Title: Development and *In Vitro*/*In Vivo* Evaluation of Zn-pectinate Microparticles Reinforced with Chitosan for the Colonic Delivery of Progesterone

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Source: *Drug Delivery, 23 (7), 2541-2554 (2015), DOI: 10.3109/10717544.2015.1028602, http://dx.doi.org/10.3109/10717544.2015.1028602*

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The colon is a promising target for drug delivery owing to its long transit time of up to 78 h, which is likely to increase the time available for drug absorption. Progesterone has a short elimination half-life and undergoes extensive first-pass metabolism, which results in very low oral bioavailability (~ 25%). To overcome these shortcomings, we developed an oral multiparticulate system for the colonic delivery of progesterone. Zn-pectinate/chitosan microparticles were prepared by ionotropic gelation and characterized for their size, shape, weight, drug entrapment efficiency, mucoadhesion and swelling behavior. The effect of cross-linking pH, cross-linking time and chitosan concentration on progesterone release were also studied. Spherical microparticles having a diameter of 580-720 μm were obtained. Drug entrapment efficiency of ~75-100% was obtained depending on the microparticle composition. Microparticle mucoadhesive properties were dependent on the pectin concentration, as well as the cross-linking pH. Progesterone release in simulated gastric fluids was minimal (3–9%),

followed by burst release at pH 6.8 and a sustained phase at pH 7.4. The in vivo study revealed that the microparticles significantly increased progesterone residence time in the plasma and increased its relative bioavailability to ~168%, compared to the drug alone. This study confirms the potential of Zn-pectinate/chitosan microparticles as a colon-specific drug delivery system able to enhance the oral bioavailability of progesterone or similar drugs.