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Effect of different polymers on avanafil–β-cyclodextrin inclusion complex: *in vitro* and *in vivo* evaluation☆

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ABSTRACT

In this study, we examined the effect of different polymers on the chemical, physical and pharmacokinetic properties of avanafil–β-cyclodextrin (β-CD) inclusion complex. Equimolar mixtures of drug and β-CD were used to prepare 25 ternary drug–β-CD-polymer inclusion complexes using five different polymers, polyethylene glycol (PEG 4000), polyvinyl pyrrolidone (PVP K-30), chitosan, hydroxypropylmethyl cellulose, and hydroxyethyl cellulose, each in five different concentrations, 1, 3, 5, 7, and 10% (w/w). The addition of 10% (w/w) PEG 4000 resulted in a significant decrease of drug solubility, where the infrared spectra and differential scanning thermograms revealed an interaction between PEG 4000 and avanafil which hindered drug inclusion. In contrast, addition of 7% (w/w) PVP K-30 facilitated drug inclusion as concluded from differential scanning thermograms, X-ray diffraction patterns and scanning electron micrographs. This resulted in a subsequent improvement in drug solubility and *in vitro* dissolution. This formula was chemically and physically stable for 6 months under accelerated storage conditions. The formula had a relative bioavailability of 125.56% in rabbits as compared to conventional commercially available avanafil tablets (Spedra®).

1. Introduction

Avanafil is an inhibitor of phosphodiesterase enzyme type 5 (PDE5) used for treatment of erectile dysfunction. It was recently approved by US Food and Drug Administration (FDA) and European Medicines Agency (European Medicines Agency, 2013; US Food and Drug Administration, 2012). It's characterized by its rapid onset and it exhibits visual side effects to a lower extent than other PDE5 inhibitors (Alwaal et al., 2011; Limin et al., 2010). It is poorly soluble in water and has relatively low bioavailability of 38%–41% (Burke and Evans, 2012). Complexation with cyclodextrins (CDs) is a well-established method to improve aqueous solubility of drugs (Loftsson et al., 2004). β-CD has the lowest aqueous solubility among all CDs. Nevertheless, owing to its low price, β-CD is the most commonly used agent in pharmaceutical preparations where it represents 54.8% of the CDs used in marketed medicines (Kurkov and Loftsson, 2013; Szejtli, 1998). Drug/CD inclusion complexes are usually prepared by simple unit processes such as precipitation, kneading, solvent evaporation, lyophilization and spray drying of solutions or suspensions of the components (Challa et al., 2005; Giordano et al., 2001). Hydrophilic auxiliary polymers may be added during preparation of drug-CD complexes to enhance wetting, dispersibility and amorphization in order to improve drug solubility (Ammar et al., 2006; Srivalli and Mishra, 2015; Taupitz et al., 2013). However, contradictory effects may result from certain drug-polymer and CD-polymer interactions. Polyethylene glycol 4000 (PEG 4000), polyvinyl pyrrolidone K-30 (PVP K-30), chitosan, hydroxypropylmethyl cellulose (HPMC) and hydroxyethyl cellulose (HEC) are among the most common hydrophilic polymers involved in the preparation of drug-CD inclusion complexes (Kurkov and Loftsson, 2013). In this study, we examined the

Abbreviations: PDE5, phosphodiesterase enzyme type 5; FDA, Food and Drug Administration; CD, cyclodextrin; PEG, polyethylene glycol; PVP, polyvinyl pyrrolidone; HPMC, hydroxypropylmethyl cellulose; HEC, hydroxyethyl cellulose; HPLC, high performance liquid chromatography; $K_{s(1:1)}$, stability constant; CE, complexation efficiency; Q_5, percentage drug released at 5 minutes; $D.E._{(0-30)}$, dissolution efficiency (0–30 min); ANOVA, analysis of variance; FT-IR, Fourier-Transform infrared; PXRD, powder X-ray diffractometry; RDC, relative degrees of crystallinity; DSC, differential scanning calorimetry; SEM, scanning electron microscopy; C_{max}, peak plasma concentration; T_{max}, time to peak plasma concentration; $AUC_{(0-\infty)}$, area under plasma concentration-time curve extrapolated to infinity; MRT, mean residence time; K_e, elimination rate constant.

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effects of these polymers on solubility, *in vitro* release and crystalline properties of avanafil-β-CD inclusion complex. The study involved stability as well as *in vivo* assessment of a selected formula.

2. Materials and methods

2.1. Materials

Avanafil was purchased from Arcadia biotechnology (Shanghai, China), PVP K-30 was purchased from Loba Chemie (Mumbai, India), PEG 4000 was purchased from Oxford Laboratory Pharmaceuticals (Mumbai, India), chitosan was purchased from Carl Roth (Karlsruhe, Germany), β-CD, HPMC, HEC, sodium dihydrogen phosphate, disodium hydrogen phosphate, *n*-hexane, ethyl acetate, methanol and high-performance liquid chromatography (HPLC) grade acetonitrile were purchased from Sigma-Aldrich (Cairo, Egypt), absolute ethanol was purchased from Piocheme (Cairo, Egypt), hydrochloric acid was purchased from El-Nasr Pharmaceuticals (Cairo, Egypt), dapoxetine HCl and transparent hard gelatin capsule shells size (0) were supplied by Center of Applied Research and Advanced Studies, faculty of pharmacy, Cairo university.

2.2. Preparation of ternary inclusion complexes

Equimolar mixtures of avanafil and β-CD were used to prepare 25 ternary avanafil-β-CD-polymer inclusion complexes using five different polymers; PEG 4000, PVP K-30, chitosan, HPMC and HEC, each in five different concentrations; 1, 3, 5, 7 and 10% (w/w) (Table 1). Solvent evaporation technique was adopted for preparation of the inclusion complexes where solutions of 1.6 mM concentration of each of avanafil and β-CD were prepared with different (w/w) concentrations of polymers in 60% v/v methyl alcohol, and the combined drug-β-CD-polymer solutions were evaporated at 80 °C under vacuum in rotavap (Laborota 4000 efficient; Heidolph, USA) (Soliman et al., 2016). Binary drug-β-CD complex and drug-polymer solid dispersions were prepared as control formulas.

2.3. Drug content

An accurately weighed amount of each of the prepared formulas (equivalent to 5 mg avanafil) was dissolved in 100 mL 50% (v/v) ethanol and filtered through a 0.45-μm membrane filter. The drug content was determined spectrophotometrically at a λ_{max} of 311 nm (UV-1601 PC; Shimadzu, Japan). Two sided *t-test* was used to investigate whether there were significant differences between the average drug contents and the hypothetical value.

2.4. Solubility determination

Excess amount of each of the prepared formulas was mechanically shaken in 10 mL distilled water for 24 h at room temperature (SW-20C; Tulabo, USA). The supernatant was filtered through a 0.45-μm membrane filter prior to dilution with equal volume of ethanol. Drug solubility was determined spectrophotometrically at a λ_{max} of 311 nm. Two sided *t-test* was used to compare avanafil solubility of each formula with that of the binary avanafil-β-CD complex. Phase-solubility graphs were plotted to show the effect of polymers concentration on avanafil solubility.

2.5. Phase-solubility study

The study was carried out based on the method proposed by Higuchi and Connors (1965). The study involved preparation of 1.6 mM solutions of avanafil in 60% (v/v) methanol in addition to increasing concentrations of β-CD (0, 0.4, 0.8, 1.2 and 1.6 mM). The study was performed in absence and in presence of 195 mg PVP K-30. The mixtures were dried in rotavap and the products were examined for avanafil solubility as described above. The study was done in replicates and the molar solubility of avanafil was plotted versus molar concentration of β-CD. Assuming 1:1 complex formation, the stability constant ($K_{s(1:1)}$) and the complexation

Table 1
Compositions of ternary avanafil-β-cyclodextrin-polymer inclusion complexes and their solubility values.

Formula	Type of polymer	Polymer concentration (% w/w)	Mean solubility μg/mL (±SD, n = 2)
1A	Polyethylene glycol 4000	1	16.35 ± 0.03
3A	Polyethylene glycol 4000	3	16.57 ± 0.26
5A	Polyethylene glycol 4000	5	20.48 ± 0.14
7A	Polyethylene glycol 4000	7	22.01 ± 0.60
10A	Polyethylene glycol 4000	10	10.00 ± 0.09
1B	Polyvinyl pyrrolidone K-30	1	20.45 ± 0.34
3B	Polyvinyl pyrrolidone K-30	3	23.71 ± 0.09
5B	Polyvinyl pyrrolidone K-30	5	25.94 ± 0.54
7B	Polyvinyl pyrrolidone K-30	7	36.29 ± 0.88
10B	Polyvinyl pyrrolidone K-30	10	26.54 ± 0.94
1C	Chitosan	1	20.34 ± 0.57
3C	Chitosan	3	27.42 ± 0.57
5C	Chitosan	5	15.13 ± 0.06
7C	Chitosan	7	19.97 ± 0.26
10C	Chitosan	10	25.16 ± 0.11
1D	Hydroxypropylmethyl cellulose	1	28.58 ± 0.77
3D	Hydroxypropylmethyl cellulose	3	24.53 ± 0.68
5D	Hydroxypropylmethyl cellulose	5	21.36 ± 0.17
7D	Hydroxypropylmethyl cellulose	7	17.31 ± 0.37
10D	Hydroxypropylmethyl cellulose	10	32.72 ± 0.31
1E	Hydroxyethyl cellulose	1	26.79 ± 0.15
3E	Hydroxyethyl cellulose	3	25.61 ± 0.79
5E	Hydroxyethyl cellulose	5	26.20 ± 0.20
7E	Hydroxyethyl cellulose	7	21.33 ± 0.65
10E	Hydroxyethyl cellulose	10	25.64 ± 0.03