improvement of the membrane's selectivity in organic liquid separations applications. Wan states that the process also serves to reduce the hydrophilicity of the membranes, and that by use of the crosslinking agents no unreacted hydroxy groups are left after reaction, nor are any hydroxy groups introduced by the crosslinking agent. Such membranes would not be suitable for use with water solutions, or solutions with appreciable amounts of water.

The membranes in the Wan patent have rejection values for oils of molecular weights in the range of from about 300 -600 Daltons of 55%-90%. (Molecular weight data from concurrent patent US 4,510,047.) These rejections are not suitable for the high value added products of pharmaceutical manufacturers.

Beer et al, in US Patent 5,739,316, claims a process for making a cross-linked cellulose hydrate ultrafiltration membrane comprising contacting a cellulose hydrate membrane with an aqueous alkaline solution of a water soluble diepoxide. Besides being limited to water soluble diepoxides, Beer teaches away from the use of organic solvents in the reactions as being technically difficult and expensive. Moreover, Beer states as an objective of his invention a process that does not modify the high flux of the membrane. This means that the membranes so produced would not have increased rejection from the initial ultrafiltration membrane.

Charkoudian, in US patent Applications 11/199491 and 10/414988 teaches crosslinked and crosslinked and charged cellulose ultrafiltration membranes that retain the ultrafiltration structure of the membranes.

US Patent 6,113,794 describes a nanofiltration composite membrane comprising a substrate ultrafiltration membrane formed from non-cross-linked ethylenically unsaturated nitrile polymer, and a porous coating of a cross-linked hydrophilic polymer having a molecular weight of 20,000 to 2,000,000 and containing reactive functional groups, formed from an aqueous solution of the polymer containing 1.5-2.5% w/w of the polymer. The patent is directed to chitosan coated membranes that are completely dried before being crosslinked. This will produce a dense film rather than a porous membrane.

The US 6,113,794 patent cannot be used with dipolar aprotic solvents such as N-methyl pyrrolidone or dimethylacetamide because such solvents will dissolve the support layer and destroy the composite membrane.

Guo et al in Chinese Chemical Letters, Vol 5, (10) pp 869-872 1994 reports on crosslinking large pore cellulose membranes with DMSO aqueous alkaline solutions of epoxyl propane chloride (epichlorohydrin). These membranes were used for affinity separations. Such large pore membranes would not be suitable for small molecule separations, and there is no teaching that the method could be used to make ultrafiltration or NF membranes.

Several patent applications and articles have been published by authors primarily associated with GKSS Research Center. These all appear to be based on the same technology. This method (WO 97/20622) coats a substrate membrane with a low solids solution of cellulose-hydroxyether, such as hydroxyethylcellulose or hydroxypropyl cellulose, and then crosslinks the coating with aldehyde, preferably a dialdehyde to the point of water insolubility. In an article in JAOCS Vol 76#1, pp83-87 1999, Zwijnenberg et al report on nanofiltration of vegetable oils in acetone using composite membranes with a “cellulose-type top-layer.” In Membrane Technology #107 pp5-8 1999, Ebert et al report on nanofiltration of vegetable oils in solvents with “cellulose-type” membranes in which the performance of the cellulose type membranes is influenced by the crosslinking conditions. Cellulose hydroxyethers are a different class of material from regenerated cellulose, as can be seen by the referenced authors describing the material as cellulose-like. Cellulose hydroxyethers are water soluble and can be expected to behave differently from regenerated cellulose membranes in operation. The membranes made from cellulose hydroxyethers are formed from thin dense layers and will have a different structure than the regenerated cellulose made by phase separation methods.

The inventors of the present invention have found that by using a porous ultrafiltration membrane as a precursor, and carefully controlling reaction conditions so as to maintain sufficient hydrophilic nature of the membrane, they can produce a solvent stable cellulose nanofiltration membrane capable of operating at satisfactory flux in

the kind used in the original solution may be added to the concentrated solute to produce a purer solution relative to the original feed, now that low molecular impurities have been removed by passage through the membrane.

Detailed Description of the Invention

The inventive nanofiltration membrane comprises a crosslinked cellulosic membrane, preferably integral with a support layer. The cellulosic membrane is made from a cellulosic ultrafiltration membrane preferably made by the process of US Patent 5,522,991 (which is incorporated herein by reference). The change in the membrane caused by the crosslinking reaction is from a membrane that separates primarily by size (ultrafiltration) to one where other interactions between the pore materials and the solutes play an important role in rejection of solutes. In nanofiltration, the forces on the solute molecule that retard entrance of solute into the pores, or transport through the porous nature of the membrane derive from the nature of the membrane material and the intimacy of solute to the pore surface. Charge and dielectric constant effects on the solute and solvent in the pores affect transport through the pores in a manner absent in the large pores of ultrafiltration membranes. Therefore, when making a nanofiltration membrane by the process of the present invention, the pore size was reduced to obtain a porous structure in which solute-membrane material interactions were important, and where rejection simply by size was not the only mechanism.

Supports suitable for the present invention can be made from polymer such as polyethylene, polypropylene, or polyether-ether ketone (PEEK) capable of operation in dipolar aprotic (e.g. DMSO, DMF, NMP) solvents. Supports need to combine porosity for flow, mechanical strength and flexibility and resistance to swelling or dissolution by organic solvents. Supports may be non-woven or woven fabrics made from, for example, polyolefins, polyethylene terephtalate, or fluorinated polymers such as polytetrafluoroethylene. A preferred support is a microporous membrane. A more preferred support is a microporous membrane made from ultrahigh molecular weight polyethylene (UPE) produced by the process described in US Patent 4,778,601.

Cellulose membranes can be formed by immersion casting of a cellulose acetate or other cellulose ester polymer solution onto a support. The cellulose ester is then

Crosslinker concentration in the reaction solution is about 5% by weight to about 60% by weight, with a preferred range of about 10% to about 40% by weight.

A skilled practitioner will determine the reaction based on reaction temperature and reaction conditions. Generally, the reaction will take place at a faster rate at higher temperatures. A larger reaction vessel will require more time to reach the reaction temperature and to cool down. Higher pressures may be used to increase reaction rate. Depending on the reaction vessel, the practitioner may use a continuous flow, stirred tank or other means to improve contact of reactants to the membrane and thereby control the reaction. Higher concentrations will increase reaction rate. Crosslinker type as well as solvent will also play a role in determining reaction time. Hydroxyl ion activity is another important reaction condition.

Preferred reaction times are from about two to about one hundred hours with preferred reaction times of about 4 to about 24 hours. The reaction can be run at room temperature, and up to about 60°C, with preferred temperatures being from 25°C to about 50°C. One of ordinary skill in the art will be able to modify or reduce this time by increasing for example the mass transfer rates, by using a continuous web or by further increasing reaction rates by adjusting temperature, concentrations and other like parameters.

When a multifunctional epoxy is used, the reaction is run at basic conditions. Sodium or potassium hydroxides are generally used. Typically about 0.1 M to about 1 M hydroxide solutions are used. The skilled practitioner will be able to balance the reaction against alkaline deterioration of the cellulose. Higher hydroxide concentrations and higher reaction temperatures will accelerate alkaline deterioration, lower concentrations of hydroxide and lower temperatures will slow deterioration rate as well as crosslinking reaction rate.

Powderlink 1174, Cymel 385 and similar crosslinking agents (multifunctional N-methyl methoxy compounds) crosslink cellulose through the hydroxyls on the cellulose with an acid catalyst, such as toluenesulfonic acid. Other similar acid catalysts are organic sulfonic acids and non-oxidizing mineral acids. Weak or moderately acid conditions, of pH about 2 to 4, are appropriate. A preferred catalyst is Cycat 4040, a sulfonic acid catalyst available from Cytec Industries. While more acidic conditions may

Examples

A. Aqueous Solutions

PLCCC is a cellulose ultrafiltration membrane made by Millipore Corporation of Billerica, Massachusetts. It has a rated molecular weight cutoff as specified in the manufacturer's literature of 5000 Daltons.

BUDGE is butanediol diglycidylether used as a crosslinking agent.

EDGE is Ethylene glycol diglycidylether used as a crosslinking agent.

Example 1

A piece of PLCCC membrane 85mm x 165mm, is treated with a solution of 40 grams of ethyleneglycol diglycidylether(EDGE) dissolved in 60 grams 0.1 M NaOH for 6 hours at 40 degrees C by rolling the membrane with the EDGE solution in a glass jar placed in a temperature controlled TECHNE HB1D hybridizer. The membrane is washed three times with 200 cc of Milli-Q® water. It is stored until use in 200 cc of Milli-Q® water containing 0.01% sodium azide to prevent bacterial contamination. (Membrane #1).

Membrane 1 was tested for its rejection of neutral dextrans and its buffer flux according to the Dextran Test described above. The molecular weight at which 90% of the dextrans are rejected (R90) is tabulated in Table 1 along with the value for the PLCCC control. Also shown in Table 1 is the buffer flux for Membrane 1 and the PLCCC control.

Membrane 1 was tested for its ability to reject $MgSO_4$ according to the Retention Test described above. A 0.2% aqueous $MgSO_4$ solution was prepared and its conductivity measured to give 2.34 milliSiemens (mS). The membrane was placed in a high pressure filtration stirred cell. The 0.2% feed solution was passed through Membrane 1 at a pressure of 50psi and a stirring rate of 150 rpm. The conductivity of the filtrate was 0.68 mS which corresponds to a concentration of 0.04% $MgSO_4$. This is a reduction of about 80% of the feed $MgSO_4$. The flux of this membrane during the nanofiltration experiment was 0.24 lmh/psi. This data is given in Table 2.

Membrane 1 was also tested for its ability to reject raffinose according to the Retention Test described above. Raffinose is a small sugar molecule with a molecular weight of 594 Daltons. A 0.1% aqueous raffinose solution was prepared a processed using the same cell and settings as for the MgSO4 experiment above. The feed solution and the filtrate were analyzed for their raffinose concentration by HPLC using a refractiveindex (RI) detector. A 91% reduction in raffinose concentration was recorded after being processed with membrane 1. This data is shown in Table 2.

B. Organic Solutions

Example 2

A piece of PLCCC membrane, 85mm x 165mm, is treated with a solution of 20 grams of butanediol diglycidylether(BUDGE) dissolved in 40 grams N-methylpyrrolidone and 40 grams of 0.5M NaOH for 90 hours at 24 degrees C by rolling the membrane with the BUDGE solution in a glass jar placed in a temperature controlled hybridizer. The membrane is washed once with 200 cc of methanol and twice with 200cc of Milli-Q® water. It is stored until use in 200cc of Milli-Q® water containing 0.01% sodium azide to prevent bacterial contamination. (Membrane #2.)

Membrane 2 was tested for its rejection of neutral dextrans and its buffer flux according to the Dextran Test described above; these values are given in Table 1.

Membrane 2 was tested for its ability to reject raffinose in isopropyl alcohol (IPA) according to the Retention Test described above. A 0.1% solution of raffinose in IPA was processed with Membrane 2 at 50psi. After passing through Membrane 2, the concentration was reduced to 0.029%. This is a decrease of 71% relative to the feed concentration. These data along with the flux and stir rate are shown in Table 3.

The dramatic difference in rejection seen for raffinose in DMAC compared tp isopropyl alcohol demonstrates that pore size alone does not control rejection, but that the interaction of solute/membrane is important.

Example 3

A piece of PLCCC membrane, 85mm x 165mm, is treated with a solution of 40 grams of butanediol diglycidylether(BUDGE) dissolved in 40 grams N-methylpyrrolidone and 40 grams of 0.5M NaOH for 40 hours at 24 degrees C by rolling the membrane with the BUDGE solution in a glass jar placed in a temperature controlled hybridizer. After this period of time this solution was discarded and a fresh solution with the same composition was introduced for 5 hours at 40 degrees C. The membrane is washed once with 200 cc of methanol and twice with 200cc of Milli-Q® water. It is stored until use in 200cc of Milli-Q® water containing 0.01% sodium azide to prevent bacterial contamination. (Membrane #3).

Membrane 3 was tested for its rejection of neutral dextrans and its buffer flux according to the Dextran Test described above; these values are given in Table 1.

Membrane 3 was tested for its ability to reject raffinose in N-methylpyrollidone (NMP) according to the Retention Test described above. A 0.1% solution of raffinose in IPA was processed with Membrane 3 at 50psi. After passing through Membrane 3, the concentration was reduced to below the detection limit of the HPLC equipment which is 0.005%. This corresponds to a decrease of at least 95% relative to the feed concentration. These data are listed in Table 3.

Example 4

A piece of PLCCC membrane, 85mm x 165mm, is treated with a solution of 40 grams of ethyleneglycol diglycidylether(EDGE) dissolved in 60 grams 0.25M NaOH for 4 hours at 40 degrees C by rolling the membrane with the EDGE solution in a glass jar placed in a temperature controlled hybridizer. The membrane is washed three times with 200 cc of Milli-Q® water. It is stored until use in 200cc of Milli-Q water containing 0.01% sodium azide to prevent bacterial contamination. (Membrane #4.)

Membrane 4 was tested for its rejection of neutral dextrans and its buffer flux according to the Dextran Test described above. The molecular weight at which 90% of the dextrans are rejected (R90) is tabulated in Table 1 along with the value for the

2	**BUDGE**	**0.1% Raffinose/IPA**	**0.1**	**0.001**	**90**	**0.008**
3		**0.1% Raffinose/NMP**	**0.1**	**<0.005**	**>95**	**0.01**
1		**0.1% Raffinose/NMP**	**0.1**	**<0.005**	**>95**	**0.01**

Prophetic Charged Nanofiltration Membranes

Example 1 — Negatively Charged 1

A piece of Membrane #1, 85mm x 165mm, is treated with a solution of 22.5 grams of bromopropylsulfonic acid sodium salt (BPSA) in 100 grams of 0.5M NaOH for 4 hours at 25 degrees C by rolling the membrane with the BPSA solution in a glass jar placed in a temperature controlled hybridizer. The membrane is washed three times with 200 cc of Milli-Q® water. It is stored until use in 200cc of Milli-Q® water containing 0.01% sodium azide to prevent bacterial contamination. (Negatively Charged Membrane #1).

Example 2 — Negatively Charged 2

The same BPSA reaction conditions as in Example 1 are employed except for reaction time which is allowed to proceed to 16 hours. This produces a sulfonic acid modified membrane with a higher amount of negative charge compared to 1 above. (Negatively Charged Membrane #2).

Example 3 —Positive Charge 1

A piece of Membrane #1, 85mm x 165mm, is treated with a solution of 15 grams of a 70-75% aqueous solution of glycidyltrimethylammonium chloride (GTMAC), 10 grams of 1 M NaOH, and 75 grams of water for 3 hours at 25 degrees C by rolling the membrane with the GTMAC solution in a glass jar placed in a temperature controlled hybridizer. The membrane is washed three times with 200 cc of Milli-Q® water. It is stored until use in 200cc of Milli-Q® water containing 0.01% sodium azide to prevent bacterial contamination. (Positively Charge Membrane #1.)

Example 4 —Positive Charge 2

The same GTMAC reaction conditions as in Example 1 is employed except for reaction time which was allowed to proceed to 16 hours. This produces a quaternary ammonium modified membrane with a higher amount of positive charge compared to 1 above. (Positively Charged Membrane #2).

What we claim:

1. A method of forming an organic solvent resistant hydrophilic nanofilter having a porous support integral with a crosslinked hydrophilic cellulose ultrafiltration membrane, comprising:
    (a) providing a microporous support made from a polymer selected from polyethylene, polypropylene, polyether ether ketone, polyolefins, polyethylene terephthalate, fluorinated polymers, and ultrahigh molecular weight polyethylene;
    (b) providing a cellulose solution;
    (c) contacting said microporous support with said cellulose solution;
    (d) forming an ultrafiltration cellulose membrane having a molecular weight cutoff (MWCO) values of 10,000 Daltons (D) or less on said support;
    (e) providing a reactant solution containing a multifunctional crosslinking agent dissolved in an aqueous solvent, an organic solvent, or an aqueous-organic solvent mixture, said multifunctional crosslinking agent comprising a butanediol diglycidyl ether or ethylene glycol diglycidylether;
    (f) contacting said ultrafiltration cellulose membrane on said support with said reactant solution; and
    (g) crosslinking said ultrafiltration cellulose membrane on said support by reacting said multifunctional crosslinking agent in the reactant solution through hydroxyl groups in the cellulose, under conditions whereby sufficient hydroxyl groups present in the cellulose are left unreacted resulting in a hydrophilic crosslinked cellulose membrane containing nanofilter, wherein said nanofilter retains solutes greater than about 200 Daltons.

2. The method of claim 1, further comprising after step (g) attaching a negative surface charge or a positive surface charge to the surfaces of said hydrophilic crosslinked cellulose membrane.

3. The method of claim 1, Wherein the reactant solution in step (e) further comprises a charge modifying reactant for providing a negative surface charge modifying reactant for providing a negative surface charge or a positive surface charge to the surfaces of said hydrophilic crosslinked cellulose membrane.

4. The method of claim 1, wherein said microporous support is selected from the group consisting of a polymeric woven fabric, polymeric non-woven fabric and polymeric membrane.

5. The method of claim 1, wherein said microporous support comprises an ultrahigh molecular weight polyethylene microporous membrane.

6. The method of claim 1, wherein said microporous support comprises polyethylene, polyethylene terephthalate or a fluorinated polymer.

7. The method of claim 1, wherein said cellulose solution comprises a cellulose ester solution.

8. The method of claim 7, wherein said cellulose ester is cellulose acetate.

9. The method of claim 8, wherein in said cellulose acetate is hydrolyzed to cellulose.

10. The method of claim 1, wherein said crosslinking agent is present from 5% by weight to 60% by weight of the reactant solution.

11. A method of forming an organic solvent resistant hydrophilic crosslinked cellulose containing nanofilter for removing or concentrating organic or inorganic solutes from aqueous, organic, or aqueous-organic solvent solutions comprising:

(a) providing an ultrahigh molecular weight polyethylene microporous membrane support
(b) providing a cellulose solution;
(c) contacting said support with said cellulose solution;
(d) forming an ultrafiltration cellulose membrane having molecular weight cutoff (MWCO) values of 5,000 Daltons (D) or less on said support;
(e) providing a reactant solution containing a multifunctional crosslinking agent, wherein said crosslinking agent is present from about 10% by weight to 40% by weight of the reactant solution, said multifunctional crosslinking agent comprising butanediol diglycidyl ether or ethylene glycol diglycidylether;
(f) contacting said cellulose membrane with said reactant solution forming an ultrafiltration cellulose membrane thereon;

(g) crosslinking said ultrafiltration cellulose membrane on said support by reacting said multifunctional crosslinking agent in the reactant solution through hydroxyl groups in the cellulose under conditions whereby sufficient hydroxyl groups present in the cellulose are left unreacted resulting in a hydrophilic crosslinked cellulose nanofilter having a molecular weight cut-off of 200 Da, and

(h) sealing the nanofilter in a pressure holding device.

12. The method of claim 11, wherein said cellulose solution comprises a cellulose ester solution.

13. The method of claim 11, further comprising attaching a negative surface charge or a positive surface charge to the surfaces of said hydrophilic crosslinked cellulose membrane in step (g).

14. The method of claim 11, wherein the pressure holding device includes a spiral wound module, a pleated cartridge, or a plate and frame type cassette.

15. A method of forming a pressure filtration holding device containing a hydrophilic crosslinked cellulose nanofilter used to remove or concentrate organic or inorganic solutes greater than about 200 Daltons from a feed solution, comprising:

(a) providing a microporous support having an upstream facing side and downstream facing side, made from a polymer selected from polyethylene, polypropylene, polyether ether ketone, polyolefins, polyethylene terephthalate, fluorinated polymers, and ultrahigh molecular weight polyethylene;

(b) providing a cellulose solution;

(c) contacting said microporous support with said cellulose solution;

(d) forming an integral ultrafiltration cellulose membrane having molecular weight cutoff (MWCO) values of 10,000 Daltons (D) or less on the upstream facing side of said support;

(e) providing a reactant solution containing a multifunctional crosslinking agent, said multifunctional crosslinking agent comprising butanediol diglycidyl ether or ethylene glycol diglycidylether;

(f) contacting said ultrafiltration cellulose membrane on said support with said reactant solution;

(g) crosslinking said ultrafiltration cellulose membrane on said support by reacting said multifunctional crosslinking agent in the reactant solution through hydroxyl groups in the cellulose, under conditions whereby sufficient hydroxyl groups present in the cellulose are left unreacted resulting in a hydrophilic crosslinked cellulose nanofilter;

(h) providing a pressure filtration holding device;

(i) placing said nanofilter in said pressure filtration holding device; and

(j) sealing the nanofilter in the device, wherein the upstream facing side of the nanofilter is the feed side and the downstream facing side of the nanofilter is the permeate side, such that when a feed solution stream is introduced to the upstream facing side, solutes greater than about 200 Daltons are retained on the upstream side of the nanofilter.

16. The method of claim 15, wherein the pressure holding device includes a spiral wound module, a pleated cartridge, or a plate and frame type cassette.

17. The method of claim 15, wherein said microporous support comprises an ultrahigh molecular weight polyethylene microporous membrane.