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Research Article

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Nanosuspension versus cyclodextrin inclusion of ciprofloxacin for solubility and dissolution enhancement

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ABSTRACT

Objective of this research is to evaluate solubility and dissolution of ciprofloxacin using current nanotechnology and classical cyclodextrin inclusion complex approach. Ciprofloxacin nanosuspension was prepared by anti solvent precipitation method using pluronic F68 as stabilizer. Phase solubility study of ciprofloxacin was carried out alone and with addition of different amount of beta-cyclodextrin. Solubility studies showed linear increase in aqueous solubility of ciprofloxacin with increase in concentration of beta cyclodextrin. Inclusion complex of ciprofloxacin was prepared by kneading method. Both nanosuspension and inclusion complexes were compared with ciprofloxacin for physicochemical characteristics using FT-IR spectroscopy, solubility and dissolution profiles. In vitro dissolution studies revealed there is no significant difference between dissolution profiles of inclusion complexes and nanosuspension however; both showed more than two fold higher dissolution as compared to that of pure ciprofloxacin. The finding revealed no significant difference between these two techniques for enhancing solubility and dissolution of ciprofloxacin

Keywords: Ciprofloxacin, nano-suspension, cyclodextrin, solubility, dissolution.

INTRODUCTION

The formulation development and efficient delivery of poorly water-soluble drugs has always been a challenge. It has been estimated that more than 40% of the discovered drugs are poorly water-soluble [1]. Bioavailability and performance of such drugs are usually low as their absorption is dissolution rate limited. Moreover, such drugs often have an incomplete or erratic absorption profile thus highly variable bioavailability. Subsequently, prediction, estimation and control of pharmacological response are often difficult. Significant food effect is also very common on bioavailability of poorly soluble drug. Thus it is evident that solubility of the drug is a critical factor in achieving an optimum formulation of any drug so as to get better therapeutic profiles [2, 3]. Several techniques are available to improve the solubility of poorly soluble drugsin order to improve their bioavailability and performance such as classical and conventional solid dispersion techniques [4], molecular inclusion complexation with cyclodextrins [5], co-solvency with alcohol or surfactants[6] and co-grinding [7].Of the available techniques, molecular inclusion complexation with natural cyclodextrin is supposed to be one of the most widely used classical technologies to increase the aqueous solubility of poorly water-soluble drugs. Cyclodextrins (CDs) are torus shaped cyclic oligomers consisting of 6 (α),7 (β) or 8 (γ-CD) glucose units with a-1,4-linkages with a hydrophobic cavity and a hydrophilic exterior [8]. These macromolecules are able to form inclusion complexes with many drugs by taking up the drug molecule or some lipophilic moiety of the molecule, into their central cavity [9-11].

Cyclodextrincomplexation technique is simple, economical;in addition to easy commercialization capability [12-14]. Formulation as nano-suspension is an attractive and promising alternative for solublization and delivery of poorly soluble drugs. Nano-suspension consists of the pure poorly water-soluble drug without any matrix material suspended in dispersion. Nanosuspensions are submicron colloidal dispersions of nano-sized drug particles stabilized by surfactants. The formulations consist of water, drug, and one or more generally regarded as safe excipients [15, 16].

Ciprofloxacin is a broad spectrum second generation fluoro-quinolone antibiotic which is effective against gram positive and gram negative bacteria. It kills bacteria by interfering with topoisomerase which stops synthesis of DNA and of protein [17]. It is practically insoluble in water and sensitive to sunlight losing its antibacterial activity. Objective of this research is to investigate the solubility of ciprofloxacin by cyclodextrins inclusion complexes or by nanosuspension techniques. Both beta-cyclodextrin complexation[18-20] as well as nanosuspension are known to improve solubility or therapeutic activities of the enclosed ciprofloxacin [21]. However, there is no study which explores these methods based on simplicity, efficiency and lack of demerits. In this paper we formulate and compare the solubility enhancement by nano-suspension and cyclodextrin inclusion techniques.

EXPERIMENTAL SECTION

Ciprofloxacin basewas obtained as gift from Riyadh Pharma. (Riyadh, Saudi Arabia). β-cyclodextrin and Pluronic F68 were purchased from Sigma-Aldrich (St Louis, MA, USA).Other solvent likeethanol, methanol, dicloromethane, sodium chloride, disodium hydrogen phosphate, sodium hydroxide were of analytical grades.

Phase Solubility Study

Excess amount of ciprofloxacin was incubated at 37 °C and 100 RPM in biological shaker with 0-16 mM of beta cyclodextrins solutions. Suspensions were filtered were filtered through a 0.2 μm pore size membrane filter (Cellulose acetate filter, Sartorius, Germany), after reaching equilibrium.The concentrations of dissolved ciprofloxacin in water/ cyclodextrins mixtures were determined by absorption spectroscopy using UV-VIS spectrophotometer (V-630 Gasco, Japan) at 270 nmafter appropriate dilution.

Preparation of Inclusion Complex

One mole of ciprofloxacin was kneaded for 15 minutes in mortar with one mole of beta cyclodextrin in by adding sufficient amount of water. Dough was then dried at 60°C in hot air oven, scraped and stored for further analysis.

Characterization of Inclusion Complex

Inclusion complexes were compared with pure drug for physicochemical characteristics using FT-IR, solubility and dissolution profile.

For solubility study, samples containing equivalent amount of ciprofloxacin were suspended in distilled water and placed in biological shaker at 37°C 72 hours. Samples were filtered and absorbance of filtrate was measured by UV-VIS spectrophotometer at 270 nm. For dissolution profile, equivalent amount of ciprofloxacin were compressed with Avicel 102 and magnesium stearate as pellet. Dissolution study was carried out in USP II apparatus using phosphate buffer pH 6.8 as media. Samples were collected at 0, 10, 20, 30, 40, 60 and 120 minutes. Samples were filtered, diluted and analyzed by UV-VIS spectrophotometer at 270 nm.

Fourier Transform Infra-Red Spectroscopy

The Fourier transform infra-red spectroscopy (FT-IR) spectra of pure drug and inclusion complexes were recorded on the FT-IR (Alpha, Germany) using the potassium bromide (KBr) disc technique.

Dissolution Studies of Inclusion Complex

In vitro dissolution studies were carried out in USP dissolution apparatus II using 900 ml of the dissolution medium constituting of phosphate buffer pH 6.8 and 1% sodium lauryl sulphate (SLS) at 37ºC). Speed was adjusted to 100 rpm. The samples were withdrawn periodically over a period of 2 hours and analyzed using Shimadzu UV spectrophotometer UV-1601 (Japan).

Preparation of Nano-Suspension

Accurately weighed amount of ciprofloxacin was dissolved in 5 ml of dichloromethane by using ultra-sonicator (Bandelin, Germany). This drug solution was then injected into anti-solvent (22.5 ml water) in the presence of 0.1% w/v aqueous pluronic F68 as stabilizer. Rapid addition of solution to such anti-solvent leads to rapid super-saturation of drug in the solution, and formation of ultrafine amorphous or crystalline drug. Ultrasonic energy was employed for preparing a stable suspension with minimum particle size.

RESULTS AND DISCUSSION

Ciprofloxacin solutions in concentration range of 0.5-10 µg.ml^{-1}followed beer lambert law with a correlation coefficient of 0.996 (Fig.1).Phase solubility diagram of ciprofloxacin in aqueous solutions of beta cyclodextrin is shown in Fig.2. Ciprofloxacin solubility was increased linearly as a function of amount of beta cyclodextrin.

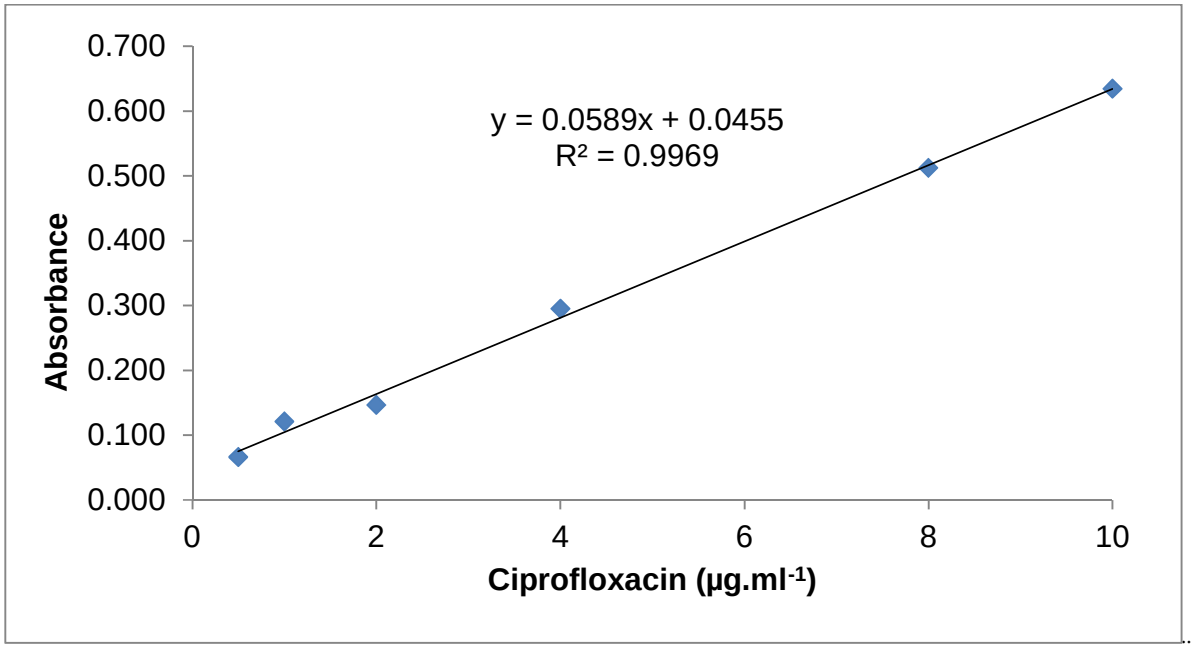

Fig 1: Calibration plot of ciprofloxacin

***In vitro* Dissolution profiles**

The dissolution profiles of ciprofloxacin alone and from formulations were carried out in USP dissolution apparatus II. Dissolution profiles of all tested samples are shown in Fig. 3.The dissolution studies revealed that about 40% and 70% ciprofloxacin were released within two hours from pure drug and physical mixture respectively; however it was almost completely released from inclusion complexes and nanosuspension.

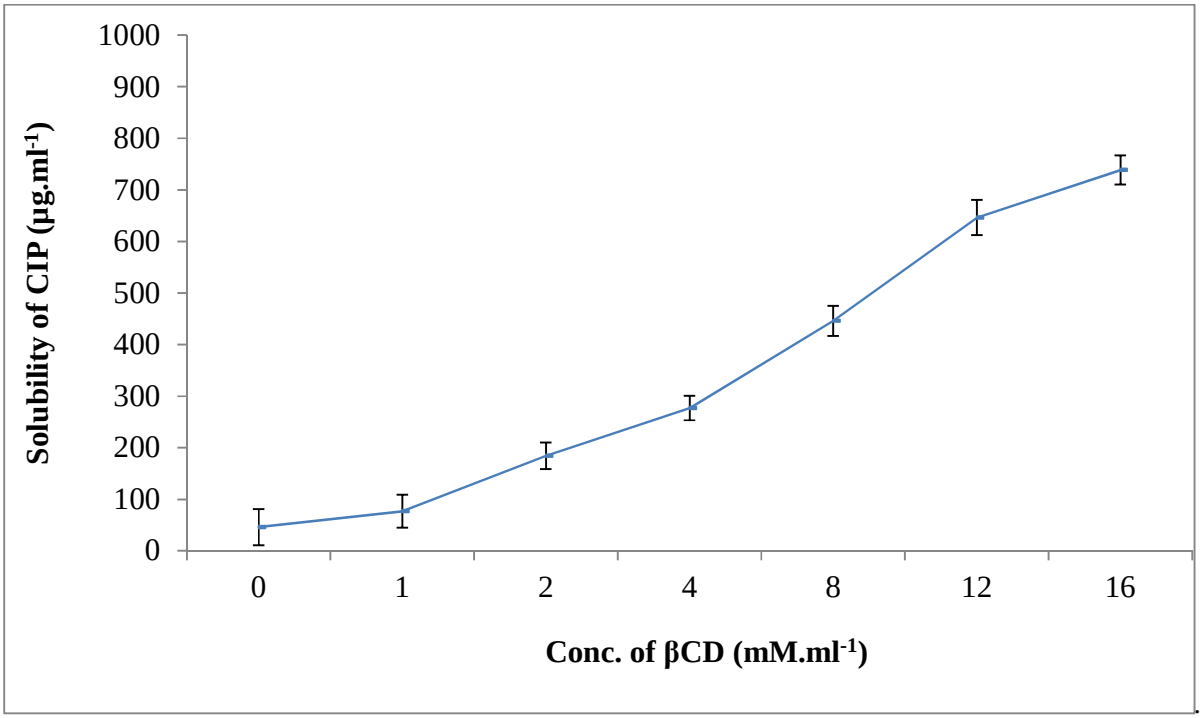

Fig 2: Phase solubility of ciprofloxacin in aqueous solutions of beta-cyclodextrin (n=3±SD)

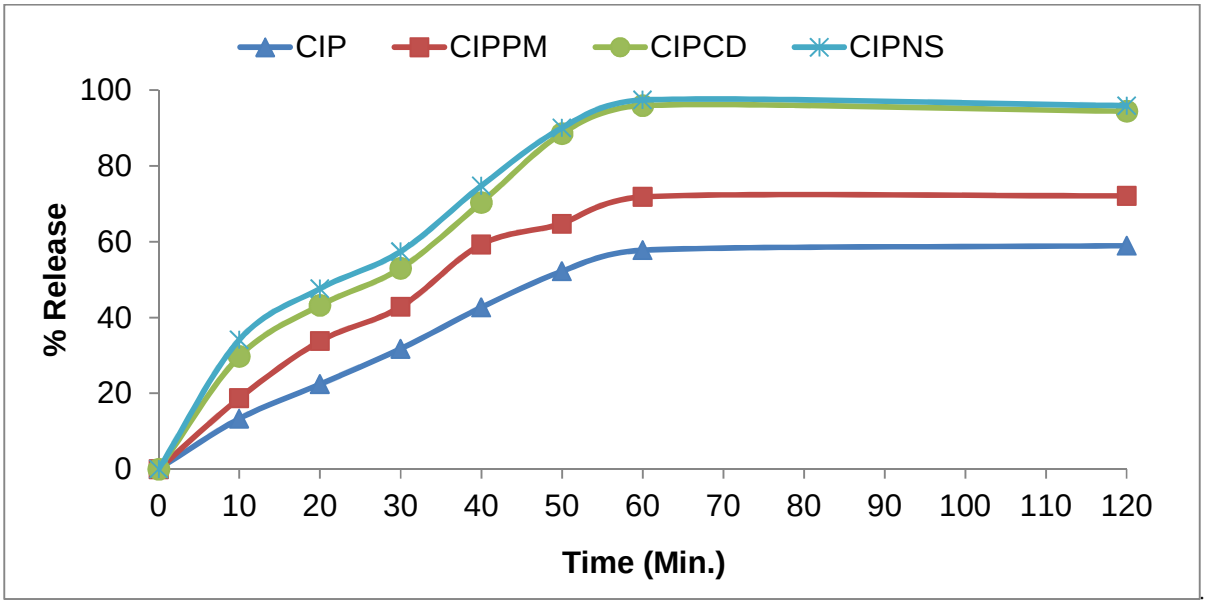

Fig 3: Dissolution profiles of pure ciprofloxacin and formulations (CIP: pure ciprofloxacin; CIPPM: physical mixture of ciprofloxacin and beta cyclodextrin; CIPCD:Kneaded inclusion complex of ciprofloxacin and beta cyclodextrin; CIPNS: Nano-suspension of ciprofloxacin)

FTIR spectroscopy

IR curves of pure components (CIP and BCD), physical mixtures (PM), inclusion complex prepared by kneading method (KD) and nanosuspension (NS) are shown in Fig.4. These curves were indicative of formation of inclusion complex in solid state. The disappearance of sharp peaks of CIP might be attributed to an amorphous state and/or to an inclusion complexation.

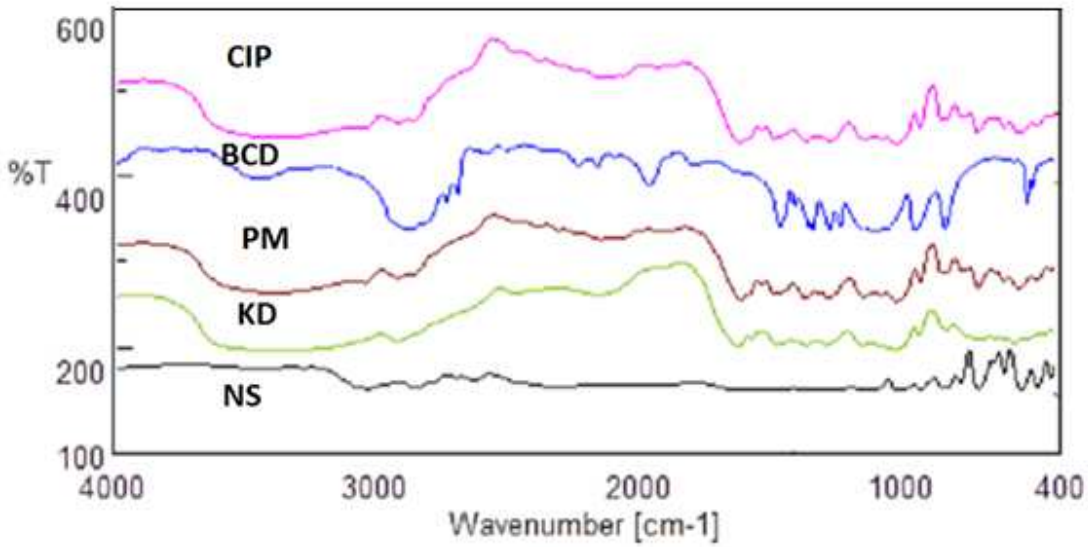

Fig 4: FT-IR profiles of pure ciprofloxacin and formulations (CIP: pure ciprofloxacin; BCD: beta cyclodextrin; PM: physical mixture of ciprofloxacin and beta cyclodextrin; KD:Kneaded inclusion complex of ciprofloxacin and beta cyclodextrin; NS: Nano-suspension of ciprofloxacin)

CONCLUSION

Solubility studies showed linear increase in aqueous solubility of ciprofloxacin with increase in concentration of beta cyclodextrin. *In vitro* dissolution studies revealed there is no significant difference between dissolution profiles of inclusion complexes and nanosuspension however; both showed more than two fold higher dissolution as compared to that of pure ciprofloxacin. The finding revealed no significant difference between these two techniques for enhancing solubility and dissolution of ciprofloxacin therefore it is recommended that cyclodextrin complexation be preferred over nanosuspension owing to its simplicity and absence of use of any surfactant or harsh solvent.

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