4.2.5.2.3 INTRA-VAGINAL RINGS pdf

1: Pudendal cleft â€" Wikipedia Republished // WIKI 2

Intra-vaginal Rings 3. Intra-vaginal Rings - Designs 4. Intra-vaginal Rings - Designs 5. Intra-vaginal Rings - Drug Release Profiles In vitro In vivo 6.

The core is positioned in the vaginal ring body suitably prior to use in order to substantially avoid initial bursts of drug into the tissues of the subject and resultant side effects such as nausea and vomiting. Representative drugs include contraceptive agents and other steroidal substances for use in hormone replacement therapy. Also disclosed are methods for preparing the vaginal rings, kits for assembling the vaginal rings, and methods of using the vaginal rings to achieve intravaginal delivery of drugs to a female. Description The present invention is directed to intravaginal drug delivery devices and methods for producing such devices, and more particularly, devices for intravaginal administration of contraceptive agents and agents for hormone replacement therapy. Typically, they are made of a silicone elastomer and contain a drug released by diffusion though the elastomer. The most common commercial applications have been to deliver low doses of steroids for post-menopausal vaginal conditions. They have also been under development for use in contraception and hormone replacement therapy. Vaginal rings have also been used to administer spermicides, as well as a variety of locally or systematically active medicaments. Vaginal rings have provided several advantages in that their use is controlled by the female; they allow for a better regulated dose of drug without attention by the user; and they avoid the destruction by the intestine and by first pass through the liver of an appreciable portion of the daily dosage of some steroids compared to their orally delivered counterparts. The use of a vaginal ring to deliver drugs requires a ring design that regulates the release rate so as to provide the user with the appropriate daily dose. Among the important factors governing release are the solubility of the drug in the ring elastomer, the surface area of the drug reservoir, the distance the drug must diffuse through the ring body to reach its surface and the molecular weight of the drug. If very high release rates are desired, they can be attained by a drug load at the ring surface as is characteristic of the homogeneous matrix ring design. This design, however, suffers from rapidly declining release rates as the distance the drug must travel to reach the ring surface increases as the drug load near the surface is depleted. If moderately high release rates are needed to provide the appropriate dose, a design which modulates release rate by imposing a layer of drug-free elastomer between the drug reservoir and the ring exterior is appropriate. This may be attained by coating a homogeneous ring, or to conserve drug, by incorporating a drug-free core, a shell design may be used. If an even lower release rate is desired, the drug may be confined to a small diameter at the center of the ring "core ring". Finally, the drug-loaded core may not encircle the ring but instead be of short length. Numerous types of vaginal rings have been described in the patent and non-patent literature alike. Patent 4,, is directed to a core-type vaginal ring based upon a curable silicon rubber composition, and which results in controlled release of therapeutic agents in a human or animal body. The rings are made by extruding a first composition containing a therapeutic agent and a first elastomer-forming silicon composition to provide a core; extruding a second composition containing a second elastomer-forming silicon composition to provide a sheath enclosing the core; bringing together end portions of a piece of extruded core and sheath to form a ring; effectively cross-linking the extruded core; and effectively cross-linking the extruded sheath. Vaginal rings have been used experimentally to deliver the contraceptive agent, ethynylestradiol. However, an undesirable percentage of women who have used vaginal rings for this purpose had complained of nausea and vomiting, particularly from the first cycle of use of the rings due to an initial burst of steroid release. The manufacture of the so-called "core" rings presents additional problems. One problem is the physical one of placing the cores in the ring body by techniques adapted to facile manufacture. Another is that drugs with reactive groups such as ethynyl, amino groups, or sulfhydryl groups may prevent vulcanization of preferred silicone polymers. One method of introducing short lengths of drug-loaded cores is to mold a half ring with a center groove, place the core in the groove, change molds and inject the second half of the ring. This technique, while feasible, requires two molding steps for manufacture of the ring body. It also limits elastomer choice when dealing with reactive drugs such as ethynylestradiol. Hence, a need remains for a vaginal ring that does not cause nausea and

vomiting, and other problems associated with some devices, while still providing the other advantages that vaginal rings have offered. Preferred drugs include contraceptive agents such as progestational compounds e. In a more preferred embodiment, the core contains two drugs, more preferably two contraceptive agents, e. In yet other preferred embodiments, the vaginal ring contains a plurality e. The vaginal ring has an overall diameter of from about 4 mm to about 10 mm. The core has a cross-sectional diameter of from about 1. The hollow channel of the vaginal ring may also contain a sealant such as a silicone medical grade adhesive e. Another aspect of the present invention is direction to the use of a vaginal ring in the preparation of a medicament for drug administration according to claim Yet another aspect of the present invention is directed to a kit which contains a suitably shaped vaginal ring body comprising a first polymeric material having at least one hollow internal channel defining an opening to the exterior of said body and which channel is adapted to receive an intravaginally administerable drug-containing core through the opening, and at least one core to be positioned in the channel, wherein the core contains a pharmaceutically effective amount of an intravaginally administerable drug dispersed in a second polymeric material, wherein the first and second polymeric materials may be the same or different, the channel being sealed. The sealant is preferably a medical grade adhesive such as a polymethylsiloxane having methyldiacetoxysilyl end groups. The applicator is preferably a syringe. The vaginal rings and the methods of the present invention offer several additional advantages over prior art drug delivery mechanisms. They provide for a substantially constant release of drug as compared to oral or injectable modes of drug administration, and they maintain the potency of drugs that are susceptible to destruction as they pass from the intestine through the liver immediately after absorption from the gut. A further aspect of the present invention is directed to the methods of preparing the vaginal ring by the relatively simple procedures of claims 29 and The core is prepared by mixing the drug with an elastomeric material, followed by molding and then vulcanizing. The core may be vulcanized in situ in the ring body, depending upon whether the drug is one in which the initial burst is to be avoided. For example, in cases where initial drug bursts are to be avoided, the ring body and core are vulcanized separately, and the cores are introduced into the channels suitably prior to use. In embodiments where an initial drug burst is not a problem, the core may be vulcanized in situ in the ring body subsequent to its introduction into the channel. In these embodiments, the drug-containing core may be effectively introduced by injecting a mixture of the drug, the second polymeric material and a suitable catalyst into, the hollow internal channel of the vaginal ring body so that the drug-containing core is formed in situ. In preferred embodiments, the diameter of the core relative to the channel may vary slightly; it may be substantially equal to or slightly greater or smaller than the channel diameter. In preferred embodiments, the core diameter is substantially equal to or even slightly greater than that of the channel, such that following insertion or formation of the core into the channel, surface contact is maintained between the outer longitudinal surfaces of the core and the surface of the channel. The method is less time consuming and more easily mechanized than current methods. Therefore, the core may be inserted into the ring body during the manufacturing process, or packaged separately and inserted suitably prior to use, in accordance with other aspects of the present invention. The invention, and preferred features thereof, is defined in the appended claims Shell ring 10, illustrated in Figs. Thus, the steroid load is in a zone beneath the ring surface but not extending to the center of the ring. Shell rings were developed to deliver a lesser dose than that which would be initially delivered by homogenous ring 20, illustrated in Fig. In the homogenous ring, the drug is substantially uniformly dispersed throughout the volume of the vaginal ring. If even lower doses are desired, the drug or steroid load may be delivered via a so-called core ring, as illustrated in Fig. The drug load is contained totally in core 24 of ring A modification of the core ring is illustrated in Fig. Vaginal core ring 30, having a total diameter of 58 mm, and a cross-sectional diameter of 7. Each of cores 32 and 34 has a cross-sectional diameter of 2 mm. Applicants have unexpectedly found that the nausea and vomiting that has typically occurred in some women shortly after beginning use of a vaginal ring with an ethynylestradiol-containing core 30 is due to the initial burst of drug from the ring caused by the accumulation of the drug in the ring body between the core and the outer surface of the ring during post-manufacture storage. These experimental results are described in detail in Example 1. The vaginal rings of the present invention, on the other hand, eliminate or substantially alleviate undesirable side effects such as nausea and

vomiting often associated with the use of vaginal drug delivery systems containing estrogens. As illustrated in Fig. By the term "ring", it is meant any continuous curved or torous shape that does not compromise ease of administration insertion , comfort, esthetic appeal, or efficacy. By the term "internal", it is meant that there is no portion of the core which is exposed to or in contact with the outer surface of the ring body once the vaginal ring is fully assembled and the opening is sealed , such that when administered, the drug will diffuse from the core directly into the tissue of the subject. In preferred embodiments, the core is inserted into the channel suitably prior to use i. By the phrase "suitably prior to use," it is meant that the drug-containing core is positioned in the hollow channel at a time such that accumulation of the drug in ring body 40 i. In preferred embodiments, the core is positioned in the channel no later than about 4 days prior to use, more preferably within about 24 hours prior to use, and most preferably substantially immediately prior to use. In some unusual situations, however, core insertion may be conducted even more than one week prior to administration of the vaginal ring of the present invention. For example, vaginal rings fully assembled at least ten days prior to use, and which are stored at temperatures substantially below room temperature, e. The vaginal ring may also contain a pharmaceutically effective amount of at least one vaginally administerable drug, preferably uniformly dispersed in the first polymeric material. Core 44, illustrated in Fig. The first and second polymeric materials may be the same or different. Suitable first and second polymeric materials for use in the present invention are compatible with each other and the drug e. Preferred polymeric materials are silicone elastomers, particularly polydimethylsiloxanes and derivatives e. The structural integrity of the ring body may be enhanced by the addition of a particulate material such as fumed silica or diatomaceous earth. The sealant closes the channel after core placement and may also be used to form a firm bond between the ring body and the core, and to serve as a lubricant during core insertions. It also minimizes diffusion of the drug through the axial ends of the core. Preferred sealants include medical grade adhesives such as polydimethylsiloxanes, and particularly those having methyl diacetoxysilyl end groups which vulcanize upon exposure to moisturized air. The intravaginally administered drug s contained in the core s and optionally the vaginal ring include any physiologically or pharmacologically active substance that because of its potency and solubility in the ring elastomer, can be released in adequate doses from ring bodies with central drug-bearing cores, particularly cores of less that 60 mm cumulative length. Among drugs meeting these criteria, those used chronically and those with a low acceptable dose range are particularly apt candidates. Examples include contraceptive steroids, and certain steroids for hormone replacement therapy. By the term "pharmaceutically effective," it is meant an amount which is sufficient to effect the desired physiological or pharmacological change in the subject. This amount will vary depending upon such factors as the potency of the particular drug, the desired physiological or pharmacological effect, and the time span of the intended treatment. Those skilled in the pharmaceutical arts will be able to determine such amount for any given drug in accordance with standard procedures. In a preferred embodiment wherein the drug is a contraceptive agent, the "pharmaceutically effective" amount is an amount sufficient to result in contraception for a predetermined time period, which is generally from about 3 months to about 1 year. In general, this amount is in the range from about 5. Greater amounts of drug can be advantageously achieved by omitting particulate filler materials in the core polymeric material. The ring body may contain a plurality of drug-containing cores. The drug contained in each of cores 54, 56 and 58 may be the same or different. In addition, one or two of the cores may contain a drug, an initial burst of which would not cause undesirable side effects in a patient, so that the core s containing such drug may be inserted such as by injection into the ring body after molding of the ring body and prior to packaging and storage. The vaginal ring bodies of the present invention are prepared using a single molding step. In one preferred embodiment, the first polymeric material is cast in a mold having removable, rod-like inserts extending therein, which when removed, form channels into which the drug-containing core will be inserted. The thus-molded ring body is then vulcanized in accordance with standard techniques. Vulcanization can be conducted at room temperature or at elevated temperatures, and, if necessary, in the presence of a suitable catalyst such as heavy metals e. The drug-containing core is also prepared in accordance with standard techniques such as extrusion and injection molding. In a preferred embodiment, the drug is mixed with the second polymeric material, and the mixture is injected into a suitably shaped mold, and then vulcanized.

4.2.5.2.3 INTRA-VAGINAL RINGS pdf

2: USB2 - Bicyclic aza compounds as muscarinic M1 receptor agonists - Google Patents

Pros and Cons of Contraceptive Vaginal Rings Table I. Physical and pharmacological characteristics of the main models of combined and progestin-only contraceptive vaginal rings.

C alkyl optionally substituted with 1 to 6 fluorine atoms; C cycloalkyl optionally substituted with one or two methyl groups; Ccycloalkyl-CH2â€" wherein the C cycloalkyl moiety is optionally substituted with one C alkyl group and wherein one carbon atom of the Ccycloalkyl moiety may optionally be replaced by an oxygen atom; cyclopropyl-C alkyl; and methyl-bicyclo[2. A compound according to Embodiment 1. For example, if the condition is pain, then the effective therapeutic amount is an amount sufficient to provide a desired level of pain relief. The desired level of pain relief may be, for example, complete removal of the pain or a reduction in the severity of the pain. In formula 1 , X1 and X2 are saturated hydrocarbon groups which together contain a total of five to nine carbon atoms and which link together such that the moiety: The hydrocarbon group may be fully saturated or may contain one or more carbon-carbon double bonds or carbon-carbon triple bonds, or mixtures of double and triple bonds. The hydrocarbon group may be a straight chain or branched chain group or may consist of or contain a cyclic group. Thus the term non-aromatic hydrocarbon includes alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenyl alkyl and so on. Bicyclic cycloalkyl groups include bridged ring systems such as bicycloheptane, bicyclooctane and adamantane. In the definitions of R1, R3 and R4 above, where stated, one or two but not all, carbon atoms of the non-aromatic hydrocarbon group may optionally be replaced by a heteroatom selected from O, N and S and in the case of R1 and R4 oxidised forms thereof. It will be appreciated that when a carbon atom is replaced by a heteroatom, the lower valencies of the heteroatoms compared to carbon means that fewer atoms will be bonded to the heteroatoms than would have been bonded to the carbon atom that has been replaced. Thus, for example, replacement of a carbon atom valency of four in a CH2 group by oxygen valency of two will mean that the resulting molecule will contain two less hydrogen atoms and replacement of a carbon atom valency of four in a CH2 group by nitrogen valency of three will mean that the resulting molecule will contain one less hydrogen atom. In each such replacement, at least one carbon atom of the hydrocarbon group must remain. Salts Many compounds of the formula 1 can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulfonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula 1 include the salt forms of the compounds as defined in Embodiments 1. The salts are typically acid addition salts. The salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods such as methods described in Pharmaceutical Salts: Properties, Selection, and Use, P. Heinrich Stahl Editor , Camille G. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used. Acid addition salts as defined in Embodiment 1. Examples of acid addition salts falling within Embodiment 1. D-glucuronic , glutamic e. Where the compounds of the formula 1 contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of formula 1. The compounds of the invention may exist as mono- or di-salts depending upon the pKa of the acid from which the salt is formed. The salt forms of the compounds of the invention are typically pharmaceutically acceptable salts, and examples of pharmaceutically acceptable salts are discussed in Berge et al. However, salts that are not pharmaceutically acceptable may also be prepared as intermediate forms which may then be converted into pharmaceutically acceptable salts. Such non-pharmaceutically acceptable salts forms, which may be useful, for example, in the purification or separation of the compounds of the invention, also form part of the invention. Stereoisomers Stereoisomers are isomeric molecules that have the same molecular formula and sequence of bonded atoms but which differ only in the three-dimensional orientations of their atoms in space. The stereoisomers can be, for example, geometric isomers or optical isomers. Geometric Isomers With geometric

isomers, the isomerism is due to the different orientations of an atom or group about a double bond, as in cis and trans Z and E isomerism about a carbon-carbon double bond, or cis and trans isomers about an amide bond, or syn and anti isomerism about a carbon nitrogen double bond e. Accordingly, in another embodiment Embodiment 1. Optical Isomers Where compounds of the formula contain one or more chiral centres, and can exist in the form of two or more optical isomers, references to the compounds include all optical isomeric forms thereof e. The optical isomers may be characterised and identified by their optical activity i. Where compounds of the invention exist as two or more optical isomeric forms, one enantiomer in a pair of enantiomers may exhibit advantages over the other enantiomer, for example, in terms of biological activity. Thus, in certain circumstances, it may be desirable to use as a therapeutic agent only one of a pair of enantiomers, or only one of a plurality of diastereoisomers. In one general embodiment Embodiment 1. For example, in one embodiment Embodiment 1. In another embodiment Embodiment 1. The invention also provides mixtures of optical isomers, which may be racemic or non-racemic. Thus, the invention provides: Isotopes The compounds of the invention as defined in any one of Embodiments 1. Similarly, references to carbon and oxygen include within their scope respectively 12C, 13C and 14C and 16O and 18O. In an analogous manner, a reference to a particular functional group also includes within its scope isotopic variations, unless the context indicates otherwise. For example, a reference to an alkyl group such as an ethyl group also covers variations in which one or more of the hydrogen atoms in the group is in the form of a deuterium or tritium isotope, e. The isotopes may be radioactive or non-radioactive. In one embodiment of the invention Embodiment 1. Such compounds are preferred for therapeutic use. Compounds containing such radioisotopes may be useful in a diagnostic context. Solvates Compounds of the formula 1 as defined in any one of Embodiments 1. Preferred solvates are solvates formed by the incorporation into the solid state structure e. Examples of such solvents include water, alcohols such as ethanol, isopropanol and butanol and dimethylsulphoxide. Solvates can be prepared by recrystallising the compounds of the invention with a solvent or mixture of solvents containing the solvating solvent. Whether or not a solvate has been formed in any given instance can be determined by subjecting crystals of the compound to analysis using well known and standard techniques such as thermogravimetric analysis TGE , differential scanning calorimetry DSC and X-ray crystallography. The solvates can be stoichiometric or non-stoichiometric solvates. Particularly preferred solvates are hydrates, and examples of hydrates include hemihydrates, monohydrates and dihydrates. Accordingly, in further embodiments 1. For a more detailed discussion of solvates and the methods used to make and characterise them, see Bryn et al. Alternatively, rather than existing as a hydrate, the compound of the invention may be anhydrous. Therefore, in another embodiment Embodiment 1. Crystalline and Amorphous Forms The compounds of any one of Embodiments 1. Whether or not a compound exists in a crystalline state can readily be determined by standard techniques such as X-ray powder diffraction XRPD. Crystals and their crystal structures can be characterised using a number of techniques including single crystal X-ray crystallography, X-ray powder diffraction XRPD , differential scanning calorimetry DSC and infra red spectroscopy, e. The behaviour of the crystals under conditions of varying humidity can be analysed by gravimetric vapour sorption studies and also by XRPD. Determination of the crystal structure of a compound can be performed by X-ray crystallography which can be carried out according to conventional methods such as those described herein and as described in Fundamentals of Crystallography, C. This technique involves the analysis and interpretation of the X-ray diffraction of single crystal. In an amorphous solid, the three dimensional structure that normally exists in a crystalline form does not exist and the positions of the molecules relative to one another in the amorphous form are essentially random, see for example Hancock et al. Accordingly, in further embodiments, the invention provides: Prodrugs The compounds of the formula 1 as defined in any one of Embodiments 1. For example, some prodrugs are esters of the active compound e. Such esters may be formed by esterification, for example, of any hydroxyl groups present in the parent compound with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required. For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative. Complexes and Clathrates Also encompassed by formula 1 in Embodiments 1. Biological Activity and Therapeutic Uses The compounds of the present invention have

activity as muscarinic M1 receptor agonists. A significant advantage of compounds of the invention is that they are highly selective for the M1 receptor relative to the M2 and M3 receptor subtypes. Compounds of the invention are neither agonists nor antagonists of the M2 and M3 receptor subtypes. For example, whereas compounds of the invention typically have pEC50 values of at least 6 preferably at least 6. Accordingly, in Embodiments 2. Methods for the Preparation of Compounds of the Formula 1 Compounds of the formula 1 can be prepared in accordance with synthetic methods well known to the skilled person and as described herein. Accordingly, in another embodiment Embodiment 3. A the reaction of a compound of the formula 10 wherein R3, R4, R5, X1 and X2 are as defined in any one of Embodiments 1. C converting one compound of the formula 1 to another compound of the formula 1. In process variant A , the reaction may be carried out in the presence of a reagent of the type commonly used in the formation of amide bonds. Carbodiimide-based coupling agents are advantageously used in combination with 1-hydroxyazabenzotriazole HOAt L. Ber, , , A preferred amide coupling agent is HATU. The coupling reaction is typically carried out in a non-aqueous, non-protic solvent such as acetonitrile, dioxane, dimethylsulphoxide, dichloromethane, dimethylformamide or N-methylpyrrolidinone, or in an aqueous solvent optionally together with one or more miscible co-solvents. The reaction may optionally be carried out in the presence of a non-interfering base, for example a tertiary amine such as triethylamine or N,N-diisopropylethylamine. As an alternative, a reactive derivative of the carboxylic acid, e. The acid chloride is typically reacted with the compound of formula R1R2NH in the presence of a base such as sodium bicarbonate. The acid chloride can be prepared using standard methods, for example by treatment of the acid with oxalyl chloride in the presence of a catalytic amount of dimethylformamide. Process variant B is typically carried out in an aprotic solvent such as dichloromethane or dichloroethane in the presence of a non-interfering base such as triethylamine. The reaction may be conducted at room temperature. Intermediate compounds of the formula 10 can be prepared by the series of reactions shown in Scheme 1 below.

4.2.5.2.3 INTRA-VAGINAL RINGS pdf

3: Gynecological devices market Transparency Market Research by Jess Bruce - Issuu

Vaginal rings come in one size that fits most women. The correlation between breast cancer and the use of vaginal rings is under investigation, but recent literature suggests that the hormones used in vaginal rings has little, if any, relation to the risk of developing breast cancer.

The entire contents of each of the prior applications are incorporated herein by reference. Thus, a C alkyl group contains from 1 to 6 carbon atoms, a C cycloalkyl group contains from 3 to 6 carbon atoms, a O alkoxy group contains from 1 to 4 carbon atoms, and so on. Examples of such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert butyl, n-pentyl, isopentyl, neopentyl or hexyl and the like. Examples of such groups include methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy and the like. Examples of such groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and the like. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl and the like. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Examples of such groups include cyclobutyl, cyclopentyl, cyclohexyl, and the like. Examples of such groups include cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene or cyclooctene and the like. Examples of such groups include fluoroethyl, trifluoromethyl or trifluoroethyl and the like. Examples of such groups include difluoromethoxy or trifluoromethoxy and the like. In general, such groups may be monocyclic or bicyclic and may contain, for example, 3 to 12 ring members, more usually 5 to 10 ring members. Examples of monocyclic groups are groups containing 3, 4, 5, 6, 7, and 8 ring members, more usually 3 to 7, and preferably 5 or 6 ring members. Examples of bicyclic groups are those containing 8, 9, 10, 11 and 12 ring members, and more usually 9 or 10 ring members. Where reference is made herein to carbocyclic and heterocyclic groups, the carbocyclic or heterocyclic ring can, unless the context indicates otherwise, be unsubstituted or substituted by one or more substituents for example molecular fragments, molecular scaffolds or functional groups as discussed herein. The carbocyclic or heterocyclic groups can be aryl or heteroaryl groups having from 5 to 12 ring members, more usually from 5 to 10 ring members. In such polycyclic systems, the group may be attached by the aromatic ring, or by a non-aromatic ring. Saturated carbocyclic groups include cycloalkyl groups as defined below. Partially saturated carbocyclic groups include cycloalkenyl groups as defined below, for example cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl. Saturated heterocyclic groups include piperidine, morpholine, thiomorpholine. Partially saturated heterocyclic groups include pyrazolines, for example 2-pyrazoline and 3-pyrazoline. Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings, or two fused five membered rings. Each ring may contain up to five, e. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five. Examples of five membered heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, triazole and tetrazole groups. One further example of a five membered heteroaryl group includes thiadiazole. Examples of six membered heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine. A bicyclic heteroaryl group may be, for example, a group selected from: Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazothiazole e. Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuran, benzthiophene, benzimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran,

indole, isoindole, indolizine, indoline, isoindoline, purine e. One further example of a bicyclic heteroaryl group containing a six membered ring fused to a five membered ring includes imidazopyridine. Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups. Examples of polycyclic aryl and heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydronaphthalene, tetrahydroisoquinoline, tetrahydroquinoline, dihydrobenzthiene, dihydrobenzfuran, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole, 4,5,6,7-tetrahydrobenzofuran, indoline and indane groups. One further example of a polycyclic heteroaryl group containing an aromatic ring and a non-aromatic ring includes tetrahydrotriazolopyrazine e. A nitrogen-containing heteroaryl ring must contain at least one ring nitrogen atom. Each ring may, in addition, contain up to about four other heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, for example 1, 2 or 3, more usually up to 2 nitrogens, for example a single nitrogen. Examples of nitrogen-containing heteroaryl groups include, but are not limited to, pyridyl, pyrrolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, furazanyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl e. Examples of nitrogen-containing polycyclic heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydroisoquinolinyl, tetrahydroquinolinyl, and indolinyl. Examples of carbocyclic aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl groups. Examples of non-aromatic heterocyclic groups are groups having from 3 to 12 ring members, more usually 5 to 10 ring members. Such groups can be monocyclic or bicyclic, for example, and typically have from 1 to 5 heteroatom ring members more usually 1, 2, 3 or 4 heteroatom ring members , usually selected from nitrogen, oxygen and sulphur. The heterocyclic groups can contain, for example, cyclic ether moieties e. Particular examples include morpholine, piperidine e. In general, preferred non-aromatic heterocyclic groups include saturated groups such as piperidine, pyrrolidine, azetidine, morpholine, piperazine and N-alkyl piperazines. In a nitrogen-containing non-aromatic heterocyclic ring the ring must contain at least one ring nitrogen atom. The heterocylic groups can contain, for example cyclic amine moieties e. Particular examples of nitrogen-containing non-aromatic heterocyclic groups include aziridine, morpholine, thiomorpholine, piperidine e. The carbocyclic and heterocyclic groups can be polycyclic fused ring systems or bridged ring systems such as bicycloalkanes, tricycloalkanes and their oxa- and aza analogues e. For an explanation of the distinction between fused and bridged ring systems, see Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience, pages , Examples of non-aromatic carbocyclic groups include cycloalkane groups such as cyclohexyl and cyclopentyl, cycloalkenyl groups such as cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl, as well as cyclohexadienyl, cyclooctatetraene, tetrahydronaphthenyl and decalinyl. The heterocyclic groups can each be unsubstituted or substituted by one or more substituent groups. For example, heterocyclic groups can be unsubstituted or substituted by 1, 2, 3 or 4 substituents. Where the heterocyclic group is monocyclic or bicyclic, typically it is unsubstituted or has 1, 2 or 3 substituents. Examples of N-linked imidazolyl groups include imidazolyl. Particular Embodiments of the Invention Examples of ring systems encompassed by the definition Aa are shown in the following formulae I A- I O, wherein the nitrogen atom demonstrates the point of attachment with the urea group: The group I L can be any tautomer of imidazole e. In one embodiment, Aa or Ab is a group other than pyrazole. In one embodiment, A is the group I A which can be optionally substituted by one or more e. In one embodiment, Aa represents a monocyclic aromatic carbocyclic or heterocyclic ring system having for example a 5, 6 or 7 membered ring e. In a further embodiment, Aa represents a 6 membered carbocyclic ring. In a yet further embodiment, Aa represents a phenyl group i. In a further embodiment, Aa or Ac represents a pyridyl group i. In a yet further embodiment, Aa or Ac represents a ring system of formula I B optionally substituted by one or more e. In a one embodiment, Aa or Ab represents a thiazolyl group, isothiazole group or imidazole group optionally substituted by one or more e. In a further embodiment, Aa or Ab represents a thiazolyl group i. In a yet further embodiment, Aa or Ab represents a ring system of formula I P or I Q optionally substituted by one or more e. In one embodiment, Aa or Ac or Ad represents a 6 membered

monocyclic aromatic carbocyclic or heterocyclic ring system e. Also disclosed is, Aa or Ac or Ad represents a 6 membered monocyclic aromatic carbocyclic or heterocyclic ring system e. In one embodiment, Aa or Ac represents a 6 membered monocyclic aromatic carbocyclic or heterocyclic ring system e. In a further embodiment, Aa or Ad represents unsubstituted phenyl. In one embodiment, Aa is as defined in Ab. In another embodiment, Aa is as defined in A. In another embodiment, Aa is as defined in Ad. Also disclosed is, R1 represents hydrogen or C alkyl e.

4.2.5.2.3 INTRA-VAGINAL RINGS pdf

4: Sensors | November - Browse Articles

Issuu is a digital publishing platform that makes it simple to publish magazines, catalogs, newspapers, books, and more online. Easily share your publications and get them in front of Issuu's.

Advanced Search Abstract The effect of trimegestone-based and norethisterone-based hormone replacement therapy HRT regimens on the endometrial vascularity compared with that of the endometrium of the natural cycle were evaluated using immunohistochemical techniques. Endometrial vascular space area, diameter and number were defined in the functionalis layer of the endometrial samples from postmenopausal women who either completed a randomized, double blind, dose-ranging study of continuous oral micronized oestradiol 2 mg daily with trimegestone 0. The control samples were LH-dated endometrial biopsies. NET-based HRT was associated with a higher number of smaller vascular spaces compared with the trimegestone-treated endometrium or that of the natural cycle. There was no dose-dependent effect in the four dose groups of trimegestone. In conclusion, norethisterone may exert a different effect on angiogenesis to that of trimegestone on endometrial vascular development. CD34 , endometrium , hormone replacement therapy , norethisterone , trimegestone Introduction Postmenopausal sex steroid administration is associated with initiation of withdrawal bleeding. This irregular bleeding may respond to an increase in the dose of progestogen administered, but with the majority of progestogens, such dose-dependent modulation of uterine bleeding is associated with a higher incidence of adverse effects, such as bloatedness, mastalgia, fluid retention and mood swings. Progesterone inhibits endothelial cell proliferation Vazquez et al. Morphological changes in the endometrial blood vessels may be one of the factors responsible for bleeding. Gaps start to appear between the endothelial cells in the premenstrual phase Sixma et al. Endometrial blood vessels undergo different morphological changes under the effect of different sex steroids. There is controversy in the literature regarding the vascular density in the natural cycle. Authors reported no variation in the vascular density with different phases of the natural cycle, and therefore concluded that there is no correlation between vascularity and stromal development Shaw et al. On the other hand, a significant increase was found in the vascular surface area, diameter and total number of capillaries in the secretory phase compared with the proliferative phase Ota et al. In a recent study Al-Azzawi et al. Women on cyclical sequential norethisterone NET , exhibited two patterns of bleeding: CD34 is a glycoprotein expressed on haematopoietic progenitor cells, in the basement membrane of the vascular endothelium Traweek et al. The CD34 antigen was chosen for detection, although not an exclusive marker of endothelial cells, in preference to Von Willebrand factor, which gives a weaker staining, or the less specific antigen Ulex europaeus Traweek et al. The aim of this study was to establish the vascular morphometric changes using the endothelial cell marker, CD34, i in the natural cycle, ii in response to trimegestone-based HRT in a dose ranging study, and iii to compare the changes in vascular morphometry between two sequential HRT regimens: The clinical indications for the hysterectomies were: All women were given urinary LH surge detection kit tests First Response; Carter Wallace Limited, Folkstone, UK , which were used during the month preceding the endometrial biopsy or hysterectomy. The technique used to obtain endometrial samples from hysterectomy specimens was as follows: The study materials were from slice B. Endometrial samples were taken from a specific area of the uterus to maximize consistency, since the fundus is recognized to be the most hormone responsive area of the endometrium. Area B was specifically chosen as this avoided the lateral edge of the fundal endometrium, which may sometimes undergo tubal epithelial metaplasia. These biopsies were dated both by LH surge and the date of the last menstrual period, and were examined by two independent pathologists who were blinded to the LH surge and menstrual dates. They characterized the specimens according to the criteria of Noyes Noyes et al. Where all agreed, the specimen was included as a control sample. HRT-treated endometrial samples This study involved women on two progestogen regimens: The protocol was approved by the local ethics committees and all patients signed an informed consent. This cohort of women recruited in our centre was part of a multicentre double blind dose-ranging study population of women. None had received any form of sex steroid treatment for 6 weeks before the commencement of study medications. Those who had ever used oestradiol implants were excluded.

4.2.5.2.3 INTRA-VAGINAL RINGS pdf

Tests for liver and renal function were performed and those women with abnormalities were excluded. All women over the age of 50 years had a normal mammogram within 3 years and normal cervical smears within the previous 6 months. General, breast and pelvic examinations were conducted to confirm normality. Endometrial biopsies were obtained using a vabra curette, and sampling only the functional layer, on day 24 of the last treatment cycle. The exclusion criteria and the safety parameters were as in group i. The tissue specimens were obtained from the corpus region, and the hysterectomy was performed between day 11 and 21 of the commencement of norethisterone phase of the third treatment cycle. The sections were then incubated with the primary antibody, 1: Specimens were washed with phosphate buffered saline PBS for 20 min between the steps. To test for the binding specificity of the secondary antibody, the primary antibody was omitted. The positive control was stained with CD34 and there was no background reaction, while the negative control did not show any staining. All fields examined were restricted to the functionalis layer. All the vascular spaces positive for CD34 were measured, and that included the collapsed blood vessels since they were lined by CD34 positive endothelium. The actual measurements of the vascular diameter included the distance spanned from the outer edge of the CD34 positive membrane of one side of the vessel to the outer edge of the CD34 positive membrane of the other side. The measurements were averages of the maximum and minimum diameter. Statistics The data did not fulfil the assumptions necessary for using the analysis of variance and t-test, therefore the non-parametric Kruskalâ€"Wallis and Mannâ€"Whitney tests were used. Results In the trimegestone-based HRT group, women were randomized to one of the four dose groups and completed the study; seven women did not start treatment after randomisation and were withdrawn from the study: Thirty-eight women did not complete the study, of whom only nine withdrew due to irregular bleeding. There was no statistically significant difference between the number of patients who were assigned to, or those who withdrew from, each trimegestone dose group. The total number of the endometrial samples obtained at the end of the study was , as two women declined to have a biopsy at the end of the study. In the NET-based HRT, 25 women completed 3 months of treatment and all had regular withdrawal bleeding prior to their scheduled hysterectomy. Trimegestone-treated endometrium Figure 1b The mean percentage vascular space area and average vascular diameter were higher in the high dose group 0. There was a lower mean number of vascular spaces the higher the dose of trimegestone, but this trend was not statistically significant Figure 2c. There was no statistically significant difference in the vascular parameters studied between women who bled on the day of the biopsy compared with those who had not bled by then data not shown. There was no evidence of a difference in the endometrial vascularity between the trimegestone-treated endometrium and the natural cycle. There was no evidence of apparent difference in the vascular parameters studied between women who had bled by the day of the biopsy and those who had not data not shown. The timing of the uterine specimen in relation to NET administration had no effect on the endometrial vascularity. Discussion In this study, the morphometric features of endometrial microvasculature of the functionalis layer in four phases of the natural cycle and in endometrial samples obtained from women treated with HRT, using two different progestogens are presented. CD34 antigen is also expressed on endothelial cells of lymphatics; however, there is no indication in the literature that sex steroids modify lymphangiogenesis. A similar decrease in the number of vascular spaces in early luteal phase has been reported Rogers et al. This may be due to the number of fields examined per biopsy, which they did not state, or due to the small number of specimens examined. Moreover, the endometrial samples in the control group of this study were highly characterized by the agreement of four parameters, viz. New vessel formation involves degradation of the basement membrane by the action of collagenase and plasminogen activators secreted by the endothelial cells. Endothelial cells then migrate through these openings formed in the basement membrane as a loose sprout. A lumen is formed by curvature of the endothelial cells, followed by division of the endothelial cells, and then canalization as the sprouts join each other Findlay, The major stimulus of angiogenesis is hypoxia Adair et al. Capillaries, including those of the endometrium, are lined by a continuous single layer of endothelial cells arranged over a basement membrane. Pericytes surround some of these endothelial cells which form projections that make contact with endothelial cells. Ultrastructurally, endothelial cells show changes in activity and size according to the phase of the menstrual cycle Roberts et al. Oestrogen and progesterone receptors have not been found in endometrial

endothelium Critchley et al. Therefore, it is plausible to postulate that steroidal modulation of changes in cellular activity and morphology may be mediated indirectly through changes in extracellular matrix proteins Ingber and Folkman, , integrins Vitola et al. They are present in the extracellular matrix and attached to proteoglycans on the cell surface. VEGF acts synergistically with angiopoietin-1, to induce sprout formation Koblizek et al. Basic FGF is expressed in glandular epithelial and stromal cells, although there were no changes in expression across the phases of the natural cycle Ferriani et al. However, there is increased glandular and stromal expression of bFGF in simple and complex hyperplasia, where it may stimulate the synthesis of plasminogen activator by the endothelial cells Mignatti et al. The involvement of extracellular matrix proteins Ingber and Folkman, was highlighted by the finding of cycle regulation of thrombospondine-1 in the endometrium. Thrombospondine-1, a multifunctional extracellular matrix glycoprotein, is a suppressor of angiogenesis in vitro and in vivo, and is regulated by progesterone Iruela-Arispe et al. Increased microvascular density was noted in endometria of women treated with levonorgestrel subdermal implants Rogers et al. On the other hand, medroxyprogesterone acetate administration was found to suppress angiogenesis in endometrial cancer transplant experiments Jikihara et al. Orally administered medroxyprogesterone acetate was shown to reduce microvascular density in women with endometrial hyperplasia Abulafia et al. A known difference between levonorgestrel and medroxyprogesterone acetate is that the former possesses much higher androgenic effect than the latter. In this study trimegestone, with the characteristic of very low androgen receptor binding, behaved in a manner similar to progesterone in the natural cycle, as reflected by the vascular morphometric parameters. The androgenic progestogen norethisterone, on the other hand, affected microvascular density in a manner analogous to subdermal levonorgestrel implants, although levonorgestrel administration was continuous and not cyclical. This suggests that androgen receptor activation probably plays an important role in modulating angiogenesis. An example has been demonstrated Watson et al. Moreover, norethisterone may be converted to ethinyloestradiol Fotherby, , thereby augmenting the oestrogenic stimulation of the endometrium. It can be argued that the regional variation in endometrial development could underlay the difference in the endometrial vascular parameters observed between trimegestone and norethisterone treated endometrium. In this study, the endometrial biopsies from the NET-based HRT were obtained from the corpus region of the hysterectomy specimens, while in the trimegestone groups, a vabra curettage was used, which would sample tissues from different parts of the uterine cavity. Therefore, such differences may be expected to result in a lower number of vascular spaces compared with the NET-treated endometrium, but as such does not explain the prevalence of smaller vascular diameter in the latter group. There is a difference in the duration of the two types of progestogens, as trimegestone was given for 6 months, while cyclical NET was given for 3 months. There is no information in the literature on vascular morphometry defined by CD34 overtime. However, it has been found Hickey et al. Nevertheless, it should be pointed out that the essential difference is the continuous administration of levonorgestrel in a previous study Hickey et al. The endometrial vascular morphometry as studied by CD34 did not explain the different patterns of bleeding in these two HRT regimens, as there was no difference in the endometrial biopsies obtained from women who bled on the day of the biopsy and those who had not bled by then. In conclusion, NET-based HRT was associated with a higher number of smaller vascular spaces than in the trimegestone treated endometrium or that of the natural cycle, and therefore it opens the question for further assessment of the mechanism of vascular development in the endometrium to help in the optimization of future therapeutics. Mean and SD of the vascular parameters in the endometrium of the natural cycle, trimegestone-treated or norethisterone-treated NET cycles Vascular parameters Endometrium of the natural cycle Trimegestone dose group.

4.2.5.2.3 INTRA-VAGINAL RINGS pdf

5: EPB1 - Intravaginal rings with insertable drug-containing core - Google Patents

platforms suitable for intra-vaginal administration are hydro-gels, vaginal tablets, pessaries/suppositories, particulate systems, and intra-vaginal rings.

Also provided are pharmaceutical compositions containing the compounds, processes for their preparation and novel chemical intermediates. Background of the Invention Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes within the cell Hardie and Hanks The Protein Kinase Facts Book. The kinases may be categorized into families by the substrates they phosphorylate e. Sequence motifs have been identified that generally correspond to each of these kinase families e. Protein kinases may be characterized by their regulation mechanisms. These mechanisms include, for example, autophosphorylation, transphosphorylation by other kinases, protein-protein interactions, protein-lipid interactions, and protein-polynucleotide interactions. An individual protein kinase may be regulated by more than one mechanism. Kinases regulate many different cell processes including, but not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation and other signalling processes, by adding phosphate groups to target proteins. Phosphorylation of target proteins occurs in response to a variety of extracellular signals hormones, neurotransmitters, growth and differentiation factors, etc. The appropriate protein kinase functions in signalling pathways to activate or inactivate either directly or indirectly , for example, a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor. Aurora Kinases Three members of the Aurora kinase family have been found in mammals so far Nigg, Nat. Aurora kinase A is believed to play a part in mitotic checkpoint control, chromosome dynamics and cytokinesis Adams et al. The kinases are located at the centrosomes of interphase cells, at the poles of the bipolar spindle and in the mid- body of the mitotic apparatus. The other two currently known Aurora kinases are Aurora B also referred to in the literature as Aurora 1 and Aurora C also referred to in the literature as Aurora 3. The Aurora kinases have highly homologous catalytic domains but differ considerably in their N-terminal portions Katayama et al, Cancer Metastasis Rev. The substrates of the Aurora kinases A and B have been identified as including a kinesin-like motor protein, spindle apparatus proteins, histone H3 protein, kinetochore protein and the tumour suppressor protein p Aurora A kinases are believed to be involved in spindle formation and become localised on the centrosome during the early G2 phase where they phosphorylate spindle- associated proteins Prigent et al. Hirota et al, Cell, , found that cells depleted of Aurora A protein kinase were unable to enter mitosis. Furthermore, it has been found Adams, that mutation or disruption of the Aurora A gene in various species leads to mitotic abnormalities, including centrosome separation and maturation defects, spindle aberrations and chromosome segregation defects. Aurora kinase A is generally expressed at a low level in the majority of normal tissues, the exceptions being tissues with a high proportion of dividing cells such as the thymus and testis. However, elevated levels of Aurora kinases have been found in many human cancers Giet et al. Furthermore, Aurora A kinase maps to the chromosome 2Oq 13 region that has frequently been found to be amplified in many human cancers. Thus, for example, significant Aurora A over-expression has been detected in human breast, ovarian and pancreatic cancers see Zhou et al. Moreover, lsola American Journal of Pathology , has reported that amplification of the Aurora A locus 20q13 correlates with poor prognosis for patients with node-negative breast cancer. High levels of Aurora A kinase have also been found in renal, cervical, neuroblastoma, melanoma, lymphoma, pancreatic and prostate tumour cell lines Bischoff ef al. Royce et al Cancer. Reichardt et al Oncol Rep. It was hypothesized that amplification of the Aurora 2 gene may be a non-random genetic alteration in human gliomas playing a role in the genetic pathways of tumourigenesis. Results by Hamada et al Br. In a study by Gritsko et al Clin Cancer Res. High protein levels of Aurora A correlated well with elevated kinase activity. Results obtained by Li ef al Clin. Similarly, it has been shown that Aurora A gene amplification and associated increased expression of the mitotic kinase it encodes are associated with aneuploidy and aggressive clinical behaviour in human bladder cancer. Investigation by several groups Dutertre and Prigent , MoI. For example overexpression of Aurora A in mouse

embryo fibroblasts can reduce the sensitivity of these cells to the cytotoxic effects of taxane derivatives. Therefore Aurora kinase inhibitors may find particular use in patients who have developed reistance to existing therapies. On the basis of work carried out to date, it is envisaged that inhibition of Aurora A kinase will prove an effective means of arresting tumour development. It has also been shown that there is an increase in expression of Aurora B in tumour cells compared to normal cells Adams et al. One report suggests that overexpression of Aurora B induces aneuploidy through increased phosphorylation of histone H3 at serine 10, and that cells overexpressing Aurora B form more aggressive tumours and have a higher tendency to form metastatic tumours Ota et al. Aurora B is required for both spindle checkpoint function and metaphase chromosome alignment in human cells Adams et al. Consequently, after a brief delay cells exit mitosis without dividing and with a 4N DNA content, whereupon they rapidly lose their proliferative potential. In the study, the Aurora kinase inhibitor blocked cancer cell proliferation, and also triggered cell death in a range of cancer cell lines including leukaemic, colorectal and breast cell lines. In addition, it has shown potential for the treatment of leukemia by inducing apoptosis in leukemia cells. In the study, dose-dependent tumour growth inhibition was demonstrated in HCT tumour bearing mice and PC-3 tumour bearing mice versus vehicle treated mice. FLT3 FMS-like tyrosine kinase 3 FLT3 is a receptor tyrosine kinase involved in the proliferation, differentiation and apoptosis of hematopoietic and non-hematopoietic cells Scheijen and Griffin, Oncogene 21 , and Reilly, British Journal of Haematology , Activation of these downstream signalling molecules by phosphorylation leads to the proliferative and pro-survival effects of FLT3 Gilliland and Griffin and Levis and Small, Leukemia 17 9 , Other ligand independent activating mutations of FLT3 have recently been described, contributing to the leukaemic transformation in AML. FLT4 has been found to be expressed in a variety of human malignancies including lung adenocarcinoma Li et al. Expression of FLT4 has also been shown to correlate with the different stages of cervical carcinogenesis Van Trappen et al. Expression levels of VEGF-C and FLT4 were found to correlate with the stage and lymph node metastasis and survival of cancer patients with lung adenocarcinomas. Amongst the compounds disclosed in the article are 2,5-diphenyl-1H-imidazole carboxylic acid amide and 2-phenylthiophenyl-1H-imidazolecarboxylic acid amide. Amongst the compounds disclosed in the article is 2,5-diphenyl-oxazolecarboxylic acid amide. One of the compounds exemplified in the article is 2-phenyl 3,4,5-trimethoxy-phenyl -oxazole carboxylic acid amide. JP and JP Yoshitomi disclose diaryl imidazoles as analgesic and anti-inflammatory agents. The compound 2-4-fluorophenyl 4-methoxyphenyl -1 H- imidazolecarboxylic acid amide is specifically disclosed. The compound 2- 4-methylphenyl phenyl-oxazolecarboxylic acid amide is specifically disclosed as a chemical intermediate. Summary of the Invention The invention provides compounds that have kinase modulating or inhibiting activity, and which it is envisaged will be useful in preventing or treating disease states or conditions mediated by the kinases. The compounds of the invention are defined and described below and in the claims appended hereto. Accordingly, in one aspect, the invention provides a compound which is an amide of the formula 1: In one embodiment, the invention provides a compound which is an amide of the formula 1a: In one sub-group of compounds, a and b are both 0 and therefore the compound is an amide of the formula 2: Within formula 2 , one group of compounds consists of amides of the formula 2a: Another group of compounds consists of amides of the formula 2b: A farther group of compounds consists of amides of the formula 2c: In another subgroup of compounds, a is 1 and b is 0 and therefore the compound is an amide of the formula 3: Within formula 3 , one group of compounds consists of amides of the formula 3a: In a further sub-group of compounds, a is 0 and b is 1 and therefore the compound is an amide of the formula 4: Within formula 4 , one group of compounds consists of amides of the formula 4a: Further aspects of the invention and particular and preferred embodiments of the invention are as set out below or as defined in the claims appended hereto. General Preferences and Definitions In this specification, references to formula 1 include not only formula 1 perse but also formulae 1a , 2 , 2a , 2b , 2c , 3 , 3a , 4 , 4a and 5 and sub-groups, examples or embodiments thereof, unless the context requires otherwise. Thus for example, references to therapeutic uses, pharmaceutical formulations and processes for making compounds, where they refer to formula 1 , are also to be taken as referring to formulae 1a , 2 , 2a , 2b , 2c , 3 , 3a , 4 , 4a and 5 and sub- groups, examples or embodiments thereof. Similarly, where preferences, embodiments and examples are given for compounds of

the formula 1 , they are also applicable to formulae 1a , 2 , 2a , 2b , 2c , 3 , 3a , 4 , 4a and 5 unless the context requires otherwise. As used herein, the term "modulation", as applied to the activity of a kinase such as FLT3, FLT4 or an Aurora kinase, is intended to define a change in the level of biological activity of the kinase s. Thus, modulation encompasses physiological changes which effect an increase or decrease in the relevant kinase activity. In the latter case, the modulation may be described as "inhibition". The term "upregulation" as used herein in relation to a kinase is defined as including elevated expression or over-expression of the kinase, including gene amplification i. References herein to a disease state or condition being "mediated" by a particular kinase are intended to operate limitatively so that the various disease states or conditions to which the term is applied are those in which the kinase in question plays a biological role. The following general preferences and definitions shall apply to each of the moieties T, Ar1, Ar2, R1 to R4 and any sub-definition, sub-group or embodiment thereof, unless the context indicates otherwise. The term "halogen" as used herein refers to fluorine, chlorine, bromine and iodine and does not include astatine. The term "aryl" as used herein refers to a carbocyclic ring or group having aromatic character and the term "heteroaryl" is used herein to denote a heterocyclic group having aromatic character. The terms "aryl" and "heteroaryl" e. The term covers polycyclic ring systems in which all of the fused rings are aromatic as well as ring systems where one or more rings are non-aromatic, provided that at least one ring is aromatic. In polycyclic systems containing both aromatic and non-aromatic rings fused together, the group may be attached to another moiety e. Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings or two fused five membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulphur and oxygen. The heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five. Examples of five membered heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, triazole and tetrazole groups. Examples of six membered heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine. A bicyclic heteroaryl group may be, for example, a group selected from: Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazothiazole e. Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuran, benzothiophene, benzimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzothiazole, benzisothiazole, isobenzofuran, indole, isoindole, indolizine, indoline, isoindoline, purine e. A further example of a six membered ring fused to a five membered ring is a pyrrolopyridine group such as a pyrrolo[2,3-b]pyridine group. Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, chromene, isochromene, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups. Examples of polycyclic aryl and heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydronaphthalene, tetrahydroisoquinoline, tetrahydroquinoline, dihydrobenzothiophene, dihydrobenzofuran, 2,3-dihydro-benzo[1 ,4]dioxine, benzo[1 ,3]dioxole, 4,5,6,7-tetrahydrobenzofuran, indoline, isoindoline and indane groups. Examples of carbocyclic aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl groups.

4.2.5.2.3 INTRA-VAGINAL RINGS pdf

6: [Full text] Development of polyether urethane intravaginal rings for the sustained | DDDT

In this study intra-vaginal rings containing. oestradiol have been used to examine the feasibility of vaginal administration of oestradiol. The rings were inserted in post-menopausal women. Plasma concentrations of oestrone and oestradiol were analysed by radioimmunoassay (RIA).

Wahab Human Reproduction vol. Gaps start 1To to appear between the endothelial cells in the premenstrual whom correspondence should be addressed at: The effect of trimegestone-based and norethisterone-based Endometrial blood vessels undergo different morphological hormone replacement therapy HRT regimens on the changes under the effect of different sex steroids. Endometrial vascular of the endothelial cells, reflecting an increase in endothelial space area, diameter and number were defined in the permeability Johannisson et al. Given orally, levonorgestrel 0. The control samples levonorgestrel implants Norplant induced an increase in were LH-dated endometrial biopsies. Authors reported no variation in that of the natural cycle. There was no dose-dependent the vascular density with different phases of the natural cycle, effect in the four dose groups of trimegestone. In conclu- and therefore concluded that there is no correlation between sion, norethisterone may exert a different effect on angio- vascularity and stromal development Shaw et al. On the other hand, development. In a recent study Al-Azzawi et al. Women on cyclical sequential bleeding is irregular Habiba et al. This irregular norethisterone NET , exhibited two patterns of bleeding: Al-Azzawi progenitor cells, in the basement membrane of the vascular Included in the study were healthy women aged 45â€”65 years mean endothelium Traweek et al. None had received any form of sex marker of endothelial cells, in preference to Von Willebrand steroid treatment for 6 weeks before the commencement of study factor, which gives a weaker staining, or the less specific medications. Those who had ever used oestradiol implants were antigen Ulex europaeus Traweek et al. Tests for liver and renal function were performed and those The aim of this study was to establish the vascular morpho- women with abnormalities were excluded. All women over the age metric changes using the endothelial cell marker, CD34, i in of 50 years had a normal mammogram within 3 years and normal the natural cycle, ii in response to trimegestone-based HRT cervical smears within the previous 6 months. General, breast and in a dose ranging study, and iii to compare the changes in pelvic examinations were conducted to confirm normality. Endometrial biopsies were obtained using a vabra curette, and trimegestone-based and the widely used, NET-based. The exclusion criteria hysterectomy specimens. The clinical indications for the hysterectom- and the safety parameters were as in group i. The tissue specimens ies were: None of these women had received performed between day 11 and 21 of the commencement of norethis- any hormonal treatments for 2 months prior to the procurement of terone phase of the third treatment cycle. The technique used to obtain endometrial specimens were incubated in microwave oven W in citrate samples from hysterectomy specimens was as follows: The Glostrup, Denmark to minimize non-specific reactivity. The sections study materials were from slice B. Endometrial samples were taken were then incubated with the primary antibody, 1: Area B was specifically chosen as this avoided the were washed with phosphate buffered saline PBS for 20 min lateral edge of the fundal endometrium, which may sometimes between the steps. Endometrial sections were incubated with biotin- undergo tubal epithelial metaplasia. Controls were included using mouse immuno- the phase of the endometrial development. To test for the binding specificity of the secondary antibody, last menstrual period, and were examined by two independent the primary antibody was omitted. The positive control was stained pathologists who were blinded to the LH surge and menstrual dates. Where all agreed, the specimen was included as a control sample. All the megestone 0. The actual measurements of the vascular diameter dose-ranging study, for six treatment cycles. The protocol was included the distance spanned from the outer edge of the CD34 approved by the local ethics committees and all patients signed an positive membrane of one side of the vessel to the outer edge of the informed consent. This cohort of women recruited in our centre CD34 positive membrane of the other side. The measurements were was part of a multicentre double blind dose-ranging study population averages of the maximum and minimum diameter. Statistics The data did not fulfil the assumptions necessary for using the analysis of variance and t-test, therefore the non-parametric Kruskalâ€” Wallis and Mannâ€”Whitney tests

were used. Results In the trimegestone-based HRT group, women were randomized to one of the four dose groups and completed the study; seven women did not start treatment after randomisation and were withdrawn from the study: Thirty-eight women did not complete the study, of whom only nine withdrew due to irregular bleeding. There was no statistically significant difference between the number of patients who were assigned to, or those who withdrew from, each trimegestone dose group. The total number of the endometrial samples obtained at the end of the study was , as two women declined to have a biopsy at the end of the study. In the NET-based HRT, 25 women completed 3 months of treatment and all had regular withdrawal bleeding prior to their scheduled hysterectomy. The mean percentage vascular space area was significantly lower in the early luteal phase compared with the late luteal and Figure 1. The average diameter b and in the norethisterone-based HRT c. There was no statistically significant difference in the Trimegestone-treated endometrium Figure 1b vascular parameters studied between women who bled on the The mean percentage vascular space area and average vascular day of the biopsy compared with those who had not bled by diameter were higher in the high dose group 0. There was no evidence of a difference there was no statistically significant difference between the in the endometrial vascularity between the trimegestone-treated four dose groups Figure 2a,b. There was a lower mean endometrium and the natural cycle. There was no evidence of apparent difference in the vascular parameters studied between women who had bled by the day of the biopsy and those who had not data not shown. The timing of the uterine specimen in relation to NET administration had no effect on the endometrial vascularity. Discussion In this study, the morphometric features of endometrial micro- vasculature of the functionalis layer in four phases of the natural cycle and in endometrial samples obtained from Figure 2. Open circles are used for the mean percentage vascular space area in the individual women. Open circles are used for the mean diameter of the vascular space in the individual women. Open circles are used for the mean number of the vascular spaces in the individual woman. The use of CD34 staining technique is more ovaries Ferrara et al. They are present in the staining, where it is difficult to identify the microvasculature, extracellular matrix and attached to proteoglycans on the cell which when constricted or small may blend with the surround- surface. CD34 antigen is small patches of immunostaining were found around some also expressed on endothelial cells of lymphatics; however, blood vessels, in the glandular epithelium and in the stromal there is no indication in the literature that sex steroids modify cells Gargett et al. VEGF acts synergistically with lymphangiogenesis. This may be due to the number of fields However, there is increased glandular and stromal examined per biopsy, which they did not state, or due to expression of bFGF in simple and complex hyperplasia, where the small number of specimens examined. Moreover, the it may stimulate the synthesis of plasminogen activator by the endometrial samples in the control group of this study were endothelial cells Mignatti et al. The involvement of extracellular matrix proteins Ingber date of the last menstrual period, urinary LH surge, and the and Folkman, was highlighted by the finding of total agreement of two independent histopathologists to the cycle regulation of thrombospondine-1 in the endometrium. Thrombospondine-1, a multifunctional extracellular matrix New vessel formation involves degradation of the basement glycoprotein, is a suppressor of angiogenesis in vitro and membrane by the action of collagenase and plasminogen in vivo, and is regulated by progesterone Iruela-Arispe activators secreted by the endothelial cells. Endothelial cells et al. A lumen is formed by curvature of women treated with levonorgestrel subdermal implants of the endothelial cells, followed by division of the endothelial Rogers et al. On the other hand, Findlay, Orally administered medroxyprogesterone acetate by a continuous single layer of endothelial cells arranged over was shown to reduce microvascular density in women with a basement membrane. Pericytes surround some of these endometrial hyperplasia Abulafia et al. Capillaries lack muscle layer; however, progesterone acetate is that the former possesses much higher capillaries and small vessels consist of one or two endothelial androgenic effect than the latter. Ultrastructurally, endothelial cells show cycle, as reflected by the vascular morphometric parameters. Therefore, it is plausible to postulate that steroidal an important role in modulating angiogenesis. An example has modulation of changes in cellular activity and morphology been demonstrated Watson et al. Al-Azzawi vascular parameters observed between trimegestone and nor- growth factor is essential for corpus luteum angiogenesis. In this Findlay, J. Raven Press, New York, pp. Therefore, such differences may be expected to result acetate on secondary spreading of

4.2.5.2.3 INTRA-VAGINAL RINGS pdf

endometrial cancer. Invasion Metastasis, in a lower number of vascular spaces compared with the NET- 9, â€" There is a difference in the duration of the two types of Gold, L. There is no information for paracrine and autocrine action. However, it has been found Hickey et al. Nevertheless, it should be immunocytochemical localization in normal and endometriotic tissues. Blackwell Science, et al. Thrombospondin-1, an inhibitor of angiogenesis, is regulated by progesterone in the human endometrium. Cambridge University Press, Cambridge, pp. Pitman Press, Bath, UK, pp.

4.2.5.2.3 INTRA-VAGINAL RINGS pdf

7: Gynecological devices market in Transparency Market Research by Jess Bruce - Issuu

Vaginal rings are efficient for patients and doctors Vaginal rings are effective Intra-vaginal rings (IVR's) A new drug delivery system with a year track record.

Description - - Intravaginal use of methylB,16B-methylenenorspiroxenones, intravaginal rings comprising methylBJ6B-methylenenorspiroxenones, and use thereof in contraception The present invention relates to the subject matter characterized in the patent claims, i. Among them, oral contraception pill is the most frequently used contraceptive method in many countries. However, there is a demand for the development of new, long-acting reversible contraceptives LARC that require minimal medical guidance and patient compliance compared to oral contraceptives. New LARCs like intrauterine devices e. However they are implanted and removed by an invasive procedure. In contrast intravaginal rings can be inserted into the vagina by the user herself. They provide a continuous release of the active ingredient over a period from several weeks up to one year. Therefore intravaginal rings have been under clinical investigation over the last 45 years. Such intravaginal rings are devices made of flexible and drug-permeable silicone elastomers that release the active agent s to the vaginal mucosa for a certain period of time at a defined rate [for details see Brache et al. Semin Reprod Med ; Fertil Steril ; Since then, several clinical trials with IVR releasing different progestins such as progesterone, nestorone, levonorgestrel and other progestins were published see below. However, estrogens are associated with potential risks such as a slightly increased risk of thrombosis and certain side effects such as loss of libido, nausea, and headache. Contraceptive efficacy of progestin-only contraceptives like progestin-only pills POPs is thought to depend primarily on cervical mucus thickening, making the cervix impermeable for sperm [Roland et al. Adv Contracept ; Other discussed mechanisms of action are interference with fallopian tube motility, thus inhibiting egg transport, changes in the uterine endometrium, interfering with blastocyst implantation and ovulation inhibition[Brache et al. Contraception ; 50 6 Suppl 1: Nevertheless, contraceptive efficacy is lower than that of combined oral contraceptives. Irregular bleeding and spotting is the main reason for discontinuation of presently available synthetic progestin-only contraceptives which undermines the use of these valuable contraceptives. A multicenter clinical trial with a intravaginal ring releasing 20 micrograms per day of levonorgestrel for at least 90 days was performed over The one year pregnancy rate was 4. However, the overall discontinuation rate at 1 year was It consists of a homogeneous mixture of soft, flexible silicone elastomers and micronized progesterone. It has been developed by Population Council as a contraceptive method for lactating woman. The ring is to be used continuously and replaced every 3 months plus two weeks. IVR removal should be rare and include intercourse and ring cleaning, but reinsertion within 2 h is mandatory. Overall, three of breastfeeding women became pregnant while using this method during 10, women-months of exposure, which is comparable to the efficacy of a copper-T intrauterine device. Although women using the progesterone releasing IVR experienced a lactational amenorrhea of approximately 6 months, vaginal bleeding has been reported to be fairly common in the first 30 days after insertion of progesterone IVR [Nath et al. However, there are no data on the contraceptive efficacy and irregular bleeding and spotting in non-lactating woman. No pregnancies were observed in women-months and postpartum amenorrhea was prolonged while breastfeeding performance and infant growth were not different from those observed in a previous comparative group of TCu IUD users. The 1-year continuation of use was high However, menstrual disturbances were also associated with this ring, more so in the lower doses, while the higher dose had reduced bleeding. In summary, progestin-only IVR are useful contraceptives in lactating women with high contraceptive efficacy and acceptable irregular bleeding pattern. However, in contrast to non-lactating woman lactating woman possess a reduced fertility and a postpartum amenorrhea and hence currently available progestin-only IVR are not suitable contraceptives for non-lactating woman. Object of invention It is therefore an object of the present invention to provide a progestin-only contraceptive intravaginal ring which ensures sustained local cervical mucus blockage and contraceptive efficacy in lactating and in non-lactating woman comparable to the contraceptive efficacy of oral contraceptives while systemic effects on the ovarian cycle and the endometrium are minimized, which results in reduced irregular bleeding

and spotting. Description of invention The object of invention is achieved according to the invention by the intravaginal use of compounds of general formula I - - formula I wherein R6 and R7 are a hydrogen atom or together are an a-methylene group, namely by the intra vaginal use of Compound A: Detailed description of the invention In a study with intravaginal rings releasing Compound A , methyl,methylenenor spiroxenone, which was placed into the vagina of monkeys, the inventors were able to demonstrate a surprising dissociation of a local action at the cervix mucus and a systemic action as shown by inhibition of ovulation and effects on the cervix and the endometrium. Higher doses progressively abolished menstruation with a dose dependency identical to that of ovulation inhibition. The marked strong dissociation of high local versus low systemic activity and the high gestagenic efficacy of the substances are sufficient for causing a contraceptive action only due to the local effects. Systemically caused side effects, such as those occurring with the use of other gestagens, may thus be prevented or at least greatly reduced. Owing to the high local gestagen concentration, a more rapid onset of contraceptive efficacy and better bleeding control can also be expected. Owing to the properties of Compound A and B , these are very well suited for intravaginal use in contraception. Preference is given here to intravaginal administration by means of an intravaginal ring. The terms intravaginal ring, vaginal ring, and IVR are used synonymously. The application in an IVR provides a convenient formulation with low variability in drug release rate, avoiding hepatic first-pass metabolism of the drug substance and improving treatment compliance since no daily recall of drug intake is required. In contrast, the contraceptive principle of the progestin- only pill POP requires an exact dosing schedule to ensure a reliable contraceptive effect. In that aspect, continuous administration with an IVR is of great advantage. The core and the membrane can be formed from the same or different biocompatible polymers. The core or the membrane or both can comprise the drug substance. A number of different hormone releasing IVR are known from the literature, e. The IVR can be manufactured in accordance with standard techniques described in the art e. The design and manufacture of an exemplary IVR is described in example 1. Human size rings can be produced in a similar way as described in example 1. Variations can be made with respect to the surface area of the drug releasing part to adjust it to the desired dose. Adjustment of membrane thickness and material can also be needed. According to the invention the IVR can be continuously used for at least one month up to one year, preferably for three month to six month. Continuous use includes that the IVR can be taken out intermittently for 1 up to 4 hours for e. Alternatively according to the invention the IVR can be used in such a way that it is used during the menstruation-free phase of the respective cycle and not used during menstruation; e. The release of a compound from the IVR is described by the release rate. Release rate means the average amount of active drug substance released from the IVR within 24 hours that is available for - - absorption by the surrounding tissue. A person skilled in the art will know that the average release rate from IVR can decrease over the period of application. The in vitro release rate is routinely used in the art to characterize hormone - containing IVR. The term dose and release rate are used synonymously in this patent application. According to the invention, a long-term release IVR is used to ensure constant average release rates over several weeks or months up to one year. Long-term release IVR means any IVR suitable for administration of drugs over a prolonged period of time avoiding fluctuations of drug levels normally induced by short-term release formulations e. A considerably increased potential release of active ingredients shortly after insertion so called burst effect of long-term release IVR is known to a person skilled in the art. IVR showing such a burst effect shortly after insertion are also considered to be claimed according to the invention even if during the duration of the burst effect the release rate is increased. Owing to the burst effect, the IVR according to the invention may achieve the desired release rates according to the invention only one, two or three days after insertion of the IVR into the vagina, in exceptional cases only after a week. To a person skilled in the art, it is known that application of an IVR can lead to a change decrease in the daily release rate over the period of administration. IVR which exhibit such a change are considered to be claimed as long as sufficient compound is released. According to the invention, the release rate of Compound A and B needs to be high enough to ensure local contraceptive efficacy but low enough to avoid systemic side effects. Such a release rate can be achieved by choosing the appropriate parameters for the design of the membrane and core of the IVR such as polymer composition, membrane thickness, and membrane surface area. An further embodiment of the invention is a

4.2.5.2.3 INTRA-VAGINAL RINGS pdf

intravaginal ring for use in contraception. Determination of the release rate of an IVR releasing of Compound A and production of the intravaginal rings for the in vivo study For an in vivo study with cynomolgus monkeys, Compound A -releasing intravaginal rings adapted to the size of the cynomolgus monkeys were manufactured. The rings had an outer diameter of 14 mm and a cross-section of 2. The rings contained a core of compound A and elastomer. Said core was coated by a release- controlling membrane. The intended drug dosages were achieved by appropriate selection of the materials for the core and the membrane and by adjusting the drug concentration and the surface area of the Compound A -containing core in combination with the membrane thickness. Suitable selection of these parameters makes it possible to control the release of Compound A over periods of more than 3 weeks. Placebo rings were likewise produced. The properties and materials of these IVR are summarized in Table 1. The matrix of Compound A comprising core was made of silicone elastomer polydimethylsiloxane and the inert core was made of fluorosilicone elastomer poly 3,3,3-trifluoropropylmethylsiloxane. The Compound A -containing core was produced by mixing micronized Compound A and the silicone elastomer in a mixer. The mixture was shaped in a mold to give a small elastic rod having a thickness of 1. The fluorosilicone elastomer core was extruded to give a small elastic rod having a thickness of 1. Membrane - - Two drug-release-controlling membrane tubes were produced by tube extrusion. The wall thickness of the tube the membrane thickness was about 0. Assembly of the ring The Compound A core was cut into four lengths: The inert fluorosilicone elastomer core was cut into appropriate lengths so that a total core length of 35mm was achieved. The ring was put together by pushing the core segment s into the swollen membrane tube. The tube was shaped into a ring by overlapping and gluing. A small PE piece was applied in the ring joint to give better ring shape. After evaporation of the solvents, the tube contracted and compressed the parts tightly. The solutions were changed daily in the first week and twice in the following weeks. The detection wavelength for Compound A was mm. Three rings were tested in parallel. Results The rings were tested in vitro for up to 34 days. The starting release rates were about 4 times higher than the final steady release rate which was achieved within one week. The in vitro release rate of Compound A is depicted in figure 1.

4.2.5.2.3 INTRA-VAGINAL RINGS pdf

8: Vaginal ring - Wikipedia

The vaginal ring is easy to use. Squeeze the ring between your thumb and index finger and gently push it into your vagina. When you first begin using the ring, use back-up birth control in addition to the ring, like a condom, for the first seven days after you insert the vaginal ring.

Editor who approved publication: Both IVRs were fabricated by hot-melt injection molding. Surface-modified matrix IVRs with polyvinylpyrrolidone or poly vinyl alcohol coatings exhibited significantly reduced burst release on the first day 6. Reservoir IVR segments designed to release lower amounts of HCQ displayed near-zero-order release kinetics with an average release rate of The IVR segments had no significant effect on cell viability, pro-inflammatory cytokine production, or colony formation of vaginal and ectocervical epithelial cells. Microbicides containing active agents that can be topically applied to the vagina are currently being investigated for use as HIV prophylactic strategies. One possible approach is to formulate therapeutic drugs into intravaginal rings IVRs. IVR drug delivery systems have been marketed since for hormone replacement therapy, but the use of IVRs as microbicides is relatively new. Several IVR medical devices have been developed preclinically for the purpose of sustained release of either single antiretroviral drugs or multiple drugs. In the case of hydrophilic drugs, the ideal polymer for IVR fabrication should satisfy several conditions. First, it should provide high drug solubilization capacity so that a sufficient quantity of the drug could be incorporated into the IVR formulation. Second, the polymer should be able to control the drug release based on properties such as water swellability and drug diffusion within the polymeric matrix. Last, its mechanical and chemical properties should allow the IVR to remain within the vaginal lumen without eliciting tissue damage, and the selected polymer should be stable in the acidic vaginal environment pH, 3. HCQ, a lysosomotropic amine and a hydroxyl derivative of chloroquine, has been used for the treatment of acute malaria 15 and autoimmune diseases such as lupus 16 and rheumatoid arthritis. We report, for the first time to our knowledge, the fabrication and in vitro characterization of two IVR medical devices surface-modified matrix and reservoir segmented IVRs , which can provide sustained release and varying release rates high and low of HCQ for more than 14 days. In addition, stability of HCQ within the matrix IVR formulation and effect of drug-free IVRs on the viability of vaginal and cervical epithelial cells in vitro were investigated in the current study. The polymer was dissolved by stirring the mixture at room temperature for 6 hours. The drug-containing PUA solution was allowed to mix overnight. The films were then placed on high vacuum and considered free of methylene chloride when the film mass remained constant over the course of 24 hours. These dimensions have been previously evaluated for use in humans and macaques, respectively. Each segment was coated twice following this process before it was used for release or stability studies. Afterwards, all the content was transferred into a 5 mL syringe attached to another 5 mL syringe via a 1. After complete dissolution, dimethylacetamide was added to fill up to volume, and the sample was vortexed. A known amount of drug was added to the mixture and placed back on the shaker for another 4 hours. The solution was then filled to volume with dimethylacetamide, followed by vortexing. Drug extraction was performed on the polymer solution containing a known amount of HCQ, using the same method described earlier. Extraction samples were diluted times before subjection to the HPLC analysis described later. The mobile phase consisted of methanol, acetonitrile, and 58 mM sodium phosphate dibasic buffer 4: Flow rate was maintained at 1. The retention time of HCQ was approximately 5. Sink conditions were maintained by replacing the entire release medium daily. The pH of the daily release medium was monitored for the entire study period. The weight and the dimensions length and diameter of each segment were recorded both at the beginning and the end of the study. Release study was performed under the same conditions described earlier. Weights and cross-sectional diameters of IVRs were measured using an analytical balance and digital caliper, respectively. The cells were cultured in keratinocyte-serum free medium K-SFM containing 0. IVR segment elution medium preparation The effect of drug-free IVR segments on cell viability was evaluated using an elution assay. Lipopolysaccharide from Escherichia coli Drug-free K-SFM was used as negative control. Colony formation assay Colony formation assay was performed similar to other reported studies. After 2 hours of cell

attachment, medium was replaced with 4 mL of either regular medium negative control or elution medium collected at different intervals. Thereafter, the medium was discarded and the colonies were gently washed once with warm PBS solution. The cells were fixed and stained using a mixture of 6. After gentle rinsing, formed colonies containing more than 50 cells 37 were manually counted under a microscope. The colony-forming efficiency was calculated by dividing the average number of colonies with the number of cells inoculated further normalized to the negative control and expressed as a percentage of the negative control. The n-value refers to number of replicates performed for each study. Table 1 Dimensions and weight of fabricated small-size matrix intravaginal rings Note: During the entire study period, HCQ release followed a typical matrix drug diffusion release pattern 34 in all matrix systems developed in the current study, which is characterized by a first-day burst release followed by a rapid drug elution phase and then a continuous decelerated release phase. Within the first 24 hours, burst releases of During the 18 day study period, a total of Data were scaled up to represent the release from a full-size small IVR. Inset graphs show daily release rates of different HCQ loadings from day 10 to day Although the first-day burst release was further decreased to Similarly, matrix IVR segments fabricated from the lower swellable polymer PUD showed a reduced daily HCQ release profile with a decreased first-day burst release During the entire release study, there were no significant changes in pH observed in the daily collected release medium data not shown , indicating that the released HCQ did not alter the pH of the release buffer. Figure 3 PUA matrix intravaginal ring accelerated stability test. The segments began to absorb water within 24 hours in buffer, with the noncoated segments reaching an equilibrated swelled state no significant weight increase within 2 days Figure 4. Compared with their initial dry weights, the equilibrated swelled weights of the noncoated, PVP-coated, and PVA-coated segments were However, the latency in reaching the equilibrated state was observed in both types of coated segments Figure 4 , suggesting that swelling may be affected by the PVP or PVA coatings. The reduced swelling resulted in a reduced increase in the weights of the coated segments Figure 4 Swelling test of PUA matrix intravaginal ring segments. Noncoated segments reached equilibrated state no significant mass change after 2 days, whereas PVP- or PVA-coated segments reached equilibrated state after 5 days of incubation. In vitro cytotoxicity evaluation The in vitro biocompatibility of the matrix IVRs developed was evaluated Figure 5. Figure 5 In vitro biocompatibility evaluations of hot-melt intravaginal ring segments. A MTS assay was performed to determine cell viability. Cells cultured in drug-free medium were used as negative control; 1 M acrylamide prepared in culture medium was used to induce cell death as a positive control. E Colony formation assay was performed to determine the cell proliferation potential after cell incubation with elution medium for 12 days. Cells cultured in drug-free medium were used as a negative control. Discussion The vaginal route has been used for the administration of a wide range of therapeutic agents for women, such as those for contraception and those for the treatment of local vaginal infections. Compared with oral route of administration, vaginal delivery avoids gastric irritation, 35 bypasses hepatic first-pass metabolism, and can achieve relatively higher drug concentrations in vaginal mucosal tissues while reducing systemic uptake. Among these delivery strategies, the IVR dosing regimen can provide sustained drug delivery, allowing therapeutic effects to be obtained using lower daily doses, which provides effective local drug concentrations at the vaginal mucosa without causing systemic toxicity. Studies have demonstrated that the inhibition of T-cell activation by HCQ is through the inhibition of T-cell-receptor-induced up-regulation of the T-cell activation marker CD Although Sperber and colleagues reported that cell viability was not affected when T-cell or monocytic cell lines were treated with 0. In addition, intravaginal delivery of HCQ for the prevention of HIV infection may potentially reduce the development of multidrug resistance because of its combination of effects on both host cells and virus. For example, HCQ has modulatory effects on host immunity 29 and can directly affect HIV replication via the impairment of posttranslational activities such as glycosylation of gp In a typical matrix-based IVR, the drug is uniformly dispersed within the elastomeric polymer matrix. Drug is eluted from the matrix in the radial direction via passive diffusion mechanism. During the drug elution process from a matrix IVR device, the drug will undergo simple diffusion out of the device into the vaginal fluid. As the drug depletion zone increases, the surface area of the drug core exposed to the fluid decreases, resulting in a declining drug release profile. The burst release effect is commonly observed in matrix-based IVRs.

Furthermore, the hydrophilic nature and high swelling properties of the PUA could be another reason contributing to the burst effect. Because it takes less time to hydrate the polymeric matrix compared with hydrophobic PUs, the polymeric matrix can swell, allowing a sudden increase in drug diffusion. PUs with higher water swellability demonstrated higher drug release rates. We believe less water was able to penetrate the PUA, allowing for a slower hydration of the drug core and resulting in reduced drug release. Although further investigation is necessary to understand the mechanism of this action, the observed delayed swelling of PUA in the coated IVR segments could be attributed to the decelerated water penetration into the PUA matrix as a result of the presence of hydrophilic PVP and PVA coating. Another strategy for overcoming the burst release would be to alter the design of IVR from matrix to reservoir-based. Reservoir-type IVRs have been investigated for the controlled release of various compounds in preclinical microbicide development. Studies were performed using res-IVR segments, rather than a full-size res-IVR to save on the cost of drugs and polymers. Theoretically, the use of IVR segments should not demonstrate any significant difference in release rates, polymeric swelling, or drug diffusion mechanism. PUs with varying water swellability were investigated for their effects on HCQ release. Reservoir-based IVRs have been shown to demonstrate a first-day burst effect, followed by a constant release profile. Furthermore, it was the first time, to our knowledge, to show that preformulating HCQ into a semisolid mixed with the rate-controlling agent, a high-viscosity HPMC, burst release could be eliminated Figure 2F and G. In addition to providing sustained drug release, an ideal IVR formulation should demonstrate a high degree of stability during storage and excellent biocompatibility. These results are consistent with the forced degradation studies performed by Saini and Bansal, whereby it was demonstrated that HCQ was only unstable under photolytic alkaline conditions. Furthermore, the PU used for IVR development should also exhibit good stability without any compromise to the mechanical properties of the IVR while being exposed to an acidic humidified environment. Previous studies have shown that IVRs fabricated from PUD did not demonstrate any changes in mechanical property elastic modulus or drug release profile in vitro or in vivo after being exposed to acidic conditions during a 90 days study period. Previously failed microbicide trials using cellulose sulfate and nonoxynol-9 were a result of the disruption of tight junctions and the induction of inflammation in the FGT, characterized by elevated IL-1 and IL-8 expression. In the current study, there was no significant induction of pro-inflammatory cytokines or reduction in cell viability, further supporting the fact that our IVR delivery system is noncytotoxic Figure 5A and B. Using the vaginal and ectocervical epithelial cells, drug-free IVR segments had no significant effect on the viability of epithelial cells even up to 30 days of incubation.

4.2.5.2.3 INTRA-VAGINAL RINGS pdf

Designing the user interface 6th edition and 5th edition Ships routeing supplement, 1975 Electrolyte imbalances and drugs Noodle doodle box adapted and translated by Anita and Alex Page F. Bloch: Notes on the Radiation Field of the Electron Essentials Of Academic Success Plus Guide To Apa One Lucky Bastard Fundamentals of fluoroscopy The Morphology of the Tigre Noun (London Oriental Series) Southern writers and the New South movement, 1865-1913 Self-Consistent Field Introduction to veterinary bacteriology The book of hours Numerical studies of frontal motion in the atmosphere. The Essential Handbook of Social Anxiety for Clinicians Something About the Author v. 78 Psychopathology of serial murder Vital records of Wrentham, Massachusetts, to the year 1850 . Pathways to the present Wayward wizard by Mary Kay McComas. 1. From Cooper to Hawthorne-excessive America 25. Extremity trauma Dan Garza and Gregory W. Hendey Industrial relations in Australia. Solid waste disposal: Policies for the Western Area Of Christs speaking inwardly to the Faithful Soul i The Joint Stock Book Information processing in motor skills The blood of Spain. Child abuse, acrying shame Hero of hacksaw ridge book All about Sniffing Aquarium fishes; their beauty, history, and care. Pharmaceutical regulatory affairs an introduction for life scientists Rules and regulations of the Advocates Association of Montreal Spring Grove State Hospital (Images of America (Arcadia Publishing (Images of America (Arcadia Publishing Camp fear (Shivers) Vs apte sanskrit english dictionary Food lion printable job application First uprising of the Emigrants Capt. Fremonts plan / Communication skills for cosmetologists