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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 September 2003 (25.09.2003)

PCT

(10) International Publication Number
WO 03/077952 A1

(51) International Patent Classification[7]: A61K 47/36, A61P 27/00

(21) International Application Number: PCT/EP03/02760

(22) International Filing Date: 17 March 2003 (17.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

02006085.1	18 March 2002 (18.03.2002)	EP
0229019.5	12 December 2002 (12.12.2002)	GB
0230033.3	23 December 2002 (23.12.2002)	GB

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Wien (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KIS, György Lajos** [CH/CH]; Keberlistrasse 21, CH-8273 Triboltingen (CH). **SCHOCH, Christian** [CH/CH]; Lindenweg 15, CH-4132 Muttenz (CH). **LOHMANN, Dieter** [CH/CH]; Mittelweg 56, CH-4142 Münchenstein (CH).

(74) Agent: **GROS, Florent**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/077952 A1

(54) Title: TOPICAL COMPOSITION COMPRISING A CYCLOFRUCTAN, A CARRIER AND A DRUG

(57) Abstract: The present invention relates in particular to a drug delivery system comprising a cyclofructan, a drug and a polymeric carrier.

TOPICAL COMPOSITION COMPRISING A CYCLOFRUCTAN, A CARRIER AND A DRUG

Compositions Comprising Cyclofructan

The present invention relates especially to a drug delivery system comprising a cyclofructan, a drug and at least one carrier.

A problem associated with topical administration of a drug is the drug permeability through tissue and the topical tolerability. Typically, for ocular and mucus tissue, permeability and tolerability play a significant role both with respect to the active and inactive ingredients. This problem is now surprisingly solved by providing a drug delivery system comprising a cyclofructan (CFR), a drug and at least one carrier selected from a bioerodible polymer and a bioadhesive polymer. CFR in a composition as described hereinafter provides an enhanced drug permeability through tissue, in particular in ocular and mucus tissue.

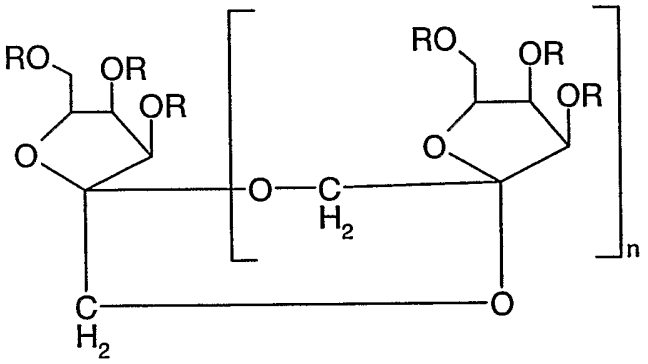
Since a drug is often washed off from ocular and mucus tissue, this additional problem is addressed in the present invention. This is now solved by providing a drug delivery system which enables sustained and prolonged drug delivery, which drug delivery system contains a polymeric carrier selected from a bioerodible polymer and/or a bioadhesive polymer.

Accordingly, the present invention pertains to a composition comprising a cyclofructan (CFR), a drug and at least one carrier selected from a bioerodible polymer and a bioadhesive polymer. As used herein, such a composition represents a drug delivery system.

Cyclofructan (CFR) is known in conjunction with medicinal products. JP 5310805 (Mitsubishi) describes the use of CFR in a pharmaceutical preparation providing a clathrate function. Similar, JP 6298807 (Mitsubishi) describes the use of CFR to increase the solubility of a pharmaceutically effective drug.

In a first aspect the present invention relates to the use of a CFR to enhance drug permeation through tissue, and to the use of CFR to enhance drug penetration into tissue, wherein said tissue is preferably selected from ocular tissue and mucus tissue, and wherein said drug is typically administered topically to said tissue. Said use is preferably within the context of the manufacture of a drug delivery system which contains said CFR, further being tailor-made for a disease being preferably treatable by topical treatment.

Cyclofructan contains fructose units being connected by beta-(1 → 2) linkages and may be depicted e.g. in formula I,



(I)

wherein n is from 5 – 11,
R is independently from each other H, alkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkylen-carbonyl, alkylcarbonyl, alkylcarbamoyl, R'_3Si, or R is a saccharide minus the hydrogen atom from a hydroxy group,
wherein R' denotes independently of each other alkyl and phenyl, preferably methyl and phenyl, more preferably methyl.

In an above CFR, at least one R shall denote H.

Cyclofructan (CFR) is typically consisting of 6 to 12 fructose units, preferably 6 – 10 units, also preferably 6 - 8 units, mixtures of 6, 7 and 8 units, most preferably 6 and 7 units. As used herein, the number of fructose units in a CFR are definded by the number directly following the three letters CFR, e.g. 6 fructose units in a cyclofructan shall be depicted as CFR6, 7 units as CFR7, and so on.

The degree of substitution in a CFR of formula I is typically described as a percentage of substitution and refers to the percentage of being different from H. An R being different from H is typically randomly distributed. The degree of substitution is generally from 5 – 99.5%, preferably 5 – 90%, more preferably from 10 – 50%, also preferably from 12 – 45%, and in particular from 15 – 30%. Full substitution with R being different from H (100%) may be very difficult to obtain.

In a preferred aspect R is methyl and the degree of substitution is from 5 – 99.5%, and shall also preferably refer to entirely methylated CFR.

In a highly preferred aspect all R denote H (degree of substitution is 0%).

Alkyl has up to 20 carbon atoms and may be linear or branched. Suitable examples include dodecyl, octyl, hexyl, pentyl, butyl, propyl, ethyl, methyl, 2-propyl, 2-butyl and 3-pentyl. In a preferred definition, alkyl has up to 12 C-atoms and more preferably up to 6 C-atoms. Preferred examples are butyl, propyl, ethyl, and methyl, more preferably ethyl, and methyl, most preferably methyl.

Alkoxy has up to 20 carbon atoms and may be linear or branched. Alkoxy has preferably up to 12 carbon atoms, in particular up to 6 carbon atoms and is, for example, methoxy, ethoxy, propoxy, butoxy, tert-butoxy or hexyloxy.
Preferred examples are methoxy, ethoxy, propoxy, butoxy, more preferably methoxy, ethoxy, in particular methoxy.

Aminoalkyl maybe linear or branched and has up to 20 carbon atoms, preferably up to 12 carbon atoms, and in particular 2 to 6 carbon atoms. Examples for aminoalkyl are aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, aminooctyl or aminodecyl.
Preferred examples are aminoethyl, aminopropyl, aminobutyl, aminopentyl, and aminohexyl. An amino group may additionally be substituted by one or two alkyl group, e.g. for aminoethyl, an addressed substitution may read as N-methylaminoethyl, or N,N-dimethylaminoethyl.

Hydroxyalkyl maybe linear or branched and has up to 20 carbon atoms, preferably up to 12 carbon atoms, and in particular 2 to 6 carbon atoms. Examples for hydroxyalkyl are hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxyhexyl, hydroxyoctyl or hydroxydecyl.
Preferred examples are hydroxyethyl, hydroxypropyl, hydroxybutyl, and hydroxyhexyl.

Alkylene has up to 20 carbon atoms and may be linear or branched. Suitable examples include decylene, octylene, hexylene, pentylene, butylene, propylene, ethylene, methylene,

2-propylene, 2-butylene and 3-pentylene. In a preferred definition, alkylene has up to 12 C-atoms and more preferably up to 6 C-atoms.

Carboxyalkyl may be linear or branched and has up to 20 carbon atoms, preferably up to 12 carbon atoms, and in particular up to 6 carbon atoms. Preferred examples are carboxymethyl, carboxyethyl, carboxypropyl, in particular carboxymethyl.

Alkoxyalkylen-carbonyl may be linear or branched and has up to 20 carbon atoms, preferably up to 12 carbon atoms, and in particular up to 6 carbon atoms. Preferred examples are methoxymethylen carbonyl, methoxyethlyen carbonyl, methoxypropylen carbonyl, ethoxymethlyen carbonyl, ethoxyethylen carbonyl, in particular methoxymethylen carbonyl and methoxyethlyen carbonyl.

Alkylcarbonyl may be linear or branched and has up to 20 carbon atoms, preferably up to 12 carbon atoms, and in particular up to 6 carbon atoms. Preferred examples are methlycarbonyl, ethylcarbonyl, and propylcarbonyl, in particular ethylcarbonyl and methylcarbonyl.

Alkylcarbamoyl may be linear or branched and has up to 20 carbon atoms, preferably up to 12 carbon atoms, and in particular up to 6 carbon atoms. Preferred examples are methylcarbamoyl, ethylcarbamoyl, and propylcarbamoyl, more preferably ethylcarbamoyl.

As used herein, a saccharide shall mean a monosaccharide , disaccharid or trisaccharide.

A monosacharide is understood to be an aldopentose, aldohexose, aldotetrose, ketopentose or ketohexose.

Examples of an aldopentose are D-ribose, D-arabinose, D-xylose and D-lyose; examples of an aldohexose are D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose, D-talose, L-fucose and L-rhamnose; examples of a ketopentose are D-ribulose and D-xylulose; examples of a tetrose are D-erythrose and threose; and examples of a ketohexose are D-psicose, D-fructose, D-sorbose and D-tagatose.

A preferred monosaccharide residue is for example fructosyl, glucosyl, mannosyl or mixtures thereof.

Examples of a disaccharide are trehalose, maltose, isomaltose, cellobiose, gentiobiose, saccharose, lactose, chitobiose, N,N-diacetylchitobiose, palatinose and sucrose. Maltose is a preferred disaccharide.

Raffinose, panose and maltotriose may be mentioned as examples of a trisaccharide. Panosyl is a preferred trisaccharide residue.

As used herein, preferred substituents R in a compound of formula (I) are H, alkyl and hydroxylakyl substituents, more preferred is H, alkyl with up to 6 carbon atoms and hydroxyalkyl with up to 6 carbon atoms, even more preferred is H, methyl and hydroxypropyl, highly preferred is H and methyl, even more preferred is H.
Another preferred R substituent R is selected from H and a monosaccharide, more particular H, fructosyl, and glucosyl.

A preferred cyclofructan ring size is CFR 6, CFR7, CFR8, and mixtures of CFR6,7,8. In an example of a mixed cyclofructan, a CFR 6,7,8, contains 75% CFR6, 20% CFR7 and 5% CFR8 of total weight percent cyclofructan. An above preferred CFR is further preferably CFR6, CFR7, CFR8, and mixtures of CFR6,7,8, wherein R denotes H (degree of substitution is 0%).

As used herein, a drug is in particular selected from the group consisting of:

- Anti-angiogenic drugs, such as VEGF-inhibitors, PKC-inhibitors and the like, e.g. N-benzoylstaurosporine, 1-(3-Chloroanilino)-4-(4-pyridylmethyl)phthalazine,
- Anti-inflammatory drugs, such as steroids, e.g. dexamethasone, fluorometholone , hydrocortisone, prednisolone; or so-called non-steroidal anti-inflammatory drugs (NSAID) such as COX-inhibitors, e.g. diclofenac, valdecoxib, lumiracoxib, ketorolac, or indomethacin;
- Anti-allergic drugs, selected e.g. from FK506, 33-epi-chloro-33-desoxy-ascomycin, cromolyn, emadine, ketotifen, levocabastine, lodoxamide, norketotifen, olopatadine, and rizabene;
- Drugs to treat glaucoma (in particular intraocular pressure treatment), selected e.g. from latanoprost, 15-keto-latanoprost, unoprostone isopropyl, betaxolol, clonidine, levobunolol and timolol;

- Anti-infective drugs, e.g. selected from ciprofloxacin, chloramphenicol, chlortetracycline, gentamycin, lomefloxacin, neomycin, ofloxacin, polymyxin B and tobramycin;
- Antifungal drugs, e.g. selected from amphotericin B, fluconazole and natamycin;
- Anti-viral drugs such as acyclovir, fomivirsen, ganciclovir, and trifluridine;
- Anesthetic drugs, e.g. selected from cocaine hydrochloride, lidocaine, oxybuprocaine and tetracaine hydrochloride;
- Myopia preventing/inhibiting drugs such as pirenzepine, atropine and the like;
- Miotics, e.g. selected from carbachol, pilocarpine and physostigmine;
- Carbonic anhydrase inhibitors, e.g. selected from acetazolamide and dorzolamide;
- Alpha blocking agents, e.g. selected from apraclonidine and brimonidine; and
- Antioxidants and/or vitamins, e.g. selected from ascorbic acid, α-tocopherol, α-tocopherol acetate, retinol, retinol acetate, and retinol palmitate.

Preferred drugs are selected from:
Anti-angiogenic drugs, anti-inflammatory drugs, anti-allergic drugs, drugs to treat glaucoma, and myopia preventing/inhibiting drugs.

Further preferred are anti-angiogenic drugs, anti-inflammatory drugs, anti-allergic drugs, drugs to treat glaucoma, anti-infective drugs, anti-fungal drugs, anti-viral drugs, anesthetic drugs, myopia preventing/inhibiting drugs, miotics, carbonic anhydrase inhibitors, alpha blocking agents antioxidants and/or vitamins.

In another aspect, and depending on the polymeric carrier, the drug delivery system of the present invention may at room temperature (approximately 22-25°C) be in a solid state, and is in particular selected from a tablet, a film, a rod, a bar, a capsule, a corneal shield. a corneal ring, an implant, an insert, an intra-ocular lens, a therapeutic contact lens, a mini tablet , a mini-disc, and a pellet. Preferably said drug delivery system is selected from a rod, a bar, a capsule, a corneal shield. a corneal ring, an implant, an insert, an intra-ocular lens, a therapeutic contact lens, and a mini-disc, and even more preferred from a corneal shield. a corneal ring, an implant, an insert, an intra-ocular lens, a therapeutic contact lens, and a mini-disc.

As used herein, polymeric carriers suitable for drug delivery systems are for example selected from

- a matrix of a bioerodible polymer being selected from the group consisting of polyhydroxy-acids, such as polylactic acid and polyglycolic acid; polyesters, polyorthoesters, polyanhydrides, polycyanoacrylates, natural gums, such as acacia gum and arabic gum; celluloses, such as carboxymethylcellulose; methacrylate (co)polymers such as Eudragits, e.g. Eudragit RL PO, Eudragit RS PO; and/or
- a bioadhesive polymer being selected from the group consisting of maltodextrin, celluloses, such as carboxymethyl cellulose, hydroxyethyl cellulose; chitosans; hyaluronic acid; polyacrylates e.g. carbopol; polycarbophils e.g. Noveon AA-1; polyvinylalcohol such as Mowiol 26-88; polyvinylpyrrolidone such as povidone K30.

The amount of a polymeric carrier used in a composition or a drug delivery system of the present invention is in the range of from 0.01 to approximately 99% by weight, preferably in the range of from 1 - 95% by weight, more preferably in the range of from 10 - 90% by weight, even more preferably in the range of from 15 - 85% by weight, and in the range of from 20 - 80% by weight.

The use of a drug in conjunction with a polymeric carrier and a cyclofructan provides typically a synergistic advantage of sustained drug delivery with improved drug permeability.

Accordingly, a further aspect is a drug delivery system which comprises a polymeric carrier being selected from:
A matrix of a bioerodible polymer being selected from the group consisting of polyhydroxy-acids, such as polylactic acid and polyglycolic acid; polyesters, polyorthoesters, polyanhydrides, polycyanoacrylates, natural gums, such as acacia gum and arabic gum; celluloses, such as carboxymethylcellulose; methacrylate (co)polymers such as Eudragits, e.g. Eudragit RL PO, Eudragit RS PO; and/or
A bioadhesive polymer being selected from the group consisting of maltodextrin, celluloses, such as carboxymethyl cellulose, hydroxyethyl cellulose; a cyclodextrin, chitosans; hyaluronic acid; polyacrylates e.g. carbopol; polycarbophils e.g. Noveon AA-1; polyvinylalcohol such as Mowiol 26-88; polyvinylpyrrolidone such as povidone K30:
a cyclofructan, and
a pharmaceutically effective drug.

Additional carriers might be used in the manufacture of a drug delivery system, for example by adapting said system to specific needs, e.g. ophthalmically acceptable issues, and are for example water, mixtures of water and water-miscible solvents, such as C_1- to C_7-alkanols, vegetable oils or mineral oils comprising from 0.5 to 5% by weight hydroxyethylcellulose, ethyl oleate, carboxymethyl-cellulose, polyvinyl-pyrrolidone and other non-toxic water-soluble polymers for ophthalmic uses, such as, for example, acrylates or methacrylates, such as salts of polyacrylic acid or ethyl acrylate, polyacrylamides, natural products, such as gelatin, alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar and acacia, starch derivatives, such as starch acetate and hydroxypropyl starch, and also other synthetic products, such as polyvinyl methyl ether, polyethylene oxide or mixtures of those polymers.

The concentration of an above carrier is, for example, from 1 to 100000 times the concentration of the active ingredient.

The drug delivery system of the present invention may further comprise a tonicity enhancing agent.

Tonicity enhancing agents are, for example, ionic compounds, such as alkali metal or alkaline earth metal halides, such as, for example, $CaCl_2$, KBr, KCl, LiCl, NaI, NaBr or NaCl, or boric acid. Non-ionic tonicity enhancing agents are, for example, urea, glycerol, sorbitol, mannitol, propylene glycol, or dextrose. For example, sufficient tonicity enhancing agent is added to impart an osmolality of approximately from 50 to 1000 mOsmol.

For the adjustment of the pH, preferably to a physiological pH, buffers may especially be useful. Examples of buffer substances are acetate, ascorbate, borate, hydrogen carbonate /carbonate, citrate, gluconate, lactate, phosphate, propionate and TRIS (tromethamine) buffers. Tromethamine and borate buffer are preferred buffers. The amount of buffer substance added is, typically, that necessary to ensure and maintain a physiologically tolerable pH range. The pH range is generally in the range of from 4 to 9, preferably from 4.5 to 8.5 and more preferably from 5.0 to 8.2.

The drug delivery system of the present invention may further comprise a preservative, e.g on storage or to inhibit microbial growth.

A preservative may typically be selected from a quaternary ammonium compound such as benzalkonium chloride, benzoxonium chloride or the like. Benzalkonium chloride is better described as: N-benzyl-N-(C_8-C_{18}alkyl)-N,N-dimethylammonium chloride. Examples of preservatives different from quaternary ammonium salts are alkyl-mercury salts of thiosalicylic acid, such as, for example, thiomersal, phenylmercuric nitrate, phenylmercuric acetate or phenylmercuric borate, parabens, such as, for example, methylparaben or propylparaben, alcohols, such as, for example, chlorobutanol, benzyl alcohol or phenyl ethanol, guanidine derivatives, such as, for example, chlorohexidine or polyhexamethylene biguanide, sodium perborate, Germal®II or sorbic acid. Preferred preservatives are quaternary ammonium compounds, in particular benzalkonium chloride, alkyl-mercury salts and parabens. Where appropriate, a sufficient amount of preservative is added to ensure protection against secondary contaminations during use caused by bacteria and fungi.

A drug delivery system of the present invention may additionally require the presence of a solubilizer, in particular if the active or the inactive ingredients or the active and intended inactive ingredients tend to form a suspension or an emulsion.
A solubilizer suitable for compositions of the invention is for example selected from the group consisting of tyloxapol, fatty acid glycerol polyethylene glycol esters, fatty acid polyethylene glycol esters, polyethylene glycols, glycerol ethers, a cyclodextrin (for example α-, β- or γ-cyclodextrin, e.g. alkylated, hydroxyalkylated, carboxyalkylated or alkyloxycarbonyl-alkylated derivatives, or mono- or diglycosyl-α-, β- or γ- cyclodextrin, mono- or dimaltosyl-α-, β- or γ-cyclodextrin or panosyl-cyclodextrin), polysorbate 20, polysorbate 80 or mixtures of those compounds. A specific example of an especially preferred solubilizer is a reaction product of castor oil and ethylene oxide, for example the commercial products Cremophor EL®or Cremophor RH 40®. Reaction products of castor oil and ethylene oxide appear to be particularly good solubilizers that are tolerated extremely well by the eye. Another preferred solubilizer is selected from tyloxapol and from a cyclodextrin. The concentration used depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient. For example, the concentration of the solubilizer is typically from 0.1 to 5000 times the concentration of the active ingredient.

Further excipients may be comprised in a drug delivery system of the invention, which may in particular function as a combined stabilizer/solubilizer. Such a combined additional stabilizer/solubilizer is for example a cyclodextrin. A preferred cyclodextrin is in particular

selected from the group of α-cyclodextrin, β-cyclodextrin, methyl-β-cyclodextrin, methyl-γ-cyclodextrin, γ-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, dimethyl-β- cyclodextrin and dimethyl-γ-cyclodextrin. The amount is generally in the range of from approximately 0.01 to approximately 90% by weight, more preferably in the range of from 0.1 - 20% by weight.

A drug delivery system of the invention may comprise further non-toxic excipients, such as, for example, emulsifiers, wetting agents or fillers, such as, for example, the polyethylene glycols having an average molecular weight of 200, 300, 400 and 600, or higher polyethylene glycols, also called Carbowax being designated Carbowax 1000, 1500, 4000, 6000 and 10000. Other excipients that may be used if desired are listed below but they are not intended to limit in any way the scope of the possible excipients. They are especially complexing agents, such as disodium-EDTA or EDTA, antioxidants, such as ascorbic acid, acetylcysteine, cysteine, sodium hydrogen sulfite, butyl-hydroxyanisole, butyl-hydroxytoluene or alpha-tocopherol acetate; stabilizers, such thiourea, thiosorbitol, sodium dioctyl sulfosuccinate or monothioglycerol; or other excipients, such as, for example, lauric acid sorbitol ester, triethanol amine oleate or palmitic acid ester. Preferred exipients are complexing agents, such as disodium-EDTA. The amount and type of excipient added is in accordance with the particular requirements and is generally in the range of from approximately 0.0001 to approximately 90% by weight.

The amount of CFR present in a drug delivery system of the present invention generally depends on the drug being used and is typically in the range of 0.1 – 35%, preferably from 0.5 – 25%, more preferably from 5 – 10%, and 15 – 20%, also preferably from 0.1 – 5%, 0.5 – 5% and 1-5% by total weight of a corresponding pharmaceutical composition.

Also preferred are the amount and type CFR as described in the working examples.

The invention further relates to a method of improving drug permeability through mucus tissue and/or in the ocular tissue, which method comprises the steps of:
Conventionally admixing an effective amount of a CFR , an effective amount of a drug, and at least a polymeric carrier;

optionally admixing one or more further ingredients selected from the group of buffers, tonicity enhancing agents, preservatives, solubilizers, stabilizers/solubilizers, and complexing agents;
optionally forming the above admixed components in a mold;
and
administering said admixture comprising said CFR and said drug to said tissue in need of drug treatment.

Said tissue is preferably mucus tissue and/or in the ocular tissue, such as corneal epithelial cells, and conjunctival cells. Mucus tissue is for example without limitation nasal, in the mouth, lingual, in the ear, aural, conjunctival, anal, vaginal and the like.

The improvement of drug permeation, for example in the eye, typically provides the benefit of improved tolerability and/or improved efficacy, typically in a synergistic fashion, because CFR appears to improve the bio-availability of a corresponding drug. Therefore, typically less drug is needed for obtaining a comparable pharmacological efficacy as obtained by a composition not comprising a CFR. Also, typically the onset of action of a CFR formulated composition , e.g. upon topical ophthalmic administration, appears to be improved.

The invention also relates to the use of a cyclofructan in the manufacture of a solid state medicament for the treatment of a disease being treatable by topical treatment, said disease being preferably selected from an ocular disease. Said solid state medicament comprises a CFR, a polymeric carrier suitable for solid state medicaments and a pharmaceutically effective drug.

A still further aspect is a method of improving drug permeability in mucus tissue, which method comprises the topical administration of an effective amount of a drug in appropriate admixture with a CFR to the mucus tissue of a patient in need of such treatment.

A preferred embodiment is related to an ophthalmic composition comprising a CFR, an ophthalmically acceptable polymeric carrier and an ophthalmic drug, said polymeric carrier being for example selected from cellulose derivatives, hyaluronic acid, cyclodextrins, polyvinylalcohol, polyvinylpyrrolidone, neutral Carbopol, or mixtures thereof.

The invention also relates to the use of a CFR to enhance drug permeation through tissue, and to enhance drug penetration into tissue, wherein said tissue is preferably mucus tissue, in particular ocular tissue, and wherein said drug is administered topically to said tissue.

The use of a CFR in the context with enhanced drug permeation trough tissue upon topical administration is not conditional to a special polymeric carrier, as e.g. described above. Accordingly, as used herein a carrier represents any other carrier if compatible with topical administration.

Accordingly, the invention relates to the use of a CFR in the manufacture of a topical medicament for the treatment of a disease being treatable by topical treatment, said topical medicament comprises a CFR, a carrier, preferably a polymeric carrier, and an effective amount of drug.

More preferably it pertains to the use of a cyclofructan in the manufacture of a topical ophthalmic medicament for the treatment of a disease being treatable by topical treatment, wherein said medicament comprises a CFR, a carrier, preferably a polymeric carrier and an ophthalmic drug.

Example: Increase of corneal permeation

Corneal permeation system:
The system used was a modified Valia-Chien system consisting of two water-jacketed cells for temperature control. Each cell was filled with GBR buffer (see below), stirred by a magnet and continuously gassed with Oxycarbon (5 % CO_2 / 95 % O_2). During an experiment, the cells were separated by the cornea, one cell containing the test substance dissolved in GBR and acting as donor (tear side), the other one being the acceptor (aqueous humor side).

Corneas:
Pig eyes were obtained from the local abattoir. They were kept in Dulbecco's MEM (minimal essential medium) with Glutamax-I (Gibco) on ice and used within a few hours after receipt.

Buffers:

Buffers for *in vitro* corneal permeation studies were adapted from glutathione-bicarbonate-Ringer (GBR) solution. "GBR aqueous humor" was used in the acceptor cell and "GBR tears" on the donor side for equilibration. Their composition is listed in Table 1.

Assay of corneal permeation:
On receipt from the abattoir the eye was mounted on a dissection board, cornea facing up. After checking integrity of the cornea, the sclera was incised approximately 1-2 mm from the corneal rim with a scalpel and the anterior segment was excised. The iris and lens were carefully removed with forceps without damaging the corneal structures. The cornea was then mounted between the two cells of the permeation system with the help of a pinch clamp. Immediately, 3 ml of prewarmed and gassed GBR buffer were added to each cell, carefully removing any trapped air bubbles in the cells. The system was gassed and stirred for about 30 minutes at 35° C. After equilibration, the donor side was emptied and the same amount of prewarmed formulation of active substance was added at time t=0. An aliquot of 300 µl "GBR aqueous humor" was taken at time t=0 from the acceptor cell and the missing volume was replaced by the same volume of fresh buffer. Subsequently, this procedure was repeated in the acceptor cell at predefined time points and the aliquots were analysed for active by HPLC. Both compartments were kept under constant stirring with small magnets. The usual duration of an experiment was 180 minutes which was also the time of contact of the formulation with the cornea.

Table 1: Buffers used for *in vitro* corneal permeation experiments

Constituent	GBR aqueous humor Concentration [mM]	GBR tears Concentration [mM]
NaCl	95.75	115.75
NaH_2PO_4	1.25	1.25
KCl	4	20
$CaCl_2$	2	2
$MgCl_2$	1	1
Adenosine	0.5	0.5
$NaHCO_3$	23	23
Glutathione reduced	0.3	0.3
Glucose	77.7	27.75
H_2O	q.s.	q.s.
pH	7.3-7.4*	7.3-7.4*
Osmolality	297 mOsm/kg	311 mOsm/kg

* when gassed with 5% CO_2 / 95% O_2

Corneal permeation experiments with diclofenac formulations

1) Diclofenac sodium 0.1% without thiomersal (marketed Voltaren Ophtha formulation, SDU)

Time (min)	Average permeated amount (micro-gram)	S.D.
0	0	0
30	0	0
60	0	0
90	0.215981	0.196208
120	0.689412	0.418657
180	1.979619	0.878349

2) Diclofenac sodium 0.1% with 2% HP-gamma-CD and without BAC

Time (min)	Average permeated amount (micro-gram)	S.D.
0	0	0
30	0	0
60	0.060704	0.105143
90	0.870969	0.348648
120	1.794925	0.553737
180	5.321767	1.036315

3) Diclofenac sodium 0.1% with 2% CFR6 and without BAC

Time (min)	Average permeated amount (micro-gram)	S.D.
0	0	0
30	0	0
60	2.092435	0.781957
90	6.113682	1.163991
120	11.19923	1.621378
180	21.59050	3.123698

BAC = benzalkonium chloride

HP-gamma-CD = hydroxypropyl-γ-cyclodextrin

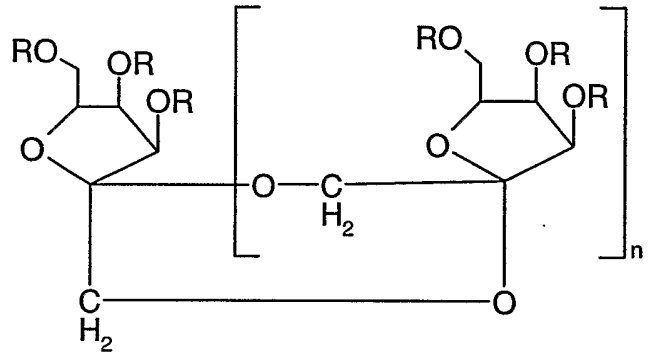
CFR6 = circular (or cyclic) hexameric cyclofructan, 6 fructose units (R=H, 0% substitution)

In the above experiments [item 2) & item 3)] the efficacy in drug permeation is directly comparable with respect to the prior art situation (HP-gamma-CD) and an embodiment of this invention, namely CFR6.

Claims:

1. Composition comprising a CFR, a polymeric carrier and a pharmaceutically effective drug.

2. Composition of claim 1, wherein said CFR is a compound of formula I,



I

wherein n is from 5 – 11,
R is independently from each other H, alkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkylen-carbonyl, alkylcarbonyl, alkylcarbamoyl, R'_3Si, or R is a saccharide minus the hydrogen atom from a hydroxy group,
wherein R' denotes independently of each other alkyl and phenyl, preferably methyl and phenyl, more preferably methyl.

3. Composition of claim 2, wherein R is H.

4. Composition of claim 2 -3, wherein said CFR is CFR 6, CFR7, CFR8, and mixtures of CFR6,7,8.

5. Composition of claim 1, wherein said drug is selected from anti-angiogenic drugs, anti-inflammatory drugs, anti-allergic drugs, drugs to treat glaucoma, anti-infective drugs, anti-fungal drugs, anti-viral drugs, anesthetic drugs, myopia preventing/inhibiting drugs, miotics, carbonic anhydrase inhibitors, alpha blocking agents antioxidants and/or vitamins.

6. Composition of claim 1, wherein said polymeric carrier is selected from:

A matrix of a bioerodible polymer being selected from the group consisting of polyhydroxy-acids, such as polylactic acid and polyglycolic acid; polyesters, polyorthoesters, polyanhydrides, polycyanoacrylates, natural gums, such as acacia gum and arabic gum; celluloses, such as carboxymethylcellulose; methacrylate (co)polymers such as Eudragits, e.g. Eudragit RL PO, Eudragit RS PO; and/or
A bioadhesive polymer being selected from the group consisting of maltodextrin, celluloses, such as carboxymethyl cellulose, hydroxyethyl cellulose; chitosans; hyaluronic acid; polyacrylates e.g. carbopol; polycarbophils e.g. Noveon AA-1; polyvinylalcohol such as Mowiol 26-88; polyvinylpyrrolidone such as povidone K30.

7. Composition of claim 6, which is at room temperature (approximately 22-25°C) in a solid state.

8. Composition of claim 1 – 7, which is a drug delivery system.

9. Drug delivery system of claim 8, which is selected from the group consisting of a rod, a bar, a capsule, a corneal shield. a corneal ring, an implant, an insert, an intra-ocular lens, a therapeutic contact lens, and a mini-disc, and
even more preferred from a corneal shield. a corneal ring, an implant, an insert, an intra-ocular lens, a therapeutic contact lens, and a mini-disc.

10. Composition of claim 1, further comprising one or more of the ingredients selected from the group of buffers, tonicity enhancing agents, preservatives, solubilizers, stabilizers/solubilizers, and complexing agents.

11. Use of a cyclofructan in the manufacture of a drug delivery system for the treatment of a disease being treatable by topical treatment, wherein said drug delivery system contains a drug, a CFR and a polymeric carrier which carrier is selected from:
A matrix of a bioerodible polymer being selected from the group consisting of polyhydroxy-acids, such as polylactic acid and polyglycolic acid; polyesters, polyorthoesters, polyanhydrides, polycyanoacrylates, natural gums, such as acacia gum and arabic gum; celluloses, such as carboxymethylcellulose; methacrylate (co)polymers such as Eudragits, e.g. Eudragit RL PO, Eudragit RS PO; and/or

A bioadhesive polymer being selected from the group consisting of maltodextrin, celluloses, such as carboxymethyl cellulose, hydroxyethyl cellulose; a cyclodextrin, chitosans; hyaluronic acid; polyacrylates e.g. carbopol; polycarbophils e.g. Noveon AA-1; polyvinylalcohol such as Mowiol 26-88; polyvinylpyrrolidone such as povidone K30.

12. Method of improving drug permeability in mucus tissue, which method comprises the topical administration of an effective amount of a drug in appropriate admixture with a CFR to the mucus tissue of a patient in need of such improved treatment.

13. Use of a CFR in the manufacture of a topical medicament for the treatment of a disease being treatable by topical treatment, said topical medicament comprises a CFR, a carrier, preferably a polymeric carrier, and an effective amount of drug.

14. Use of a CFR in the manufacture of a topical ophthalmic medicament for the treatment of a disease being treatable by topical treatment, wherein said medicament comprises a CFR, a carrier, preferably a polymeric carrier and an ophthalmic drug.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/02760

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/36 A61P27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1995, no. 05, 30 June 1995 (1995-06-30) -& JP 07 053347 A (MITSUBISHI KASEI CORP), 28 February 1995 (1995-02-28) abstract example 1, 2	1-5,7,8, 10,13
P,X	EP 1 273 286 A (ROHM & HAAS ;ISP INVEST INC (US)) 8 January 2003 (2003-01-08) '0001!	1-4,8,13
A	WO 97 10805 A (CIBA GEIGY AG ;KIS GYOERGY LAJOS (CH); FETZ ANDREA (CH); SCHOCH CH) 27 March 1997 (1997-03-27) page 3, second to last paragraph	1-14

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 May 2003	28/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Borst, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/02760

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 018, no. 448 (C-1240), 22 August 1994 (1994-08-22) -& JP 06 141856 A (MITSUBISHI KASEI CORP), 24 May 1994 (1994-05-24) abstract ---	1-14
A	PATENT ABSTRACTS OF JAPAN vol. 018, no. 448 (C-1240), 22 August 1994 (1994-08-22) -& JP 06 141879 A (MITSUBISHI KASEI CORP), 24 May 1994 (1994-05-24) abstract ---	1-14
A	IMMEL S ET AL: "Cyclofructins with six to ten beta-(12)-linked fructofuranose units: Geometries, electrostatic profiles, lipophilicity patterns, and potential for inclusion complexation" CARBOHYDRATE RESEARCH, ELSEVIER SCIENTIFIC PUBLISHING COMPANY. AMSTERDAM, NL, vol. 313, no. 2, December 1998 (1998-12), pages 91-105, XP004155558 ISSN: 0008-6215 page 99, right-hand column, paragraph entitled "Inclusion complexation potential" - page 102, left-hand column first paragraph -----	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/02760

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1(iv) PCT).

2. [X] Claims Nos.: –
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

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

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 2 is not clear (Article 6 PCT).
According to formula (I) of claim 2 the individual monosaccharides are not fructose units, since they lack the methylene-group in position 1 (cf. for comparison IMMEL S ET AL: 'Cyclofructins with six to ten beta-(12)-linked fructofuranose units: Geometries, electrostatic profiles, lipophilicity patterns, and potential for inclusion complexation': page 92). The search has been carried out in respect of claim 2 for cyclofructanes containing fructose units being connected by beta (1, 2) linkages (cf. description on file: page 1, last paragraph).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/02760

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 07053347 A	28-02-1995	NONE	
EP 1273286 A	08-01-2003	CA 2390952 A1	02-01-2003
		CN 1397269 A	19-02-2003
		EP 1273286 A2	08-01-2003
		JP 2003040734 A	13-02-2003
		US 2003021847 A1	30-01-2003
WO 9710805 A	27-03-1997	AT 209896 T	15-12-2001
		AU 704925 B2	06-05-1999
		AU 6987196 A	09-04-1997
		CN 1196676 A ,B	21-10-1998
		CZ 9800800 A3	17-06-1998
		DE 69617726 D1	17-01-2002
		DE 69617726 T2	08-08-2002
		DK 862414 T3	25-03-2002
		WO 9710805 A1	27-03-1997
		EP 0862414 A1	09-09-1998
		ES 2169262 T3	01-07-2002
		HU 9900361 A2	28-10-1999
		JP 11512445 T	26-10-1999
		PL 324921 A1	22-06-1998
		PT 862414 T	31-05-2002
		TW 434023 B	16-05-2001
		ZA 9607827 A	18-03-1997
JP 06141856 A	24-05-1994	WO 9410295 A1	11-05-1994
JP 06141879 A	24-05-1994	WO 9410295 A1	11-05-1994