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TECHNIQUES IMPLEMENTED FOR SOLUBILITY AND DISSOLUTION RATE ENHANCEMENT OF KETOCONAZOLE: A REVIEW

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ABSTRACT

Ketoconazole is one of the most commonly used anti-fungal drug. Ketoconazole, is a member of imidazole containing compound that is used as a broad spectrum antifungal agent for the treatment or prevention of fungal infections especially against thrush, gastrointestinal (GI) infections, and infections of the skin, nails and scalp. Ketoconazole is available as oral tablet, cream and dandruff shampoo formulations. Ketoconazole has a high permeability and its solubility in aqueous media is not sufficient for the whole dose to be dissolved in the GI fluids under normal conditions. Formulation techniques that accelerate drug dissolution can guarantee a parallel improvement in bioavailability. Now a days different techniques are available to enhance the solubility of drug like co-solvent, solid dispersion, chemical modification of drug, liquid solid technique etc. One of the favourable strategy to improve the solubility and hence bioavailability of poorly water soluble drugs is the formulation of solid dispersion. The solid dispersion of ketoconazole were prepared by solvent evaporation method, melting method, melt solvent method, kneading method, co-grinding method, co-precipitation method, modified solvent evaporation method, spray drying, gel entrapment technique, and co-precipitation with supercritical fluid. This review article comprises of the research materialized in the field of solubility and dissolution rate enhancement of ketoconazole by solid dispersion.

INTRODUCTION

Ketoconazole is the member of imidazole class that is currently used in the treatment of systemic infections. Ketoconazole is classified in the Biopharmaceutics Classification Scheme (BCS) as a class II drug, since it has a high permeability and poor solubility. Ketoconazole is best absorbed at highly acidic levels, so antacids or other causes of decreased stomach acid levels will lower the drugs absorption. Absorption can be increased by taking it with an acidic beverage. It is very lipophilic and tends to accumulate in fatty tissues. Ketoconazole works principally by inhibiting the enzyme cytochrome P450 14-alpha-demethylase (P45014DM).

Many solubilization techniques have been described that either changes the nature of solvent environment (co-solvents systems, emulsions, micellization) or the chemical identity of the desired solute (salt formation, prodrugs); however, in comparison drugs into hydrophilic carriers is an alternate option for improving the drug bioavailability. Such dosage forms are referred to as solid dispersions [1,2].

A solid dispersion can be defined as "the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by a melting (fusion), solvent, or melting-solvent method. Aqueous solubility of any therapeutically active pharmaceutical ingredient is a vital property, which plays major role in dissolution, absorption, and bioavailability. To improve the dissolution and bioavailability of poorly water-soluble drugs, researchers have employed various techniques such as micronization, solubilisation, salt formation, complexation with polymers, changing in physical forms (amorphous), use of prodrugs and drug derivatization, pH alteration and addition of surfactants. Some studies used the solid-dispersion technique for dissolution enhancement of poorly water-soluble drugs. Among the various approaches, the solid-dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble, active pharmaceutical ingredients because it is simple, economical, and advantageous. . The half-life of ketoconazole is 3.3hrs. The drug shows low pH dependent solubility. It is practically insoluble in water, more soluble in methanol than ethanol. It is well soluble in DMSO. The melting point of Ketoconazole 146°C [1,3].

SOLUBILITY AND DISSOLUTION RATE ENHANCEMENT OF KETOCONAZOLE

It is well known that drug efficacy can be severely limited by poor aqueous solubility, leading to low dissolution rate and thus results in low absorption in the gastrointestinal tract after oral administration. The ability to increase aqueous solubility is thus a valuable aid to increase the efficacy for certain drugs [4].

Md. Sahabuddin Ansari et. al. 2014, formulated and evaluated solid dispersion of Ketoconazole with β-cyclodextrin and PEG-6000 by four different methods with an intention to improve its dissolution properties. Ketoconazole is prepared by nanocrystallization, solid dispersion, hydrotropy and Inclusion complex formation technique. In vitro release profile were evaluated and compared with standard ketoconazole. Solubility by the hydrotropy method was found to be 12.159 fold increases while by inclusion complex, solid dispersion, and crystallization method was found to be 9.644, 7.349, and 5.517 fold respectively. Dissolution profile of all four formulations (aqueous suspension) showed that the formulation prepared by the hydrotropy method has best release profile around 83.16%. Investigations of the properties of the dispersions were performed using release studies with analytical studies, Differential scanning calorimetery (DSC), and Fourier transform infrared (FTIR) [5].

Pankaj Kumar et al 2011, prepared solid dispersion of ketoconazole with Pluronic F-127 and PVP K-30 with an intention to improve its dissolution properties by melt-fusion method and solvent-evaporation method with different concentrations of Ketoconazole in the drug to carrier ratios 1:1, 1:2, 1:4, 1:6, and 1:8 respectively. Solid dispersions demonstrated a higher dissolution rate than physical mixtures and pure drug. On comparison the two formulations PVP K-30 has better dissolution rate and solubilising action on ketoconazole than third Pluronic F127 crystalline carrier with surface active property. Thus, the formulation of solid dispersions of a drug with hydrophilic carriers is a potential approach used to improve the solubility and dissolution rate of practically water-insoluble or less soluble drugs [1].

Aggarwal AK et al 2011, formulated solid dispersions of ketoconazole in ratios of 90 : 10, 70 : 30, 50 : 50, 30 : 70 and 10 : 90 by the melting method using nicotinamide as carrier to improve the solubility and dissolution rate of a poorly water-soluble drug ketoconazole. These solid dispersions were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (XRD) and Fourier transform infrared (FT-IR) spectroscopy to ascertain if there were any physicochemical interactions between drug and carrier that could affect dissolution. Solubility and dissolution studies were conducted with pure ketoconazole, physical mixtures and solid dispersions. Solubility studies indicated that nicotinamide increased significantly the solubility of ketoconazole in water. Solid state characterization indicated that there is no interaction between ketoconazole and nicotinamide in the solid state. In contrast to the very slow dissolution rate of pure ketoconazole, the dispersion of the drug in nicotinamide considerably enhanced the dissolution rate. The drug dissolution rate was highest at a drug-to-nicotinamide ratio of 10 : 90 (w/w) [6].

M.Najmuddin et al, 2010 prepared solid dispersions of ketoconazole with mannitol, polyethylene glycol (PEG) 4000 and polyethylene glycol 6000, polyvinyl pyrrolidone K-30, ß-cyclodextrin as carrier in different ratios by fusion, solvent evaporation, melt solvent and kneading method. Among these methods employed solvent evaporation method of preparing solid dispersions was found to be satisfactory as it produced good product with high drug content. Some of the dispersions prepared by the solvent evaporation method and kneading method were formulated into tablets containing ß-cyclodextrin (1:1 ratio of drug : ß-cyclodextrin) shows higher dissolution rate compared with other formulations. The increase in dissolution rate was in the order of ß-cyclodextrin > PEG-6000 > PEG-4000 > Mannitol > PVPK-30. The dissolution rate of such tablet formulations were found to release the drug at a faster rate than that of tablets prepared with drug alone [7].

Gehan Balata et al 2010, prepared inclusion complexes and solid dispersions of ketoconazole to improve its dissolution rate and its antifungal properties for the effective therapy of candidaiasis. The solvent evaporation method was used to prepare ketoconazole inclusion complexes in β-cyclodextrin with different molar ratios of drug to carrier (1: 1, 1: 2.5 and 1: 5). In addition, solid dispersions of ketoconazole in polyvinylpyrrolidone k-17 with different weight ratios of drug to carrier (1: 1, 1: 5 and 1: 10) were prepared. The dissolution of all the preparations was tested using the USP paddle method. The solubility and dissolution rates of ketoconazole were significantly increased by solid dispersions and cyclodextrin complexes as well as their physical mixtures. However, the dissolution enhancement of ketoconazole was dependent on the carriers used and the nature of presentation of ketoconazole in the carriers (physical mixture/solid dispersion/molecular inclusion). The ketoconazole-beta cyclodextrin inclusion complex at 1: 5 molar ratio showed the highest dissolution of all the preparations [8].

Taneri F et al 2010, formulated and evaluated complex to enhance the solubility, dissolution rate, and oral bioavailability of a very poorly water-soluble anti-fungal agent, ketoconazole (KET), by inclusion complexation with a highly-soluble cyclodextrin derivative, hydroxypropyl-beta cyclodextrin (HP-beta-CD). Two groups of tablets containing KET alone and KET:HP-beta-CD (1:2) kneaded product (KP) including magnesium stearate and lactopress (anhydrous and spray-dried) as an excipients were prepared by direct compression method. After the characterization studies, the in vitro dissolution studies of these tablets in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) were carried out. Tablets containing the cyclodextrin complex showed a higher in vitro dissolution rate and bioavailability compared to the tablets containing KET alone [9].

Suraj P. Agarwal et al 2008, studied for enhancement of the dissolution rate of ketoconazole through a novel complexation with fulvic acid extracted from shilajit. Complexes of fulvic acid with ketoconazole were prepared in a molar ratio of 1:0.5 and 1:1 by solvent evaporation, spray drying and physical mixing methods. The prepared complexes were characterized by differential scanning calorimetry (DSC) and X-ray diffractometry (XRD). Phase solubility and intrinsic dissolution rate study of ketoconazole with fulvic acid were carried out in phosphate buffer of pH 5 and 6 to study the interaction between ketoconazole with fulvic acid. Solvent evaporated and spray dried complexes showed significant improvement in dissolution rate as compared to ketoconazole or ketoconazole-fulvic acid physical mixture. The results indicated that the fulvic acid extracted from shilajit could be used to increase the dissolution rate and hence the bioavailability of poorly water-soluble drugs [10].

Table 1: Technique and polymers used for dissolution enhancement of ketoconazole

S. No.	Mechanism	Polymer	Reference
1.	Nanocrystallization, solid dispersion, hydrotropy and Inclusion complex formation technique.	β-cyclodextrin and PEG-6000	Md. Sahabuddin Ansari et. al. 2014,
2.	Melt-fusion method and solvent-evaporation.	Pluronic F-127 and PVP K-30.	Pankaj Kumar et al 2011
3.	Complexation	Nicotinamide.	Aggarwal AK et al 2011
4.	Solvent evaporation, melt solvent and kneading method.	PEG-4000 and 6000, polyvinyl pyrrolidone K-30,	M.Najmuddin et al, 2010
5.	Solvent evaporation method.	polyvinylpyrrolidone k-17	Gehan Balata et al 2010
6.	Complexation.	hydroxypropyl-beta cyclodextrin (HP-beta-CD).	Taneri F et al 2010
7.	Complexation	fulvic acid.	Suraj P. Agarwal et al 2008

CONCLUSION

For poorly water soluble drugs dissolution is a rate-limiting step in absorption. By improving solubility of a drug its dissolution rate can be enhanced. There is a great requirement to develop such a formulation which release drug to the required extent so that it can produce rapid and desired effect. As ketoconazole is a BCS class II drug it has low solubility but high permeability. Various methods were employed to enhance the solubility of the ketoconazole. Solid dispersion is a technique which enhances the solubility by using different polymers. Several polymers and combination may also be used to improve the solubility and dissolution rate enhancement of the ketoconazole.

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