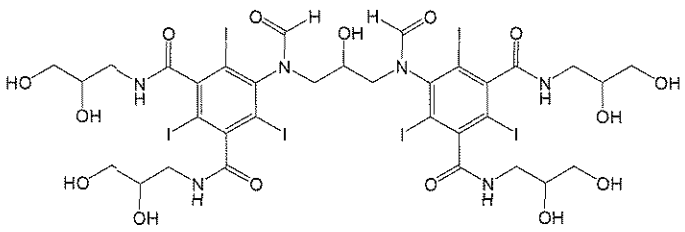
WO 2009/008734 of GE Healthcare AS discloses a new class of compounds and their use as X-ray contrast agents. The compounds are dimers containing two linked iodinated phenyl groups. The bridge linking the two iodinated phenyl groups is a straight C_3 to C_8 alkylene chain optionally substituted by one to six –OH or OCH_3 groups. A range of compounds are covered by the general formula (I) of the application and many specific compounds are suggested. Compound I, which is one specific dimeric X-ray contrast agent named Ioforminol, falling within the formula I, has been found by the applicant to have favourable properties:



Compound I: 5-[formyl-[3-[formyl-[3,5-bis(2,3-dihydroxypropylcarbamoyl)-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide.

There is a need for providing patient friendly X-ray contrast media at various concentrations *in situ*.

Brief summary ~~of the invention~~:

Disclosed herein are novel procedures, systems and excipient solutions for *in situ* provision of a contrast media at a user defined concentrations. An automated procedure according to embodiments of the current disclosure~~invention~~ provides increased user safety, flexibility and user friendliness.

~~In one aspect, i~~It is provided an aqueous, excipient solution, which solution comprises a sodium ion and a calcium ion, wherein said excipient solution is suitable for diluting a diagnostic composition comprising a contrast agent.

In one aspect, it is provided an aqueous, excipient solution comprising a sodium ion concentration of about 100 -140 mM and a calcium ion concentration of about 0.8 – 1.2 mM, wherein said excipient solution is suitable for diluting a diagnostic composition comprising a contrast agent.

In another aspect, it is provided an aqueous, excipient solution comprising a sodium ion and a calcium ion wherein the molar ratio between sodium ion concentration and calcium ion concentration is between about 80 and 175, and wherein said excipient solution is suitable for diluting a diagnostic composition comprising a contrast agent.

In another aspect, it is provided an aqueous, excipient solution consisting of Tris (Trometamol) at 10 mM, NaCa-EDTA at 0.27 mM, NaCl at 119 mM and $CaCl_2$ at1.03 mM, for diluting a diagnostic composition comprising a contrast agent.

In another aspect, it is provided a kit, comprising an aqueous, excipient solution according to an aspect of the disclosure~~invention~~ in a first container; a diagnostic composition comprising a contrast agent in a second container; and a user instruction manual.

In another ~~third~~ aspect, it is provided a method for dilution of a diagnostic composition comprising a contrast agent, which method comprises

i) determining a desired dosage amount and dosage concentration for a patient;

ii) calculating a required amount of the diagnostic composition and a required amount of the aqueous, excipient solution according to an aspect of the ~~invention~~disclosure, based on the desired dosage amount and dosage concentration;

iii) delivering the required amount of the diagnostic composition to a mixing chamber; and

iv) delivering the required amount of the excipient solution to the mixing chamber.

In other aspects of the disclosure~~invention~~, it is provided a method for producing an aqueous, excipient solution according to an aspect of the disclosure~~invention~~; a method of diagnosis, as well as a method of *in vivo* imaging detection.

In another aspect, it is provided a diagnostic composition prepared as disclosed above, wherein said composition is to be administered to a human or animal body, the body is examined with a diagnostic device and data are compiled from the examination.

In another aspect, it is provided a method of in vivo imaging detection comprising the following steps:

i) administering a detectable quantity of the diagnostic composition prepared as disclosed above;

ii) allowing the administered composition to distribute;

iii) detecting signals emitted by the contract agent of the distributed composition,

iv) generating an image representative of the location and/or amount of said signal.

In another aspect, it is provided a method for producing an aqueous, excipient solution as disclosed above, comprising

i) predicting the molar amount of sodium ion and calcium ion suitable for the excipient using a chemiometrical model, based on the salt composition of the diagnostic formulation;

making the aqueous, excipient solution according to the predicted molar amount of sodium ion and calcium ion.

Detailed description of the invention:

In diagnostic imaging procedures where contrast agents are administered to a patient, it is desirable that the amount of contrast agent used may be adjusted based on the individual patient. Thus, the contrast agent concentration and injection volume best suited for the individual can be achieved. Factors that affect the right concentration and injection volume for any patient may depend on, for example, the type of examination, age, weight or physical health of the patient.

Aspects of the invention provide novel procedures, systems and excipient solutions for *in situ* generation of a contrast media at a user defined concentrations. Thus, a contrast agent may be manufactured at one higher concentration, and the user (hospital/doctor) may dilute to a desired concentration just prior to use. However, the isotonicity of the solution is maintained throughout the concentration range.

Isotonicity – A solution is isotonic with human blood plasma if no net water migration takes place over the blood cell membranes after mixing the solution with human blood. This means

Claim 29: A ~~method of diagnosis comprising administering a~~ diagnostic composition prepared according to claim 26, wherein said composition is to be administered to a human or animal body, the body is examined~~examining the body~~ with a diagnostic device and data are compiled~~compiling data~~ from the examination.

Claim 30: A method of in vivo imaging detection comprising the following steps;

i) administering a detectable quantity of the diagnostic composition prepared according to claim 26;

ii) allowing the administered composition to distribute;

iii) detecting signals emitted by the contract agent of the distributed composition,

iv) generating an image representative of the location and/or amount of said signal.

Claim 31: A method as claimed in claim 30 wherein the method is a method of coronary arteriography.

Claim 32: A method for producing an aqueous, excipient solution of claim 1, comprising

i) predicting the molar amount of sodium ion and calcium ion suitable for the excipient using a chemiometrical model, based on the salt composition of the diagnostic formulation;

ii) making the aqueous, excipient solution according to the predicted molar amount of sodium ion and calcium ion.