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(54) **BIOSTABILITY OF POLYMERIC STRUCTURES**

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(57) **ABSTRACT**

A biocompatible polymeric material is prepared by forming a three dimensional cross-linked structure of a biocompatible polymeric material such as a polyether or polycarbonate polyurethane and solvent extracting the material with a swelling solvent such as MEK which swells the material by up to 150%. The solvent swollen polymeric material is then de-swelled with a non solvent such as water which is miscible with the extraction solvent. The process produces polymeric materials which do not produce leachables and thereby have properties that are suitable for implantation.

BIOSTABILITY OF POLYMERIC STRUCTURES

[0001] This invention relates to biocompatible polymeric structures suitable for long term implantation within a living human body, and as a substratum for cell, tissue and organ growth technologies.

BACKGROUND OF THE INVENTION

[0002] Extensive investigations have been undertaken over many years to find materials that will be biologically and chemically stable towards body fluids and body tissue. This area of research has become increasingly important with the development of various objects and articles which can be implanted into a living body, such as pacemaker leads, vascular grafts, mammary prostheses, pacemaker bodies, probes, catheters and the like. Understanding the interactions between the host cells, tissue structures, physiological fluids biological agents and synthetic materials has become an area of intense research in recent years.

[0003] A serious limitation associated with the processes and materials available to the biomedical designer today is the fact that virtually all materials available today require some level of additives. An additional limitation of current materials is that polymerization reactions are far from perfect and generate materials which contain low molecular weight material, oligomers, unreacted monomers, catalysts, stabilizers and a host of other additives within the material. Irrespective of the source, these chemicals present a serious problem as they can leach into the tissue surrounding the implant.

[0004] Among the most important implantation material available today are the polyurethane's, silicones, fluoropolymers, and the polyesters. All of these classes of material suffer from the liberation of leachables. Among the most important of these materials are the polyurethanes. The polyurethane family of materials is unsurpassed in the area of soft tissue implantable materials. Attempts have been made to make porous structures from these materials for application as tissue scaffolds. While these porous structures have been implanted successfully it has hitherto been impossible to control the tissue growth process with any precision. One of the primary reasons for this has been the evolution of toxic leachables from the materials.

[0005] Thus, while there are some polymeric materials available for use in medical implant technologies there is a need for an improved technology for producing polymeric materials with enhanced biostability and biocompatibility.

[0006] This invention therefore is directed towards providing process and material technologies that can produce leachable free polymer systems with properties suitable for implantation.

STATEMENTS OF INVENTION

[0007] According to the invention there is provided a process for preparing a biocompatible polymeric material comprising the steps of:

[0008] forming a three dimensional cross-linked structure of a biocompatible polymeric material; and

[0009] solvent extracting the polymeric material with an extraction solvent, the solvent being a solvent which generates a volumetric swelling and having a solubility parameter of from 17 to 27 $MPa^{0.5}$.

[0010] The solvent extraction technique involves extracting the polymer in the presence of a swelling solvent. In a preferred embodiment the solvent swells the material of the implant by more than 30%, more preferably by more than 100% and still more preferably by more than 150%.

[0011] Ideally the solubility parameter of the solvent extraction system is selected for compatibility with the solubility parameter of the polymeric material or its phases. Preferably the solubility parameter of the solvent extraction system is within ±4 $MPa^{1/2}$ of the solubility parameter of the polymer or its phases.

[0012] Most preferably the solubility parameter is from 18-24 $MPa^{1/2}$.

[0013] In a preferred embodiment the hydrogen-bonding component of the solvent solubility parameter is in excess of 3 $MPa^{1/2}$.

[0014] In a preferred embodiment the solvent solubility parameter is selected such that it is similar to that of material leachables.

[0015] In a preferred embodiment the solvent is miscible with water. In another embodiment the solvent has a vapour pressure in excess of 2 kPa. More preferably the vapour pressure is in excess of 5 kPa. Even more preferably the vapour pressure is in excess of 10 kPa. The vapour pressure of MEK is 12.6 kPa, while the vapour pressure of THF is 21.6 kPa at room temperature.

[0016] Preferably the solvent selected has a low content of stabilizers and other additives and is non-reactive. MEK is the preferred solvent due to its excellent ability to swell cross-linked polyurethanes, its miscibility with water, its high vapour pressure, its stability and it can be obtained at high level of purity.

[0017] In a preferred embodiment of the invention the method includes the step of removing residual solvent from the structure, after solvent extraction. Preferably residual solvent is removed by treatment with water. Alternatively the solvent is removed by freeze drying or by thermally induced phase separation.

[0018] The biocompatible material may for example be a polyether polyurethane, a polycarbonate urethane, a polydimethylsiloxane urethane, a polyester urethane, a fatty acid derived polyurethane, a polybutadiene polyurethane, a urethane urea of any of the above or mixtures. Preferably the polyurethane is a polyether polyurethane, a polycarbonate polyurethane or a polydimethylsiloxane polyurethane.

[0019] In one case the material is in the form of a medical implant. The implant may be a septal defect occluder, a vessel occluder, a vessel defect occluder, a mammary prosthesis, a muscle bulking agent, a gynecological implant, a vascular graft, an embolising implant, a pacemaker housing cover, or an embolic filter.

[0020] The material may be in the form of a porous substratum for cell growth, tissue growth, organ growth or organ reconstruction.

[0021] In the case of a polyurethane biomaterial/scaffold the article may be formed from an organic diisocyanate, a

polyol, a chain extender and a blowing agent. A cross-lining agent may be employed to enhance the cross-linking of the material. A catalyst and surfactant may also be employed. The blowing agent is preferably water. For tissue engineering applications, the ratios of the reaction components are selected to promote the formation of a three dimensional porous molecular structure of polyurethane biomaterial.

[0022] The article may be processed by a metering and mixing process, wherein the chemical components are aggressively mixed and dispensed into a vessel and chain extension and blowing reactions occur substantially simultaneously.

[0023] Typically the article is processed by a reactive moulding process, wherein the chemical components are mixed and dispensed into a vessel wherein chain extension occurs.

[0024] Preferably the polyurethane scaffold has a pore size of from 10 microns to 300 microns. Ideally the scaffold has a pore size of between 35 microns to 200 microns.

[0025] Further details of the invention are set out in the claims.

DETAILED DESCRIPTION

[0026] The biocompatible, leachable free polyurethanes of this invention are derived from organic diisocyanates and polyols. The reaction step converts the chemical precursors into a 3 dimensional molecular cross-linked structure. A 3-dimensional network of this kind is insoluble and intractable.

[0027] The fact that the biomaterial is a three dimensional structure at a molecular level allows it to be processed aggressively to remove leachable chemicals from the material. Low molecular weight chemicals have the potential to leach from the article and result in toxic reactions in living cells. The severity of the inflammation, following implantation of a synthetic material, is strongly dependent on the type and quantity of chemicals that can migrate from the implant to the surrounding tissue. The processes of the invention expand the biomaterials volume at a molecular level. This expansion facilitates the removal of leachables such as monomers, oligomers, high molecular weight linear polymers, catalysts, surfactants, and other additives. The solvent extraction process also reduces any internal stresses within the material. The solvent expands the material by separating the molecular chains and suspending the chains in a solvent matrix. This loss of interchain attraction seriously compromises the mechanical properties of the matrix during the extraction step. The 3-dimensional cross-links however provide the materials with molecular memory and prevent the molecular structure from being completely solubilised. The recovery step removes the solvent and de-swells the material to its original state.

[0028] While the polymer is in the swollen state, the molecular chains can orient themselves into preferred relaxed conformation. These relaxations are limited by the cross-links such that no gross structural change is observed. This process allows the polymer chains to relieve any internal stresses. Relieving internal stress within the polyurethane increases the resistance of the material to phagocyte mediated oxidative degradation.

[0029] It is worth noting that with the process of the invention there is always two phase in the system. The solvent never succeeds in dissolving the cross-linked polymer phase.

[0030] Where a very high level of material purity is required, as in tissue engineering applications, multiple solvent swelling extractions may be carried out. These extractions preferably use solvents that have an affinity for different leachables. Low solubility parameter solvents have an affinity for surfactant leachables. Moderate solubility parameter solvents are used to remove the bulk of the leachables including soft phase monomers, oligomers and diols. High solubility parameter solvents have an affinity for hard phase monomers, dimers, oligomers and amine catalysts. In general the affinity of a particular leachable to a solvent must be off set against the ability of the solvent to swell the matrix. Higher swelling ratio solvents tend to be most effective in removing a wide spectrum of leachables.

[0031] The process of the invention is specifically designed to the treatment of polyurethane polymers. More specifically the invention is designed to treat polyurethane porous structures and scaffolds. However it is recognised that the principles of the invention can be applied to other materials. Indeed, most cross-linked polymer materials can be treated by the processes of the invention. The optimum swelling solvents will naturally have different solubility parameters to those specified for polyurethanes.

[0032] This process enhances the material biocompatible for use as an implantable medical device or as a 3 dimensional matrix for use as a cell scaffold in tissue engineering applications. Altering the chemical precursors and the processing conditions of the material may alter the pore size and the density of the material, as required, to meet the requirements of the application.

[0033] The process for the removal of leachables consists of the following general steps:

[0034] The scaffold is immersed in the swelling solvent and placed in an ultrasonic chamber for a minimum of six hours. The ultrasonic bath facilitates solvent penetration of the scaffold and assists in the migration of leachables from the polymer into the solvent.

[0035] Following the preliminary step, the solvent is diluted by the drop wise addition of non-solvent, miscible with the solvent over a period of 1-3 hours.

[0036] The concentration of solvent should be less than 5% after the addition of non-solvent. The scaffold is then immersed in pure non-solvent for 7-8 hours.

[0037] The scaffold is dried in an oven for 72 hours to remove all traces of the non-solvent.

[0038] This process is carried out in a fashion whereby material is subjected to minimal mechanical stress during the processing. This is particularly important during the swollen phase.

[0039] Achieving incredibly low levels of leachables may require multiple solvent swelling extraction steps. Different solvents may be used in each extraction steps.

[0040] Leachable levels can be measured gravimetrically or analytically (chromatography). HPLC grade water extraction of the materials or scaffold at 40° C. should produce a leachables content less than 1.0 mg per g. More preferably the water extracted leachables content is less than 10 μg per g: Even more preferably the water extracted leachables content is less than 0.1 μg per g. Extraction times in excess of 12 hours should be employed. These levels are near or below the level of detection for many analytical systems and may be demonstrated by extrapolation.

[0041] In another embodiment the exposure of the processed scaffold to a solvent whose solubility parameter is between 18 $MPa^{1/2}$ and 24 $MPa^{1/2}$, at 40° C., should produce a leachables content less than 10.0 mg per g in the solvent. More preferably the solvent extracted leachables content is less than 100 μg per g. Even more preferably the solvent extracted leachables content of the scaffold is less than 10.0 μg per g. Suitable solvents for this assessment of polyurethane biomaterials include MEK, DMA and THF.

[0042] Solvents that provide the maximum swelling are preferred per this invention. The volume swelling during solvent extraction should be above 30%. Preferably the solvent swelling should be in excess of 100%. Even more preferable is solvent swelling in excess of 150%. The level of solvent swelling decreases as the average molecular weight between cross-links decreases. However a minimum cross-link density is necessary to provide solvent swelling memory.

[0043] The molecular weight between cross-links of the material should preferably be between 300 and 6,000. Preferably the molecular weight between cross-links of the material is between 800 and 2,000. At very high cross-link densities the ability of the polymer to swell in the presence of a swelling solvent is diminished. At very low cross-ink densities large amounts of the polymer structure become solubilised. This creates recovery problems or results in a loss of structure.

[0044] The 3-dimensional molecular structure is important to achieving the physical and chemical characteristics of the invention. The three dimensional aspect is achieved with polyurethane's either by incorporating a trifunctional entity within the formulation or by employing an isocyanate index in excess of 1. Linear polymer systems cannot be subjected to such an aggressive solvent extraction since the use of a solvent with a similar solubility parameter will cause both the polymer and it's leachables to dissolve.

[0045] The implications of a leachable free scaffold are very significant. It means that the response of cells, the foreign body system and the immune system to the scaffold is geometry, morphology and surface chemistry driven. It means that the tissue structures, which propagate through the scaffold in vivo, depend on where the scaffold is placed, the geometry, morphology or surface chemistry characteristics of the scaffold and the chemical environment. The chemical environment can be altered with growth factors, chemo-attractants or other agents, which alter the path of tissue structure development. These features ensure the maintenance of phenotype. This is critical in both in vivo and in vitro applications. These issues are described in detail in our co-pending PCT Application No. _____ filed May 8, 2000, the entire contents of which are herein incorporated by reference (SALV20).

[0046] In conventional implant applications the biocompatible polyurethanes of this invention are useful for the manufacture of catheters, vascular grafts, septal occluders, vessel occluders, embolisation devices, mammary prosthesis, pacemaker housing covers, a stent cuffs, a stent covering, a tissue bridge, a vessel defect occluder, a muscle bulking agent, a gynecological implant, a vascular graft, an embolic filter and other such implant and blood contacting devices.

[0047] In one case the material is in the form of a medical implant. The material may be in the form of a porous substratum for cell growth, tissue growth, organ growth or organ reconstruction.

[0048] The biostable polyurethanes of this invention are based on organic diisocyanates, polyols, and diol, diamine or water chain extenders and combinations thereof.

[0049] To manufacture and process linear polymers into required geometries, normally requires the use of additives and catalysts, which cannot be removed completely by conventional solvent extraction. The 3 dimensional materials, detailed in this invention can be laser machined into the required geometries.

[0050] Details on the chemistry of the invention are as follows.

[0051] The organic diisocyanates are of the general formula:

$$R\text{-}(NCO)_n$$

[0052] R is an aliphatic, aromatic, cycloaliphatic, or an aliphatic-aromatic hydrocarbon entity containing between 4 and 24 carbon atoms and "n" varies between 2.0 and 3. More preferably, R contains between 4 and 15 carbon atoms. Where n is 2, a polymer with a linear molecular structure may be produced. A three dimensional molecular network may be produced where n varies from 2.0 to 3.0. Ideally n should be 2.

[0053] Examples of suitable isocyanates include: p-phenylene diisocyanate, tetramethylene diisocyanate, cyclohexane 1,2-diisocyanate, m-tetramethylxylene diisocyanate, hexamethylene diisocyanate, 2,4 diphenylmethane diisocyanate, 4,4 diphenylmethane diisocyanate, 2,4 toluene diisocyanate, 2,6 toluene diisocyanate, cyclohexane 1,4 diisocyanate, isophorone diisocyanate, 4,4-dicyclohexylmethane diisocyanate, 4,4-dicyclohexylmethane diisocyanate, and mixtures of the above.

[0054] More ideally the following isocyanates can be used to manufacture suitable materials; 2,4 diphenylmethane diisocyanate, 4,4 diphenylmethane diisocyanate, 2,4 toluene diisocyanate, 2, 6 toluene diisocyanate, cyclohexane 1,4 diisocyanate, isophorone diisocyanate, 4,4-dicyclohexylmethane diisocyanate, and mixtures of the above.

[0055] Even more ideally, 4,4 diphenylmethane diisocyanate, with a low 2,4 isomer content is used.

[0056] A wide variety of polyols may be used per this invention. These include polyether polyols, polyester polyols, polycarbonate polyols, silicone based polyols, fatty acid derived polyols, polybutadiene polyols.

[0057] The molecular weights of the polyols is in excess of 400 and less than 6000. More preferably the molecular weight is between 600 and 2500.

[0058] Polyether polyols, PDMS polyols and polycarbonate polyols are preferred for long term implantation applications. Polyether polyols that may be used include products obtained by the polymerisation of cyclic oxide, for example, ethylene oxide, propylene oxide, butylene oxide, or tetrahydrofuran.

[0059] Useful polyether polyols include polytetramethylene glycols obtained by the polymerisation of tetrahydrofuran. Polyols of differing molecular weights can be used together in a single formulation. Multiple polyols can be used in a single formulation.

[0060] The polyurethanes of this invention are based on diol, diamine, alkanolamine, water chain extenders or mixtures of these. Diol chain extenders react with isocyanate to generate urethane linkages. Most diols or diamines make suitable chain extenders. Examples of such chain extenders include, ethylene glycol, 1,4 butanediol, diethylene glycol, triethylene glycol, 1,2 propane diol, 1,3 propane diol, 1,5 pentane diol, ethylene diamine, 1,4 diaminobutane, 1,6 diaminohexane, 1,7 diaminoheptane, 1,8 diaminooctane, and 1,5 diaminopentane.

[0061] Useful catalysts are widely available in the marketplace and include organic and inorganic salts of bismuth, lead, tin, iron, antimony, cadmium, cobalt, aluminum, mercury, zinc, cerium, molybdenum, vanadium, copper, manganese and zirconium, as well as phosphines and tertiary amines.

[0062] Tertiary amines are an important class of catalyst in which the nitrogen atom is not directly attached to an aromatic ring. Examples of tertiary armines are: triethylamine, N,N,N',N'-tetramethylenediamine, N-N,N',N'-tetramethyl-1,3-butanediamine, bis-2-dimethylaminoethyl ether, N,N-dimethylcyclohexylamine, N,N-dimethylbenzylamine, N-methylmorpholine, N-ethylmorpholine, 1,4-diazabicyclo-[2.2.2] octane and the like.

[0063] Standard cross-linking agents may also be employed to improve the cross-linked aspect of the material. TEA is an exemplary example.

[0064] The chemistry and process for some preferred polyether and polycarbonate polyurethanes is described in more detail in our co-pending PCT application No. _____ filed May 8, 2000, the entire contents of which are herein incorporated by reference (SALV12).

[0065] The one shot process, the quasiprepolymer method or the prepolymer method, can be used to prepare the polyurethanes of this invention.

[0066] Different solvents are available for carrying out this process. The solubility parameter and hydrogen bonding parameters of the solvent will affect the suitability of the solvent. The solubility of the solvents of the invention is typically in the region of 17-27 $MPa^{1/2}$. More preferably the solubility parameter is from 18-24 $MPa^{1/2}$. The solvent system used for the extract system should have a solubility parameter in the same range as that of the biomaterial or scaffold.

[0067] Solvents that may be used include methylethyl ketone, tetrahydrofuran, 1,2-dichloroethane, propan-2-ol, and combinations of the above. Many other solvents have suitable properties and could equally be employed.

EXAMPLE A

[0068] Preparation of polyether polyurethane biomaterials suitable for solvent extraction.

[0069] Polyol Preparation.

[0070] In the preparation of the polyol resin the following raw materials are added to a heated round bottom flask and mixed;

Raw material	Quantity (php)
PTMEG (MW 1000)[1]	100
Triethanolamine[2]	4.60
Water[3]	2.56
1,4 Butanediol[4]	8.05
BF 2270[5]	1.0
RC Catalyst 105[6]	2.96
Desmorapid PP[7]	0.34
Kac/Deg[8]	0.73

[1]Terathane (Du Pont)
[2]Sigma Aldrich
[3]Sigma Aldrich
[4]Sigma Aldrich
[5]Th GoldSchmidt
[6]DABCO and Diethylene Glycol (Sigma Aldrich) at a ratio of 33.3:66.7
[7]Whitchem
[8]Potassium acetate and Diethylene Glycol (Sigma Aldrich) at a ratio of 30:70

[0071] The materials are mixed at 50-60° C. for a minimum of 25-30 minutes.

[0072] The polyol resin is stored in containers, under a blanket of nitrogen gas.

[0073] An isocyanate pre-polymer is prepared from flake MDI (Desmodur from Bayer) and PTMEG (Terathane 1000 MW from DuPont). The amount of MDI and polyol used yield a NCO % content by weight of 15.6% and can be readily determined by those skilled in the art. A number of polyether polyurethane biomaterials are prepared at varying isocyanate indices using techniques described in our copending patent. The following isocyanate index materials were reacted and cured in a cylindrical mould; 0.95, 0.99, 1.04, 1.08, 1.13, 1.18, 1.23 and 1.29. The samples were cut to a length of 15 mm and had a diameter of 21.5 mm.

[0074] Solvent Extraction.

[0075] A 250 ml wide necked conical flask was filled with MEK to the 250 ml mark. A separate flask was used for samples of each index. Five samples were placed in each flask. The flasks were stoppered and placed in a water filled ultrasonic bath. The bath was at room temperature. The flasks were sonified for 6 hours. After the 6 hours the samples were removed from the flask by pouring the contents into a sieve. The samples were rinsed in water and placed in an oven at 80° C. to dry. The samples were weighed at 30 minute intervals until the weight stabilised. The weight loss for each sample was measured.

[0076] Note: The materials processed in this experiment suffered from shrinkage. This was overcome in more recent experiments by using a larger vessel, adding the water as non-solvent to the extraction vessel over a period of 3 hours to achieve a solution concentration of <5%. This avoids the mechanical deformation associ-

ated with sieving and the differential shrinkage associated with drying the material while it is still solvent swollen. The procedure was further optimised by placing the samples in water for 6-8 hours. This step removes virtually all the solvent prior to the drying step.

[0077] The following table details the average % weight losses at the various isocyanate indices.

Isocyanate Index	Average % weight loss
0.95	21.7%
0.99	13.5%
1.04	7.2%
1.08	5.5%
1.13	4.8%
1.18	5.5%
1.23	10.3%
1.29	9.8%

[0078] The minimum weight loss for polyether polyurethane biomaterial was achieved with an isocyanate index of 1.13. This was achieved with swelling of the biomaterial to 150%. It is concluded from this example that the formation of a cross linked structure is most efficiently achieved at an isocyanate index of 1.13.

[0079] Cytotoxicity

[0080] This biomaterial scored zero when subjected to the Cytotoxicity test as outlined in ISO standard 10993-5. This is the lowest possible score with this test method. This means that when cell growth media, previously incubated with the biomaterial, supported the growth of L-929 cells and did not induce a cytopathic effect. Media incubated with cytotoxic materials induce cytopathic effects when incubated with L-929 cells. The extent of cytopathic effect can be correlated to the cytotoxicity of the biomaterial.

[0081] In vivo Response

[0082] This polyether polyurethane biomaterial was also implanted in the gluteal muscle of rats and left for up to 6 months. The histological analysis conducted on the explants indicated that the implant was well tolerated in the animal model and did not induce any adverse inflammatory response.

[0083] The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

1. A process for preparing a biocompatible polymeric material comprising the steps of:

forming a three dimensional cross-linked structure of a biocompatible polymeric material; and

solvent extracting the polymeric material with an extraction solvent, the solvent being a solvent which generates a volumetric swelling and having a solubility parameter of from 17 to 27 $MPa^{0.5}$.

2. A process as claimed in claim 1 including the step of de-swelling the solvent swollen polymeric material.

3. A process as claimed in claim 2 wherein the polymeric material is de-swelled by contacting the solvent swollen polymeric material with a non-solvent which is miscible with the extraction solvent.

4. A process as claimed in any of claims 1 to 3 including the step of drying the polymeric material to substantially remove solvent residues.

5. A process as claimed in claim 4 including the step, prior to drying, of extracting the polymeric material with water.

6. A process as claimed in any of claims 1 to 5 wherein the polymeric material is extracted with a number of extraction solvents.

7. A process as claimed in claim 6 wherein the solvent extractions are carried out sequentially.

8. A process as claimed in any preceding claim wherein the solubility parameter of the extraction solvent is within ±4 $Mpa^{0.5}$ of the solubility parameter of the polymeric material or its phases.

9. A process as claimed in any preceding claim wherein the vapour pressure of the extraction solvent is greater than 2 kPa at 25° C.

10. A process as claimed in claim 9 wherein the vapour pressure of the extraction solvent is greater than 5 kPa at 25° C.

11. A process as claimed in claim 10 wherein the vapour pressure of the extraction solvent is greater than 10 kPa at 25° C.

12. A process as claimed in any preceding claim wherein the extraction solvent has a polar component of its solubility parameter in excess of 3 $MPa^{0.5}$.

13. A process as claimed in any preceding claim wherein the solvent has a solvability parameter of from 18 to 24 $MPa^{0.5}$.

14. A process as claimed in any preceding claim wherein the swelling solvent swells the material by more than 30%.

15. A process as claimed in claim 14 wherein the swelling solvent swells the material by more than 100%.

16. A process as claimed in claim 14 or **15** wherein the swelling solvent swells the material by more than 150%.

17. A process as claimed in any of claims 1 to 16 wherein the extraction solvent is water miscible.

18. A process as claimed in any of claims 1 to 17 wherein the extraction solvent includes tetrahydrofuran (THF).

19. A process as claimed in any of claims 1 to 19 wherein the extraction solvent includes methyl ethyl ketone (MEK).

20. A process as claimed in any of claims 1 to 15 wherein the solvent extraction step is carried out for a period of at least 2 hours at room temperature.

21. A process as claimed in any preceding claim wherein the solvent extraction step is carried out at a temperature in excess of 20° C.

22. A process as claimed in any preceding claim wherein the solvent extraction step is carried out in an ultrasonic bath.

23. A process as claimed in any of claims 3 to 22 wherein the non solvent is water.

24. A process as claimed in any of claims 3 to 22 wherein the non solvent is and alcohol.

25. A process as claimed in any of claims 3 to 24 wherein the non solvent is added to the solvent swollen polymeric material in an amount and at a rate to maintain a low concentration gradient.

26. A process as claimed in any of claims 3 to 25 wherein the de-swelling is carried out at a temperature of less than 40° C.

27. A process as claimed in any preceding claim wherein the polymeric material is a polyether polyurethane.

28. A process as claimed in any of claims 1 to 26 wherein the polymeric material is a polycarbonate urethane.

29. A process as claimed in any of claims **1** or **26** wherein the polymeric material is a polydimethyl-siloxane urethane.

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