

Title: Thermosensitive Bioadhesive Gels for the Vaginal Delivery of Sildenafil Citrate: *In Vitro* Characterization and Clinical Evaluation in Women Using Clomiphene Citrate for Induction of Ovulation

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Objective: *The objective of this study is to develop and characterize in situ thermosensitive gels for the vaginal administration of sildenafil as a potential treatment of endometrial thinning occurring as a result of using clomiphene citrate for ovulation induction in women with type II eugonadotrophic anovulation. While sildenafil has shown promising results in the treatment of infertility in women, the lack of vaginal pharmaceutical preparation and the side effects associated with oral sildenafil limit its clinical effectiveness.*

Methods: *Sildenafil citrate in situ forming gels were prepared using different grades of Pluronic[®] (PF-68 and PF-127). Mucoadhesive polymers as sodium*

alginate and hydroxyethyl cellulose were added to the gels in different concentrations and the effect on gel properties was studied. The formulations were evaluated in terms of viscosity, gelation temperature (Tsol-gel), mucoadhesion properties, and in vitro drug release characteristics. Selected formulations were evaluated in women with clomiphene citrate failure due to thin endometrium (Clinicaltrial.gov identifier NCT02766725).

Results: The T_{sol}-gel decreased with increasing PF-127 concentration and it was modulated by addition of PF-68 to be within the acceptable range of 28–37 °C. Increasing Pluronic[®] concentration increased gel viscosity and mucoadhesive force but decreased drug release rate. Clinical results showed that the in situ sildenafil vaginal gel significantly increased endometrial thickness and uterine blood flow with no reported side effects. Further, these results were achieved at lower frequency and duration of drug administration.

Conclusion: Sildenafil thermosensitive vaginal gels might result in improved potential of pregnancy in anovulatory patients with clomiphene citrate failure due to thin endometrium.

Keywords

Sildenafil; Pluronic; thermosensitive gel; clomiphene failure; thin endometrium; ovulation induction.