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ORIGINAL ARTICLE

Ternary Complexation of Fluconazzole with Cyclodextrin

Shahid Jamil*, Md.Khalid Anwer, Mohammed Almalki, Mohammad Javed Ansari, Mohammad Muqtader Aqhmad, Ramadan Al- Shdefat
Department of Pharmaceutics, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, Kingdom of Saudi Arabia
*Corresponding Author's Email: shahidjamil07@gmail.com

ABSTRACT
In an attempt to improve the solubility of fluconazole, its inclusion complexation was tried with Hydroxy propyl-β-cyclodextrin (HP-β-CD) in presence of ternary component PVP using kneading technique. Phase solubility studies confirmed a stoichiometry of 1:1 (fluconazole:HP-β-CD) molar ratio with an A_L-type of phase solubility curve. These inclusion complexes were confirmed by FTIR, XR-D studies. In vitro release studies showed a promising result when complexed in ternary system.
***Keywords**: Fluconazole, Cyclodextrin, PVP, Solubility, Enhancement*

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INTRODUCTION

Fluconazole is a broad-spectrum antifungal agent, active by both oral and intravenous routes, for the treatment of superficial and systemic infections. Insufficient aqueous solubility of fluconazole at the gastrointestinal pH, would be the rate-determining step in the gastric absorption of these drugs leading to very poor bioavailability [1].Improvement of its dissolution properties is essential because the *in vitro* dissolution behavior of fluconazole is closely related to its bioavailability. The use of cyclodextrins (CDs) as host molecule for Inclusion Complex was one of the most useful technique for improving the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host) [2-3].

The Hydroxy propyl-β-Cyclodextrins (HP-β-CD) has been frequently used to enhance the solubility and dissolution rate of water insoluble and slightly soluble drugs in an effort to increase oral bioavailability. However it has some limitation for incorporating amount into drug formulation due to cost, production capability and toxicity [2-3].

To overcome this limitation by addition of small amounts of PVP polymers to the system, which causes an increase in complexation efficiency, while requiring smaller amounts of HP-β-CD [4-5]. The synergistic effect of water soluble polymer and HP-β-CD on solubilization of drug results in ternary complex formation [6].

The purpose of the present study, to enhance the solubility of fluconazole by complexation technique with cyclodextrin having ternary complex.

MATERIALS AND METHODS

Materials

Fluconazole and HP-β-CD were purchased (from Fluka). Polyvinylypyrrolidone (PVP) was purchased from (Sigmal Aldrich). All chemicals and solvents used in this study were of analytical grade. Freshly prepared double distilled water was used throughout the work.

Phase solubility study

Excess amount of fluconazole were added to 5.0mL of distilled water containing increasing concentrations of HP-β-CD with 1% PVP (20-80 mM). The resulting dispersions were stirred using a water bath at 37 °C and 100 RPM for 72 h and then filtered through a 0.45µm membrane. Aliquots of the supernatant were diluted with distilled water and fluconazole content was measured in triplicate by UV/Vis spectroscopy at 260 nm (7).

Preparation of inclusion complex

The required quantities of the Fluconazole: HP-β-CD in the molar ratio (1:1) and 1% w/w PVP were weighed accurately following the above described phase solubility study procedure. A homogenous paste of HP-β-CD/PEG was prepared in a mortar by adding water: ethanol mixture (1:1) in small quantities for ternary system. Fluconazole powder was then added to this paste in portions, with continuous kneading, for 4hrs. An appropriate quantity of water: ethanol mixture (1:1) was added further to maintain suitable consistency of the paste. This paste was dried in a hot air oven at 40°–50° for 4 hours. The dried complexes were then powdered and passed through sieve No. 44 and stored in airtight containers till further use [8-9].

Characterization of complexes

Prepared complexes were characterized by using techniques such as FT-IR and XRD.

Fourier transforms infrared spectroscopy (FT-IR)

The FTIR spectra of samples were recorded on the on an ALPHA FT-IR Spectrometer (OPTIK,USA) using the potassium bromide (KBr) disc technique. Samples equivalent to 2mg of Fluconazole were mixed with potassium bromide (about 100 mg) in a clean glass pestle and mortar and were compressed to obtain a pellet. Baseline was corrected and the samples were scanned against a blank KBr pellet background at a wave number ranging from 4000-400 cm^{-1}.

X-ray diffraction of solid complexes (X-RD)

X-ray diffractionpatteren of samples was obtained by using X-ray diffractometer (Altima IV Regaco, Japan). The scanningrate was 4°/min. The voltage/current used was 30 kV/25 mA and the target/filter (monochromator) was copper.

In-vitro release studies

The dissolution behaviors of complex were compared with those of pure fluconazole powder. The release studies were conducted according to the USP XXVI rotating basket method in a dissolution apparatus. In order to maintain sink conditions, the samples, equivalent to 100 mg of fluconazole were placed into hard gelatin capsules. The drug were analyzed in simulated gastric fluid (pH 1.2). The stirring speed was 75 rpm, and the temperature was maintained at 37 °C. The samples (10 mL) were withdrawn and analyzed by UV/Vis spectroscopy. The same volume of fresh medium was replaced. Experiments were carried out in triplicate.

RESULTS AND DISCUSSION

Phase-solubility study

The phase-solubility diagram obtained for fluconazole/HP-β-CD complex with 1% PVP showed a linear relationship between increases in the solubility of fluconazole and HP-β-CD concentration. According to Higuchi and Connors, these curves can be classified as AL type (Fig.1) and favors 1:1 ratio complexation.

Characterization of complexes

Fourier transforms infrared spectroscopy (FT-IR)

Variations in peaks were observed in the absorption spectra of complex corresponding to the drug in the region of 400-1600 cm^{-1} which resulted from the overlapping of the drug and HP-β-CD (Fig.2). It could be understood, a shift and reduced in peak intensity probably due to inclusion of drug into HP-β-CD cavity.

X-ray diffraction of solid complexes (X-RD)

XRD pattern of fluconazole and 1:1 complex in Fig.3, revealed several intense peaks however, these peaks are absent or reduced in intensity in 1:1 complex as compared to fluconazole alone. This indicated inclusion of drug into HP-β-CD cavity.

***In-vitro* release studies**

The ***in vitro*** release studies was carried out for ternary complex in both simulated gastric fluid (pH 1.2) (Fig 4). Release of fluconazole alone was found to be 35% in 60mins at pH 1.2. Release of kneaded complex was increased to 65% (about 2 fold).

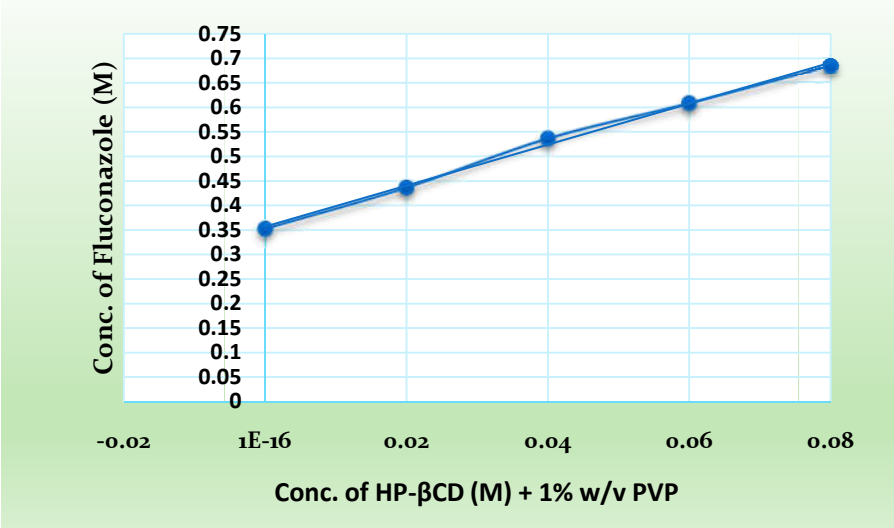

Fig. 1: Phase-solubility diagram of Fluconazole with HP-β-CD + 1% PVP

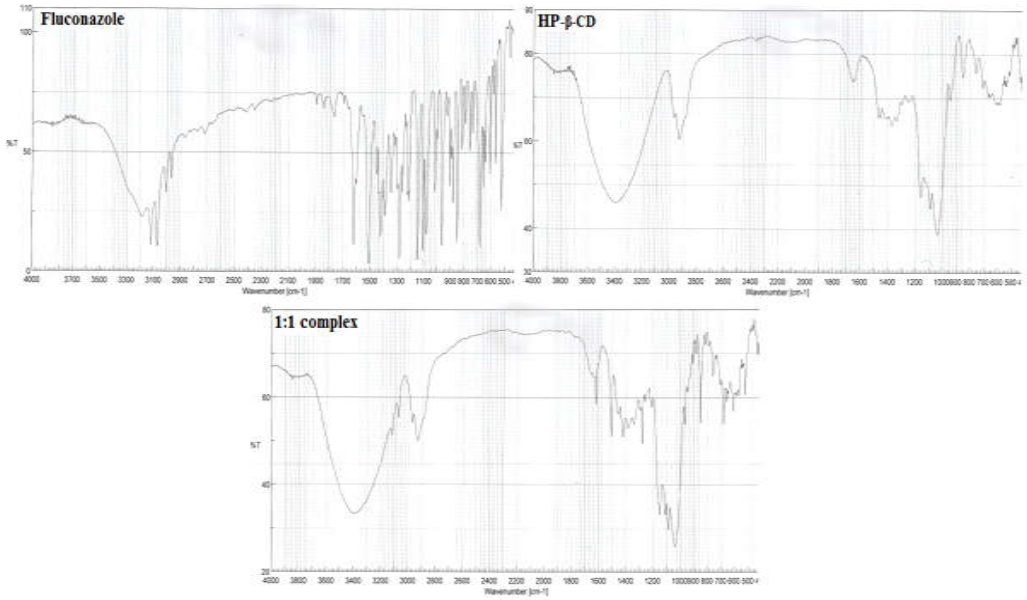

Fig. 2: FT-IR spectra of drug and complex

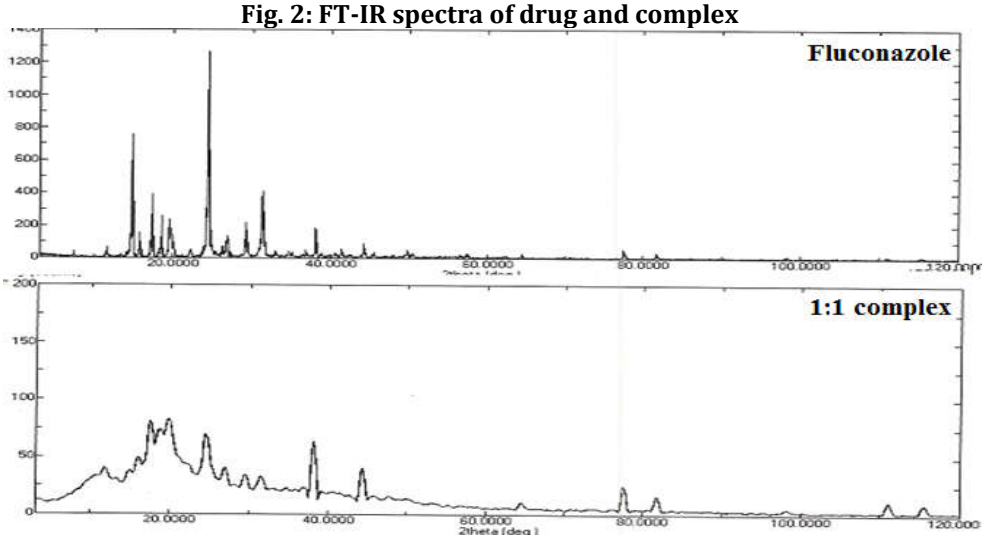

Fig. 3: XRD spectra of drug and complex

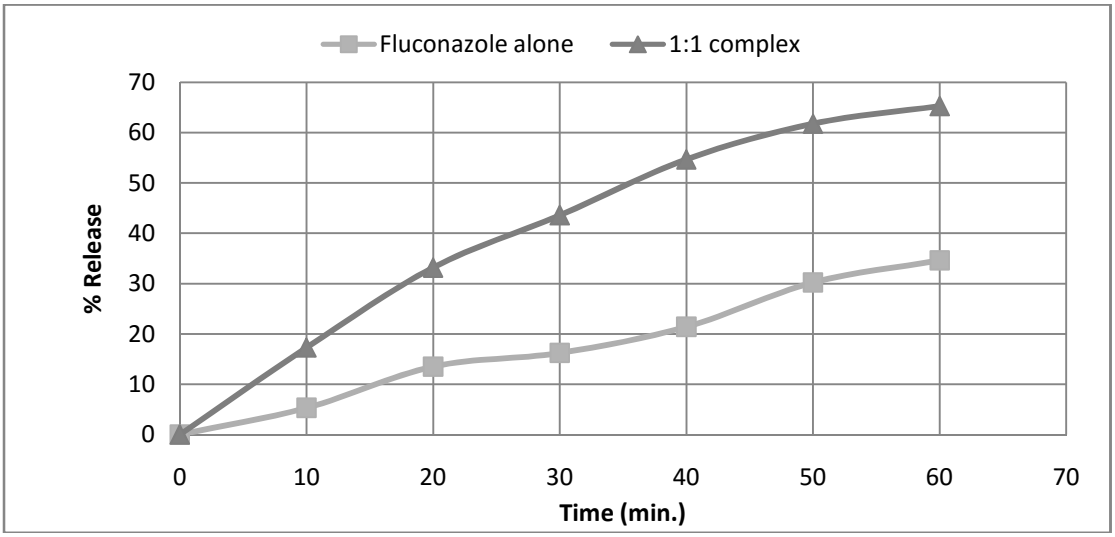

Fig. 4 : Release rate profile at pH 1.2

CONCLUSION

In this study, poorly soluble drug, fluconazole was successfully incorporated in HP-β-CD with PVP by kneading technique. Developed complex may be a suitable carrier for the possible oral delivery. A significant drug release was observed when fluconazole complexed. Hence, by using HP-β-CD and PVP polymer as complexing agent, a reduction of dose and dose frequency of fluconazole is possible.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

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