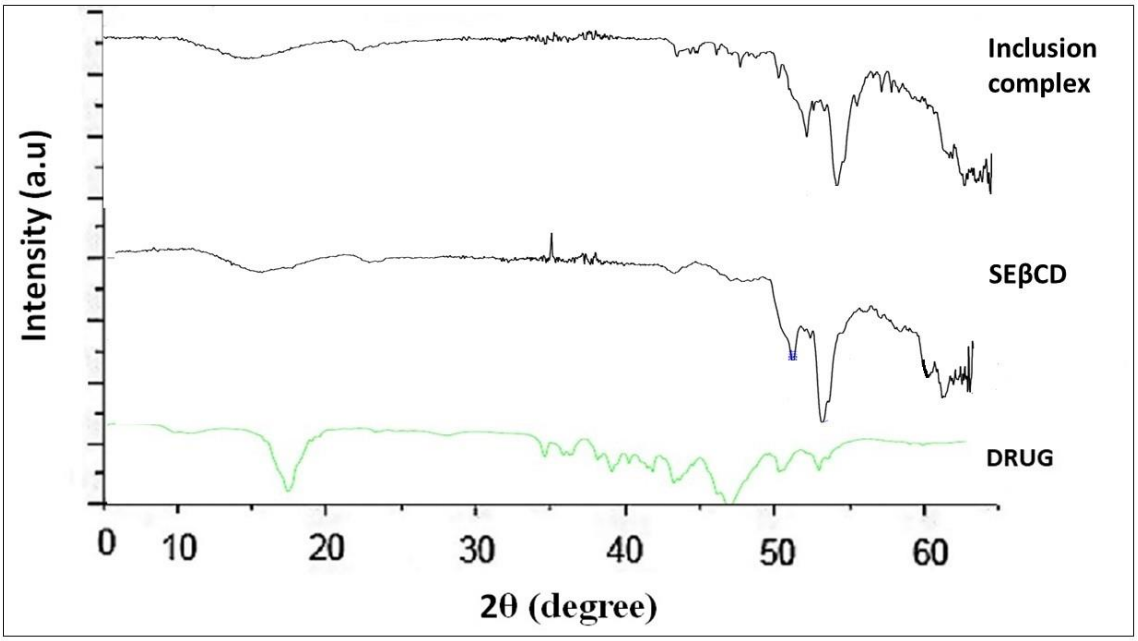

Figure 3. FT-IR spectra of Drug (ILO), SEβCD and inclusion complex.

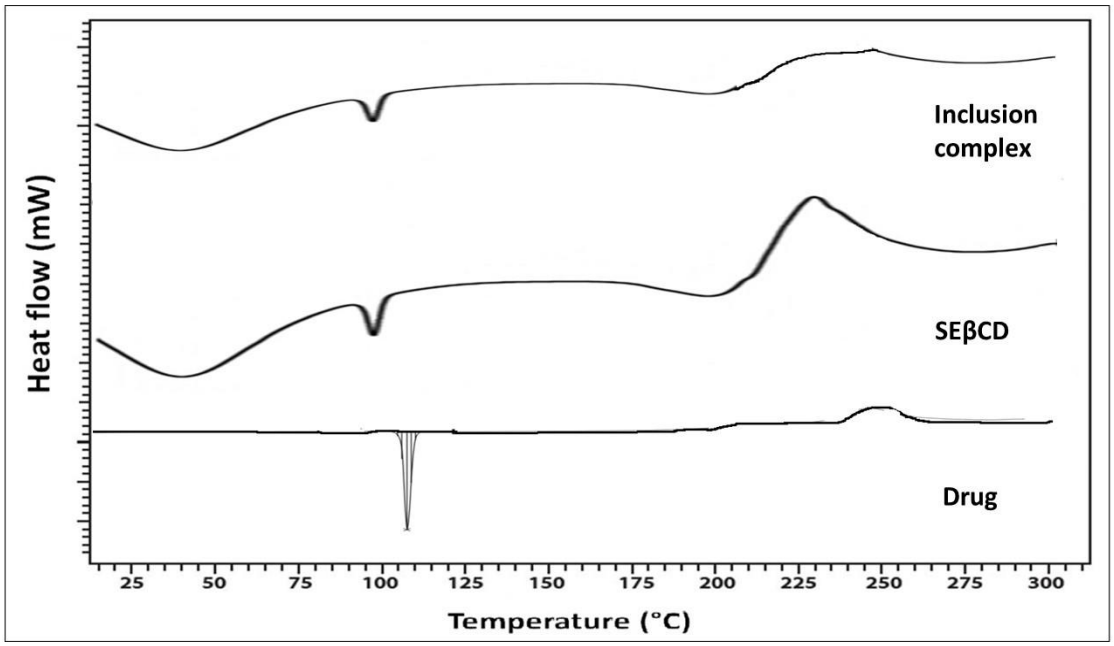

Figure 4. DSC thermogram of Drug (ILO), SEβCD and inclusion complex.

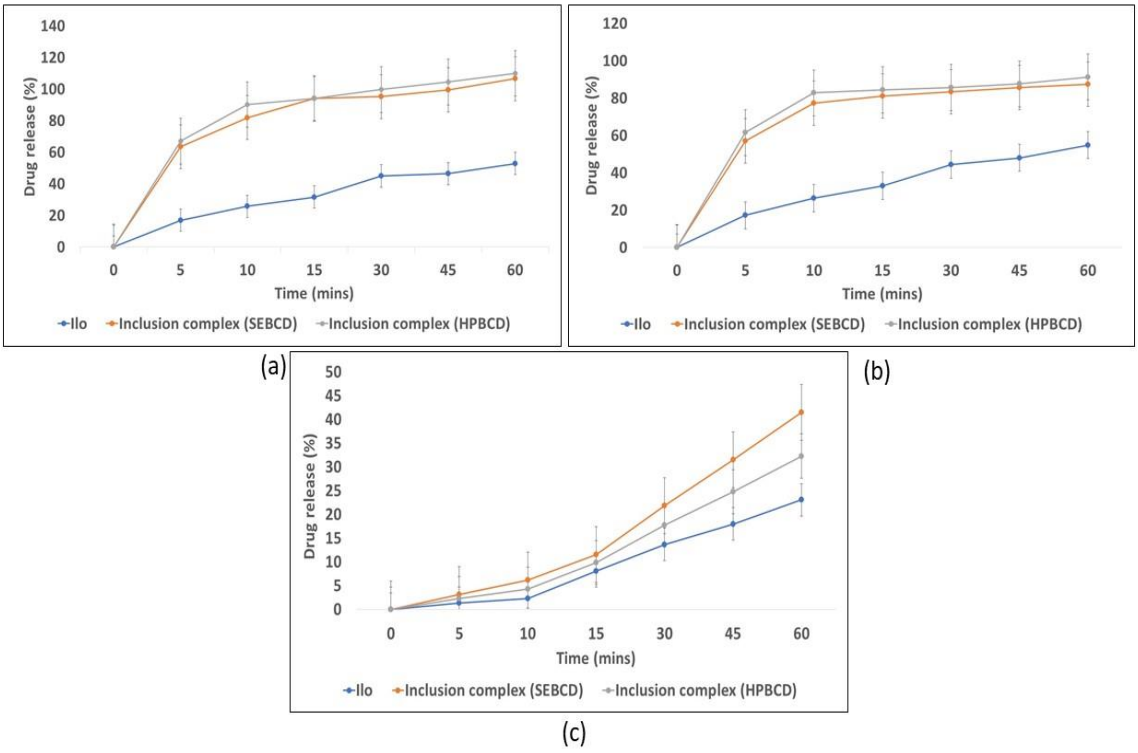

Figure 5. Multimedia dissolution of a drug (ILO) and inclusion complex ($p \leq 0.05$, Mean±SD, n=3).

Table 1. Phase solubility studies of inclusion complex.

Parameters	Observation
Slope	0.0063
R^2	0.9918
y-intercept (S_0)	0.051
K_c (M^{-1})	124.31
CE	0.0063

3.3. Mathematical Components

An equation:

$$\mathbf{CE=}\ \frac{\boldsymbol{Slope}}{(\boldsymbol{1-slope})} \quad \textbf{(1)}$$

Where CE is complexation efficiency

$$K_C=\ \frac{Slope}{S0\ (1-slope)} \quad (2)$$

Where K_c is stability constant, S_0 is the solubility of ILO only.

4. Conclusions

In this research article, we evaluated the inclusion of SEβCD to enhance the solubility of the drug. Thermal analysis (DSC) and FT-IR depict the reduction in crystallinity and increase host-guest interaction, suggesting the inclusion of complex formation. SEβCD displayed improved complexation efficacy and solubility, more stability, as detected from the FT-IR study. The inclusion complex might be attributed to the enhanced dissolution of the drug. Thus, it can be concluded that SEβCD based inclusion complexes can lead to an increase in solubility, which may enhance the drug's bioavailability.

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Author Contributions: "Vaishali Londhe and Rupali Bhadale conceived and designed the experiments; Rupali Bhadale performed the experiments; Vaishali Londhe and Rupali Bhadale analyzed the data; SERB, Cyclolab, Symed lab, and SPP SPTM contributed reagents/materials/analysis tools; Rupali Bhadale wrote the paper."

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ILO: Iloperidone
SEβCD: sulfobutyl ether-β-cyclodextrin
BCS: Biopharmaceutical Classification Systems
ATR-FTIR: Attenuated total reflection- Fourier-transform infrared spectroscopy
DSC: Differential scanning calorimetry
CE: Complexation efficiency
Kc: stability constant

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