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(54) Title: A NOVEL INTRAUTERINE DEVICE WITH CONTROLLED COPPER RELEASE

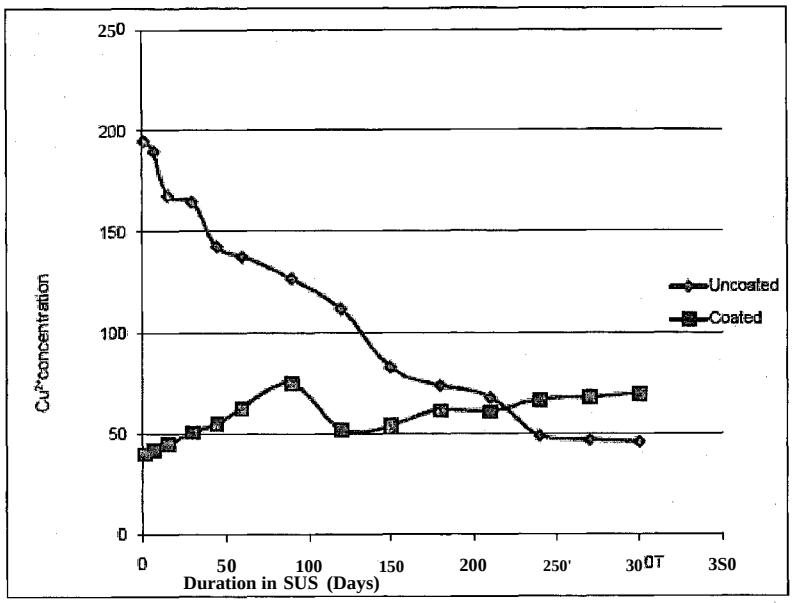

Figure 1: Cu2+ release rate against time for uncoated Cu-T380 A and coated Cu-T 380A

(57) Abstract: **A** novel intrauterine contraceptive device of the present invention is developed to surmount the problem prevailing with the conventional contraceptive device. The IUD of the present invention is covered with a thin layer of a biodegradable/bioabsorbable polymer, to control the excessive release of copper ion in the early stage and to minimize bleeding and pain after insertion. The polymer thin layer has a controlled degradation rate and advantageously degrades over a period of time say between one month and five month in the uterus environment.

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A NOVEL INTRAUTERINE DEVICE WITH CONTROLLED COPPER RELEASE

FIELD OF INVENTION;

The invention relates generally to the field of contraceptive devices, particularly designed for intrauterine insertion. The device of the present invention more specifically concerns with copper containing intrauterine device **covered with a thin layer of a biodegradable polymer.**

BACKGROUND OF THE INVENTION:

IUDs or intrauterine devices are a type of contraceptive medical device placed in the uterus. IUDs are safe and effective methods of long-term reversible contraception. Copper IUDs, which were first marketed in the early 1970s, represent an important contraceptive option for nearly 160 million women worldwide [1]. The design and copper content as well as placement of the copper on IUDs could affect their effectiveness and side effects. The presence of this foreign body in the uterus makes the endometrium to release leukocytes and prostaglandins. These substances are hostile to both sperm and eggs. It is reported that the presence of copper increases this spermicidal effect [2, 3].

The most widely used IUDs are copper-bearing IUDs (Cu-IUD). The enhanced contraceptive effect of Cu-IUD is attributed to the copper ions released by the corrosion of copper in the uterus [4]. The contraceptive effectiveness of Cu-IUD is related to the surface area of copper on the device. Moreover they do not affect breastfeeding, interfere with intercourse, or have hormonal side effects. The minimum amount of copper ions required for contraceptive action is 25-80 micrograms per day [5].

The main limitation of Cu-IUD is their tendency to cause excessive pain and heavy menstrual bleeding in the initial days of insertion as a result of the burst release of copper ions into the uterus [6, 7]. This side effects decrease over time period [8]. Nevertheless the usage of Cu-IUDs is very less (except in Chine) owing to the above mentioned reason. In OOIndia, the government supports the Cu-T380A as the suitable IUD. The studies indicate that the copper ion release in 380A is much more compared to the other copper-bearing Ts like 220B and 220C, of course due to less amount of copper.

In WO Patent No 2010082197 dated July 22, 2010, an Intra Uterine Ball (IUB) device comprising a hollow sleeve for at least partial insertion into the uterine cavity and an elongate conformable member comprised of shape memory alloy which is adapted to conform into a predetermined three dimensional ball - like configuration within the uterine cavity, with useful for a gynecological procedure or treatment has been disclosed.

In the Journal of Biomedical materials Research Part B: Applied Biomaterials, Vol. 80B, Issue 1, 220-225 (2006), the Cu^{2+} release rate of nano and micro copper/low density polyethylene as an intrauterine device in the uterine solution was disclosed. Both types of composites exhibited burst release behavior of Cu^{2+} within the first month of incubation, but nanocomposites showed steady release of Cu^{2+} ions.

In an article presented in the journal Contraception 70 (2004) 153-157, nanocopper/low density polyethylenes as a potential copper carrier in IUDs have been reported. The composite offered a reduction in large initial release of Cu^{2+} ions provided with continuous release in amounts effective for contraception.

In WIPO Patent No. WO/2006/108065, disclosure is made on degradable implantable medical device in the form of graft implants, vascular implants, non vascular implants, wound closure implants, sutures, drug delivery implants, biologic delivery implants, urinary tract implants, inter-uterine implants, organ implants, bone implants, dental implants and spinal disks.

In European Patent No. NL 1024660 (C2), a copper containing carrier with a coating that releases a hemostatic agent has been reported. An independent claim of this patent discloses the production of the device which includes partial insertion of the carrier into a container containing the hemostatic agent, removal of the carrier from the container and fixing the hemostatic agent to the carrier.

Taking into consideration of all the above facts, the researchers have tried to develop newer varieties of IUDs over the period of time. The non-acceptance of the copper-bearing IUDs due to the bulk release of copper ions (100-150micrograms per day) in the initial days after insertion can be overcome by controlling the release rate by suitable means. In all the conventional system and prior art, the contraceptive intrauterine device does not disclose on the use of any biodegradable polymer coating over the device.

The present invention speaks about coating the copper bearing IUD with a polymer which is biocompatible and regulate the release of Cu^{2+} ions in such a way to ensure the concentration required for contraception.

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SUMMARY OF THE INVENTION

The present invention relates to intrauterine devices and more specifically concerns with copper containing intrauterine device covered with a thin layer of a biodegradable/bioabsorbable polymer, which degrade over a clinically relevant period of time, to minimize the burst release of copper ions. Due to coating, biodegradable/bioabsorbable polymer thin film according to the present invention can prevent the copper ions from being excessively released in the early stage immediately after insertion, which contributes, to bleeding and pain, and after that, can gradually release the copper ions over a delayed period as the biodegradable/bioabsorbable polymer thin layer is degraded. The polymer thin layer degrades in the uterus environment within a clinically relevant time period, such as approximately fifteen days to five month. The devices at least partially degrade in the uterus environment in less than one week, such as a few days, one day, a few hours, one hour or less. For example, the device may have at least a portion which degrades at a controlled degradation rate to approximate dissolution at or within one month.

The biodegradable/bioabsorbable polymer is one or more compounds selected from the group consisting of poiyglycolide (PGA), polylactide (PLA), poly caprolactone (PCL), and their copolymers, derivatives and copolymers of poly(amino acid), polyanhydride and polyorthoesters, , PVA (polyvinyl alcohol)chitosan or their blends or composites. The biodegradable/bioabsorbable polymer has a weight-average molecular weight ranging from about 100 g/mol to about 1,000,000 g/mol. The thickness of the biodegradable/ bioabsorbable polymer coating is from about 10 μm to about 10mm.

Degradation of the polymer thin layer may occur in multiple phases, such as a slower degradation rate in one phase and a faster degradation rate in another phase or in the reverse

order. The biodegradable polymer coated copper-T will release copper ions to the surrounding aqueous medium at a release rate of 10 to 100 micrograms of copper ions per day. Therefore, the coated copper-T of the present invention can be effectively used for controlled copper ion release for contraception.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is the graph to illustrate the variation of Cu^{2+} release rate for polymer coated Cu-T380 A and uncoated Cu-T 380A in simulated uterine solution (SUS) **for a period of 10 months**

DESCRIPTION OF THE INVENTION;

The present invention provides a new and improved reversible contraceptive copper bearing intrauterine device, comprising of a biodegradable/bioabsorbable thin film coated copper- T. The purpose of using this thin film coated copper-T is to control and minimize the burst release of copper ions after the insertion of the device in the uterine environment. The biodegradable thin film coated in the IUD reduces the copper ions release rate during the early stage. Another advantageous effect of the present invention, while reducing the burst release of copper ions, it avoids over bleeding and pain which may usually occur in conventional intrauterine devices. As the biodegradable/bioabsorbable polymer thin layer is degraded over time, it renders gradual release of the copper ions. Degradation of the polymer thin layer may occur in multiple phases, such as a slower degradation rate in one phase and a faster degradation rate in another phase or in the reverse order.

The biodegradable/bioabsorbable polymer according to the invention, is a non erodible polymer selected from one or more compounds of a group consisting of polyglycolide (PGA), polylactide (PLA), poly caprolactone (PCL), and their copolymers, derivatives and copolymers of poly (amino acid), polyanhydride and polyorthoesters, PVA (polyvinyl alcohol) chitosan or their blends or composites at different proportions/ratios.

According to another embodiment of the present invention, the biodegradable/bioabsorbable polymer selected has a weight-average molecular weight ranging from about 100 g/mol to about 1,000,000 g/mol and the organic solvent is selected from the group consisting of tetrahydrofuran, methylene chloride, chloroform, ethyl acetate, hexafluoroisopropanol and acetone and their combinations.

The biodegradable/bioabsorbable polymer is used in an amount of about 5 wt % to about 75 wt % based on the weight of the organic solvent. The thickness of the biodegradable/ bioabsorbable polymer coating varies between 10 μm to about 10 mm. The biodegradable/bioabsorbable polymer coated copper-T will release copper ions to the surrounding aqueous medium at a release rate variable within a range of 10 to 100

micrograms of copper ions per day. The biodegradable polymer coated copper-T can avoid the excessive release of copper ions immediately after insertion and will gradually release the copper ions over a delayed period as the biodegradable/bioabsorbable polymer thin layer is degraded.

The polymer thin layer degrades in the uterus environment within a clinically relevant time period, such as approximately fifteen days to five month. The devices at least partially degrade in the uterus environment in less than one week, such as a few days, one day, a few hours, one hour or less. For example, the device may have at least a portion which degrades at a controlled degradation rate to approximate dissolution at or within one month.

The biodegradable/ bioabsorbable polymer coated copper-T will release copper ions to the surrounding aqueous medium at a uniform release rate, which is required for providing contraception. The biodegradable/bioabsorbable polymer coated copper-T will be beneficial since there is no side effect arising from bulk release of copper ions. The IUD of the present invention is made of polyethylene frame over which the copper releasing units are present.

The insertion method of biodegradable/ bioabsorbable polymer coated copper-T is the same as such for uncoated Cu-T insertion. The IUD member in its three dimensional configuration has a diameter which is significantly higher than the diameter of the cervical canal thereby expulsion of IUD member from the uterine cavity is prevented.

Initial studies were conducted by coating the stem of Cu-T 380A with poly (lactide-co-glycolide) in ethyl acetate. For the determination of Cu^{2+} ion release from the device, both the uncoated Cu-T 380A and coated Cu-T 380A of the present invention were suspended and incubated in 50 ml simulated uterine solution (SUS) at temperature of 30 +/- 10°C. The variation of Cu^{2+} release in SUS for both the devices is shown in figure 1. It can be seen that the initial copper release from coated Cu-T 380A is around 58 microgram/day and that of Cu-T 380A is around 114 microgram/day. Table 1 shows the release of Cu^{2+} for coated and **uncoated** Cu-T 380A. Thus the copper release from the device of the present invention is very less which makes the users comfortable.

Table 1: Cu^{2+} release for coated Cu-T 380A and uncoated Cu-T380 A

Time Period	Concentration of Sample	
	Coated Cu T	**Uncoated** Cu T
After 24 hours	40	195
After 7 days	42	190
After 15 days	45	168
After 30 days	51	165
After 45 days	55	143
After 2 months	63	138

After 3 months	75	127
After 4 months	52	112
After 5 months	54	83
After 6 months	62	74
After 7 months	61	68
After 8 months	67	49
After 9 months	68	47
After 10 months	70	46

Toxicology studies have proven that the new system is not cytotoxic. Preclinical evaluation studies such as Genotoxicity, Acute systemic toxicity, Hemolytic property, Sensitization tests and implantation tests are conducted to prove safety of the device and obtained positive results

While the foregoing written description of the invention enables one of ordinary skill to make and use what is considered presently to be the best mode thereof, those of ordinary skill will understand and appreciate the existence of variations, combinations, and equivalents of the specific embodiment, method, and examples herein. The invention should therefore not be limited by the above described embodiment, method, and examples, but by all embodiments and methods within the scope and spirit of the invention as claimed

WE CLAIM

1. A novel intrauterine device (IUD) adaptable to insertion in the uterine cavity for the controlled release of copper ions comprising a copper- T coated with a thin layer of a biodegradable / bioabsorbable polymer

2. The IUD of claim 1, is made of polyethylene frame over which the copper releasing units are present

3. The IUD according to claim 1, wherein said biodegradable polymer coated copper-T avoids the excessive release of copper ions immediately after insertion of said IUD in the uterus environment

4. The IUD according to claim 1, gradually releases the copper ions over a delayed period as the said biodegradable polymer thin layer is degraded

5. The IUD according to claim 1, wherein the said biodegradable polymer coated copper-T releases copper ions at a uniform release rate required for providing contraception

6. The IUD of claim 1, has no side effect arising from bulk release of copper ions such that the use of said biodegradable polymer coated copper-T will be beneficial.

7. The IUD according to claim 1, member in its three dimensional configuration has a diameter which is significantly higher than the diameter of the cervical canal such that the expulsion of said member from said uterine cavity is prevented

8. A method of preparing biodegradable thin film coated copper- T comprising: dissolving biodegradable polymer in an organic solvent, to prepare a thin film coat over the copper-T using the said biodegradable polymer for the controlled release of copper ions

9. The biodegradable polymer according to claim 8; is one or more compounds selected from the group consisting of polyglycolide (PGA), polylactide (PLA), poly(lactide-glycolide) copolymer (PLGA), poly caprolactone (PCL), poly(lactide- □ -caprolactone) copolymer (PLC), derivatives and copolymers of poly(amino acid), polyanhydride and polyorthoesters.

10. The method according to claim 8, wherein the biodegradable polymer has a weight-average molecular weight ranging from about 5000 g/mol to about 1,000,000 g/mol.

11. The method according to claim 8, wherein the organic solvent is selected from the group consisting of tetrahydrofuran, methylene chloride, chloroform, ethyl acetate, hexafluoroisopropanol and acetone.

12. The method according to claim 8, wherein the biodegradable polymer is used in an amount of about 10 wt % to about 30 wt % based on the weight of the organic solvent.

13. The composition according to claim 8, wherein the biodegradable polymer coating is from about 10 μm to about 1mm thick.

14. The biodegradable polymer coated copper-T according to claim 8, will release copper ions to the surrounding aqueous medium at a release rate of 10 to 100 micrograms of copper ions per day.

Applicant: HLL Lifecare Limited **Total No. of Sheet: 1**

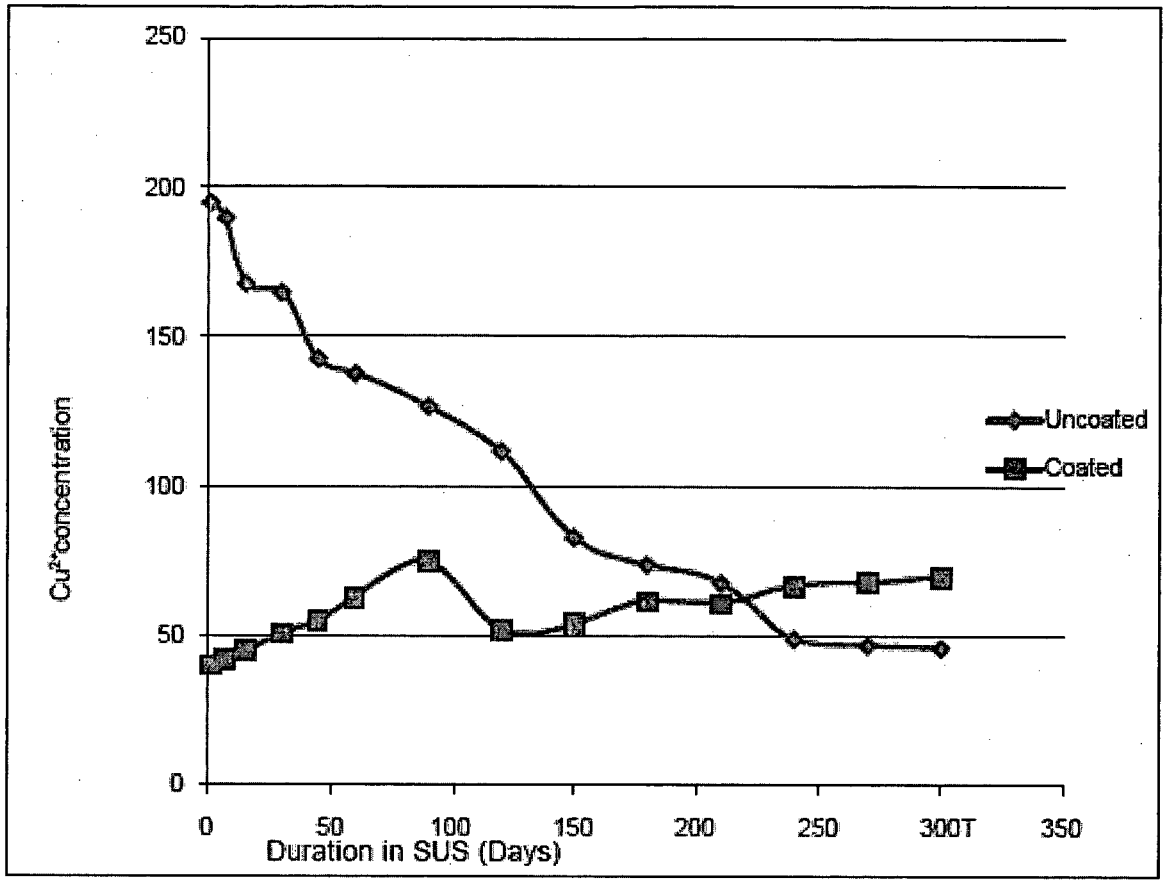

Figure 1: Cu2+ release rate against time for uncoated Cu-T380 A and coated Cu-T 380A