Technical Report:
Improvement of Dissolution Properties of Ketoconazole Using a New Excipient (LoxOral™) in Comparison with Microcrystalline Cellulose

Abstract: Ketoconazole is an imidazole antifungal drug that can be administered orally and is characterized by low solubility-high permeability (class II by BCS). The capability of a new excipient, LoxOral, manufactured by PCCA, to enhance the dissolution of drugs with poor water solubility was investigated by USP dissolution testing and compared to microcrystalline cellulose (MCC). The capsules containing ketoconazole in LoxOral produced a higher in vitro dissolution when compared to corresponding mixture with MCC. It was also the only combination which complied with the USP dissolution specification for the drug (80.78% at 30 min). The results suggest that LoxOral, is a useful and powerful excipient tool to accelerate dissolution and potentially improve the oral bioavailability of drugs with poor water solubility.

Purpose:
The purpose of this study was to evaluate the potential of LoxOral to enhance the dissolution properties of ketoconazole and to evaluate its utility in comparison to MCC delivery systems.

Introduction:
Poor aqueous solubility of an active pharmaceutical ingredient (API) is one of the most pressing problems in pharmaceutical R&D, with as many as 90% of new API candidates in this category (Lobmann et al., 2013). Dissolution rate in the gastrointestinal tract is the rate limiting factor for the absorption of many of these drugs (Zimmermann et al., 2009), which may limit their bioavailability after oral administration (Holm et al., 2011).

In order to enhance the dissolution of poorly water-soluble drugs, an increasing number of pharmaceutical formulation technologies are being developed to address this drug development challenge (Uchiyama et al., 2013). Many pharmaceutical studies have focused their attention on the production of multifunctional excipients, once the choice of excipients becomes critical in terms of delivery system functionality and quality. Excipients with multiple functional properties confer many advantages such as manufacturing efficiency and reduced production costs (Builders et al., 2010).

Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as pulp from fibrous plant material, with mineral acids (Gohel et al., 2007). It is widely used as a filler, disintegrant and binder of oral tablets, pellets and capsules (Nikolakakis et al., 2006). MCC is considered one of the most useful fillers due to its excellent compatibility at low pressures, high dilution potential, chemical inertness and compatibility with most drugs (Kalita et al., 2013). However, according to Chamsai & Srimomnsak (2013), most drugs prepared with MCC show a tendency toward prolonged release due to a lack of disintegration.

LoxOoral, manufactured by PCCA, is an innovative excipient for use in capsule formulations. It improves dissolution of all types of APIs, including drugs with poor water solubility. It is gluten- and casein-free, Sodium Lauryl Sulfate (SLS)-free, lactose-free, soy-free, dye-free and magnesium stearate-free. It also contains an ingredient (isomalt) which has shown potential prebiotic effects (Gibson et al., 2010). LoxOoral is an all-in-one base with improved dissolution, excellent flowability and reduced static. It is minimally hygroscopic, resisting moisture absorption and providing optimal stability.

Ketoconazole, an imidazole antifungal agent, is administered both orally and topically. It is known to be orally active in the treatment of systemic blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, paracoccidioidomycosis, and tinea of skin and nails (Van den Mooter et al., 2001). According to the Biopharmaceutic Drug Classification System (BCS) proposed by Amidon et al. (1995), ketoconazole is a class II drug, characterized by low solubility—high permeability. It is difficult to dissolve in water, and gastrointestinal fluids under normal conditions (Van den Mooter et al., 2001). Furthermore, ketoconazole exhibits solubility which is strongly pH dependent (Dressman & Reppas, 2000). It has been reported that poor water solubility can cause problems with drug release and bioavailability in various pharmaceutical forms and there have been numerous efforts to resolve this issue (Balata et al., 2010).

Methodology:
Materials: Ketoconazole (lot number C150885) was obtained from PCCA (Houston, TX, USA), as well as the excipients LoxOoral and MCC.

Methods: Dissolution studies of the capsule dosage form containing ketoconazole were performed using a USP Apparatus 2 (rotating paddle method) (Distek Symphony 7100, North Brunswick, NJ), according to the USP monograph of the drug (US Pharmacopeia, 2000). The test was conducted on 12 capsules (6 capsules LoxOoral and 6 capsules MCC). An accurately weighed amount of ketoconazole (400 mg) plus LoxOoral (108.9 mg), or the excipient MCC (80 mg), were placed in gelatin capsules. Each capsule was then placed in a dissolution media containing 900 mL of 0.1 N HCl (pH 1.2). The paddle rotation speed was kept at 50 rpm and the dissolution medium maintained at 37°C. In all experiments, samples (5 mL) were withdrawn at 10, 20, and 30 minutes and replaced by 5 mL of fresh pre-warmed 0.1 N HCl (pH 1.2). Samples were then filtered with an Acrodisc® syringe - 0.45 µm HT Tuffryn membrane - diluted with the same medium and ketoconazole content analyzed using UV spectrophotometry (IMPLEN NanoPhotometer 300) at 270 nm. The cumulative percentage of the API released from the preparations was calculated using calibration equations.
Results and Discussion:
In Figure 1, dissolution profiles of ketoconazole, obtained from in vitro tests with two different excipients, are shown. The dissolution rate was higher for the system containing ketoconazole and LoxOral when compared to the dispersion system containing ketoconazole and MCC. The dissolution specification for ketoconazole has been stated in the USP as not less than 80% of the labeled amount of the drug within 30 min in 0.1N HCl (pH 1.2). Only the LoxOral formulation complied with the USP dissolution specification. The dissolved amount of drug at 30 min was 80.78%.

The increased drug release from the LoxOral formulation possibly resulted from a partial dissolution of the drug in the excipient, solubilization effects of LoxOral, and improved wettability in dissolution media because of the excipient’s amphiphilic character.

![Ketoconazole](image1)

**Figure 1.** Dissolution profiles of ketoconazole from capsules containing different excipients, LoxOral and microcrystalline cellulose (MCC).

Conclusions:
LoxOral was shown to be a successful excipient to improve the dissolution rate of ketoconazole. The increase in rate would potentially provide rapid bioavailability and onset of action after the drug is taken orally. LoxOral-based formulations have proven to be a most promising delivery system for oral bioavailability enhancement of BCS Class II drugs such as ketoconazole.

Financial Disclosure:
PCCA is the full sponsor of the study.

References:


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