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# Dual-responsive lidocaine *in situ* gel reduces pain of intrauterine device insertion

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Potassium hydroxide (Pubchem CID: 14797)
HCl (Pubchem CID: 313)
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ABSTRACT

The most effective and safe contraceptive method, intrauterine devices (IUDs), is still underutilized due to the pain barrier during IUD insertion. Lidocaine, a well-known local anesthetic, can be used to relieve IUD insertion pain. This study aimed at formulation, *in vitro*, *in vivo* and clinical evaluation of a novel lidocaine dual-responsive *in situ* gel. Pluronic and Gelrite® were used as thermosenstive and ion-activated polymers, respectively. *In situ* gels containing 2% lidocaine, pluronics and/or Gelrite® were prepared. The optimized dual-responsive formula ($F_5$) was clear, with 95% drug content, free flowing at room temperature and gel at vaginal temperature ($T_{gel}$ of 28 °C). This optimized dual-responsive *in situ* gel was found to be superior to single-responsive one due to presence of Gelrite®, imparting resistance to dilution effect of simulated vaginal fluids. DSC thermograms revealed no interaction between formulation components. Biocompatibility study showed no degeneration, necrosis or inflammation. Optimized dual-responsive *in situ* gel was further evaluated for pain reduction efficiency via a pilot randomized, double-blinded, placebo-controlled clinical trial showing ease of self-administeration by patients and significant pain reduction induced at all steps of IUD insertion. In conclusion, lidocaine dual-responsive *in situ* gel can be effectively used in prevention of pain during IUD insertion.

## 1. Introduction

Intrauterine devices (IUDs) are highly effective and safe long-acting reversible contraceptive method (Peipert et al., 2011). Once inserted, IUDs have a low rate of discontinuation, however, they are underutilized worldwide with only 14.3% of total contraception use (Kulier et al., 2007; O'Brien et al., 2008; Peipert et al., 2011; Suhonen et al., 2004). One of the reasons of their underutilization is the discomfort and pain associated with IUD insertion steps of speculum insertion, tenaculum application, manipulation of the cervix and passage of IUD through the endocervical canal (Lopez et al., 2015; McNicholas et al., 2012; Weston et al., xxxx). Moreover, the fear of encountered pain is itself an obstacle, making IUDs unpopular as a contraception method (Lopez et al., 2015).

The main strategy reported for relieving the pain and discomfort of IUD insertion is the use of local anesthetics (Lopez et al., 2015). Nonsteroidal anti-inflammatory drugs and cervical ripening agents such as misoprostol have also been used for the same purpose, but were found to be of minor efficacy (Lopez et al., 2015). Among local anesthetics, lidocaine has been frequently investigated, mostly due to its favorable pharmacokinetic properties of rapid onset and intermediate duration of action (Ogle and Mahjoubi, 2012). For controlling IUD insertion pain, lidocaine was studied in the form of EMLA cream, gel, 4% viscous solution and 10% spray (Abbas et al., 2017; Aksoy et al., 2016; Tavakolian et al., 2015; Tornblom-Paulander et al., 2015). However, for many of these preparations, some limitations and non-significant reduction in pain score was reported (Lopez et al., 2015; McNicholas et al., 2012; Rapkin et al., 2016). The 10% spray, which is designed to be effective and easily applied but still non self-administered, was not thoroughly studied, as pain was only measured at certain steps of IUD insertion. Additionally, the study lacked any pain measurement after the completion of IUD insertion (Aksoy et al., 2016). For the 4% viscous

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solution, although effective pain reduction was achieved, discomfort was reported with 40% of women during the application (Tornblom-Paulander et al., 2015). Finally, while lidocaine gel (2%) was self-administered to the participants, it had no significant pain reduction during IUD insertion. Surprisingly, there was no sufficient pharmaceutical information about this 2% self-administered gel preventing us from relating the clinical result with the dosage form design (Rapkin et al., 2016). Accordingly, many literatures are calling for further investigation of lidocaine topical formulations (Allen et al., xxxx; Grimes et al., xxxx).

Attempting to solve this problem, we propose the use of novel lidocaine *in situ* hydrogel to relieve IUD insertion pain. These *in situ* hydrogels are stimuli-sensitive hydrogels that are free flowing aqueous solutions and rapidly transform into gels triggered by physical stimuli (e.g. temperature, light, electrical field and magnetic field) or chemical stimuli (e.g. pH and ions). Unlike conventional gels, presence of the preparation in the liquid form offers two main advantages. First, ease of vaginal application, allowing self-administration of the preparation. Second, the liquid spreads quickly, efficiently coating the entire surface of the vaginal tissue (Chang et al., 2002; Mauck et al., xxxx). Subsequent transformation of the liquid into a viscous gel on the mucosal tissue increases its residence time and adhesion, contributing to efficacy of the preparation (Ibrahim el et al., 2012).

In this study, self-administered lidocaine dual-responsive *in situ* gel was developed, characterized and tested. Combining two different stimuli-sensitive polymers in one system enhances the *sol-to-gel* transition and the overall responsiveness of the system (Qiu and Park, 2001). The two polymers are Pluronic and Gelrite®, responding to alteration in temperature and ionic strength, respectively. Different formulations containing lidocaine hydrochloride were prepared by varying the weight ratios of pluronic and Gelrite®. Prepared formulations were evaluated for their physical properties, safety and clinical efficacy.

## 2. Material and methods

### 2.1. Material

Lidocaine HCl was obtained as a gift from MUP Co. (Cairo, Egypt). Pluronic F-127 (PF-127), Pluronic F-68 (PF-68) and benzalkonium chloride were obtained from Sigma Chem. Co. (MO, USA). Gelrite® (gellan gum) was obtained from Kelco division of the Merck Sharp and Dohme (NJ, USA). Sodium chloride, calcium hydroxide, potassium hydroxide, glucose, urea, lactic acid and acetic acid were obtained from ADWIC, El-nasr Chemical Co. (Cairo, Egypt). Glycerol and hydrochloric acid were purchased from Alpha Chemicals Co. (Cairo, Egypt).

### 2.2. Preparation of lidocaine HCl dual-responsive in situ gel

A clear homogenous solution of PF-127 and PF-68 was obtained according to cold method (Schmolka, 1972). Gelrite® at different concentrations was dispersed in one third of the total amount of water of the preparation. The dispersions were heated to 95 °C ± 5 for 20 min while stirring, and then allowed to cool at room temperature (RT) during stirring. The pluronic/Gelrite® solution was prepared by dispersing the required amount of Gelrite® solution in the desired concentration of pluronics while stirring. Finally, Lidocaine HCl 2% was added to the preparation. All solutions were prepared on weight basis. The composition of the different formulations is shown in Table 1.

### 2.3. Determination of clarity and drug content

The clarity of the formulations was determined visually. Drug content was measured for the different formulations, in their liquid form, where a certain volume of the formulation was diluted to 100 mL with distilled water. The lidocaine HCl absorbance was measured using at 263 nm against blank prepared similarly (UV spectrophotometer, Jenway, UK). From these readings, the drug concentration was calculated.

**Table 1**
Composition of lidocaine dual-responsive *in situ* gel.

| Formula Code | Ingredients (%W/V) | | | |
|---|---|---|---|---|
| | Lidocaine HCl | PF-127 | PF-68 | Gelrite® |
| $F_1$ | 2 | 16 | 5 | 0 |
| $F_2$ | 2 | 16 | 5 | 0.3 |
| $F_3$ | 2 | 16 | 5 | 0.6 |
| $F_4$ | 2 | 18 | 5 | 0 |
| $F_5$ | 2 | 18 | 5 | 0.3 |
| $F_6$ | 2 | 18 | 5 | 0.6 |
| $F_7$ | 2 | 20 | 5 | 0 |
| $F_8$ | 2 | 20 | 5 | 0.3 |
| $F_9$ | 2 | 20 | 5 | 0.6 |

### 2.4. Gelation temperature ($T_{gel}$) measurement

Fixed volume of each formulation (10 mL) was put into a glass container and placed in water bath at RT. The sample temperature was elevated slowly under continuous stirring using a small magnetic bar. Once the magnetic bar stopped moving due to gel formation, the thermometer reading was recorded. The temperature at which the magnetic bar ceases to move, indicating gel formation is known as gelation temperature ($T_{gel}$).

### 2.5. Rheological studies

Rheological behavior of the different formulations, upon change in temperature and ionic strength, was studied using a DV-III Ultra viscometer, (RV model, Brookfield, USA). The spindles used were 07 for liquids and 96 for gels. Measurements were carried out at spindle speed of 40 rpm. For formulations containing only pluronic (no Gelrite®), effect of temperature on the viscosity was studied at different temperatures: 4 °C, 25 °C (RT), and 37 °C (vagina temperature). In case of pluronic/Gelrite® formulations, the rheological behavior of the samples was investigated as a function of both temperature and ions. First, the viscosity of solution was measured at 4 °C and 25 °C. Then, at 37 °C, the viscosity of the samples was measured with the help of a diffusion cell (2.4 cm internal diameter). The formulation was placed on top of a dialysis membrane, then immersed in 100 mL of simulated vaginal fluid (SVF) for a certain time period, after which viscosity measurements were taken. SVF was prepared according to a previously method (Owen and Katz, 1999). Briefly, to 1 L of distilled water, 3.5 g NaCl, 1.4 g KOH, 0.22 g $CaOH_2$, 2 g lactic acid, 1 g acetic acid, 0.16 g glycerol, 0.4 g urea, and 5 g glucose were added and dissolved. The pH of the mixture was then adjusted to 4.5 using HCl.

### 2.6. In vitro release studies

*In vitro* release from dual-responsive *in situ* gel was done using a standard semi-permeable cellophane membrane (Ibrahim el et al., 2012). One-gram solution of the tested formulation was weighed over the membrane of the dialytic tube and the tube was gentlyimmersed in SVF (100 mL). Then, the experiment was done in a shaking water bath, which is adjusted conditions at 75 spm and 37 ± 0.2 °C. Aliquots were withdrawn at certain time points. The cumulative drug release percent was calculated by measuring the absorbance of the aliquots using UV spectrophotometer at 263 nm against a blank gel similarly treated.

### 2.7. Kinetic analysis of the release data of lidocaine from the in situ gel

To determine the mechanism of the release of lidocaine HCl from their different *in situ* forming gels, kinetic models such as zero and first