Research Article

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PREPARATION AND EVALUATION OF INCLUSION COMPLEXES OF FELODIPINE

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ABSTRACT

Studies were carried out on the complexation of felodipine with β-cyclodextrin(β-CD) and hydroxypropyl β-cyclodextrin(HP β-CD) with the objective of developing a new oral dosage form with enhanced dissolution rate and bioavailability. Equimolar drug-cyclodextrin binary systems were prepared according to three different techniques (physical mixing, kneading and solvent evaporation) and were characterized by infrared, FTIR studies and comparative *in-vitro* studies. The drug solubility improvement obtained by the different binary systems varied from a minimum of 2.5 times up to a maximum of 120 times, depending on both the cyclodextrin type and the method of preparation. Phase solubility studies indicated formation of 1:1 M complex for HP β-CD. Apparent stability constant (K_c) was found to be 582.78 M^{-1} for HP β-CD complexes. Solid complexes of felodipine-HP β-CD at 1:1 M prepared by kneading method exhibited the highest dissolution rate and dissolution efficiency values than the pure drug and other complexes. It can be reasonably expected that the obtained drug dissolution rate improvement will result in an increase in its bioavailability, with the possibility of reducing dose and side effect.

Keywords: Felodipine, β-cyclodextrin, HP β-cyclodextrin, Physical mixture, Kneading method, Solvent evaporation method

Introduction:

Felodipine (FD), an antihypertensive agent, a second-generation calcium antagonist of the 1, 4-dihydropyridine (DHP) type, lowers blood pressure by selective dilatation of arterial smooth muscles in peripheral resistance vessels. Natural CDs are cyclic oligosaccharides, containing 6 (α-

cyclodextrin), 7 (β-cyclodextrin) or 8(γ-cyclodextrin) α-1, 4-linked glucopyranose units, with hydrophilic outer surface and hydrophobic cavity. Inclusion complexes improve stability, solubility, dissolution rate and bioavailability.

Felodipine has significant therapeutic potential in treating hypertension. Unfortunately though it has good therapeutic potential, it is poorly water soluble. It comes under Class II drugs which have low solubility and high permeability. The extent of its absorption after ingestion and its ability to be distributed into various body tissues determines its ability to exert action *in vivo*. In previous studies, it was reported that oral bioavailability of felodipine is < 20%. To improve dissolution rate and bioavailability of poorly water soluble drugs, researchers have employed various techniques such as micronisation, complexation, solid dispersion, salt formation, and others.

Formation of inclusion complexes is a method which has several advantages such as good enhancement in solubility and the use of conventional equipment. Inclusion complexes include the use of hydrophilic polymers which on contact with the medium dissolve rapidly, resulting in the fine precipitation of the drug.

The present investigation aims at improving the bioavailability of felodipine by the formation of inclusion complexes. This study aims to improve dissolution rate of FD in aqueous solution through formation of inclusion complexes with β-cyclodextrin (β-CD) and HP β-cyclodextrin(HP β-CD) and to thereby improve its oral bioavailability. The aim of the present work is to improve the pharmaceutical properties of felodipine, like its solubility, dissolution rate and oral bioavailability, which will improve their biological activity.

Experimental work:

Materials:

Felodipine (99.4%) from Ranbaxy Laboratory Limited (India), β-CD and HP β-CD was obtained as a gift sample from FDC Limited, Mumbai. All other reagents and solvents were of analytical grade and double distilled water was used throughout the study.

Phase solubility studies:

In phase solubility studies, an excess of FD was added to 50 ml volumetric flask containing distilled water (25 ml) with successively increasing quantities (0,2,4,6,8,10,12 mM) of β-CD and HP β-CD. Flasks were sealed and brought to solubility equilibrium at room temperature after shaking for 72 h. After equilibrium, the

content of each flask was filtered through a Millipore membrane (0.45 µm). The filtrated solution was appropriately diluted and the amount of dissolved FD was determined spectrophotometrically at 362 nm **(**ELICO, Model SL-159). Apparent 1:1 M stability constant (Kc) was calculated from the phase solubility diagram as

$Kc = slope/S_0(1\text{-}slope)$

Where S_0 is solubility of FD in absence of CDs.

Complex preparations:

Inclusion complexes of FD and carrier (β-CDs, HP β-CDs) are prepared in the following ratios 1:0.5, 1:1, 1:1.5 and 1:2.

Physical mixing method:

The physical mixtures of FD and carrier (β-CDs, HP β-CDs) in 1:0.5, 1:1, 1:1.5 and 1:2 ratios were prepared by simple trituration for 1 h in a glass mortar, passed through sieve no.100 and stored in a desiccator.

Kneading method (KN):

In this method, accurately weighed quantities of carriers (β-CDs, HP β-CDs) in the stated proportions were carefully transferred into test tubes, and dissolved in chloroform and water mixture. To these solutions, accurately weighed quantities of FD were added, and allowed to dissolve. The solution was transferred to a petridish, the solvent was allowed to evaporate at 50±10ºc until constant weight was obtained. Then they are kept in desiccator for 24 hours. The mass obtained in each case was crushed, pulverized, and sifted through 100 mesh.

Solvent evaporation method:

In this method, accurately weighed quantities of carriers (β-CDs, HP β-CDs) in the stated proportions were carefully transferred into boiling test tubes, and dissolved in chloroform. To these solutions, accurately weighed quantities of FD were added, and allowed to dissolve. The solution was transferred to a petridish; the solvent was allowed to evaporate at 50±10ºc until constant weight was obtained. Then they are kept in a desiccator for 24 hours. The mass obtained in each case was crushed, pulverized, and sifted through 100 mesh.

Characterization of prepared complexes:

IR-Spectroscopy:

IR spectra of FD and their complexes were determined by KBR pellet method by Perkin Elmer FT-IR series model-1615 spectrophotometer.

In-Vitro Dissolution Studies

In vitro dissolution of FD inclusion complexes was studied in USPXXII type II dissolution apparatus. Dissolution medium was phosphate buffer pH 6.5 with 0.1% SLS (900 ml) and it was maintained at 37±0.5^{o}C.

Samples (5 ml each) of dissolution medium were withdrawn by syringe fitted with pre-filter at known intervals and were analyzed for drug release by measuring at 362 nm after suitable dilution. The volume withdrawn at each interval was replaced with fresh quantity of dissolution medium.

Results and Discussion:

Phase solubility studies:

Phase solubility diagram for complex formation between FD and CDs (βCD and HP βCD) in water is A_L type (Fig. 1), which illustrates solubility enhancement capability of CD. Aqueous solubility of FD increased linearly (r=0.965 & 0.994) as a function of βCD and HP βCD concentration with K_c of 567.45 M^{-1} & 582.78 M^{-1}. The solubility increased approximately 15-fold and 20-fold for βCD and HP βCD respectively.

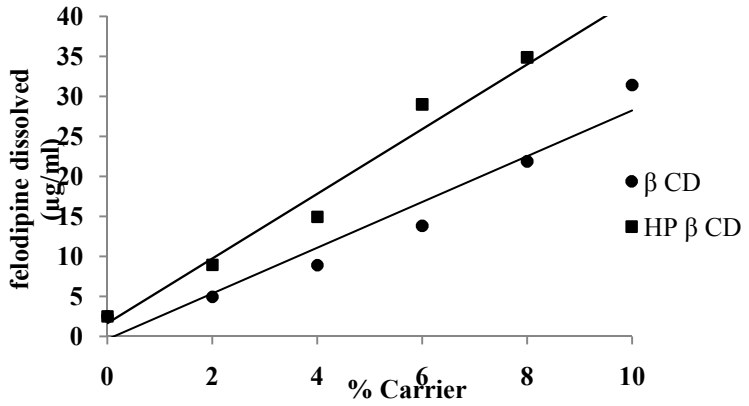

Fig 1: Phase solubility diagram of felodipine in β-CD and HP β-CD

FTIR-Studies:

In the FT-IR spectra of FD (Fig- 2, 2.1 and 2.2) absorption peaks were observed at 3371.06 cm^{-1} and 2980.13 cm^{-1} due to amine and alkyl strectching respectively. In HP β-CD, absorption peaks were at 3401.88 and 1031.60 due to O-H & C-O-C strecting respectively. In the spectra of formulation containing drug, HP β-CD at 1:1 M ratio which was prepared by kneading method, the peak due to alkyl stretching was obtained at 2930.29 and 3372.07 indicating no interaction between drug and HP β-CD.

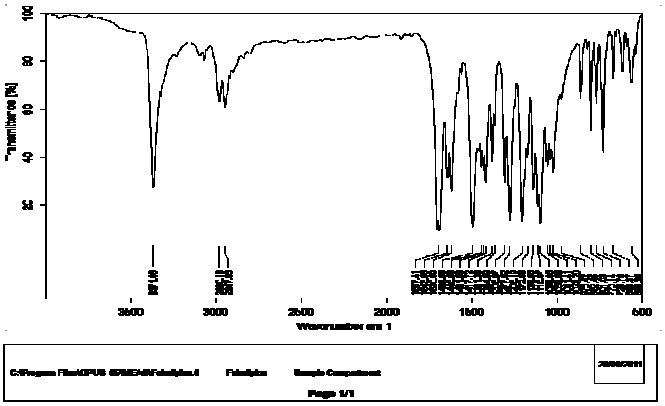

Fig.2:FT-IR spectrum of Pure drug Felodipine

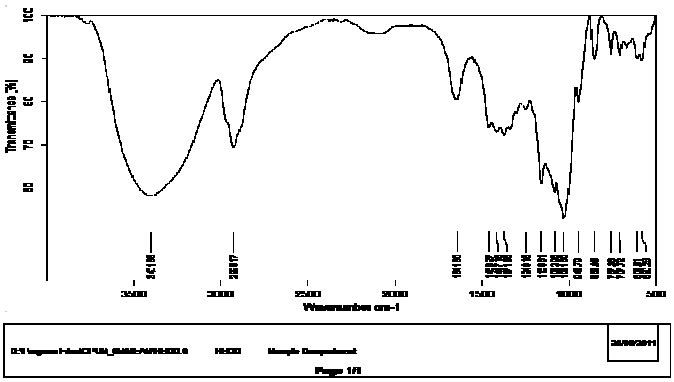

Fig.2.1:FT-IR spectrum of Pure HP β CD

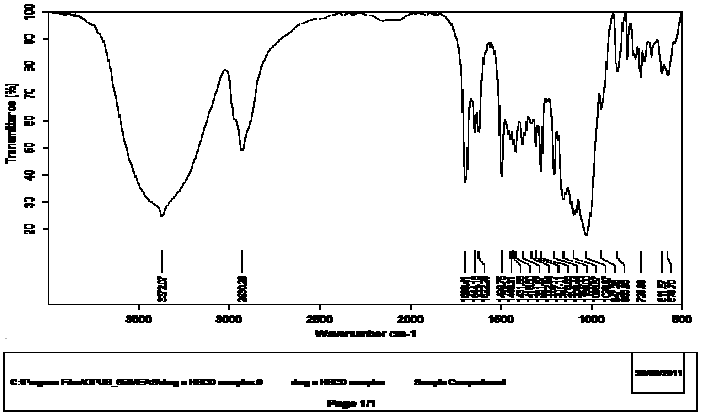

Fig.2.2: FT-IR spectrum of drug and HP β- CD 1:1 Kneading product

In Vitro Dissolution Studies:

All the complexes exhibit a faster dissolution rate than pure FD (Fig-3 and 3.1). According to these results, pure drug released less than 75% of the active content by the end of 1 hour because of its poor solubility. At the same time, physical mixtures of β-CD and HP β-CD of different ratios released the 100% active content at 20 min (1:2) and 10 min (1:1) respectively. The inclusion complexes of β-CD (1:2) and HP β-CD (1:1) prepared by kneading method released more than 95% of the drug within 5 min, indicating that the solubility of the drug was greatly increased by kneading method. From the results it is observed that the dissolution rate was increased more by kneading method than by all other techniques. This is because of higher hydrophillicity and wetting property of β-CD and HP β-CD. The order of dissolution rate enhancement was physical mixing < solvent evaporation < kneading method. When the dissolution enhancement efficacy was compared, the order obtained among the solid dispersions is HP β-CD > β-CD.The inclusion complexes made with HP β-CD exhibited higher dissolution rate than β-CD at lower proportions, hence HP β-CD complex at the ratio of 1:1 was optimized.

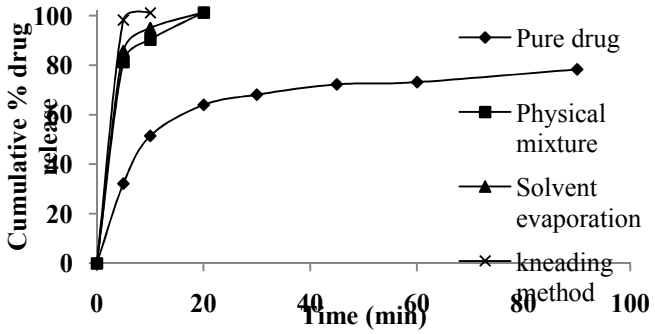

Fig.3: Comparison of dissolution profiles of felodipine- β-CD complexes (1:2) ratio

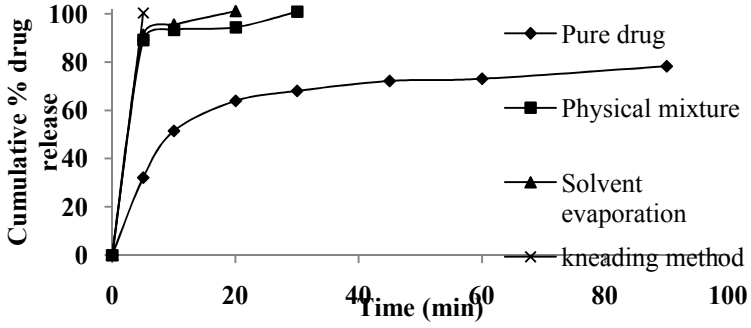

Fig 3.1: Comparison of dissolution profiles of felodipine- HP β-CD complexes (1:1) ratio**.**

Conclusions:

HP β-CD can be used to prepare FD inclusion complexes. Solubility of FD in pH 6.5 phosphate buffer was improved greatly as a result of complex formation with HP β-CD in comparison to pure FD. A marked increase in the dissolution of inclusion complex was observed with HP β- CD at 1:1 M prepared by kneading method. FD-CD complexation results in an increase of solubility and dissolution rate for the drug suggesting a possible enhancement of its oral bioavailability.

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