INCLUSION COMPLEX OF ANTI-TUBERCULAR RIFAMPICIN WITH BETA-CYCOLODEXTRIN OR 2-HYDROXY-PROPYL BETA-CYCOLODEXTRIN AND A PROCESS FOR PRODUCING THE SAME
as to applicant’s entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published:
— with international search report
— with amended claims and statement

For two-letter codes and other abbreviations, refer to the “Guidance Notes on Codes and Abbreviations” appearing at the beginning of each regular issue of the PCT Gazette.
Technical Field

The present invention relates to an inclusion complex comprising Rifampicin and cyclodextrin useful as drug in tuberculosis. The present invention also relates to synthesis of Rifampicin- cyclodextrin inclusion complexes, which find use in tuberculosis therapy as drug delivery systems.

Background Art

Rifampicin is the international nonproprietary name and other names used are Rifamycin AMP, Rifampin and Rifaldazine. Rifampicin is designated by IUPAC rules as 2,7- (epoxy pentadeca [ 1, 11, 13 ]trienimino ) naphtho [ 2, 1-b ]furan 1, 11 ( 2H )- dione 5,6, 9, 17, 19, 21- hexa hydroxy -23- methoxy -2, 4, 12, 16, 18, 20, 22 - hepta methyl -8- [ N- ( 4- methyl -1-piperazinyl ) formimidoyl ] – 21 – acetate.

Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities. CDs can be used in drugs either for complexation or as auxiliaries such as diluents, solubilisers or tablet ingredients (Comprehensive Supramolecular Chemistry, Vol 3, Szejtli J, Osa T, Pergamon, UK, 1996). The advantage of using CDs mainly comes from their inclusion complex formation. The complexation can protect the molecule and can eventually have considerable pharmaceutical potential. Various advantageous effects of inclusion complex formation are as follows.

i) Incompatible drugs can be mixed when one of them is complexed with CDs.

ii) The release rate of drugs can be controlled.

iii) The solubility of water insoluble drugs can be improved.

iv) The instability of drugs in water / acidic stomach conditions can be improved as the rate of hydrolysis, photo decomposition, auto catalytic reactions etc. are considerably reduced.

iv) Percutaneous or rectal absorption can be improved by the enhanced release of drugs from ointments or suppository bases. Thus, CD- inclusion complexes of drugs have several advantages.

The inclusion complex formation can be identified by powder X-ray diffraction patterns and IR spectroscopy (Comprehensive Supramolecular Chemistry, Vol 3, Szejtli J, Osa T, Pergamon, UK, 1996).
The recent finding (Chronicle Pharmabiz, p.28, Dec.20, 2001) of impaired bioavailability of Rifampicin in the presence of Isoniazid in fixed dose combinations (FDCs) due to decomposition of Rifampicin in the stomach before it is absorbed into the body has prompted us to make inclusion complexes of Rifampicin with β-cyclodextrin and (2-hydroxypropyl)-β-cyclodextrin and characterize them. They have the potential to be used as new drug delivery systems for stability and slow release. However, the combinations reported so far are only dispersions of Rifampicin and cyclodextrin (East. Pharm., p.133, vol. 41(492), 1998), but the inclusion complexes have not yet been isolated and characterized.

Accordingly, studies were undertaken to make the inclusion complexes of Rifampicin with β-cyclodextrin (β-CD) and 2-hydroxypropyl-β-cyclodextrin (HP-β-CD).

**Objects of the invention**

The main object of the invention is to establish a inclusion complex comprising Rifampicin and cyclodextrins for the treatment of tuberculosis.

Another object of the present invention, is to establish a process for the formation of Rifampicin with β-CD or HP-β-CD for possible use as drug delivery system.

Another object of the present invention is to establish a process for the formation of inclusion complexes of cyclodextrins with large size molecules.

**Brief description of the accompanying drawings**

In the drawings accompanying this specification,

**Fig 1** represents the structures of β-cyclodextrin and (2-Hydroxypropyl) - β-cyclodextrin.

**Fig 2** represents Rifampicin.

**Summary of the invention**

Accordingly, the present invention provides an inclusion complex of Rifampicin with cyclodextrin as an anti-tubercular drug. In addition, the present invention provides a process for the synthesis of inclusion complexes of the anti-tubercular drug "Rifampicin" with β-CD or HP-β-CD and characterization of these inclusion complexes.

**Detailed of the Invention**

Accordingly, the present invention provides an inclusion complex of Rifampicin with cyclodextrin as an anti-tubercular drug.
In an embodiment of the invention provides an inclusion of complex, wherein the cyclodextrin used is selected from β-cyclodextrin and 2-hydroxy propyl cyclodextrin.

Still another embodiment, the inclusion complex is characterized by X-ray diffraction and Infrared studies and the inclusion of complex has following physical and chemical characteristics.

Still another embodiment, the inclusion complex enhances the bioavailability and solubility of the drug Rifampicin.

Still another embodiment, the inclusion complex and the drug exist in an encapsulated form leading to controlled release of the drug.

Yet another embodiment, the inclusion complex has an improved stability of Rifampicin in fixed dose combination.

Yet, another embodiment, the inclusion complex of the present invention, gives a new approach to anti-tuberculosis therapy containing fixed dose combination.

One more embodiment of the invention provides a process for preparation of inclusion complexes of Rifampicin with β-cyclodextrin, the said process comprising adding Rifampicin to cyclodextrin and grinding in an agate mortar to form an uniform powdery material of Rifampicin-dextrin inclusion complex.

Another embodiment, the encapsulation of the drug under solid condition is achieved which enhances bioavailability and solubility.

In another embodiment of the invention, provides a process for the preparation of inclusion complexes of Rifampicin with β-cyclodextrin (β-CD) or 2-Hydroxypropyl β-cyclodextrin (HP-β-CD) which comprises a phenomenon of converting a free drug into an encapsulated form under solid state conditions.

Still another embodiment, the cyclodextrins forms inclusion complexes with Rifampicin an anti TB drug, are β-CD or HP-β-CD.

Still another embodiment, the formation of cyclodextrin complexes with Rifampicin and these may be β-CD or HP-β-CD.

In an embodiment of the invention provides an inclusion complex of Rifampicin with cyclodextrin as an anti-tubercular drug.

In another embodiment of the present invention, the substrate forming inclusion complex with cyclodextrins is the anti-tubercular drug “Rifampicin”.

In another embodiment of the present invention, the cyclodextrins which form inclusion complexes with “Rifampicin” are β-cyclodextrin which is a cyclic
oligosaccharide consisting of seven glucose units and 2-Hydroxypropyl-β-cyclodextrin (HP-β-CD) which is a β-cyclodextrin substituted with hydroxypropyl group at 2-position. HP-β-CD has also been used as a drug carrier due to its low toxicity, high tolerance and excellent solubilizing and stabilizing abilities. HP-β-CD has generally been found to be safe and no adverse effects were observed in human studies. (Comprehensive Supramolecular Chemistry, Vol 3, Szejtli J, Osa T, Pergamon, UK, 1996).

As a result of above, an intensive study conducted by the inventors with the aim of achieving the afore mentioned objectives, a process for the synthesis of inclusion complexes of the anti-tubercular drug, Rifampicin with β-cyclodextrin (β-CD) or 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) has been achieved for the first time.

Accordingly, the present invention deals with the synthesis of inclusion complexes of the anti-tubercular drug, Rifampicin with β-CD or HP-β-CD. The synthesis of each compound has been described in detail.

The process involves the inclusion complex formation of Rifampicin with cyclodextrins. The cyclodextrins (Fig-1) are cyclic oligosaccharides possessing hydrophobic cavities and mimic enzymes in their capability to bind substrates selectively and catalyze chemical reactions. β-Cyclodextrin consists of seven glucose units linked by α-1,4 glycosidic bonds into a macrocycle with a hydrophobic cavity. HP-β-CD is a substituted β-CD at 2-position with a 2-hydroxy propyl group. Each cyclodextrin has its own ability to form inclusion complexes with specific guests into the hydrophobic cyclodextrin cavity. The most important pharmaceutical application of cyclodextrins is to enhance the solubility and bioavailability of drug molecules.

The inclusion complexes of the anti-tubercular drug, Rifampicin with cyclodextrins were prepared by adding Rifampicin in equimolar ratio to the respective cyclodextrins and intimately grinding the mixture using mortar and pestle for varying reaction times ranging from five to eight hours. The following examples are given by way of illustration and therefore should not construe the limit of the scope of the present invention.

**EXAMPLE 1**

Rifampicin-β-cyclodextrin inclusion complex:

The cyclodextrin inclusion complex was prepared by the grinding method under solid state conditions. β-Cyclodextrin (13.79 g) was taken in an agate mortar and Rifampicin (10g) was added while mixing intimately. The ingredients were continuously
ground ranging from 5-8 hrs to form a uniform powdery material. The inclusion complex of "Rifampicin" with β-cyclodextrin thus formed has been characterized by the powder X-ray diffraction patterns and IR spectral data. The inclusion complex has been identified by comparing its X-ray and IR spectral data with Rifampicin and β-CD.

**Powder X-ray Studies:**

**Instrument:** Powder X-ray Diffractometer, Siemens / D-5000

The powder X-ray diffractograms were measured in 2θ angles.

The most significant measurements are as follows:

**β-CD:**

4.3, 6.2, 8.9, 10.4, 12.6, 18.6, 22.6, 27.0, 35.2

**Rifampicin:**

7.8, 9.5, 10.9, 12.6, 15.8, 16.9, 19.6, 21.3, 26.0

Rifampicin-β-cyclodextrin complex (**Rif- β-CD**):

4.3, 8.7, 10.6, 12.6, 15.7, 18.8, 25.5, 35.2, 46.4

In the inclusion complex, some significant peaks are either shifted, disappeared or some new peaks have appeared. The peaks at **18.8** and **22.6** in β-CD have disappeared in the complex. The peaks at **4.3, 12.6** and **27.0** in β-CD have been reduced in intensity in the complex. The new peaks that appeared in the complex are at **18.6, 25.5** and **46.4**

Similar comparison of data with Rifampicin is as follows.

The following peaks of Rifampicin that disappeared in the complex are **9.5, 10.9, 19.6** and **26.0**. The significant peaks of Rifampicin at **12.6, 15.8, 16.9** and **21.3** are reduced in intensity.

**Infrared spectral studies:**

**Instrument:** Perkin Elmer Spectrum RX/Ft IR system 500-3500 cm⁻¹

The IR spectra of the drug Rifampicin complex with β-CD and also the individual drug Rifampicin have been recorded as KBr pellets.

The inclusion complex formation has also been proved by IR spectroscopy. Bands due to the included part of the guest molecule have shifted or their intensities altered. The acetoxy C=O vibration at **1728.2 cm⁻¹** and carbonyl C=O absorption at **1730.4 cm⁻¹** of Rifampicin have been shifted to lower frequency and appear as single peak at **1722.2 cm⁻¹** where as the amide NH-C=O shows only a minor shift from **1651.2 cm⁻¹** to **1647.8 cm⁻¹**.
However, only a small shift was observed for C=C vibration from 1566.4 cm\(^{-1}\) in the drug to 1565.1 cm\(^{-1}\) in the complex. This clearly indicates the formation of inclusion complex of Rifampicin with β-CD.

**EXAMPLE 2**

**Rifampicin –2-Hydroxypropyl β- cyclodextrin inclusion complex:**

To Rifampicin (10 g) in an agate mortar, 2- hydroxypropyl β-cyclodextrin (16.77 g) was added and ground well for periods ranging from 5 to 8 hrs to form an uniform powdery material. The inclusion complex of the drug thus formed was isolated and characterized.

**Powder X-ray studies:**

Rifampicin with 2- hydroxypropyl β-cyclodextrin (HP-β-CD) complex has been confirmed by comparing its data of X-ray diffraction pattern with the parent drug and HP-β-CD.

The important peaks are shown hereunder.

**2-HP-β-CD:**

4.8, 11.6, 17.4, 19.1, 23.1, 29.1, 33.0, 35.0, 39.9

Rifampicin-2-hydroxy propyl-β-cyclodextrin inclusion complex (Rif- 2HP- β-CD):

1.4, 5.9, 12.8, 14.2, 16.3, 18.2, 21.4, 25.8, 30.6 and 31.8

Comparison of the data of the complex with Rifampicin and HP-β-CD are as follows. The following peaks of Rifampicin at 7.8, 9.5 and 10.9 have disappeared in the complex. The peak at 21.3 was reduced in intensity as compared to Rifampicin. As compared to HP-β-CD, new peaks have appeared at 14.2, 25.8 and disappearance of the peaks at 4.8 and 11.6 was observed. The peak at 23.1 was reduced in intensity.

Thus the difference in the X-ray diffraction patterns of the inclusion complexes of the drug Rifampicin with β-CD and HP-β-CD and that of the individual components by the appearance of new peaks, disappearance of some peaks and also reduction in intensity of some more peaks as described above clearly indicates the formation of inclusion complex of Rifampicin with β-CD and HP-β-CD.

**Infrared spectral studies:**

Infrared spectral studies have also been carried out to confirm the formation of inclusion complex.
The IR spectrum of RIF-HP-β-CD complex shows the merging of the acetoxyl C=O at 1728.2 cm\(^{-1}\) and carbonyl C=O absorption at 1730.4 cm\(^{-1}\) of Rifampicin to give a single peak at a lower frequency 1719.8 cm\(^{-1}\), whereas the amide NH-C=O absorption of Rifampicin at 1651.2 cm\(^{-1}\) shifts to a lower frequency at 1648.4 cm\(^{-1}\). A significant shift in C=C absorption band from 1566.4 cm\(^{-1}\) to 1562.8 cm\(^{-1}\) has also been observed. This data clearly indicates the formation of inclusion complex of Rifampicin with HP-β-CD.

The main advantages of the present invention are:

1) The inclusion complex of Rifampicin with β-CD and HP-β-CD protects the drug and this can have considerable pharmaceutical potential.

2) It may be possible to control the release rate of the anti-tubercular drug, Rifampicin.

3) There is also a possibility of improving the stability of Rifampicin in fixed dose combinations (FDCs)

4) This invention may give new approach to anti-tuberculosis therapy containing FDCs.
Claims

1. An inclusion complex of Rifampicin with cyclodextrin as an anti-tubercular drug.

2. An inclusion of complex as claimed in claim 1, wherein the cyclodextrin used is selected from β-cyclodextrin and 2-hydroxy propyl cyclodextrin.

3. An inclusion complex as claimed in claim 1 is characterized by X-ray diffraction and Infrared studies.

4. An inclusion complex as claimed in claim 1, produces enhanced bioavailability and solubility of the drug Rifampicin.

5. An inclusion complex as claimed in claim 1, wherein the drug exists in an encapsulated form.

6. An inclusion complex as claimed in claim 1, leads to controlled release of the drug.

7. An inclusion complex as claimed in claim 1, has an improved stability of Rifampicin in fixed dose combination.

8. An inclusion complex as claimed in claim 1, gives a new approach to anti-tuberculosis therapy containing fixed dose combination.

9. A process for preparation of inclusion complexes of Rifampicin with β-cyclodextrin, the said process comprising adding Rifampicin to cyclodextrin and grinding in an agate mortar to form an uniform powdery material of Rifampicin-cyclodextrin inclusion complex.

10. A process as claimed in claim 9, wherein cyclodextrin used is selected from β-cyclodextrin and 2-hydroxy propyl cyclodextrin.

11. A process as claimed in claim 9, wherein the encapsulation of the drug under solid condition is achieved.

12. A process as claimed in claim 9, wherein the inclusion complex obtained has enhanced bioavailability and solubility.

13. A process as claimed in claim 9, wherein the inclusion complex obtained has the property of controlled release of the drug Rifampicin.
14. A process as claimed in claim 9, wherein the inclusion complex obtained has improved stability of Rifampicin in fixed dose combination.

15. A process for the preparation of inclusion complex as claimed in claim 9, of Rifampicin with β-cyclodextrin (β-CD) or 2-Hydroxypropyl β-cyclodextrin (HP-β-CD) which comprises a phenomenon of converting a free drug into an encapsulated form under solid state conditions.

16. The process as claimed in claim 15, the cyclodextrins forming inclusion complexes with Rifampicin an anti TB drug, is β-CD or HP-β-CD.
AMENDED CLAIMS
[received by the International Bureau on 26 February 2004 (26.02.04); original claim 9 amended; remaining claims unchanged (2 pages) ]

1. An inclusion complex of Rifampicin with cyclodextrin as an anti-tubercular drug.

2. An inclusion of complex as claimed in claim 1, wherein the cyclodextrin used is selected from β-cyclodextrin and 2-hydroxy propyl cyclodextrin.

3. An inclusion complex as claimed in claim 1 is characterized by X-ray diffraction and Infra red studies.

4. An inclusion complex as claimed in claim 1, produces enhanced bioavailability and solubility of the drug Rifampicin.

5. An inclusion complex as claimed in claim 1, wherein the drug exists in an encapsulated form.

6. An inclusion complex as claimed in claim 1, leads to controlled release of the drug.

7. An inclusion complex as claimed in claim 1, has an improved stability of Rifampicin in fixed dose combination.

8. An inclusion complex as claimed in claim 1, gives a new approach to anti-tuberculosis therapy containing fixed dose combination.

9. A process for preparation of inclusion complexes of Rifampicin with β-cyclodextrin, the said process comprising adding Rifampicin to cyclodextrin and grinding in an agate mortar for a time period in the range of 5-8 hours to form an uniform powdery material of Rifampicin-dextrin inclusion complex.

10. A process as claimed in claim 9, wherein cyclodextrin used is selected from β-cyclodextrin and 2-hydroxy propyl cyclodextrin.

11. A process as claimed in claim 9, wherein the encapsulation of the drug under solid condition is achieved.

12. A process as claimed in claim 9, wherein the inclusion complex obtained has enhanced bioavailability and solubility.

13. A process as claimed in claim 9, wherein the inclusion complex obtained has the property of controlled release of the drug Rifampicin.
14. A process as claimed in claim 9, wherein the inclusion complex obtained has improved stability of Rifampicin in fixed dose combination.

15. A process for the preparation of inclusion complex as claimed in claim 9, of Rifampicin with β-cyclodextrin (β-CD) or 2-Hydroxypropyl β-cyclodextrin (HP-β-CD) which comprises a phenomenon of converting a free drug into an encapsulated form under solid state conditions.

16. The process as claimed in claim 15, the cyclodextrins forming inclusion complexes with Rifampicin an anti TB drug, is β-CD or HP-β-CD.
STATEMENT UNDER ARTICLE 19

XP-001145510
Kuchekar et al. describes the preparing solid dispersion of rifampicin using solvents like chloroform. Present invention discloses the inclusion complex of rifampicin with β-cyclodextrin or 2-hydroxypropyl β-cyclodextrin and the process thereof. Solid dispersions are basically dilution/distribution of the compound in a solid (inert) matrix. On contrary, inclusion complexes are prepared by positioning a particular compound in a specific area or in a cavity in solid matrix. Since the present invention is concerned with the inclusion complex of Rifampicin it is totally different from the solid dispersions of Kuchekar et al. Moreover, the process for the preparation of solid dispersion disclosed by Kuchekar involves common solvent evaporation method wherein the β-cyclodextrin is carrier and chloroform is the solvent. However, the process in the present invention is solid mixing and no way similar to the above mentioned cited art.

WO-02/32459
Shastri et al. discloses the biological activity of bioactive agents such as Rifampicin etc., may be increased by complexation with cyclodextrin. However, it does not describe the synthesis of inclusion complex of Rifampicin with either cyclodextrin or 2-hydroxypropyl β-cyclodextrin. It can be envisaged that most of the organic molecules can be complexed with
cyclodextrins but the complexation takes place from outside of the cyclodextrin by interaction with the hydroxyl groups without actually forming the inclusion complex or by the formation of inclusion complex with the hydrophobic cavity of cyclodextrin or it can also be through inclusion into channels of cyclodextrin formed by the association of cyclodextrin molecules. Apart from this, it is not possible to presume the "geometric compatibility" of Rifampicin with various cyclodextrins until and unless one actually isolates and characterizes the complex to show that it is indeed an inclusion complex into the hydrophobic cavity of cyclodextrin. Thus shastri et al. have concentrated only on the biological activity of complexes such as chlorhexidine, tetracycline, tobramycin or gentamicin with cyclodextrin and the cited art of Shastri et al does not throw any light whether rifampicin can actually form complex by inclusion in to the hydrophobic cavity of β-cyclodextrin or 2-hydroxy propyl β- cyclodextrin.

WO 0054751
The cited art relates to producing solid dosages form, containing one physiologically compatible polymer binding agent, one drug and cyclodextrin, which is obtained by mixing and plasticizing. However, this process does not describe the process and isolation of inclusion complexes of rifampicin and cyclodextrin. The ingredients used in the cited art are completely different from the present invention and moreover, the processing temperature in the cited art is 220°C whereas in the present invention is carried out at room temperature. Thus the product and process of the present invention is distinct from the cited art.

XP-002232706
The above reference deals only with Clathrate compounds of drugs which are not structurally similar with Rifampicin and hence a person skilled in this art will not be able to anticipate and prepare the inclusion complex with Rifampicin. The clathrate compounds work on a principle of charge transfer between molecules which leads to clathrate complexes. Where as the
inclusion complexes work on porosity and permeability which is strictly/steric process. Thus the process is completely different.

Since, the present invention meets all the criteria of formation of inclusion complex of Rifampicin into the hydrophobic cavity of cyclodextrin which nobody else has done so far and has the potential to become a drug delivery system.
Figure 1

R = H; β-Cyclodextrin
R = 2-Hydroxypropyl;
2-Hydroxy propyl-
β-Cyclodextrin
RIFAMPICIN

Figure 2
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7  A61K31/496  A61K47/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7  A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
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* Special categories of cited documents:

*A* document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search:
26 February 2003

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