Ternary Complexation of Fluconazole with Cyclodextrin

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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_s-type of phase solubility curve. These inclusion complexes were confirmed by FTIR, XRD studies. In vitro release studies showed a promising result when complexed in ternary system.

Keywords: Fluconazole, Cyclodextrin, PVP, Solubility, Enhancement

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). Polyvinylpyrrolidone (PVP) was purchased from (Sigma 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
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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)
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).

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.

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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
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.

REFERENCES