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Studies on the preparation, characterization, solubility and stability of cefadroxil - β-cyclodextrin inclusion complexes

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Cefadroxil - β-Cyclodextrin dispersions were prepared with a view to study the influence of β-CD on the solubility and dissolution rate of this poorly soluble drug. Phase-solubility profile indicated that the solubility of Cefadroxil was significantly increased in the presence of β-cyclodextrin and was classified as AL-type, indicating the 1:4 stoichiometric inclusion complexes. Physical characterization of the prepared systems was carried out by differential scanning calorimetry (DSC), X-ray diffraction studies (XRD) and IR studies. Solid state characterization of the drug β-CD binary system using XRD, FTIR and DSC revealed distinct loss of drug crystallinity in the formulation, ostensibly accounting for enhancement of dissolution rate.

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Keywords: P^H, Cefadroxil, Dissolution, β-cyclodextrin, Kneading method

1. Introduction

The therapeutic effectiveness of a drug depends upon the ability of the dosage forms to deliver the medicaments to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. Some drugs having poor bioavailability are with poor aqueous solubility and or slow dissolution rate in the biological fluids. Cefadroxil is a first generation cephalosporin anti-bacterial drug that is the para hydroxyl derivative of cefalexin, and is used similarly in the treatment of mild to moderate susceptible infections and bitter taste. Upon prolonged use of this drug will cause darkened tongue, difficulty in breath in, fever, itching, severe diarrhea etc [1]. Applications of CDs in oral drug delivery include improvement of drug bioavailability due to increased drug solubility, improvement of rate and extent of dissolution and /or stability of the drug at the absorption site**,** reduction of drug induced irritation, taste masking, etc. ß- Cyclodextrin (ß-CD) is cyclic malto oligosaccharides in which the glucose units are linked by a- 1, 4 glycoside bonds. [2].The peculiar arrangement of the glucose units imparts the molecule a cone like structure, which makes the exterior of the cone hydrophilic and interior of the cone hydrophobic in nature. This characteristic of the polymer enables encapsulation of the drug in the cavity resulting in the improvement in the solubility, drug release as well as taste masking. They have hydrophobic central cavity and a hydrophilic outer surface [2]. CDs have been found to be very useful in enhancing the solubility of poorly water-soluble drugs owing to the formation of inclusion complex of the drug in its hydrophobic cavity [3-7]. The most common natural CDs are Cyclodextrins, ß cyclodextrin and γ cyclodextrin, which are formed by six, seven, and eight glucose units, respectively. Apart from these naturally occurring CDs, various derivatives are also available [8-9].which may produce better solubility when complexes [10,11] but cost and toxicity factors poses limitation in their use. Amongst the various available CDs, ß Cyclodextrins (_ß -CD) are the cheapest and are nontoxic when adminsitered orally. Present study is an attempt to form inclusion complexes of Cefadroxil with ß-CD to improve solubility of the drug.

2. Materials and methods

Cefadroxil was a product of Aurobindo pharma, Hyderabad. All other chemicals were of analytical grade and used without further purifications. Measurements of pH were performed using a calibrated Elico pH meter. Cefadroxil concentrations were determined at 311 nm using Shimadzu UVspectrophotometer. As a starting point for this study, the solubility of Cefadroxil as a function of pH was studied. A series of buffer solutions from pH range 2.4 to 9.2 were prepared and Cefadroxil was added in sufficient quantity to saturate each solution. To avoid change in concentration due to evaporation, the solutions were kept in vials sealed with teflon lined screw caps and wrapped with paraffin. All solutions were then placed on a test tube rotator for mixing. They were checked daily for the saturation and pH was adjusted as necessary. To ensure the attainment of equilibrium, all solutions were shaken for one week. The solutions were then diluted as appropriate and absorbance determined spectrophotometrically at 311 nm.

Determination of Stability Constant (K)

Complexation studies were performed according to the method reported by Higuchi. An excess amount of Cefadroxil was added to the aqueous solution of various concentrations (0.05-0.005 m M/L) of ß-CD solution (molecular weight = 1135). The contents were stirred for45 hours at 37°C ± 2°C. After equilibrium, the samples were

Filtered and absorbance was measured at 311 nm (UV/ VIS spectrophotometer, Japan). The apparent stability constant was calculated for this complex using the equation.12-15

Preparation of inclusion complexes [13-14]

The complexes were prepared in 1:1 molar ratio by following methods-

Spray drying method (SPR)

Cefadroxil and ß-CD were dissolved in water and the mixture was stirred at 100 rpm for 3 hours. The mixture was spray dried using Labultima (Model) spray dryer. Inlet temperature was 120^0C and outlet temperature was 1000C.

Kneading method (KN)

Cefadroxil was added to aqueous paste of ß-CD and the mixture was levigated for 45 min. The paste was dried at 500C and the dried mass was pulverized and sieved through # 60 mesh.

Characterization of solid complexes [14-15]

The complexes were characterized and evaluated by the following methods

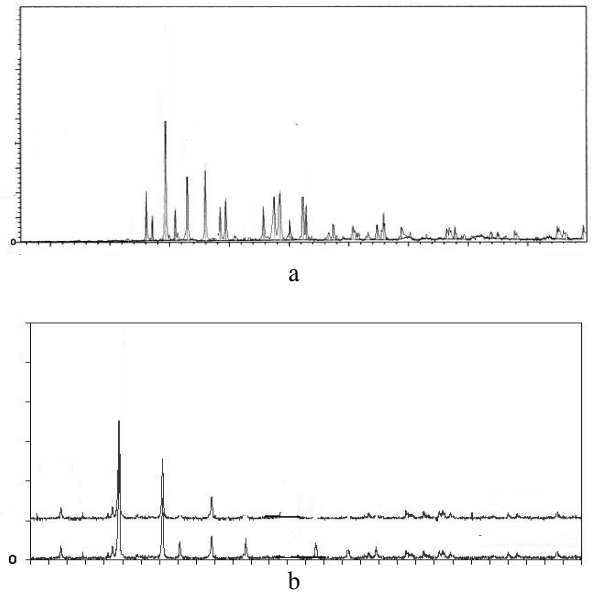

Fig. 1 a. XRPD of Cefadroxil - β Cyclodextrins, b. XRPD of Cefadroxil - β Cyclodextrins.

Differential Scanning Calorimetry (DSC)

Thermal behavior of Cefadroxil, ß-CD, and each inclusion complex was examined by using a DuPont (Wilmington, DE) model 910 thermal analyzer.

Powder X-ray diffraction studies (XRPD)

XRPD of the samples was performed using a high-power X ray Diffractometer RU-200B from M/s Riguao, (Tokyo, Japan).

Fourier Transform Infra Red spectroscopy (FT-IR)

FT-IR spectral studies were carried on FT-IR 460 PLUS by JASCO series II instrument using DRIFT method (JASCO Analytical Instruments, Madison, WI).

3. Evaluation

Phase solubility study

Phase-solubility studies were performed by the method of Higuchi and Connors.[16] Cefadroxil, in constant amounts (5 mg) that exceeded its solubility, was transferred to screw capped vials containing 15 ml of aqueous solution of *β*-CD or at various molar concentrations(0, 3.0, 6.0, 9.0, 12.0, and 15.0 µm). The contents were stirred on rotary shaker for 72 hrs. at 37 ^{0}C ± 0.1 ^{0} C and 1200 rpm. The time duration was fixed based on pilot experiment and found to be sufficient to achieve equilibrium of mixture. After reaching equilibrium, samples were filtered through a 0.36 µm membrane filter, suitably diluted and analyzed spectrophotometrically for drug content at 311 nm UV/Visible spectrophotometer,. Solubility studies were performed in triplicate.

Preformulation studies

Preformulation studies were performed on free drug and complexes to assess the suitability of the complexes for capsule dosage forms. Bulk density, Tapped density,

percentage compressibility, angle of repose of the drug and the complexes were found out. Thermo grams of the pure drug, BCD and 1:1 complex were recorded by analyzing the samples by differential thermal analysis. Solubility of the drug and the complex in phosphate buffer pH 6.8 were determined.

***In-vitro* dissolution studies**

Dissolution of drug from capsules

The dissolution profile was studied using USP dissolution rate test apparatus employing paddle stirrer. In 900 ml dissolution medium (2 hrs using 0.1 N HCl and the medium was replaced with phosphate buffer pH 7.4), a sample of 25 mg drug equivalent complex (1:1m, 1:2m) was placed and set rpm at 100 and temperature +37^0 C. Aliquots of 5 ml was withdrawn at 10mts intervals of time and replaced with the same medium and analyzed at 311 nm by using uv visible spectrophotometer.

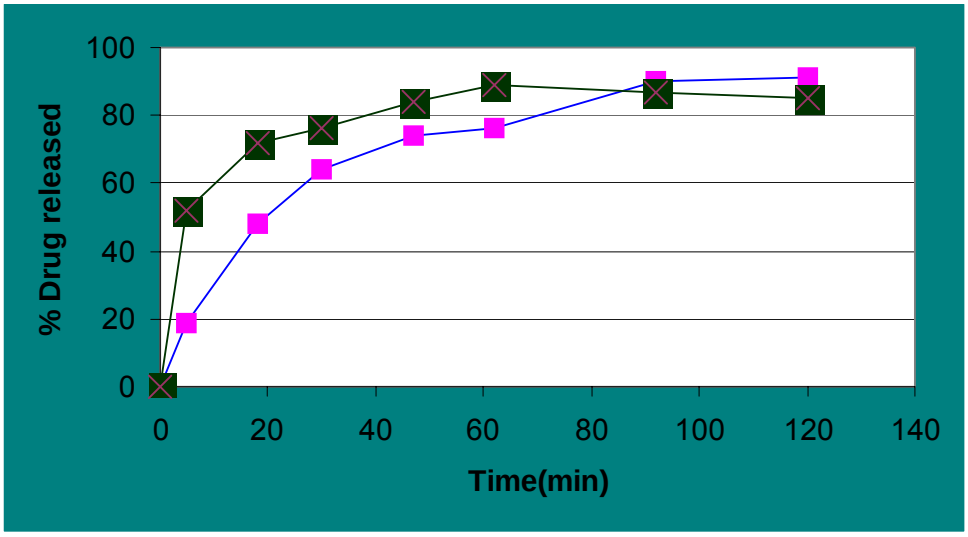

Fig. 2. Dissolution Profiles of Cefadroxil and its complexes with β-Cyclodextrins.

Formulation studies

Tablets containing 50 mg of Cefadroxil were prepared by direct compression using different excipients like Lactose monohydrate, colloidal silicon dioxide, and magnesium stearate. Tablets containing complexes (equivalent to 50 mg Cefadroxil) prepared by kneading and co evaporation method were also prepared similarly using less quantity of lactose. The blend was compressed on a six-station single rotary machine using round-shaped, flat punches to obtain tablets having thickness 10–12 mm and hardness 9–14 kg/cm2. The tablets were studied in 6 replicates for release profile of Cefadroxil using the same method described in dissolution studies.

Analysis of Cefadroxil - β-Cyclodextrins inclusion complexes

Quantitative IR analyses of each sample were performed using sodium chloride (NaCl) discs referenced to a potassium bromide background on a FT-IR instrument. The IR spectra for all the 1:2 and 1:3 (molar ratio) Cefadroxil / β-cyclodextrin freeze dried preparations are essentially the same. In each case significant spectral change for the freeze-dried preparations only observed in the range of 2364-828cm^{-1}. Figure 2 and 3. The spectrum for Cefadroxil is characterized by peaks at 2214 cm^{-1} and 1432 cm^{-1}. A broad band at 1852cm-1 characterizes the spectrum for β cyclodextrin, which is due to the glycosidic linkages. The spectrum for the physical mix and kneaded preparation are more or less the summation of those for the biphenyl rings of Cefadroxil at 1043cm^{-1} & 1365 cm^{-1}. The cyclodextrin glycosidic peak is unchanged in the presence of Cefadroxil both as freeze preparation and as a physical mixture.

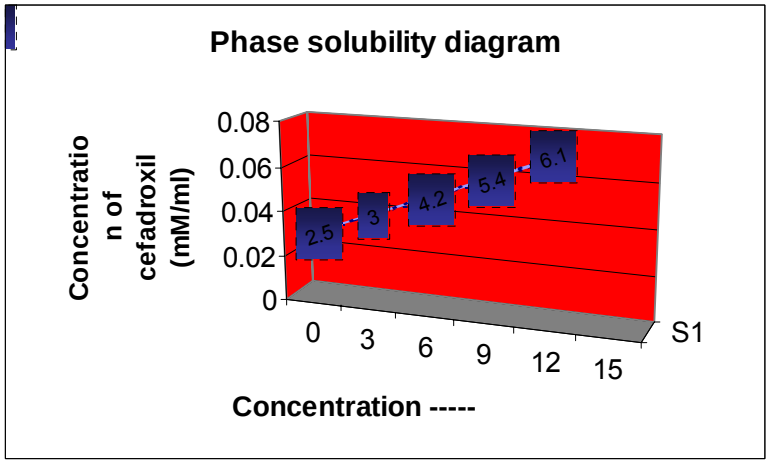

Fig. 3. Phase solubility diagram

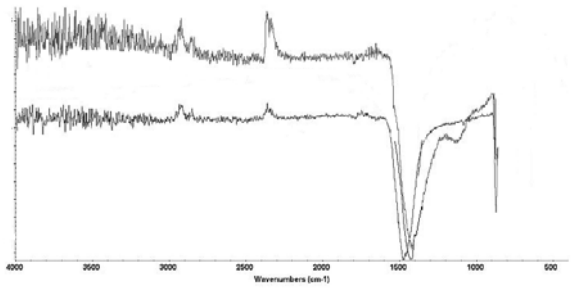

Fig. 4. FT-IR spectrum of Cefadroxil - β Cyclodextrins preparation in 1:2 ratios.

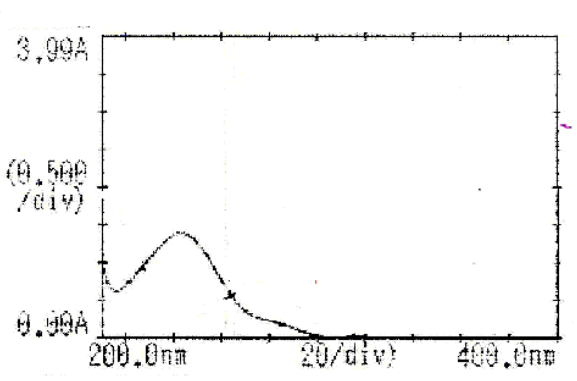

Fig. 5. UV spectrum of Cefadroxil β-cyclodextrin in the region of 311nm.

4. Results and discussion

The present study involves the influence of inclusion complexes of β-cyclodextrin on

solubility of Cefadroxil.Phase solubility diagram for Cefadroxil -ß-CD system in water shown linear increase in solubility of Cefadroxil with increasing concentration of ß-CD. Since the slope of the diagram was less than 2 (1.654), the complex stoichiometry was assumed to be 1:3.The stability constant (K) found to be 89.41. The low value of stability constant for the inclusion complex may be due to the large size of Cefadroxil and it can be suggested that the interaction between ß-CD and Cefadroxil is not strong resulting in partial complexation of drug in ß-CD cavity. The DSC graph of pure Cefadroxil drug powder showed a sharp endotherm near 3217C, which is indicative of its melting temperature. In the thermogram of ß-CD, two endothermic peaks were observed. Loss of water occurs in the temperature range between 1654 C and 17534C and near 2165C, the endothermic peak corresponding to ß-CD fusion is observed. The XRPD pattern of Cefadroxil showed peaks that were intense and sharp, indicating its crystalline nature. Inclusion complexes KN showed undefined, broad, diffused peaks with low intensities. Though this signifies an amorphous nature, a few sharp peaks having less intensity were observed. The inclusion complexes SPR showed peaks of diminished intensity suggesting almost complete amorphization of the drug. (fig.1) Since FTIR is a highly sensitive method of analysis; all spectra of complexes show some or other changes from parent spectra, i.e. pure drug and ß-CD. Drug spectrum shows the spectrum for Cefadroxil is characterized by peaks at 2214 cm^{-1} and 1432 cm^{-1}. A broad band at 1852cm^{-1} characterizes the spectrum for β cyclodextrin, which is due to the glycosidic linkages. The spectrum for the physical mix and kneaded preparation are more or less the summation of those for the biphenyl rings of Cefadroxil at 1043cm^{-1} & 1365 cm^{-1}.The UV spectrum for Cefadroxil consists of two peaks, one at 287nm and other at 311 nm (not very prominent). The molar absorptivities at these wavelengths were determined as 0.3761, 0.2542 respectively. The point of inflexion at 311nm (ε = 0.7612) has been assigned to butane group by reference to the UV spectrum. The dissolution studies was carried out with Cefadroxil and it's complexes and physical mixture using dissolution medium 0.1 N HCl. 60 min (dissolved within 90 min), time to dissolve 50% drug (t_{50}%) and mean dissolution time are reported in Table 2. The data revealed the onset of dissolution of pure Cefadroxil was very low in (14.28 % within 19 min). It is evident that the dissolution rate of pure Cefadroxil is very high (39.53 % in 2 hr.) Moreover, Cefadroxil diffusion rate was higher from the control-saturated solution. Moreover, although drug diffusion was very similar for all the freeze-dried products, Cefadroxil diffusion rate slightly decreased as the β-CD amount increased.

Table 1. Solubility of Pure Cefadroxil Stability constant (Kc), and Correlation Coefficient (R^2).

Medium	G	Kc (M−1)	R^2
pH 2.1	0.562	163	0.9983
pH 5.0	0.318	354	0.7803
pH 8.5	0.271	416	0.9265

Table 2. Dissolution Efficiency and Dissolution Percentage Values at 30 and 90 Minutes and Time.

	DE30	DP35	DE50	DP90	$T_{50\%}$
Cefadroxil	6.43	8.63	48.42	65.21	>79
PM	8.53	22.54	31.54	57.31	>55
FD	25.85	53.43	69.03	81.43	< 45

*CD-Cefadroxil dissolution efficiency; DP- dissolution percentage; $t_{50\%}$, time to dissolve 50% of drug; Cefadroxil; PM, physical mixture; and FD, freeze-dried. CD was calculated from the area under the dissolution curve at 30 and 90 minutes and is expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time.

5. Conclusion

Results obtained during this study showed that β-CD is able to improve Cefadroxil dissolution properties. The best results were obtained from freeze-dried product, in

which a true inclusion of Cefadroxil with β-CD was confirmed by studies both in the solid and liquid phase. Despite their different solubility, drug diffusion through a model silicone membrane was higher for the saturated drug solution than the freeze-dried inclusion complexes that were able to stabilize the system leading to a more regular diffusion profile.The solubility of Cefadroxil can be increased either by the addition of Cefadroxil with β-CD or by adding pH lowering agents.

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