



# A Comparison of the Bioaccessibility of Micronized and Milled Progesterone in an In Vitro Model of the Gastrointestinal System

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## Purpose

The purpose of this study was to determine the bioaccessibility (estimated bioavailability) and dissolution profile of compounded oral special micronized progesterone when compared to compounded oral milled (non-micronized) progesterone in a simulated in vitro model of the human upper gastrointestinal (GI) tract.

## Introduction

Hormonal replacement therapy (HRT) has been used extensively to treat the symptoms caused by decreased estrogen production following menopause (Ryan & Rosner, 2001). Estrogen therapy is frequently used in HRT and its pro-proliferative effects on the endometrium are counterbalanced by the use of progesterone, which is known to modulate the growth-stimulatory effects of estrogen (Yang *et al.*, 2011). Results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial recommend that oral micronized progesterone be the first choice for estradiol opposing therapy in postmenopausal women (Miller *et al.*, 1995; Barret-Connor *et al.*, 1997).

Progesterone is a drug with poor aqueous solubility and therefore has a limited dissolution rate. It can have its absorption and bioavailability significantly altered depending on the physical characteristics of the drug and the vehicle used for oral administration (Hargrove *et al.*, 1989). Several reports have demonstrated that micronization of progesterone facilitates aqueous dissolution in the small intestine (Bolaji *et al.*, 1993), and that the absorption and serum concentration of progesterone are enhanced by micronization (Hargrove *et al.*, 1989). Special micronized progesterone has a smaller particle size than milled (non-micronized) progesterone.

## Methods

Particle size distribution testing of both special micronized and milled (non-micronized) progesterone was performed by using laser light scattering method. The mean particle size distribution was determined using laser diffraction volume-based calculations. The bioaccessibility of the different forms of progesterone was examined using the dynamic, multi-compartmental in vitro TIM-1 gastrointestinal model (TNO, Zeist, The Netherlands), which simulates the gastrointestinal (GI) tract from the stomach to the small intestine (Figure 1) with dynamic conditions of healthy human adults in a fasting state with normal gastric and intestinal secretions. The analysis was performed in duplicate (n=2) at 37°C, as described previously (Dickson *et al.*, 2012). A 100 mg capsule of special micronized progesterone and a 100 mg capsule of milled (non-micronized) progesterone were added to the TIM-1 system per run. Both capsule formulations contained Methocel E4M to create the prolonged release rate and LoxOral as the excipient base. Samples were collected from the jejunum and the ileum at 60, 120, 180, 240 and 300 min using a semipermeable Spectrum membrane filtration unit with a cut-off of 0.05 µm. The ileum effluent samples collected hourly (5 samples/run) and residues remaining in each compartment were also collected and dissolved 1:1 with ethanol.

Progesterone concentrations in each sample were measured using LC MS and the total amount of progesterone recovered from each compartment was calculated with correction for recovery. Release from special micronized progesterone capsule into a simulated gastrointestinal fluid (SGIF) model was determined in a USP Apparatus 2, operating at 55 rpm and 37°C. Cumulative amount of progesterone released over a 24 h period was assayed directly using HPLC at 242 nm.

## Results and Discussion

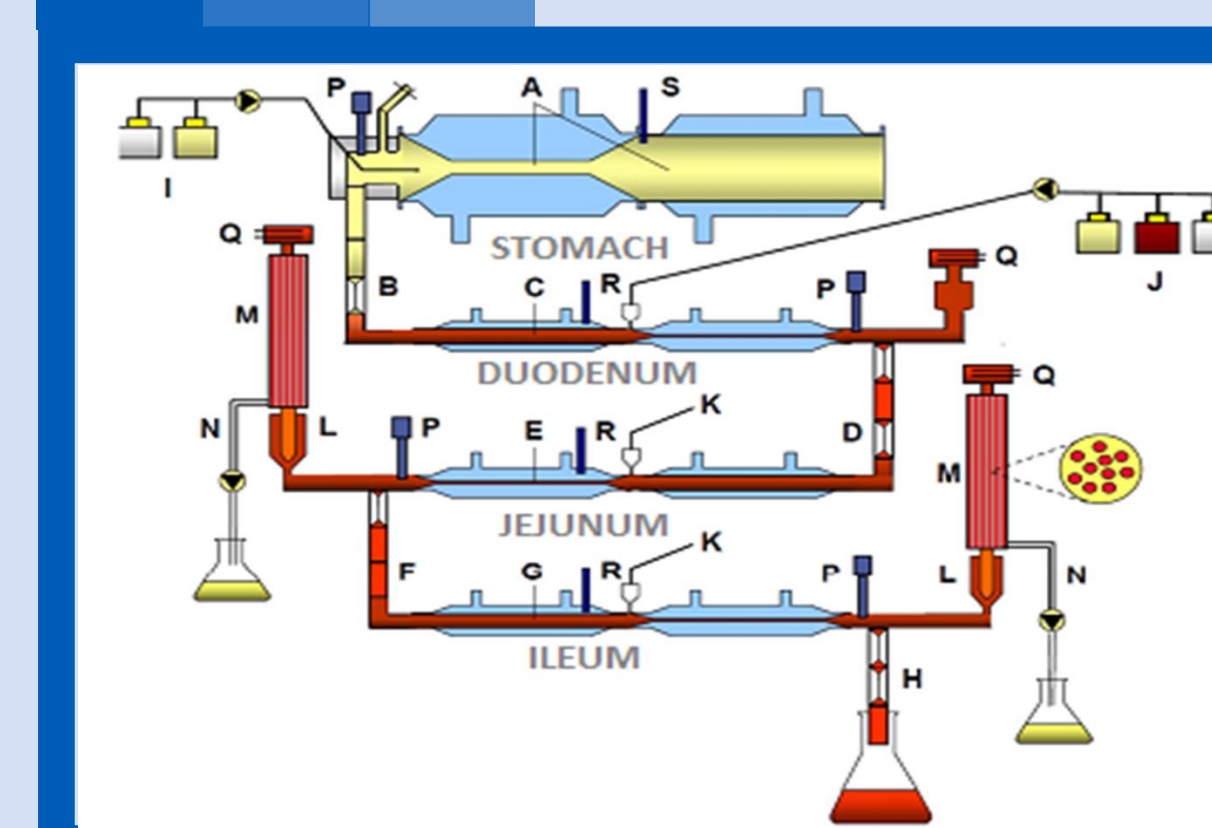
The mean particle size of special micronized progesterone was considerably smaller (5.38 µm) than that of milled (non-micronized) progesterone (92.31 µm). The overall bioaccessibility of special micronized progesterone (21.8%) was substantially higher than that of milled (non-micronized) progesterone (1.9%) (Figure 2), while the total amount of progesterone residue was higher for milled (non-micronized) progesterone (86.7%) than for special micronized progesterone (72.1%) (Figure 3). As bioaccessibility can be used to estimate the bioavailability of a drug, this data suggests that special micronized progesterone has a greater bioavailability, and therefore a greater potential for efficacy, than milled (non-micronized) progesterone.

The dissolution profile of special micronized progesterone in a sustained release formulation containing LoxOral, exhibited rapid increase up to 480 min and achieved a maximum dissolution of 9.83% at 1440 minutes (Figure 4), which is similar to the approximately 10% progesterone released from Prometrium® 100 mg capsules (Liu *et al.*, 2010), the only currently FDA approved bioidential progesterone for prevention of endometrial hyperplasia in postmenopausal women.

## Conclusion

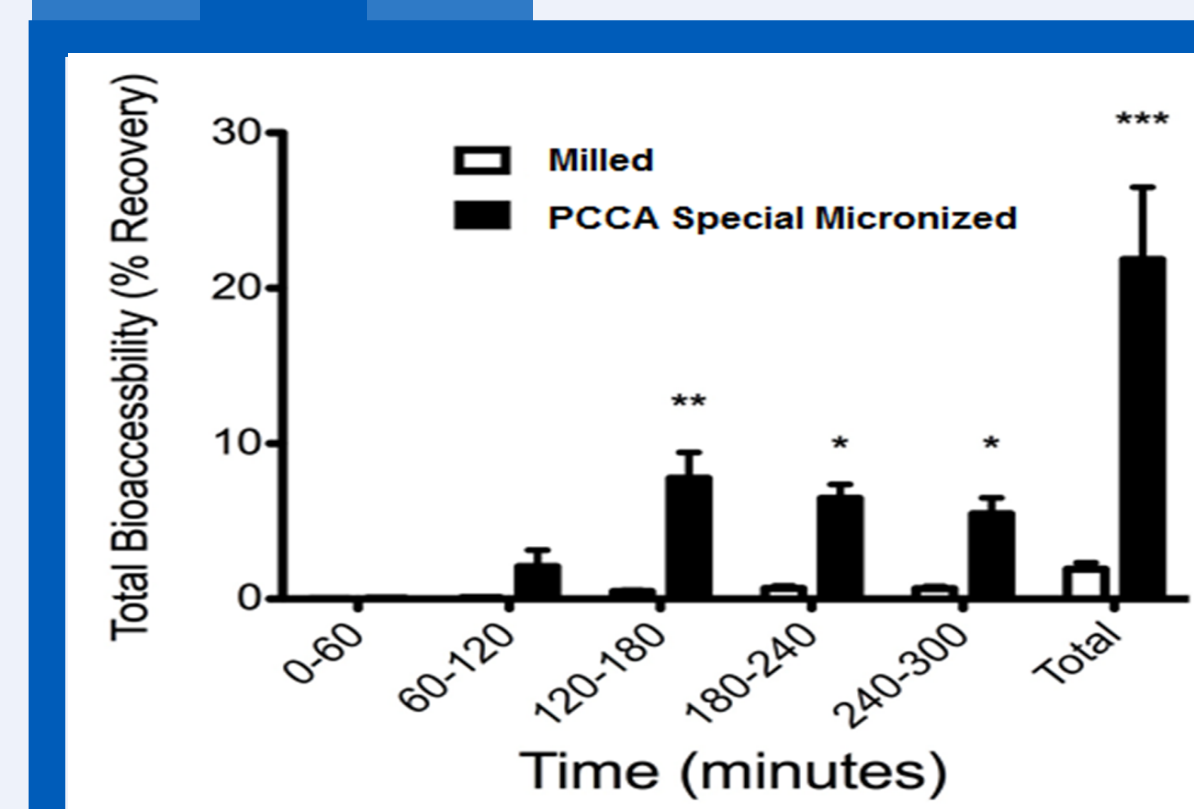
This study provides the first assessment of progesterone bioaccessibility (estimated bioavailability) from a compounded formulation using the dynamic gastrointestinal TIM-1 system. Oral compounded special micronized progesterone using Methocel E4M to create the prolonged release rate and LoxOral as the excipient showed an enhanced bioaccessibility profile determined by TIM-1 system, in addition to a similar dissolution profile to that of Prometrium 100 mg capsules, suggesting that it is a valuable option for hormone replacement therapy (HRT).

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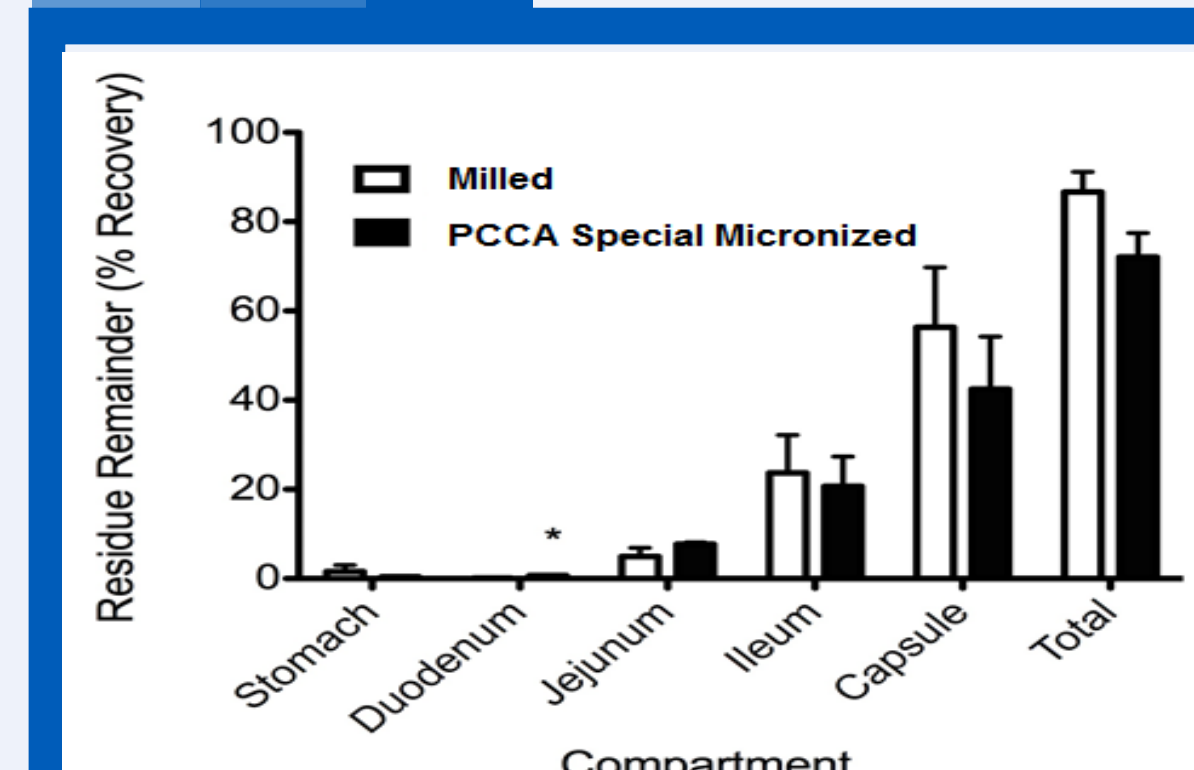
... Schematic diagram of the dynamic, multi-compartmental model of the stomach and small intestine (TIM-1): A. stomach compartment; B. pyloric sphincter; C. duodenum compartment; D. peristaltic valve; E. jejunum compartment; F. peristaltic valve; G. ileum compartment; H. ileo-caecal sphincter; I. stomach electrolytes, HCl and enzyme secretion; J. bile, pancreatic juice and bicarbonate secretion; K. jejunum/ileum electrolyte secretion; L. pre-filter; M. hollow fibre membrane; N. filtrate pump; P. pH electrodes; Q. level sensor; R. temperature sensor; S. pressure sensor.

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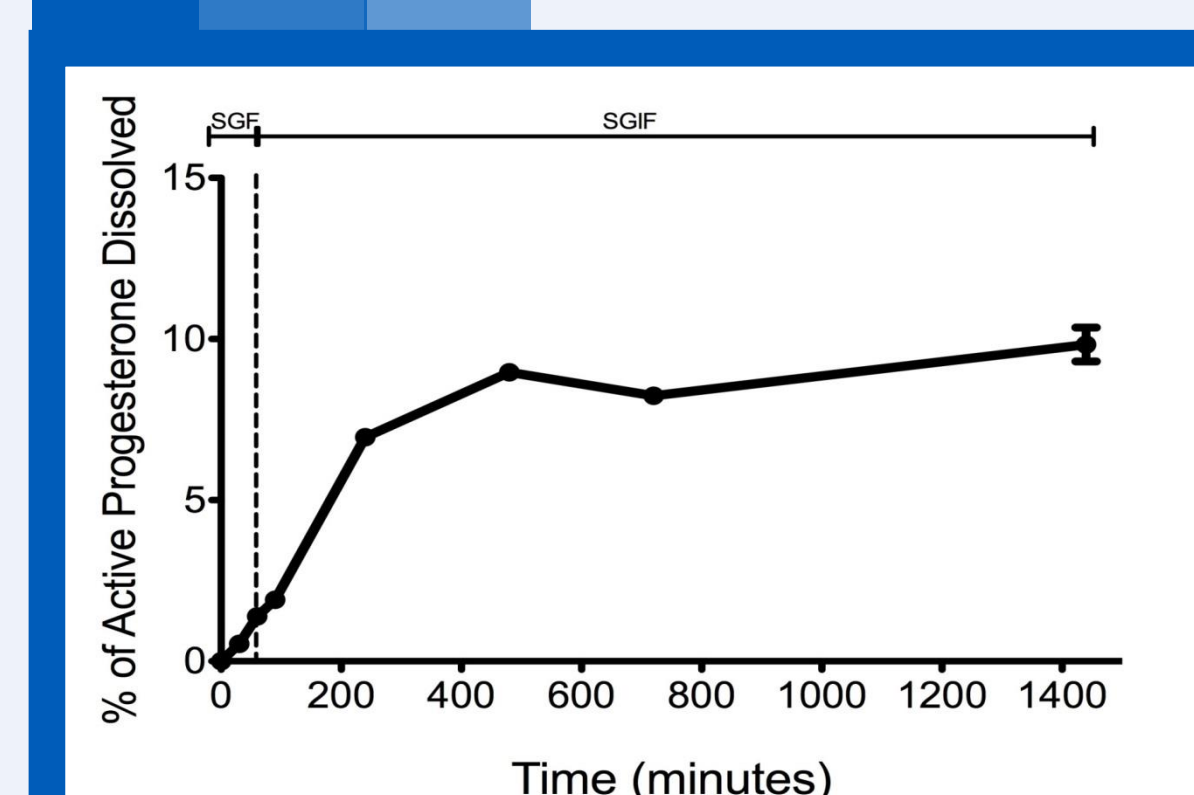
... Overall bioaccessibility (jejunum + ileum) of oral special micronized progesterone and oral milled (non-micronized) progesterone over time in the TIM-1 simulated GI tract model system. Each of the 100 mg SR progesterone capsules were subjected to the stomach (60 min), the duodenum (10 min), the jejunum (80 min) and the ileum (150 min) compartments. Samples were withdrawn every 60 min until 5 h and were assayed for progesterone concentration. Mean ± SD. \*\*\* P < 0.001; \*\* P < 0.01; \* P < 0.05.

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... Special micronized progesterone residue and milled (non-micronized) progesterone residue present in specific compartments of the TIM-1 simulated GI tract system after completed TIM-1 run. Residues from each compartment were collected separately upon completion of each TIM-1 run. Mean ± SD. \* P < 0.05.

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... Dissolution profile of special micronized oral progesterone following incubation for up to 1440 min in SGF and SGIF. Results are displayed as mean ± SD.



For the complete studies along with the references listed hereby, please refer to :  
<http://www.pccarx.com/about-pcca/pcca-studies/studies>

