Abstract:
A composition comprising a diindolyl methane compound and a cyclooligosaccharide. In addition, a formulation of such a composition as well as to the use of such composition or formulation to treat genital warts and/or neoplastic diseases of the reproductive organs is disclosed.
DIINDOLYL METHANE COMPOSITIONS, FORMULATIONS AND USE THEREOF

FIELD OF THE INVENTION

In one aspect, the present invention is directed to a composition comprising a diindolyl methane compound and a cyclooigosaccharide. In other aspects, this invention is directed to a formulation of such a composition as well as to the use of such composition or formulation to treat genital warts and/or neoplastic diseases of the reproductive organs.

BACKGROUND OF THE INVENTION

Human papillomavirus infection is one of the most commonly sexually transmitted infectious diseases. It is believed that more than 50% of the sexually active population may become infected with human papilloma virus (HPV) during their lifetime. HPV infections can frequently cause benign hyperplasia, and in some cases, can initiate the development of malignant tumors of the anogenital area: cancer of the cervix, vulva, vagina, etc. Infection with HPV is known to induce cervical intraepithelial neoplasia (CIN) that is considered as pre-cancerous condition. HPV DNA (mainly 16 and 18 types) is associated with a high degree of carcinogenic risk, and is found in 50-80% of the samples of moderate and severe dysplasia of the squamous epithelium of the cervix and in 90% of invasive cancers.

Cancer of the cervix (cervical cancer) is one of the most prevalent cancers in women. Every year in the world there are nearly half a million new cases of this disease of which 270,000 are deadly. The incidence of and mortality caused by cervical cancer is 16.2 and 9 per 100,000 population, respectively.

Important HPV mediated medical problems include benign manifestations of exophytic and endophytic lesions of various parts of the epithelium of the vulva, vagina and cervix, as well as the surrounding skin and mucous membranes, including the anus. Exophytic forms (genital warts) can be substantially diverse in appearance and size, and often are additionally complicated by secondary bacterial infections and accompanied not only psychological, but also physical suffering of the patient. Genital warts are also a cause of refractory Atego respiratory papillomatosis in children due to vertical transmission of the virus from an infected mother to child.
Conventional methods of treatment of genital warts and pre-cancerous neoplastic diseases of the reproductive organs caused by HPV currently include chemical destruction, surgical excision or ablation. These methods are often accompanied with complications, require the use of expensive medical equipment and are not always effective. As a result a large number of young women with clinical picture of HVP infections become carriers of the infection and pose a risk to sexual partners as well as to unborn children.

Unfortunately, there are no approved drugs on the market that are able to selectively affect the pathological appearance of HPV infections. While it has been attempted to treat HPV infections by using interferons (IFNs) - proteins produced by cells of the immune system in response to the stimulation by viral antigens - in most cases, even long-term IFN therapy did not lead to clinical improvement. (New Advances in Interferon Therapy of Cancer. Scott Wadler and Edward L. Schwartz. The Oncologist August 1997, Vol. 2 , No. 4 pp. 254-267) . It has been shown that the resistance to IFN HPV-infected cervical cells is determined by an increased level of expression of the oncoprotein E7, an intracellular inactivating factor of IFN regulation.

It has recently been proposed that a chemical compound, indole-3-carbinol ("I3C"), a phytonutrient isoflavonoid produced by cruciferous vegetables, may exhibit certain anticancer activity (Cell Cycle. 2005 Sep; 4(9): 1201-15. 2005 Sep 6 .Molecular targets and anticancer potential of indole-3-carbinol and its derivatives. Aggarwal BB1, Ichikawa H.). Safea et al. (Cancer chemotherapy with indole-3-carbinol, bis(3'-indolyl)methane and synthetic analogs Cancer Letters Volume 269, Issue 2, 8 October 2008, Pages 326-338), suggest that the long-term use of this compound prevents the development of tumors of the intestines, lungs, and organs of the female reproductive system. I3C has also been indicated to be capable of potentiating antitumor effect of many medicines, and reduces the mutagenic activity of carcinogens (Wang et al, Enhanced Efficacy of Gemcitabine by Indole-3-carbinol in Pancreatic Cell Lines: The Role of Human Equilibrative Nucleoside Transporter, Anticancer Research October 2011 vol. 31 no. 10 3171-3180)

A study of I3C antitumor activity in estrogen-dependent tissues and organs (mammary gland, endometrium and cervix), demonstrated cyclic changes in the level of cell proliferative activity. (Meng et al, J Nutr. 2000 Dec; 130(12):2927-31. Indole-3-carbinol is a negative regulator of estrogen receptor-alpha signaling in human tumor cells). On one hand, I3C has a
strong anti-estrogenic effect, stimulating the formation of antiproliferative 2-hydroxyestrone, thus improving the ratio of 2-hydroxyestrone /16α-hydroxyestrone in favor of the former; on the other hand, I3C prevents the phosphorylation of cytoplasmic proteins participating signal transduction induced by EGF. Another important mechanism of the antitumor action of I3C is its ability to induce apoptosis - "programmed death" of tumor cells through a system of bax-bcl.

Cervical cancer associated with HPV has been investigated as a potential target for therapy of I3C. Promising results were reported using a model of transgenic mice containing an integrated genome of HPV-16. It was found that the addition of I3C in the diet of these mice suppresses 17α-estradiol and inhibits the development of cervical cancer (Lawrence, J. A., et al (2000), Clinical development of estrogen modulators for breast cancer chemoprevention in premenopausal vs. postmenopausal women. J. Cell. Biochem., 77: 103-114.).

Further studies have confirmed the diversity of antitumor activities of I3C in HPV-transformed cell of the cervical epithelium. It was indicated that in vitro and in vivo:

1) I3C reduces estradiol-dependent induction of oncogene E7, reducing the level of expression of the oncoprotein E7 and the hormone-dependent proliferation of infected cells;

2) I3C normalizes the metabolism of estradiol in cells infected with HPV, reducing the formation of carcinogenic metabolite 16α-ONE, stimulating the expression of HPV oncogenes; and


Unfortunately, I3C is extremely unstable in the human digestive tract as it readily undergoes oligomerization upon its consumption in the acidic environment of stomach. The main product of this process is its dimeric form, 3,3'-diindolylmethane (DIM). As demonstrated by pharmacokinetic and metabolism studies, under the influence of the acidic environment of the stomach orally dosed I3C almost instantly turns into DIM (Ameson DW, Hurwitz A,

Recent experimental studies have shown the ability of DIM to cause apoptosis of cervical HPV-infected keratinocytes in vitro. In three investigated cell lines of cervical cancer DIM demonstrated several times greater efficiency than I3C; the IC50 was 50-60 uM for DIM and 200 uM for I3C, respectively (Indole-3-Carbinol and Diindolylmethane Induce Apoptosis of Human Cervical Cancer Cells and in Murine HPV16-Transgenie Preneoplastic Cervical Epithelium. Da-Zhi Chen, Mei Qi, Karen J. Auborn, Timothy H. Carter J. Nutr. 2001; 131:3294-3302).


While such studies indicate that DIM and related compounds could be effectively used to treat genital warts and/or neoplastic diseases of the reproductive organs, the implementation of such a treatment has been hindered by the poor solubility and resultant poor bioavailability of DIM. In particular, it has been difficult to provide a formulation of DIM which exhibits desirable uniformity of release, a property which is highly desirable to effectively employ such compound in a therapeutic manner.

While certain formulations of DIM have been proposed to address these issues, such formulations have not been shown to be effective and exhibit certain undesirable side effects. Thus, Zeligs (US Patent 8080577) discloses vaginal suppositories comprising DIM for the treatment of leishmaniasis, produced by heating cetostearyl, the primary alcohol, with an active substance, and with the addition of ceramides or their derivatives, with the subsequent introduction of the mixture with triglyceride base and molded candles. Somewhat similarly, Zeligs (US Patent 6,689,387) discloses suppositories of diindolyl methane compounds useful for the treatment of mastalgia and endometriosis. Unfortunately, these suppositories do not provide sufficiently long exposure of the active substance that is necessary for the treatment CIN induced by HPV infection, as the treatment of neoplastic disorders requires a considerable time. In addition, a long-term use of triglyceride as suppository matrix cause ulceration of the...
mucous membranes. Recently, a new type of vaginal suppository has been suggested with improved residence time in the administration site (Kiselev V.I., Russian Patent, RU 2 318 510; Kiselev V.I., WO 2010/027294). However, as is shown in Example 20 of the present application, linear release of DIM is not achieved upon dissolution of this product.

Thus, there is a need for improved formulations of diindolyl methane compounds which will provide enhanced efficacy. Accordingly, it is an object of this invention to provide an effective formulation of a composition comprising a diindolyl methane compound which exhibits a desirable, long term release profile and which does not contain triglycerides in an amount which can lead to ulceration of the mucous membranes after long term exposure.

SUMMARY OF THE INVENTION

In one aspect, the present invention is directed to a composition comprising:
   a) a diindolyl methane compound; and
   b) a cyclooligosaccharide.

In another aspect, this invention is directed to a formulation comprising:
   a) a diindolyl methane compound;
   b) a cyclooligosaccharide; and
   c) one or more pharmaceutically acceptable excipients.

In yet another aspect, this invention is directed a method of treating genital warts and/or neoplastic diseases of the reproductive organs by administering to a patient in need of such treatment an effective amount of a composition comprising:
   a) a diindolyl methane compound;
   b) a cyclooligosaccharide; and
   c) optionally, one or more pharmaceutically acceptable excipients.

In another aspect, this invention is directed to the use of a composition as defined herein in the manufacture of a medicament for the treatment of genital warts and/or neoplastic diseases of the reproductive organs.

In another related aspect, this invention is directed to the use of a composition as defined herein for treating genital warts and/or treating neoplastic diseases of the reproductive organs.
Yet, in another aspect, this invention is directed to a medicament in the form of a suppository, a film, a tablet, a cream or a foam, wherein said medicament comprises:

a) a diindolyl methane compound; and
b) a cyclooligosaccharide.

**DETAILED DESCRIPTION OF THE INVENTION**

In one aspect, the present invention is directed to a composition comprising a diindolyl methane compound; and a cyclooligosaccharide.

Diindolyl methane compounds which may be employed in the practice of this invention include 3,3'-diindolyl methane (DIM), hydroxylated DIM, methoxylated DIM, 2-(indol-3-ylmethyl)-3,3'-diindolylmethane (LTR), hydroxylated LTR, methoxylated LTR, 5,5'-dimethyldiindolyl methane, 2,2'dimethyldiindolyl methane, 5,5'-dichlorodiindolyl methane, imidazolelyl-3,3'-diindolylmethane, nitro-substituted imidazolelyl-3,3'-diindolylmethane, 2,10 dicarbethoxy-6-methoxy-5,7-dihydro-indolo-[2,3-b]carbazole, 6-ethoxycarbonyloxy5,7-dihydro-indolo-[2,3-b]carbazole, 2,10-dicarbethoxy-6-ethoxycarbonyloxy-5,7-dihydro-indolo-[2,3-b]carbazole, 2,6-dicarbethoxy-3,3'-dimethyl-13,14-diindolylmethane as well as mixtures thereof.

Cyclopolysaccharides which may be employed in the practice of this invention include cyclodextrins, cyclomannins, cycloaltrins, cyclofructans and the like. In general, cyclopolysaccharides comprising between 6 and 8 sugar units are preferred.

Among the preferred cyclopolysaccharides which may be employed are cyclodextrins. Cyclodextrins are cyclic oligo-1-4-alpha-D-glucopiranoses consisting of at least 6 sugar units. The most widely known are cyclodextrins containing six, seven or eight sugar units. Cyclodextrins containing six sugar units are known as alpha-cyclodextrins, those containing seven sugar units are known as beta-cyclodextrins and those consisting of eight sugar units are known as gamma-cyclodextrins. Particularly preferred cyclopolysaccharides are beta-cyclodextrins.

The cyclopolysaccharides employed in the practice of this invention may be charged or non-charged. Non-charged cyclopolysaccharides do not have their hydroxyl groups substituted with a charged moiety. Illustrative of such a non-charged polysaccharide is hydroxypropyl beta-cyclodextrin.
As is employed herein the term "charged cyclopolysaccharide" refers to a cyclopolysaccharide having one or more of its hydroxyl groups substituted with a charged moiety. Such moiety may itself be a charged group or it may comprise an organic moiety (e.g., a C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkyl ether moiety) substituted with one or more charged moieties. Such charged polysaccharides may be anionic or cationic.

Although the anionic cyclopolysaccharides which may be employed may comprise any one or mixture of anionic groups, in general it is preferred that such compound comprise a carboxyl, sulfonyl, or sulphate group. Preferred anionic cyclopolysaccharides include sulfobutyl ether beta-cyclodextrin, sodium carboxymethylated-beta-cyclodextrin, sodium O-phosphated-beta-cyclodextrin, succinyl-(2-hydroxy)propyl-beta-cyclodextrin, sodium sulfopropylated-beta-cyclodextrin, and sodium O-sulfated-beta-cyclodextrin with sulfobutyl ether beta-cyclodextrin being particularly preferred.

Although the cationic cyclopolysaccharides which may be employed may comprise any one or mixture of cationic groups, in general it is preferred that such compound comprise an amino, a guanidine or a quaternary ammonium group. Illustrative of the amino-cyclodextrins which may be employed are amino-alpha-cyclodextrins, amino-beta-cyclodextrins, and amino-gamma-cyclodextrins, preferably having a substitution level of between about 4 and about 10. Preferred amino-cyclodextrins of this type include hexakis(6-amino-6-deoxy) alpha-cyclodextrin, heptakis(6-amino-6-deoxy) beta-cyclodextrin, octakis(6-amino-6-deoxy) gamma-cyclodextrin. Other cationic cyclopolysaccharides which may be employed include guanidino-cyclodextrins, preferably having a substitution level of between about 4 and about 10, such as heptakis(6-guanidino-6-deoxy) beta-cyclodextrin; alkylamino-cyclodextrins, preferably having a substitution level of between about 4 and about 10, such as 6-deoxy-6-(3-hydroxy)propylamino beta-cyclodextrin; and alkylammonium-cyclodextrins, preferably having a substitution level between 4 and 9, such as 2-hydroxy-N,N,N-trimethylpropanammonium-cyclodextrin.

Particularly preferred cationic polysaccharides include hexakis(6-amino-6-deoxy) alpha-cyclodextrin, heptakis(6-amino-6-deoxy) beta-cyclodextrin, octakis(6-amino-6-deoxy) gamma-cyclodextrin, heptakis(6-guanidino-6-deoxy) beta-cyclodextrin, octakis(6-guanidino-6-deoxy) gamma-cyclodextrin, 2-hydroxy-N,N,N-trimethylpropanammonium-cyclodextrin and 6-deoxy-6-(3-hydroxy)propylamino beta-cyclodextrin.
In certain embodiments, the cyclopolysaccharide is a charged cyclopolysacharide which is stabilized by the addition of an oppositely charged cyclopolysaccharide. In the event that the first charged cyclopolysaccharide is substituted with an anionic group, the stabilizing agent is a cationic cyclopolysaccharide. Conversely, in the event that the first charged cyclopolysaccharide is substituted with a cationic group, the stabilizing agent is an anionic cyclopolysaccharide.

In one particularly preferred embodiment of this invention, the first charged cyclopolysaccharide comprises sulfobutyl ether beta-cyclodextrin and the stabilizing agent comprises heptakis(6-amino-6-deoxy) beta-cyclodextrin.

The ratio of a diindolyl methane compound to cyclopolysaccharide is typically between 0.5:1 and 1:1000 by weight; and is more typically between 0.5:1 and 1:10 by weight.

The compositions of this invention exhibit unexpectedly enhanced aqueous solubility, coupled with unexpectedly robust control of release of the diindolyl methyl compound from the composition. In particular, the compositions of this invention exhibit a desirable linearity of release when compared with existing DIM formulations (see, for example, Example 20 below).

The formulations of this invention comprise a) a diindolyl methane compound; b) a cyclooligosaccharide; and c) one or more pharmaceutically acceptable excipients.

Such formulations may be in the form of suppositories, creams, rinsing solutions, films, and the like.

In one embodiment the formulation is a suppository that comprises DIM, a lipophilic base, and an antioxidant. In another embodiment the formulation further comprises an emulsifier and/or another solubilising agent. In third embodiment the composition further comprises a bioadhesive component. In another yet embodiment a gelling agent is included in the formulation. A preservative may also be included. Preferably, such suppository formulations compositions do not comprise components, such as triglycerides, in an amount which can lead to ulceration of the mucous membranes upon long term exposure.

In another set of embodiments the formulation is a cream. Such composition typically comprises an oily or aqueous base, an emulsifying agent, and optionally a preservative.

Another yet embodiment comprises a tablet or capsule insert. Such formulation may include a diluent, binder, disintegrant, glidant, lubricating agent, and an antoadherant.
Another set of embodiment comprises gel. In such formulations a gelling agent, a humectant, a preservative and a vehicle are typically present.

In another embodiment the formulation is a foam or spray. Such formulation typically comprises an emulsifier, a propellant blend, and a vehicle.

In another embodiment the formulation is a film. The film formulation typically comprises film former, plasticizer, humectant, and a solvent.

Illustrative of the pharmaceutically acceptable excipients which may be employed in the formulations of this invention include those in the following list (as published in Compendium of pharmaceutical excipients for vaginal formulations. S. Garg, et al, Pharmaceutical Technology, Drug delivery, 2001, 14-24, available on the website of Pharmtech):

**Excipient, Category (concentration in %), Regulatory Status**

Absorbent cotton absorbent sutures in tampons 8, 13, 25

Acacia suspending agent (5-10); emulsifier (5-10); tablet binder (1-5); pastille 1, 3, 8, 25

Adipic acid acidifier; urethane foams -

Adonitol sugar -

Agarose gelling agent; thickening agent -

Alcohol solvent 1, 3, 5-7, 9-14, 16-19, 21-26

Alkyl fumarate buffering agent -

Allantoin adsorbent; clarifying agent (1-2); emulsion stabilizer (1.0); 1, 3, 6-11, 13-14, 16-18, 20, 23, 25

suspending agent (0.5-5.0)

Alum, potassium astringent; antiseptic 1, 8, 25

Aluminium magnesium adsorbent (10-50); binder (2-10); disintegrant (2-10); 3, 25

silicate (Veegum) suspending agent (1-10); emulsifier (2-5); thickening agent (2-10)

Aluminium sulfate acidifier; mineral carrier for adsorbed vaccines 13, 25

Arabitol sugar -

Ascorbic acid antioxidant (0.01-0. 1) G, 1, 3v, 3-26

Barium sulfate diagnostic aid (radiopaque medium) 1, 8, 13, 25
Bentonite adsorbent (1-2); emulsion stabilizer (1.0); suspending agent (0.5-5.0); I, 1, 3, 6-11, 13-14, 16-18, 20, 23, 25
viscosity enhancer
Benzalkonium chloride preservative (0.01-0.02) 1, 3, 3v, 4, 7-9, 11-12, 14, 16-18, 20, 23-26
Benzethonium chloride preservative (0.01-0.02) 7, 16, 19, 25
Benzoic acid preservative (0.1-0.2) G, 1-26
Benzy alcohol preservative (0.2); solubilizer (>5); disinfectant (10) 1, 3, 7-9, 11-14, 16-20, 23’25
Beta cyclodextrin stabilizing agent; solubilizing agent 25
Boric acid astringent; antimicrobial preservative 3, 8, 25
Butylated hydroxyanisole antioxidant (0.005-0.02) G, 3, 9, 13, 14, 17, 25
Butylated hydroxytoluene antioxidant (0.5-1.0) G, 3, 8-10, 13, 17-19, 23, 25
Calcium acetate food stabilizer; buffering agent 3, 8, 25
Calcium carbonate diluent; buffering and dissolution aid in dispersible tablets; G, 1- 4, 6-21, 23-26
bulking agent in sugar coating
Calcium lactate buffering agent; preservative I
Carbomer (Carbopol) emulsifying agent (0.1-0.5); gelling agent (0.5-2.0); suspending agent 3, 14, 17, 25
(0.5-2.0) tablet binder (5-10)
Cellulose diluent (0-100); binder (5-20); disintegrant (5-15); glidant (1-2) G, 3, 8-11, 14, 18, 20, 23, 25
Ceteth-20 (Polyoxy- emulsifying agent; wetting agent; solubilizer; antifoaming agent; I ethylene 20 cetyl ether) vaginal tampons
Cetostearyl alcohol stiffening agent; emulsifying agent; gelling agent (10); 1, 3, 3v, 6, 8, 10, 13, 21, 25, 26
(Cetearyl alcohol) suppository base
Cetyl alcohol coating agent; emulsifying agent (2-5); stiffening agent (2-10); 1, 3, 6, 8-10, 14, 16-19, 23, 25-26
emollient (2-5); water absorption base (5)
Cetyl dimethicone copolyol antifoaming agent -
Cetyl esters wax cold cream base (12.5); stiffening agent (1-20); emollient 25
Cetyl palmitate emulsion/cream base; stiffening agent; emollient I
Cetyl pyridinium chloride preservative 25
Chamomile tea soothing agent -
5 Chitosan gelling agent; sustained-release formulations -
Cholesterol emulsifying agent (0.3-5.0); emollient 1, 4, 6, 16, 21, 25
Choleth emulsion/cream base I
Citric acid acidifier; sequestering agent (0.3-2.0); effervescent formulations; G, 1, 3-14, 16-26
10 antioxidant synergist
Cocoa butter suppository/ointment base 3, 8, 25
(Theobroma oil)
Coconut oil glycerides suppository/ointment base 8
Collagen absorbent sutures in medicated tampons 8, 25
15 Colloidal Silicon dioxide adsorbent; anticaking agent; glidant (0.1-0.5); suspending and G, 1, 3, 8-14, 16-18, 20, 23, 25
thickening agent (2-10); tablet disintegrant; emulsion stabilizer (1-5)
Copper sulfate astringent, antiseptic 8, 25
20 Corn oil (maize oil) solvent 3, 8, 25
Cremophor emulsifier; solubilizer 25
Cros pivodone tablet disintegrant (2-5) 14, 17, 25
Cystine wound healing 8
Dextrin suspending agent; binder; diluent G, 1, 3, 5, 6, 9, 10, 16, 17, 25, 26
Dextrose diluent; toxicity adjusting agent; sweetening agent 3V, 1-5, 8-11, 13-4, 17-20, 22-26
25 Diacetin plasticizer; softening agent; solvent -
Diacetyl phosphate phospholipids for liposomes -
Dibasic calcium phosphate diluent G, 1-3, 8-14, 16-20, 22-23, 25-26
Dichlorodifluoromethane aerosol propellant 17, 25
Dichlorotetrafluoro-ethane aerosol propellant 17, 25
(Cryofluorane)
Diethylaminoethyl cream base -
stearamide
Diglycol stearate emulsifying agent; dispersing agent I
Disodium edetate chelating agent G, 2, 3, 8, 9, 11-14, 16-20, 23-26
Dulcitol (Galactitol) pharmaceutical aid -
EDTA chelating agent; antioxidant synergist (0.005-0.1); preservative synergist 21, 25
(0.01-0.1)
Egg albumin jellying agent G
Ethyl cellulose coating agent (1-3); tablet binder (1-3); viscosity enhancer G, 3, 8, 17, 25
Ethylene glycol humectant; solvent; cosolvent I
Fragrance (RBD-9819) fragrance I
Gelatin hard and soft capsules; microencapsulation; base for paste, pastilles, 1, 3-14, 16-26
Glycine buffering agent 8, 3, 13, 25
Glycogen animal starch -
Hibitane acetate preservative 3, 5, 8, 10, 15, 18, 23
Hydrochloric acid acidifier G, 1-3, 3v, 5, 7-14, 16-25
Hydrogen peroxide antiseptic; deodorant; cleansing agent 8, 3, 13, 25
Hydrogenated palm oil emulsion/cream base -
glyceride
Hydrogenated tablet and capsule diluent; lubricant (1-6); binder G, 16, 25
vegetable oil
Hydrous lanolin emulsifying agent; ointment base 1, 3, 4, 6, 8-10, 13-14, 16, 18, 19, 21-23, 25
Hydroxyethyl cellulose thickening agent; gelling agent; binding agent; film former 3, 8, 9, 10-12, 18, 20, 23, 25
Hydroxyethyl methacrylate viscosity enhancer; hydrogel ingredient -
Hydroxymethyl cellulose gelling agent; thickening agent I
Hydroxypropyl cellulose coating agent (3-5); film former; emulsifying agent; sustained-release matrix (15-35); thickening agent; suspending agent; stabilizing agent G, 3, 8-10, 12, 14, 16, 18, 20, 23, 25
Hydroxypropylmethyl film former (2-10); tableting aid (2-10); suspending and thickening cellulose agent (0.45-1); emulsifier; gelling agent (2-10) G, 3, 8, 9, 11, 14, 16, 18, 20, 23, 25
Inositol sugar, supports epithelialization -
Isopropyl myristate detergent (0.003-0.03); topical creams and lotions (1-10); emollient;
oleaginous vehicle; skin penetrant 1, 3, 8, 13, 25
Isopropyl palmitate detergent (0.005-0.02); perfume (0.2-0.8); emollient; oleaginous vehicle;
solvent 3, 8, 25
Lactic acid acidifier; topical preparations (0.015-6.6) G, 1, 3-14, 16-21, 23-26
Lactose tablet and capsule excipient (65-85); vaginal suppository and emulsion 1-3, 3v, 5-14, 16-26
Lanolin emulsifying agent; ointment base 3v, 1-14, 16-26
Laureth (Polyoxyethylene emulsifier; solubilizing agent; wetting agent I
Lecithin; emulsifying agent; solubilizing agent; suppository base
Light mineral oil emollient; solvent; tablet and capsule lubricant; oleaginous vehicle
Magnesium stearate tablet and capsule lubricant (0.25-5)
Maltodextrin film coating (2-10); tablet binder (2-40); viscosity enhancing agent
Diluent
Maltose (liquid glucose) coating agent (10-20); binder (5-10); sweetening agent (20-60)
Mannitol sweetening agent; diluent (20-90); thickening agent (1-7); plasticizer in G, 1,
soft gelatin capsules; tonicifier
Massa estarinum suppository base 1, 3, 3v, 8-12, 14, 18-20, 23, 25
Massupol suppository base 1, 3, 3v, 8-12, 14, 18-20, 23, 25
Methyl cellulose emulsifying agent (1-5); suspending agent (1-2); binder (2-6); tablet
coating (0.5-5); tablet disintegrant (2-10); sustained-release tablet matrix
(5-75); gelling agent
Methyl paraben preservative (0.1-0.18) G, 1, 3-4, 7-14, 16-21, 23, 25-26
Methyl stearate cream base
Microcrystalline cellulose disintegrant (5-15); diluent (20-90); adsorbent (20-90); anti-
G, 3, 8, 9, 11-14, 16-18, 20, 23, 25
adherent (5-20)
Mineral oil emollient; solvent (1-32); tablet and capsule lubricant; oleaginous G, 3v, 1-
14, 16-26
vehicle (0.1-95)
Myristic acid cream base; sustained-release preparations I
N 3 chloroallyl antiseptic I
methenamine chloride
Nitric acid acidifier I, 3
Novata suppository base 1, 3, 3v, 8-12, 14, 18-20, 23, 25
Octyl dodecanol vaginal emulsion; cream and suppository I
Oxyquinoline sulfate chelating agent; deodorant; antiseptic 25
Palm kernel oil suppository/ointment base I, 3
Palm oil suppository/cream base I
Panthenol vitamin 25
Peanut oil solvent; oleaginous vehicle 1, 3, 3v, 6-11, 13-14, 16-20, 23, 25
Pegicol 5 oleate water-miscible cream base I
Pegoxol 7 stearate water-miscible cream base I
Phenylethyl alcohol preservative (0.25-1.0) 19, 25
Phosphoric acid acidifier; synergistic antioxidant; solvent 8, 13, 25
Piperazine hexahydrate solubilizer, stabilizer (for estrogen) I, 8
Poloxylene stearates emulsifying agent (0.5-10); solubilizing agent; wetting agent; tablet 1, 4, 10, 12, 16, 23, 25
lubricant (1-2); ointment base (7)
Polyacrylamide gelling agent (4) -
Polycarboxophil gelling agent; controlled release; bioadhesive; viscosity modifier; 25
complexing agent; moisture enhancer
Polyethylene suppository base I
Polyethylene glycol suppository/ointment base; plasticizer; solvent; tablet and capsule 1-4, 6-10, 12, 14, 16, 18-21, 23, 25, 26
lubricant
Polyethylene glycol emulsifying agent 1, 4, 10, 12, 16, 23-25
(Polyoxyxyl stearate)
Polyethylene oxide sustained-release formulation I, 25
Polyglyceryl methacrylate matrix former -
Polyoxyethylene - gelling agent (15-50); fat emulsifier (0.3); flavor solubilizer (0.3); I, 3, 25
Polyoxypropylene spreading agent (1); stabilizing agent (1-5); suppository base (4-6 or copolymer (Pluronic/90); tableting aid (5-10); wetting agent (0.01-5)
Poloxamer
Polysorbates emulsifier (1-15); solubilizing agent (1-10); wetting agent (0.1-3) G, 1, 3-6, 8-14, 25, 16, 18-21, 23
Polyvinyl alcohol coating agent; surfactant; viscosity enhancing agent; film former; topical 12, 17, 25, 26
lotions (2.5)
Potassium bitartarate acidifier -
Potassium carbonate alkalinizer; effervescent formulations I
Potassium hydroxide alkalinizer I, 8
Potassium sorbate preservative (0.1-0.2) G, 3, 9, 14, 18, 23, 25
Povidone (Polyvinyl suspending agent (.5); tablet binder; diluent; coating agent (0.5-5) G, 3, 9, 14, 18, 23, 25
pyrrolidone)
Pregelatinized starch diluent (5-75); tablet binder (5-20); tablet disintegrant (5-10) 3, 25
Promulgen D emulsion/cream base I
propellant A31 propellant -
Propyl paraben preservative (0.02-0.1) G, 1, 3-4, 6-11, 13-14, 16-21, 23, 25, 26
Propylene glycol humectant (15); preservative (15-30); solvent or cosolvent (5-80) G, 1, 3, 3v, 4, 6-14, 16-20, 23-26
Propylene glycol emulsion base
monostearate
Quillaia saponins emulsifier 3
Rayon absorbent sutures in tampons, surgical aid 25
Ricinoleic acid used in contraceptive jellies -
Salvoderm pink perfume perfume -
SD Alcohol 40 solvent -
Silica gel disintegrant in vaginal capsules (2-5); tableting aid I
Silicone polymers oleaginous ointment base; antifoaming agent; lubricant, wetting agent; I, 3, 8, 13, 25
(Polydimethylsiloxane/ adhesives; surfactant; vaginal rings Dimethicone/ Simethicone)
Sodium alginate stabilizer (1-3); suspending agent (1-5); disintegrant (2.5-10); binder G, 1, 3, 8-10, 14, 17, 18, 23, 25 (1-3); viscosity enhancer (5-10)
Sodium ascorbate antioxidant G, 9, 13, 25
Sodium benzoate preservative (0.02-0.5); tableting aid (2-5) G, 1-9, 11-14, 16-26
Sodium bicarbonate alkalinizer (10-40); effervescent preparations (25-50) G, 3v, 1-26
Sodium carbonate buffering agent; effervescent preparations I, 8, 25
Sodium carboxymethyl emulsifying agent (0.25-1.0); gelling agent (4-6); tablet binder (1-6) G, 1, 3, 4, 6-9, 11-14, 16-19, 21, 23, 25, 26
cellulose
Sodium chloride humectant, tableting aid (5-80), capsule diluent (10-80); flocculating G, 3v, 1-26
agent for suspensions (.1), isotonic solutions (.0,9)
Sodium cetearyl sulfate surfactant 8 (sodium cetostearyl sulfate)
Sodium citrate buffering agent (0.3-2); sequestering agent (0.3-2) G, 1, 3, 3v, 5-26
Sodium dibasic phosphate buffering agent; sequestering agent G, 1-3, 6-14, 16-21, 23, 25, 26
Sodium dihydrogen citrate buffering agent -
Sodium ethyl paraben preservative 3, 5, 9, 16, 25
Sodium hyaluronate viscosity enhancing agent -
Sodium hydroxide alkalinizer I, 8, 13, 25
Sodium lactate alkalinizer 1, 8, 13, 25
Sodium lauryl sulfate anionic emulsifiers (0.5-2.5); solubilizer (at critical micelle G, 1-4, 6-9, 11-13, 16, 18, 21, 23, 25, 26
concentration .0.25); tablet lubricant (1-2); wetting agent (1-2)
Sodium metabisulfite antioxidants (0.01-1) G, 1-3, 3v, 6-9, 12, 13, 16-19, 24-26
Sodium monobasic alkalinizer; sequestering agent; emulsifying agent G, 3v, 1-5, 8-14, 17-20, 23, 25, 26
phosphate
Sodium propionate preservative (5-10) G, 3v, 9, 19, 25
Sodium propyl paraben preservative 3, 9, 13, 14, 25
Sodium starch glycolate tablet and capsule disintegrant 3, 13, 14, 17, 25
Sorbic acid preservative (0.05-0.2) G, 1-3, 6, 8-10, 12, 14, 17-18, 23, 25-26
Sorbitan esters emulsifier (1-50); solubilizer (1-10); wetting agent (0.1-3) 3, 12, 16, 17, 23, 25, 26
(stearates, laurates, oleates, and palmitates)
Sorbitol humectant (3-15); plasticizer (5-20); vehicle in sugar-free liquid G, 1, 3, 6-14, 16-18, 20, 21, 23, 25, 26
formulations (20-70); tableting aid (25-90)
Spermaceti wax ointment/emulsion base; emollient; stiffening agent I
Stannous chloride reducing agent I, 8
Starch (potato, maize) glidant; diluent; disintegrant (3-15); tablet binder (5-25) G, 3v, 1-14, 16-21, 23-26
Stearic acid tableting aid (1-3) G, 1-7, 9, 12-14, 16-17, 19, 21, 23, 25-26
ointment and cream base (1-20)
emulsifying and solubilizing agent
Stearyl alcohol stiffening agent; emollient; weak emulsifying agent; tableting aid 3, 8, 9, 14, 16, 17, 25
Succinic acid acidifier I
Sucrose tablet binder (2-67); suspending agent; viscosity enhancer G, 1-3, 5-14, 16-21, 23-26
Suppocire suppository base 1, 3, 3v, 8-12, 14, 18-20, 23, 25,
Synthetic fiber composed base material for tampons - of polyester, polypropylene, nylon, or acrylic resin
Talc dusting powder (90-99); glidant and tablet lubricant (1-10); diluent (5-30) G, 1, 3, 3v, 5-14, 16, 18-22, 24-26
Tartaric acid acidifier; sequestering agent; antioxidant synergist; effervescent formulations G, 1, 3-4, 6-14, 16-21, 23-26
Tartrazine (FD&C coloring agent I yellow #5)
Tertiary butyl hydroquinone antioxidant (.0.02) -
Titanium dioxide coating agent; pigment 1-4, 8-9, 11-14, 16-18, 20, 23, 25, 26
Tragacanth suspending agent; viscosity modifier G
Triacetin plasticizer (10-35) G, 8, 25
Triethanolamine alkalinizer; emulsifying agent (2-4); humectant; solvent; polymer
plasticizer 1, 3-4, 6-7, 9, 12, 14, 16-19, 23, 25-26
(Trolamine)
Trihydroxystearate cream base I
Urea antiseptic I, 3, 8, 13, 25
Vitamins A, D, and E vitamins 1, 3, 13, 25
Water solvent 1-3, 3v, 5-14, 16-21, 23-26
White ceresin wax (white stiffening agent; tablet and capsule coating agent G, 23, 25
microcrystalline wax)
White soft paraffin absorption base component (10-50); emollient; pasticizer (5-50) 1,
3v, 3-5, 7, 9-10, 12-14, 16-21, 23-26
(Petrolatum)
White wax stiffening agent (5-20); emulsifying agent; polishing agent for sugar G, 1-3,
3v, 6-14, 16-21, 23, 25-26
(bleached bees' wax) coating; sustained-release formulations; helps in adjusting
melting point
of suppositories
Witepsol (Wecobee) suppository base 1, 3, 3v, 8-12, 14, 18-20, 23, 25,
Xanthan gum bioadhesive; stabilizing agent; suspending agent; viscosity enhancer G, 1,
8, 17, 25
Xylitol sweetening agent; pharmaceutical aid G, 6, 8, 16, 25

**Abbreviations:** G: GRAS, 1: inactive ingredients guide, Pharmacopeias, 1: Austrian, 2:
Belgian, 3: British, 3v: British (veterinary), 4: Brazilian, 5:
Chinese, 6: former Czechoslovakian, 7: Egyptian, 8: European, 9: French, 10: German, 11:
Greek, 12: Hungarian, 13: Indian, 14: Italian, 15: International, 16: Japanese, 17: Mexican, 18:
United States, 26.
In another aspect, this invention is directed a method of treating genital warts and/or neoplastic diseases of the reproductive organs by administering to a patient in need of such treatment an effective amount of a composition comprising:

a) a diindolyl methane compound;

b) a cycloooligosaccharide; and

c) optionally, one or more pharmaceutically acceptable excipients.

The dose of the composition typically ranges from 100 to 600 mg per day, given once or twice per day daily, depending upon the status of the disease involved. Thus, an initial treatment is typically between 100 mg and 200 mg per day. The treatment duration is generally ranges from 90 days to 180 days, until the disease symptoms disappear and complete regression occurs according to the above listed diagnostic methods. However, if the disease progression is still ongoing a higher dose of 400 mg or 600 mg per day of the composition may be considered. However, the use of currently accepted surgical methods of treatment may additionally be employed.

It is to be understood that each component, compound, substituent, or parameter disclosed herein is to be interpreted as being disclosed for use alone or in combination with one or more of each and every other component, compound, substituent, or parameter disclosed herein.

It is also to be understood that each amount/value or range of amounts/values for each component, compound, substituent, or parameter disclosed herein is to be interpreted as also being disclosed in combination with each amount/value or range of amounts/values disclosed for any other component(s), compounds(s), substituent(s), or parameter(s) disclosed herein and that any combination of amounts/values or ranges of amounts/values for two or more component(s), compounds(s), substituent(s), or parameters disclosed herein are thus also disclosed in combination with each other for the purposes of this description.

It is further understood that each lower limit of each range disclosed herein is to be interpreted as disclosed in combination with each upper limit of each range disclosed herein for the same component, compounds, substituent, or parameter. Thus, a disclosure of two ranges is to be interpreted as a disclosure of four ranges derived by combining each lower limit of each range with each upper limit of each range. A disclosure of three ranges is to be interpreted as a disclosure of nine ranges derived by combining each lower limit of each range
with each upper limit of each range, etc. Furthermore, specific amounts/values of a component, compound, substituent, or parameter disclosed in the description or an example is to be interpreted as a disclosure of either a lower or an upper limit of a range and thus can be combined with any other lower or upper limit of a range or specific amount/value for the same component, compound, substituent, or parameter disclosed elsewhere in the application to form a range for that component, compound, substituent, or parameter.

EXAMPLES

The following Examples are provided to illustrate the invention in accordance with the principles of this invention, but are not to be construed as limiting the invention in any way except as indicated in the appended claims.

Example 1

3,3'-diindolylmethane (DIM) was mixed with aqueous sulfobutyl ether betacyclodextrin (SBEC) solution at 23°C at the ratio 1 to 3 w/w. The resulting suspension was filtered through a 0.22 µm filter, and a clear filtrate solution was obtained.

Example 2

3,3'-diindolylmethane (DIM) was mixed with aqueous sulfobutyl ether betacyclodextrin (SBEC) solution at temperature above 60°C at the ratio 1 to 3 w/w. The resulting suspension was filtered through a 0.22 µm filter, and a clear filtrate solution was obtained.

Example 3

3,3'-diindolylmethane (DIM) was mixed with aqueous sulfobutyl ether betacyclodextrin (SBEC) solution at 23°C at the ratio 1 to 3 w/w and sonicated. The resulting suspension was filtered through a 0.22 µm filter, and a clear filtrate solution was obtained.

Example 4

3,3'-diindolylmethane (DIM) was mixed with aqueous sulfobutyl ether betacyclodextrin (SBEC) solution at 23°C at the ratio 1 to 3 w/w and was microwaved. The resulting suspension was filtered through a 0.22 µm filter, and a clear filtrate solution was obtained.
Example 5

a) 3,3'-diindolylmethane (DIM) was mixed with aqueous hydroxypropyl beta-cyclodextrin (HPCD) solution at about 60°C at the ratio 1 to 3 w/w. The resulting suspension was filtered through a 0.22 μm filter, and a clear filtrate solution was obtained.

b) An excess of 3,3'-diindolylmethane (DIM) was mixed with aqueous hydroxypropyl beta-cyclodextrin (HPCD) solution at 23°C at the ratio 1 to 3 w/w and was sonicated. The resulting suspension was filtered through a 0.22 μm filter, and a clear filtrate solution was obtained.

c) 3,3'-diindolylmethane (DIM) was mixed with aqueous hydroxypropyl beta-cyclodextrin (HPCD) solution at 23°C at the ratio 1 to 3 w/w and was microwaved. The resulting suspension was filtered through a 0.22 μm filter, and a clear filtrate solution was obtained.

Example 6

A vaginal suppository was produced by blending the following ingredients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diindolylmethane + SBEC</td>
<td>0.05 g + 0.15 g</td>
</tr>
<tr>
<td>Tallow type &quot;A&quot;</td>
<td>1.73 g</td>
</tr>
<tr>
<td>Kollidon CL</td>
<td>0.02 g</td>
</tr>
<tr>
<td>Butylhydroxyanisole</td>
<td>0.01 g</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2.15 g</td>
</tr>
</tbody>
</table>

Example 7

A vaginal suppository was produced by blending the following ingredients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diindolylmethane + HPCD</td>
<td>0.1 g + 0.3 g</td>
</tr>
<tr>
<td>Tallow type &quot;A&quot;</td>
<td>1.67 g</td>
</tr>
<tr>
<td>Kollidon CL</td>
<td>0.02 g</td>
</tr>
<tr>
<td>Butylhydroxyanisole</td>
<td>0.01 g</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2.15 g</td>
</tr>
</tbody>
</table>
Example 8

A vaginal suppository is produced by blending the following ingredients: DIM plus SBECED, polyethylene glycol 400 and 3350, Polysorbate 80, albicans glycerin, lactic acid, cover made up of gelatin, glycerin, water, methyl paraben, propyl paraben, and color.

Example 9

Vaginal suppositories containing are produced by blending:
DIM plus SBECED with polyethylene glycols 400, 1450, 3350, and 8000.

Example 10

A vaginal gel is produced containing: DIM plus HPCD, water, glycerin, mineral oil, Polycarbophil, hydrogenated palm oil, Carbomer 934P, methyl paraben, sorbic acid, and NaOH.

Example 11

A vaginal gel is produced containing: DIM plus HPCD, type A gelatin, purified corn, starch, hydroxypropylmethyl cellulose, glycerine, and water.

Example 12

A vaginal gel is produced containing: DIM HPCD, cellulose gum, lactic acid, methyl paraben, povidone, propylene glycol, water, sorbic acid, and sorbitol solution

Example 13

A vaginal gel is produced containing: DIM plus SBECED, Carbomer 934P, EDTA, methyl paraben, propyl paraben, propylene glycol, and sodium hydroxide.

Example 14

A vaginal cream is produced containing: DIM plus HPCD, lactose, propylene glycol, stearic acid, diglycol stearate, methyl paraben, propyl paraben, trolamine, and lactic acid.

Example 15

A vaginal cream is produced containing: DIM plus SBECED, Benzyl alcohol, cetyl stearyl alcohol, 1-oatyl dodecanol, Polysorbate 60, water, and sorbitan monostearate.
Example 16

A vaginal cream is produced containing: DIM plus SBECD, Benzyl alcohol, cetearyl alcohol, cetyl esters wax, octyldodecanol, Polysorbate 60, water, and sorbitan monostearate.

Example 17

A vaginal film is produced containing: DIM SBECD, Glycerine, and polyvinyl alcohol.

Example 18

A vaginal foam is produced containing: DIM SBECD, Benzoic acid, cellulose gum, cetyl alcohol, glacial acetic acid, methyl paraben, perfume, phosphoric acid, polyvinpropellant A 31, propylene glycol, water, sorbic acid, searamidoethyl diethylamine, and stearic acid.

Example 19

A vaginal tablet is produced containing: DIM plus HPCD, Lactose, microcrystalline cellulose, hydroxypropylmethyl cellulose, silicon dioxide, magnesium stearate, corn starch, lactic acid, and crospovidone.

Example 20

A composition of this invention containing 0.1 g of DIM with 0.3 grams of hydroxypropyl beta-cyclodextrin was formed into a suppository by formulating it as follows:

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diindolylmethane + HPCD</td>
<td>0.1 g + 0.3 g</td>
</tr>
<tr>
<td>Tallow type &quot;A&quot;</td>
<td>0.67 g</td>
</tr>
<tr>
<td>Kollidon CL</td>
<td>0.2 g</td>
</tr>
<tr>
<td>Butylhydroxyanisole</td>
<td>0.01 g</td>
</tr>
</tbody>
</table>

The resultant composition was tested in a dissolution test and compared with a control composition (described in Kiselev V.I., RU 2 3 1 5 10) as set forth below:

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,3'-Diindolylmethane</td>
<td>0.1 g</td>
</tr>
<tr>
<td>Tallow type &quot;A&quot;</td>
<td>2.02 g</td>
</tr>
<tr>
<td>Kollidon CL</td>
<td>0.02 g</td>
</tr>
<tr>
<td>Butylhydroxyanisole</td>
<td>0.01 g</td>
</tr>
</tbody>
</table>
The dissolution study was carried out at 25°C in 500 ml of vaginal simulation fluid as described in Owen, D.H. et al. *A vaginal fluid stimulant*. Contraception 1999, 59 (2), 91-95 additionally containing 10% w/v Poloxamer 407 to assure an adequate comparison of the test and control samples. The testing was performed in 500 ml of the fluid using USP Apparatus 2 in paddle configuration at the rotation rate of 50 rpm.

The amount of DIM released into the fluid was assayed by HPLC as described in (Kiselev V et al. (2013) *Polymer Based Nano Formulation of Diindolylmethane with High Oral Bioavailability* J Nanomed Nanotechol 4: 162. doi:10.4172/2157-7439.1000162). Each series were repeated 4 times, and the mean values +/- SEM were calculated.

The results are shown in Table 1 below:

**Table 1.** Results of dissolution test for composition of Example 7 and Control composition.

<table>
<thead>
<tr>
<th>Time, mini</th>
<th>Composition of the example, mg per 100 mg of DIM</th>
<th>SEM</th>
<th>Control composition, mg per 100 SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>15</td>
<td>1.31;</td>
<td>25</td>
</tr>
<tr>
<td>45</td>
<td>30</td>
<td>2.12;</td>
<td>55</td>
</tr>
<tr>
<td>60</td>
<td>45</td>
<td>3.49;</td>
<td>83</td>
</tr>
<tr>
<td>90</td>
<td>55</td>
<td>0.23;</td>
<td>85</td>
</tr>
<tr>
<td>120</td>
<td>64</td>
<td>5.16;</td>
<td>88</td>
</tr>
<tr>
<td>150</td>
<td>75</td>
<td>5.21;</td>
<td>90</td>
</tr>
<tr>
<td>300</td>
<td>100</td>
<td>5.09;</td>
<td>100</td>
</tr>
</tbody>
</table>

These results indicate that the dissolution of the control composition was nonlinear, characterized by an initial fast release phase within the first hour followed by slow release phase. In contrast, the release of the drug from the composition of this invention was linear and well predictable within the experimental conditions used.
CLAIMS:

1. A composition comprising:
   a) a diindolyl methane compound; and
   b) a cyclooligosaccharide,

2. The composition of claim 1 wherein the diindolyl methane compound is selected from the group consisting of 3,3'-diindolyl methane (DIM), hydroxylated DIM, methoxylated DIM, 2-(indol-3-ylmethyl)-3,3'-diindolylmethane (LTR), hydroxylated LTR, methoxylated LTR, 5,5'-dimethylidiindolyl methane, 2,2'dimethyliindolyl methane, 5,5'-dichlorodiindolyl methane, imidazoleyl-3,3'-diindolylmethane, nitro-substituted imidazoleyl-3,3'-diindolylmethane, 2,10 dicarbethoxy-6-methoxy-5,7-dihydro-indolo-[2,3-b]carbazole, 6-ethoxycarbonyloxy5,7-dihydro-indolo-[2,3-b]carbazole, 2,10-dicarbethoxy-6-ethoxycarbonyloxy5,7-dihydro-indolo-[2,3-b]carbazole, 2,6-dicarbethoxy-3,3'-dimethyl-13, 14-diindolylmethane and mixtures thereof.

3. The composition of claim 2, wherein the diindolyl methane compound is 3,3'-diindolyl methane.

4. The composition of any one of claims 1-3, wherein the cyclooligosaccharide is a beta-cyclodextrin.

5. The composition of claim 1, wherein the cyclooligosaccharide is a non-charged cyclooligosaccharide.

6. The composition of claim 5, wherein the cyclooligosaccharide is hydroxypropyl beta-cyclodextrin.

7. The composition of claim 1, wherein the cyclooligosaccharide is a charged cyclooligosaccharide.

8. The composition of claim 7, wherein the beta-cyclodextrin is sulfobutyl ether beta-cyclodextrin or hydroxypropyl beta-cyclodextrin.

9. The composition of any one of claims 1-8, wherein the weight ratio of diindolyl methane compound to cyclooligosaccharide, is between 1:0.5 and 1:1000.

10. A formulation comprising the composition of any one of claims 1-9 and a pharmaceutically acceptable excipient.
11. The formulation of claim 10, wherein said formulation is in the form of a suppository, a film, a tablet, a cream or a foam.

12. A method of treating genital warts and/or neoplastic diseases of the reproductive organs by administering to a patient in need of such treatment an effective amount of the composition of any one of claims 1-8.

13. The method of claim 12, wherein the daily dosage of diindolyl methane compound is from 100 to 600 mg per day.

14. The method of claim 13, wherein the daily dosage of diindolyl methane compound is from 100 to 200 mg per day.

15. The method of claim 13, wherein the daily dosage of diindolyl methane compound is from 400 to 600 mg per day.

16. Use of the composition according to any one of claims 1-8, in the manufacture of a medicament for the treatment of genital warts and/or neoplastic diseases of the reproductive organs.

17. The use of claim 16, wherein said medicament is formulated for a daily dosage of the diindolyl methane compound from 100 to 600 mg per day.

18. The use of claim 16, wherein said medicament is formulated for a daily dosage of diindolyl methane compound from 100 to 200 mg per day.

19. The use of claim 16, wherein said medicament is formulated for a daily dosage of diindolyl methane compound from 400 to 600 mg per day.

20. Use of the composition according to any one of claims 1-8, for treating genital warts and/or treating neoplastic diseases of the reproductive organs.

21. The use of claim 20, comprising a daily dosage of diindolyl methane compound from 100 to 600 mg per day.

22. The use of claim 20, comprising a daily dosage of diindolyl methane compound from 100 to 200 mg per day.

23. The use of claim 20, comprising a daily dosage of diindolyl methane compound from 400 to 600 mg per day.
24. A medicament in the form of a suppository, a film, a tablet, a cream or a foam, wherein said medicament comprises:
   a) a diindolyl methane compound; and
   b) a cyclooligosaccharide.

25. The medicament of claim 24, wherein said medicament comprises a daily dosage from 100 to 600 mg of the diindolyl methane compound.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 47/40 (2006.01), A61K 31/404 (2006.01), A61P 15/00 (2006.01), A61P 17/12 (2006.01), A61P 35/00 (2006.01), C07D 209/08 (2006.01), C08K 5/3417 (2006.01), C08L 5/16 (2006.01)

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)

IPC: A61K 47/40 (2006.01), A61K 31/404 (2006.01), A61P 15/00 (2006.01), A61P 17/12 (2006.01), A61P 35/00 (2006.01), C07D 209/08 (2006.01), C08K 5/3417 (2006.01), C08L 5/16 (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 2006/083458 A2 [ZELIGS, M. A.] 10 August 2006 (10-08-2006) (see paragraphs [0020], [0095], [0115], [0116], [0104], [0152], Example 6.3 and claims 1, 6, 14 and 20)</td>
<td>1-11, 24 and 25 12-23</td>
</tr>
<tr>
<td>X</td>
<td>WO 2011/104625 A1 [ALAKHOV, V. et al.] 1 September 2011 (01-09-2011) (see Example 4)</td>
<td>1-4, 7-10, 24 and 25 12-23</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search
25 August 2016 (25-08-2016)

Date of mailing of the international search report
19 September 2016 (19-09-2016)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage 1, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 819-953-2476

Authorized Officer
Owen Terreau (819) 639-9384
International application No.
PCT/IB2016/053722

INTERNATIONAL SEARCH REPORT

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ✔ Claim Nos.: 12-15
   because they relate to subject matter not required to be searched by this Authority, namely:
   Claims 12-15 are directed to a method for treatment of the human or animal body by surgery or therapy, which the International Searching Authority is not required to search under PCT Rule 39.1(iv). However, this Authority has carried out a search based on the alleged effect or purpose/use of the product defined in claims 12-15.

2. ✗ Claim Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ✗ Claim Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ✗ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ✗ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ✗ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:

4. ✗ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

Remark on Protest 

The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

No protest accompanied the payment of additional search fees.
<table>
<thead>
<tr>
<th>Patent Document</th>
<th>Publication Date</th>
<th>Patent Family Member(s)</th>
<th>Publication Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>US6399645B1</td>
<td>04 June 2002</td>
<td>None</td>
<td></td>
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