IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

STUDIES ON INCLUSION COMPLEXES OF CILNIDIPINE WITH β-CYCLODEXTRIN

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ABSTRACT

Cilnidipine is a dihydropyridine class of calcium-channel blocker. Cilnidipine prevents intracellular calcium influx and results in vasodilatation. Prescribed for the medical management of hypertension in adults. Cilnidipine is BCS Class II drug having low solubility and high permeability. Its bioavailability is 64-90%. In present study attempt has been made to prepare and characterize inclusion complexes of drug with Beta Cyclodextrin (β-CD). The phase solubility analysis indicated the formation of a 1:1 molar inclusion complex of drug with β-CD. Apparent stability constant (K_C) was 1578 K^{-1} for β-CD complex. The inclusion complexes were prepared by two different methods viz. coprecipitation, and kneading method. The prepared complexes were characterized using dissolution study, FTIR and X-ray diffractometry. The inclusion complex prepared with β-CD by kneading method exhibited greatest enhancement in solubility and fastest dissolution (T_{90} = 20 min.) of Cilnidipine

Key Words:

Cilnidipine, inclusion complex, βCD, enhancement in solubility

INTRODUCTION

Cilnidipine is a dihydropyridine class of calcium-channel blocker. Cilnidipine prevents intracellular calcium influx and results in vasodilatation. Prescribed for the medical management of hypertension in adults. Cilnidipine is BCS Class II drug having low solubility and high permeability. Its bioavailability is 64-90%.which limits its dissolution and consequently its bioavailability. Thus it is important to enhance the solubility and dissolution rate of Cilnidipine to improve its oral bioavailability.

Many approaches such as modification of drug crystal form, addition of cosolvents, addition of surfactants, inclusion complexes with cyclodextrins (CD) may be used to increase solubility, dissolution and bioavailability of drug.

The objective of the present study is to investigate the possibility of improving the solubility and dissolution rate of Cilnidipine by complexation with β-CD. The complexes of Cilnidipinewith β-CD were prepared by using different methods like Kneading, co-precipitation,. Formation of complex was confirmed by phase solubility analysis, Fourier transform infrared (FTIR), dissolution study.

MATERIALS AND METHODS

Materials

Cilndipine (Emcure Pharmaceuticals Pvt. Ltd., Pune), β-Cyclodextrin (Signet Chemical Corporation, Mumbai) were used. All other chemicals and reagents used were of analytical grade.

Methods

Phase solubility analysis

Phase solubility studies were performed to determine stoichiometric proportions of Cilndipine with β-CD. This data was used to determine stability constant of complexes. Phase solubility study was performed as per Higuchi and Connors. For this, stock solution of 0.01M β-CD was prepared separately using distilled water. These stock solutions were diluted with distilled water to give molar solutions in the range of 2 to 10 mM for β-CD. Five ml of each molar solution was filled in screw-capped vials and the excess quantity of drug was added to each vial separately. The vials were kept for shaking at ambient temperature for 48 hrs using a lab shaker (Remi). The supernatant solutions were collected carefully and filtered using Whatman filter paper (No.41). The concentration of drug in filtered solutions was determined using UV visible spectrophotometer. No change in λ max of drug was found after complexation with cyclodextrins, hence absorbances of resultant solutions were recorded at 253 nm, which is λ max of drug. From slope and intercept value (S_0) of phase solubility curve stability constant (Kc) was determined.

$$Kc = Slope / [S_0 (1- Slope)]$$

Preparation of Physical mixture and Inclusion complexes

Physical mixture method

The required molar (1:1) quantities of drug and β-CD were weighed accurately and mixed together thoroughly in a mortar with vigorous trituration for about an hour. These mixtures were then passed through sieve no. 44 and finally were stored in airtight containers till further use.

Preparation of inclusion complexes

Inclusion complexes of Cilndipine were prepared by following different methods.

1) Kneading method

The required quantities of drug and β-CD were weighed accurately in 1:1 molar ratio. A homogeneous paste was prepared in a mortar by adding water: methanol mixture (1:1) in small quantities with continuous kneading for three hours. An appropriate quantity of water: methanol mixture (1:1) was added further to maintain suitable consistency of paste. This paste was dried in hot air oven at 45^0- 50^0C for 24 hours. The dried complexes were then powdered and passed through sieve no. 44 and stored in airtight containers till further use.

2) Co precipitation method

The required molar (1:1) quantities of drug and β-CD were dissolved in methanol and water respectively. The solution of drug was added drop wise into β-CD solution. The contents were continuously stirred for 6 hours and finally were dried at 45^0- 50^0C for 48 hours, collected and stored in airtight containers till further use.

Characterization of inclusion complexes

Inclusion complexes were characterized using following analytical techniques.

1) Drug content estimation

The quantities of inclusion complex equivalent to 10 mg of Cilndipinewere dissolved in Water: Methanol mixture (1:1). Appropriate dilutions were made and drug content of each complex was calculated from UV absorbance recorded at λmax 253 nm.

2) Solubility studies

Solubility study was performed according to method reported by Higuchi and Connors.Excess quantities of inclusion complexes were added to 25 ml distilled water taken in stoppered conical flasks and mixtures were shaken for 24 hrs in rotary flask shaker. After shaking to achieve equilibrium, 2 ml aliquots were withdrawn at 1 hr intervals and filtered through Whatman filter paper no. 41. The filtrate was analysed spectro-photometrically at 253 nm. Shaking was continued until three consecutive readings were same.

3) IR spectral analysis

Infra red spectra of drug and inclusion complexes were recorded by KBr method using Fourier Transform Infrared Spectrophotometer (FTIR-8400s).

4) X – ray diffraction (XRD) study

The X-ray diffraction pattern of the selected inclusion complexes was compared with that of the pureCilndipine. This was done by measuring 2ø in the range of 4 to 50^0 with reproducibility of $\pm 0.001^0$ on a X ray diffractometer (Philips). The XRD patterns were recorded automatically using rate meter with time constant of 2×10^2 pulse/second and with the scanning speed of 2^0 (2ø)/min.

5) Dissolution study of Cilnidipine and its inclusion complexes

Dissolution of inclusion complexes (equivalent to 20 mg of Cilnidipine) was studied using USP XXII six station dissolution apparatus (Type II). The dissolution was carried out in 900 ml of 0.1N HCl at 37 ± 0.5 ^{0}C at 50 rpm. Aliquots of 10 ml were withdrawn periodically and replaced with 10 ml of fresh dissolution medium. The concentrations of drug in samples were determined by measuring absorbance at 253nm. Cumulative percent drug released was determined at each time point. Pure drug was used as a control. The t_{90} (time required for 90% dissolution of drug) (Table 1) of various inclusion complexwas calculated.

System	% Drug Content	Solubility (mg/100 ml)	T_{90} (min)
Cilnidipine (Alone)	----	2± 0.24	>90
Cilnidipine: βCD (PM)	99.39 ± 0.71	4.9 ± 0.87	>90
Cilnidipine: βCD (CP)	94.95 ± 0.77	10.1 ± 1.51	22
Cilnidipine: βCD (KN)	97.48 ± 0.56	19.0 ± 1.09	20

Table 1: Comparison of various parameters for Cilnidipine inclusion complex

* PM- Physical mixture, CP- Coprecipitation method, KN- Kneading method,

RESULTS AND DISCUSSION

Phase solubility analysis

Phase solubility study was done to determine the stoichiometric proportion of Cilnidipine with complexing agent β-CD. The phase solubility analysis indicated formation of a 1:1 molar inclusion complex of drug with β-CD. Apparent stability constant (K_C) was 1578 K^{-1} for β-CD complex.

Characterization of Cilnidipineinclusion complex

All **i**nclusion complexes prepared by different methods such as kneading method, coprecipitation method were found to be free flowing powders.

1) Estimation of drug content

Physical mixture and inclusion complexes showed 94- 100 % drug content. (Table 1)

2) Solubility study

The saturation solubility of inclusion complexes of Cilnidipine with β-CD are indicated in Table 1**.** Cyclodextrin and their derivatives have proved to be powerful solubilizers for many poorly water-soluble drugs by forming inclusion complexes. In present work, significant enhancement in the solubility of drug was observed for all inclusion complexes with β-CD. The findings indicate that inclusion complexes prepared with β-CD showed greater enhancement in solubility. The inclusion complexes prepared by different methods showed different saturation solubility values. This may be because of variable degree of complexation. Inclusion complexes prepared by kneading method showed higher saturation solubility than those prepared by other methods.

3) IR spectral analysis

IR Spectra of pure drug and inclusion complexes of Cilnidipine with β-CD prepared by different methods are given in Fig. 1. The spectra of inclusion complexes and physical mixtures of components revealed disappearance of characteristic peaks of aromatic C-H stretching, N-H stretching and Amide at 3250 cm^{-1}, 3400 cm^{-1} and 1670 cm^{-1}respectively. Therefore, it suggests that vibrating and bending movements of guest molecule that is Cilnidipine were restricted due to formation of inclusion complex. It may be aromatic ring portion of Cilnidipine, which has been included into the cavity of Beta cyclodextrin. IR spectra thus suggest the possibility of formation of inclusion complexes.

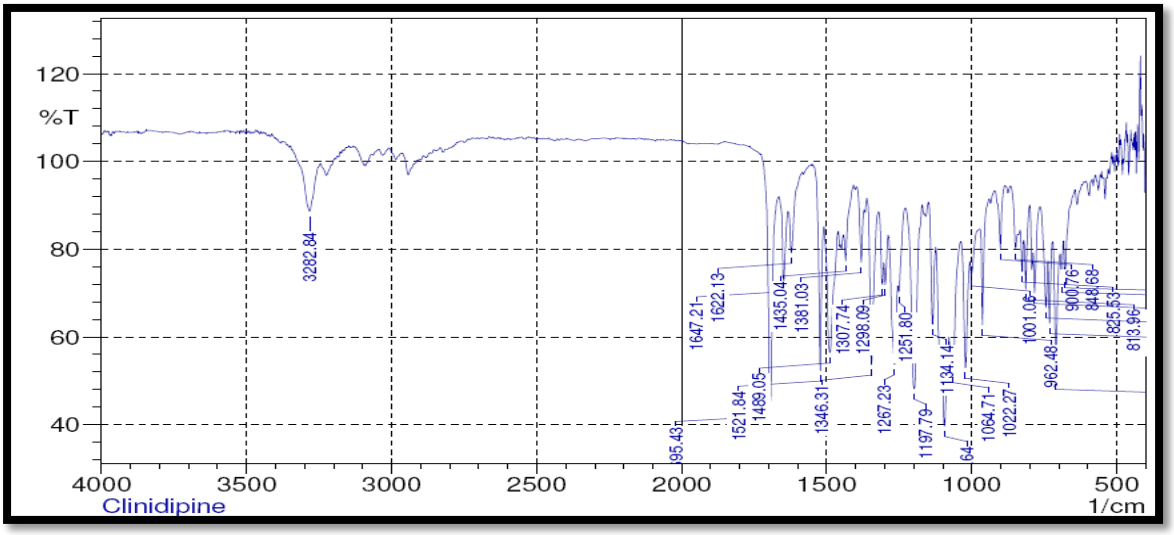

Fig. 1: IR spectra of Cilnidipine

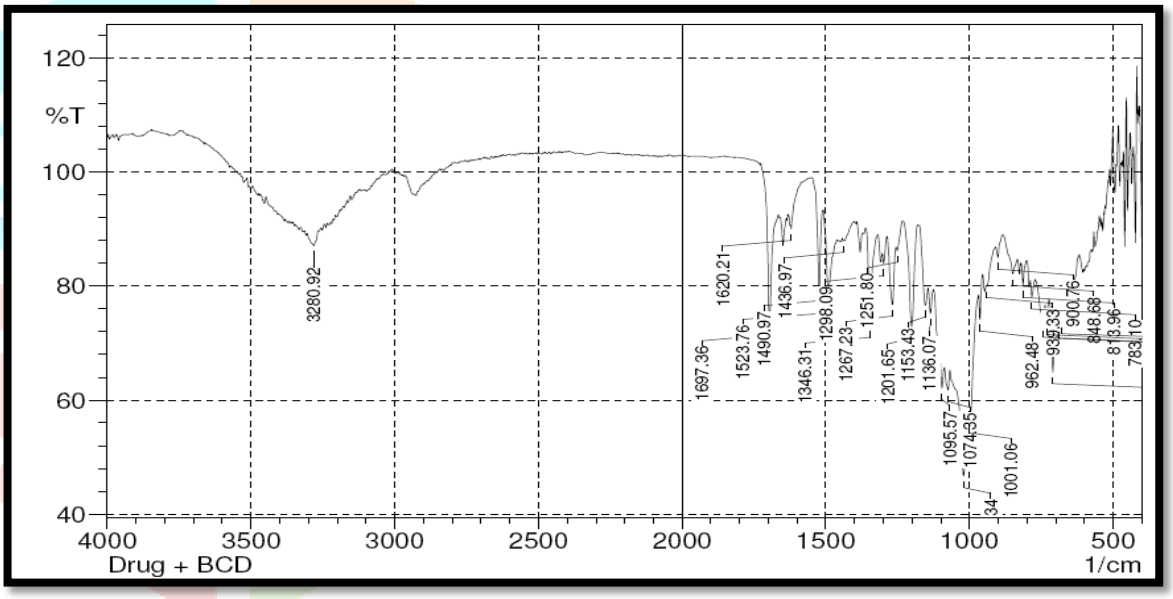

Fig. 1: IR spectra of Cilnidipine β- CD inclusion complex prepared by kneading method

4) X – ray diffraction (XRD) study

The inclusion complexes of drug prepared with β- CD by kneading method showed highest enhancement in solubility and fastest dissolution profile than any other methods (Table 1). Hence the same inclusion complex was characterized further by XRD study. Cilnidipine, β-CD and inclusion complexes of drug with β-CD prepared by kneading method were subjected to XRD analysis (Fig 2). Many broad peaks of very low intensity were observed which indicates pure drug existed as microcrystalline particles. However no sharp peaks were detected. The X-ray diffraction pattern for inclusion complexes was characterized by complete absence of any diffraction peaks for the drug, suggesting probable transformation of microcrystalline form into an amorphous state.

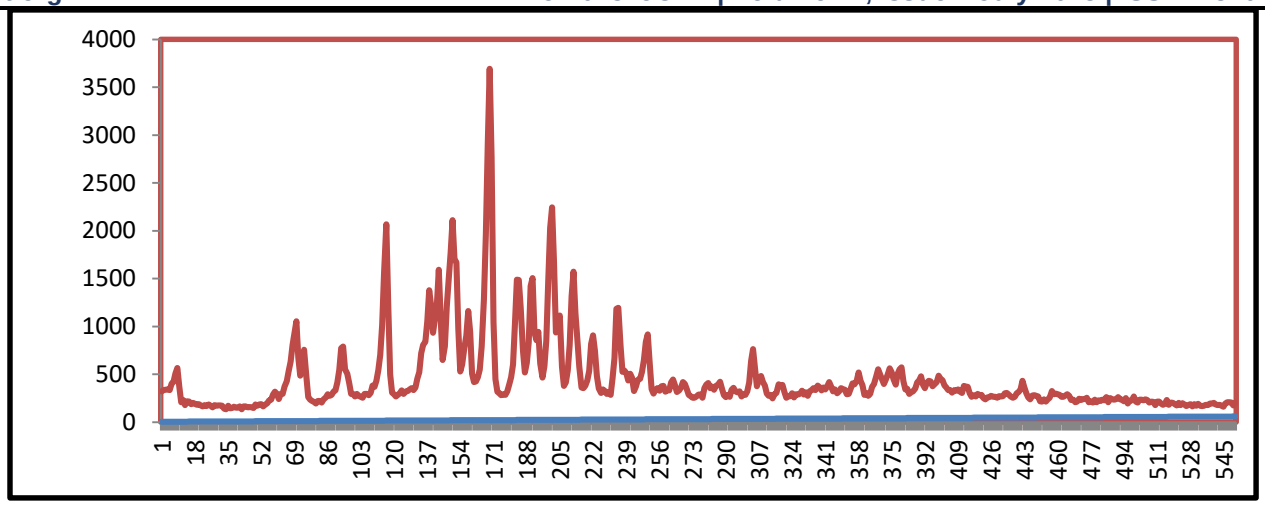

Fig. 2: A XRD pattern for Cilnidipine (pure)

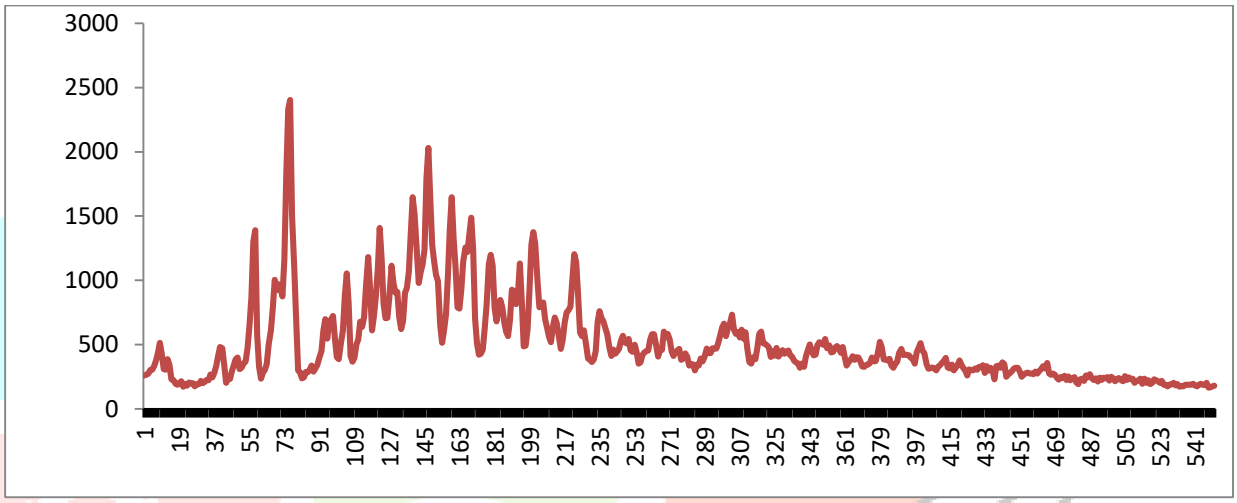

Fig. 2: XRD pattern for Cilnidipine and β- CD inclusion complex prepared by kneading method

5) Dissolution study of Cilnidipine and its complexes:

The inclusion complexes of Cilnidipine with β-CD produced pronounced enhancement in its dissolution. From Table 1, T_{90} value for physical mixture and inclusion complexes was found to be less than pure drug. Thus β-CD helps in enhancing the dissolution rate of Cilnidipine (Fig. 3).

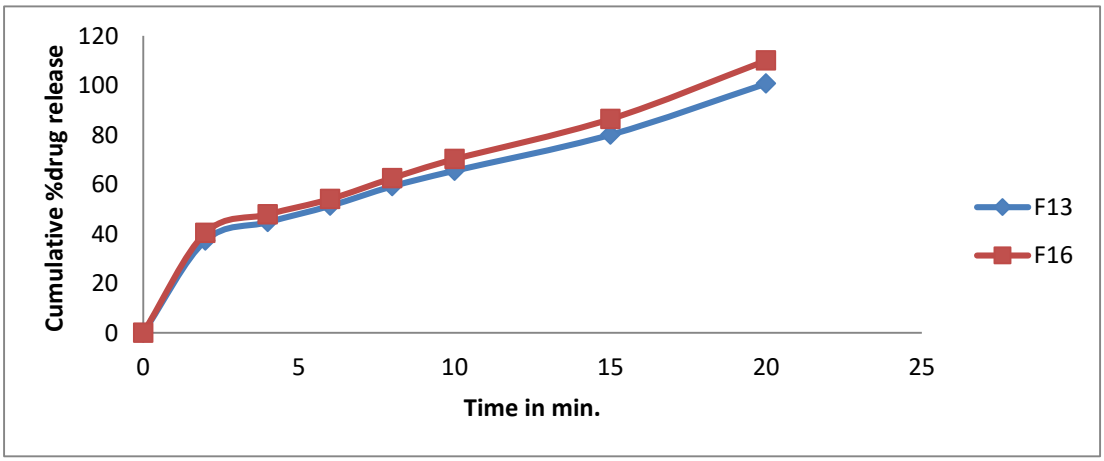

Fig.3: Dissolution profiles of Inclusion complexes of Cilnidipine and BetaCyclodextrin prepared by different methods

CONCLUSION

Phase solubility data suggests 1:1 molar complex formation of Cilnidipine with β-CD (A_L type curve). All complexes showed increase in saturation solubility and dissolution than drug alone. The enhancement in dissolution profiles has been attributed to formation of an inclusion complex in the solid state and reduction in the crystallinity of the product as confirmed by XRD study. The inclusion complexes of drug prepared with β- CD by kneadingmethod showed highest enhancement in solubility (19 mg/100ml) and fastest dissolution profile (T_{90} = 20 min). Kneading method is of particular interest for industrial scale preparation as it has major advantage of shorter reaction time and higher yield of product.However further *in vivo* studies are needed to correlate the effect of increasing solubility of Cilnidipine with its bioavailability.

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