chromatography and crystallization, and wherein monomeric impurities are removed.

Summary

A process has been sought wherein the crude dimeric contrast agent is purified providing a high yield, wherein crystallisation of crystals is avoided, which is easy to scale up and which provides a purified agent in short time. A process has now been identified using membrane technology to remove monomeric compound impurities and salts from the crude product of dimeric X-ray contrast agents.

Accordingly, ~~in a first aspect~~ the disclosure provides a process for the purification of a crude dimeric X-ray contrast agent product comprising the step of

i) passing a solution of the crude product across a membrane (M1) such that monomeric compound impurities and salts cross the membrane (permeate, P1) and the dimeric X-ray contrast agent passes over the membrane (retentate, R1)

providing a purified dimeric X-ray contrast agent.

In a first aspect, there is provided a process for the purification of a crude dimeric X-ray contrast agent product comprising the steps of

i) passing a solution of the crude product across a membrane M1 such that monomeric compound impurities and salts cross the membrane to form a permeate P1 and the dimeric X-ray contrast agent passes over the membrane to form a retentate R1,

providing a purified dimeric X-ray contrast agent.

~~In a second aspect, there is provided a composition comprising a dimeric contrast agent purified according to the process as disclosed above, together with at least one physiologically tolerable carrier or excipient.~~

Brief Description of the drawings

Figure 1 shows the process of the first aspect wherein a crude product is purified by separating purified product from monomeric impurities and salts.

Detailed Description of the Preferred Embodiments

Surprisingly it has been found possible to provide an industrially viable process, useful also in large scale, wherein both monomeric impurities and salts are separated from the dimeric contrast agent by using membrane separation.

The crude dimeric X-ray contrast agent product to be purified by the process of the invention is the product obtained from the syntheses, in a raw non-purified state. This crude product is preferably in the form of a solution, wherein the solvent comprises the solvent used in the last step of the synthetic route. The solvent is e.g. water or an alcohol or mixtures thereof, and this may comprise water, 2-

Claims

1. A process for the purification of a crude dimeric X-ray contrast agent product comprising the steps of

   i) passing a solution of the crude product across a membrane (M1) such that monomeric compound impurities and salts cross the membrane to form a (permeate, P1) and the dimeric X-ray contrast agent passes over the membrane to form a (retentate, R1),

providing a purified dimeric X-ray contrast agent.

2. A process as claimed in claim 1 wherein the dimeric X-ray contrast agent has a molecular weight of 1400-1700 Da.

3. A process as claimed in claim 1 wherein the dimeric X-ray contrast agent is loforminol or Iodixanol.

4. A process as claimed in any of the claims 1 to 3 wherein the monomeric compound impurities have a molecular weight of less than 900 Da.

5. A process as claimed in any of the claims 1 to 4 wherein the retentate (R1) of the step (i) is retained and collected.

6. A process as claimed in any of the claims 1 to 5 wherein the purified dimeric X-ray contrast agent obtained holds a purity of at least 98 %.

7. A process as claimed in any of the claims 1 to 6 wherein a membrane (M1) is used having a cut-off size between 950 and 1200 Da.

8. A process as claimed in any of the claims 1 to 7 comprising a second step

   ii) wherein the permeate from step i) (P1) is passed across another membrane (M2) such that salts cross this membrane to form a (permeate, P2) and the monomeric compound impurities passes over the membrane to form a (retentate, R2), and wherein the retentate R2 is retained.

9. A process as claimed in any of the claims 1 to 8 wherein the permeate ~~(~~P1~~)~~ from step i), or the retentate ~~(~~R2~~)~~ from step (ii), is subject to another round of purification by repeating step (i) of the process to recover dimeric X-ray contrast agent lost in the first round.

10. A process as claimed in claim 8 wherein the retentate R2 is transferred to the crude product and mixed with this, or is combined with a feed stream from the crude product, before repeating step i).

~~11. A composition comprising a dimeric contrast agent purified according to the process as claimed in any of the claims 1 to 10, together with at least one physiologically tolerable carrier or excipient.~~