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(57) Abstract

A process aimed at concentrating and purifying raw aqueous solutions of water-soluble non-ionic organic compounds, preferably those which are useful as contrast enhancing agents in diagnostic procedures, such as for example X-ray, NMR and ultrasound diagnosis, through the use of techniques of tangential filtration on membranes is disclosed. This process also allows the recovery of valuable reactants in excess and of reaction solvents, if any, and it is particularly useful for purifying expensive non-ionic iodinated compounds, which now have been widely used in X-ray imaging.

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PROCESS OF CONCENTRATION AND PURIFICATION OF ORGANIC COMPOUNDS

This invention relates to a process aimed at concentrating and purifying raw aqueous solutions of water-soluble non-ionic organic compounds, preferably those which are useful as contrast enhancing agents in diagnostic procedures, such as for example X-ray, NMR and ultrasound diagnosis, through the use of techniques of tangential filtration on membranes. This process also allows the recovery of valuable reactants in excess and of reaction solvents, if any. It is particularly useful for purifying expensive non-ionic iodinated compounds, which now have been widely used in X-ray imaging.

The introduction in X-ray diagnosis of contrast media containing non-ionic iodinated compounds as opacifying agents represented a remarkable progress in the state of the technique, so far that, these media will eventually substitute the traditional iodinated ionic products (see: Grainger and Dawson, Clinical Radiology, 1990, 42, 1-5).

However the synthetic processes and, particularly, the final purification of these products are more complex and expensive than those previously used to obtain the ionic contrast media. In fact, neutral iodinated opacifying agents differ from the ionic ones because they cannot be isolated and purified by precipitation from water due to their high solubility in this solvent. Hence, the following problems must still be conveniently solved: the removal of ionic

species, usually inorganic salts, situated in the final reaction mixture, the recovery of valuable reagents in excess and of the water-soluble reaction media. A preferred technique to be performed (see patents: DE 1909439, GB 1472050, EP 26281) is the one based on the submission of the raw solutions of the contrast media to a complex series of operations such as:

- preliminary removal of the solvent, usually dimethylacetamide (DMAC) or dimethylformamide (DMF), by evaporation,
- dilution by water of the residue,
- extraction of the residual reaction medium, preferably with a chlorinated solvent,
- elution of the aqueous phase on a system of columns of cationic and anionic ion-exchange resins,
- concentration of the eluate by evaporation,
- crystallization of the crude residue from hydroalcoholic mixtures in order to remove the last impurities of neutral type.

The drawbacks related to this type of process are clear. For instance, large purification plants for ion-exchange resins are needed and their running is extremely complex and expensive. In addition, a large quantity of thermal energy is required for the concentration of the considerable volumes of water to be used. It is also foreseen the use, the recovery and the removal of polluting and toxic organic solvents such as the chlorinated ones. Last but not least, the concentration of extremely diluted solutions causes the corresponding concentration of impurity traces and the submission of the final product to a long-lasting

thermal treatment.

Another process which can be carried out (see patents: EP 83964, WO 8908101) implies the purification of raw solutions of non-ionic contrast media through preparative liquid chromatography. This technique is extremely complex and expensive too, and in addition it is unsuitable for a generalized industrial application.

Up to now, nobody has used ultra- or nanofiltration techniques in order to purify the above mentioned compounds. The process of this invention performs, for the first time, this technique on highly concentrated solutions of water-soluble neutral iodinated contrast agents, by obtaining extremely favourable and absolutely unexpected results if compared to the common knowledge.

It is known that organic impurities with low relative mass and/or inorganic salts can be removed from aqueous diluted solutions through tangential filtration processes by using ultrafiltration (U.F.) or nanofiltration (N.F.) membranes (Bungay P.M., Lansdale H.K., De Pinho M.N., "Synthetic Membranes: Science, Engineering and Applications", D. Reidel, C 181, 1986 and Applegate L.E., "Membrane Separation Process", Chem. Eng., pages 63-89, 11.06.1984). As these membranes are partially permeable to substances which have relative masses below a given value, part of impurities with lower relative mass permeates together with water, allowing, beyond the concentration of the desired product, a partial purification too. Higher levels of purification can be achieved by performing, subsequently to the concentration stage, a dilution

stage with water of the non-permeated solution (retentate). This stage, named diafiltration, involves the make-up/dilution of the retentate with de-ionized water. The diluted retentate is filtered again through the filtrating membrane in order to allow the permeation of residual impurities.

The main drawback of this technique is that, in order to obtain a high level of purity, large amounts of make-up water have to be added to the retentate, i.e. high dilutions are required. That involves considerable equipment size, as a large membrane surface is needed. In addition, if the recovery of some permeated species is needed, and this is the case, the permeate has to be thermally concentrated with heavy energy consumptions and thermal stress.

The use of large solvent volumes brings about also a consequent loss of valuable product. The rejections of the membranes, available on the market, to products with relative mass lower than 2000 (such as non-ionic iodinated contrast media) are unsufficiently high, so that the final yield of the purification process is lower than the one obtained through known methods. This flaw is particularly serious because the cost of the product to be purified is very high and yield reductions cannot be accepted.

Another limiting factor of the process is given by the unfeasibility of the separation, if DP, which is the osmotic pressure difference across the membrane (DP corresponds to the difference of osmotic pressure between the retentate and the permeate) exceeds the maximum working pressure of the membrane module, which

usually ranges between 2.5 and 4 MPa. On the other hand, it is known (from Bungay P.M., "Synthetic Membranes", cited ref., pages 110-112) that useful permeate flow rates can be obtained only when the working pressure overcomes DP by 1 or 2 MPa. For this reason, solutions recording a DP transmembrane pressure higher than 2.5 MPa are not conveniently purified by nano- or ultrafiltration. In this respect, Table 1 shows the foreseeable situation, considering the cited literature, for a raw solution containing for example, the (L)-5-(2-hydroxy-propionyl)amino-2,4,6-triiodo-bis-(1,3-dih ydroxy-isopropyl)isophtalamide [IOPAMIDOL, Bracco's Patent GB 1472050, Example 1, compound A].

TABLE 1: Foreseeable osmotic and transmembrane pressures for aqueous solutions containing IOPAMIDOL, sodium chloride (NaCl), 2-amino-1,3-propandiol (APD), dimethylacetamide (DMAC), operating at 20°C.

Components	Foreseen rejections a)	Solution A concentrations (Mol/l)	Solution B concentrations (Mol/l)
Iopamidol	0.99	0.70	0.20
NaCl	0.20	2.10	0.60
APD	0.40	1.68	0.48
DMAC	0.30	4.58	1.31
Total osmotic pressure (MPa)	b)	26.8	7.6
ΔΠ transmembrane pressure (MPa)	c)	8.6	2.4

a) rejection values for each component have been derived from the data supplied by manufacturer of the membrane type which was used (NANOFILM^{TM} NF40, FilmTec Corporation/Dow Chemical), or experimentally from aqueous solutions of the pure components.

b) the osmotic pressure of the solution to be

purified has been calculated according to Van't Hoff's equation (Bungay P.M., "Synthetic Membranes", cited ref., pages 109-153).

c) the foreseeable transmembrane pressure has been calculated by difference between the osmotic pressure of the retentate and of the permeate.

When using a solution of Iopamidol 0.7M (Solution A), a very high osmotic pressure and a definitely unfavourable DP transmembrane pressure are foreseen, while the maximum concentration of the same compound, useful in principle for an acceptable purification, is foreseen at 0.2 Mol/l (Solution B). This concentration limit is too low and will eventually have a negative impact on volumes of liquid to be used and consequently on the equipment sizes and the economic running of the same.

One would have expected that ultrafiltration or nanofiltration applied to non-ionic iodinated contrast media solutions would be either impossible, due to extremely high pressure, or uncompetitive in comparison with the known methods when worked with diluted solutions.

On the contrary, the process of this invention recorded excellent and fully unexpected degrees of purification and recovery of the desired products, thanks to the realization of an innovative filtrating unit which can be run in a non-traditional way, that's to say, by using highly concentrated solutions of the contrast agent and limited water volumes for the make-up of the retentate while keeping the system working pressure within the usual values for the operation. The

filtration apparatus has been built by connecting two filtrating groups in series, as shown in the enclosed Figure 1. The second group is analogous to the first one, but has a smaller size and has been designed to recover the small amounts of iodinated compound which remain in the permeate from the first stage, without losses of final product. The ratio between the membrane surfaces of the two filtrating units (unit one /unit two) can range from 1.5 to 6, preferably from 2.5 to 4. Suitable membranes can be sorted out among the commercial ones featuring a rejection to sodium chloride (measured at concentrations of 2000 ppm, pressure of 1.6 MPa, temperature of 25°C) not higher than 85%, preferably lower than 70%, and rejection to raffinose higher than 85%, preferably higher than95%. By way of example, thin-layer membranes can be cited and particularly: TFM™ G-5 (Desal), NANOFILM™ NF40 (FilmTec/Dow Chemical), ROMEMBRA™ SU-200S, SU-220S, SU-600 (Toray), NTR 7410, NTR 4550 (Nitto), MOLSEP™ DRA-4020 (Daicel), OSMOTICS OSMO 411TM012, 411TMX02, 411TBQ01, or asymmetrical polysulphone membranes i.e., PSRO (Millipore). Of course, if the skilled technician uses other types of membranes with similar features, the results are immediate, so, the above mentioned list is absolutely non-limiting for this invention. Tangential filtrating units can be tubular or preferably equipped with flat or spiral wound membranes.

Working temperatures range from 10°C to 90°C according to the membrane used, preferably from 25°C to 45°C.

Working pressures range from 1.5 to 5.5 MPa, preferably from 2 to 3.5 MPa.

The filtrating unit is connected to an evaporation-condenser group to recover the solvents, if any, and to concentrate, before their recovery, salts, valuable reactants in excess and reaction by-products, which are in the permeate. In addition, it can be integrated in the latter phase, with a guard of small-volume ion-exchange resins, providing the full elimination of last traces of ionic species, if still present. The running of these columns does not involve substantial energy consumption or considerable extra-costs, due to their limited size.

This filtrating unit can be surprisingly run under conditions of extremely high concentrations of the contrast agent. In fact, aqueous solutions to be treated usually contain: non-ionic water-soluble iodinated compounds at concentrations ranging between 15 and 60% in weight (w/w), preferably between 20 and 50%, inorganic salts, such as chlorides, bromides, iodides, sulphites of alkaline or alkaline-earth metals or of ammonium or alkylammonium with a relative mass lower than about 150, organic compounds, generally aminoalcohols with a relative mass lower than about 200, water-soluble solvents, such as for instance di-methylacetamide, dimethylformamide, ethanol, dimethylaminoethanol in concentrations not higher than 25% (w/w), preferably not higher than 15%.

The raw solution containing contrast agent, inorganic salts, organic compounds at a relative mass lower than about 200 and solvents (DMAC, DMF and so on)

is pumped on the membranes of the first filtrating group. Water, salts, organic compounds at relative mass lower than 200 and solvents, if any, permeate through the membranes and the retentate, partially concentrated and purified as to contrast agent, is recycled at the first stage after dilution with a little amount of de-ionized make-up water. The permeate, which still contains small amounts of the iodinated compound, proceeds towards the second filtrating group. From here, the new retentate is streamed back to the first filtrating group in order to fully purify the recovered contrast medium, while the permeate of the second filtrating group consists of an aqueous solution of salts, organic compounds to be recovered, solvents, if any, and is contrast-agent free.

This solution is concentrated by evaporation and submitted to the recovery of valuable species in it.

The make-up water, used during the diafiltration stage, does not usually exceed 12 kg per mole of the iodinated compound, preferably is less or equal to 8 kg/mol.

The degree of purification obtained by this process is such that the total amount of residual impurities in the final recycled retentate does not exceed 10% of the initial one, preferably 5%. The filtration parameters, in particular the solution and dilution water feed rates, as well as the retentates flow rates and, of course, the operative pressures, are to be experimentally chosen in correlation with the filtration membranes size and porosity in order to obtain the above mentioned purity degrees.

The final recycled retentate can be percolated, if necessary, on the small guard of columns of ion-exchange resins to remove any traces of inorganic salts before being submitted to crystallization of the final product.

According to the process of this invention the purification levels obtained as a function of the amount of make-up water fed during the diafiltration step, are surprisingly better than the foreseeable ones, as reported in Table 2.

TABLE 2 Percentage residue levels of impurities in an aqueous solution containing Iopamidol, NaCl, APD, DMAC, referred to the amount of the make-up water added per mole of Iopamidol

Make-up water (l) per mole of Iopamidol	Percentage residue impurities a)					
	NaCl b) (rejection 0.2)		ADP b) (rejection 0.4)		DMAC b) (rejection 0.3)	
	c)	d)	c)	d)	c)	d)
0	100	100	100	100	100	100
6	38.3	2.1	48.7	9.0	43.2	3.5
12	14.7	0.1	23.7	0.6	18.6	0.3

a) calculated by considering equal to 100 the amounts of initial impurity.

b) rejection values for each component have been derived from the data supplied by the membrane manufacturer of NANOFILM^{TM} NF40, or experimentally by aqueous solutions of the pure component.

c) foreseeable values according to the equation (Aptel P., Clifton M., "Synthetic Membranes", cited ref., pages 249-305):

$$C_A = C°_A \cdot \exp\left[-Vw/V°(1-R_A)\right]$$

where:

Vw = make-up water volume

V° = retentate volume

C_A = concentration of component A

$C°_A$ = initial concentration of component A

R_A = membrane rejection to component A.

d) experimental values.

The process of this invention allows, for the first time, the concentration and the purification of raw solutions of X-ray water-soluble non-ionic opacifying agents in a simple, economic and environmentally acceptable way.

In particular, it allows higher recovery yields of the contrast compound and the other valuable components, the elimination of large amounts of basic and acid reactants needed for regenerating the ion-exchange resins, beyond their total removal, and a remarkable reduction of the steam necessary for the concentration of the eluates. Finally, it avoids extracting the reaction medium with organic toxic solvents such as chlorinated solvents. All this implies considerable operating advantages from the economical and environmental point of view.

Table 3 shows the advantages that the process of this invention brings to the state of the art for the purification of 1000 kg of Iopamidol.

TABLE 3 Total consumption of the process of desalination of 1000 kg of Iopamidol through tangential filtration and recovery of valuable by-products. Comparison with the state of the art.

	Process according to the invention	Process according to the state of the art
	kg	kg
Steam	9,500	16,500
De-ionized water	10,000	83,000
HCl 32%	720	4,000
NaOH 30%	664	4,400
Water cooling	220,000	360,000

The process of this invention can be also applied to solutions of any non-ionic water-soluble contrast agents, either for use in X-ray or for use in NMR diagnosis.

In particular it can be preferably applied to the solutions of any non-ionic water-soluble iodinated compounds, even if they are monomers, dimers o trimers.

The following experimental examples describe the advantages of this invention without limiting it. The further possible changes of the indicated parameters are absolutely clear to the skilled technician.

EXAMPLE 1

Purification of (L)-5-(2-hydroxy-propionyl)amino-2,4,6-triiodo-bis-(1,3-dihydroxy-isopropyl)-isophtalamide (Iopamidol: patent GB 1472050, Example 1).

70 kg of an aqueous solution containing 15.5 kg of Iopamidol (22%, w/w), 2.3 kg of sodium chloride, 1.6 kg of sodium acetate, 4.4 kg of 2-amino-1,3-propandiol and 12 kg of dimethylacetamide are fed in the tank of the

two-stage filtrating plant, which is equipped with a total of 4m of a TFM™ DESAL-G-5 membrane (one 2.5" x 40" spiral module for the first stage, and one 2.5" x 21" spiral module for the 2nd stage). In a first step (1.5 h), the solution is concentrated up to about 37 kg, by operating at 30°C at a working pressure of 3 MPa and at a recirculation rate of 750 l/h for both stages. Then, the diafiltration stage begins by continually reintegrating the water through a dosing pump. The process is stopped after 6.5 h when the conductivity falls under 1000 mS/cm and the final retentate, containing 99.6% of the initial Iopamidol (HPLC determination), is percolated on a couple of columns of ion-exchange resins and subsequently crystallized. 14.6 kg of pure product, complying with the requested analytical features (purification yield: 94.2%), are obtained.

The permeate, weighting approximately 120 kg, contains less than 0.4% of the initial Iopamidol and more than 96% of the other initial species in the mixture. The permeate gets through the recovery stage of valuable components. The recovery is quite simple and cheap thanks to the relatively small amount of diluting water.

EXAMPLE 2

Purification of 5-(N-methyl-hydroxyacetyl)amino-2,4,6-triiodo-bis-(2,3-dihydroxy-propyl)-isophtalamide (Iomeprol: EP 26281, Example 11).

50 kg of an aqueous solution containing 14.2 kg of Iomeprol (28%, w/w), 1.9 kg of sodium chloride, 1.5 kg

of sodium acetate, 0.9 kg of 1-amino-2,3-propandiol and 15 kg of dimethylaminoethanol are fed in the tank of the filtrating unit equipped with 4 m of NANOFILM™ NF40 membrane in spiral wound modules, as described in Example 1. The purification is carried out in the same way as in Example 1. 13.2 kg of pure product are obtained (overall purification yield: 93%).

EXAMPLE 3

Purification of 1,3-bis-[3-(L-2-hydroxy-propionyl)amino-5-(1,3-dihydroxy-is opropyl)aminocarbonyl-2,4,6-triiodo-benzoyl-amino]-2-hydrox ypropane (Italian Patent Application n° 22088 A/90, Example 1).

40 kg of an aqueous solution containing 14.8 kg of the above mentioned product (37% w/w), 1.1. kg of sodium chloride, 2.4 kg of sodium acetate and 0.5 kg of 1,3-diamino-2-hydroxypropane are purified with the procedure described in Example 1. 14.4 kg of pure product are obtained (purification yield: 97.3%).

TABLE 4 Average percentage composition of fluids described in Figure 1.

Components	Fluids (% composition in weight)						
	a)	d)	g)	h)	i)	l)	m)
Contrast agent	25	traces	50	50	traces	-	-
Inorganic salts	5	4	traces	-	25	-	-
Exceeding reactives	7	4	1	traces	50	-	-
Organic solvent	13	7	-	-	-	50	1
H_2O	50	85	49	50	25	50	99

CLAIMS

1. A method for the concentration and purification of non-ionic organic compounds from their aqueous solutions, wherein their concentration ranges from 15 to 60% by weight and which contain, as dissolved impurities, mineral salts and/or water-soluble residual unconsumed organic reactants and/or water-soluble organic solvents, this method involving separating said impurities by continuously feeding said solutions into the first stage of a two-stage, cascade connected, tangential filtration apparatus, using permeable filtration membranes, in which the filtrate/permeate from the first stage is passed to a second stage for further filtration, the retentate from this second stage, together with a proportion of water for dilution, is continuously recycled to the retentate of the first stage, characterized in that the proportion of said diluting water does not exceed 12 kg per mole of the neutral organic compound being subject to purification and that the filtration parameters, i.e. the solution and dilution water feed rates, as well as the operative pressures and the retentates flow rates, are chosen in correlation with the filtration membranes size and porosity grade so that the degree of purification of said organic compound present in the final recycled retentate from the first stage is such that the total amount of residual impurities therein does not exceed 10% of the initial one.

2. A process, according to claim 1, characterized in that the filtration apparatus has a filtrating unit in

which the second filtration stage is smaller than the first one and the ratio of the membrane surfaces of the first and the second unit ranges from 1.5 to 6, preferably from 2.5 to 4.

3. A process, according to claim 1, wherein the filtrating membranes are characterized by sodium chloride rejections lower than 85%, preferably lower than 70% and by raffinose rejections higher than 85%, preferably higher than 95%.

4. A process, according to claim 1, wherein the filtrating membranes are chosen among the following ones:
TFM™ G-5 (Desal),
NANOFILM™ (FilmTec/Dow Chemical),
ROMEMBRA™ SU-200S or SU-2205 or SU-600 (Toray),
NTR 7410 or NTR 4550 (Nitto),
MOLSEP™ DRA-4020 (Daicel),
OSMOTIC™ OSMO411TM01, or 411TMX02 or 411TBR01,
PSRO (Millipore).

5. A process, according to claim 1, wherein the working temperature of the filtrating units ranges from 10° to 90°C, preferably from 25° to 45°C.

6. A process, according to claim 1, wherein the working pressures of the filtrating units range from 1.5 to 5.5 MPa, preferably from 2 to 3.5 MPa.

7. A process, according to claim 1, wherein the filtration apparatus is equipped with an evaporation-condenser unit to recover volatile components and is also optionally integrated with a guard of anionic and cationic ion-exchange resins connected in series in order to avoid any ionic impurity traces in the

final recycled retentate from the first filtrating unit.

8. A process, according to any previous claims, wherein the water-soluble non-ionic organic compound concentration ranges from 15 to 60% in weight, preferably from 20 to 50%, the amount of make-up water, used for the diafiltration step, is lower than 12 kg of water per mole of organic compound, preferably lower than 8 kg per mole, and the total amount of the impurities in the final recycled retentate from the first filtrating unit is less than 10% of the initial one, preferably less than 5%.

9. A process according to claims 1 to 8, wherein the water-soluble non-ionic organic compounds are usually employed as contrast enhancing agents in diagnostic procedures, preferably in X-ray, NMR and/or ultrasound diagnostics.

10. A process according to claim 9, wherein said organic compounds are water-soluble non-ionic iodinated compounds.

11. A process, according to claim 10, wherein said iodinated organic compounds are opacifying X-ray agents, which are preferably monomeric or dimeric. The impurities in the reaction mixture usually are inorganic salts such as chlorides, bromides, iodides or sulphites of alkaline or alkaline-earth metals or of ammonium or alkylammonium ions with relative mass lower than 150, organic reactants in excess such as aminoalcohols with relative mass lower than 200 and water-soluble organic solvents such as dimethylacetamide, dimethylformamide, dimethylaminoethanol, ethanol.

12. A process, according to claim 11, wherein the X-ray opacifying agent is the compound (L)-5-(2-hydroxy-propionyl)amino-2,4,6-triiodo-bis-(1,3-dihydroxy-iso-propyl)isophtalamide.

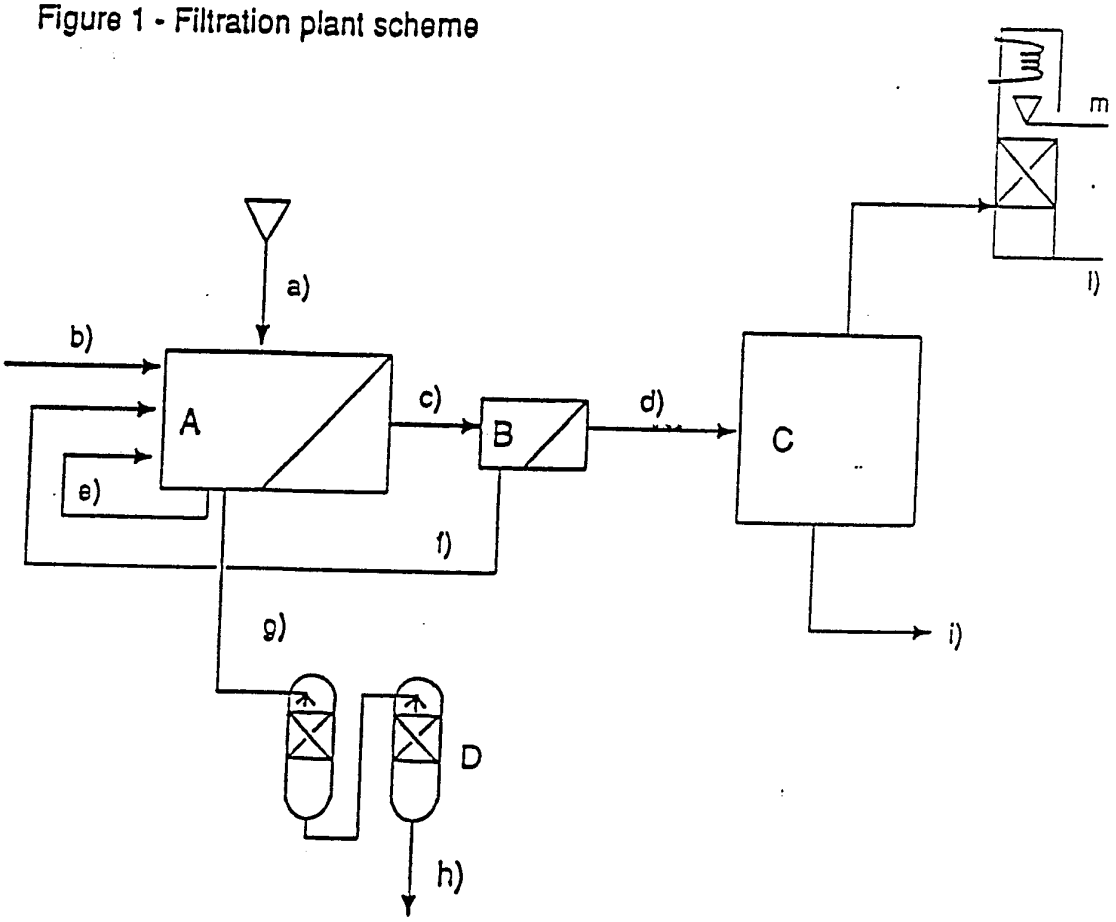
13. A process, according to claim 11, wherein the X-ray opacifying agent is the compound 5-(N-methyl-hydroxyacetyl)amino-2,4,6-triiodo-bis-(2,3-dihydroxy-propyl)-isophtalamide.

14. A process, according to claim 11, wherein the X-ray opacifying agent is the compound 1,3-bis-[3-(L-2-hydroxy-propionyl)amino-5-(1,3-dihydrox y-isopropyl)aminocarbonyl-2,4,6-triiodo-benzoyl-amino]-2-hydroxypropane.

15. A tangential filtration plant to performing the process of claim 1, characterized in that it substantially comprises a two filtrating units, cascade connected, in which the ratio between the membrane surfaces of unit one and unit two ranges from 1.5 to 6, preferably from 2.5 to 4 and which also comprises an evaporation-condenser unit and which optionally comprise a guard of anionic and cationic ion-exchange resins.

Sheet of drawing no. 1

Figure 1 - Filtration plant scheme



A = Filtrating units 1st stage
B = Filtrating unit: 2nd stage
C = Evaporating unit
D = Cationic and anionic resin column
a) = Raw solution of iodinated contrast medium
b) = Make-up water
c) = First permeate (to the second stage)
d) = Final permeate (to the evaporator)
e) = First stage/unit retentate
f) = Second stage/unit retentate
g) = Final retentate (containing the purified contrast medium)
h) = Eluate (to the recovery of the contrast medium)
i) = Residue (to the recovery of valuable compounds)
l) = Reaction solvent (to the recovery)
m) = ~~Steam~~ Water

INTERNATIONAL SEARCH REPORT

PCT/EP 92/00341

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 B01D61/02

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	B01D ; C02F ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US,B,524 806 (BASF WYANDOTTE CORPORATION) 2 March 1976 see abstract see column 1, line 9 - line 18 see column 2, line 40 - line 62 see column 3, line 24 - column 4, line 7 see column 5, line 43 - column 6, line 42 see column 7, line 41 - line 59 see column 9, line 51 - column 10, line 63 see figure 2 ---	1,5,6,15
A	US,A,3 836 457 (WESTINGHOUSE ELECTRIC CORPORATION) 17 September 1974 see the whole document ---	1-3,6,8, 15

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° Special categories of cited documents :[10]

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IV. CERTIFICATION

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08 APRIL 1992	23.06.92
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EUROPEAN PATENT OFFICE	STEVNSBORG N.

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