

Technical Report:

Effect of LoxOral[®] and Lactose on *In Vitro* Dissolution Studies of Progesterone Sustained Release Capsules



Abstract:

Progesterone is a hormonal steroid used as a lipophilic drug model for evaluation of the effect of two different excipients, LoxOral and lactose monohydrate, on *in vitro* sustained release drug from pharmaceutical compounded oral capsules. The study was performed over time by monitoring the percentage of progesterone dissolved in simulated gastro-intestinal fluids (SGIF), employing the USP dissolution apparatus 2. In such fluid, the amount of progesterone dissolved increased rapidly up to 480 min from both oral drug delivery systems, although the dissolution rate profiles were statistically similar. The satisfactory and comparable dissolution performances of both progesterone capsule formulations confirm the interchangeability between the two excipients. Nevertheless, the versatile oral base, LoxOral, has advantages over traditional lactose since the compounding process of progesterone formulations becomes easier due to its excellent flowability, reduced static and minimum hygroscopicity.

Introduction:

In vitro drug release and dissolution testing play an important role in pharmaceutical formulation development and quality control. Poorly soluble candidate molecules constitute a major challenge for the formulation development since the insufficient solubility causes problems for *in vitro* and *in vivo* assays, with consequent increased risk of attrition and costs (Di *et al.*, 2012), besides low solubility and low dissolution rate often lead to poor bioavailability (Sarnes *et al.*, 2013). The trend in the pharmaceutical industry is to produce more and more compounds that exhibit high lipophilicity and poor water solubility, categorizing into Biopharmaceutical Classification System (BCS) classes II and IV (Vogt *et al.*, 2008).

Progesterone is a naturally occurring steroid hormone used in the treatment of endometrial hyperplasia and secondary amenorrhea in postmenopausal women as part of a hormone replacement therapy. The drug, a BCS class II compound, suffers from poor aqueous solubility due to its highly lipophilic structure (cLog P 4.0) (Miller, 2009). Its oral absorption can be significantly improved by the physical characteristics of the progesterone and the vehicle used in the dosage form. Progesterone for oral administration has been delivered in a micronized form in order to improve the dissolution rate and oral absorption (Hargrove *et al.*, 1989).

A variety of strategies have been adopted to increase the aqueous solubility of lipophilic drugs which include the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrin, nanoparticle and solid dispersions (Saxena *et al.*, 2013). Recent studies have approached the use of amphiphilic excipients as both drug delivery systems and solubilization agents to improve the aqueous solubility of many of these drugs (McCrary *et al.*, 2013).

Following the trend of the need for a new generation of versatile excipients as oral drug delivery system to enable increased bioavailability of most drug candidates (Lipp, 2013), PCCA developed LoxOral. This innovative multifunctional excipient for capsule formulations allows enhanced dissolution rate of all types of active pharmaceutical ingredients (APIs), aggregating excellent physical and chemical stability. LoxOral composition, that confers amphiphilic character to the excipient, consists of: isomalt, glyceryl behenate, poloxamer and sodium stearyl fumarate.

The focus of the present research was to investigate the effect of two different excipients, LoxOral and lactose monohydrate, on the progesterone sustained release from capsules through *in vitro* dissolution rate studies in simulated gastro-intestinal fluids (SGIF). Progesterone was selected as a model of a lipophilic drug with poor aqueous solubility and dissolution rate, being an ideal candidate for study of solubility enhancement by using LoxOral as an excipient. Lactose monohydrate is one of the most commonly used fillers although it provides poor powder flowability and is shown to interact negatively with various drug actives (Ferreira, 2008). Methocel (hypromellose) is one of the most widely used mean of providing prolonged release of API in a solid oral dosage form due to form a hydrophilic matrix system (Novak *et al.*, 2012).

Methodology:

Materials: Special Micronized Progesterone (lot number C152389) was obtained from PCCA (Houston, TX, USA), as well as the excipients Methocel[®] E4M Premium CR (hypromellose USP, lot number C155691), LoxOral (lot number 1309189) and Lactose Monohydrate (lot number C156659).

Methods: The study of the progesterone sustained release from gelatin capsules was performed *in vitro* in the SGIF employing the USP Apparatus 2 (rotating paddle method) (Distek Symphony 7100, North Brunswick, NJ), according to the protocol described by Hamoudi *et al.* (2011) with minor modifications. The following formulations composed of 100 mg of progesterone were tested in duplicate: progesterone in LoxOral/Methocel E4M capsules and progesterone in lactose monohydrate/Methocel E4M capsules. Each capsule was introduced into 500 mL of simulated gastric fluid (SGF) without pepsin pH 1.2, at 37°C under stirring at a speed of 55 rpm. After 60 min, 500 mL of pre-warmed simulated intestinal fluid (SIF) without enzyme pH 6.8 were added. For each formulation, samples of 6 mL were withdrawn at different times of incubation over 24 h (30, 60, 90, 240, 480, 720 and 1440 min) and were immediately filtered through an Acrodisc[®] syringe - 0.45 µm HT Tuffryn membrane. An equal volume of fresh pre-warmed SGF (first time-point) or SGIF at 37°C was then replaced to maintain a constant volume. The progesterone was assayed directly in the filtered samples, without dilution, by HPLC (detection wavelength = 242 nm). The cumulative percentage of the API released was calculated.

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Results and Discussion:

The effect of LoxOral and lactose monohydrate as excipients on the *in vitro* dissolution of progesterone from capsules is shown in Figure 1. The progesterone was released sustainably and only the amount dissolved in SGIF was quantified.

Comparing the amount dissolved of progesterone from both capsule formulations, there was not much difference caused by LoxOral and lactose monohydrate as excipients on the drug release and solubilization. The dissolution rate was statistically similar for both delivery systems and influenced by the dissolution time, but not by the type of medium (SGF and SGIF). The proportion of progesterone dissolved from capsules increased rapidly up to 480 min (8 h), achieving the maximum of 9.83% (LoxOral formulation) and 9.55% (lactose monohydrate formulation) in 1440 min (24 h).

These cumulative progesterone releases in SGIF at the end of 24 h from PCCA formulations were similar to approximately 10% progesterone release from PROMETRIUM[®] oral capsules (100 mg progesterone in peanut oil, Abbott Inc.) (Liu *et al.*, 2010)

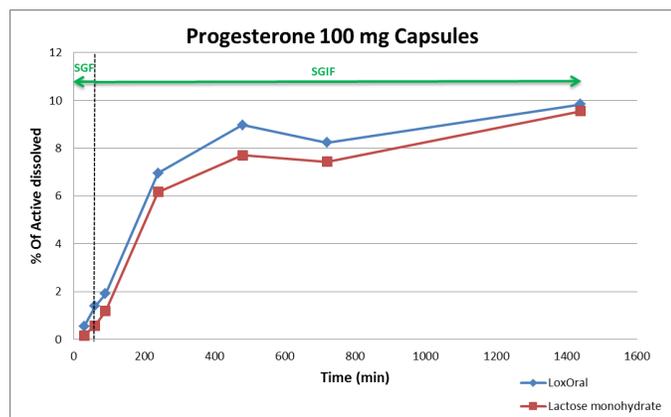


Figure 1. Percentage of progesterone dissolved obtained from capsules containing different excipients, LoxOral and lactose monohydrate, combined with Methocel E4M. Formulations were incubated 60 min in SGF (simulated gastric fluid) before addition of SIF (simulated intestinal fluid) to give the final SGIF (simulated gastro-intestinal fluid).

Conclusions:

LoxOral and lactose monohydrate oral delivery systems showed similar *in vitro* sustained progesterone release profile from capsules. Based on the satisfactory and comparable dissolution performances of both progesterone capsule formulations, there is a great potential of interchangeability between LoxOral and lactose monohydrate as excipients of sustained release progesterone capsules. However, PCCA's new oral base, LoxOral, confers advantages in the process of compounding progesterone formulations in comparison with the traditional lactose, since it is a base with enhanced quality attributes such as, excellent flowability, reduced static and minimum hygroscopicity.

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