



(51) International Patent Classification:

A61K 47/48 (2006.01) A61P 35/00 (2006.01)
A61K 9/14 (2006.01)

(21) International Application Number:

PCT/SE2015/000055

(22) International Filing Date:

9 September 2015 (09.09.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1400427-9 10 September 2014 (10.09.2014) SE

(71) Applicant: DOUBLE BOND PHARMACEUTICALS
AB [SE/SE]; Virdings Alle 32B, S-754 50 Uppsala (SE).(72) Inventor: LOKOT, Igor; Ferlingsgatan 59 NB, LGH 1001,
S-754 28 Uppsala (SE).(74) Agent: CONIMAR AB; Box 2086, 141 02 Huddinge
(SE).(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ,
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU,
TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

(54) Title: TARGETED DELIVERY OF HYDROPHILIC DRUGS

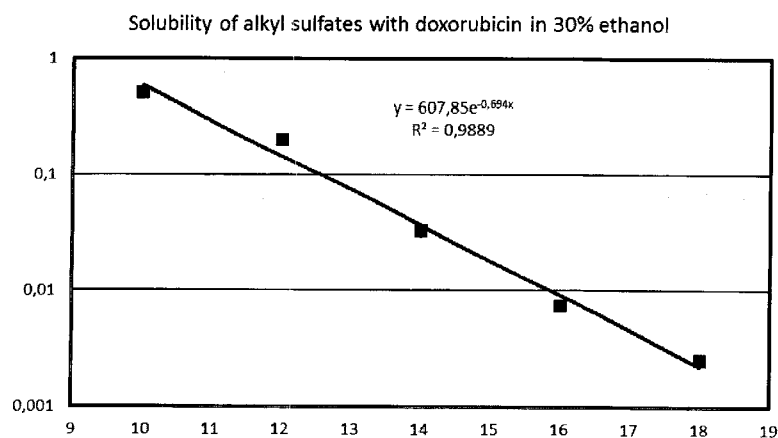


Fig. 1

(57) Abstract: A pharmaceutical composition in form of an aqueous colloid or an aqueous suspension of particles up to a size of 100 µm comprises or consists of amphiphilic sulfonate or sulfate of a hydrophilic cancer drug having a solubility in water or aqueous body fluid of less than 0.1 % by weight. Also disclosed are the particles in powderous form, methods for their production and for the production of the colloid and the courser suspension, a method of treating liver cancer, in particular solid liver cancer tumours, by administration of the pharmaceutical composition, and a method of designing a composition according to the invention.

TARGETED DELIVERY OF HYDROPHILIC DRUGS

FIELD OF THE INVENTION

5 The present invention relates to the administration of hydrophilic drugs to the liver of a human or animal, and to a solid liver tumour. More specifically the present invention relates to the administration of hydrophilic drugs, in particular anti-cancer drugs.

10 BACKGROUND OF THE INVENTION

 The therapeutic window represents the range of drug dosages by which a disease can be treated efficiently and safely. It ranges from the dosage at which a noticeable therapeutic effect is seen to that at which the therapeutic benefit is
15 neutralized by adverse effects.

 The majority of anticancer drugs have a narrow therapeutic window. In addition it is often a tiny fraction of an administered dose that reaches the site to be treated. Upon systemic administration by oral ingestion or intravascular injection, the medication is distributed throughout the body via the circulation resulting in the
20 entire body being affected. Ideally, the medication should be directed exclusively to a desired body site such as an organ or tissue in need of treatment. Such targeted administration would avoid harming the rest of the body. This kind of administration seeks to direct the medication to tissues of interest while avoiding substantial amounts thereof reaching tissues that do not require treatment.

25 An example of drugs which need to be directed to a specific body site is the anti-cancer drug doxorubicin. It is generally accepted that the therapeutic potential of doxorubicin could be significantly improved by targeted drug delivery since its dangerous side effects thereby could be avoided or at least substantially
30 reduced. The most dangerous side effect of doxorubicin is damage to the heart. When the cumulative dose of doxorubicin reaches 550 mg/m², the risk of developing cardiac side effects increases dramatically. Doxorubicin cardiotoxicity is characterized by a dose-dependent decline in mitochondrial oxidative phosphorylation. Reactive oxygen species generated by the interaction of
35 doxorubicin with iron can damage myocytes causing myofibrillar loss and cytoplasmic vacuolization. Excessive damage of this kind may result in the death of the patient. It is therefore desirable to keep the cardiac concentration of doxorubicin as low as possible.

40 Liver cancer is one of a number of malignancies in which administration of doxorubicin is indicated. More specifically, liver cancer can be treated by targeted (or local) administration in a procedure known as transarterial chemoembolization. In this procedure doxorubicin is administered through a catheter directly to

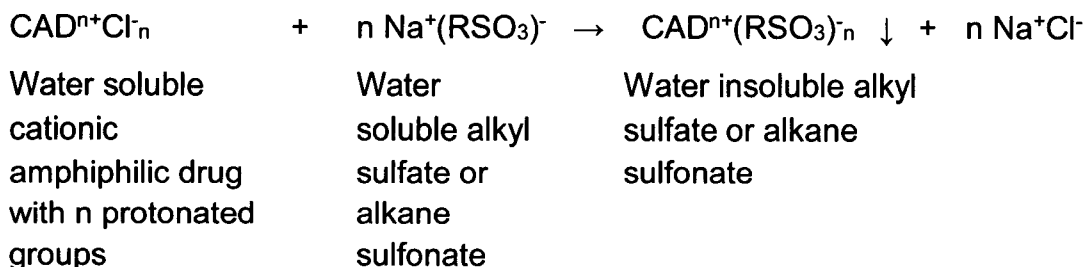
artery(ies) feeding the diseased portion of the liver while arteries supplying portions of the liver not affected by the disease are blocked by, for instance, gelatin sponge.

Isolated liver perfusion is one approach for targeted delivery of drugs to the liver. It comprises a surgical procedure during which the circulation of blood to the liver is separated from general circulation and separately perfused with blood. After separation the drug is injected into the blood by which the liver is being perfused, allowing a higher concentration of chemoterapeutical agent(s) to be used than with systemic administration. This invasive procedure is however technically complicated and not safe.

Many pharmacologically active agents such as the aforementioned anti-cancer drugs are weak bases in that they comprise one or more amino groups. For this reason they form salts with strong and weak acids, and are usually administered in salt form. The solubility of their common pharmaceutically acceptable salts, in particular their hydrochlorides, hydrobromides, phosphates, sulfates, lactates, tartrates, etc. in aqueous body fluid is usually higher than the solubility of the free base. Therefore aqueous solutions of such salts are used for intravenous infusion rather than an aqueous solution of the respective base.

For administration to the liver of a person or animal anti-cancer drugs of this kind are provided in a cationic amphiphilic form (in the form of a salt with a pharmaceutically acceptable acid). This manner of administration is applied but not limited to anti-cancer drugs such as, for instance, anthracyclines (doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone), vinca alkaloids (vinblastine, vincristine, vinorelbine), amsacrine, topotecan and irinotecan. If a pharmacologically active agent comprises more than one amino group two or more of them may be protonated and form salts with an acid.

Cationic amphiphilic drugs (CAD) of the aforementioned kind react with amphiphilic anionic surfactants, such as alkyl sulfates or alkane sulfonates, to form water insoluble complexes.



While still meeting the definition of a salt of an organic base with an organic or inorganic acid, the water insoluble complexes are to some extent additionally linked by non-covalent forces.

OBJECTS OF THE INVENTION

A primary object of the invention is to provide a pharmaceutical composition for targeted administration to the liver of an anti-cancer drug comprising one or more amino functions, which is lacking one or more of the drawbacks of known compositions of the drug or at least exhibits them to a lesser extent.

Another object of the invention is to provide a pharmaceutical composition for targeted administration to a solid liver tumour of an anti-cancer drug comprising one or more amino functions, which is lacking one or more of the drawbacks of known compositions of the drug known in the art or at least exhibits them to a lesser extent.

A further object of the invention is to provide a method of designing pharmaceutical compositions of this kind that will provide, after intravenous administration, a desired target concentration of the drug in the liver or the solid liver tumour.

Additional objects of the invention will become evident from the study of the following short description of the invention, of preferred embodiments thereof, and of the appended claims.

SUMMARY OF THE INVENTION

The present invention is based on the insight that aqueous suspensions of particles of amphiphilic compounds, in particular of straight chain alkyl sulfonates and straight chain alkane sulfates of hydrophilic anti-cancer drugs comprising amino function(s), are valuable forms by which these drugs can be administered in a manner concentrating their therapeutic effect to the liver or the solid liver tumour, i.e., targeting the liver or solid tumour. Thus, by targeting is understood preferential delivery to the liver so as to achieve a higher drug concentration (w/w) in liver tissue, including liver cancer tissue, than in other tissues. An important feature of straight chain alkyl sulfonates and of straight chain alkane sulfates of hydrophilic anti-cancer drugs is their low solubility in water and aqueous body fluid of less than 0.1 mg/mL at 25 °C.

A possible explanation of the biology behind the invention, which is however in no way binding, is that upon administration of a particulate aqueous suspension of an anti-cancer drug of this kind to the systemic circulation or the liver or a solid liver tumour the drug particles will reach, within a given period of time, an equilibrium distribution in the body. Their solubility in aqueous media is very low but not nil. They will therefore slowly dissolve in body fluid until an equilibrium determined by their solubility is reached. Since the dissolved material is irreversibly transformed chemically to degradation products more material is dissolved over time to maintain

the equilibrium. As long as the equilibrium is fed by dissolving material a steady state concentration of the drug is maintained locally.

The present invention is furthermore based on the insight that aqueous colloids of amphiphilic straight chain alkyl sulfonates of hydrophilic anti-cancer drugs comprising amino function(s) and of amphiphilic straight chain alkane sulfates of hydrophilic anti-cancer drugs comprising amino function(s) are particularly valuable forms by which these drugs can be administered in a manner concentrating their therapeutic effect to the desired organ, in particular the liver, or to the desired solid tumour, i.e., targeting the organ or solid tumour. Aqueous colloids are constituted by particles or comprise particles of a size of up to about 10000 nm.

An important property of aqueous colloids of the invention is their low sedimentation rate. In general the sedimentation rate of a given sort of particle increases with particle size. It may however be prevented from increasing and even be decreased by increasing the viscosity of the aqueous phase and/or by changing a surface property of the particles, such as, for instance, surface roughness.

The present invention provides solid particles of a salt of a hydrophilic cancer drug comprising one or more amino groups and a water soluble alkyl sulfate or alkane sulfonate or a mixture of two or more of such sulfates or sulfonates. An important feature of the salt is its low solubility in water. In other words, the salts of the invention are substantially insoluble. By "substantially soluble" is understood a solubility in water or aqueous body fluid of less than 0.1 % by weight, in particular of less than 0.05 or 0.02 by weight.

The present invention provides a method of producing said solid particles of a water insoluble salt of a hydrophilic cancer drug with a water soluble alkyl sulfate or alkane sulfonate or with a mixture of two or more of such sulfates or sulfonates.

The present invention furthermore provides a pharmaceutical composition comprising one or more amphiphilic sulfonates and/or sulfates of the invention and a liquid carrier. The composition can be administered by any suitable route, such as by intraarterial, intraperitoneal, intramuscular, transdermal or intravenous administration. Administration of a bolus comprising an aqueous colloid of the amphiphilic sulfonates and sulfates of the invention is preferred.

The present invention also provides a method of producing a pharmaceutical composition comprising a water insoluble salt of a hydrophilic cancer drug and a water soluble alkyl sulfate or alkane sulfonate or of a mixture of two or more of such sulfates or sulfonates in form of solid particles.

The composition of the invention may further comprise a buffer and pharmaceutically acceptable excipients such as osmolality controlling agent and viscosity controlling agent. Due to the method of production used the composition additionally contains a salt or corresponding ions consisting of the cation of the

water soluble alkyl sulfate or alkane sulfonate and of the anion of the anti-cancer drug. The use of alkali alkyl sulfates and of alkali alkane sulfonates, in particular of sodium and potassium alkyl sulfates and alkane sulfonates, is preferred.

- 5 The amphiphilic particulate sulfonates and sulfates of the invention consist of a pharmacological agent D possessing anti-cancer activity comprising from 1 to 4 amino groups of which one or more is protonated, and of one or more sulfate or sulfonate anion. They are represented by formulae (1) and (2):



- 10 wherein R^1 is straight chain C_6 - C_{30} alkyl; R^2 is straight chain C_6 - C_{30} alkyl; n is an integer from 1 to 4.

- It is preferred for R^1 and R^2 to be straight chain C_{10} - C_{20} alkyl, more preferred to be straight chain C_{12} - C_{18} alkyl, even more preferred to be about straight chain C_{16} alkyl. In consequence, R^1 can be any of straight chain C_{12} , C_{13} , C_{14} , C_{15} ,
15 C_{16} , C_{17} , C_{18} alkyl; R^2 is any of straight chain C_{12} , C_{13} , C_{14} , C_{15} , C_{16} , C_{17} , C_{18} alkyl.

A preferred particle size of 90 % of the colloid particles is 10000 nm or less, more preferred of 5000 nm or less.

- According to a preferred aspect of the invention particles of larger size than colloid particles and their aqueous suspensions are comprised by the present
20 invention, such as particles of a size of up to 10 μ m or 50 μ m and even up to 100 μ m, and their suspensions.

- The particles of the invention can be separated from the aqueous phase by, for instance, centrifugation or cryoprecipitation. If separated by centrifugation accompanying salt or corresponding ions consisting of the cation of the water
25 soluble alkyl sulfate or alkane sulfonate and of the anion of the anti-cancer drug are eliminated with the aqueous phase. The resulting powder (additionally dried, if necessary) retains the particle size of the colloid to at least 50 %, more preferred to at least 80 %. To facilitate re-suspension in an aqueous media, the powder can comprise a re-suspension facilitating agent such as glucose, lactose or albumin.
30 Alternatively the particles of the invention can be produced by evaporation, including cryoprecipitation, of the aqueous media; in such case they will be admixed with accompanying salt comprising the cation of the water soluble alkyl sulfate or alkane sulfonate and the anion of the anti-cancer drug; if desired they can be admixed with resuspension facilitating agent.

- 35 According to another preferred aspect of the invention, colloid particles of the invention can be comprised by micro carrier particles having affinity, such as by including appropriate antibody structures, to a surface antigen of the tumour to be treated.

Preferred pharmacologically active agents D of the amphiphilic sulfonates and sulfates of the invention include but are not limited to doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone, viniblastine, vincristine, vinorelbine, amsacrine, topotecan, irinotecan.

5 According to a further preferred aspect of the invention, suitable anti-cancer agents for preparing amphiphilic sulfonates and sulfates of the invention other than the aforementioned ones are of similar hydrophilicity as doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone, viniblastine, vincristine, vinorelbine, amsacrine, topotecan, irinotecan.

10 According to the present invention is also disclosed a method of treating liver cancer in a person, comprising administering to said person a therapeutically effective amount of the pharmaceutical composition of the invention or of a pharmaceutical composition comprising amphiphilic particulate sulfonate or sulfate powder of the invention. A preferred method of administration is by infusion or
15 injection into a vein or artery, in particular into the portal vein or hepatic artery. Another preferred method of administration is to a solid liver tumour by infusion or injection into the peripheral circulation. A third preferred method of administration is by infusion or injection directly into a solid liver tumour. According to a preferred aspect of the invention administration is by a bolus or by several boli is preferred.
20 One aspect of administration to the liver or liver tumour is by infusion or injection into a vein or artery, in particular into the portal vein or hepatic artery.

 According to the present invention is provided a drug delivery system for convenient and non-invasive intravenous administration capable of providing a desired concentration of the drug over extended periods of time, such as for more
25 than one hour or six hours or even a day or more. Such concentration is provided and maintained in the liver or in a solid liver tumour or other tissue. According to a preferred aspect of the invention the invention provides a method of controlling the ratio of distribution of a drug between the liver and other organs and tissues.

 In this application, unless otherwise stated, the term "liver disease"
30 (hepatic disease) comprises primary liver cancer (for example hepatocellular carcinoma and/or cholangiocarcinoma, angiosarcoma, hemangiosarcoma of the liver), secondary malignancies (i.e. secondary lesions that have metastasized from primary cancers in the gastrointestinal tract and other organs, such as the kidneys, lungs, breast, or prostate); inflammation of the liver caused by virus (viral hepatitis),
35 liver toxins (e.g. alcoholic hepatitis), autoimmunity (autoimmune hepatitis) or hereditary conditions; liver cirrhosis caused by excessive alcohol consumption.

 According to the invention is also disclosed a method of designing a pharmaceutical composition for providing, during a predetermined period, a therapeutic target of a person or animal selected from liver and solid liver tumour
40 with a predetermined concentration of a sulfate or sulfonate of a pharmacologically

active agent D comprising from 1 to 4 amino groups represented by formula (1) or (2) or a mixture of these agents:



5 wherein R^1 is straight chain C_6 - C_{30} alkyl; R^2 is straight chain C_6 - C_{30} alkyl; n is an integer from 1 to 4; wherein the method comprises:

- i) determining the solubility of $D_n^+(R^1SO_3^-)_n$ and/or $D_n^+(R^2OSO_3^-)_n$ for various carbon chain lengths X , Y in an aqueous solvent;
- 10 ii) determining the correlation between the solubility of said sulfate or sulfonate of said pharmacologically active agent and the expected concentration of said pharmaceutically active agent D in the therapeutic target upon administration of said pharmacologically active agent D to the subject or animal;
- 15 iii) defining a target solubility of said sulfate or sulfonate of said pharmacologically active agent in said solvent based on a desired concentration of said pharmaceutically active substance D in said organ or tissue;
- iv) determining the carbon chain length(s) X , Y corresponding to said target solubility;
- 20 v) providing a sulfate or sulfonate of said pharmacologically active agent comprising the so determined the carbon chain length(s) X , Y ;
- vi) providing a fluid carrier;
- vii) combining said sulfate or sulfonate of said pharmacologically active agent comprising the so determined the carbon chain length(s) X , Y with the fluid carrier in an amount capable of maintaining said concentration during said period.
- 25

According to a preferred aspect of the invention the solubility is determined in an aqueous organic solvent, such as an aqueous alcohol, in particular aqueous ethanol in a concentration of from 5 % to 50 %, preferably from 10 % to 30 % (v/v). Other water miscible solvents such as low molecular weight ketones, amides, esters, amides, and sulfoxides may also be used.

According to a preferred aspect of the invention the pharmaceutical composition comprises a mixture of at least two different sulfates or sulfonates of the invention represented by formula (1) or (2) or at least two different sulfates or sulfonates of which one is represented by formula (1) and the other by formula (2).

A preferred pharmacologically active substance D is selected from the group consisting of doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone,

viniblastine, vincristine, vinorelbine, amsacrine, topotecan, irinotecan. It is also preferred for the composition to comprise a colloid.

A preferred fluid carrier is water or an aqueous media in which the sulfate or sulfonate of said pharmacologically active agent D is insoluble or substantially insoluble. By "substantially soluble" is understood a solubility of less than 0.1 % by weight, in particular of less than 0.05 or 0.02 by weight. The composition may be designed for intraarterial, intraperitoneal, intramuscular, transdermal or intravenous administration. The steps above may be performed in any suitable order.

A preferred form of said sulfate or sulfonate of the pharmacologically active agent D is a powder of a mean particle size (N) of up to 100 μm , preferably up to 50 μm or 10 μm or 5 μm . A preferred form of said pharmaceutical composition is an aqueous suspension, in particular an aqueous colloid.

According to the present invention is also disclosed a method of producing the pharmaceutical composition of the invention, the method comprising: providing a first aqueous solution of a salt of said anti-cancer drug with an inorganic or organic acid that is not amphiphilic; providing a second aqueous solution comprising an amount of a sodium or potassium salt of an alkyl sulfonate of the formula $(\text{Na or K})^+(\text{R}^1\text{SO}_3)^-$ or of an alkane sulfate of the formula $(\text{Na or K})^+(\text{R}_2\text{OSO}_3)^-$ equivalent to the amount of said salt; mixing said first and second solutions. While other than sodium and potassium salts can be used in the method, their use is not preferred. It is preferred for R^1 to be straight chain $\text{C}_6\text{-C}_{30}$ alkyl; R^2 is straight chain $\text{C}_6\text{-C}_{30}$ alkyl; n is an integer from 1 to 4. It is preferred for R^1 and R^2 to be straight chain $\text{C}_{10}\text{-C}_{20}$ alkyl, more preferred straight chain $\text{C}_{12}\text{-C}_{18}$ alkyl, most preferred about straight chain C_{16} alkyl.

According to the present invention is furthermore disclosed the use of the composition of the invention comprising an anti-cancer agent of the group consisting of doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone, viniblastine, vincristine, vinorelbine, amsacrine, topotecan, irinotecan for targeted delivery to the liver of a person or animal.

According to the present invention is also disclosed the use of the amphiphilic particulate sulfonate powder of the invention comprising an anti-cancer agent of the group consisting of doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone, viniblastine, vincristine, vinorelbine, amsacrine, topotecan, irinotecan for the manufacture of a medicament comprising a pharmaceutical composition capable of targeted delivery to the liver of a person or animal.

The invention will now be illustrated in greater detail by a number of non-limiting examples thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

- Fig. 1 is a graph illustrating the dependence of the solubility of doxorubicin alkyl sulfate in 30% aqueous ethanol on alkyl chain length;
- 5 Fig. 2 is a graph illustrating the dependence of the solubility of doxorubicin alkane sulfonate in 30% aqueous ethanol on alkyl chain length;
- Fig. 3 is a graph illustrating the dependence of the solubility of mitoxantrone alkyl sulfate in 30% aqueous ethanol on alkyl chain length;
- 10 Fig. 4 is a graph illustrating the dependence of the solubility of mitoxanthrone alkane sulfonate in 30% aqueous ethanol on alkyl chain length;
- Fig. 5 is a graph illustrating the dependence of the solubility of irinotecan alkane sulfonate in 10% aqueous ethanol on alkyl chain length;
- Fig. 6 is a graph illustrating the dependence of the solubility of vinorelbine alkane sulfonate in 20% aqueous ethanol on alkyl chain length;
- 15 Fig. 7 is a graph illustrating the dependence of doxorubicin concentration in the liver of Wistar rats 2 h post bolus injection on the solubility of doxorubicin alkane sulfate and sulfonate in 30% aqueous ethanol;
- Fig. 8 is a graph illustrating the relationship between the solubility of non-covalent complexes of doxorubicin in 30 % aqueous ethanol and the increase of doxorubicin concentration in Californian rabbit liver 0.5 h post intravenous injection;
- 20 Fig. 9 are graphs illustrating doxorubicin concentration in the liver and the heart upon intravenous injection of 5 mg/kg aqueous doxorubicin hydrochloride and of 1.25 mg/kg of the composition of the invention according to Example 1.
- 25

Exponential (for Figs. 1-6) and logarithmic (for Figs. 7 and 8) trendlines and their equations were obtained by means of Microsoft Excel software.

DESCRIPTION OF PREFERRED EMBODIMENTS

30

General procedures. *Materials and methods.*

Solubility in aqueous ethanol was determined by centrifuging an adequate amount of freshly obtained colloid at 3000 rpm for 30-90 min, decanting the supernatant, adding 10 mL water and shaking the mixture, then repeating
35 centrifugation, shaking and washing 3 times. The centrifugate from the final

centrifugation was air dried for 72 h at room temperature followed by drying *in vacuo* for 24 h. A portion of the dried centrifugate (20 mg) was resuspended in 6 mL aqueous ethanol by stirring at room temperature for 24 h. The mixture was centrifuged at 3000 rpm for 10 min and the supernatant filtered through a 0.2 micrometer filter to remove aggregates of undissolved solid product. The solubility of the compound was determined by a UV method.

The composition used for *in vivo* investigation was freshly prepared or had been obtained by dilution of a concentrate. For *in vivo* investigation, female Wistar rats 60-75 days old weighing 300 g $\pm$ 30g were selected. Four animals were used for testing one composition. The doxorubicin compositions were administered via single bolus injections into the tail in an amount of 5 mg/kg doxorubicin. Immediately after sacrificing the rat bodies were deep-frozen in liquid nitrogen.

Determination of the bio-distribution of doxorubicin in liver tissue. Five or six pieces of liver tissue of a total weight of about 1g were taken from different parts of a liver. The samples were homogenized with a solution of aqueous ethanol containing HCl for 20 s at 7000 rpm and for 10 s at 11000 rpm. The homogenate was vortexed for 30 min and centrifuged at 3000 rpm for 30 min. The supernatant was treated with a solution of monochloroacetic acid and incubated for 1 h. The mixture was centrifuged at 15000 rpm for 15 min. Doxorubicin concentration in the final supernatant was determined by fluorometric analysis.

EXAMPLE 1. Preparation of colloid doxorubicin alkyl sulfate and alkane sulfonate

To a solution of doxorubicin hydrochloride (50 mL, 1 mg/mL) in 5% aqueous dextrose in an Erlenmeyer flask was added at room temperature a solution of a 5-10 % molar excess of $\text{Na}^+(\text{R}^1\text{SO}_3)^-$ or $\text{Na}^+(\text{R}^2\text{OSO}_3)^-$ and in the same solvent as for doxorubicin hydrochloride. Instead of 5 % aqueous dextrose can be used in this and the other examples Ringer solution or 0.9% saline or phosphate-buffered saline or another aqueous solution of an osmolality from 270 to 300 mOsm/L. The process of colloid formation was monitored visually. After completing of the addition the mixture was vortexed or shaken for an additional time period varying from 30 min to 7 days. The colloid then was either directly used or placed for storage in a refrigerator. Concentration of doxorubicin in the compositions was determined by a UV method at 495 or 233 nm. For sampling, an aliquot of the colloid was diluted with methanol (excess of methanol > 20:1).

EXAMPLE 2. Preparation of colloid mitoxantrone alkyl sulfates and alkane sulfonates

To a vigorously stirred solution of mitoxantrone dihydrochloride (40 mL, 0.2 mg/mL) in 5% dextrose in water in an Erlenmeyer flask was added at room

temperature a solution containing 0.03 mmol of $\text{Na}^+(\text{R}^1\text{SO}_3)^-$ or $\text{Na}^+(\text{R}^2\text{OSO}_3)^-$ in the same solvent as for mitoxantrone dihydrochloride. The formation of a black colloid was monitored visually. The colloid slowly disintegrated into a black precipitate and a pale supernatant. After completing of the addition the mixture obtained stirred for additional time (from 1 to 7 days). The colloid composition was either used directly or stored in a refrigerator for later use. The concentration of mitoxantrone in the colloid was determined by a UV method at 662, 611 or 242 nm. For sampling an aliquot of the colloid was diluted with methanol to >20:1.

10 **EXAMPLE 3. *Preparation of colloid irinotecan alkyl sulfates and alkane sulfonates***

To a vigorously solution of irinotecan hydrochloride trihydrate (5 mL, 4 mg/mL) in deionized water was added at room temperature a solution containing $\text{Na}^+(\text{R}^1\text{SO}_3)^-$ or $\text{Na}^+(\text{R}^2\text{OSO}_3)^-$ in deionized water. The formation of a colloid was monitored visually. After completing of the addition the mixture obtained stirred for 2 days and the mixture was centrifuged 10 min at 3000 rpm. On standing the white colloid slowly disintegrated into a white precipitate and a nearly colourless supernatant. The supernatant was replaced by 5 % aqueous dextrose. The precipitate was re-suspended in water by vortexing for 10 min. The composition obtained then was either directly used or stored in a refrigerator for future use. The concentration of irinotecane in the colloid or modified colloid was determined by a UV method at 360, 255 or 220 nm. For sampling an aliquot of the product was diluted with methanol (excess of methanol >20:1).

EXAMPLE 4. *Preparation of colloid vinorelbine alkyl sulfates and alkane sulfonates*

25 To a vigorously stirred solution of vinorelbine tartrate (2 mL, 5 mg/mL) in 5% aqueous dextrose in an Erlenmeyer flask was added at room temperature a solution of one equivalent of $\text{Na}^+(\text{R}^1\text{SO}_3)^-$ or $\text{Na}^+(\text{R}^2\text{OSO}_3)^-$ in the same solvent as for vinorelbine tartrate. The formation of a colloid was monitored visually. After completing of the addition the mixture obtained was vortexed or shaken for 7 days. On standing the colloid slowly disintegrated into a precipitate and a clear supernatant. The colloid was either used directly or stored in a refrigerator for future use. The concentration of vinorelbine in the colloid was determined by a UV method at 268 or 212 nm. For sampling an aliquot of the colloid was diluted with methanol (excess of methanol >20:1).

35

EXAMPLE 5. *Solubility of colloid doxorubicin alkyl sulfates and alkane sulfonates in 30% aqueous ethanol*

Solubility was determined in accordance with the general method described under *Materials and Methods*. The results are summarized in Table 1 and presented in Figs. 1 and 2.

5 **Table 1. Solubility of colloid doxorubicin alkyl sulfates and alkane sulfonates in 30 % ethanol (v/v)**

Generic formula of anion	Alkyl chain length, n	Solubility, mg/mL
$C_nH_{2n+1}OSO_3^-$	10	0.50769
	12	0.20560
	14	0.03281
	16	0.00729
	18	0.00260
$C_nH_{2n+1}SO_3^-$	10	1.06429
	12	0.23953
	14	0.04596
	16	0.01194
	18	0.00279

EXAMPLE 6. Solubility of colloid mitoxantrone alkyl sulfates and alkane sulfonates in 30% aqueous ethanol

10 The solubility was determined in accordance with the general method described under *Materials and Methods*. The results are summarized in Table 4 and presented in Figures 3 and 4.

Table 2. Solubility of colloid mitoxantrone alkyl sulfates and alkane sulfonates in 30 % ethanol (v/v)

Generic formula of anion	Alkyl chain length, n	Solubility, mg/mL
$C_nH_{2n+1}OSO_3^-$	8	1.34798
	10	0.29487
	12	0.06813
	14	0.00203
	16	0.00020
$C_nH_{2n+1}SO_3^-$	8	0.78058
	10	0.17582
	12	0.06484
	14	0.00720
	16	0.00020

EXAMPLE 7. Solubility of irinotecan alkane sulfonates in 10% aqueous ethanol

The solubility was determined in accordance with the general method described under *Materials and Methods*. The results are summarized in Table 3 and Fig. 5.

5 Table 3. Solubility of colloid irinotecan alkane sulfonates in 30 % ethanol (v/v)

Alkyl chain length, n	Solubility, mg/mL
10	0.83483
12	0.15453
14	0.07064
16	0.01476

EXAMPLE 8. Solubility of colloid vinorelbine alkane sulfonates in 20% aqueous ethanol

10 The solubility was determined according to the general method described, cf. *Materials and Methods*. The results are summarized in Table 4 and Fig. 6.

Table 4. Solubility of colloid inorelbine alkane sulfonates in 20% aqueous ethanol

Alkyl chain length, n	Solubility, mg/mL
10	1.11868
12	0.25692
14	0.06731
16	0.01977

EXAMPLE 9. In vivo analysis of distribution of doxorubicin in the liver of Wistar rats

15 An aqueous solution of doxorubicin hydrochloride, an aqueous colloid of doxorubicin alkane sulfate and an aqueous colloid of doxorubicin alkyl sulfonate were administered via a single bolus injection into the tail. Animals were sacrificed after 2 hours after administered via a single bolus injection into the tail; total doxorubicin dose 5 mg/kg. The concentration of doxorubicin in a liver was determined according to the procedure described above.

20 The results are summarized in Table 5 and Fig. 7.

Table 5. *In vivo analysis of distribution of doxorubicin in Wistar rat liver*

Anion of doxorubicin salt	Conc. of doxorubicin, $\mu\text{g/kg}$ (SDI)	Solubility in 30% ethanol, mg/mL	Increase of doxorubicin concentration in liver tissue, times
Cl^-	11.47 ± 2.98	(1)	(1)
$(\text{C}_{12}\text{H}_{25}\text{OSO}_3)^-$	7.15 ± 2.07	0.20560	0.64
$(\text{C}_{14}\text{H}_{29}\text{OSO}_3)^-$	21.45 ± 4.33	0.03281	1.87
$(\text{C}_{16}\text{H}_{33}\text{OSO}_3)^-$	31.77 ± 2.82	0.00729	2.77
$(\text{C}_{12}\text{H}_{25}\text{SO}_3)^-$	9.52 ± 1.03	0.23953	0.83
$(\text{C}_{16}\text{H}_{33}\text{SO}_3)^-$	29.75 ± 3.51	0.01194	2.60

EXAMPLE 10. *In vivo analysis of distribution of doxorubicin in Californian rabbit liver*

- 5 Colloid non-covalent complexes of doxorubicin and doxorubicin hydrochloride were administered at a slow flow rate of 1 ml/mi to Californian rabbits into the marginal ear vein, the total doxorubicin dose being 5 mg/kg. The animals were sacrificed 0.5 h post administration. The concentration of doxorubicin in a liver was determined in accordance with the procedure described above. For results, see
- 10 Table 6 and Fig. 8.

Table 6. *Distribution of doxorubicin in the liver of Californian rabbits*

Anion of doxorubicin salt	Conc. of doxorubicin, $\mu\text{g/kg}$ (SDI)	Solubility in 30% ethanol, mg/mL	Increase of doxorubicin concentration in liver tissue, times
Cl^- (Doxorubicin)	0.392 ± 0.128	(1)	(1)
$\text{C}_{12}\text{H}_{25}\text{OSO}_3$	0.496 ± 0.201	0.20560	1.27
$\text{C}_{14}\text{H}_{27}\text{OSO}_3$	0.776 ± 0.301	0.03281	1.98
$\text{C}_{16}\text{H}_{33}\text{OSO}_3$	1.141 ± 0.203	0.00729	2.91
$\text{C}_{12}\text{H}_{25}\text{SO}_3$	0.423 ± 0.078	0.23953	1.08
$\text{C}_{12}\text{H}_{25}\text{SO}_3$	1.128 ± 0.148	0.01194	2.88

EXAMPLE 11. *Preparation of a colloid comprising doxorubicin sulfonates with a desired solubility in 30% aqueous ethanol*

- 15 This example illustrates the preparation of colloids of the invention with desired solubility in a particular solvent. The following parameters were set: *active*

agent: doxorubicin; *anion*: alkane sulfonate with even number of carbon atoms;
solvent: 30% aqueous ethanol; *desired solubility*: 0.1 mg/mL.

The calculation was based on the assumption that the number of carbon atoms in an alkane sulfonate radical of medium chain length is additive.

- 5 The calculation was furthermore based on the assumption of a continuous function for solubility y in 30% aqueous ethanol.

Following function (f_1), which was obtained from Example 5 (cf. Fig. 2) represents relationship between number of carbon atoms x and solubility y .

$$y=f_1(x)=1754.71710 \exp(-0.74429 x) \text{ (eq. 1)}$$

- 10 Function (f_2) allows to perform a reverse calculation, i.e. determine the number of carbon atoms X from a given solubility Y :

$$x=f_2(y)=-1/0.7442855697 \ln(y/1754.71709855) \text{ (eq. 2)}$$

For the solubility of $y = 0.1$ mg/mL, the function f_2 gives x as equal to 13.20628.

- 15 Based on the assumption of an additive effect of the number of carbon atoms in the radicals the ratio of C_{12} and C_{14} sulfonates behaviour (the pair of sulfonates with solubilities closest to the desired one) to provide the suggested $C_{13.20628}$ radical:

- 20 One equivalent of $C_{13.20628}$ is equal to a mixture of 0.397 equivalents of C_{12} and 0.603 equivalents of C_{14} .

A mixture of doxorubicin sulfonates with the determined ratio of C_{12} and C_{14} was prepared in accordance the typical method described in Example 1. The solubility was determined in accordance with the general method which is described above, and was found 0.098713 mg/mL.

25

EXAMPLE 12. Intravenous delivery of a composition of the invention targeted to the liver of Californian rabbits

- 30 The doxorubicin composition of the invention according to Example 1 ($R = C_{16}$ sulfonate) was administered to Californian rabbits by injection into the ear vein at a concentration of 1.25 mg doxorubicin/kg body weight. For comparison aqueous doxorubicin hydrochloride was administered in the same manner at a concentration of 5.0 mg doxorubicin/kg body weight. As shown by Fig. 9 the composition of the invention is about four times more efficient in regard of delivery of doxorubicin to the liver than prior art aqueous doxorubicin hydrochloride, whereas there is no
- 35 difference in regard of delivery to the heart.

Claims

1. Pharmaceutical composition in form of an aqueous colloid comprising or consisting of solid particles of amphiphilic particulate sulfonate or amphiphilic particulate sulfate of a hydrophilic cancer drug, the particles having a solubility in water or aqueous body fluid of less than 0.1 % by weight, in particular of less than 0.05 or 0.02 by weight, and wherein 90 % or more of the particles have a size of 10000 nm or less, in particular of 5000 nm or less.
2. The composition of claim 1, wherein the solid particles are of amphiphilic sulfonate particles.
3. The composition of claim 1, wherein the solid particles are of amphiphilic sulfate particles.
4. The composition of claim 2 or 3, further comprising buffer and/or pharmaceutically acceptable excipient such as osmolality controlling agent and viscosity controlling agent.
5. The composition of claim 2, wherein an amphiphilic particulate sulfonate consists of a pharmacologically active anti-cancer agent D comprising from 1 to 4 amino groups of which one or more is protonated, and of a corresponding number of sulfate or sulfonate anion.
6. The composition of claim 3, wherein an amphiphilic particulate sulfate consists of a pharmacologically active anti-cancer agent D comprising from 1 to 4 amino groups of which one or more is protonated, and of a corresponding number of sulfate or sulfonate anion.
7. The composition of claim 2, wherein the amphiphilic particulate sulfonate is represented by formula (1): $D^{n+}(R^1SO_3)^{-n}$ (1);
wherein R^1 is straight chain C₆-C₃₀ alkyl; R^2 is straight chain C₆-C₃₀ alkyl; n is an integer from 1 to 4.
8. The composition of claim 3, wherein the amphiphilic particulate sulfate is represented by formula (2): $D^{n+}(R_2OSO_3)^{-n}$ (2);
wherein R^1 is straight chain C₆-C₃₀ alkyl; R^2 is straight chain C₆-C₃₀ alkyl; n is an integer from 1 to 4.
9. The composition of claim 7 or 8, wherein R^1 and R^2 is straight chain C₁₀-C₂₀ alkyl, more preferred to be straight chain C₁₂-C₁₈ alkyl, most preferred about C₁₆.
10. The composition of any of claims 5-9, wherein D is selected from the group consisting of doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone, vinblastine, vincristine, vinorelbine, amsacrine, topotecan, irinotecan.

11. A method of producing the pharmaceutical composition of any of claims 2, 4, 5, 7, 9, 10 comprising: providing a first aqueous solution of a salt of said hydrophilic anti-cancer drug with an inorganic or organic acid that is not amphiphilic; providing a second aqueous solution comprising an amount of a sodium or potassium salt of an alkyl sulfonate of the formula $(\text{Na or K})^+(\text{R}^1\text{SO}_3)^-$ equivalent to the amount of said salt; mixing said first and second solutions.
12. A method of producing the pharmaceutical composition of any of claims 3, 4, 6, 8, 10 comprising: providing a first aqueous solution of a salt of said hydrophilic anti-cancer drug with an inorganic or organic acid that is not amphiphilic; providing a second aqueous solution comprising an amount of a sodium or potassium salt of an alkyl sulfonate of the formula of an alkane sulfate of the formula $(\text{Na or K})^+(\text{R}^2\text{OSO}_3)^-$ equivalent to the amount of said salt; mixing said first and second solutions.
13. The method of claim 11, wherein R^1 is straight chain $\text{C}_6\text{-C}_{30}$ alkyl and n is an integer from 1 to 4.
14. The method of claim 11, wherein R^2 is straight chain $\text{C}_6\text{-C}_{30}$ alkyl; n is an integer from 1 to 4.
15. The method of claim 13, wherein R^1 is straight chain $\text{C}_{10}\text{-C}_{20}$ alkyl, more preferred straight chain $\text{C}_{12}\text{-C}_{18}$ alkyl, most preferred about C_{16} .
16. The method of claim 14, wherein R^1 and R^2 is straight chain $\text{C}_{10}\text{-C}_{20}$ alkyl, more preferred straight chain $\text{C}_{12}\text{-C}_{18}$ alkyl, most preferred about C_{16} .
17. Amphiphilic particulate sulfonate powder consisting of or comprising a pharmacologically active agent D comprising from 1 to 4 amino groups of which one or more is protonated and a number of sulfate or sulfonate anion corresponding to the number of protonated amino groups, represented by formula (1): $\text{D}^{n+}(\text{R}^1\text{SO}_3)^{-n}$ (1); wherein R^1 is straight chain $\text{C}_6\text{-C}_{30}$ alkyl and n is an integer from 1 to 4.
18. The amphiphilic particulate sulfonate powder of claim 17, wherein R^1 is straight chain $\text{C}_{10}\text{-C}_{20}$ alkyl, more preferred straight chain $\text{C}_{12}\text{-C}_{18}$ alkyl, most preferred to be about straight chain C_{16} alkyl.
19. The amphiphilic particulate sulfonate powder of claim 18 of a particle size of up to $100\text{ }\mu\text{m}$ or up to $50\text{ }\mu\text{m}$ or up to $10\text{ }\mu\text{m}$.
20. The amphiphilic particulate sulfonate powder of any of claims 17-19 comprising a re-suspension facilitating agent and/or sodium or potassium salt of hydrochloric or hydrobromic acid.
21. Amphiphilic particulate sulfate powder consisting of or comprising a pharmacologically active agent D comprising from 1 to 4 amino groups of

which one or more is protonated and a number of sulfate or sulfonate anion corresponding to the number of protonated amino groups, represented by formula (2): $D^{n+}(R^2OSO_3)^{-}_n$ (2); wherein R^2 is straight chain C_6 - C_{30} alkyl and n is an integer from 1 to 4.

- 5 22. The amphiphilic particulate powder of claim 20, wherein R^1 is straight chain C_{10} - C_{20} alkyl, more preferred straight chain C_{12} - C_{18} alkyl, most preferred straight chain C_{16} alkyl.
- 10 23. The amphiphilic particulate powder of claim 21, wherein R^2 is straight chain C_{10} - C_{20} alkyl, more preferred straight chain C_{12} - C_{18} alkyl, most preferred straight chain C_{16} alkyl.
24. The amphiphilic particulate sulfate powder of any of claims 21-23 of a particle size of up to 100 μm or up to 50 μm or up to 10 μm .
- 15 25. The amphiphilic particulate sulfonate powder of any of claims 17-20 or the amphiphilic particulate sulfate powder of any of claims 21-24 comprising a re-suspension facilitating agent and/or sodium or potassium salt of hydrochloric or hydrobromic acid.
- 20 26. A method of designing a pharmaceutical composition for providing, during a predetermined period, as a therapeutic target, the liver of a person or animal, with a predetermined concentration of a sulfate or sulfonate of a pharmacologically active agent D comprising from 1 to 4 amino groups represented by formula (1) or (2) or a mixture of these agents:



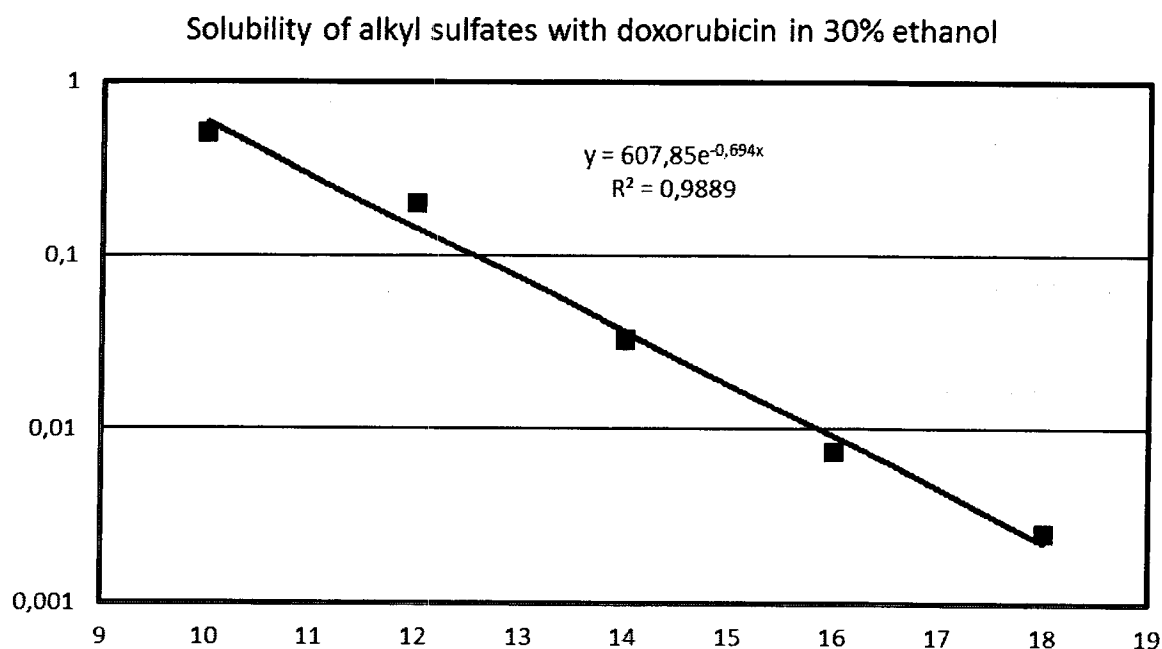
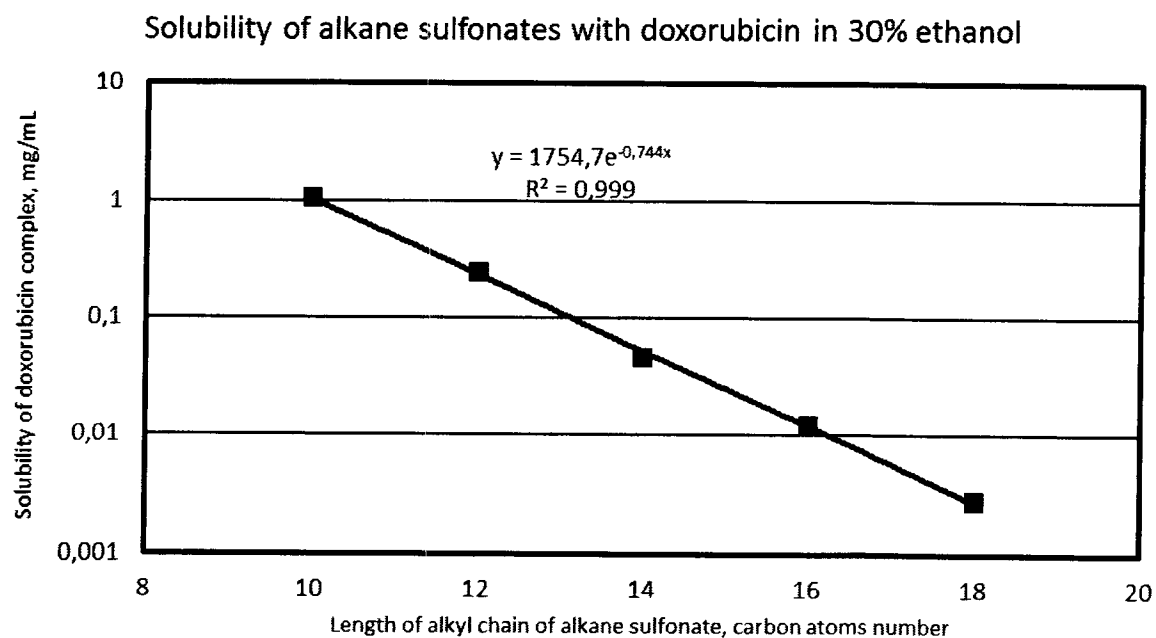
25 wherein R^1 is straight chain C_6 - C_{30} alkyl; R^2 is straight chain C_6 - C_{30} alkyl; n is an integer from 1 to 4; wherein the method comprises:

- i) determining the solubility of $D^{n+}(R^1SO_3)^{-}_n$ and/or $D^{n+}(R^2OSO_3)^{-}_n$ for various carbon chain lengths X , Y in an aqueous solvent;
- 30 ii) determining the correlation between the solubility of said sulfate or sulfonate of said pharmacologically active agent and the expected concentration of said pharmaceutically active agent D in the therapeutic target upon administration of said pharmacologically active agent D to the subject or animal;
- 35 iii) defining a target solubility of said sulfate or sulfonate of said pharmacologically active agent in said solvent based on a desired concentration of said pharmaceutically active substance D in said therapeutic target;

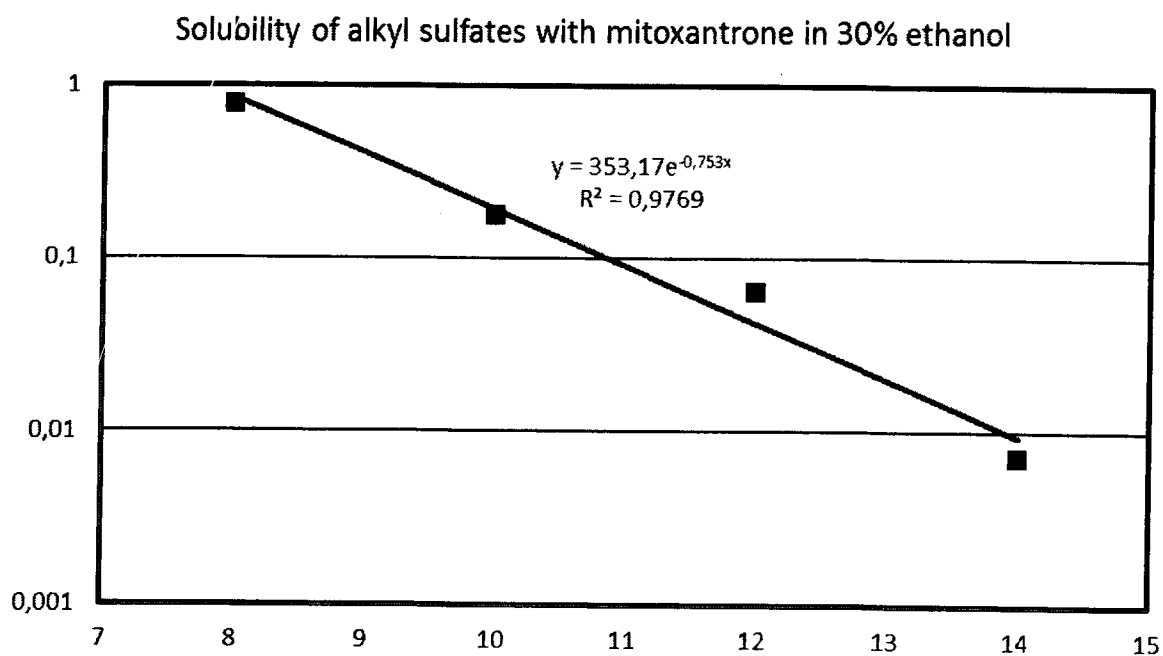
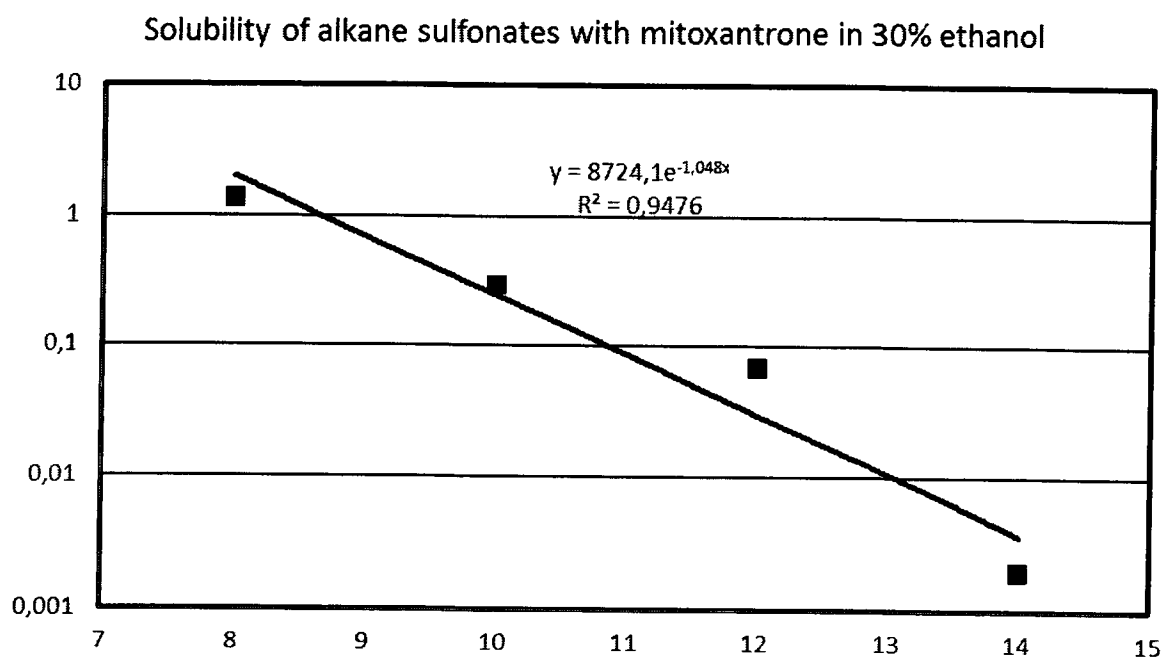
- iv) determining the carbon chain length(s) X, Y corresponding to said target solubility;
 - v) providing a sulfate or sulfonate of said pharmacologically active agent comprising the so determined the carbon chain length(s) X, Y;
 - 5 vi) providing a fluid carrier;
 - vii) combining said sulfate or sulfonate of said pharmacologically active agent comprising the so determined the carbon chain length(s) X, Y with the fluid carier in an amount capable of maintaining said concentration during said period in said target.
- 10 27. The method of claim 26, wherein the solubility is determined in an aqueous organic solvent, such as an aqueous alcohol, in particular aqueous ethanol in a concentration of from 5 % to 50 %, preferably from 10 % to 30 % (v/v).
- 15 28. The method of claim 26 or 27, wherein D is selected from the group consisting of doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone, vinblastine, vincristine, vinorelbine, amsacrine, topotecan, irinotecan.
- 20 29. A method of treating cancer in a person, comprising administrating to said person a therapeutically effective amount of the pharmaceutical composition of any of claims 1, 2, 4, 5, 7, 9, 10 or of the pharmaceutical composition of any of claims 1, 3, 4, 6, 8-10 or of a pharmaceutical composition comprising amphiphilic particulate sulfonate powder of any of claims 17-20 and 25 or amphiphilic particulate sulfate powder of any of claims 21-25.
- 30 30. The method of claim 29, wherein administration is by infusion or injection into a vein or artery, in particular into the portal vein or hepatic artery.
- 25 31. The method of claim 29, wherein administration is to a solid liver tumour by infusion or injection into the peripheral circulation.
32. The method of claim 29, wherein administration is by infusion or injection directly into a solid liver tumour.
33. The method of any of claims 29-32, wherein administration is by a bolus or by several boli.
- 30 34. Use of the composition of any of claims 1 to 10 for targeted intravenous delivery to the liver of a person or animal of an anti-cancer agent of the group consisting of doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone, vinblastine, vincristine, vinorelbine, amsacrine, topotecan, irinotecan.
- 35 35. Use of the amphiphilic particulate sulfonate powder of any of claims 17 to 25 comprising an anti-cancer agent of the group consisting of doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone, vinblastine, vincristine, vinorelbine, amsacrine, topotecan, irinotecan for the manufacture of a

medicament comprising a pharmaceutical composition capable of targeted intravenous delivery to the liver of a person or animal.

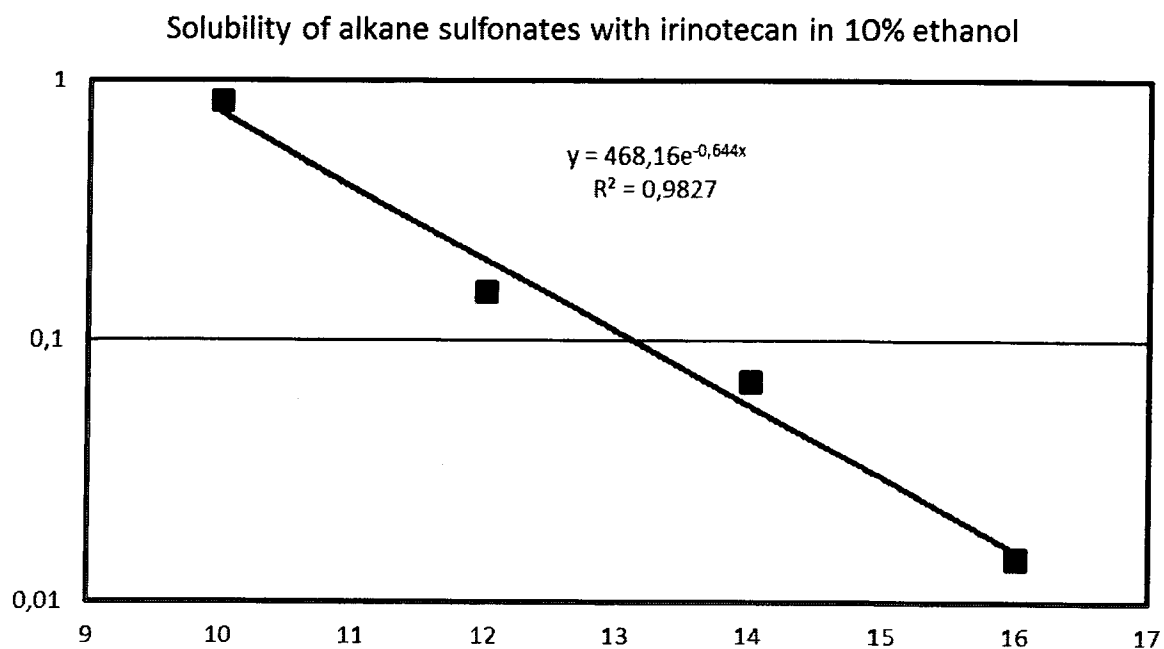
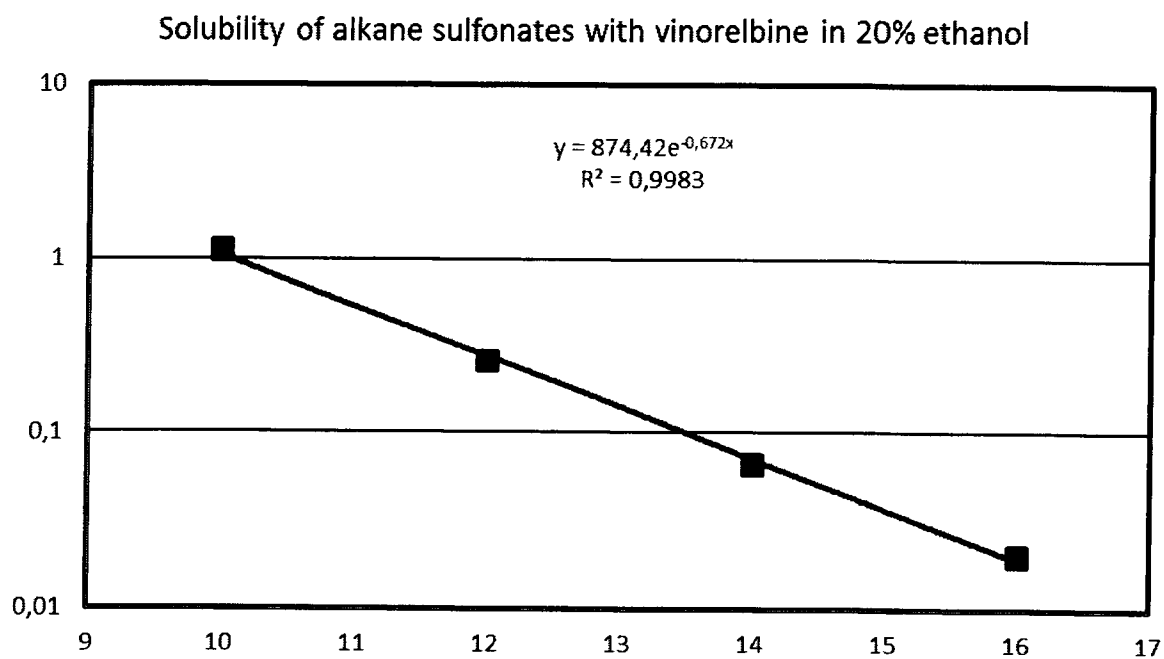
1/5

**Fig. 1****Fig. 2**

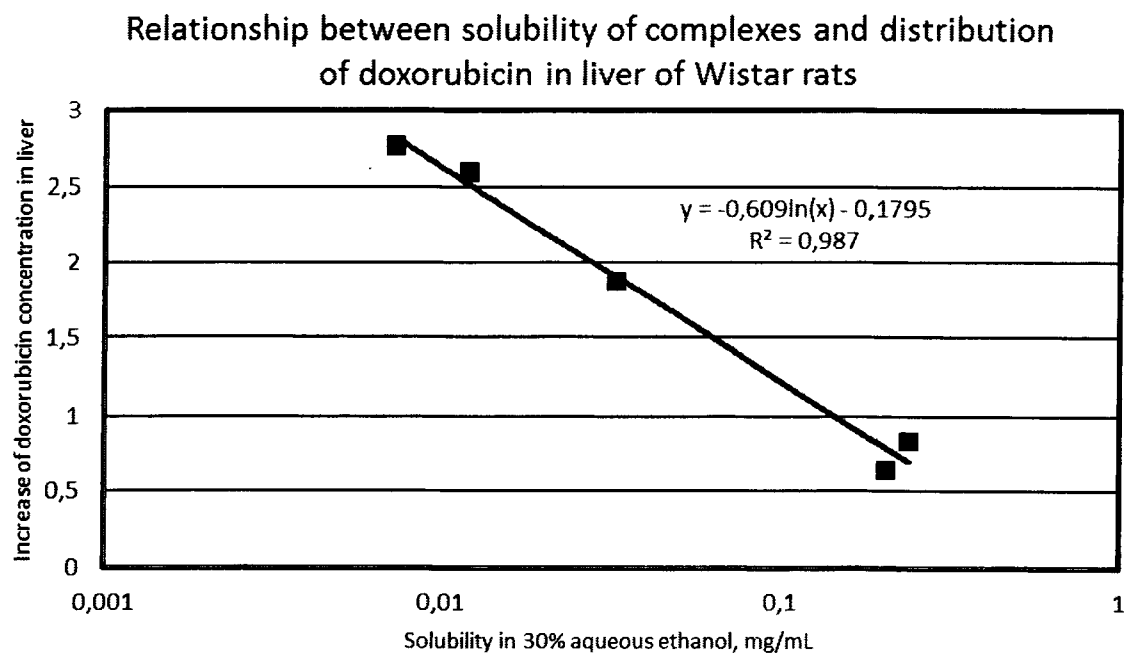
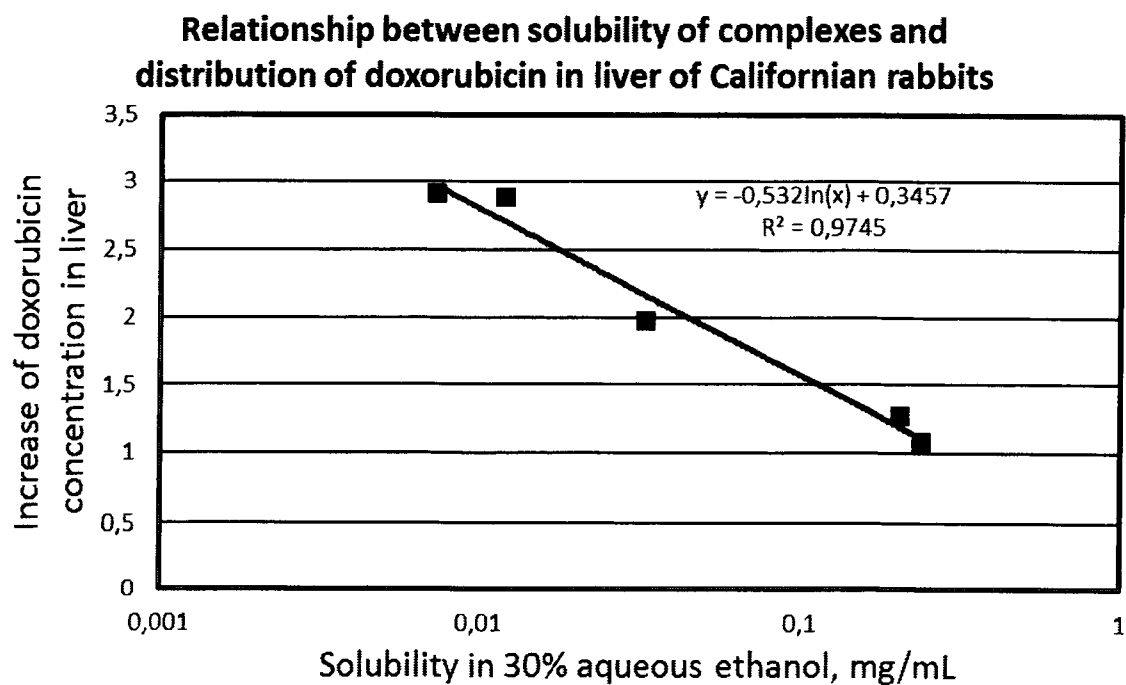
2/5

**Fig. 3****Fig. 4**

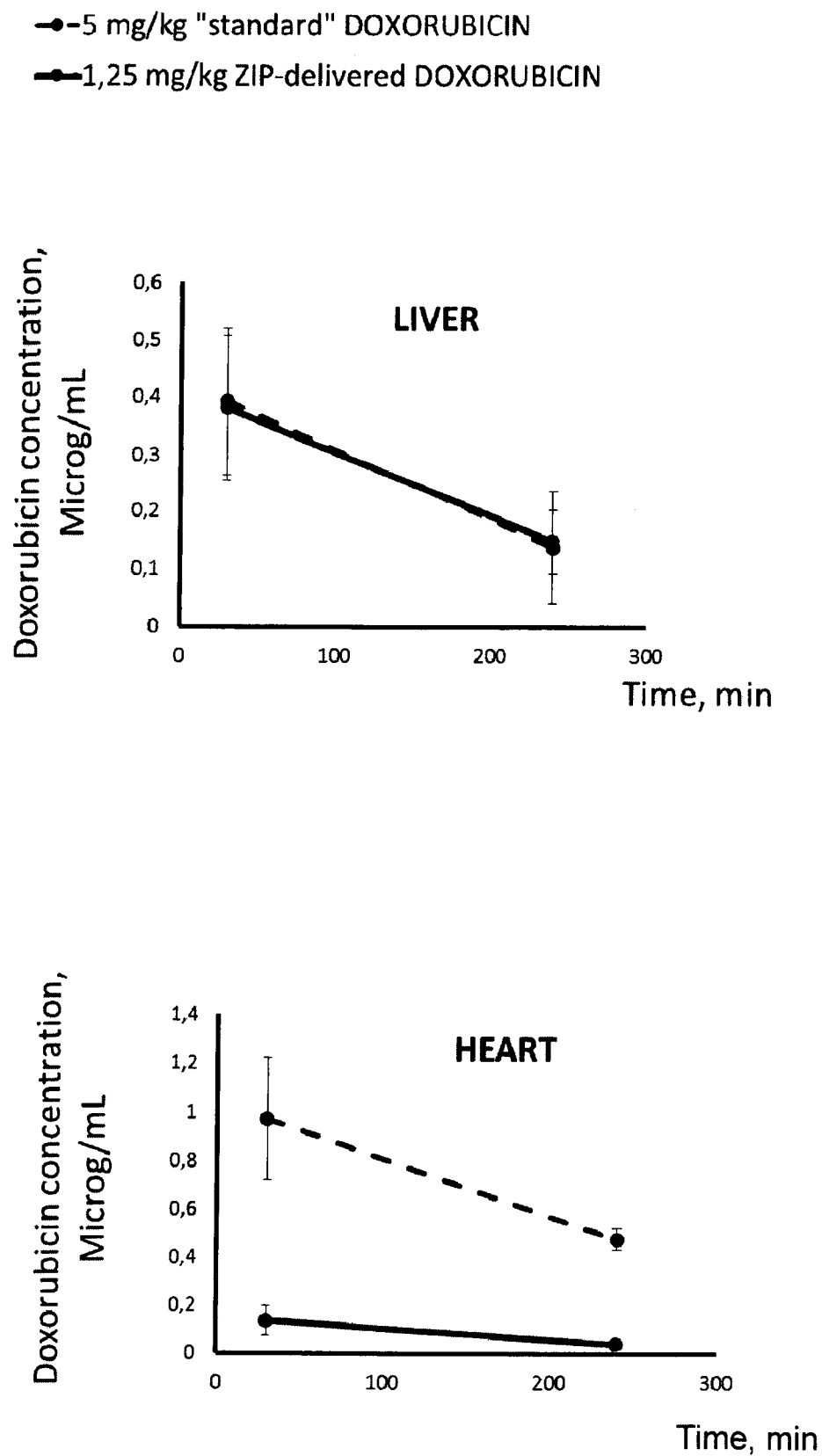
3/5

**Fig. 5****Fig. 6**

4/5

**Fig. 7****Fig. 8**

5/5

**Fig. 9**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2015/000055

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K, A61P

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

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, PAJ, WPI data, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GU, Xinyi "A novel approach to formulation of anticancer drugs in nanoparticles". Dissertation. The University of Michigan. 2008; pages 39-68, 164-165 --	1-35
X	WO 2009100222 A1 (QPS LLC ET AL), 13 August 2009 (2009-08-13); paragraphs [0007]-[0009], [0011], [0017], [0031]; claims 1, 15, 17, 19; examples 2-3, 11-13 --	1-35
X	WO 03099346 A2 (ANGIOTECH PHARM INC ET AL), 4 December 2003 (2003-12-04); page 43, line 21 - page 44, line 6 --	1-35

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

11-12-2015

Date of mailing of the international search report

11-12-2015

Name and mailing address of the ISA/SE

Patent- och registreringsverket
Box 5055
S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86

Authorized officer

Andreas Gustafsson

Telephone No. + 46 8 782 28 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2015/000055

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ENACHE, M. et al "Coupled spectral and electrochemical evaluation of the anticancer drug mitoxantrone-sodium dodecyl sulfate interaction". International Journal of Pharmaceutics. 2010, vol. 390, no.2, pages 100-106; abstract; Sections 1-2, 4 --	1-35
X	WO 9947543 A2 (UNIV TECHNOLOGY CORP ET AL), 23 September 1999 (1999-09-23); page 4, line 6 - line 12; page 8, line 30 - page 9, line 21; page 10, line 7; page 10, line 28 - page 11, line 18; page 11, line 30 - page 12, line 3; page 12, line 21 - page 13, line 1; page 16, line 31 - page 17, line 15 --	1-35
A	KR 20140095438 A (UTAH INHA DDS & ADVANCED THERAPEUTICS RES CT), 1 August 2014 (2014-08-01); (abstract) Retrieved from: WPI database; Original document: paragraphs [0013]-[0017] --	1-35
A	WO 2009078756 A1 (ARDENIA INVESTMENTS LTD ET AL), 25 June 2009 (2009-06-25); whole document --	1-35
A	GB 2415904 A (CHIRON CORP - (B) CHIRON CORP [US] ET AL), 11 January 2006 (2006-01-11); abstract; claims 1-43 --	1-35
A	US 20120269722 A1 (LEWIS ANDREW LENNARD ET AL), 25 October 2012 (2012-10-25); abstract; paragraph [0003]; claims 1-2, 4-7, 13, 21-24 -- -----	1-35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2015/000055

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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. ☒ Claims Nos.: **29-34**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 29-34 relate to a method for treatment of the human or animal body by therapy, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.
2. ☐ 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:
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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically 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 and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Continuation of: second sheet**International Patent Classification (IPC)****A61K 47/48** (2006.01)**A61K 9/14** (2006.01)**A61P 35/00** (2006.01)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE2015/000055

WO	2009100222 A1	13/08/2009	AU	2009212373 A2	17/02/2011
			CA	2714514 A1	13/08/2009
			CN	102131483 A	20/07/2011
			EP	2244679 A1	03/11/2010
			JP	2011511088 A	07/04/2011
			JP	5737949 B2	17/06/2015
			TW	200936167 A	01/09/2009
			TW	I400090 B	01/07/2013
			US	20100034801 A1	11/02/2010
			US	8586103 B2	19/11/2013

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE2015/000055

WO	03099346 A2	04/12/2003	AT	515277 T	15/07/2011
			AU	2003234670 A1	12/12/2003
			AU	2010201996 A1	10/06/2010
			BR	0311285 A	27/04/2007
			CA	2484761 A1	04/12/2003
			CN	1688349 A	26/10/2005
			CN	101134119 A	05/03/2008
			CN	100341589 C	10/10/2007
			DE	60328486 D1	03/09/2009
			DK	1509256 T3	23/11/2009
			EP	2075014 B9	01/02/2012
			ES	2369640 T3	02/12/2011
			ES	2330326 T3	09/12/2009
			HK	1082435 A1	11/04/2008
			IL	165120 A	31/05/2010
			JP	2010158545 A	22/07/2010
			JP	2005527302 A	15/09/2005
			KR	20100110378 A	12/10/2010
			MX	PA04011651 A	07/03/2005
			NZ	575452 A	26/03/2010
			NZ	536308 A	31/01/2009
			RU	2341296 C2	20/12/2008
			RU	2004137816 A	27/06/2005
			US	8372420 B2	12/02/2013
			US	20040043052 A1	04/03/2004
			US	8425927 B2	23/04/2013
			US	20130224276 A1	29/08/2013
			US	20110129513 A1	02/06/2011
			US	20100082003 A1	01/04/2010
			US	20080241217 A1	02/10/2008
			US	20080145514 A1	19/06/2008
			US	20080113000 A1	15/05/2008
			US	20080089952 A1	17/04/2008
			US	20070270447 A1	22/11/2007
			US	20060127438 A1	15/06/2006
			ZA	200409291 A	28/04/2010
WO	9947543 A2	23/09/1999	AU	3108299 A	11/10/1999
			CA	2324254 A1	23/09/1999
			EP	1073419 A2	07/02/2001
			JP	2002506876 A	05/03/2002
KR	20140095438 A	01/08/2014	WO	2014116043 A1	31/07/2014

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE2015/000055

WO	2009078756 A1	25/06/2009	AU	2008339100 A1	25/06/2009
			BR	PI0821741 A2	16/06/2015
			CA	2709267 A1	25/06/2009
			CN	101945670 A	12/01/2011
			EA	201070625 A1	30/12/2010
			EA	018636 B1	30/09/2013
			EP	2231192 A1	29/09/2010
			JP	2011507839 A	10/03/2011
			JP	5466173 B2	09/04/2014
			KR	20100103588 A	27/09/2010
			MX	2010006907 A	10/11/2010
			NZ	586853 A	29/06/2012
			US	20110123607 A1	26/05/2011
			US	8765173 B2	01/07/2014
			WO	2009078803 A1	25/06/2009
GB	2415904 A	11/01/2006	HK	1086757 A1	27/04/2007
US	20120269722 A1	25/10/2012	US	20130243695 A1	19/09/2013
			US	20090022804 A1	22/01/2009
			US	20060204583 A1	14/09/2006
			US	20040161466 A1	19/08/2004
			US	8455003 B2	04/06/2013
			US	8221793 B2	17/07/2012
			US	7442385 B2	28/10/2008