Preparation and in-vitro characterization of Risperidone-cyclodextrin inclusion complexes as a potential injectable product

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ABSTRACT

Background and the purpose of the study: This investigation deals with risperidone cyclodextrin (CD) complexation for parenteral administration to improve its aqueous solubility which would be beneficial over immediate and sustained release formulations available in market especially for agitated and non-cooperative psychotic patients.

Methods: The phase solubility study of the drug with β-CD, hydroxypropyl (HP)-β-CD and γ-CD was conducted and CDs with higher stability constants were selected for complexation. The complexes of Risperidone with β-CD and HP-β-CD were prepared by precipitation and vacuum drying methods, respectively. Fourier transform-infrared, X-ray diffraction and differential scanning calorimetry techniques were used for characterization of complexes. Drug precipitation study of complex's solution in water for injection and 100 ml of 0.1 M pH 7.4 phosphate buffer saline and stability study in accelerated condition were also carried out.

Results: The stability constants of the CD were in the following order: β-CD (341.953±11.87 M^{-1}) > HP-β-CD (170.817± 5.93 M^{-1}) > γ-CD (93.716 ± 3.25 M^{-1}). CDs with high stability constants were selected to prepare the drug CD complex. The complexation efficiencies of β-CD and HP-β-CD were 95.23 ± 2.27% and 97.59 ±1.97%, respectively. Both types of CDs exhibited complexation at 1:2 molar stoichiometric ratio. The drug precipitation study indicated complete solubility (100% drug dissolution) without a trace of precipitate within 5 mins. The complexes were found to be stable for a period of 3 months under accelerated stability conditions.

Major conclusion: Stable complexes of risperidone were successfully formulated using both β-CD and HP-β-CD by simple and highly efficient methods of complexation for parenteral administration.

Keywords Risperidone, cyclodextrin, complexation, parenteral formulation, solubility enhancement

INTRODUCTION

Cyclodextrins (CDs) are well known inclusion-complexing agents for both small and large molecules (1, 2). Some derivatives like hydroxypropylated and sulfobutylated CDs have largely superseded the natural CDs like α, β and γ-CDs in pharmaceutical research and development (3, 4). In pharmaceutical industry, they are mainly used for solubility enhancement of water insoluble drugs and also for the enantio-separation of drug enantiomers by capillary electrophoresis (5, 6).

The present investigation deals with 'Risperidone' a benzisoxazole derivative psychotropic agent which is lipophilic in nature, practically insoluble in water and exhibits a pH dependent solubility. It is soluble in 0.1 N HCl, slightly soluble at pH 4.0 and sparingly soluble at pH 7.0-10.0. It is a potent drug used frequently in the treatment of schizophrenia and bipolar mania (7). The oral administration of the drug may not be possible in the case of a non-cooperative agitated patient with acute psychotic attack (8). In such critical cases, parenteral administration of the drug is the most suitable alternative (9). Unfortunately, injections of this drug to manage such situations are not currently available in the market except the long acting risperidone injection formulation (microparticulate formulation of PLGA) which has the drawback of lack of initial drug release (< 1% of dose) for the first 3 weeks after injection (7). Hence, the immediate release injection of drug can be used as a supplement to provide the loading dose of the drug. Apart from its extrapyramidal side effects (7) could be avoided by bypassing hepatic first pass metabolism when given by parenteral route rather than its oral administration. However, due to its water insolubility, a sterile suspension for injection may be possibly fabricated which requires additional excipients to stabilize the system.

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Moreover, the suspended particles of the drug may be effective only after a lag time, which is required to undergo solubilization in the blood. In contrast, a solution for injection of the drug minimizes the use of additives in the formulation and drug is present in a readily available form which would be effective immediately. The solubility enhancement of risperidone by addition of tartaric and benzoic acids has been reported for oral administration where solution was adjusted to pH 3-4 as drug has higher solubility in acidic rather than in alkaline pH (10). In another study, risperidone resin complexation was carried out to improve dissolution rate of the drug by enhancing wetting, or increase in the solubility in the presence of resin, or many other factors such as modification of micro-environmental pH (11). Adequate characterization used commonly in the industrial practice to confirm the complexation, as well as long term stability studies of the complex have not been reported earlier for Risperidone cyclodextrin complexes (12,13). Therefore, the objective of the present study was to improve the aqueous solubility of the drug by complexation with cyclodextrin, to carry out in-depth characterization of the complex and ensure the stability of the product under accelerated conditions which can be effectively used as a dry powder for injection to treat critical cases of acute psychotic disorders.

MATERIAL AND METHODS

Materials

Risperidone and γ-CD (Cavamax W8 Pharma) were gift of Jubilant Organosys Ltd (India) and Wacker Chemicals Ltd (UK), respectively. β-CD (Kleptose) and HP-β-CD (Kleptose HPB) were obtained as gift samples from Roquette Ltd (UK). Other chemicals of analytical grades including acetonitrile, sodium hydroxide and potassium dihydrogen phosphate were purchased from RFCL Ltd (India).

Phase solubility study of risperidone with cyclodextrins

Excess amount of Risperidone was added to 10 ml of CD solutions (γ-CD and HP-β-CD in concentrations of 5.0-50.0 mM and β-CD in concentration of 1.0-10.0 mM) in deionized water and filled in a series of 25 ml tightly closed volumetric flasks. The flasks were shaken for 48 hrs at room temperature on a rotary flask shaker (EXPO HI-Tech, Mumbai, India) followed by equilibration for 12 hrs. The solutions were filtered using 0.45 µ nylon disc filters and diluted suitably. The drug content was estimated by HPLC method (Agilent 1100 Series) (14). The system set up was as follows: mobile phase: buffer: acetonitrile (65 : 35) with pH of 6.8, column: inertsil C18 150X4.6 mm, run time: 10 min, flow rate: 1.0 ml/min, retention time: 6 min, injection volume: 10 µl and wavelength: 238 nm. The apparent stability constants were calculated from the phase solubility diagram using following equation:

K_c=Slope / S_0 (1-Slope)

Preparation of risperidone β-CD complex by precipitation method

Phosphate buffer of pH 10.5 was prepared as per USP specifications. To prepare Risperidone β-CD complex, solution of 14 mM β-CD was prepared in above mentioned buffer (9.352 mg in 600 ml) (12) and treated with 492.6 mg of Risperidone and the conical flask was kept on rotary flask shaker for 48 hrs followed by equilibration for 12 hrs. The resulting precipitates were filtered using Whatman Filter paper No. 41 and dried in vacuum oven at 50 °C for 6 hrs.

Preparation of risperidone HP-β-CD complex by vacuum drying method

The solution of 13.99 g HP-β-CD in 100 ml of deionized water and solution of 2.05 g of risperidone in 20 ml of ethanol were prepared and then both solutions were mixed to allow complexation of risperidone with HP-β-CD. This combination was then kept on a rotary flask shaker for 48 hrs followed by equilibration for 12 hrs. Finally, the suspension was filtered using G2 sintered glass filter and filtrate was dried in a rotary vacuum dryer (Buchi Rotavapor® R-205, Switzerland) at 60 °C till a dry powder was obtained (~ 4 hrs).

Drug content estimation

For drug content estimation, 4 mg equivalent of Risperidone was transferred into a dry 100 ml volumetric flask, and treated with 50 ml of deionized water and sonicated in ultrasonic water bath (Imeco ICW Pvt. Ltd., Pune) for 30 min while swirling occasionally. Then the solution was allowed to cool to room temperature and finally the volume was made up to the mark using water. Five milliliters of the above solution was diluted to 100 ml with mobile phase and analyzed by HPLC.

Characterization of CD Complexes

Evaluation by Fourier Transform Infra Red Spectroscopy

Infrared spectra of the complexes, physical mixtures and the individual components were obtained using fourier transform infra-red (FT-IR) spectrophotometer (Spectrum One, Perkin Elmer Instruments). The pellets were prepared on KBr press, and the spectra were recorded over the wave number 4000 to 400 cm^{-1}.

Evaluation by X-Ray Diffractometry

The X-ray diffraction (XRD) patterns of the complexes, physical mixtures and the individual components were recorded using Philips XPERT-PRO X-Ray diffractometer having X'Celerator detector. Samples were irradiated with

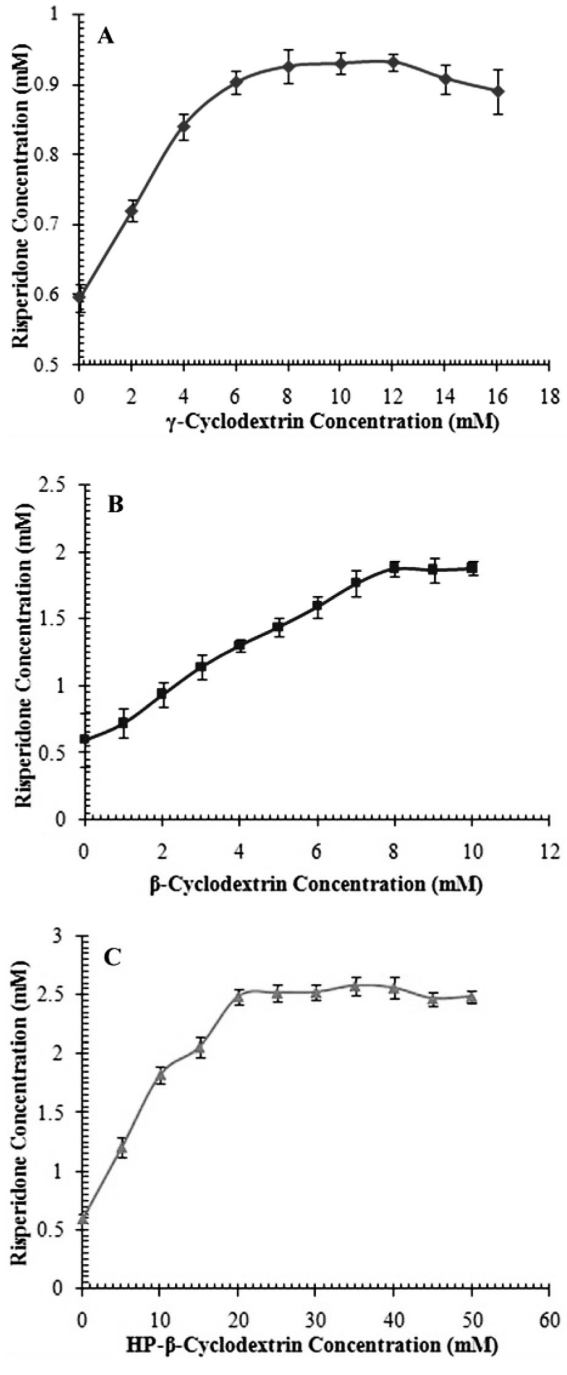

Figure 1. Phase Solubility Study of Ris peridone with (A) γ-Cyclodextrin, (B) β-Cyclodextrin and (C) HP- β-Cyclodextrin

monochromatized Cu Kα radiation (1.5406 Å) after passing through nickel filters and were analyzed between 40° and 2° (2θ) with scan step size 0.0167 in spinning condition and number of scan steps were 2274. The applied voltage and current were 45 KV and 40 mA, respectively.

Evaluation by Differential Scanning Calorimetry

The thermal behavior of the complexes, physical mixtures and the individual components was determined by using differential scanning calorimetry (DSC) equipped with an intra-cooler and a refrigerated cooling system (Q 1000, TA Instruments, Delaware, USA). Indium standard was used to calibrate the DSC temperature. Each sample was placed in an aluminum pan and then crimped with an aluminum cover to provide hermetically sealed samples (1-2 mg). The heating rate was 10 °C/min. All measurements were performed over 25–350 °C. Nitrogen was purged at the rate of 50 ml/min through cooling unit.

In vitro drug precipitation study

The drug-CD complex equivalent to 10 mg of risperidone was dissolved in 10 ml of water for injection at room temperature to obtain a clear transparent solution. After filtration through 0.45 µm nylon filter, 5 ml of the solution was diluted to 100 ml with 0.1M phosphate buffer saline of pH 7.4 and maintained at 37±0.5 °C on a water bath (15). One-half milliliter of the medium was withdrawn at every 5 mins interval for duration of 30 mins, filtered through 0.45 µm nylon filter, diluted appropriately with mobile phase and analyzed by HPLC. The remaining solution of the complex was kept at room temperature in tightly closed flask for 10 days and checked for drug content or precipitation at the end of the period.

Stability studies

The complexes of risperidone with β-CD and HP-β-CD were separately packed in glass vials closed with rubber stoppers and aluminium seals, and kept at 40 °C and 75% relative humidity in stability chamber (Narang Scietific Works Pvt. Ltd., New Delhi, India) for a period of 3 months as per ICH guidelines. Samples withdrawn at 1, 2 and 3 months were analyzed for the moisture content using Moisture Analyzer, LJ16 (Mettler Toledo International Inc. USA). The drug content was also determined at each sampling interval.

RESULTS AND DISCUSSION

Phase Solubility Study of Risperidone with CDs

The phase solubility study of Risperidone with three different types of CDs i.e., γ, β-CD and HP-β-CD (Figure 1) showed the increase in drug solubility by increase in the CD concentration in solutions indicating the occurrence of complexation in all the three cases and the obtained phase diagrams were of Bs type (16). The initial ascending portions of the curve can be attributed to the interaction of the drug with CD resulting in the formation of complex which has higher solubility than the drug alone. When the solubility limit of the formed complex exceeds, the ascending linear portion starts leveling off, forming a plateau. Further addition of CD results in the

Table 1. Stability Constants of Risperidone Cyclodextrin Complex (n=3).

Cyclodextrins	Intrinsic solubility of Risperidone (mM/L)	Slope	Stability Constant Kc (M^{-1})
γ-Cyclodextrin	0.596 ± 0.20	0.0529	93.716 ± 3.25
β-Cyclodextrin	0.596 ± 0.20	0.1693	341.953 ± 11.87
HP-β-Cyclodextrin	0.596 ± 0.20	0.0924	170.817 ± 5.93

The results are expressed as mean +/- SD

precipitation of a microcrystalline complex. By the increase in the concentration of γ-CD/β-CD, the complex continues to form in the plateau region and subsequently precipitates from the saturated solution. In the case of γ-CD, increase in CD concentration above 12 mM does not result in further improvement of the solubility of the drug as the saturation level of the complex is achieved in the medium. At this point, there is always a tendency of the saturated molecule to precipitate by the process of nucleation and crystallization which results in extraction of the solubilized complex from the solvent and thus the drug concentration reduces (Figure 1 A).

The apparent stability constant, K_c of the complex was estimated from the initial linear portion of the phase solubility diagram. The stability constants for γ-CD, β-CD and HP-β-CD are given in table 1. Statistical analysis of stability constants using one way ANOVA with Tukey Kramer multiple comparison test showed that the type of CD has significant effect on the values of stability constant ($p < 0.001$). Thus, from phase solubility studies, it can be concluded that all three CDs form complex successfully with the drug and the values of stability constants indicate that the complexation ability of risperidone with the CDs under study is in the order: β-CD > HP-β -CD > γ-CD The trend of stability constants could be explained on the basis of water solubility of CDs in relation to cavity size. The water solubility of β-CD, HP-β-CD and γ-CD are 18, 500 and 232 mg/ml, respectively and cavity size of β-CD and HP-β-CD are 6.0 – 6.5 Å and that of γ-CD is 7.5 – 8.3 Å (17). The highest stability constant of β-CD is due to its lowest solubility where the dissociation of drug from β-CD is slower in comparison to other CDs. However in the case of HP-β-CD, its solubility is highest and its cavity size is smaller than γ-CD, which results in slower escape of the drug molecule from the cavity upon dilution with aqueous medium. Due to relatively high stability constants of β-CD and HP-β-CD in comparison to γ-CD, the former CDs were selected for preparation of drug-CD complexes.

Inclusion complexation of Risperidone with β-CD

Risperidone-β-CD complex was prepared by precipitation method using phosphate buffer of pH 10.5 as the complexation medium. For the weak electrolytes, the strength of binding to a CD is dependent on the charged state of the drug, which is dependent on dissociation constant/s of the drug and the pH of its environment. In complexation with neutral CDs, the ionized or charged form of a molecule shows poor binding compared to the non-ionized or neutral form (18, 19). For example, it has been demonstrated (20, 21) that there was a decrease in complexation of molecules with HP-β-CD as the substrate becomes ionized. This decrease in stability was attributed to the overall increase in the hydrophilicity of the substrate upon ionization which reduces the substrates eliminate interaction with the more hydrophobic cavity of the CD. Therefore, conditions favoring the ionization of drug substances will increase the fraction of non-complexed molecules in solution. Thus, at pH 10.5, risperidone [pka_1 and pKa_2 are 3.1and 8.1, respectively (12)] prefers to be in non-ionic state which is more apolar in nature than ionic state of drug molecule which is favorable state for maximum inclusion complexation. Aqueous medium has been preferred for complexation because its polarity would act as a driving force for complexation as the guest or portion of the guest which complexes with the cavity of the CD is apolar and associates much more readily with the apolar cavity of the CD than with water.

Inclusion complexation of Risperidone with HP- β-CD

Risperidone-HP-β-CD complex was prepared by vacuum evaporation method with aqueous-alcoholic complexation medium where ethanol was added to increase the solubility of drug in the medium. A small amount of water miscible solvent was used to assist eliminate dissolution of guests and to increase the rate of complexation reaction. A polar solvent which does not complex with the cavity is preferred to minimize competition for the cavity with the guest. Upon addition of the dissolved guest to the solution of CD, the guest becomes solubilized or dispersed as a fine precipitate. In the latter case, a long stirring or complexation time is required, but complexation occurs more rapidly if the guest were still in the form of large crystals. Excessive amount of solvent reduces the driving force for complexation by reducing the difference in polarity between the cavity of the CD and the bulk solution, which may result in good solubilization of the guest, without complexation. Vacuum evaporation of the non-aqueous solution of CD and drug results in complexation as the solvent is

Table 2. Efficiency of complex of cyclodextrins with risperidone (n=6).

Type of CD	Weight of complex (mg)	Amount of Risperidone Complexed		% Complexation Efficiency	Amount of Complex containing 1 mg Drug	Molar Ratio Obtained
		Theoretical amount (mg)	Practical amount (mg)			
β-CD	10.4	1.593	1.517 ± 0.036	95.23 ± 2.27	6.86 ± 0.17	1:2
HP-â-CD	10.7	1.369	1.336 ± 0.027	97.59 ± 1.97	8.01 ± 0.16	1:2

The results are expressed as mean +/- SD

removed by evaporation and this process forces the drug to move into another hydrophobic environment i.e. CD cavity.

Determination of the Drug content of complexes

Both complexes showed very high drug content when analyzed by dissolving in 0.1N HCl as shown in table 2. There was no statistically significant difference ($p>0.05$) between encapsulation efficiency of β-CD and HP-β-CD when compared using t-test. Therefore, both CDs can be employed for formulation of the complex with Risperidone.

Characterization of the prepared CD Complexes

X-Ray Diffractometric Evaluation

X-ray pattern of diffraction (XRPD) of Risperidone, β-CD, their physical dispersion and Drug-β-CD complex are shown in figure 2 (A) and of similar samples with HP-β-CD in figure 2 (B). The XRPD pattern of the drug contained a number of sharp peaks which is indicative of its crystallanity with two prominent peaks of high intensity at $2\theta = 14.22°$ and $2\theta = 21.33°$, while the diffraction pattern of β-CD also shows a number of characteristic peaks. The diffraction pattern of the complex is quite different from pattern of physical mixture of drug and β-CD which shows the sum of both the patterns. In XRPD of the complex, most of the characteristic peaks of risperidone disappeared and some were reduced in intensity i.e. the peaks at $2\theta=14.22°$ and $2\theta=21.33°$, but overall it resembles the pattern of β-CD, which indicates a successful inclusion of risperidone in β-CD. The sharp peaks of complex confirmed its crystalline nature.

The diffraction pattern of HP-β-CD showed a diffused pattern indicating its amorphous nature. The XRPD of physical dispersion has all the peaks of risperidone summed up with peaks of HP-β-CD. The pattern of complex is similar to that of HP-β-CD pattern with only a few peaks of risperidone whose intensity was reduced. The complex is also amorphous in nature similar to the HP-β-CD, as it has same diffused XRD pattern.

Differential Scanning Colorimetric Evaluation

Thermal behavior of risperidone, β-CD, their physical dispersions and Drug-β-CD complex studied by DSC are shown in figure 3 (A) and of similar samples with HP-β-CD in figure 3 (B). The DSC curve of the drug shows a sharp endothermic peak at 170.29 °C and a small gradual exotherm at 210 °C indicating onset and gradual decomposition and of β-CD shows fractional loss of water at 90-155 °C, melting at 301 °C and decomposition afterwards. The DSC curve of their physical mixtures shows the sum of endotherms of drug as well as β-CD. However thermal behavior of Risperidone-β-CD complex shows fractional loss of water between 70 °C and 160 °C followed by melting at 301 °C and decomposition afterwards which indicate formation of complex because it does not have any endotherm around 170 °C. Results confirm the complexation of risperidone with β-CD.

The DSC curve of HP-β-CD shows fractional loss of water at 50-150 °C and there was melting by decomposition after 300 °C. The DSC curve of its physical mixture with risperidone shows the sum of endotherms of both molecules. However, thermal behavior of Risperidone-HP-β-CD complex shows fractional loss of water at 50-167 °C and decomposition after 300 °C indicating formation of complex as it also misses the endotherm of drug at 170 °C and confirms the complexation of risperidone with HP-β-CD.

Fourier-Transform Infrared Spectrophotometric Evaluation

The infrared spectra of risperidone, β-CD, their physical dispersion and drug-β-CD complex are depicted in figure 3 4(A) and of similar samples with HP-β-CD in figure 3 4(B). Risperidone spectrum shows a prominent band at 3058.1 cm^{-1} corresponding to the aromatic C–H stretching and at 2941.7 cm^{-1} and 2757.1 cm^{-1} due to aliphatic C–H stretching. A prominent band at 1651.6 cm^{-1}corresponds to C=O stretching of the aryl acids and bands at 1535.2 cm^{-1} and 1448.2 cm^{-1} related to C=C & C=N stretchings. Bands at 1412.9 cm^{-1} are due to aliphatic C-H bending and at 958.7, 866.5 and 817.6 cm^{-1} due to aromatic C-H bending. Other bands at 1351.5 cm^{-1} and 1130.7 cm^{-1} corresponds to C-N stretching and C-F stretching respectively. The IR spectrum of risperidone-β-CD complex is entirely different from risperidone, while it closely resembles the spectrum of β-CD. The characteristic bands of risperidone either have disappeared or reduced in intensity. The same is true with risperidone-HP-β-CD complex which has spectrum similar to HP-β-CD but with a few bands of risperidone decreased

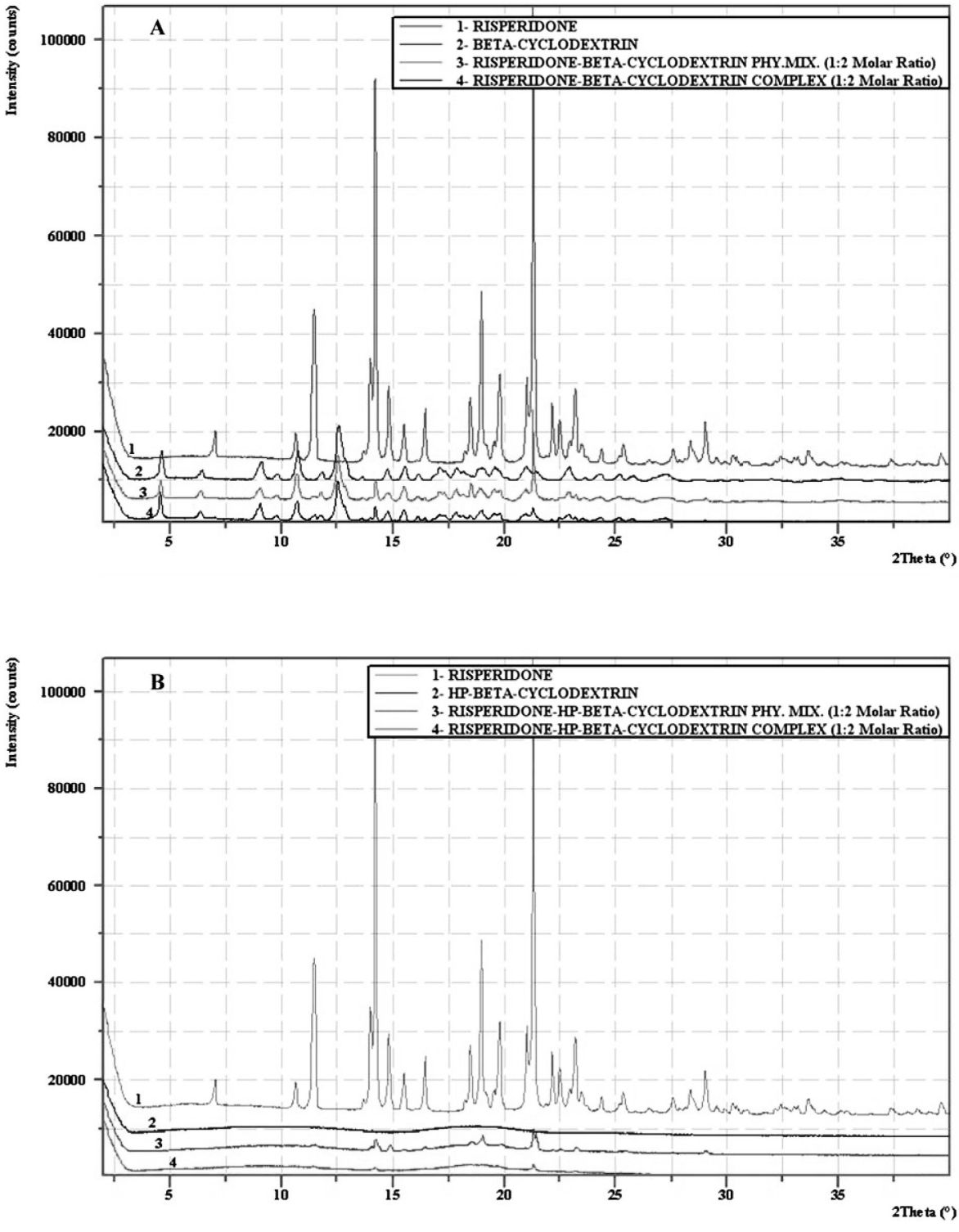

Figure 2. Comparison of X-Ray Diffractograph of: (A) Risperidone, β-CD, their physical mixture and complex in 1:2 molar ratio; (B) Risperidone, HP-β-Cyclodextrin, their physical mixture and complex in 1:2 molar ratio.

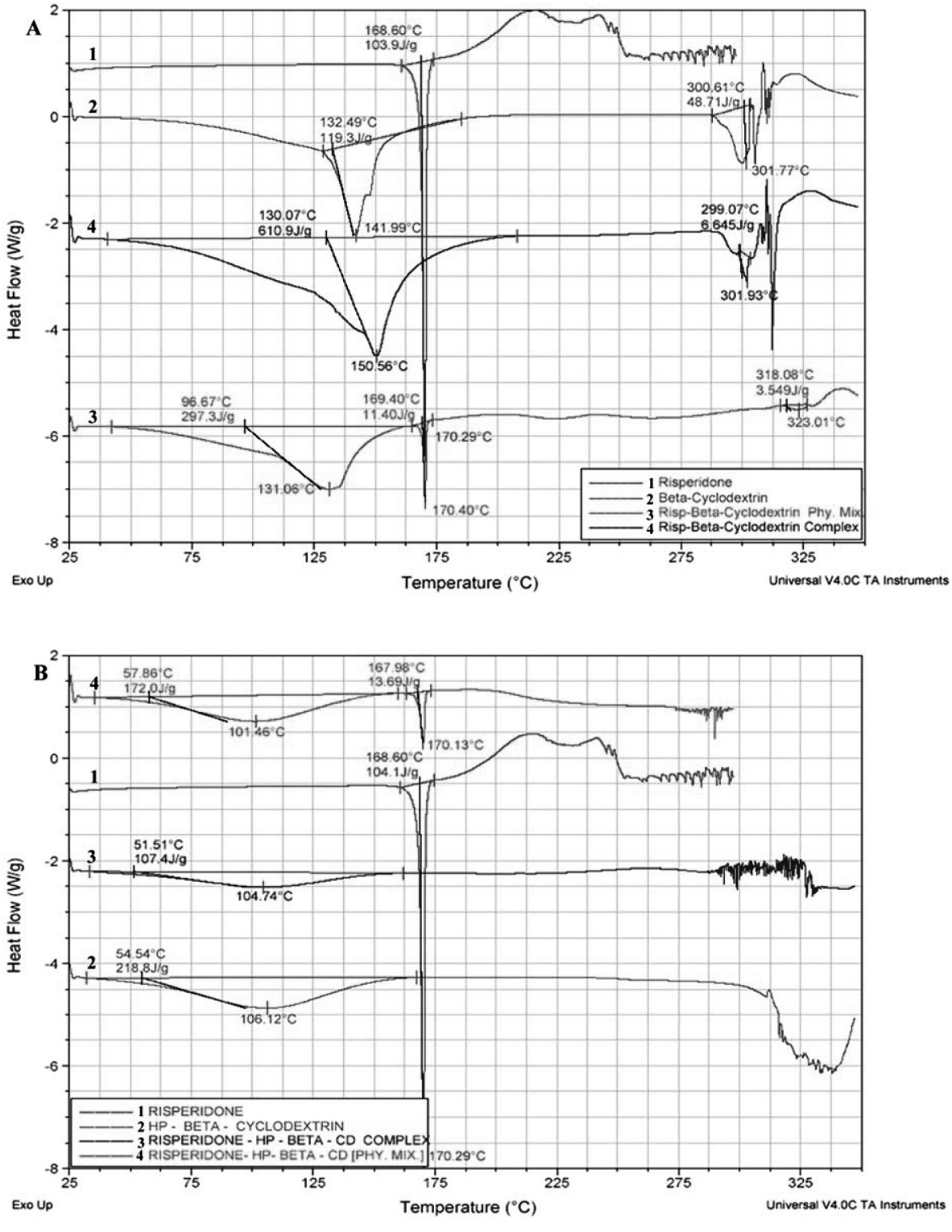

Figure 3. Comparative DSC thermographs of: (A) Risperidone, β-CD, their physical mixture and complex in 1:2 molar ratio; (B) Risperidone, HP-β-CD, their physical mixture and complex in1:2 molar ratio

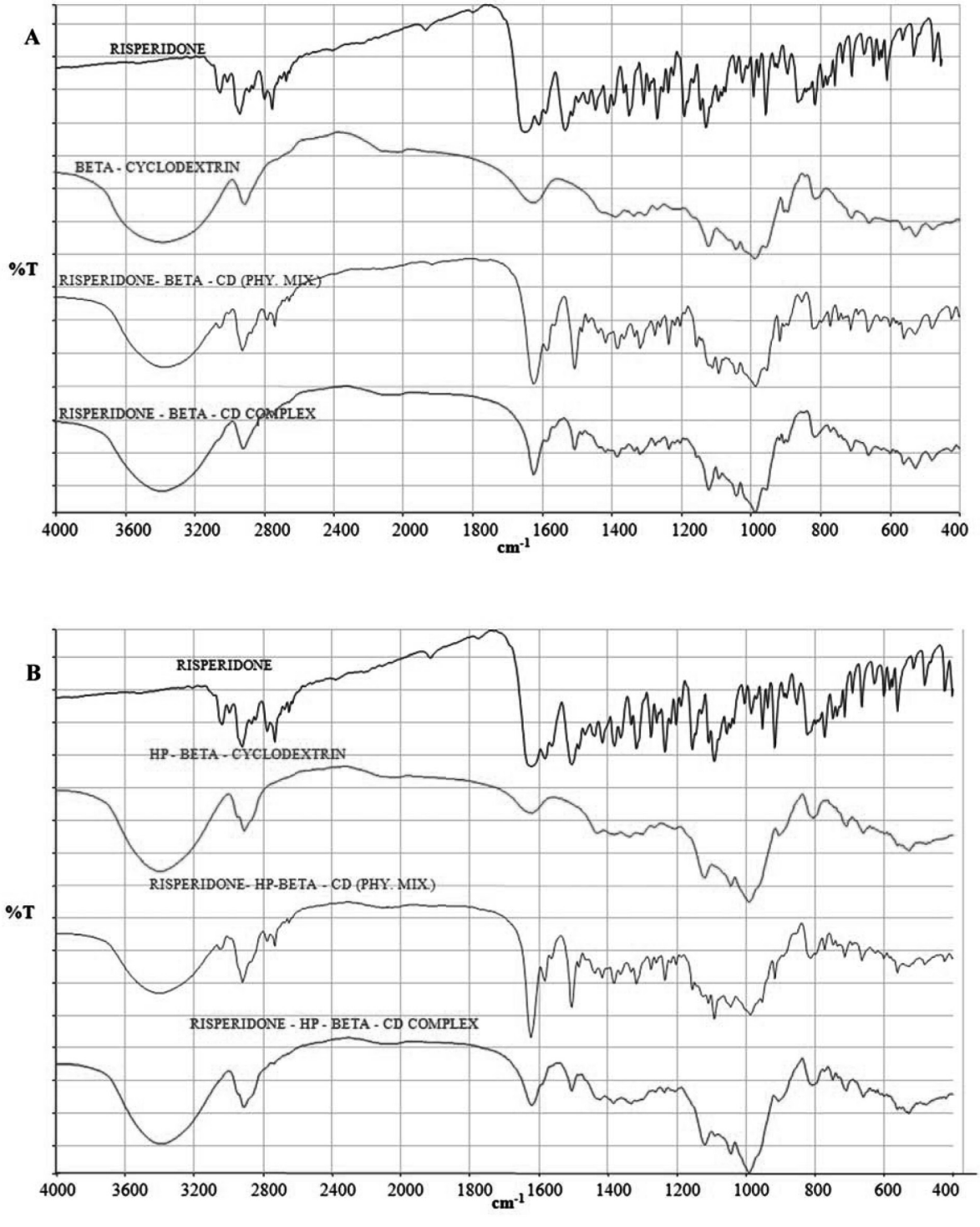

Figure 4. Comparative diagram of FT-IR Spectra of: (A) Risperidone, β-CD, their physical mixture and complex in 1:2 molar ratio; (B) Risperidone, HP-β-CD, their physical mixture and complex in 1:2 molar ratio.

Table 3. Stability data of drug cyclodextrin complex (n=3).

Month	Moisture content (%)		Drug content (%)	
	Risperidone β- CD	Risperidone HP-β-CD	Risperidone β- CD	Risperidone HP-β-CD
0	1.2 ± 0.3	1.5 ± 0.3	99.67 ± 0.58	99.21 ± 0.45
1	1.0 ± 0.2	1.2 ± 0.4	99.19 ± 0.75	98.94 ± 0.69
2	1.5 ± 0.1	1.4 ± 0.1	100.29 ± 0.32	99.81 ± 0.47
3	1.3 ± 0.2	1.3 ± 0.3	99.53± 0.67	98.72 ± 0.41

The results are expressed as mean +/- SD

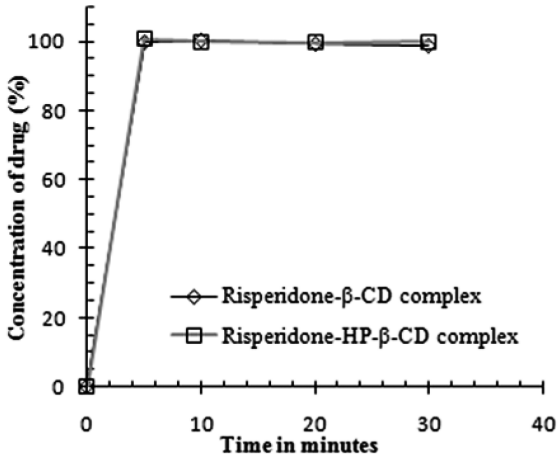

Figure 5. Concentration of drug in 100 ml pH 7.4 PBS.

in intensity probably due to the restriction inside the CD cavity.

In vitro drug precipitation study

Due to low drug solubility at alkaline pH, there may be chances that upon parenteral administration the drug released from a highly soluble complex precipitates out in the blood and blocks the blood vessels which may be fatal. Therefore, the in-vitro drug precipitation study was carried out to ascertain the lack of precipitation in the blood after the complex is administered parenterally as solution in water for injection. Figure 5 shows the complete release and stable concentration of the drug during 30 mins which means that no drug was precipitated out from the solution upon dilution with 100 ml of the buffer. This study indicates the safety of the product for parenteral application.

Stability Study

No change in color of samples was observed during storage. The drug and moisture contents (Table 3) were compared statistically using One way ANOVA with Bartlett test and no significant difference was found ($p > 0.05$) in either complex even after 3 months of accelerated stability study. This indicates a stable product and suitability of the sealed glass vial as the packing material for the present formulation.

CONCLUSION

In the present investigation, an injectable formulation of Risperidone was successfully formulated by complexation with both β-CD and HP-β-CD using a simple and highly efficient method and the complexation was confirmed by FTIR, XRD and DSC. The stability of complexes was found to be satisfactory.

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