(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 June 2011 (23.06.2011)

PCT

(10) International Publication Number
WO 2011/073995 A2

(51) **International Patent Classification**:
A61K 9/00 (2006.01)

(21) **International Application Number**:
PCT/IN2010/000790

(22) **International Filing Date**:
6 December 2010 (06.12.2010)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
2879/MUM/2009 14 December 2009 (14.12.2009) IN

(71) **Applicant** *(for all designated States except US)*: **LINCOLN PHARMACEUTICALS LIMITED** [IN/IN]; Nirav Complex, Opposite Navrang High School, Naranpura, Ahmedabad 380 014, Gujarat (IN).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **PATEL, Rajni, Gulabdas** [IN/IN]; Lincoln Pharmaceuticals Ltd., Nirav Complex, Opposite Navrang High School, Naranpura, Ahmedabad 380 014, Gujarat (IN). **PATEL, Jigar, Hasmukhbhai** [IN/IN]; Lincoln Pharmaceuticals Ltd., Nirav Complex, Opposite Navrang High School, Naranpura, Ahmedabad 380 014, Gujarat (IN). **SHAH, Arun, Chimanlal** [IN/IN]; Lincoln Pharmaceuticals Ltd., Nirav Complex, Opposite Navrang High School, Naranpura, Ahmedabad 380 014, Gujarat (IN). **NAIK, Shardul, Arunkumar** [IN/IN]; Lincoln Pharmaceuticals Ltd., Nirav Complex, Opposite Navrang High School, Naranpura, Ahmedabad 380 014, Gujarat (IN).

(74) **Agent**: **NAIR, Gopakumar, G.**; Gopakumar Nair Associates, 3rd Floor, 'Shivmangal', Near Big Bazaar, Akurli Road, Kandivali (East), Mumbai 400 101, Maharashtra (IN).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2011/073995 A2

(54) **Title**: LIQUID VAGINAL SPRAY OF PROGESTERONE

(57) **Abstract**: Disclosed herein a liquid vaginal spray composition comprising natural/synthetic progesterone along with unique blend of solvent/co-solvent and anti-oxidants useful for treating secondary amenorrhea, threatened or habitual abortions and infertility.

"LIQUID VAGINAL SPRAY OF PROGESTERONE"

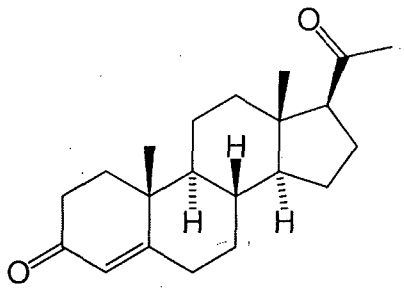
TECHNICAL FIELD OF THE INVENTION:

The present invention relates to a liquid vaginal spray dosage form that provide local as well as systemic effect, comprising therapeutically effective amount of natural/synthetic progesterone, useful for treatment of secondary amenorrhea, threatened or habitual abortions and infertility.

BACKGROUND OF THE INVENTION:

Progesterone also known as P4 (pregn-4-ene-3,20-dione), is a C-21 steroid hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen.

Chemically, Progesterone is pregn-4-ene-3,20-dione having structural formula as follows:



Progesterone is commonly manufactured from the plant called *Dioscorea mexicana*, belonging to yam family. *Dioscorea mexicana* produces large amounts of a steroid called diosgenin, which can be converted into progesterone in the laboratory.

Progesterone exerts its primary action through the intracellular progesterone receptor although a distinct, membrane bound progesterone receptor has also been postulated. Progesterone and its analogues have many medical applications both to address acute situations and to address the long-term decline of natural progesterone levels.

Progesterone is poorly absorbed by oral ingestion unless micronised and in oil, or with fatty foods; it does not dissolve in water.

Progestogens were originally developed because they were capable of being absorbed into the blood when ingested in pill form, whereas progesterone itself was not orally absorbed. Recently, however, it has been found that micronization of progesterone (making very tiny crystals of the progesterone) enhances absorption from the gastrointestinal tract. Thus micronized progesterone is now sometimes being used for menopausal hormone replacement therapy instead of progestogens. Birth control pills still have progestogens as the active progesterone-like component.

The vaginal route of progesterone administration provides many advantages such as easy administration, lack of local pain, avoids liver first-pass metabolism, rapid absorption and has no systemic side-effects. Consequently, the vagina has a large potential for absorption, and through the 'uterine first-pass effect' vaginal administration results in higher uterine progesterone concentrations.

In view of the above, vaginal administration of progesterone results in high concentration of the hormone at the uterine level (first uterine passage), which may be advantageous for certain indications such as HRT (Hormone Replacement Therapy).

WO2008154240 discloses a solid, compressed pharmaceutical composition, containing only progesterone or progesterone combined with estradiol, to be administered vaginally in the form of tablet.

WO2004080413 discloses a formulation for the transdermal or transmucosal administration of an active agent comprising testosterone along with estrogen or progestin for the treatment of hypogonadism, female sexual desire disorder, female menopausal disorder, and adrenal insufficiency.

US2005181045 discloses the preparation of pharmaceutical composition containing micronized progesterone in the form of tablet, for vaginal delivery.

An article titled "Efficacy of Oral Micronized Progesterone when Applied via Vaginal Route" by Roungsin Choavaratana and Darapa Manoch discloses the comparative study of the efficacy of oral micronized progesterone when applied by the vaginal route. The authors conclude that the serum progesterone level achieved when micronized progesterone capsule was administered as a vaginal suppository is significantly higher than the level achieved by oral administration.

US6077531 discloses a medicament based on estradiol and progesterone intended for the treatment of menopausal pathology.

In view of the above state of art, the present inventors have come up with a composition in a liquid vaginal spray dosage form comprising natural/synthetic progesterone to provide relatively better effect and quick absorption than other dosage forms like vaginal capsules or tablets. Further, the novel mode of delivery is useful for treatment of threatened or habitual abortions and infertility and provides better patient compliance as compare to painful intramuscular injections, as it is in solution form.

SUMMARY OF THE INVENTION:

In accordance with the above, the present invention provides a liquid vaginal spray dosage form to provide local as well as systemic effect, comprising therapeutically effective amount of natural/synthetic progesterone useful for treatment of secondary amenorrhea, threatened or habitual abortions and infertility.

In a preferred aspect, the invention provides a liquid vaginal spray dosage form comprising therapeutically effective amount of natural/synthetic progesterone in association with a unique blend of solvents and co-solvents, useful for treatment of secondary amenorrhea, threatened or habitual abortions and infertility.

The composition of the present invention afford a better patient compliance, better bioavailability, when compared to painful intramuscular injections, vaginal capsules or tablets as the present formulation is in solution form that can administered by spraying method.

DETAILED DESCRIPTION OF THE INVENTION:

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

In one embodiment, the present invention provides a liquid vaginal spray dosage form to provide local as well as systemic effect, comprising therapeutically effective amount of natural/synthetic progesterone, useful for treatment of secondary amenorrhea, threatened or habitual abortions and infertility.

In a preferred embodiment, the present invention provides, a composition which is in a liquid vaginal spray dosage form comprising therapeutically effective amount of natural/synthetic progesterone in association with a unique blend of solvents and co-solvents, useful for treatment of secondary amenorrhea, threatened or habitual abortions and infertility. The said liquid vaginal spray dosage form is dispensed in a form of mist.

The composition of the present invention has better patient compliance than vaginal tablets or capsule or painful intramuscular injection as the current formulation is dispensed in a mist form to cover a larger area of vaginal cavity with very small amount of dispensed volume, thus increasing the bioavailability of the said composition.

Accordingly in a preferred embodiment, the present invention describes a novel liquid spray composition comprising therapeutically active amount of natural/synthetic progesterone administered via vaginal route in combination with unique blend of solvents and co-solvents and anti-oxidants.

Suitable Synthetic progesterone is selected from the group of Hydroxy Progesterone Caproate, Hydroxy Progesterone acetate, Levonorgestrel, Medroxyprogesterone / Medroxyprogesterone 17-acetate, Norethisterone, Dienogest, Desogestrel, Drospirenone, Dydrogesterone, Ethisterone, Etonogestrel, Ethynodiol diacetate, Gestodene,

Gestonorone, Lynestrenol, Megestrol, Melengestrol, Norelgestromin, Norethynodrel, Norgestimate, Norgestrel, Norgestrienone, Tibolone and the like.
The natural progesterone used in the present invention is micronized.

The natural/synthetic progesterone used in the present invention is present in an amount of 50-300 mg.

Suitable solvents and co-solvents are selected from group of Benzyl benzoate and Ethyl oleate, polyethylene glycol, propylene glycol, glycofurol, ethyl alcohol, Polyoxyl-35-castor oil, Macrogol 15 Hydroxystearate, diethylene glycol monoethyl ether, Caprylocaproyl Macrogolglycerides, Glyceryl Caprylate/ Caprate, Caprylic/Capric acid and the like. The solvents/ co-solvent are present in an amount of 20% to 80%.

Suitable anti-oxidants are selected from group of BHA (Butylated hydroxyanisole), BHT (Butylated hydroxytoluene), Propyl Gallate and the like. The anti-oxidant is present in an amount of 0.01% to 0.2%.

In another embodiment, the invention provides a spray dispenser comprising therapeutically effective amount of natural/synthetic progesterone in association with a unique blend of solvents and co-solvents. The composition is filled in a convenient container that can give the formulation in form of fine droplets or mist. The dispenser assembly is specifically designed to provide drug dispensing directly into vagina in unit dosage form, thus enabling easy delivery in to vaginal orifice.

In an embodiment, the metered dose spray dispenser comprises a pump engine, wherein, a pump, a bottle and actuator are installed in the pump engine. The pump is made of transparent material, has 100 % leak proof system and higher filling line productivity that allows for fine sprays, absence of contact between formulations and springs, fast priming, very efficient pre compression mechanism providing high spray performances. The actuator provides for a reliable spray discharge during each and every dosage period.

The metered dose spray dispenser was optimized and the optimization of the same was tested by Spray pattern test, Spray content uniformity, Priming/repriming test.

In an embodiment, the present invention provides a composition which is in a liquid vaginal spray dosage form comprising therapeutically effective amount of natural/synthetic progesterone in association with a unique blend of solvents and co-solvents, wherein the said composition does not crystallizes at very low temperature during storage.

In a further embodiment, the present invention provides a method of treating Secondary amenorrhea, threatened or habitual abortions and infertility, which comprises administering 'an effective amount' of the 'natural/synthetic progesterone' to the subject suffering affected by secondary amenorrhea, threatened or habitual abortions and infertility. The subject mentioned herein is human.

The invention further discloses use of the 'spray composition of the invention comprising natural progesterone or synthetic progesterone' intended to reduce symptoms associated with secondary amenorrhea, threatened or habitual abortions and infertility.

The Pilot Clinical Trial to study improved efficacy of Progesterone Vaginal Spray of present invention on human subjects with secondary amenorrhea was conducted.

This trial has been performed according to ICH - GCP guidelines and schedule Y. Total 17 patients were screened and 10 patients were enrolled into trial. Patients were informed about the spray, dose and the way of administration along with the time of enrollment. There was no serious or adverse event occurred throughout the trial. Patients Case Report Forms (CRF) was filled during and after completion of the dosage regimen of six alternative days for each patient respectively. The data was collected, compared and analysed from the Case Report Form (CRF). All the Patients showed spotting/ bleeding within predicted days. All patients have completed the study successfully. The present study shows that Progesterone Vaginal Spray is highly effective in patients of secondary Amenorrhea and following advantages were observed:

a) Length of nozzle which has been used in administering progesterone vaginal spray is optimized to insert the nozzle of device (5.4 cm) which can deliver the drug at exact required site into vagina where as in case of other formulations, the

applicator is very long, e.g. suppository (approx. 11 cm) which produces more risk and fear to the patients.

b) The intensity of burning sensation is very minor and comfort level is higher in case of product of the present invention as compared to suppository. Many a times, patients remove suppositories immediately after inserting into vagina because of unbearable burning sensation.

c) Patients show spotting/bleeding within 12 to 17 days after the treatment. Thus, faster recovery period in comparison with other peer products.

d) Product is non-sticky as compared to suppository. Therefore, patients feel easy to administer and more comfortable after application. In this product, drug gets absorbed without leaving sticky inert particles behind.

e) This product is more patient compatible than suppositories from all 17 patients 10 patients who started treatment with this product completed full course of treatment. This is not the case with suppositories which are sometimes washed off and removed by the patients after administration.

The following example, which includes preferred embodiments, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purpose of illustrative discussion of preferred embodiments of the invention.

DESCRIPTION OF DRAWING:

Figure 1: Component of Spray Dispenser (Pump, Bottle, Actuator) and color figure is the pump engine of Spray Dispenser.

EXAMPLES:

Example 1:

Hydroxy Progesterone Caproate	250 mg
Benzyl benzoate	50% to 80%
Ethyl oleate	20% to 50%
BHA	0.015% to 0.1%

BHT	0.015% to 0.1%
Propyl Gallate	0.005% to 0.05%

Manufacturing Procedure for Example 1:

Step 1:

Dissolving Hydroxy Progesterone Caproate into half the quantity of ethyl oleate & benzyl benzoate.

Step 2:

Dissolving BHT, BHA & propyl gallate in ethyl oleate (remaining quantity)

Step 3:

Adding step-1 in to step-2

Step 4:

Final solution subjected to filling.

Example 2:

Hydroxy Progesterone acetate	250 mg
Benzyl Benzoate	50% to 80%
Ethyl oleate	20% to 50%
BHA	0.015% to 0.1%
BHT	0.015% to 0.1%
Propyl Gallate	0.005% to 0.05%

Manufacturing Procedure for Example 2:

Step 1:

Dissolving Hydroxy Progesterone acetate into half the quantity of ethyl oleate & benzyl benzoate

Step 2:

Dissolving BHT, BHA & propyl gallate in ethyl oleate (remaining quantity)

Step 3:

Adding step-1 in to step-2

Step 4:

Final solution subjected to filling.

Example 3:

Natural micronized progesterone	100mg to 200 mg
Benzyl benzoate	50% to 80%
Ethyl oleate	20% to 50%
BHA	0.015% to 0.1%
BHT	0.015% to 0.1%
Propyl Gallate	0.005% to 0.05%

Manufacturing Procedure for Example 3:

Step 1:

Dissolving Natural micronized progesterone into half the quantity of ethyl oleate & benzyl benzoate.

Step 2:

Dissolving BHT, BHA & propyl gallate in ethyl oleate (remaining quantity)

Step 3:

Adding step-1 in to step-2

Step 4:

Final solution subjected to filling.

Example 4:

The Pilot Clinical Trial to study improved efficacy of Progesterone Vaginal Spray in patients with secondary amenorrhea.

Investigational Product: Natural Micronized Progesterone

Dose: Progesterone 100mg/0.8gm.

Mode of administration: Vaginal

Duration of treatment: 17 days

Dose: Progesterone Vaginal spray (4 spray) intravaginally every other day for six days.

Results:

Among all 10 patients of secondary amenorrhea, 50 % patients observed repeated Spotting/heavy bleeding on 13^{th} day, moreover 20%, 10%, 10% and 10% patients observed repeated Spotting/heavy bleeding on 14^{th} day, 15^{th} day, 16^{th} day and 17^{th} day

respectively (Table 1) which is better efficacious in comparison to 17 days therapy as in the case of other commercial formulations of vaginal Progesterone (e.g Suppository). Only 3 patients each observed the side effect like mild post oocyte pain, abdominal pain and mild irritation respectively.

Table 1: Percentage of spotting/bleeding after treatment with Progesterone Vaginal Spray

Table1 : Percentage of spotting/bleeding after treatment with Progesterone vaginal spray

Patient initial	Age	Lab examination		Evaluation of withdrawal Bleeding																		Side effects	Adverse Effects
		TSH test	Prolactin Test	No bleeding						Isolated spotting /mild bleeding						Repeated spotting/Heavy bleeding							
				Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17		
AS	24	Negative	Negative	√	√						√								√	√	√	No	No
RS	23	Negative	Negative							√							√	√	√	√	√	Mild post Oocyte pain	No
SM	21	Negative	Negative	√	√	√	√	√													√	No	No
RT	28	Negative	Negative	√	√							√	√							√	√	Abdominal Pain	No
DJ	30	Negative	Negative							√							√	√	√	√	√	No	No
RJ	24	Negative	Negative	√							√							√	√	√	√	Mild irritation	No
MS	24	Negative	Negative							√							√	√	√	√	√	No	No
NS	31	Negative	Negative	√	√														√	√	√	No	No
MJ	28	Negative	Negative													√	√	√	√	√	√	No	No
RG	23	Negative	Negative							√							√	√	√	√	√	No	No

We claim,

1. A liquid vaginal spray composition comprising:
   a) Natural or Synthetic progesterone in an amount of 5% to 50%;
   b) Unique blend of solvent/co-solvent in an amount of 20% to 90% and
   c) Anti-oxidants in an amount of 0.01% to 0.2%.
2. The spray composition according to claim 1, wherein synthetic progesterone is selected from the group of Hydroxy Progesterone Caproate, Hydroxy Progesterone acetate, Levonorgestrel, Medroxyprogesterone / Medroxyprogesterone 17-acetate, Norethisterone, Dienogest, Desogestrel, Drospirenone, Dydrogesterone, Ethisterone, Etonogestrel, Ethynodiol diacetate, Gestodene, Gestonorone, Lynestrenol, Megestrol, Melengestrol, Norelgestromin, Norethynodrel, Norgestimate, Norgestrel, Norgestrienone, Tibolone and the like.
3. The spray composition according to claim 1, wherein solvent/co-solvent are selected from group of Benzyl benzoate and Ethyl oleate, polyethylene glycol, propylene glycol, glycofurol, ethyl alcohol, Polyoxyl-35-castor oil, Macrogol 15 Hydroxystearate, diethylene glycol monoethyl ether, Caprylocaproyl Macrogolglycerides , Glyceryl Caprylate/ Caprate, Caprylic/Capric acid and the like.
4. The spray composition according to claim 1, wherein anti-oxidants are selected from group of BHA (Butylated hydroxyanisole), BHT (Butylated hydroxytoluene), Propyl gallate and the like.
5. Method of treating Secondary amenorrhea, threatened or habitual abortions and infertility, which method comprises administering 'an effective amount' of the spray composition according to claim 1 to the subject suffering from Secondary amenorrhea, threatened or habitual abortions and infertility.
6. The method according to claim 6, wherein said subject is human.
7. A metered dosing spray dispenser to deliver the composition of claim 1.

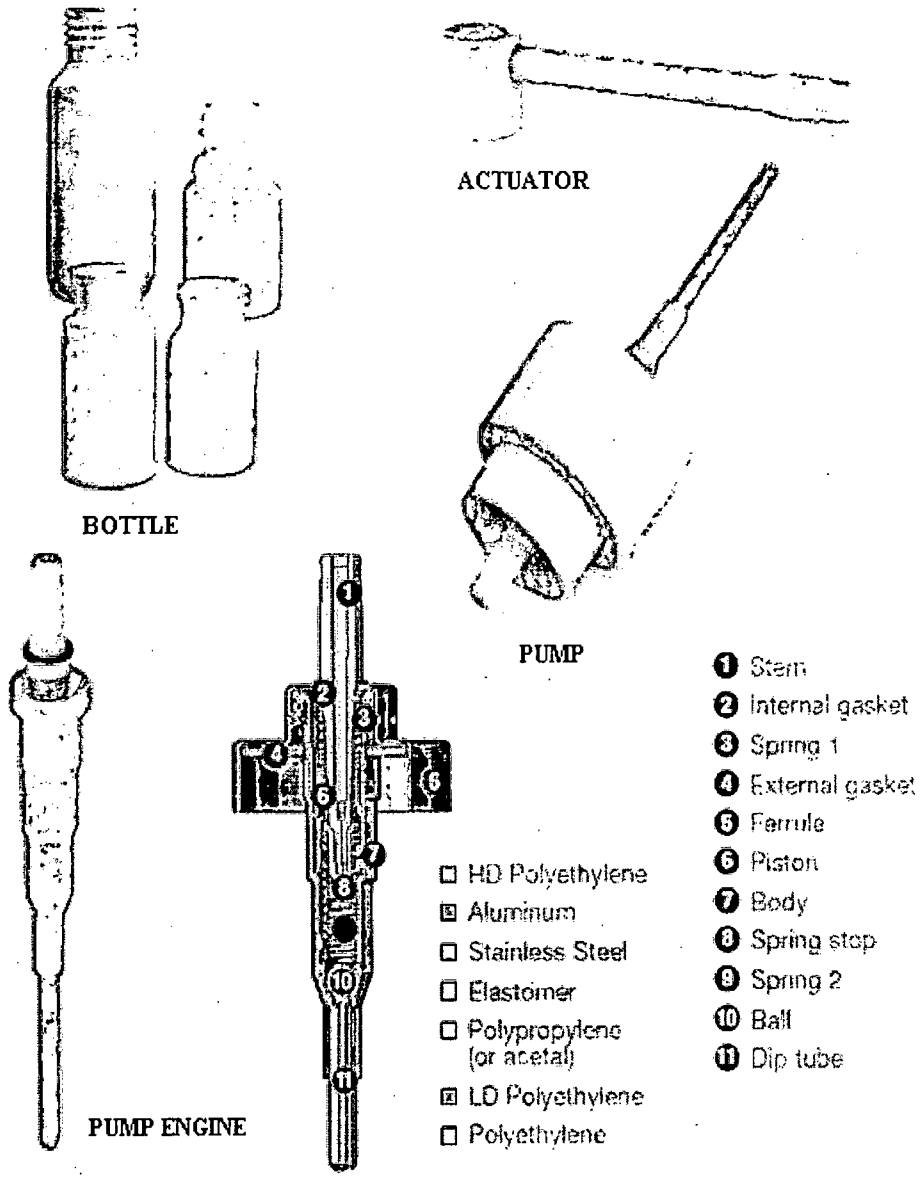

ACTUATOR
BOTTLE
PUMP
PUMP ENGINE
HD Polyethylene
Aluminum
Stainless Steel
Elastomer
Polypropylene (or acetal)
LD Polyethylene
Polyethylene
1 Stem
2 Internal gasket
3 Spring 1
4 External gasket
5 Ferrule
6 Piston
7 Body
8 Spring stop
9 Spring 2
10 Ball
11 Dip tube

Figure 1