

Original research article

Controlled release of copper from an intrauterine device using a biodegradable polymer

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Abstract

Background: The adverse effects of copper intrauterine devices (IUDs) such as abnormal bleeding, pain and cramps may be due in part to the burst release of copper ions during the first few months of usage. This study focuses on controlling the initial burst release of copper ions.

Study design: This study evaluated in vitro release rates of copper for a period of 1 year from standard CuT380 IUDs ($n=6$) and from CuT380 IUDs coated with poly(DL-lactide-co-glycolide) (PLGA) films ($n=6$). This study characterized the coated device for its morphological changes during degradation of film by scanning electron microscopy (SEM).

Results: CuT380 IUDs coated with PLGA film with a thickness of 0.10 ± 0.02 mm showed a reduced initial copper release (40–80 mcg/day) compared with uncoated CuT380 IUDs (150–200 mcg/day). Statistically significant ($p<.05$) results were obtained at different time intervals during the overall study period of 1 year. SEM images showed degradation of coating.

Conclusion: Coating a CuT380 IUD with biodegradable polymer reduced the initial copper release without affecting release at 1 year. Clinical trials are required to determine whether this could reduce side effects such as bleeding and pain associated with copper containing IUDs.

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Keywords: Copper intrauterine device; Biodegradable polymer; PLGA; Controlled release

1. Introduction

Copper T intrauterine devices (IUDs) represent an important contraceptive option for a very large number of women, about 160 million worldwide. The IUD, which is the most frequently used long-acting reversible contraceptive method in the world, is used by 14% of women of reproductive age [1]. A major drawback of copper IUDs is the high incidence of increased bleeding and pain following insertion. This may be related to a high initial release of copper [2–4]. It is also reported that 67% of women using CuT380 complained about menstrual side effects within the first year of use [5].

The corrosion rate of IUD is extremely high in the first few days after the insertion, which is the so-called burst release of cupric ions [6–8]. It is also reported that the high corrosion rates of the TCu380A IUD and TCu220C IUD in simulated uterine solution (SUS) were obtained after the first

and the third days of immersion in the solution, respectively [9]. According to literature, burst release could contribute to abnormal bleeding [2,10,11]. Arancibia et al. [12] demonstrated that a burst release of copper ions occurs in the first few months after insertion, and then the release rate decreases and stabilizes gradually. Hubacher et al. [13] suggested that side effects like bleeding and pain decrease over time, which might mean that the burst release of copper is one of the causal factors.

Yang et al. [14] studied the effects of low-density polyethylene (LDPE) film on the properties of copper/LDPE composites for intrauterine contraceptive device to reduce burst release of copper. Alvarez et al. [15] also studied the effect of pretreatment with organic inhibitors to reduce burst release of copper ions. In order to control the burst release of copper ions, we designed a safe, biodegradable coating over the copper wire for controlling the release and achieving the recommended levels of copper for contraceptive effect that is reported to be in a range from 20 to 80 mcg/day [16].

Due to good biodegradability, biocompatibility and proper mechanical properties, poly(DL-lactide-co-glycolide)

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(PLGA) 75/25, a biodegradable polymer approved by the Food and Drug Administration [17], was selected for this purpose. The degradation products are easily metabolized in the body and are eliminated as carbon dioxide and water [18].

In this work, we engineered PLGA film and coated over the stem part of copper T to modulate the burst release of copper ions from the copper T device. The morphological changes during degradation of film coating over the copper T were studied through scanning electron microscopy (SEM) analysis. The biodegradable polymer coating may prevent burst release, which in turn may decrease side effects.

2. Materials and methods

2.1. Preparation of coated CuT380 IUD

Preparation of CuT380 IUD coated with PLGA film (coated CuT380) involves preparation of PLGA film, coating of PLGA film onto CuT380 IUD (uncoated CuT380), packing and sterilization. Uncoated CuT380 is sourced from HLL Lifecare Ltd, India, who is a manufacturer of copper T prequalified by the United Nations Population Fund.

PLGA 75/25 (Corbion Biomaterials, Netherlands) was dissolved in ethylacetate under stirring. Solvents like tetrahydrofuran, methylene chloride, chloroform, ethyl acetate, hexafluoroisopropanol and acetone are found to be good solvents for the selected polymer PLGA. Based on the extent of solubility and its low toxic potential, ethyl acetate was selected as the ideal candidate out of the mentioned solvents. As per International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Q3C guidelines, ethyl acetate solvent comes under class 3 solvents [19] that are regarded as less toxic and of lower risk to human health. Different (w/v) concentration (10%, 30% and 50%) of solutions were prepared and checked for the suitability of release and film formation ability with three different methods of coating such as dip coating, spray coating and film wrapping. PLGA solution, 10% (w/v), was finalized for coating by film wrapping, after optimization.

The polymer film (PLGA film) prepared with a thickness of 0.10 ± 0.02 mm was sized into desired dimensions ($3 \text{ cm} \times 1 \text{ cm}$) and then was wrapped over the copper wire on the stem part of uncoated CuT380 to obtain the finished product coated CuT380 (Fig. 1).

The finished product coated CuT380 was packed in Tyvek pouch as primary packaging and then subjected to sterilization by gamma radiation as per the standard International Organization for Standardization 11137 at a dose of 25 kGy.

2.2. Characterization of coated CuT380

The gamma-sterilized coated CuT380 was characterized for its morphological changes during degradation of film by SEM, release of copper ions by UV.

2.2.1. PLGA film degradation

The surface morphology of coated CuT380 samples was examined using Zeiss EVO 18 and HITACHI S2400 scanning electron microscope. The samples were sputter-coated with an Au–Pd mixture to ensure conductivity. The coated CuT380 samples were suspended and incubated in 50 mL of SUS at a temperature of $37.0 \pm 0.1^\circ\text{C}$ with 70 rpm. At predetermined time points, the samples were withdrawn and dried for 24 h to investigate polymer film degradation by SEM.

2.2.2. Estimation of copper ions

To compare the release behavior of coated CuT380 and uncoated CuT380, the release rate of copper was studied in the same environmental conditions. The coated CuT380 ($n=6$) and uncoated CuT380 ($n=6$) samples were suspended and incubated in 50 mL of SUS a temperature of $37.0 \pm 0.1^\circ\text{C}$ with 70 rpm.

The composition of SUS (g/L) is as follows: 4.97, NaCl; 0.224, KCl; 0.167, CaCl_2 ; 0.25, NaHCO_3 ; 0.50, glucose; 0.072, $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ [4,8,20]. The intrauterine pH is reported in the range from 6.0 to 7.9 [8]. Considering the abovementioned fact, tests were conducted in SUS at pH 6.3, which represents the condition with high copper corrosion rate [8].

Samples were taken after different exposure time (1, 7 and 30 days initially and subsequently every month) and refreshed with SUS. The samples of incubated SUS solution

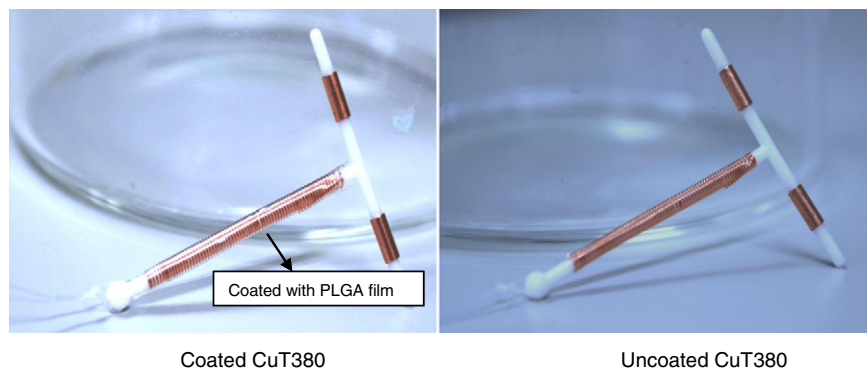


Fig. 1. Images of coated CuT380 and uncoated CuT380.

were added to chelating agent (diethyl ammonium salt of diethyl dithiocarbamic acid, with a concentration of 8×10^{-3} mol/L) [20] and Cu^{2+} concentration was analyzed by absorbance measurements using a UV spectrophotometer (model: Shimadzu 1700) with an absorption maximum at 448 nm.

An unpaired, two-tailed *t* test was used to test the significance of difference in the release between coated CuT380 and uncoated CuT380. A *p* value of .05 was defined to be statistically significant.

3. Results

3.1. Characterization of coated CuT380

3.1.1. PLGA film degradation

The erosion and degradation of PLGA film are considered as the factors influencing release of copper ions and are controlled by the physical properties of the film. Degradation of PLGA film occurs by bulk erosion [21]. The PLGA film started developing pores on it and the number of pores and its size increased over time leading to degradation of the film as observed in the micrograph pictures (Fig. 2).

3.1.2. Estimation of copper ions

Fig. 3 shows the release profile of coated CuT380 and uncoated CuT380 samples for 360 days. The initial release of copper (after 24 h) from coated CuT380 is 40 mcg/day (mean \pm S.D., $n=6$) and that of uncoated CuT380 is around 195 mcg/day ($n=6$). The release was statistically significant at a level of *p* value $< .05$ when student unpaired *t* test was used. The results demonstrate that the initial release rate of copper ions in uncoated CuT380 was very high (195 mcg/day) and decreased gradually in 30 days (165 mcg/day) and maintain a constant release after 180 days (40–80 mcg/day). The initial burst release of copper ions in uncoated CuT380 is thus clear, whereas, in coated CuT380, the release of copper ions was controlled at a rate of 40–80 mcg/day throughout the study period of 360 days.

4. Discussion

The adverse effects of copper IUDs such as abnormal bleeding, pain and cramps may be due in part to the burst release of copper ions during the first few months of usage. This study focuses on controlling this initial burst release of copper ions.

We developed here a coated CuT380 and demonstrated a better control of the burst release observed with the standard CuT380 IUD.

The coating material PLGA becomes more attractive as compared to natural hydrophilic polymer because the release profile of the drug (copper ions) can be controlled by diffusion and the erosion of the polymer. Our results illustrate the release pattern of PLGA film on erosion.

In correlation with Arancibia et al. [12], our research on in vitro copper release also demonstrates that the burst release

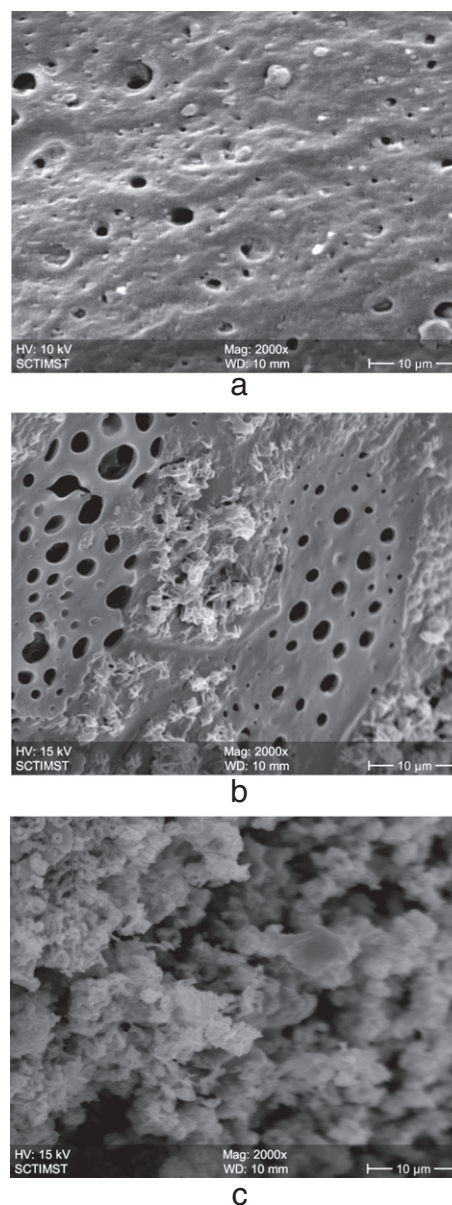


Fig. 2. SEM micrographs of PLGA film on coated CuT380 kept in SUS for (a) 1 day, (b) 20 days and (c) 40 days.

of copper ions from uncoated CuT380 occurs only in the initial few months and then decreases and stabilizes gradually throughout the study period. The copper release study shows a controlled release of copper ions from coated CuT380 from the first day that is maintained (40–80 mcg/day) throughout the study period of 360 days. Thus, the drawback of the copper-bearing IUDs due to the initial burst release of copper ions (150–200 mcg/day) in the initial days after insertion can be overcome by controlling the release rate as observed in coated CuT380. The initial cupric ion release from the coated CuT380 is significantly less than that of the existing uncoated CuT380, which may lead to less side effects related to burst release [22,8]. This needs to be clinically evaluated and will be reported later.

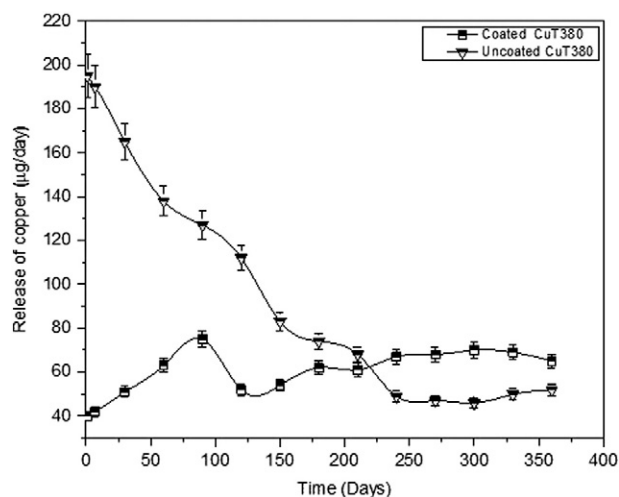


Fig. 3. Release of copper from coated CuT380 and uncoated CuT380 (mean±S.D., $n=6$).

5. Conclusion

Copper corrosion from uncoated CuT380 after 24 h is thrice than that of the coated CuT380. These differences in the cupric ion release among the two IUDs decrease over time, and after a period of 4–5 months, both exhibit approximately equal release rate that is proved to be effective for contraception. In view of the abovementioned results, coated CuT380 may provide a new and improved reversible contraceptive method, which is expected to minimize the burst release of copper ions. We described an approach to suppress burst release and clinical testing is warranted.

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