Summary ~~of the invention~~

After having performed extensive research, the inventors have found that specific formulations comprising a lyophilized composition comprising cidofovir, hydroxyethylcellulose (HEC) or hydroxypropylmethylcellulose (HPMC) and optionally a plasticizer present a valuable and advantageous alternative for the existing cidofovir formulations.

Therefore, in a first~~an~~ aspect, the present disclosure~~invention~~ relates to a sheet-shaped lyophilized composition comprising:

(a) cidofovir in an amount between 0.1 and 5.0 mg/cm^2;

(b) hydroxyethylcellulose (HEC) or hydroxypropylmethylcellulose (HPMC) in an amount between 1.0 and 17.0 mg/cm^2; and optionally

(c) a plasticizer in an amount between 0 and 5.0 mg/cm^2,

In a preferred embodiment, the lyophilized composition according to the present disclosure~~invention~~ comprises:

(a) cidofovir in an amount between 0.1 and 5 mg/cm^2, preferably between 2.0 and 5.0 mg/cm^2;

(b) HEC in an amount between 1.0 and 17.0 mg/cm^2, preferably between 7.0 and 10.5 mg/cm^2; and

(c) a plasticizer in an amount between 0.5 and 4.0 mg/cm^2.

Preferably, the HEC is selected from the group consisting of: HEC H4000, HEC 250M, HEC 250HX and HEC 250HHX, most preferably HEC 250M or HEC 250 HX.

In other preferred embodiments, the lyophilized composition according to the present disclosure~~invention~~ comprises:

(a) cidofovir in an amount between 0.1 and 5 mg/cm^2;

(b) HPMC in an amount between 1.0 and 17.0 mg/cm^2; and

(c) a plasticizer in an amount between 0.0 and 5.0 mg/cm^2.

Preferably, the HPMC is selected from the group consisting of HPMC E5, HPMC E15, HPMC 4000 and HPMC K15, most preferably HPMC E5, or HPMC E15.

The inventors have surprisingly found that such formulations form, after lyophilisation, a dry, solid, easy to manipulate and malleable porous matrix which presents itself as a sponge-like structure.

In contrast to the previously known creams or gels, the composition according to the ~~invention~~present disclosure displays excellent cidofovir stability. Hence, and advantageously, the compositions according to the ~~invention~~present disclosure can be stored at ambient (room) temperature, in contrast to gels and creams, which need to be stored refrigerated.

Moreover, in contrast to the preparation of films a heating step is absent during the preparation of the compositions according to the present ~~invention~~disclosure, thereby eliminating the risk of heat-mediated cidofovir degradation.

The addition of a small amount of water to the lyophilized composition according to the present ~~invention~~disclosure allows for the rapid transformation of the sponge-like structure into a mucoadhesive gel without the need for agitation. It has been found that the speed of rehydration, as well as the quantity of water needed for rehydration can easily be modulated by changing the type and the concentration of the polymer. In particular, it has been found that the speed of rehydration decreases with increasing concentration of the polymer. Depending of whether a slow rehydration is needed (e.g. for slow release applications) a higher concentration of the polymer can be used in the compositions according to the ~~invention~~present disclosure. The inventors have also found that HPMC-based sponges require a lower amount of water for rehydration than HEC-based sponges, which might influence the mode of administration. HPMC-based sponges may be administered directly, i.e. without being rehydrated before application. Rehydration which may take place *in situ*, in the uterus, with the aid of a minimal amount of vaginal fluids. This is especially true for HPMC E5, HPMC E15, HPMC 4000 and HPMC K15, most particularly for HPMC E5, and HPMC E15.

The HEC-based sponges on the other hand may be rehydrated prior to administration, resulting in a gel-like composition, which can subsequently be applied into the vagina or cervix of the subject. Rehydration of the HEC-based compositions of the ~~invention~~present disclosure can be done with a larger quantity of water than for the HPMC-based compositions.

It has further been found that the viscosity of the gel which is obtained after rehydration of the compositions according to the ~~invention~~present disclosure is determined by the type and the concentration of the polymer (not by the type or the concentration of the plasticizer). This allows for easy modulation of the viscosity depending on the needs by changing the type and concentration of the polymer. In particular, the inventors have found that using the same conditions and amounts of components, the HEC-based sponges are more viscous after rehydration than HPMC-based sponges and present themselves as

gels. This is especially true for HEC H4000, HEC 250M, HEC 250HX and HEC 250HHX, most particularly for HEC 250M and HEC 250 HX.

The differences in viscosity are important in determining the way of applying the composition of the ~~invention~~present disclosure to the subject. The advantage of the HPMC-based compositions, being less viscous, is that less water is needed for the *in situ* formation of a gel-like structure. They can therefore easily be applied internally to the subject without the need for addition of water to invoke rehydration. Said rehydration will take place in situ in the body cavity of the subject, using bodily fluids. The HEC-based compositions are more viscous and have the advantage to form a gel, which can be easier applied topically to e.g. the anogenital region.

The ~~invention~~present disclosure therefore also provides a gel-like composition obtained after rehydration of the lyophilized compositions according to the ~~invention~~present disclosure, especially of the HEC-based lyophilized compositions according to the ~~invention~~present disclosure.

In an embodiment, the plasticizer in the lyophilized composition according to the ~~invention~~present disclosure, if present, is selected from the group consisting of polyethylene glycol 400 or 4000 (PEG 400 or 4000) and propylene glycol (PG). In a preferred embodiment, the plasticizer in the composition according to the ~~invention~~present disclosure, if present, is PEG, more preferably PEG 400.

In another embodiment, the lyophilized composition according to the ~~invention~~present disclosure further comprises water in an amount between 1 and 10 weight%, preferably between 1 and 8 weight%.

In an embodiment, the lyophilized composition according to the ~~invention~~present disclosure further comprises NaOH. NaOH is generally added to the composition before lyophilization in order to promote the solubilization of cidofovir. In a further embodiment, the compositions according to the ~~invention~~present disclosure have a pH between 6 and 8, preferably between 6.5 and 7.5 before lyophilization and after rehydratation of the matrix.

Preferably, the HPMC in the compositions according to the ~~invention~~present disclosure is selected from the group consisting of HPMC E5, HPMC E15, HPMC 4000 and HPMC K15; the HEC

in the compositions according to the ~~invention~~present disclosure is selected from the group consisting of: HEC H4000, HEC 250M, HEC 250HX and HEC 250HHX.

The inventors have shown that in contrast to lyophilized placebo compositions comprising various cellulose derivatives such as HPMC, NaCMC, or HEC, which all form malleable sponges, only HPMC- and HEC-based compositions are capable of forming malleable sponges after lyophilization when cidofovir is added.

Unexpectedly, other tested compositions, based on other polymers, such as NaCMC, Carbomer 974P or HPC in the presence of cidofovir do either not form malleable sponges, or present other unfavorable characteristics, such as being very rigid and/or brittle, being too sticky or not adherent at all, showing structural defects or show slow or difficult rehydration. The inventors have shown that the addition of cidofovir alters the structural and functional characteristics of the lyophilized sponges.Furthermore, the inventors have shown that the addition of cidofovir in the compositions according to the ~~invention~~present disclosure alters the pore structure of the sponge, in comparison with placebo sponges. In particular, it was found that cidofovir seems to weaken the pore structure, especially in case of the HPMC based compositions.

In one ~~aspect~~embodiment, the ~~invention~~present disclosure relates to the lyophilized composition as described herein for use in topical drug delivery especially for treating all pathologies linked to infections with human DNA-viruses such as Herpes, Pox, Papillomavirus, Adenoviruses, Smallpox viruses, preferably by HPV, CMV, BK-virus, Smallpox, HSV, or VZV, or accompanying pathologies such as those selected from the group comprising: virus induced lesions or warts of the vagina, cervix, anogenital region, mucosa, epithelium of the oral sphere, or skin, precancerous lesions and/or neoplasms or cancers caused by viral infection, more specifically to the cervix or the mucosal surface of the cervix. In particular, HPV infections and pathologies are envisaged. The term "pathologies linked to HPV or DNA-virus infections" encompasses, but is not limited to: HPV or DNA-virus induced lesions or warts of the cervix, uterus, anogenital region, or skin, precancerous lesions and/or neoplasms or cancers caused by HPV or DNA-virus infection, more specifically to the cervix or the mucosal surface of the cervix. In another ~~aspect~~embodiment, the ~~invention~~present disclosure relates to the lyophilized composition as described herein for use in treating human papillomavirus (HPV) infection. In yet another ~~aspect~~embodiment, the ~~invention~~present disclosure relates to the lyophilized composition as described herein for use in treating cervical cancer. The

present disclosure~~invention~~ also provides for methods of treating HPV or DNA-virus infection, using the lyophilized compositions according to the present disclosure~~invention~~. Administration of said compositions can be done directly, by inserting the lyophilized composition into the cervix, e.g. on a vaginal inserter or fixed to a vaginal or uteral cap. Alternatively, the composition according to the present disclosure~~invention~~ can be rehydrated prior to its administration and subsequently in the cervix applied as a gel-like composition. The treatment can be repeated a number of times in order to prevent, reduce or eliminate the pathologies linked to HPV or DNA-virus infections as defined herein, more in particular HPV or DNA-virus infections, or HPV or DNA-virus induced lesions, precancerous lesions, or cancers, especially cervical cancer.

In a second aspect of the present disclosure, there is provided the lyophilized composition as defined herein for use in medicine, preferably for use in medicine, preferably for use in treating infection with human DNA-virus such as Herpes virus, Pox virus, Papilloma virus, Adenovirus, Smallpox virus, or Human papillomavirus (HPV), or accompanying pathologies such as those selected from the group comprising: virus induced lesions or warts of the vagina, cervix, anogenital region, mucosa, epithelium of the oral sphere, or skin, precancerous lesions and/or neoplasms or cancers caused by HPV infection, more specifically to the cervix or the mucosal surface of the cervix.

In a third aspect of the present disclosure, there is provided a gel-like composition obtained after rehydration of the lyophilized composition as defined herein for use in medicine, preferably for use in treating infections with human DNA-viruses such as Herpes, Pox, Papillomavirus, Adenoviruses, Smallpox viruses, or Human papillomavirus (HPV) infection or accompanying pathologies such as those selected from the group comprising: virus induced lesions or warts of the vagina, cervix, anogenital region, mucosa, epithelium of the oral sphere, or skin, precancerous lesions and/or neoplasms or cancers caused by viral infection, more specifically to the cervix or the mucosal surface of the cervix.

In a fourth aspect of the present disclosure, there is provided the lyophilized composition as defined herein for use in treating human DNA virus infection or accompanying pathologies, wherein the composition is rehydrated before administration.

In a fifth aspect of the present disclosure, there is provided the lyophilized composition as defined herein, for use in treating human DNA virus infection or accompanying pathologies , wherein the composition is not rehydrated before administration.

In a sixth aspect of the present disclosure, there is provided the lyophilized composition as defined herein, or the gel-like composition as defined herein, for use in topical drug delivery to the vagina, cervix, anogenital region, mucosa, epithelium of the oral sphere, or skin.

In a seventh aspect of the present disclosure, there is provided a method for producing the lyophilized composition as defined herein, comprising the steps of (a) dispersing HEC or HPMC in water to obtain a homogenized composition; (b) optionally dispersing plasticizer in the composition obtained in step (a) to obtain a homogenized composition; (c) dispersing cidofovir and optionally adding NaOH 2M solution in the composition obtained in step (b) or alternatively the composition obtained in step (a) if no plasticizer is added to obtain a homogenized composition; (d) lyophilizing the composition obtained in step (c), wherein plasticizer needs to be added in step (b) when HEC is used in step (a).

In a further embodiment~~aspect~~, the present disclosure~~invention~~ relates to methods for producing the lyophilized composition as described herein, comprising the steps of:

(a) dispersing a polymer in water to obtain a homogenized composition;

(b) optionally dispersing a plasticizer in the composition obtained in step (a) to obtain a homogenized composition;

(c) dispersing cidofovir and optionally adding NaOH 2M solution in the composition obtained in step (b) or alternatively the composition obtained in step (a) if no plasticizer is added to obtain a homogenized composition;

(d) lyophilizing the composition obtained in step (c).

In a preferred embodiment of the method of the present disclosure~~invention~~,

(a) cidofovir is added in an amount between 0.1 and 5.0 mg/cm^2;

(b) hydroxyethylcellulose (HEC) or hydroxypropylmethylcellulose (HPMC) is added in an amount between 1.0 and 17.0 mg/cm^2; and optionally

(c) a plasticizer is added in an amount between 0 and 5.0 mg/cm^2,

wherein between 0.5 and 4.0 mg/cm^2 of said plasticizer is present when HEC is used.

In a particularly preferred embodiment of the method according to the present disclosure~~invention~~,

(a) cidofovir is added in an amount between 0.1 and 5 mg/cm², preferably between 2.0 and 5.0 mg/cm²;

(b) HEC is added in an amount between 1.0 and 17.0 mg/cm², preferably between 7.0 and 10.5 mg/cm²; and

(c) a plasticizer is added in an amount between 0.5 and 4.0 mg/cm².

Preferably, the HEC in the compositions according to the present disclosure~~invention~~ is selected from the group consisting of: HEC H4000, HEC 250M, HEC 250HX and HEC 250HHX, most preferably HEC 250M and 250HX.

In a further embodiment, the homogenized composition obtained in step (c) comprises NaOH in an amount between 0.10 to 0.30 weight%, preferably about 0.20 or 0.21 %, before lyophilisation.

In other preferred embodiments, the lyophilized composition according to the present disclosure~~invention~~ comprises:

(a) cidofovir is added in an amount between 0.1 and 5 mg/cm^2;

(b) HPMC is added in an amount between 1.0 and 17.0 mg/cm^2; and

(c) a plasticizer is added in an amount between 0.0 and 5.0 mg/cm^2.

Preferably, said HPMC is selected from the group consisting of HPMC E5, HPMC E15, HPMC 4000 and HPMC K15, most preferably HPMC E5 and E15.

In a further embodiment, the homogenized composition obtained in step (c) comprises NaOH in an amount between 0.10 to 0.30 weight%, preferably about 0.20 or 0.21 %, before lyophilisation.

Preferably, said plasticizer is selected from the group consisting of polyethylene glycol 400 or 4000 (PEG 400 or 4000) and propylene glycol (PG). In a preferred embodiment, the plasticizer in the composition according to the present disclosure~~invention~~, if present, is PEG, more preferably PEG 400.

In a further embodiment, the homogenized composition obtained in step (c) comprises between 0.35 and 3.5 weight% of HEC or HPMC. In particular embodiments, the homogenized composition obtained in step (c) comprises between 1 and 2.5 weight% HEC and between 0.2 and 1 weight% plasticizer. In other particular embodiments the homogenized composition obtained in step (c) comprises between 0.35 and 3.5 weight% HPMC and between 0 and 1 weight% plasticizer. In yet another embodiment, the homogenized composition of step (c) comprises between 0.10 and 1.5 weight% cidofovir. In an embodiment, the homogenized composition obtained in step (c) has a pH between 6 and 8, preferably between 6.5 and 7.5.

In a further embodiment, the homogenized composition obtained in step (c) comprises NaOH in an amount between 0.10 to 0.30 weight%, preferably about 0.20 or 0.21 %, before lyophilisation.

In an embodiment, the lyophilization for producing the compositions according to the present disclosure~~invention~~ can be performed in a crystallizer, or in a mould, or in any other known device or reactor that can be used to make a sheet-like lyophilized composition of the present disclosure~~invention~~.

In an eighth aspect of the present disclosure, there is provided a method of preparing a gel-like composition as defined herein, comprising the step of rehydrating the lyophilized composition as defined herein.

In a ninth aspect of the present disclosure, there is provided a sheet-shaped solid porous malleable matrix obtained by lyophilization of an aqueous composition, said aqueous composition comprising between 1 and 17 mg/cm^2 HEC or HPMC, between 0 and 5 mg/cm^2 plasticizer, and between 0.1 and 5 mg/cm^2 cidofovir, wherein between 1.5 and 3 mg/cm^2 of said plasticizer is present when HEC is used.

Another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a sheet-shaped solid porous malleable matrix obtained by lyophilization of an aqueous composition, said aqueous composition comprising between 0.35 and 3.5 weight% HEC or HPMC, between 0 and 1 weight% plasticizer, and between 0.10 and 1.5 weight% cidofovir.

In particular embodiments this matrix comprises between 1 and 2.50 weight% HEC, between 0.2 and 1 weight% plasticizer, and between 0.10 and 1.5 weight% cidofovir.

In other particular embodiments this matrix comprises between 0.35 and 3.50 weight% HPMC, between 0 and 1 weight% plasticizer, and between 0.10 and 1.5 weight% cidofovir.

In an embodiment, this matrix comprises between 1 and 17 mg/cm² HEC or HPMC, between 0 and 5 mg/cm² plasticizer, and between 0.1 and 5 mg/cm² cidofovir.

In particular embodiments, this matrix comprises between 7 and 10.5 mg/cm² HEC, between 1.5 and 5 mg/cm² plasticizer, and between 0.1 and 5 mg/cm² cidofovir, preferably with HEC 250M or HEC 250HX as the polymer.

In other particular embodiments, this matrix comprises between 1 and 17 mg/cm² HPMC, between 0 and 5 mg/cm² plasticizer, and between 0.1 and 5 mg/cm² cidofovir, preferably with HPMC E5 or E15 as the polymer.

In a tenth aspect of the present disclosure, there is provided a drug delivery applicator, comprising the sheet-shaped lyophilized composition as defined herein or the matrix as defined herein.

A further embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a drug delivery applicator, comprising the sheet-shaped lyophilized composition or the malleable matrix according to the present disclosure~~invention~~ as described herein disposed on a drug-impermeable barrier.