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Physicochemical Characterization and Dissolution Enhancement of Loratadine–Hydroxypropyl-β-cyclodextrin Binary Systems

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Abstract:
Loratadine, a Class II drug is a second generation antihistaminic agent, which is poorly water soluble with low bioavailability. Loratadine is practically insoluble in water and as such it exhibits poor variable oral bioavailability. Loratadine needs enhancement of solubility and dissolution rate to improve its oral bioavailability and therapeutic efficacy. In the present investigation, studies were carried out on loratadine with an objective of enhancing its solubility and its dissolution rate. Solid binary systems of loratadine with HP-β-CD were prepared using co-grinding, kneading, and coevaporating methods, and the physical mixture was prepared for comparison. Among the various approaches to enhance the solubility and dissolution rate of poorly soluble drugs complexation with cyclodextrin is an effective and industrially accepted technique. The specific objective of the study is to prepare, evaluate the complex and to characterize it by FTIR, SEM and DSC studies.All the binary systems showed superior dissolution as compared to pure loratadine, but the kneaded product exhibited the best dissolution profile with complete drug release within 30 min and saturation solubility of the drug was increased to more than 10 times. . Hence, it was suggested that complexation of loratadine with HP-β-CD may be used as an approach to change the drug from Biopharmaceutics Classification System BCS Class II to BCS Class I.
Key Words: Loratadine, Hydroxypropyl-β-cyclodextrin, kneading, binary complexes.

INTRODUCTION:

Cyclodextrins are cyclic (α-1,4)-linked oligosaccharides of α-Dglucopyranose, containing a relatively hydrophobic central and hydrophilic outer surface. Cyclodextrins are used to increase the solubility of water insoluble drugs, through inclusion complexation.[1-2] Natural cyclodextrins have been used extensively for this purpose. However, they are characterized by a relatively low solubility in water, which limits their application. Hence, chemically modified cyclodextrins are gaining considerable interest to improve the physicochemical properties of cyclodextrin.[3] Cyclodextrin are known to form an inclusion complex with many drugs of appropriate molecular size and polarity in hydrophobic drug molecules. The resulting complex generally leads to an improvement in some of the properties of drugs in terms of solubility, bioavailability and tolerability. Poorly water soluble drugs are generally associated with slow drug absorption leading eventually to inadequate and variable bioavailability.

Loratadine is a second generation nonsedating tricyclic H1 antihistamine drug which prevents and suppress seasonal and perennial allergic rhinitis, allergic dermatitis, urticaria and occular allergy. Loratadine is practically insoluble in water (BCS Class II) drug.[4, 5] However, its very low water solubility and hydrophobic nature represent a rate-limiting step in its absorption from solid dosage formulations and can be the cause of reduced and variable bioavailability which are the disadvantages for its oral administration, because the drug may suffer a reduced therapeutic efficacy.[6, 7] In recent years, cyclodextrin complexation has been successfully used to improve solubility, dissolution rate and bioavailability and to reduce undesired side effects.[8]

Amorphous cyclodextrin such as hydroxypropyl-β-cyclodextrin are useful for inhibition of polymorphic transition and crystallization rates of poorly water soluble drugs during storage, which can consequently maintain the higher dissolution characteristics and oral bioavailability of the drugs. It has received special attention because of its abilities of solubility, wetting, complexing, low cost and less toxicity.[9] Through cyclodextrin complexation it should be possible to move this drug in class I (high permeability and good solubility) by improving its dissolution properties without modifying its intrinsic ability to permeate bio-membranes.[10]

So the attempts has been made to prepare drug-cyclodextrin complex of 1:1 and 1:2 molar ratios by four different techniques (physical mixing, co-grinding, solvent evaporation and kneading) to investigate the influence of the preparation methods on the final product and to select the system allowing

the greatest improvement of Loratadine dissolution properties. The obtained solid samples were characterized by Differential Scanning Calorimetry, Fourier transform infra red spectroscopy, Scanning electron microscopy and evaluated for solubility and dissolution rate properties.

MATERIALS AND METHODS

Materials

Loratadine (LRT) was obtained as gift sample by Shreeji pharmaceuticals (Gujarat,India) Hydroxypropyl-β-cyclodextrin, croscarmellose sodium(CCS), crospovidone (CLP), sodium starch glycollate(SSG) was procured from Shree Ram Chemicals, Ghaziabad. All other chemicals and materials were of analytical grade and were used as such.

Methods

Preparation of drug -Cyclodextrin inclusion complex[11]

Loratadine, HP-β-Cyclodextrin binary complexes were prepared at 1:1 and 1:2 molar ratios, respectively, as described in detail below.

Physical mixture:

Previously weighed drug and cyclodextrins mixture was blended in glass mortar for about an hour and passed through sieve no.85 to get Physical mixture and stored in dessicator over fused calcium chloride.

Co-grinding:

The drug-Cyclodextrin physical mixtures properly triturated in glass mortar pestle for 20 minutes and passed through 85 mesh size sieve and thus co-ground product was obtained.

Co-evaporation:

Loratadine and HP-β-CD in different molar ratios were dissolved in ethanol to get a clear solution. The resulting solution at ambient temperature was stirred until complete evaporation of the solvent takes place. Then the resulting preparation were kept in a dessicator for at least 48 hr and then grounded in a glass mortar and passed through sieve no.100 and stored in a dessicator over fused calcium chloride.

Kneading method:

HPβCD was wetted in a glass mortar with ethanol- water 50% (v/v) solution until a paste was obtained (about 30% of the total weight of cyclodextrin and loratadine). The required amount of loratadine was then slowly added and the slurry was kneaded for about 45 min. Further, the product was dried under vacuum for 24 hrs and stored in a dessicator over fused calcium chloride.

Characterization of inclusion complexes:

Differential scanning calorimetry (DSC):

DSC measurements were performed using Perkin-Elmer (DSC7), IIT, Delhi differential scanning calorimeter with a thermal analyzer. All accurately weighed samples (1-4mg of loratadine or its equivalent) were placed in sealed aluminium pans, before heating under nitrogen flow (20 ml/min) at a scanning rate of 10^0 C min^{-1}, from 25^0C to 200^0C.An empty aluminium pan was used as reference. The equipment was periodically calibrated with the help of indium.

Scanning electron microscopy (SEM):

The surface morphology of raw materials and binary systems was examined with the help of scanning electron microscope (Phillips 1500).The samples were fixed on brass stub using double-sided tape and then samples were surrounded by silver steak and made electrically conductive by coating in a vacuum with thin layer of gold. The photographs were taken with camera at an excitation voltage of 20KV at magnification of 5000X.

Fourier transforms infrared spectroscopy (FTIR):

Fourier transform infra-red spectra of the samples were obtained using Shimadzu 8300, (Japan), and FT/IR-4100 type A spectrophotometers. The samples were previously ground and mixed thoroughly with KBr, an infra red transparent matrix, using a 1% (w/w) dilution. Scans were obtained at a resolution of 16 cm^{-1} from 400-4000 cm^{-1}.

Evaluation of inclusion complexes:

Drug content:

Inclusion complexes equivalent to 10 mg of Loratadine was dissolved in 0.1N HCL. Appropriate dilutions were made and drug content of each complex was observed at 277.5 nm spectrophotometrically.

Saturation solubility of the complex:

Solubility study was performed according to

method reported by Higuchi and Connors. Inclusion complexes were added in excess quantities to 25 ml distilled water which was taken in stoppered conical flasks and mixtures were shaken for 24 hours in a shaker. After sufficient shaking to achieve equilibrium, 2 ml aliquots were withdrawn at 1 hr intervals and filtered through what man filter paper. The filtrate obtained was analyzed spectrophotometrically. Shaking was continued until three consecutive readings were same.

Dissolution studies:

The dissolution profiles were carried out by using USP II apparatus (paddle type) dissolution apparatus. The dissolution media consisted of 900 ml of (distilled water) pH 6.8. Powdered samples containing 10 mg of Loratadine equivalent in complexed form and physically mixed form were used. The stirring speed was 50±2 rpm and the temperature was maintained at 37±0.2^{0}C. Aliquot equal to 5 ml of dissolution medium was withdrawn at specific time intervals, filtered and was suitably diluted and absorbance of solution was checked spectrophotometrically to determine the drug release.

RESULTS AND DISCUSSION

Differential scanning calorimetry (DSC):

Thermal analysis shows evidence of inclusion complexation. When host-guest complex is formed the melting, boiling and sublimation point generally shifts to different temperature or disappear within the temperature range where cyclodextrin is decomposed.

The DSC thermogram of Loratadine was typical of crystalline anhydrous substance, exhibiting a sharp endothermic peak at 134.9^0 C corresponding to the melting point of the drug as shown in figure.1. The thermo grams of HP-β-CD showed a very broad endothermic effect, which attained a maximum around 70^0-100^{0}C due to release of water molecule as shown in figure.2. The physical mixture of drug and cyclodextrin endothermic peak was found at 133.11 along with the broad peak of cyclodextrin as shown in figure.3. The phase transition thermal profile of Loratadine was broadened and size was reduced with a concomitant shift to lower temperature (132.44^{0}C) with HP-β-CD in kneading method of 1:2 ratio as shown in figure.4. This indicates the formation of an amorphous nature and molecular encapsulation of drug in the cyclodextrin cavity.

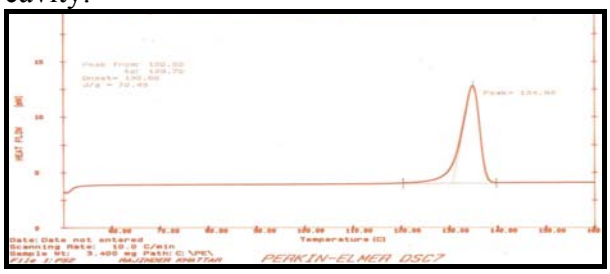

Fig.1. DSC thermogram of loratadine

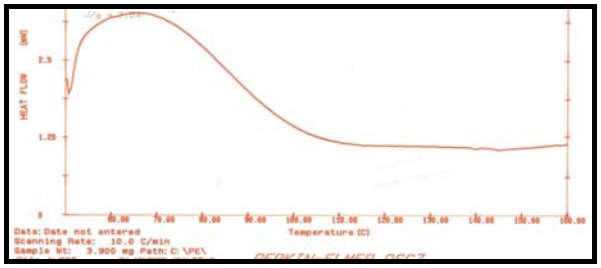

Fig.2. DSC thermogram of HPβCD

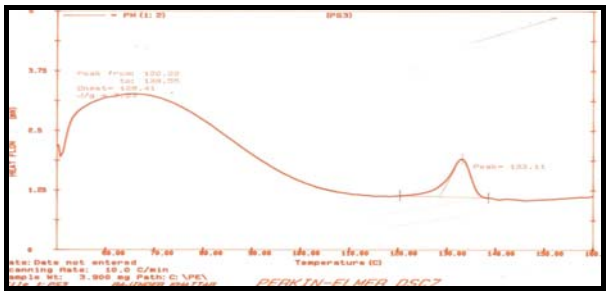

Fig.3. DSC thermogram of physical mixture(1:2)

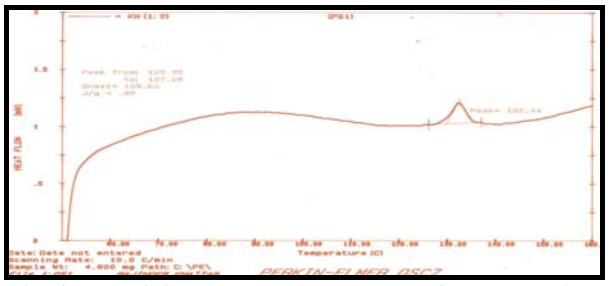

Fig.4. DSC thermogram of kneading method(1:2)

Scanning electron microscopy (SEM):

The HPβCD particles (Fig.6) had a spherical shape. The drug powder (Fig.5)consisted of irregular rod like crystals. The photomicrographs of kneaded complex had (Fig.7)shown the complex morphology, that is, aggregation, it suggests the existence of an amorphous product with the presence of a single component in the complex, which

proves the maximum or complete complex formation.

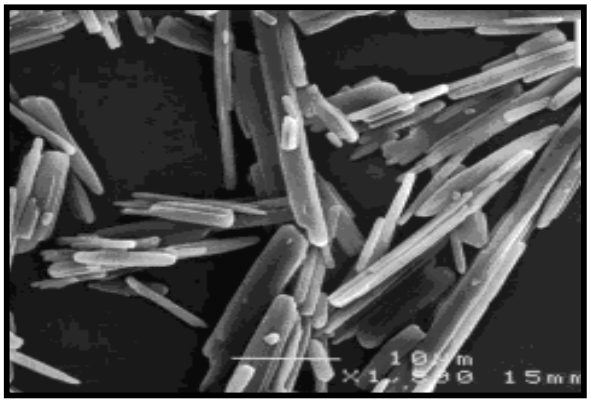

Fig:5. SEM of Loratadine

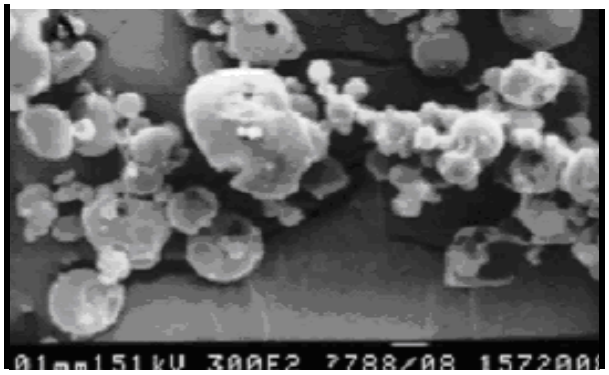

Fig:6. SEM of HPβCD

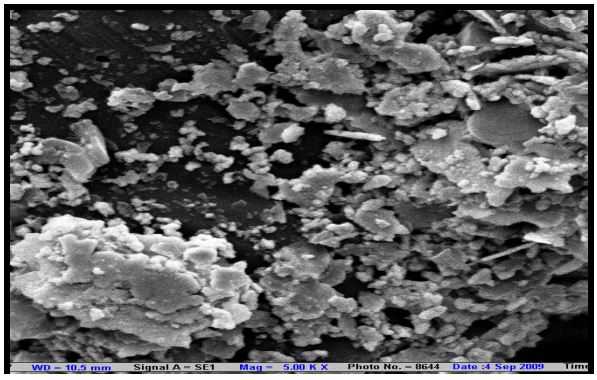

Fig:7. SEM of kneaded complex(1:2)

Fourier transform infrared spectroscopy (FTIR):

The frequency of vibrations of band depends on the masses of atoms and bond stiffness, and any factor that influences the stiffness will also alter the frequency of vibration. It is a tool to determine the complexation. The spectral changes were evaluated by subtraction of the spectrum of HP-β-CD from the spectra of the samples. The spectra of the products involving different molar ratios and preparation methods did not differ appreciably.The FTIR spectra of Loratadine bands are almost completely obscured by very intense and broad CD bands. The drug spectra showed C≡N stretch at 2196.7, C=O stretch at 1703.03, C=N stretch at 1643.24,C=C ring stretch at 1434.94,C-N vibration at 1226.64,C-O stretch at 997.13 and =C-H at 862.12.For all the products, the characteristic C=O stretching frequencies at 1703.03 cm^{-1} were shifted to lower wavenumbers, and the typical C-O stretching at 1226.64 cm^{-1} was shifted to higher range. Patterns of physical mixtures show approximate superimposition of the patterns of the cyclodextrins and the drug. The shift in the C=O stretching to lower frequency i.e. 1670.05cm^{-1} which presumably masked possible shifts to the drug carbonyl group stretching. This dramatic change was probably correlates the formation of intermolecular hydrogen bonds between the guest and host molecules. It seems that when the carbonyl group is joined by hydrogen bonds, the stretching band is shifted to lower frequency due to weakening of the carbonyl double bond radical. This change also indicates that the vibration of guest molecule (Loratadine) is restricted due to the formation of an inclusion complex. These leads to surmise that −COO group provides the complex-forming bonds and that complex formation alters the hydrogen-bonded cyclic dimer structure of the carboxyl group.

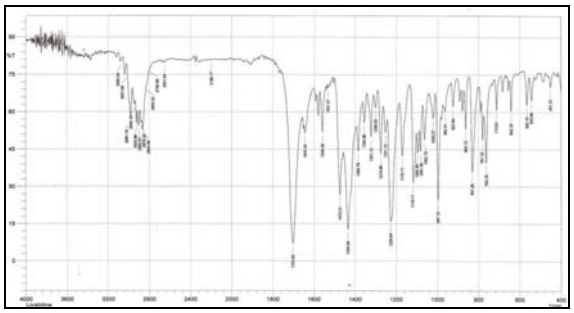

Fig:8. FTIR spectra of loratadine

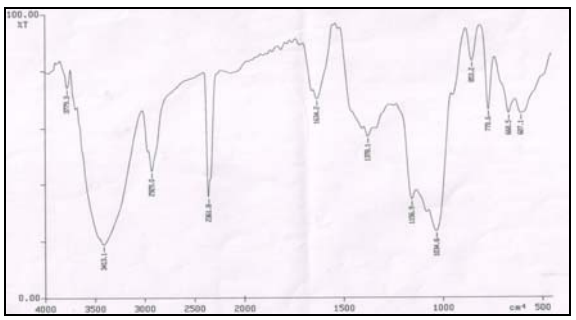

Fig:.9. FTIR spectra of HPβCD

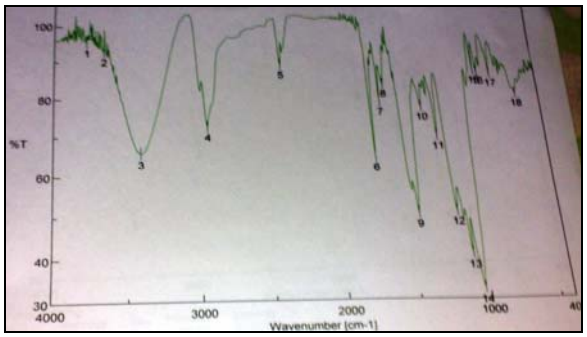

Fig:10. FTIR spectra of physical mixture(1:2 ratio)

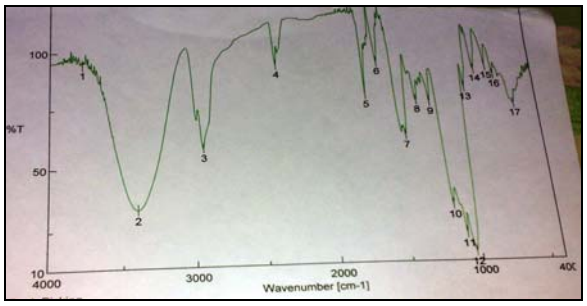

Fig:11. FTIR spectra of co-grinding(1:2ratio)

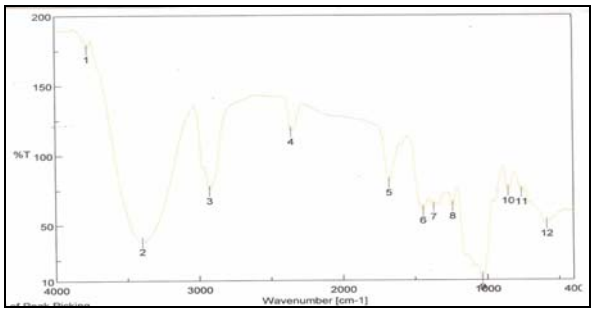

Fig:12. FTIR spectra of solvent evaporation (1:2 ratio)

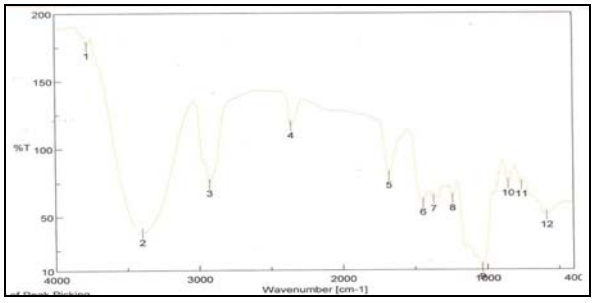

Fig:13. FTIR spectra of kneading method (1:2 ratio)

Drug Content:

Drug content of all the complexes was found in between 90.89-99.50.

Saturation Solubility:

The saturation solubility of inclusion complex of Loratadine with HPβCD were found to be 0.088±0.35g/100ml which is far superior to solubility of pure drug 0.0075±0.28g/100ml in distilled water.

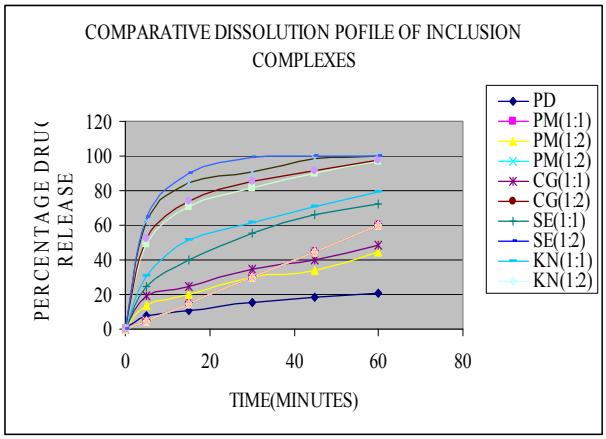

Fig:14.Comparative Dissolution profile of pure drug with inclusion complexes

(PD=Pure Drug,PM=Physical mixture,CG=Co-grinding,SE=Solvent Evaporation,KN=Kneading)

CONCLUSION

Preparation of loratadine-HP-β-cyclodextrin binary complex by using cheap lab scale method resulted in effective complexation with saturation solubility upto more than 10 times. The inclusion complex of drug showed better dissolution profile as compared to pure drug. This in turn, can have improved bioavailability

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Table -Dissolution characteristics of inclusion complexes

Parameters	P.D	PM(1:1)	PM(1:2)	CG(1:1)	CG(1:2)	SE(1:1)	SE(1:2)	KN(1:1)	KN(1:2)
%DR 5 min	8.04	14.22	19.08	24.30	30.60	49.60	62.10	52.20	64.80
%DR 15 min	11.12	20.23	24.76	40.33	51.47	70.47	84.94	74.19	90.36
%DR 30 min	15.2	29.89	34.40	55.16	61.65	81.66	90.81	85.30	99
%DR 45 min	18.5	33.65	39.63	66.36	70.99	90.11	98.51	91.17	99.68
%DR 60 min	20.92	44.64	48.35	72.32	79.38	97	99.75	97.97	99.98

%DR= Percentage drug release, P.D= Puredrug, PM=Physical mixture, CG=Co-grinding, SE=Solvent evaporation, KN=Kneading.

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