Enhancement of Solubility of Rilpivirine by Inclusion Complexation with Cyclodextrins

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ABSTRACT
Rilpivirine having lowest water solubility indicates class II drugs of BCS. These classes of drugs could potentially exhibit dissolution rate limited absorption. The objective of the present study is to improve the solubility and dissolution of Rilpivirine through inclusion complexation with βCD and HPβCD. Solid binary systems of Rilpivirine with βCD and HPβCD were prepared by solvent evaporation and kneading methods at 1:1 and 1:2 M ratios. The prepared solid binary systems were studied in solution state by phase solubility, in vitro dissolution rate and solid state by FTIR and XRD. The dissolution parameters were studied by using dissolution software PCP Disso V3. The drug content was uniform in all the solid binary systems with low SD and CV values. The apparent stability constant indicates there is a 1:1 stoichiometric complex with βCD and HPβCD. The formation of inclusion complexes with βCD and HPβCD in the solid state were confirmed by FTIR, XRD. The dissolution data clearly suggest drug release was method dependent and type of cyclodextrin. The dissolution of solid binary systems obeyed first-order kinetics and model fitted with Hixon crowel. A true inclusion complex of Rilpivirine was observed with βCD and HPβCD. Dissolution properties of solid binary systems were superior then rilpivirine alone and its corresponding physical mixtures. Overall dissolution rate was solvent evaporation > kneaded binary systems > physical mixture > pure drug. One-way ANOVA results suggest the DE³⁰ and DE⁶⁰ values were significantly higher (P<0.05) in solid binary systems when compared to physical mixture and pure drug.

Keywords: Rilpivirine, βCD, HβCD, FTIR, XRD, Solid binary systems.
INTRODUCTION
Aqueous solubility can also be an issue for some marketed drugs. More than 90% of drugs approved since 1995 have poor solubility, poor permeability or both. Approximately 16% have less than optimal solubility or almost white, white or almost colorless. The main purpose of the present study is to improve the solubility while maintaining the efficacy required. The different methods are available to enhance the dissolution and absorption rates of poorly water-soluble drugs. An inclusion complex with Cyclodextrins is one of the excellent methods used to enhance the solubility. Cyclodextrins improve the apparent drug solubility and/or dissolution of poorly water-soluble drugs through inclusion complexes with their apolar molecules or functional groups. The resulting complex hides most of the hydrophobic functionality in the interior cavity of the cyclodextrin while the hydrophilic hydroxyl groups on the external surface remain exposed to the environment. The net effect is water-soluble cyclodextrin drug complex is formed. Cyclodextrins enhance the bioavailability of insoluble drugs by increasing the drug solubility, dissolution and absorption/or drug permeability. They increase the permeability of insoluble hydrophobic drugs by making the drug available at the surface of the biological barrier e.g. skin, mucosa or eye cornea, from where it partitions into the membrane without disrupting the lipid layers of the barrier. β-cyclodextrin [11-17] appeared as white crystalline, nonhygroscopic powder having melting point of 255-263°C. Soluble in 200 parts of propylene glycol, 1 in 50 of water at 20°C, 1 in 20 at 50°C. Practically insoluble in acetone, ethanol (95%) and methylene chloride. β-cyclodextrin is considered to be nontoxic when administered orally and is primarily used in tablet and capsule formulations. In oral tablet formulations, β-cyclodextrin may be used in both wet granulation and direct compression methods. Hydroxypropyl-β-cyclodextrin [18-19] appeared as a white or almost white, amorphous or crystalline free flowing, odourless powder. It contains not less than 10.0 percent and not more than 45.0 percent hydroxypropoxy groups. HPβCD is very soluble in water. Substitution of the hydroxyl groups of the βCD disrupts the network of hydrogen bonding around the rim of the βCD. HP-β-cyclodextrin is suitable for molecular encapsulation of a sparingly water-soluble compounds to enhance the aqueous solubility. Rilpivirine is nonnucleoside reverse transcriptase inhibitor (NNRTI) which is used for the treatment of HIV-1 infections in treatment-naive patients. It is a diarylpyrimidine, a class of molecules that resemble pyrimidine nucleotides found in DNA. [20] Rilpivirine is a white powder with a molecular weight of 366.42. It is having lowest water solubility of about 10mg/ml and its logP value is 3.8, indicates class II drugs of BCS (biopharmaceutical classification systems i.e. high permeability and low solubility). These classes of drugs could potentially exhibit dissolution rate limited absorption and their dissolution rates may be improved through the preparation of solid dispersion [21] and inclusion complexes [22] therefore, Rilpivirine is suitable candidate for inclusion complexation with cyclodextrins viz., βCD and HPβCD. Cyclodextrins are known for ability to encapsulate a wide variety of drugs into their hydrophobic cavity without the formation of any covalent bonds and are widely used in the pharmaceutical field owing to their high aqueous solubility and ability to stabilize drug molecules. The main objective of the present research work Rilpivirine having lowest water solubility indicates class II drugs of BCS. These classes of drugs could potentially exhibit dissolution rate limited absorption. The objective of the present study is to improve the solubility and dissolution of Rilpivirine through inclusion complexation with βCD and HPβCD.

MATERIALS AND METHODS
Rilpivirine was procured from Strides Arc lab, Bangalore, Karnataka state. β-Cyclodextrin, HP-β-Cyclodextrin were procured as a gift sample from Yarrow chem. products. Dichloromethane was S.D. Fine chem., Mumbai. All other ingredients used were of analytical grades and distilled water was used thoroughly the studies.

EXPERIMENTAL
Preparation of solid binary systems: The following solid binary systems of Rilpivirine with βCD and HP-β-CD at 1:1 and 1:2 molar ratios are prepared by different methods.
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Physical mixtures (PM): The physical mixtures of Rilpivirine: βCD, Rilpivirine: HP-β-CD in 1:1 and 1:2 M were obtained by mixing individual components together with a spatula.
Kneading method (KNE): Accurately weighed quantities of Rilpivirine and βCD at 1:1, 1:2 molar ratios were triturated in glass mortar with small volume of dichloromethane. The thick slurry was kneaded for 1 hour and then dried at 45°C until dryness. The dried mass was pulverized and sieved through #120 and stored in desiccator until further evaluation. Similarly the solid binary systems were prepared with HP-β-CD.
Solvent evaporation method (SE): Accurately weighed quantities of Rilpivirine and βCD at 1:1, 1:2 molar ratios were dissolved in dichloromethane. The resulting mixture was stirred for 1 hour and evaporated under vacuum until dry. The dried mass was pulverized and sieved through #120 and stored in desiccator until further evaluation.
further evaluation. Similarly the solid binary systems were prepared with HP-β-CD. The formulae of physical mixture and solid binary systems are given in Table 1.

**Characterization of solid binary systems**

Detection of solid binary systems in solution state by drug content uniformity, phase solubility studies, in solid state fourier transmitted infrared (FTIR) studies, powder X-ray diffractionmetry (XRD) and *in vitro* dissolution studies.

**Drug content uniformity**

In each case physical mixture and solid binary systems equivalent to 20 mg of Rilpivirine was accurately weighed and transferred to 100 ml volumetric flask. Methanol was added and mixed to dissolve the Rilpivirine. The volume was made up to 100 ml with methanol. From this 1 ml is subsequently diluted with 0.01N HCl and make up to volume to 10 ml and Rilpivirine content was calculated from the calibration curve.

![Fig. 1: Phase solubility of Rilpivirine in 0.01N HCl.](image1)

**Phase solubility studies**

Solubility measurements were carried out according to the method described by Higuchi and Connors. The apparent stability constants ($K_{1:1}$) were calculated from phase solubility diagrams by using following equation.

$$K_{1:1} = \frac{\text{Slope}}{S_0(1 - \text{Slope})}$$

Where $S_0$ is intercept

Excess amounts of Rilpivirine were added to 15 ml βCD solution (ranging in concentration from 0.001 to 0.03 M) prepared in 0.01N HCl in a series of 25 ml stoppered conical flasks. The mixtures were shaken for 48 hour at room temperature (37°C) on a rotary shaker. Shake for 48 hour to achieve equilibrium. 2 ml aliquots were withdrawn at 48 hour followed by 2 hour intervals and filtered immediately using a 0.45μm nylon disc filter. The filtered samples were diluted and assayed for Rilpivirine by measuring absorbance at 280 nm. Shaking was continued until three consecutive estimations were the same. The solubility experiments were conducted in triplicate. The blanks were performed in the same concentrations of Rilpivirine in order to cancel any absorbance that may be exhibited by the βCD molecules. Similarly the solubility of Rilpivirine was carried out in HP-βCD solution (ranging in concentration from 0.001 to 0.03M) prepared in 0.01N HCl. The apparent stability constants were calculated from the solubility diagrams.

| Batches | Drug | Cyclodextrin | Ratio | Method |
|---------|------|--------------|-------|--------|
| F-1     | Rilpivirine | β-CD | 1:1 | PM    |
| F-2     | Rilpivirine | β-CD | 1:2 | PM    |
| F-3     | Rilpivirine | β-CD | 1:1 | KNE   |
| F-4     | Rilpivirine | β-CD | 1:2 | KNE   |
| F-5     | Rilpivirine | β-CD | 1:1 | SE    |
| F-6     | Rilpivirine | β-CD | 1:2 | SE    |
| F-7     | Rilpivirine | HP-β-CD | 1:1 | PM    |
| F-8     | Rilpivirine | HP-β-CD | 1:2 | PM    |
| F-9     | Rilpivirine | HP-β-CD | 1:1 | KNE   |
| F-10    | Rilpivirine | HP-β-CD | 1:2 | KNE   |
| F-11    | Rilpivirine | HP-β-CD | 1:1 | SE    |
| F-12    | Rilpivirine | HP-β-CD | 1:2 | SE    |

![Fig. 2: Phase solubility of Rilpivirine in 0.01N HCl.](image2)

| Batches | Amount of drug taken (mg) | Amount of drug recovered (mg) | % Drug content of Rilpivirine ± SD | Coefficient of variance |
|---------|--------------------------|-----------------------------|-----------------------------------|------------------------|
| F-1     | 20                       | 19.58                       | 97.90 ± 0.13                     | 0.139                  |
| F-2     | 20                       | 19.69                       | 98.45 ± 0.20                     | 0.206                  |
| F-3     | 20                       | 19.82                       | 99.12 ± 0.27                     | 0.272                  |
| F-4     | 20                       | 19.38                       | 98.93 ± 0.31                     | 0.313                  |
| F-5     | 20                       | 19.48                       | 97.42 ± 0.32                     | 0.328                  |
| F-6     | 20                       | 19.75                       | 98.77 ± 0.39                     | 0.394                  |
| F-7     | 20                       | 19.82                       | 99.13 ± 0.37                     | 0.373                  |
| F-8     | 20                       | 19.61                       | 98.09 ± 0.40                     | 0.407                  |
| F-9     | 20                       | 19.93                       | 99.65 ± 0.32                     | 0.321                  |
| F-10    | 20                       | 19.68                       | 98.44 ± 0.21                     | 0.213                  |
| F-11    | 20                       | 19.41                       | 97.06 ± 0.27                     | 0.278                  |
| F-12    | 20                       | 19.31                       | 97.98 ± 0.14                     | 0.142                  |

*Average of three determinations

| Molar Concentration of CD | I | II | III | Mean | SD |
|--------------------------|---|----|-----|------|----|
| 0.001                    | 0.168 | 0.169 | 0.166 | 0.167 | 0.0015 |
| 0.002                    | 0.194 | 0.193 | 0.192 | 0.193 | 0.0010 |
| 0.003                    | 0.215 | 0.214 | 0.216 | 0.215 | 0.0012 |
| 0.004                    | 0.288 | 0.287 | 0.281 | 0.285 | 0.0037 |
| 0.005                    | 0.308 | 0.311 | 0.312 | 0.310 | 0.0020 |
| 0.007                    | 0.376 | 0.377 | 0.374 | 0.373 | 0.0030 |
| 0.01                     | 0.442 | 0.443 | 0.447 | 0.444 | 0.0026 |
| 0.0123                   | 0.506 | 0.505 | 0.502 | 0.506 | 0.0040 |
| 0.015                    | 0.598 | 0.61 | 0.618 | 0.608 | 0.010 |
| 0.0175                   | 0.63 | 0.624 | 0.629 | 0.627 | 0.0032 |
| 0.02                     | 0.711 | 0.719 | 0.716 | 0.715 | 0.0040 |
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Fig. 3: FTIR spectra of pure drug Rilpivirine and F-1 to F-6 solid binary systems

Fig. 4: FTIR spectra of Pure drug Rilpivirine and F-7 to F-12 solid binary systems
Table 5: Comparative FTIR data of Rilpivirine physical mixture and solid binary systems

| Batches | -NH Stretching | CH$_3$ Stretching | C=N Stretching |
|---------|---------------|------------------|--------------|
| Rilpivirine | 2977.76 cm$^{-1}$ | 2890.38 cm$^{-1}$ | 1385.04 cm$^{-1}$ |
| F-1     | 2977.00 cm$^{-1}$ | 2890.57 cm$^{-1}$ | 1385.04 cm$^{-1}$ |
| F-2     | 2977.02 cm$^{-1}$ | 2890.65 cm$^{-1}$ | 1385.09 cm$^{-1}$ |
| F-3     | 2977.03 cm$^{-1}$ | Disappear | 1384.84 cm$^{-1}$ |
| F-4     | 2924.34 cm$^{-1}$ | Disappear | 1331.36 cm$^{-1}$ |
| F-5     | 2976.90 cm$^{-1}$ | 2890.36 cm$^{-1}$ | 1384.72 cm$^{-1}$ |
| F-6     | 2925.53 cm$^{-1}$ | 2854.48 cm$^{-1}$ | 1333.23 cm$^{-1}$ |
| F-7     | 2977.04 cm$^{-1}$ | 2890.44 cm$^{-1}$ | 1384.82 cm$^{-1}$ |
| F-8     | 2976.99 cm$^{-1}$ | 2890.60 cm$^{-1}$ | 1385.21 cm$^{-1}$ |
| F-9     | 2976.97 cm$^{-1}$ | 2890.45 cm$^{-1}$ | 1384.76 cm$^{-1}$ |
| F-10    | Disappear | 2886.62 cm$^{-1}$ | 1333.29 cm$^{-1}$ |
| F-11    | 2924.37 cm$^{-1}$ | 2855.50 cm$^{-1}$ | 1332.81 cm$^{-1}$ |
| F-12    | 2924.24 cm$^{-1}$ | 2853.41 cm$^{-1}$ | 1334.75 cm$^{-1}$ |

*Average of three determinations

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**Fig. 5:** X-ray diffraction pattern of Rilpivirine, β-CD, F-4 and F-6

**Fig. 6:** X-ray diffraction pattern of Rilpivirine, HP β-CD, F-10 and F-12

**Fig. 7:** Comparative dissolution profiles of Rilpivirine and F-1, F-3 and F-5 formulations
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Dissolution studies

In vitro dissolution studies of pure Rilpivirine, physical mixture and its solid binary systems were carried out in 900 ml of 0.01N HCl using a USPXXI type 2 dissolution rate test apparatus by the powder dispersed amount method (powder samples were spread over the dissolution medium). Sample equivalent to 20 mg of Rilpivirine, speed of 50 rpm and a temperature of 37°C were used in each test. A 5ml aliquot was withdrawn at different time intervals, filtered using a 0.45µm nylon disc filter and replaced with 5 ml of fresh dissolution medium. The filtered samples were suitably diluted, if necessary and assayed for Rilpivirine by measuring the absorbance at 280 nm. The dissolution experiments were conducted in triplicate. The results were computed by using dissolution software.

RESULTS AND DISCUSSION

Solid binary systems of Rilpivirine in βCD and HPβCD were prepared by two methods viz., kneading and solvent evaporation at 1:1 and 1:2 molar ratios. Detection of inclusion complexation was done in solution state by means of drug content uniformity, phase solubility analysis and in solid state by FTIR, powder x-ray diffractometry (X-RD) and in vitro dissolution studies.

The formulated solid binary systems were evaluated in solution state and solid state. The drug content of all batches was determined and the data was given in Table 2. The percent drug content of the solid binary systems was found to be in the range of 97.42 ± 0.32 to 99.12 ± 0.27 for F-1 to F-6 and 97.06 ± 0.27 to 99.65 ± 0.32 for F-7 to F-2 formulations. The coefficient of variation (CV) and standard deviation (SD) in the percent drug content was found to be less than 0.5% in all the batches prepared. There was no significant loss of drug during the preparation of binary systems and proportion of drug and carrier remained uniform in each batch prepared. The phase solubility data of Rilpivirine in 0.01N HCl were given in [Fig 1 and 2; Table 3 and 4]. The apparent stability constant values were 7.231M ± 0.01682 and 9.362M ± 0.1778 for βCD and HPβCD respectively. The larger constant that was observed with HPβCD indicates Rilpivirine interacts more strongly with HPβCD.

FTIR studies

Fourier transform IR spectra were recorded on a Shimadzu FTIR-281-spectrophotometer. The spectra were recorded for Rilpivirine, βCD, HPβCD, physical mixture and its solid binary systems. Samples were prepared in KBr disks prepared with a hydrostatic press at a force of 5.2T cm-2 for 3 min. The scanning range was 450-4000 cm-1 and the resolution was 1 cm-1.

Powder X-ray diffractometry

The powder X-ray diffraction patterns of pure Rilpivirine, βCD, HPβCD and selected solid binary systems were recorded by using Philips X-ray powder diffractometer (model PW 3710) employing Cr-radiation. The diffractometer were run at 2.4°/min in terms of 2θ angle.
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een Rilpivirine with HPβCD.

Table 8: Model fitting values of pure drug and F

Table 6: Dissolution data of Rilpivirine, physical mixture and its solid binary systems prepared with βCD

Table 7: Dissolution data of Rilpivirine, physical mixture and its solid binary systems prepared with HP βCD

Table 8: Model fitting values of pure drug and F-1 to F-12 formulations.

XRD studies

The compatibility between pure drug and polymers were studied by XRD. The XRD spectra of Rilpivirine, β-CD, HP-β-CD, and solid binary systems were given in Fig. 5-6.

The X-ray diffraction patterns of RIL-β-CD inclusion complexes at 1:2M ratios showed all the principle peaks of Rilpivirine and βCD. However, the peak intensities of the 1:2M inclusion complex prepared by solvent evaporation are lower than the corresponding 1:1M inclusion complex prepared by kneading method. The diffraction patterns are the sum of each component, indicating the presence of Rilpivirine in crystalline state. These results suggest no alteration in the crystal structure of Rilpivirine, but the crystallinity being modified, since the peak position (angle of diffraction) is an indication of crystal structure and the peak heights are a measure of the sample crystallinity. In case of RIL-HPβCD inclusion complexes, there was lot of decrement in the crystalline structure of Rilpivirine and in 1:2M RIL-HPβCD kneading and solvent evaporated inclusion complex only few distinguishing peak were observed indicating a strong interaction between Rilpivirine with HPβCD confirming the formation of true inclusion complex.

Dissolution studies

The in vitro drug dissolution was studied by using standard procedure and conditions. The dissolution data, dissolution profiles and model fitting data and profiles were given in Table 6-7 and Fig. 7-10. In the present investigation, dispersed amount method is used to investigate the various dissolution parameters of Rilpivirine and its inclusion complexes. The dissolution data of Rilpivirine and its inclusion complexes were studied by using dissolution software PCP DISS0 V.3.0. The dissolution data obtained were subjected to model fitting and the model which fits the observed dissolution data was evaluated by correlation coefficient (r) between the variables i.e. time (min) and dissolution rate of Rilpivirine from solid binary system.

The results of the dissolution rate studies indicated higher dissolution rate of Rilpivirine from solid binary systems than compared to Rilpivirine itself and the corresponding physical mixtures. The slight increase in dissolution rate and efficiency values recorded for the physical mixture may be explained on the basis of the solubility of the drug in aqueous cyclodextrin solutions. Since the cyclodextrins dissolve more rapidly in the hydrodynamic layer surrounding the particles of the drug.

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The $T_{50}$, RDR$_{30}$, RDR$_{60}$, DE$_{30}$, DE$_{60}$, DP$_{30}$, DP$_{60}$, MDT$_{30}$, MDT$_{60}$ values of the binary systems that were prepared by the kneading and solvent evaporation methods were relatively high when compared with the values from the physical mixtures and Rilpivirine alone. Overall the rank order of improvement in dissolution properties of Rilpivirine with different cyclodextrins is HPβCD > βCD, with ratios 1:2M > 1:1M and methods SE > KNE > PM > Pure drug. The dissolution data was model fitted using dissolution software and the best fit model was found to be Hixon crowel and the release was follows first order kinetics [Table 8].

One-way ANOVA was used to test the statistical significant difference between pure and prepared solid binary systems. Significant differences in the means of DP$_{30}$, DP$_{60}$, DE$_{30}$ and DE$_{60}$ were tested at 95% confidence. The DP$_{30}$, DP$_{60}$, DE$_{30}$ and DE$_{60}$ values of solid binary systems prepared by kneading and solvent evaporation method are significantly higher ($P<0.05$) when compared to DP$_{30}$, DP$_{60}$, DE$_{30}$ and DE$_{60}$ values of pure rilpivirine, physical mixture.

Solid binary systems of Rilpivirine in βCD and HPβCD were conveniently prepared by two methods viz., kneading and solvent evaporation at 1:1 and 1:2 molar ratios. The solubility of Rilpivirine increases linearly with an increase in the concentration of cyclodextrins giving $A_t$ type solubility diagrams. The increase in solubility in the systems is due to one or more molecular interactions between Rilpivirine and cyclodextrins form distinct species or complexes. The solubilizing efficiency of cyclodextrins is in the order of HPβCD > β-CD. Overall the rank order of improvement in dissolution properties of Rilpivirine with different cyclodextrins is HPβCD > βCD, with ratios 1:2M > 1:1M and methods SE > KNE > PM > Pure drug.

REFERENCES

1. Sanghavi NM, Choudhari KB, Matharu RS, Lattha V. Inclusion complexation of lorazepam with β-cyclodextrin. Drug Dev Ind Pharm 1993; 19(6): 701-712.
2. Hye JA, Kyounig MK, Jin-Suck C, Chong-Kook K. Effects of cyclodextrin derivatives on bioavailability of ketoprofen. Drug Dev Ind Pharm 1997; 23(4): 397-401.
3. Dhananraj MD, Santhil Kumaran K, Baskaran T, Ramamorothy SM. Enhancement of bioavailability of griseofulvin by its complexation with β-cyclodextrin. Drug Dev Ind Pharm 1998; 24(6): 583-587.
4. Maria DV, Paloma JD, Falkbr A. Interactions of griseofulvin with cyclodextrins in solid binary systems. J Pharma Sci 1998; 87(7): 891-900.
5. Gorden B, Leo JS, Mun YT. Improvement of the in vitro dissolution of praziquantel by complexation with α-, β- and γ-cyclodextrins. Int J Pharm 1999; 179(1): 65-71.
6. Jeanette L, Henning MK, Klaas K, Jaco CB. The influence of β-cyclodextrin on the solubility of chlorthalidone and its enantiomers. Drug Dev Ind Pharm 1999; 25(8): 879-884.
7. Loftsson T, Stefansson E. Effect of cyclodextrins on topical drug delivery to the eye. Drug Dev Ind Pharm 1997; 23(6): 473-481.
8. Dome VH. Interaction between cyclodextrins and ophthalmic drugs. Eur J Pharma Biopharm 1993; 39: 133-139.
9. Loftsson T, Masson M, Stefansson E. Cyclodextrins as permeation enhancers, 17th Pharmaceutical Technology Conference and Exhibition. 1997 March 24-26; Dublin, Ireland.
10. Willems L, Geest RV, DeBeule K. Itraconazole oral solution and intravenous formulations: a review of pharmacokinetics and pharmacodynamics. J Clin Pharma Ther 2001; 26(3): 159-169.
11. Sachs G, Sanchez R, Marcus R, Stock E, McQuade R, Carson W, Abou-Gharbia N, Impellizzeri C, Kaplita S, Rollin L, Iwamoto T. Rilpivirine in the treatment of HIV. J Pharmacmacia 2010 20(4): 536-546.
12. Duchene D, Wouessidjewe D. Physicochemical characteristics and pharmaceutical uses of cyclodextrin derivatives, Part-I. Pharma Techno 1990; 14(6): 26, 28, 34.
13. Duchene D, Wouessidjewe D. Physicochemical characteristics and pharmaceutical uses of cyclodextrin derivatives, Part-II. Pharma Pharm Tra 1990; 14(8): 14, 22, 24, 26.
14. Marcus EB, Matinder SH, James WS, Nicholas B. Use of 2-hydroxypropyl-β-cyclodextrin as a solubilizing and stabilizing excipient for protein drugs. Pharma Res 1991; 8(6): 792-795.
15. Somesh C, Kenneth FN. Improvement of oral bioavailability of carbamazepine by inclusion in 2-hydroxypropyl-β-cyclodextrin. Int J Pharma 1999; 85(1-3): 175-180.
16. Elshabouri MH. Physical properties and dissolution profiles of tablets directly compressed with β-cyclodextrin. Int J Pharma 1990; 63(2): 95-100.
17. Ralph F Shangraw, Girish SP, Pankaj G. Characterization of the tabletting properties of β-cyclodextrin and the effects of processing variables on inclusion complex formation, compactibility and dissolution. Drug Dev Ind Pharm 1992; 18(17): 1831-1851.
18. Muller BW, Brauns U. Hydroxy propyl-b-cyclodextrin derivatives. Influence of average degree of substitution on complexing ability and surface activity. J Pharma Sci 1986; 75:571-572.
19. Pitha, Josef. Pharmaceutical preparations containing cyclodextrin derivatives. US Patent 4727064; 8-16-88.
20. Brewster ME, Simpkins JW, Hora MS. The potential use of cyclodextrins in parenteral formulations. J Parenter Sci Tech 1989; 43: 231-240.
21. Abu TMS. Solid dispersion of poorly water soluble drugs: Early promises, subsequent problems, and recent breakthroughs. J Pharma Sci 1999; 88(10): 1058-1066.
22. Duncan QMC. The mechanisms of drug release from solid dispersions in water soluble polymers. Int J Pharma 2002; 231(2): 131-144.
23. Szente L, Szotli J. Highly soluble cyclodextrin derivatives: chemistry, properties, and trends in development. Adv Drug Deliv Rev 1999; 36: 17-28.
24. Baboot S, Agarwal SP. Rofecoxib complexation with β-CD: Influence on the anti-inflammatory and ulcerogenic activity. Die Pharmazie 2003; 58: 73-74.
25. Mukne AP, Nagarsenker MS. Triamterene-β-cyclodextrin Systems: Preparation, Characterization and In Vivo Evaluation. AAPS Pharma Sci Tech 2004; 5(1):1-9.
26. Tirucheri GS, Mitra AK. Effect of hydroxypropyl β-cyclodextrin complexation on aqueous solubility, stability and corneal permeation of acyl ester prodrugs of guanaclovir. AAPS Pharma Sci Tech 2003; 4(3):1-12.

HOW TO CITE THIS ARTICLE: Srivani, Anand Kumar Y, Raghavendra Rao NG. Enhancement of Solubility of Rilpivirine by Inclusion Complexation with Cyclodextrins. Int. J. Pharm. Sci. Drug Res. 2018; 10(1): 31-38. DOI: 10.25004/IJPSDR.2018.100106