



(51) International Patent Classification:

A61K 9/00 (2006.01) A61K 9/06 (2006.01)
A61K 47/10 (2006.01)

(21) International Application Number:

PCT/EP2013/066944

(22) International Filing Date:

13 August 2013 (13.08.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

PCT/EP2012/065822

13 August 2012 (13.08.2012)

EP

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(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, BN, 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, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
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,

[Continued on next page]

(54) Title: BIOADHESIVE FORMULATIONS FOR USE IN DRUG DELIVERY

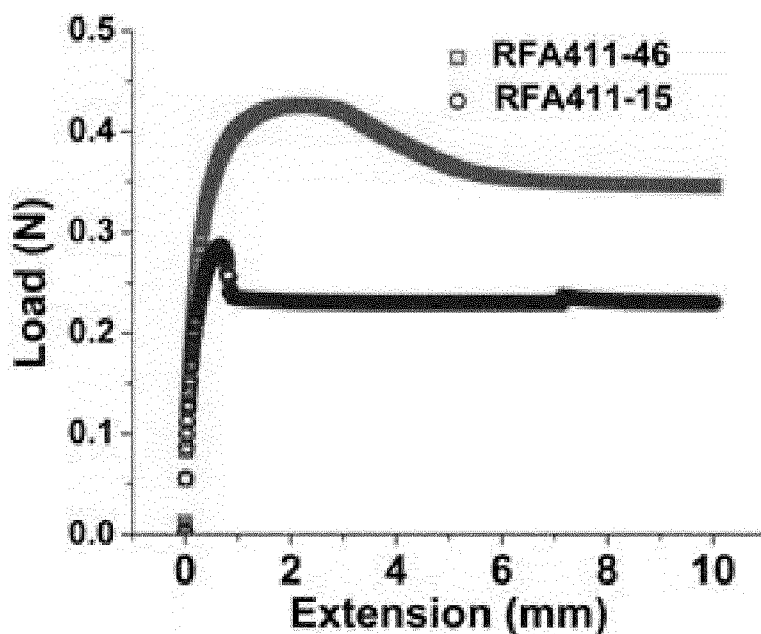


Figure 1

(57) Abstract: This invention relates to formulations having bioadhesive properties for use in drug delivery, in particular for the delivery of a drug or combination of drugs to body cavities and/or body surfaces. These are particularly suitable for the delivery of drugs to mucosal surfaces, in particular to vaginal mucosa.



GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, 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, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

BIOADHESIVE FORMULATIONS FOR USE IN DRUG DELIVERY

Technical Field of the Invention

- 5 This invention relates to formulations having bioadhesive properties for use in drug delivery, in particular for the delivery of a drug or combination of drugs to body cavities and/or body surfaces. These are particularly suitable for the delivery of drugs to mucosal surfaces, in particular the vaginal mucosa.

10 Background of the Invention

- One of the problems associated with topically applied formulations is their short duration of action which, at least in part, is due to their limited retention at the target site. Body surfaces and body cavities which have a mucous coating are particularly susceptible to this problem
15 due to the non-adherent nature of the mucosal coating and the fact this is rapidly replaced. A major problem in the delivery of drugs to body cavities and body surfaces is thus maintaining the active drug at the intended site of action for a sufficient period to achieve desired delivery of the drug and effective treatment of the condition (either at the target site or at a location remote from the delivery site in the case where the drug is intended to be
20 taken up systemically).

- Various gels are known for use in delivering drugs to body surfaces, including mucosal surfaces. Although these allow for a more uniform delivery of active, on warming to body temperature most gels have a tendency to lose their viscosity which leads to their
25 displacement. The presence of natural bodily fluids (e.g. mucosa, sweat, tears, etc.) also tends to result in their removal from the delivery site. Their limited retention reduces the therapeutic action of the active components thereby prolonging treatment periods and increasing the number and frequency of dosages required for clinical efficacy. Leakage of gels from body cavities, in particular from the vagina, is also undesirable for the patient.
30 Similar problems arise when treating other body surfaces and/or cavities, such as rectal, oral (e.g. gingival, buccal), nasal, otic, ocular, wound sites, etc.

- Thermoreversible gels have been proposed for use in improving drug delivery to mucosal surfaces. These are liquid at room temperature but form a semi-solid when warmed to body
35 temperature. For example, US 4,188,373 describes the use of Pluronic® poloxamers as

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thermally gelling polymers. Although these overcome some of the problems relating to the use of conventional gels, their bioadhesive force is weak which tends to result in detachment from the mucosal surface before treatment is complete. This is a particular problem in the vaginal cavity where the presence of vaginal fluids has a tendency to
5 displace the gel.

A particular example of a body cavity which is difficult to treat is the vaginal cavity; this is at least partly due to the exposure of the vaginal mucosa to vaginal fluids. Pessaries are most widely used for the delivery of drugs to the vagina in order to treat a range of vaginal
10 conditions. For example, these are well known for use in treating conditions such as vaginitis (a condition which is typically caused by mixed infection with *Candida spp*, *Trichomonas vaginalis* and/or *Gardnerella vaginalis*). One example of such a product is Gynomax[®], marketed by Embil Pharmaceuticals, which contains the active agents tioconazole (anti-fungal) and tinidazole (anti-bacterial and antiprotozoal). To be clinically
15 effective, especially in combating trichomoniasis, it is necessary for patients to undergo a 7-day treatment in which one pessary is administered daily. The treatment period can be reduced to 3 days by doubling the daily dose to two pessaries per day. However, the acceptability of pessaries to patients is generally low which often means that the course of treatment is not completed. Since patients tend to experience an improvement in symptoms
20 within the first 24 hours of treatment, this often leads to the situation in which the patient elects to discontinue treatment. This results in recurrence of the infection and, more significantly, development of antibiotic resistance.

A general need thus still exists for improved formulations which are capable of adhering to
25 body surfaces (both internal and external) and, in particular, to mucosal surfaces, especially where the formulation faces extensive amount of body fluids. On the other hand, there still exists a need for such formulations which are also able to provide an extended release of a wide range of actives thereby minimising the frequency of application even under the flushing effect of body fluids.

30 We have now developed pharmaceutical vehicles having improved thermoreversible and bioadhesive properties *in situ* which address the problems associated with conventional formulations for use in treating body cavities and/or body surfaces, in particular those which have been proposed for application to mucosal membranes.

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Brief Description of the Figures

Figure 1 demonstrates a tensile testing to compare the bioadhesion of the formulation of Example 2 (RFA411-15) with Universal Placebo base (RFA411-46).

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Figure 2a shows drug release (whole) in μg from the formulation of Example 2 (RFA411-15) through PVDF membrane.

Figure 2b shows drug release (diluted 10% with VFS) in μg from the formulation of Example 2 (RFA411-15) through PVDF membrane.

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Figure 3a shows drug release (whole) in % release from the formulation of Example 2 (RFA411-15) through PVDF membrane.

Figure 3b shows drug release (diluted 10% with VFS) in % release from the formulation of Example 2 (RFA411-15) through PVDF membrane.

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Figure 4a shows comparative drug release (whole) in μg from the formulation of Example 2 (RFA411-15) through porcine vaginal tissue.

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Figure 4b shows comparative drug release (diluted 10% with VFS) in μg from the formulation of Example 2 (RFA411-15) through porcine vaginal tissue.

Figure 5a shows comparative drug release (whole) in % release from the formulation of Example 2 (RFA411-15) through porcine vaginal tissue.

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Figure 5b shows comparative drug release (diluted 10% with VFS) in % release from the formulation of Example 2 (RFA411-15) through porcine vaginal tissue.

Detailed Description of the Invention

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The thermoreversible and highly bioadhesive pharmaceutical vehicles according to the present invention, following application to an internal or external body surface, undergo a thermoreversible transformation (sol-gel transition) on warming to body temperature thereby improving their retention at the target site. By appropriate selection of the active (or

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combination of actives), these also have the benefit that these continue to release the active (or actives) for an extended period of time, e.g. up to several days. As a result, the number and frequency of applications can be reduced and, in certain cases, a single dose (i.e. once only) treatment will suffice.

5

A further advantage of the pharmaceutical vehicles which have been developed is their ability to tailor or 'tune' the release profile of one or more active agents which may be dispersed or otherwise dissolved therein. This is particularly beneficial where more than one active agent is to be delivered, the different actives having different degrees of solubility in the delivery vehicle. For example, a first active which is only slightly soluble or insoluble in the vehicle may exhibit a rapid or 'burst' release following delivery to the target site, whereas a second active which is more soluble may be released more slowly from the vehicle thereby providing an 'extended' release profile. The vehicles are thus able to function not only as highly effective carriers for active agents, but also as a depot from which these can be delivered over extended periods of time.

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The pharmaceutical vehicles which have been developed are not dependent on the nature of the active agent and any compatible, pharmaceutically active substance or combination of such substances may be used. A wide range of active drug substances can therefore be delivered using these vehicles.

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In one aspect the invention provides a pharmaceutical vehicle suitable for delivering a pharmaceutically active agent to a body cavity and/or a body surface, said vehicle comprising:

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- a) a poloxamer mixture containing at least two poloxamers;
- b) a fatty acid ester derived from a C₈ to C₂₂ saturated or unsaturated fatty acid; and
- c) a glycol ether.

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Pharmaceutical compositions comprising a pharmaceutical vehicle as herein described and at least one pharmaceutically active agent, preferably a combination of active agents, form a further aspect of the invention.

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The pharmaceutical vehicles and compositions in accordance with the invention are generally liquid or semi-solid at ambient temperature (i.e. below about 30°C, preferably below about 25°C) which means that these can be applied to the desired body surface or

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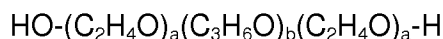
cavity, e.g. mucous membrane, by conventional means. At body temperature, these undergo a sol-gel transition to become viscous (or, in certain cases, more viscous) and to form a non-flowing gel which is capable of delivering the active agent (or active agents) as required and, preferably, for prolonged periods of time. They typically have a sol-gel transition temperature in the range of from about 25 to about 40 °C, preferably from about 25 to about 37 °C, e.g. around 35 °C.

Preferably, the formulations will be viscous liquids, gels or creams at ambient temperature. As such, these can be applied in most dosage forms, including not only topical but also those adapted for parenteral administration. For example, low viscosity liquids may be administered directly to the intended delivery site by injection. The degree of viscosity of the formulations can vary widely and will depend on a number of factors, not least the amount of any bioadhesive component(s) which may be present, the drug loading, etc. The formulations may range from thin liquids to gels; these will typically have viscosities in the range of from 1,000 to 500,000 cps at ambient temperature. Preferably, the viscosity of the formulations will lie in the range of from 80,000 to 200,000 cps, more preferably from 120,000 to 180,000 cps at ambient temperature (e.g. about 25 °C), and in the range 250,000 to 350,000 cps, more preferably from 270,000 to 300,000 cps at body temperature (e.g. in the range 35 to 40 °C) (when measured using a Brookfield Viscometer with a Spindle RV-TF @ 10 rpm for 1 minute).

In a further aspect the invention provides a method of delivering one or more active agents to a body cavity and/or body surface (e.g. a mucous membrane), said method comprising the step of providing a pharmaceutical composition as herein defined and applying said composition to the body cavity or body surface. The composition is applied in an amount sufficient to deliver a pharmaceutically effective amount of the active agent (or agents) to the intended site of treatment.

In a yet further aspect the invention provides a pharmaceutical composition as herein defined for use in a method of delivering one or more active agents to a body cavity and/or body surface (e.g. a mucous membrane). Use of components a), b) and c) in the manufacture of a medicament for use in such a method forms a further aspect of the invention.

The thermoreversible gelling properties of the vehicles and compositions arise from the use of a mixture of poloxamers. Poloxamers are a family of ethylene oxide-propylene oxide block copolymers. They may also be referred to as copolymers of polyethylene oxide (PEO) and polypropylene oxide (PPO) and may be represented by the formula:



where a and b denote the number of polyethylene oxide or polypropylene oxide units, respectively (i.e. the PEO and PPO segments). The values of a and b will vary depending on the particular grade of poloxamer. In general, each a is about 10 to about 150, preferably from 12 to 101, and b is about 20 to about 60, preferably from 20 to 56.

Ethylene oxide-propylene oxide block copolymers in which the number of polyethylene oxide units is at least about 50% of the number of units in the molecule are preferred for use in the invention, in particular those in which at least about 60%, more preferably at least about 70% of the units are polyethylene oxide. Those having approximately 70% or approximately 80% polyethylene oxide units are especially preferred. Copolymers having an average molecular weight of from about 5,000 to about 15,500, preferably from about 7,000 to about 15,500, yet more preferably from about 7,500 to about 15,000 may be used.

Suitable poloxamers for use in the invention are those sold under the tradenames Pluronic® and Lutrol® by BASF. Preferred grades of poloxamers include Poloxamer 407, Poloxamer 188, Poloxamer 124, Poloxamer 237, Poloxamer 338 and mixtures thereof, the specifications of which are detailed below:

<i>Poloxamer</i>	<i>Physical form at ambient temperature</i>	<i>a</i>	<i>b</i>	<i>Average molecular weight (g/mol)</i>
407	Solid	101	56	9,840-14,600
188	Solid	79	28	7,680-9,510
124	Liquid	12	20	2,090-2,360
237	Solid	64	37	6,840-8,830
338	Solid	141	44	12,700-14,600

Particularly preferred for use in the invention are Poloxamer 407 (available from BASF as Pluronic® F127) and Poloxamer 188 (available from BASF as Pluronic® F68).

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The poloxamer mixture contains at least two poloxamer polymers, preferably first and second poloxamers. Preferably the first poloxamer is selected from Poloxamers 407, 124, 237 and 338. More preferably, the first poloxamer is Poloxamer 407. Preferably, the second poloxamer is selected from Poloxamers 188, 124, 237 and 338. More preferably, the second poloxamer is Poloxamer 188. A preferred poloxamer combination for use in the invention is that comprising Poloxamer 407 and Poloxamer 188.

Where first and second poloxamer polymers are present, these may be present in a weight ratio of about 6:1 to about 1:6, more preferably about 2:1 to about 1:2, e.g. about 1.5:1 to 1:1.5.

The total amount of the poloxamer polymers in the vehicles and compositions herein described will generally be in the range of from 1 to 30 wt.%, preferably 20 to 30 wt.%, yet more preferably from 25 to 30 wt.%. It is generally preferred that the total amount will not exceed 30 wt.%.

The thermoreversible character of the formulation imparts a low viscosity at ambient temperature. Generally, this will thus be in liquid or semi-solid form at ambient temperature and viscous at body temperature. Administration of the formulation in liquid or semi-solid form permits ready and uniform application and distribution on the desired body surface (whether external or internal). On warming to body temperature, the more viscous form permits improved adhesion by limiting the flow of the product.

The superior bioadhesion effect of the vehicles and compositions herein described is achieved using a combination of a fatty acid ester derived from a C₈ to C₂₂ saturated or unsaturated fatty acid and a glycol ether. This specific combination notably increases bioadherence of the pharmaceutical vehicle or composition on a body surface, especially in a mucosal media. With combination of the thermogelling properties by virtue of the poloxamers, release profile of pharmaceuticals are considerably improved as demonstrated in the examples. This has particular advantages in excessively mucosal or wet media such as nasal, vaginal and buccal regions in a living body.

Examples of saturated fatty acids which may be used to form the fatty acid esters according to the invention include caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid and behenic acid. Unsaturated fatty acids which

may be used include palmitoleic acid, oleic acid, linoleic acid, linolenic acid and arachidonic acid. Preferred for use in the invention are unsaturated fatty acids, in particular oleic acid.

Particularly suitable for use in the invention are fatty acid esters of polyhydric alcohols. In such cases, the hydroxy-containing component may be partially or fully esterified with one or more fatty acid components. Suitable polyhydric alcohols include glycerol, 1,2-propanediol and 1,3-propanediol. Fatty acid esters formed from polyhydric alcohols may be mono-, di- or tri-valent. Those which comprise a single ester group (i.e. monoesters) are preferred for use according to the invention. In the case of di- or tri-esters, the fatty acid components may be the same or different. In a preferred aspect of the invention, the polyhydric alcohol is glycerol.

Examples of fatty acid esters for use in the invention in which the hydroxy-containing component is a polyhydric alcohol are glyceryl monooleate, glyceryl monolinoleate, glyceryl monolinolenate, glyceryl monostearate, glyceryl palmitostearate, and combinations thereof. Particularly preferred is glyceryl monooleate (monoolein).

The fatty acid esters for use according the invention are either commercially available or may readily be synthesized using esterification methods well known in the art. Many of the commercially available fatty acid esters are not 100% pure, but tend to contain more than about 80%, typically more than about 90% by weight of the desired fatty acid ester. Other components of the mixtures may include other fatty acid esters and other fatty acids.

Glyceryl monooleate (GMO) is available commercially from various sources, e.g. as Myverol from Kerry Bio-Science. Typically, GMO is supplied as a mixture of glycerides of oleic acid (primarily) and other fatty acids. GMO products having a monoester content of not less than 90% are preferred for use in the invention. Typically, the melting point of the mixture will lie in the range 35 to 37°C and the water content will be less than 1.0%.

The amount of fatty acid ester present in the vehicles and compositions herein described will generally be in the range of from about 0.1 to about 1 wt.%. More preferably, this will be present in an amount of less than 0.5 wt.%, e.g. in an amount in the range 0.1 to 0.3 wt.%.

Suitable glycol ethers for use in the invention include ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, propylene glycol monoethyl ether and dipropylene glycol monoethyl ether. Although a mixture of glycol ethers may be used, a single glycol ether is

preferred. Particularly preferred is diethylene glycol monoethyl ether or DGME (also known as ethoxydiglycol). DGME is a pharmaceutical grade transparent liquid (MW 134.2) with unique solubilizing properties. It has the ability not only to solubilize both hydrophilic and hydrophobic materials, but also has penetration enhancing properties. It is marketed as a highly purified liquid under the tradename Transcutol® (Gattefosse s.a., Saint Pres Cedex, France).

The amount of glycol ether present in the vehicles and compositions herein described will generally be in the range of from about 0.05 to about 1 wt.%, preferably from 0.1 to 0.6 wt.%, e.g. about 0.5 wt.%.

The bioadhesive character of the formulation improves the contact between the active or combination of actives and the body surface. This results in improved retention and increased therapeutic efficacy, thereby reducing the number of applications and the duration of treatment required. The bioadhesive nature of the formulation further limits the flow of the product once *in situ*.

Other natural or synthetic bioadhesive enhancing agents may also be present in the vehicles and compositions herein described in addition to the fatty acid ester and glycol ether components. Examples of such agents are disclosed in WO 2005/087270, the entire content of which is hereby incorporated by reference. Particularly suitable are poly(carboxylic acid-containing) based polymers, such as poly(acrylic, maleic, itaconic, citraconic, hydroxyethyl methacrylic, methoxyethyl methacrylic, methoxyethoxyethyl methacrylic or methacrylic) acid which have strong hydrogen-bonding groups, or derivatives thereof such as salts and esters. Appropriate bioadhesives having this form are available commercially (e.g. from Goodrich) as Polycarbophil, e.g. Noveon AA-1, Carbomer (Carbopol), e.g. Carbopol EX165, EX214, 434, 910, 934, 934P, 940, 941, 951, 971, 974P, 980, 981, 1342 and 1382.

Other bioadhesives which may be present include cellulose derivatives such as methyl cellulose, ethyl cellulose, methylethyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl ethyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose or cellulose esters or ethers or derivatives or salts thereof, e.g. hydroxypropyl methyl cellulose-E15 (HPMC E-15) or sodium carboxymethyl cellulose-H

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(Sodium CMC-H). Combinations of two or more cellulose derivatives may also be employed, for example HPMC E-15 and Sodium CMC-H.

Other naturally occurring or synthetic polymers may also be used for their bioadhesive properties, e.g. acacia gums, xanthan gum, guar gum, locust bean gum, tragacanth gums, karaya gum, ghatti gum, cholla gum, psillium seed gum and gum arabic; clays such as manomorphonite clays, e.g. Veegum, attapulgite clay; polysaccharides such as dextran, pectin, amylopectin, agar, carrageenan, mannan or polygalactonic acid or starches such as hydroxypropyl starch or carboxymethyl starch; lipophilic formulations containing polysaccharides, e.g. Orabase (Bristol Myers Squibb); carbohydrates such as polysubstituted with groups such as sulphate, phosphate, sulphonate or phosphonate, e.g. sucrose octasulphate; polypeptides such as casein, gluten, gelatin, fibrin glue; chitosans which are a natural polycationic copolymer consisting of glycosamine and N-acetylglucosamine units (e.g. the chloride salt, lactate or glutamate thereof) or carboxymethyl chitin; glycosaminoglycans such as hyaluronic acid and its derivatives; metals or water soluble salts of alginic acid such as sodium alginate or magnesium alginate; scleroglucan; adhesives containing bismuth oxide or aluminium oxide; atherocollagen; polyvinyl polymers such as polyvinyl alcohols, polyvinylmethyl ethers, polyvinylpyrrolidone, polycarboxylated vinyl polymers (such as polyacrylic acid); polysiloxanes; polyethers; polyalkylene oxides and glycols, e.g. polyethylene oxides and glycols; polyalkoxys and polyacrylamides and derivatives and salts thereof; polyglycolic and polylactic acid homopolymers and copolymers; glycolide and lactide copolymers, e.g. poly-L-(lactide co-glycolide); and polymeric emulsifiers, e.g. Pemulen™ polymeric emulsifiers which are high molecular weight, cross-linked copolymers of acrylic acid and a hydrophobic comonomer.

Where additional bioadhesive components are present, these will preferably be selected from: poly(carboxylic acid-containing) based polymers; tragacanth gums; pectin; carrageenan; chitosan; starches; gelatin; hyaluronic acid and derivatives thereof; cellulose derivatives; polyethylene glycols; and polymeric emulsifiers. Poly(carboxylic acid-containing) based polymers such as polyacrylic acid are especially preferred.

Where any other bioadhesive enhancing agents are present, these will typically be present in the vehicles and compositions in an amount in the range of from about 0.1 to about 1 wt.%, preferably from 0.1 to 0.5 wt.%, e.g. 0.1 to 0.3 wt.%.

Other conventional components may also be included in the vehicles and compositions herein described, for example, preservatives (e.g. propylparaben, methylparaben, phenoxyethanol, etc.), antioxidants (e.g. BHT or BHA), pH adjusters (e.g. lactic acid, etc.) anti-foaming agents (e.g. simethicone emulsion), neutralizing agents, dispersing agents, 5 penetration enhancers, solubilizers, emulsifiers, etc. These components may each be provided in an amount ranging from about 0.1 to about 15 wt.%, preferably in an amount from 0.1 to 10 wt.%, more preferably from 0.1 to 5 wt.%, e.g. from 0.1 to 1 wt.%.

Anti-foaming agents may be used to suppress foaming during manufacture of the vehicles 10 and compositions. Particularly suitable for use in this regard are simethicone-containing emulsions, e.g. Simethicone Emulsion, USP which is a non-ionic emulsion containing 30 wt.% simethicone.

Solubilizers which may be present include polyvinylpyrrolidones such as plasdone povidone 15 which is a synthetic water-soluble homopolymer of N-vinyl-2-pyrrolidone. It has adhesive, film forming and surface active properties and may be used to enhance the solubility and bioavailability of poorly soluble drugs. In certain cases, it may also function to inhibit crystal growth of an active agent.

Inorganic bases, such as sodium hydroxide, may be present to act as neutralizing agents. 20 Other compounds suitable for this purpose include potassium hydroxide, triethanolamine, aminomethyl propanol, trisamino- and tetrahydroxypropyl ethylenediamine. Amino acids such as β -alanine and lysine can also be used for neutralization and viscosity modification. Sodium hydroxide may also function as a pH adjuster.

25 Dispersing agents which may be present include propylene glycol. This is also known for its emollient, humectant and viscosity modifier properties. Alternatives to propylene glycol include glycerine, sorbitol, butylene glycol, etc.

30 Agents may also be present to function as pH adjusters in the vehicles and compositions. These aid in retaining the physical and chemical stability of the formulations. Suitable agents include lactic acid which is also particularly beneficial in the context of a product for application to the vaginal mucosa since it can help to mimic the natural vaginal microflora; normal microflora are primarily lactobacilli which produce sufficient lactic acid to acidify

vaginal secretions to a pH in the range of 3.5 to 4.5. This value is maintained by the lactobacilli which convert glycogen from exfoliated epithelial cells into lactic acid.

The various components of the compositions will generally be admixed in an aqueous system comprising water and a solvent. The solvent should be pharmaceutically acceptable and may be, for example, a C₁₋₆ alcohol, N-methylpyrrolidone, a glycol or a glycol ether (e.g. propylene glycol, 1,3-butylene glycol, dipropylene glycol, diethylene glycol or diethylene glycol monoethyl ether (DGME), or an ether (e.g. diethyl ether). Mixtures of any of these solvents may also be used. A preferred solvent system is that containing water and DGME.

At ambient temperature, the compositions herein described may take the form of a liquid, gel, paste, cream, viscous solution or dispersion. Preferably, these take the form of a liquid, cream or gel which is easy to apply. Particularly preferred are compositions which are in the form of a cream or viscous liquid (e.g. gel).

When brought into contact with a body surface, area or cavity *in vivo*, the compositions undergo a phase transition whereby to form a highly effective drug delivery system from which the active agent (or active agents) may be delivered. In a preferred embodiment, these form a depot from which the active or actives may be delivered over an extended period of time. The site to which the composition is delivered will depend on the condition to be treated and the nature of the active agent used. In this regard, it is noted that the condition to be treated may be remote from the site of application. For example, administration to the nasal cavity may be used to deliver a drug to the CNS in the treatment of central nervous system disorders. Typically, however, the condition will be one which directly affects the body surface or cavity to which the composition is applied.

A bioadhesive depot composition may be formed by administration to any body surface or body cavity, including body cavities which are artificially formed, e.g. during surgery. For example, administration may be to the surface of the skin, to a mucous membrane (e.g. the esophageal, cervical or endometrial mucosa), to a nail or nail bed (e.g. a toe or finger nail), to ophthalmic, nasal or oral surfaces (e.g. sublingual), to a body cavity such as the vaginal, rectal or buccal cavity, to a periodontal pocket or cavity, to a bone cavity, or to any body cavity which may exist prior to surgical implantation of a device or implant (examples of such devices and implants include stents, cosmetic implants, teeth and materials for filling teeth, etc.). In certain cases, however those skilled in the art will appreciate that the

composition of the present invention may be used in other medical applications such as ocular, otic, pulmoner, transdermal, intradermal and intravenous treatment and diagnosis.

In one embodiment of the invention, the compositions may also be applied to a cavity which forms part of a joint (e.g. a joint space). Where necessary or appropriate, a joint space may be formed by aspiration of the synovial fluid using methods conventionally known in the art.

The mode of application will depend on the nature of the formulation and intended site of treatment. Both topical and systemic methods of administration may be used. For example, the composition may be directly applied by methods known in the art such as spraying, dipping, rinsing, application from a pad or ball roller, intra-cavity injection (e.g. to an open cavity with or without the use of a needle), dropping (e.g. into the eye or nasal cavity), applying in the form of a patch (e.g. a bioadhesive patch for application to the surface of the skin), etc. In the case where the formulation has low viscosity at normal temperatures, this may also be administered by aerosol spray, by pump spraying or using an injector. Where the compositions are to be administered by aerosol spray, these will usually also include a suitable propellant. Volatile compounds may be used as propellants and include hydrocarbons (e.g. C₁₋₄ hydrocarbons and their fluorinated derivatives), carbon dioxide and nitrogen.

Very low viscosity or liquid formulations may also be administered parenterally, such as by injection (e.g. by intramuscular or intra-articular injection). For example, intra-articular injection may be appropriate when delivering the active to treat a condition which affects a joint (e.g. pain, inflammation or stiffness which may be associated with arthritic conditions).

Any formulation for injection should be sterile and this can be achieved by any conventional means, such as by autoclaving. The viscosity of the very low viscosity formulations should generally not exceed 5,000 cps at ambient temperature (e.g. about 20°C), and preferably should be no more than 3,000 cps under these conditions.

Methods for making the pharmaceutical vehicles and compositions herein described also form part of the invention. These may be made by methods which involve dissolving or dispersing the mixture of poloxamers in a solvent or solvent system at low temperature, e.g. at a temperature below about 25°C, preferably in the range 10-15°C, more preferably in the range 5-10°C. The fatty acid ester may similarly be dissolved or dispersed in a solvent or solvent system prior to admixing with the poloxamer mixture. The glycol ester may then be

added to the resulting mixture. In preparing the compositions containing the active agent (or agents) these may subsequently be added to the final mixture or, alternatively, these may be dispersed or dissolved in any of the components of the composition during its preparation.

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In a further aspect the invention thus provides a method for the preparation of the pharmaceutical vehicles and compositions herein described, said method comprising forming a mixture comprising: a) a poloxamer mixture containing at least two poloxamers; b) a fatty acid ester derived from a C₈ to C₂₂ saturated or unsaturated fatty acid; c) a glycol ether; and d) at least one biocompatible solvent or solvent system; and optionally dissolving or dispersing at least one active agent in the resulting mixture or in at least one of components a) to d) prior to forming said mixture.

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The vehicles herein described are suitable for the delivery of a wide range of active drug substances to body cavities and/or body surfaces. Such drug substances may be for human or veterinary use and may be used in the treatment, prophylaxis or diagnosis of a disease or condition. Amongst the substances which may be used for prophylactic purposes are vaccines. Generally speaking, any drug may be used which acts on cells and receptors (e.g. peripheral nerves, adrenergic receptors, and cholinergic receptors), the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulation system, the endocrine and hormone system, the blood circulatory system, synaptic sites, neuroeffector junctional sites, the immunological system, the reproductive system, the skeletal system, the autacid system, the alimentary and excretory systems, the histamine system, and/or the central nervous system. Drugs having a local stimulatory or inhibitory effect on enzymes or proteins, or which have such an effect on DNA and/or RNA synthesis, may also be delivered using the vehicles according to the invention.

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Drugs which may be delivered by the vehicles herein described include, for example anti-infectives, e.g. antibacterial agents such as nitroimidazoles, β -lactams and macrocyclic peptide antibiotics, antifungal agents such as polyene macrolides or azole antifungals; anti-cancer and/or anti-viral drugs such as 5-nucleoside analogues, paclitaxel and derivatives thereof; anti-inflammatories, such as NSAIDs and corticosteroids; analgesics (e.g. narcotic analgesics such as opiates and opioids); anaesthetics; cardiovascular drugs such as blood-pressure lowering or raising agents; prostaglandins and derivatives; nutrients and dietary supplements such as vitamins and minerals; proteins; peptide, protein-based and nucleic

acid-based active agents; hormones; anti-neoplastic agents; anti-histamines; antigens and antibodies; growth factors (e.g. endothelial growth factors); vaccines; vitamins; nutrients and other dietary agents such as coenzymes.

5 The drugs which may be delivered include not only those capable of exerting a therapeutic effect, but also those which may be useful in methods of diagnosis. Examples of such agents include biomarkers, radionuclides, radiolabelled compounds, contrast agents (e.g. X-ray, ultrasound and MRI contrast agents). These are particularly suitable for diagnosing conditions or disorders associated with internal body cavities, such as the vagina, rectum,
10 etc.

Other non-pharmaceutical actives may also be delivered using the formulations which are described herein. These include substances such as cosmetics, fragrances, flavours, essential oils, etc., which may be applied by spraying and which serve to provide an
15 extended release of the active component. Other actives include those having both cosmetic and therapeutic effects, e.g. sun-screens, sun-blocks and after-sun agents. Sun-screens and sun-blocks may include conventional agents, including both physical and chemical sunscreens, which are known either to absorb or scatter UV light. Active agents which provide soothing and/or moisturizing effects are particularly suitable for use in
20 formulations for application to the skin following exposure to the sun.

As described herein, in a preferred aspect of the invention the formulations are capable of extending the period of time in which a drug (or combination of drugs) is in contact with the desired target site. As such, these are particularly suitable for the delivery of actives which
25 would otherwise have a short residence time in the body, e.g. due to rapid uptake by the body and systemic clearance. By administering such agents in a vehicle according to the invention, these can be delivered for an extended period of time. This provides advantages in terms of patient compliance since it reduces the number and/or frequency of dosages required for any given treatment.

30 Suitable actives for local or systemic effect include human and veterinary drugs selected from the group consisting of adrenocorticotrophic hormone (ACTH) and its fragments, angiotensin and its related peptides, antibodies and their fragments, antigens and their fragments, atrial natriuretic peptides, bioadhesive peptides, Bradykinins and their related
35 peptides, calcitonins and their related peptides, cell surface receptor protein fragments,

- chemotactic peptides, cyclosporins, cytokines, Dynorphins and their related peptides, endorphins and P-lidotropin fragments, enkephalin and their related proteins, enzyme inhibitors, immunostimulating peptides and polyaminoacids, f[iota]bronectin fragments and their related peptides, gastrointestinal peptides, gonadotrophin-releasing hormone (GnRH) agonists and antagonist, glucagons like peptides, growth hormone releasing peptides, immunostimulating peptides, insulins and insulin-like growth factors, interleukins, lutenizing hormone releasing hormones (LHRH) and their related peptides, melanocyte stimulating hormones and their related peptides, nuclear localization signal related peptides, neurotensins and their related peptides, neurotransmitter peptides, opioid peptides, oxytocins, vasopressins and their related peptides, parathyroid hormone and its fragments, protein kinases and their related peptides, somatostatins and their related peptides, substance P and its related peptides, transforming growth factors (TGF) and their related peptides, tumor necrosis factor fragments, toxins and toxoids and functional peptides such as anticancer peptides including angiostatins, antihypertension peptides, anti-blood clotting peptides, and antimicrobial peptides; proteins such as immunoglobulins, angiogenins, bone morphogenic proteins, chemokines, colony stimulating factors (CSF), cytokines, growth factors, interferons (Type I and II), interleukins, leptins, leukaemia inhibitory factors, stem cell factors, transforming growth factors and tumor necrosis factors.
- Active agents which are suitable for topical administration, which includes buccal, sublingual, nasal, ophthalmic, dermal, rectal and vaginal delivery routes include, but are not limited to, the following: antibacterials such as chlorhexidine, chloramphenicol, triclosan, tetracycline, terbinafine, tobramycin, fusidate sodium, butenafine, metronidazole; antivirals, including acyclovir; anti-infectives such as bibrocathol, ciprofloxacin, levofloxacin; local analgesics such as benzydamine, lidocaine, prilocaine, xylocaine, bupivacaine; analgesics such as tramadol, fentanyl, sufentanyl, alfentanyl, morphine, hydromorphone, methadone, oxycodone, codeine, acetaminophen; NSAIDs such as acetylsalicylic acid, ibuprofen, flurbiprofen, naproxene, ketoprofen, fenoprofen, diclofenac, etodalac, diflunisal, oxaproxin, piroxicam, indomethacin, sulindac, tolmetin, salicylic acids such as salicylamide and diflunisal; COX-1 or COX-2 inhibitors such as celecoxib, rofecoxib or valdecoxib; nimesulide, meloxicam; corticosteroids; anticancer and immuno-stimulating agents (e.g. methylaminolevulinate hydrochloride, interferon alfa and beta); anticonvulsants (e.g. tiagabine topiramate or gabapentin); hormones (e.g. testosterone, and testosterone undecanoate, medroxyprogesterone, estradiol); growth hormones (e.g. human growth hormone), and growth factors (e.g. granulocyte macrophage colony-stimulating factor),

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immuno-suppressants (cyclosporine, sirolimus, tacrolimus); anti-virals (e.g. acyclovir), vitamin D3 and derivatives thereof; nicotine; and scopolamine.

Conditions particularly suitable for causative or symptomatic treatment by compositions herein described include conditions which affect the surface of the skin (such as eczema and herpes), eye conditions, genital infections (such as vaginitis or genital herpes), infections and conditions affecting the finger and/or toe nails (such as bacterial or fungal infections of the nails, e.g. onychomycosis or paronychia) and, more generally, any conditions resulting in inflammation, pain, itching and/or irritation at any body surface.

Conditions which affect the joints may be treated using the compositions of the invention. Such conditions include, in particular, arthritis (e.g. osteoarthritis, rheumatoid arthritis, etc.). Formulations for use in treating conditions associated with the joints may include one or more of the following active agents: NSAIDs (e.g. phenylbutazone, aspirin, indoprofen); glucocorticoids (e.g. betamethasone hydrogenphosphate disodium, betamethasone dipropionate, dexamethasone hydrogenphosphate disodium, dexamethasone-21-palmitate, prednisolone hydrogenphosphate disodium, dexamethasone acetate plus lidocaine-HCl, prednisolone acetate, rimexolone, triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide); hyaluronic acid, sodium salt, cross-linked hyaluronic acid; glucosamine; chondroitin sulphate; capsaicin; Icatibant (H0E140); Anakinra (recombination form of IL-1 receptor antagonist); and local anaesthetics (e.g. NSAIDs, morphines).

Drugs which are particularly suitable for administration in the vehicles of the invention include those within the following classes: anti-infectives, anti-inflammatories, analgesics and anaesthetics. Most preferred are anti-infectives, such as anti-fungals, anti-bacterials, anti-protozoals, etc.

The compositions herein described are particularly suitable for the treatment and/or prevention of primary and/or secondary vaginal infections, e.g. mixed vaginal infections such as those associated with acute and recurrent vulvovaginal candidiasis, bacterial vaginosis and trichomonal vaginitis and/or their causative agents. Vaginal infections due to *Candida* spp., *Gardnerella vaginalis*, *Trichomonas vaginalis*, group B and D streptococcus and the like, infections due to microorganisms causing vulvitis and vulvovaginitis, and other vaginal infections (e.g. atrophic vaginitis, allergic or irritant vulvo vaginitis, genital psoriasis (with or without clinically relevant infection), vulvitis due to Lichen sclerosis, etc.) may also

be usefully treated using the compositions herein described. They also find use in treatment of any associated symptoms such as inflammation, irritation and itch.

The compositions in accordance with the invention may also find more general use in treating primary and/or secondary genital infections in both men and women, including sexually transmitted infections, e.g. infections due to chlamydia; balanitis; penile dermatitis; herpes genitalis; gonorrhea; etc.

Vaginitis is most often caused by infection with *Candida spp.*, *Trichomonas vaginalis* or *Gardnerella vaginalis*, either singly or mixed. Certain derivatives of imidazole and nitroimidazole are known to have anti-fungal, anti-bacterial and/or anti-protozoal activity and are often used to treat such conditions. Examples of such drugs include miconazole, clotrimazole and metronidazole. Other types of drugs used in treating vaginal infections include nitrofurfuryl derivatives and various antibiotics.

Examples of suitable triazole compounds for use in the invention include terconazole, itraconazole, fluconazole, voriconazole, ravuconazole, posaconazole, hexaconazole and fosfluconazole. Of these, terconazole is preferred. It has a particularly broad spectrum of activity and has been shown to be effective against *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida pseudotropicalis*, *Candida stellatoidea* and *Candida lusitaniae*. Terconazole has the further advantage that this does not kill useful *Lactobacillus* microorganisms which form part of a healthy vaginal flora.

Anti-fungal compounds suitable for use in the compositions according to the invention include griseofulvin, nystatin, polymixin B, terbinafin and atovaquone (Meprone). Preferred anti-fungals are the imidazoles and pharmaceutically acceptable salts thereof. Suitable fungicidally active imidazole compounds include those active against *Candida albicans* such as tioconazole, butoconazole, miconazole (e.g. miconazole nitrate), ketoconazole, clotrimazole, isoconazole, saperconazole, econazole, oxiconazole, sulconazole, azanidazole, neticonazole, clomidazole, croconazole, eberconazole, flutrimazole, bifonazole and spectazole. Particularly preferred are tioconazole or butoconazole.

Other anti-fungal agents which may be used include the echinocandins (β -glucan synthase inhibitors) such as Anidulafungin, Caspofungin and Micafungin; allylamines (squalene monooxygenase inhibitors) such as Amorolfine; and benzimidazoles such as thiabendazole.

Anti-protozoal agents for use in the compositions of the invention include Paromomycin, Diclazuril (Clinacox) and Letrazuril. Preferred anti-protozoals are those which are known to be active against *Trichomonas vaginalis*. Particularly preferred anti-trichomonal drugs are those which also have anti-bacterial activity, in particular against *Gardnerella sp* and other pathogens capable of causing vaginitis, e.g. anaerobic bacteria, group B and D streptococcus and/or pathogens causing other primary or secondary vaginal/genital infections. Examples of suitable anti-protozoal agents include tinidazole, metronidazole, ornidazole, secnidazole and nimorazole. Tinidazole is particularly preferred.

Anti-bacterial agents suitable for use in the invention include those which are active against *Gardnerella sp* and other pathogens capable of causing vaginitis, e.g. anaerobic bacteria, group B and D streptococcus and/or pathogens causing other primary or secondary vaginal/genital infections. Broad spectrum antibiotics such as pivampicillin or clindamycin may usefully be included. Other suitable anti-bacterial agents include chlorquinaldol, diiodohydroxyquinoline, chloramphenicol and spiramycin (rovamycin).

In the treatment of vaginal infections, particularly those of mixed origin, combinations of actives may usefully be used. Particularly preferred for use in the invention is the combination of tinidazole and tioconazole.

It may also be advantageous to use one or more local anaesthetics in the compositions of the invention in order to alleviate the soreness associated with vaginitis. Examples of suitable anaesthetics include aptocaine, bupivacaine, butanilicaine, carticaine, cinchocaine, clibucaine, ethyl parapiperidinoacetyl-aminobenzoate, etidocaine, lidocaine (lignocaine), mepivacaine, oxethazaine, prilocaine, pyrrocaine, ropivacaine, tolycaine, vadocaine, benzocaine, pramoxine and mixtures thereof. The anaesthetic may also be used in the form of a salt, optionally in combination with the base form whereby to achieve extended release of the anaesthetic.

The local anaesthetic may be used in an amount of 0.1-10.0% by weight, preferably 1.0-7.0%. The local anaesthetic is preferably lidocaine and may be used in the form of its free base (for example in an amount of 1.0-3.0%, by weight, preferably about 1.5%) or a salt such as its hydrochloride, for example 1.5-4.0% by weight, preferably about 2%. The use of the anaesthetic at these low concentrations results in the compositions being well tolerated.

One or more wound healing or skin protectant agents may also be present in the compositions. These may be selected from demulcents, absorbents and emollients and include dimethicone (demulcent), allantoin (absorbent), sucralfate and glycerin (absorbent, demulcent and emollient). Examples of other suitable emollients include cocoa butter, white petrolatum and shark liver oil. Dimethicone has been found to be particularly advantageous in facilitating healing of the vaginal mucosa and is therefore particularly preferred for use in the compositions herein described.

In order to counter the inflammation and itching associated with vaginitis, it may be beneficial to include an anti-inflammatory and/or anti-pruritic agent such as hydrocortisone, hydrocortisone acetate, methylprednisolone aceprionate, betamethasone valerate, or the like, or a weak topical steroid and/or plant-derived anti-inflammatory bioactive such as bisabolol or chamomille. Boric acid and/or lactic acid may also advantageously be included as a further active ingredient. The compositions may also include chlorophyll as a deodorant. Other active components which may be present in any composition intended for application to the vaginal mucosa include estrogens such as estriol, conjugated estrogens and promestrien.

Anti-viral agents such as acyclovir, penciclovir, trifluridine, afovirsen, arildone, brivudine, I-docosanol, edoxudine, ganciclovir, idoxuridine, moroxydine, tromantadine and valacyclovir may also be present.

Conventional microbicides capable of preventing HIV and/or other sexually transmitted infections may also be included in the compositions herein described when these are intended for application to the vaginal mucosa. Examples of such agents include those which disrupt or otherwise disable HIV, such as surfactants, e.g. menfegol, benzalkonium chloride, docosanol, C31G (Savvy, nonoxynol-9, sodium cholate), polybiguanides, sodium dodecyl sulphate; antibiotics, e.g. gramicidin, magainins, defensins, protegrins; acidifying agents, e.g. Buffer Gel, Acidform, Lactobacillus crispatus; oxidising agents, e.g. chlorhexidine, povidone iodine, hydrogen peroxide/peroxidase gel; antibodies, e.g. anti-HIV antibodies; long-chain anionic polymers, e.g. cellulose acetate phthalate; reverse transcriptase inhibitors, e.g. UC-781, loviride, tenofovir; agents which block HIV attachment/fusion, such as long-chain anionic polymers, e.g. dextrin-2-sulphate, naphtalene sulphonate polymer (Pro 2000), carrageenan, polystyrene sulphonate, cellulose sulphate, cellulose acetate phthalate, polymeric dimandelic acid ether (SAMMA); dendrimers, e.g.

SPL7013, HIV-binding peptides/proteins, e.g. cyanovirin; T-20; lipid membrane modifiers, e.g. beta-cyclodextrin; anti-CD4 antibodies, e.g. B-12; agents which prevent intracellular HIV replication (e.g. nupurapine 16); reverse transcriptase inhibitors (e.g. UC-781, loviride, tenofovir); and plant products (e.g. Praneem, gossypol, pokeweed antiviral protein), etc.

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The compositions of the invention are also suitable for use in treating anal infections and other inflammatory conditions and associated symptoms. Active ingredients which may be present in the composition include local anaesthetics, steroidal and non-steroidal anti-inflammatory actives and antibacterials. Steroids such as hydrocortisone or its acetate may be present. Bactericides such as benzalkonium chloride and chelating agents such as EDTA can also be included. Astringents such as bismuth galate may also be present.

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The invention is also applicable to treatment of oral cavity mucosa, for example when using anaesthetic, anti-inflammatory, antibacterial, antiviral and/or wound healing active ingredients.

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Other active agents which may be provided in the compositions herein described include bromochlorosalicylanilide, methylrosaniline, tribromometacresol, polynoxylin, chlorophetanol, chlorophenesin, ticlatone, sulbentine, ethyl hydroxybenzoate, haloprogin, piroctone olamine, dimazole, tolclate, sodium thiosulfate, potassium iodide, dapson, tea tree oil, citronella oil, lemon grass, orange oil, patchouli and lemon myrtle.

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In a preferred embodiment of the invention, the compositions will comprise at least first and second actives which are both anti-infectives. For example, the first active may be an antibacterial and anti-protozoal agent, e.g. tinidazole, and the second active may be an anti-fungal agent, e.g. tioconazole.

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The quantity of active (or actives) may be readily determined by those skilled in the art and will depend on several factors, including the nature of the active(s) and of any other non-active components, the condition to be treated, and the duration of treatment, etc. In general, the actives may be used in amounts of from about 0.01 to 25% by weight, preferably from 1 to 20% by weight, more preferably from 5 to 15% by weight.

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The various drug substances which are described herein vary in their hydrophilic and hydrophobic characteristics and this will influence their release profile once the

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compositions have been delivered to the intended site of treatment. As will be described herein, appropriate selection of the drug or combination of drug substances which vary in their hydrophobic/hydrophilic nature enables the drug delivery profile of the compositions to be precisely tailored to provide the desired release characteristics.

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In a preferred embodiment of the invention, the vehicles herein described are adapted for the delivery of a combination of active drug substances which differ in their hydrophobic/hydrophilic properties.

10 Hydrophilic drug substances are those which have a tendency to interact with or be dissolved by water and other polar substances. In contrast, hydrophobic drug substances tend to be non-polar and prefer other neutral molecules and non-polar solvents; these are therefore poorly miscible or non-soluble in hydrophilic solvents such as water. As used herein, the term "hydrophilic" is generally used to refer to drug substances which have a
15 solubility in water excess of 1 wt.% under ambient conditions. Those drug substances which have a solubility in water of less than 0.1 wt.% under the same conditions are generally considered to be "hydrophobic".

The compositions may include a first active agent and a second active agent, preferably a
20 first active agent which is provided in a form which is capable of rapid release and a second active agent which is provided in a form which is capable of extended release. Following application to a body cavity or surface, the first active agent may be in a form adapted for release over a period of from 1 hour to 12 hours and the second active agent may be in a form adapted for release over a period of from 12 hours to 3 days. Preferably, the release of
25 the second active will continue for a period of from 12 hours to 7 days after the end of the release period of the first active agent.

Non-limiting examples of hydrophilic and hydrophobic actives which may be provided in the various formulations herein described, the conditions which these may be used to treat and
30 their preferred route of administration are set out in Tables 1 to 8 below. In respect of any of the conditions given, any of the actives listed may be used alone or, alternatively, in combination. Combinations of hydrophilic and hydrophobic actives are particularly preferred.

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Table 1 - Route: Vaginal

<i>Condition</i>	<i>Hydrophilic Active</i>	<i>Hydrophobic Active</i>
Vaginal conditions, e.g. vaginitis	tioconazole	Tinidazole
	Sulfanilamide	miconazole (e.g. miconazole nitrate)
	Nitrofurazone	terconazole
	Nitrofurantoin	fluconazole
	paromomycin sulfate	ketoconazole
	chloramphenicol sodium succinate	itraconazole
		clotrimazole
		butoconazole (e.g. butonconazole nitrate)
		isoconazole
		superconazole
		econazole
		oxiconazole
		sulconazole
		ornidazole
		secnidazole
		nimorazole
		griseofulvin
		Nystatin
		polymixin B
		pivampicillin
		clindamycin
		spiramycin
		terbinafin (e.g. terbinafin HCl)
		atavaquone
		paromomycin
		diclazuril
		Letrazuril
		chloroquinaldol
		diiodohydroxyquinoline
		chloramphenicol

Table 2 - Route: Topical

<i>Condition</i>	<i>Hydrophilic Active</i>	<i>Hydrophobic Active</i>
Seborrheic dermatitis	Coal tar solution	Anthralin
	Sodium sulfacetamide	Salicylic acid
		Sulfur
		Clobetasol (e.g. chlobetasol propionate)
		Fluocinonide
		Terbinafin
		Cyclopiroxamine
		Zinc pyrithione
		Climbazole
		Piroctone (e.g. piroctone olamine)
Topical pain and/or irritation (external analgesic)	Methyl nicotinate	Menthol
	Phenol	Capsaicin
		Capsicum oleoresin
		Methyl salicylate
		Natural menthol
		Purified capsaicin
		Turpentine oil
		Eucalyptus oil
Acne vulgaris		Camphor
	Resorcinol	Sulfur
		Salicylic Acid
		Benzoyl Peroxide
	Erythromycin	Isotretinoin
	Azelaic acid	Tretinoin
	Clindamycin (e.g. Clindamycin phosphate)	Benzoyl peroxide
	Sulfacetamide (e.g. Sodium sulfacetamide)	Adapalene
	Tazarotene	

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Infection (antiseptic)	Benzalkonium Chloride	Povidone-Iodine
	Phenol	Bismuth formic Iodide
	Sodium Diacetate	8-Hydroxyquinoline
	Benzethonium Chloride	Hexylresorcinol
	8-Hydroxyquinoline Sulfate	Iodine
	Cetylpyridinium Chloride	Camphor
	Alcohol	
	Merbromin	
	Sodium Hypochlorite	
	Sodium Iodide	
	Chlorohexidine Gluconate Solution	
	Hydrogen Peroxide	
	Thimerosal	
Pain	Diclofenac Sodium	Capsaicin
		Methyl Salicylate
		Menthol
		Eucalyptus
		Methyl nicotinate
		Felbinac
Topical anaesthetics	Pramoxine (e.g. Pramoxine HCl)	Benzocaine
	Povidone-Iodine	Hydrocortisone (e.g. hydrocortisone acetate)
	Cocaine HCl	Lidocaine
	Dyclonine HCl	Prilocaine
	Chloroethane	
Anti-histamines	Doxepine HCl	
Anti-infectives and antibiotics	Erythromycin	Mupirocin
	Povidone-Iodine	Mupirocin Calcium
	Clindamycin phosphate	Benzoyl peroxide
	Clindamycin	Polymyxin B sulfates
	Neomycin	Hydrocortisone acetate
	Gentamycin sulfate	Bacitracin zinc

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		Nystatin
	Sulfacetamide (e.g. sodium sulfacetamide)	
Anti-fungals	Miconazole nitrate	Sulconazole nitrate
		terbinafine hcl
		ciclopiroxolamine
		Clotrimazole
		betamethasone dipropionate
		butenafine HCl
		Nystatin
		Naftifine HCl
		Ketoconazole
		Oxiconazole Nitrate
		selenium sulfide
		Econazole nitrate
		Amphotericin B
Anti-virals	Foscarnet sodium	penciclovir
	Ganciclovir sodium	Acyclovir
		Hydrocortisone
		Imiquimod
		famcyclovir
		valcyclovir
		cidofovir
		Valcancyclovir
Anti-infectives	Povidone-Iodine	Benzoyl Peroxide
	Chlorhexidine Gluconate	Dapsone
	Sodium oxychlorosene	tetrachlorosalicylanilide
	Metronidazole	Sulfur
	mafenide acetate	
	Matenide Acetate	Hydrocortisone
Scabicides and pediculicides	Invermectin	Permethrin
		Crotamiton
		Lindane
Anti-neoplastics	Methotrexate	Fluorouracil

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		Tazarotene
		calcipotriene
		Anthralin
		Salicylic acid
		Acitetrin
Anti-pruritics	Hydroxyzine (e.g. hydroxyzine HCl)	alclometasone dipropionate
	Coal Tar	hydrocortisone
	Pramoxine (e.g. Pramoxine HCl)	flurandrenolide
	Ammonium lactate	Clobetasol propionate
	Doxepine HCl	Fluticasone propionate
		dexamethasone
		Prednicarbate
		desonide
		Betamethasone dipropionate
		Mometasone Furoate
		Halcinonide
		fluocinonide
		fluocinolone acetonide
		hydrocortisone butyrate
		hydrocortisone probutate
		diflorasone diacetate
		Clobetasol propionate
		desoximetasone
		Halobetasol propionate
		hydrocortisone valerate
		Hydrocortisone (e.g. hydrocortisone acetate)
		Crotamiton
		Clotrimazole
Anti-psoriatics	Coal Tar	Alclometasone dipropionate
	tazarotene	Hydrocortisone Acetate
	methotrexate sodium	Fluticasone propionate
		Betamethasone propionate
		Mometasone Furoate
		Clobetasole propionate

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		Methoxsalen
		anthralin
		acitretin
		cyclosporine
		Calcipotriene
Anti-seborrheics	Coal Tar	Hydrocortisone
	Sulfacetamide (e.g. sodium sulfacetamide)	selenium sulfide
		hydrocortisone butyrate
		Pyrithione zinc
		Chloroxine
Cleansing agents	Povidone-Iodine	Benzoyl peroxide
	Chlorhexidine Gluconate	Hexachlorophene
Steroids	Pramoxine (e.g. pramoxine HCl)	Alclometasone dipropionate
	Neomycin	Hydrocortisone acetate
		Hydrocortisone
		flurandrenolide
		Clobetasol propionate
		Polymyxin B Sulfates
		Fluticasone propionate
		dexamethasone
		Prednicarbate
		desonide
		betamethasone dipropionate
		Mometasone Furoate
		Halcinonide
		fluocinonide
		fluocinolone acetonide
		hydrocortisone butyrate
		hydrocortisone probutate
		Clotrimazole
		diflorasone diacetate
		Clobetasol propionate
		desoximetasone
		Benzoyl peroxide

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		Halobetasol propionate
		hydrocortisone valerate
Wart preparations	Podophyllin	imiquimod
		Podofilox

Table 3 - Route: Ophthalmic

<i>Condition</i>	<i>Hydrophilic Active</i>	<i>Hydrophobic Active</i>
Ophthalmic decongestant	Phenylephrine	Ketotifen (e.g. ketotifen fumarate)
	Naphazoline	
	Tetrahydrozoline	
	Oxymetazoline	

5

Table 4 - Route: Otic

<i>Condition</i>	<i>Hydrophilic Active</i>	<i>Hydrophobic Active</i>
Otitis externa	Boric Acid	Carbamide peroxide
	Alcohol	
	Isopropyl Alcohol	

Table 5 - Route: Dermatologic

10

<i>Condition</i>	<i>Hydrophilic Actives</i>	<i>Hydrophobic Active</i>
Dermatitis		Hydrocortisone
Dandruff, Seborrhea, Psoriasis	Coal Tar Solution	Salicylic Acid
		Sulfur
		Anthralin
		Precipitated Sulfur
		Pyrrhione zinc
		Selenium Sulfide
		Coal Tar
		Coal Tar Extract
		Tar Distillate

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		Pine Tar Oil
Topical Antifungal	Povidone-Iodine	Zinc Undecylenate
	Zinc undecylenate	Tolnaftate
		Miconazole Nitrate
		Calcium Undecylenate
		Undecylenic Acid
		Miconazole Nitrate
		Clotrimazole
Hair Regrowth	Minoxidil	Clobetasol (e.g. chlobetazol propionate)
	Coal Tar Solution	fluocinonide
		anthralin
		Coal Tar

Table 6 - Route: Topical

<i>Condition</i>	<i>Soluble Active</i>	<i>Insoluble Active</i>
Diaper Rash and Prickly Heat	8-Hydroxyquinoline Sulfate	
	Benzethonium Chloride	
	Benzalkonium chloride	
	Cetylpyridinium chloride	
Diaper rash	Clavulanate potassium	Tetrachlorosalicylanilide
		Zinc oxide
		Amoxilin
Callus, Corn, Wart, And Ingrown Toenail	Isopropyl alcohol	Salicylic Acid
	Benzoin	Poophyllum resin
	Bleomycin	imiquimod
		cantharidin
		dinitrochlorobeneine
		5-fluorouracil
Athlete's Foot	Resorcinol	Tolnaftate
	Benzoic Acid	Undecylenic acid
		Undecylenate
		Calcium Undecylenate

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		Chlorothymol
		Miconazole (e.g. miconazole nitrate)
Local pain	Lidocaine	aptocaine
	Pramoxine HCl	bupivacaine
	Procaine	Butanilicaine
	Bupivacaine HCl	carticaine
	Butanilicaine HCl	Cinchocaine
	Pyrrocaine HCl	clibucaine
		Parapiperidinoacetyl-aminobenzoate
		etidocaine
		mepivacaine
		oxethazine
		prilocaine
		pyrrocaine
		Ropivacaine
		tolycaine
		vadocaine
		benzocaine
		lignocaine

Table 7 - Route: Anorectal

<i>Condition</i>	<i>Soluble Active</i>	<i>Insoluble Active</i>
	Pramoxine (e.g. pramoxine HCl)	Hydrocortisone acetate
		Hydrocortisone
		Lidocaine
		Mesalamine

5 Table 8 - Route: Anti-dandruff Shampoos

<i>Condition</i>	<i>Soluble Active</i>	<i>Insoluble Active</i>
	Coal Tar	Ketoconazole
		selenium sulfide
		Pyrrithione zinc

		chloroxine
--	--	------------

Table 9 – Route: Nasal

<i>Condition</i>	<i>Hydrophilic Actives</i>	<i>Hydrophobic Active</i>
Anti-infectives		
	Ciprofloxacin	Levofloxacin
		Gentamycin
Analgesics & anti-inflammatory drugs		
	Fentanyl	
	Sufentanyl	
	Alfentanyl	
		Morphine
	Hydromorphone	
	Methadon	
		Oxycodone
		Codeine
	Flurbiprofen	
	Ketoprofen	
	Fenoprofen	
	Diclofenac	
	Etodolac	
	Diflunisal	
	Oxaproxin	
		Piroxicam
	Indomethacin	
	Sulindac	
	Tolmetin	
	Nimesulide	
	Meloxicam	
Anticonvulsants	Tiagabine	
		Topiramate
		Gabapentin
Hormones	Testosterone	

	Medroxyprogesterone	
	Estradiol	
		Oxytocin
Immunosuppressants	Cyclosporine	
	Sirolimus	
	Tacrolimus	
Antiemetics	Ondansetron	
	Granisetron	
	Metoclopramide	
LHRH-agonist drugs	Buserelin	
	Nafarelin	
		Leuprolide
Macromolecular drugs		Hirudin
		Glucagon
		Exenatide
		Octreotide acetate
		Calcitonin
		Heparin sodium
		Insulin
		Desmopressin
		Siyankobalamin
Antimigraine drugs		Sumatriptan
	Zolmitriptan	
	Ergotamine	
	Rizatriptan	
		Frovatriptan
	Flunarizine	
	Pizotifen	
Allergic rhinitis		Fluticasone
	Ciclesonide	
		Triamcinolone
Cardiovascular drugs	Alprenolol	
	Oxprenolol	
	Pindolol	
	Propranolol	
	Nebivolol	
	Acebutolol	

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		Atenolol
	Metoprolol	
	Nifedipine	
	Felodipine	
	Nimodipine	
	Nicardipine	
		Lisinopril
		Enalapril
		Captopril
		Perindopril
	Verapamil	
	Indapamide	
Anti-Alzheimer drugs	Donepezil	
		Galantamine
	Rivastigmine	
	Tacrine	
		Memantine
Anti-Obesity drugs	Fenfluramine	
	Benzphetamine	
	Sibutramine	
Anti-Parkinson drugs	Amantadin	
		Levodopa
	Pramipexole	
	Cabergoline	
	Selegiline	

Table 10 – Route: Buccal

<i>Condition</i>	<i>Hydrophilic Actives</i>	<i>Hydrophobic Active</i>
Antibacterial / antifungal drugs	Chlorhexidine	
	Triclosan	
		Tobramycine
		Metronidazole
Antiviral drugs		Acyclovir
Anti-infectives		

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	Ciprofloxacin	
		Levofloxacin
		Gentamycin
Local analgesic	Benzylamine	
	Lidocaine	
	Prilocaine	
	Xylocaine	
	Bupivacaine	
Analgesics & anti-inflammatory drugs	Fentanyl	
	Sufentanyl	
	Alfentanyl	
		Morphine
	Hydromorphone	
	Methadon	Oxycodone
		Codeine
	Flurbiprofen	
	Ketoprofen	
	Fenoprofen	
	Diclofenac	
	Etodolac	
	Diflunisal	
	Oxaproxin	
		Piroxicam
	Indomethacin	
	Sulindac	
	Tolmetin	
	Nimesulide	
	Meloxicam	

Any of the agents described herein may also be used in the form of their pharmaceutically acceptable salts.

5

When used to deliver drugs into a body cavity, e.g. vaginally or rectally, the compositions may be administered using a suitable applicator which may be disposable. For example, where the compositions are provided in the form of a liquid or cream, a syringe may be

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used to deliver this to the desired body cavity. The syringe may be provided with an appropriate delivery tube or needle.

5 Kits comprising a composition as herein described and an applicator adapted for delivery of the composition to a body cavity and/or body surface form a further aspect of the invention.

10 A device (e.g. a syringe) pre-loaded with at least one dose of a composition as herein described also forms a further aspect of the invention. Any such device will generally be adapted to deliver one or more doses of the product in a highly uniform manner. Typically, a single unit dose may comprise from about 1 to about 10 grams or mls of said composition, preferably from about 2 to about 7 grams or mls, e.g. from about 3 to about 5 grams or mls. Examples of suitable delivery devices include those known in the delivery of vaginal creams, such as that used in the product Gynazole-1® (available from Ther-Rx Corporation).

15

For use in topical application, the compositions may be packaged in any conventional delivery means such as tubes, containers provided with an actuated plunger, etc.

20 Due to the thermoreversible nature of the formulations herein described, these will ideally be packaged with instructions for storage below room temperature, e.g. in a refrigerator. Alternatively, or in addition, these may be housed in external packaging which provides insulation from any external temperature source.

The invention will now be described by way of the following non-limiting Examples:

25

Example 1 - Formulation

A thermo-reversible bioadhesive formulation having the following composition was prepared:

30

INGREDIENTS	INCI NAME	w/w %
<i>Phase A</i>		
<i>Thermogelling Phase</i>		
Distilled Water		43.07
Propylene Glycol, USP	Propylene Glycol, USP	1.00

Pluronic F127 NF Prill Poloxamer 407	Polyoxypropylene-polyoxyethylene block copolymer (Poloxamer 407 NF supplied by BASF)	16.00
Pluronic F68 NF Prill Poloxamer 188	Polyoxypropylene-polyoxyethylene block copolymer (Poloxamer 188 NF supplied by BASF)	11.70
<i>Phase B</i> <i>Bioadhesive Enhancer Phase</i>		
Distilled Water		7.00
Noveon AA-1 Polycarbophil	6-Polyacrylic acid polymer (supplied by Noveon)	0.25
<i>Phase C</i> <i>Polycarbophil Neutralization Phase</i>		
Sodium hydroxide, N.F. (20% solution)	Sodium hydroxide, N.F. (20% solution, supplied by J.T. Baker)	0.50
<i>Phase D</i> <i>Mucoadhesive Composition Phase</i>		
Distilled water		0.17
Myverol 18-99k	Glyceryl monooleate (supplied by Kerry Bio-Science)	0.24
Transcutol	Purified diethylene glycol monoethyl ether EP, and USP-NF (supplied by Gattefosse)	0.09
<i>Phase E</i> <i>Mucoadhesive Antifoaming and coupling enhancement Phase</i>		
Transcutol P	Purified diethylene glycol monoethyl ether EP, and USP-NF (supplied by Gattefosse)	0.50
Dow Corning Q7-2587 30% Dimethicone emulsion, USP	30% Dimethicone emulsion USP (containing 30% dimethicone USP, stearate emulsifiers, sorbic acid, benzoic acid, thickeners and water, supplied by Dow Corning)	1.00
<i>Phase F</i> <i>Actives pre- dispersion Phase</i>		
Propylene glycol, USP	Propylene glycol, USP	10.00
Plasdone K-17, PVP	Polyvinylpyrrolidone (Povidone, USP, supplied by ISP)	3.00
Tinidazole base micronized, EP	Tinidazole base micronized, EP (supplied by Selectchemie AG)	3.00
Tioconazole base micronized, PH, Eu	Tioconazole base micronized, PH, Eu (supplied by Selectchemie AG)	2.00
<i>Phase G</i> <i>Preservatives Phase</i>		
Methylparaben, NF	Methylparaben Ph Eur, BP, NF, FCC, E218	0.10
Propylparaben, Ph Eur, BP, NF, FCC, E 216	Propylparaben, Ph Eur, BP, NF, FCC, E 216	0.02
Phenoxetol, Low Phenol	Phenoxyethanol (supplied by Clariant Corporation)	0.30
<i>Phase H</i> <i>pH Balancing Phase</i>		
Lactic Acid, 88 % USP-FCC	Lactic acid, 88 % USP-FCC (adjusting pH from 5.5 to 7.00, supplied by Mallinckrodt)	0.06
		Total: 100.00

Preparation of Phase D:

Phase D of the composition having the following composition was prepared as outlined below:

5

INGREDIENTS	INCI.NAME	w/w %
<i>Phase A</i> <i>Thermogelling Phase</i>		
Distilled water	Distilled water	34.80
<i>Phase B Bioadhesive Enhancer</i> <i>Phase</i>		
Myverol 18-99 k	Glyceryl monooleate (supplied by Kerry Bio-Science)	47.20
<i>Phase C</i> <i>Polycarbophil Neutralization Phase</i>		
Transcutol P	Purified diethylene glycol monoethyl ether EP, and USP-NF (supplied by Gattefosse)	18.00
		Total: 100.00

10

The Phase A component was weighed into a suitable sized container and a moderate mechanical mixing was initiated. Heating of the Main Batch to 75-80°C was initiated. In a separate vessel Phase B (Main Batch) was mixed and heated to 75-80°C. Once both (A and B) phases were at 75-80°C, a moderate to vigorous mechanical mixing was applied and very slowly Phase A was added into Phase B. The temperature and mixing conditions were maintained for an additional 20 to 30 minutes (during which time the container was covered in order to avoid loss of water through evaporation). Mixing was maintained at a temperature of 75-80°C, and very slowly Phase C was added into the Main Batch. Once a uniform mixture was obtained, the mechanical mixing speed was decreased and the mixture allowed to cool to ambient temperature to provide the final product as a slightly yellow viscous fluid having a viscosity of 2,000 cps (measured using Brookfield Viscosometer/Spindle RV-Sp#4 at 10 rpm for 1 min).

20

0.50 % w/w of the product was provided as Phase D (Mucoadhesive Composition Phase) in the final composition.

25

Preparation of final composition:

1. The water and propylene glycol components of Phase A were weighed into a suitable sized container and a slow to moderate mechanical mixing was initiated. Cooling of
5 the mixture to 10-15°C, preferably between 5-10° was achieved by placing the container into a water bath (containing ice and water).
2. Once the temperature of the Phase A ingredients was between 10-15°C, the Pluronic F 68 NF Prill was slowly sprinkled in with slow to moderate mechanical mixing (avoiding foam formation) until a clear solution was obtained. When a clear, lump-free
10 solution was observed, the Pluronic F127 NF Prill was slowly added and mixed until the solids were in solution and/or a lump-free mixture was obtained.
3. The water component of Phase B was weighed out into a separate container and using a propeller or marine type impeller (to achieve moderate to vigorous mechanical motion) the Noveon AA1 Polycarbophil was sprinkled in. The resulting mixture was mixed
15 until a homogeneous lump-free dispersion was obtained.
4. After obtaining a homogeneous Phase B dispersion (no lumps nor "fish-eyes" are observed at this point), the mixture was added into the Main Batch (Phase A mixture) with slow to moderate mixing and maintaining the temperature conditions (10-15°C). Further mixing was carried out to achieve uniformity.
- 20 5. Once a homogeneous Main Batch mixture was obtained, Phase C (sodium hydroxide, 20% solution) was added and mixed to uniformity, whilst maintaining the low temperature conditions.
6. Phase D (0.50 % w/w) was then very slowly added into the Main Batch at 10-15°C and mixed to uniformity.
- 25 7. Once a homogeneous mixture was obtained, the Phase E ingredients we added very slowly into the Main Batch (one at a time): Transcutol then Dow Corning Q7-2587 30% Simethicone emulsion, USP. A low mechanical mixing speed was maintained at low temperature conditions, preferably at 5-10°C, until a very uniform mixture was obtained.
8. The propylene glycol, USP component of Phase F was added to a stainless steel
30 kettle equipped with a side-sweep mixer and Lightning mixer and the Plasdone K-17 component slowly sprinkled. Mixing was continued until a clear solution formed. The remainder of the Phase F ingredients (active components) were then added: Tinidazole Base, Micronized, EP and Tioconazole Base, Micronized, PH Eur. Mixing was maintained at ambient temperature conditions until a homogeneous-off white dispersion was obtained.

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9. When a homogeneous Phase F dispersion was observed, this was very slowly added into the Main Batch. Slow to moderate mechanical mixing and low temperature conditions (at 10-15°C, preferably between 5-10°C) were maintained and the composition mixed to uniformity.

5 10. One at a time the various Phase G ingredients were added: Methylparaben, NF; Propylparaben, NF; and Phenoxyethanol and the composition mixed to uniformity whilst maintaining the low temperature conditions at 10-15°C, preferably between 5-10°C.

11. The Phase H ingredient (lactic acid, 88 % USP-FCC) was added. Mixing was maintained under low temperature conditions to obtain a uniform mixture. Under slow to
10 moderate mechanical mixing, the Main Batch was then warmed to 20-25°C.

12. The resulting product was a smooth, off-white cream having a pH of 6.8 and a viscosity of 100,000 cps (measured using Brookfield Viscosometer/Spindle RV-TF at 10 rpm for 1 min). Viscosity at 35-40°C will be 30 to 60% higher due to thermoreversible effect.

15 Example 2 - Formulation

A thermo-reversible bioadhesive composition having the following composition was prepared:

INGREDIENTS	INCI NAME	w/w %
<i>Phase A Thermogelling Phase</i>		
Distilled Water		34.92
Propylene Glycol, USP	Propylene glycol, USP	2.00
Pluronic F127 NF Prill Poloxamer 407	Polyoxypropylene-polyoxyethylene block copolymer (Poloxamer 407 NF, supplied by BASF)	15.00
Pluronic F68 NF Prill Poloxamer 188	Polyoxypropylene-polyoxyethylene block copolymer (Poloxamer 188 NF, supplied by BASF)	11.00
<i>Phase B Bioadhesive Enhancer Phase</i>		
Distilled Water		6.00
Noveon AA-1 Polycarbophil	Polyacrylic acid polymer (supplied by Noveon)	0.20
<i>Phase C Polycarbophil Neutralization Phase</i>		
Sodium hydroxide, N.F. (20% solution)	Sodium hydroxide, N.F. (20% solution, supplied by J.T. Baker)	0.40
<i>Phase D Mucoadhesive Composition Phase</i>		
Distilled water	Distilled water	0.17
Myverol 18-99k	Glyceryl monooleate (supplied by Kerry Bio-Science)	0.24

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Transcutol	Purified diethylene glycol monoethyl ether EP, and USP-NF (supplied by Gattefosse)	0.09
<i>Phase E Mucoadhesive Antifoaming and coupling enhancement Phase</i>		
Transcutol P	Purified diethylene glycol monoethyl ether EP, and USP-NF (supplied by Gattefosse)	0.50
Dow Corning Q7-2587 30% Simethicone emulsion, USP	12-30% Simethicone emulsion USP (containing 30% Simethicone USP, stearate emulsifiers, sorbic acid, benzoic acid, thickeners and water, supplied by Dow Corning)	1.00
<i>Phase F Actives pre- dispersion Phase</i>		
Propylene Glycol, USP	Propylene glycol, USP	10.00
Plasdone K-17, PVP	Polyvinylpyrrolidone (Povidone, USP, supplied by ISP)	3.00
Tinidazole base micronized, EP	Tinidazole base micronized, EP (supplied by Selectchemie AG)	9.00
Tioconazole Base Micronized, PH, Eu	Tioconazole base micronized, PH, Eu (supplied by Selectchemie AG)	6.00
<i>Phase G Preservatives Phase</i>		
Methylparaben, NF	Methylparaben Ph Eur, BP, NF, FCC, E218	0.10
Propylparaben, Ph Eur, BP, NF, FCC, E 216	Propylparaben, Ph Eur, BP, NF, FCC, E 216	0.02
Phenoxetol, Low Phenol	Phenoxyethanol (supplied by Clariant Corporation)	0.30
<i>Phase H pH Balancing Phase</i>		
Lactic Acid, 88% USP-FCC	Lactic acid, 88% USP-FCC (adjusting pH from 5.5 to 7.00, supplied by Mallinckrodt)	0.06
		Total: 100.00

Preparation:

5 The composition was prepared analogously to Example 1. The resulting product was a smooth, off-white cream having a pH of 6.4 and a viscosity of 160,000 cps (measured using Brookfield Viscosometer/Spindle RV-TF at 10 rpm for 1 min). Viscosity at 35-40°C will be 30 to 60% higher due to thermoreversible effect.

Example 3 - Bioadhesive properties

10

A study was carried out to compare the bioadhesive strength of the formulation of Example 2 to that of Universal placebo gel.

The Universal placebo gel had the following composition:

<i>Component</i>	<i>w/w %</i>
Hydroxyethyl cellulose (thickening agent)	3.0
Glycerin (wetting agent)	5.0%
Methylparaben (preservative)	0.15%
Propylparaben (preservative)	0.05%
Distilled water, part 1 (solvent)	54.0%
Sodium chloride	0.03%
10% NaOH (pH adjuster)	As needed
10% HCl (pH adjuster)	As needed
Distilled water, part 2 (solvent)	q.s. to 100 %

Method for preparing Universal placebo gel:

1. The appropriate amount of distilled water (part 1) was weighted into a container and the appropriate amount of sodium chloride was added.
- 5 2. The appropriate amount of glycerin was weighed into a beaker and heated to 65 °C.
3. The appropriate amounts of methylparaben and propylparaben were weighed into the small beaker and mixed until all solids had dissolved.
4. The mixture was cooled to <35 °C, the HEC added and mixed until a homogeneous mixture was achieved.
- 10 5. With continuous propeller mixing, the mix from step 4 was added to that from step 1. Mixing was continued until a homogeneous gel was formed.
6. pH was adjusted to 4.5±0.3 by adding the appropriate pH adjustment component. The net weight of the mixture was recorded.
7. The final portion of distilled water was calculated and, with continuous mixing and side scraping, added. Mixing continued until a homogeneous system was achieved.
- 15 8. The resulting gel was covered and allowed to equilibrate at room temperature overnight. pH was then measured and, if necessary, adjusted to 4.5±0.3.

Method:

- 20 Tensile testing was performed on Instron 3342 equipped with a 0.1-10 N load cell. The assembly consisted of a movable measuring probe connected to the load cell and a fixed platform. 600 µL of gel sample was loaded on the surface of the measuring probe (2.5 cm diameter). The tissue biopsy was attached to the fixed platform using cyanoacrylate adhesive. The movable probe was lowered in order to bring the gel in contact with the

tissue. A preload of 0.5 N was applied for 60 secs following which the movable probe was raised at a constant speed of 0.1 mm/s and the force required to do so was recorded as a digital signal.

5 *Results and discussion:*

Figure 1 shows the results from tensile testing to compare the bioadhesion of the formulation of Example 2 to that of the Universal placebo base. Bioadhesion of both formulations was found to be comparable.

10 Example 4 - Drug transport kinetics

A study was carried out to evaluate the drug transport characteristics of the formulation of Example 2 as a whole and diluted with vaginal fluid stimulant (VFS) using the Static Franz cell system.

15

Materials:

Acetonitrile (Fisher Scientific)

Methanol (Fisher Scientific)

Ammonia Solution (Mallincrodt)

20 Lecithin (granular) (Spectrum)

DMSO (VWR)

Polyvinylidene-fluoride (PVDF) membrane (Millipore)

Porcine vaginal tissue

25 Methods:

Preparation of sink media: Tinidazole is a hydrophilic drug with LogP of -0.41 while tioconazole is hydrophobic with a LogP of 4.86. To study the release profile of the formulation it was necessary to produce a suitable sink media that would solubilize both the drugs released from the gel. 1% lecithin and 5% DMSO in phosphate buffered saline (pH
30 7.2) was used as a suitable sink medium that solubilized both drugs.

Diluting gel with VFS: The gel to be studied was diluted 10% with VFS in a 20 mL scintillation vial. The contents were mixed well with a spatula and left overnight for uniform mixing. The diluted gel was then used the next day for the release study.

35

Method for transport studies: The transport studies were conducted using a Franz cell system (PermeGear, Riegelsville, PA). The Franz cells were water jacketed and temperature was maintained at 37 °C throughout the experiment via a circulating water bath. 1% lecithin and 5% DMSO in phosphate buffered saline (pH 7.2) was used as the receptor medium. Permeability studies were conducted using both PVDF membrane (0.45 µm) and porcine vaginal tissue (approx. 400 to 700 µm in thickness). The volume of the receiver chamber was 15 ml of the PVDF study and 5 ml for the tissue study and was continuously stirred by a magnetic stir bar. For release studies using porcine vaginal tissue, 12 mm biopsies were cut and mounted on Franz cells with their epithelial side facing the donor chamber and the connective tissue side facing the receiver chamber. 100 mg of the gel was loaded into each donor chamber. At regular time intervals 400 µl of receptor media was removed from the receiver compartment and replaced with fresh media. Results were adjusted for the dilution of the receiver chamber and analyzed by HPLC. At the end of the study the remaining gel was extracted from the donor chamber and analyzed to obtain the mass balance.

Gel extraction from the donor chamber: At the end of the experiment, the donor chamber was rinsed 3 to 4 times with methanol in a clean beaker using a wash bottle (when using the PVDF membrane the membrane was put in the beaker containing methanol for 1 min and taken out while tissues were stored at -80 °C). The solution was transferred to a 10 ml volumetric flask. The flask was sonicated for 5 mins and vortexed for 1 min. The volume was then made up and 1 ml of the solution was filtered and transferred to HPLC for analysis.

Results:

Figures 2a, 2b, 3a and 3b show the comparative drug release (whole and diluted with 10% VFS) from the formulation through PVDF membrane.

Figures 4a, 4b, 5a and 5b show the comparative drug release (whole and diluted with 10% VFS) from the formulation through porcine vaginal tissue.

Conclusions:

Release kinetics through PVDF membrane: The formulation according to the invention shows a burst release for tinidazole and an extended release for tioconazole. The release kinetics profile did not change much with 10% dilution with VFS.

Release kinetics through porcine vaginal tissue: Drug permeability across vaginal tissue depends on the physicochemical properties of the drug therefore tinidazole being hydrophilic in nature permeated quickly through the spaces in the tissue while tioconazole because of its hydrophobic nature permeated solely by the transcellular route. Dilution with

5 VFS did not significantly affect the release pattern.

Claims:

1. A pharmaceutical vehicle comprising: a) a poloxamer mixture containing at least two poloxamers; b) a fatty acid ester derived from a C₈ to C₂₂ saturated or unsaturated fatty acid; and c) a glycol ether.

2. A pharmaceutical vehicle as claimed in claim 1, wherein the poloxamer mixture comprises at least two poloxamers which are copolymers of polyethylene oxide (PEO) and polypropylene oxide (PPO).

3. A pharmaceutical vehicle as claimed in claim 2, wherein the poloxamer mixture comprises Poloxamer 407 and Poloxamer 188.

4. A pharmaceutical vehicle as claimed in any one of the claims 1 to 3, wherein the fatty acid ester is selected from the group consisting of glyceryl monooleate, glyceryl monolinoleate, glyceryl monolinolenate, glyceryl monostearate, glyceryl palmitostearate, and combinations thereof.

5. A pharmaceutical vehicle as claimed in any preceding claim, wherein the glycol ether is selected from ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, propylene glycol monoethyl ether, dipropylene glycol monoethyl ether, and combinations thereof.

6. A pharmaceutical vehicle as claimed in claim 1, which comprises a combination of Poloxamer 407 and Poloxamer 188, glyceryl monooleate and diethylene glycol monoethyl ether (DGME).

7. A pharmaceutical composition comprising a pharmaceutical vehicle as claimed in any preceding claim and at least one active agent.

8. A composition as claimed in claim 7 which is provided in the form of a viscous liquid, cream or gel.

9. A composition as claimed in claim 7 or claim 8 which comprises a first active agent and a second active agent.

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10. A composition as claimed in claim 9, wherein the first active agent is hydrophilic and the second active agent is hydrophobic.

11. A composition as claimed in claim 9 or claim 10, wherein the first active agent is provided in a form adapted for rapid release and the second active agent is provided in a form for extended release.

12. A composition as claimed in any one of claims 9 to 11, wherein the first active agent is in a form adapted for release over a period of from 1 to 12 hours and the second active agent is in a form adapted for release over a period of up to 7 days in a body cavity and/or body surface.

13. A composition as claimed in any one of claims 9 to 12, wherein said first and second active agents are independently selected from any drug which acts on cells and receptors (e.g. peripheral nerves, adrenergic receptors, and cholinergic receptors), the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulation system, the endocrine and hormone system, the blood circulatory system, synaptic sites, neuroeffector junctional sites, the immunological system, the reproductive system, the skeletal system, the autacoid system, the alimentary and excretory systems, the histaminergic system, and the central nervous system.

14. A composition as claimed in any one of claims 9 to 13, wherein the first and second active agents are independently selected from the group consisting of anti-infectives, anti-inflammatories, analgesics and anaesthetics.

15. A composition as claimed in claim 14, wherein the first and second active agents are both anti-infectives.

16. A composition as claimed in any one of the claims 9 to 15, wherein the first active agent is selected from the group consisting of: tioconazole, sulfanilamide, nitrofurazone, nitrofurantoin, paromycin sulfate and chloramphenicol sodium succinate, and pharmaceutically acceptable salts thereof.

17. A composition as claimed in any one of claims 9 to 15, wherein the second active agent is selected from the group consisting of tinidazole, miconazole, terconazole,

fluconazole, ketoconazole, itraconazole, clotrimazole, butoconazole, isoconazole, superconazole, econazole, oxiconazole, sulconazole, ornidazole, secnidazole, nimorazole, griseofulvin, nystatin, polymixin B, pivampicillin, clindamycin, spiramycin, terbinafin, atavaquone, paromomycin, diclazuril, letrazuril, chloroquinaldol, diiodohydroxyquinoline, chloramphenicol, and pharmaceutically acceptable salts thereof.

18. A composition as claimed in any one of claims 9 to 17, wherein the first active agent is an anti-fungal agent and the second active agent is an antibacterial/anti-protozoal agent.

19. A composition as claimed in claim 18, wherein the anti-protozoal agent is selected from paromomycin, diclazuril (Clinacox), letrazuril, tinidazole, metronidazole, ornidazole, secnidazole, nimorazole, and pharmaceutically acceptable salts thereof.

20. A composition as claimed in claim 19, wherein the antibacterial/anti-protozoal agent is tinidazole

21. A composition as claimed in claim 18, wherein the anti-fungal agent is selected from griseofulvin, nystatin, polymixin B, terbinafin, atovaquone (Meprone), tioconazole, butoconazole, miconazole, ketoconazole, clotrimazole, isoconazole, seperconazole, econazole, oxiconazole and sulconazole, and pharmaceutically acceptable salts thereof.

22. A composition as claimed in claim 21, wherein the anti-fungal agent is tioconazole.

23. A method for the preparation of a pharmaceutical vehicle or composition as claimed in any one of claims 1 to 22, said method comprising forming a mixture comprising: a) a poloxamer mixture containing at least two poloxamers; b) a fatty acid ester derived from a C₈ to C₂₂ saturated or unsaturated fatty acid; c) a glycol ether; and d) at least one biocompatible solvent or solvent system; and optionally dissolving or dispersing at least one active agent in the resulting mixture or in at least one of components a) to d) prior to forming said mixture.

24. The method as claimed in claim 23, wherein the fatty acid ester is derived from a polyhydric alcohol.

25. A method as claimed in claim 24, wherein the polyhydric alcohol is glycerol.

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26. A kit comprising a composition as claimed in any one of claims 7 to 22 and an applicator adapted for delivery of said composition to a body cavity, body surface, and/or a mucosal surface.

5 **27.** A kit as claimed in claim 26, wherein the applicator is disposable.

28. A kit as claimed in claim 26 or claim 27, wherein the applicator is pre-loaded with a single unit dose of the composition.

10 **29.** A kit as claimed in claim 28, wherein a single unit dose comprises from about 1 to about 10 grams or mls of said composition.

30. A kit as claimed in any one of claims 26 to 29, wherein the applicator is a syringe.

15 **31.** A device pre-loaded with at least one dose of a composition as claimed in any one of claims 7 to 22.

32. A composition as claimed in any one of claims 7 to 22 for use in treating or diagnosis of a condition associated with a body cavity, body surface and/or mucosal surface.

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33. A composition as claimed in any one of claims 7 to 22 for use in treatment or diagnosis of a disorder by way of a topical, ophthalmic, nasal, oral, vaginal, rectal, buccal, ocular, otic, transdermal, periodontal, or intramuscular administration route.

25 **34.** A composition as claimed in claim 32 for use in treating vaginitis.

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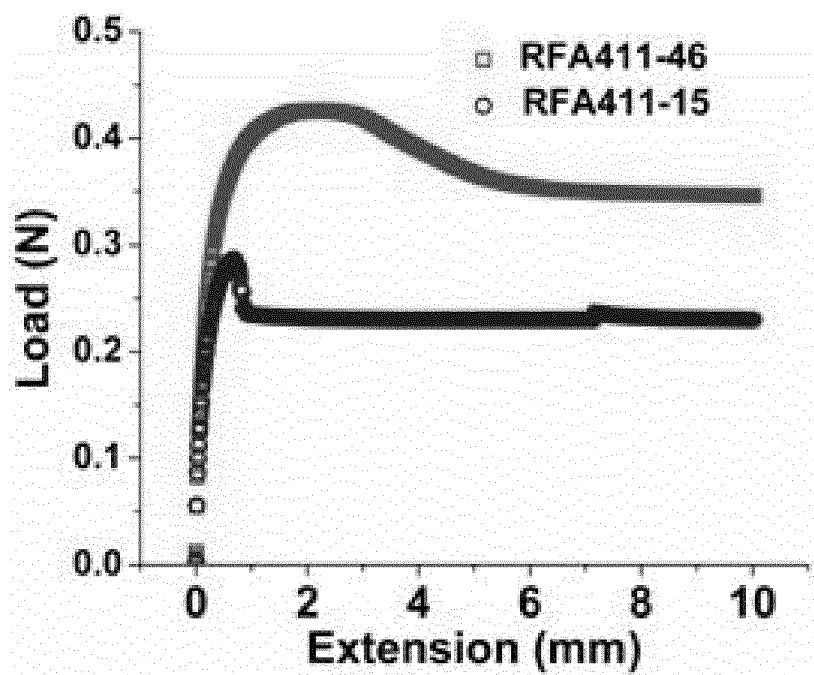
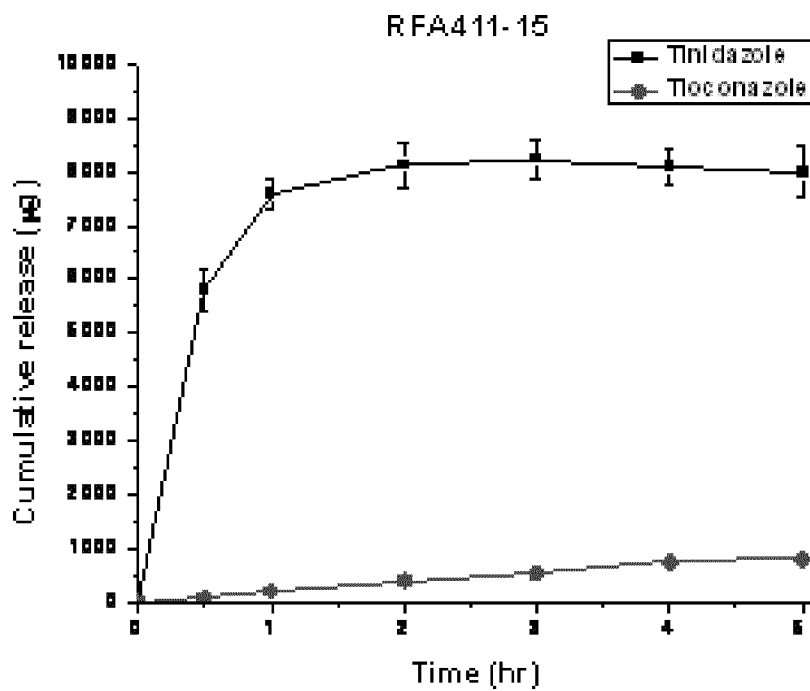
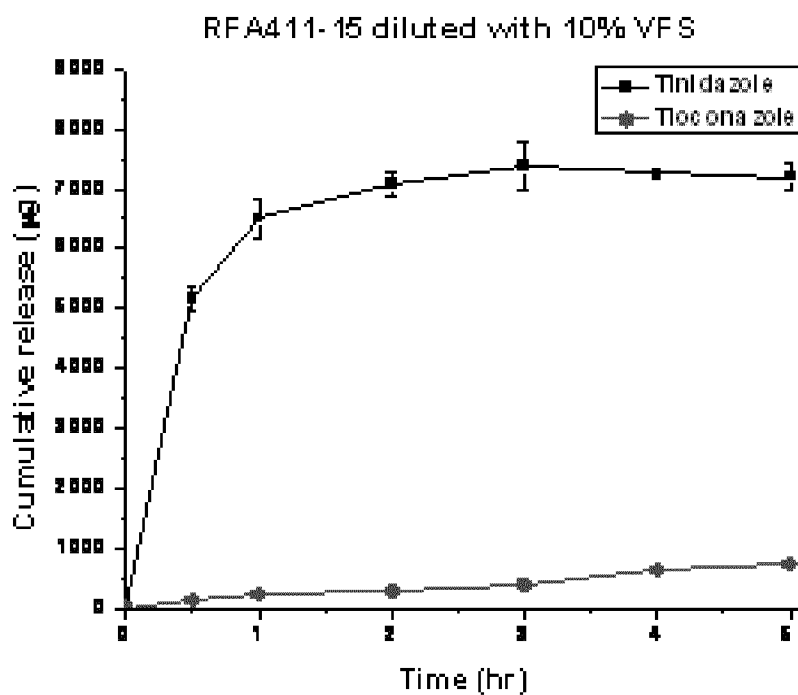
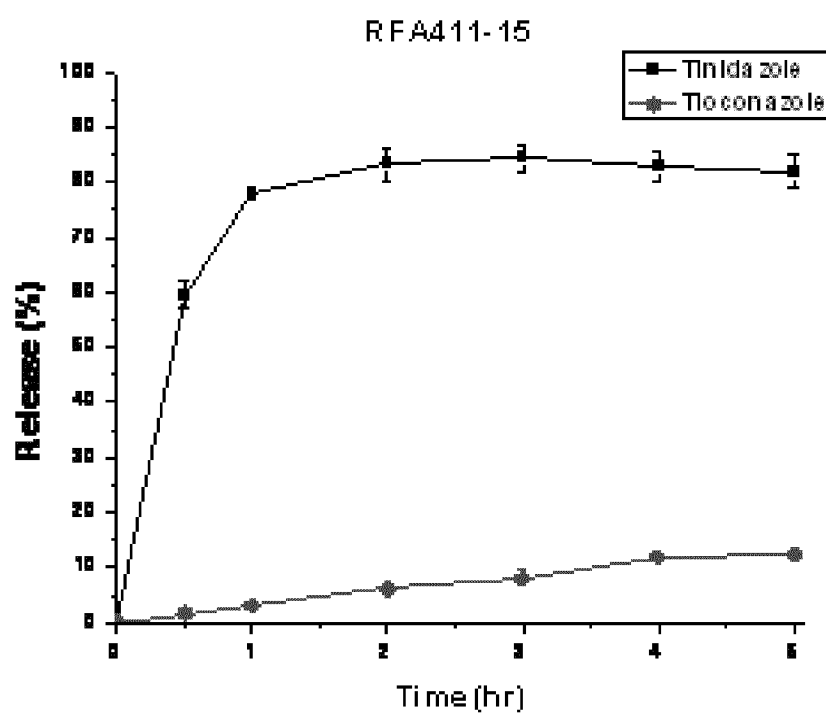
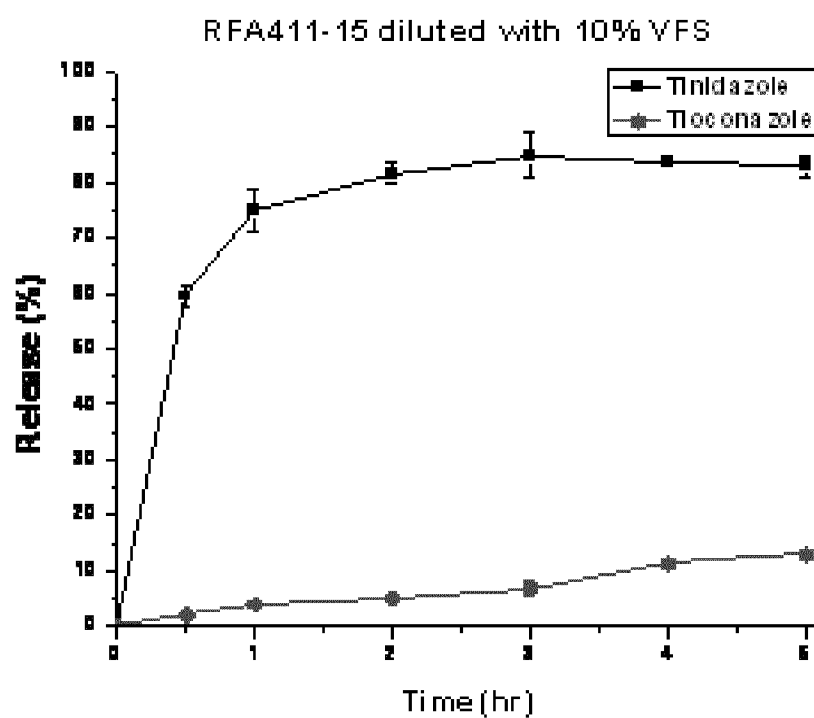
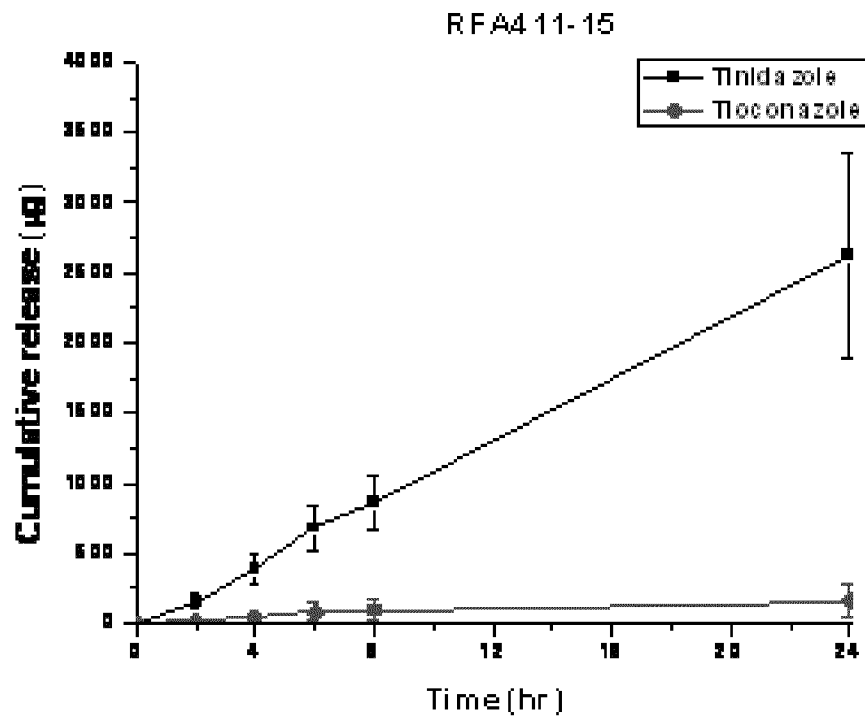
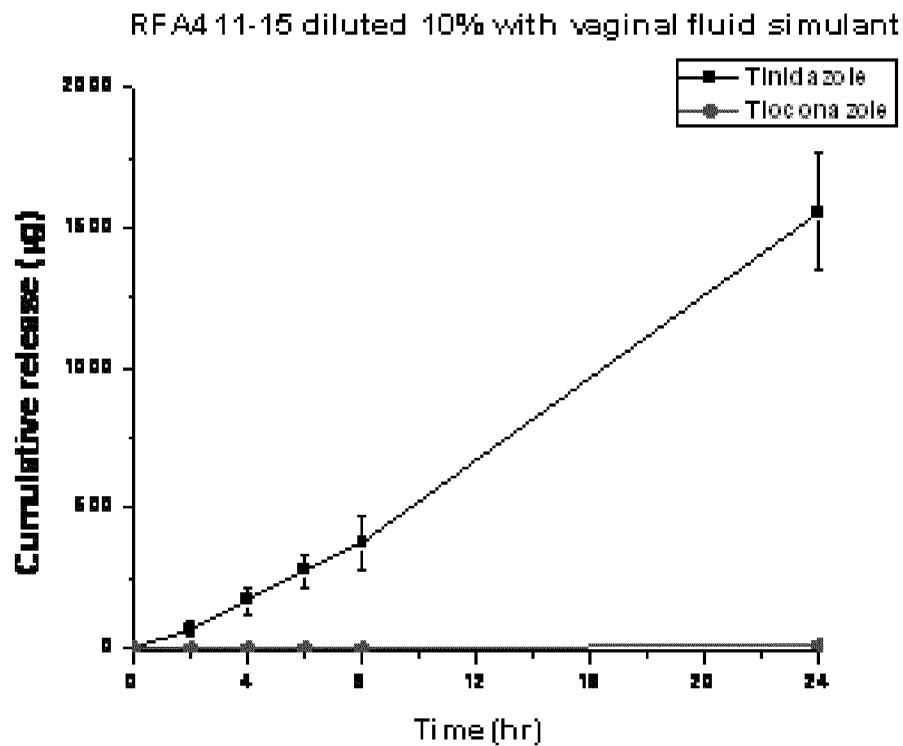
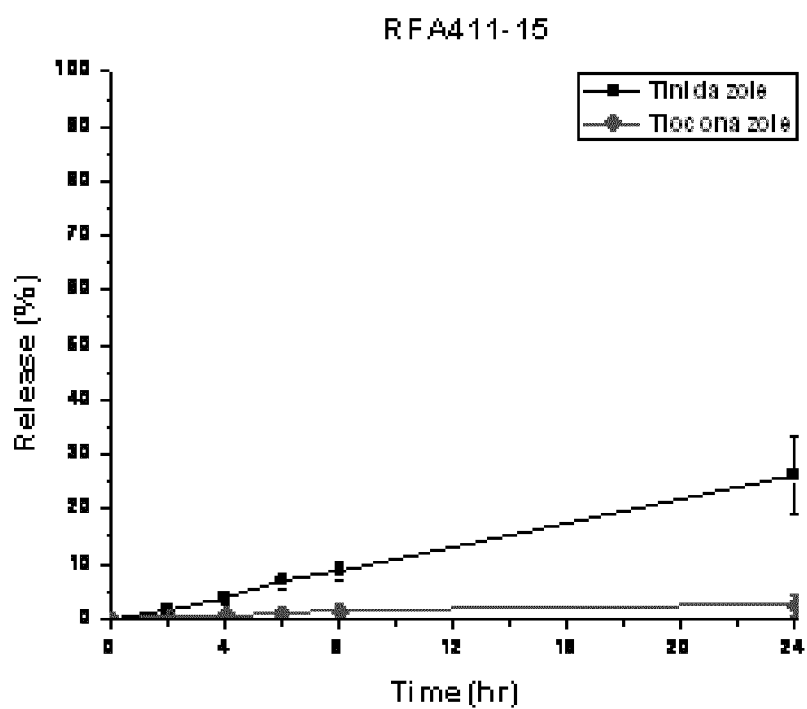
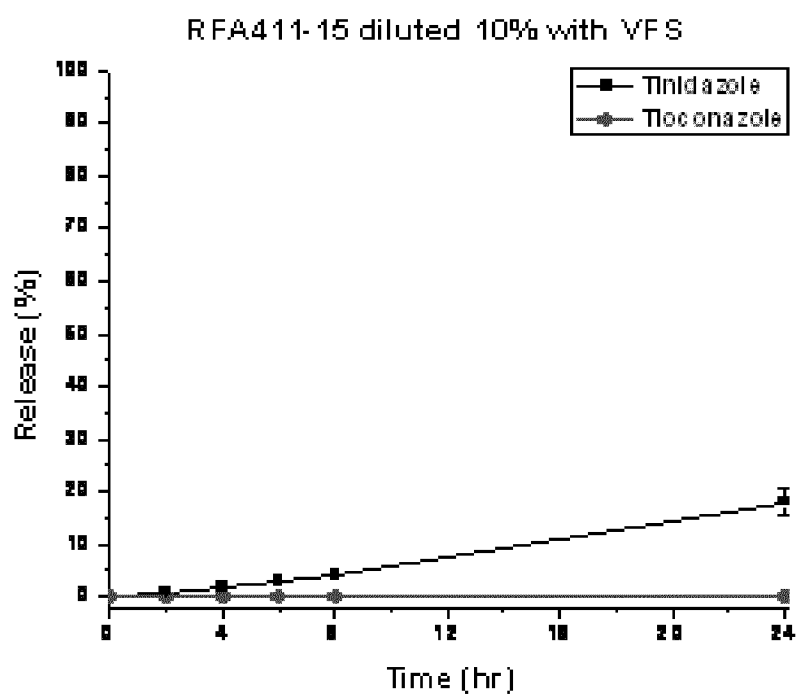


Figure 1

**Figure 2a****Figure 2b**

**Figure 3a****Figure 3b**

**Figure 4a****Figure 4b**

**Figure 5a****Figure 5b**

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/066944

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/00 A61K47/10 A61K9/06 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/087270 A1 (EDKO TRADING REPRESENTATION [TR]; EMBIL KORAL [TR]; BAKTIR GUL [TR]; F) 22 September 2005 (2005-09-22) cited in the application example 4	1-34
Y	----- WO 2006/024138 A1 (TARO PHARMA IND [CA]) 9 March 2006 (2006-03-09) claims examples 1-7	1-34
Y	----- WO 2011/121604 A2 (LINCOLN PHARMACEUTICALS LTD [IN]; PATEL RAJNI GULABDAS [IN]; PATEL JIG) 6 October 2011 (2011-10-06) claims 1-7 ----- -/-	1-34
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 9 October 2013	Date of mailing of the international search report 16/10/2013	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Schüle, Stefanie	

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/066944

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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International application No

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