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(71) Applicant *(for all designated States except US)*: **DEPARTMENT OF ATOMIC ENERGY** [IN/IN]; Anushakti Bhavan, Chhatrapati Shivaji Maharaj Marg, Mumbai 400 038, Maharashtra (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VARSHNEY, Lalit** [IN/IN]; Radiation Technology Development Section, Bhabha Atomic Research Centre, Trombay, Mumbai 400 085, Maharashtra (IN). **MAJMUDAR, Advait, Ajit, Kumar** [IN/IN]; Radiation Chemistry and Chemical Dynamics Division, Bhabha Atomic Research Centre, Trombay, Mumbai 400 085, Maharashtra (IN).

(74) Agents: **MAJUMDAR, S.** et al.; S. Majumdar & Co., 5, Harish Mukherjee Road, Calcutta 700 025 (IN).

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(54) Title: A PROCESS FOR MANUFACTURE OF HYDROGELS FOR BURN AND INJURY TREATMENT

(57) Abstract: In this invention a process for manufacture of hydrogel dressing by cross-linking aqueous solution of synthetic polymer namely poly vinyl alcohol (PVA) and natural polymer agar-agar and one or more of other natural polymers from carageenan, sodium alginate and sodium carboxymethyl cellulose, gum acacia or similar polysaccharides or protein like gelatine etc. by gamma or electron beam irradiation has been described. In the process the ingredients are dissolved in distilled/deionized water at elevated temperatures. The hot solution is poured in disposable plastic mould, closed tightly and subjected to radiation dose between 25 to 60 kGy to give final, ready to use, high water content, transparent, flexible, self adhesive gel dressing. The pre irradiated gel solution contains 5-15 % by weight of PVA, 0.5 to 5 % by weight of natural polymers and distilled water not less than 80 % by weight.

A PROCESS FOR MANUFACTURE OF HYDROGELS FOR BURN AND INJURY TREATMENT

Technical Field

This invention relates to process for manufacturing hydrogel dressings useful as dressing for burn and injuries. This invention particularly relates to a process for manufacturing hydrogel dressings based on polyvinyl alcohol.

Background and Prior Art

Hydrogels have three dimensional network structure of polymer chains holding significant amount of water. The water holding capacity of a hydrogel depends upon the basic polymer network structure, other ingredients and the production process. In spite of their very high water content, these solid hydrogels are not soluble in water.

Synthetic and natural polymers along with other chemical ingredients have been used for making hydrogels. Synthetic polymers, however, form the main base material in all these hydrogels.

Polymers employed in manufacturing hydrogels useful as burn dressings are mainly polyvinyl pyrrolidone, vinyl pyrrolidone, acrylamide, poly vinyl alcohol, polyethylene oxide, gelatin and agar-agar. Along with these polymers use of a plasticizer such as silicone oil and polyethylene glycol have been reported in US Pat. 4871490 (1989). Viscosity modifiers or adhesion improvers like cyclodextrin have also been used [J P Appln. 230659/1989]; tackiness improvers like glycerol, 1,2,3 propane-triol ; use of colouring agents [Us patent 4646730,1987]; pharmaceutically active agents, such as drugs, antibiotics have also been reported [J P 77171/1991].

Methods of making hydrogel dressings such as thawing, freezing using different solvent systems as in US Pat 4663358; use of cross-linking agents such as formaldehyde, glutaraldehyde, methylene bis acrylamide, oxidising agents [Hirai T. et. al., J.Appli Polym. Sci,46,1449,1992 & US Patent 5076265, 1991] and irradiation

as in US Patent 4871490(1989) have been used as appropriate to the raw materials. Some of the processes for making hydrogel dressings are multi stage like gel formation, cleaning, post dosing and sterilizing.

Of the various methods, irradiation is a clean process and does not require toxic chemicals like cross-linkers, initiators etc. for forming hydrogel, thereby reducing the chances of undue toxicity in the final product. Gamma radiation and electron beam are used for cross linking polymers in solid as well as in solution form and the technique is also used for sterilizing medical products. In general, on irradiating aqueous solution of PVA, some of the water molecules undergoes radiolytic decomposition forming free radicals like OH. H and e- aqueous. These radicals, mainly OH abstract hydrogen atom present on the PVA molecule to form reactive radical site on it. Two of such radical sites combine to form a cross-link. Several such cross-linked molecules form a three-dimensional network to form hydrogel. Nature of the polymer, Cross-link density and network structure determines the hydrogel qualities. The hydrogels formed with different cross-linking density and network structure, would have different characteristics with respect to its water absorption, tensile strength, elongation, distribution of pore sizes etc. Presence of natural polymers like polysaccharides and proteins like gelatin could modify these characteristics of the network structure, changes in internal volume etc., over and above imparting strength to the hydrogel. The presence of ionic groups on some of them, could significantly change the water absorption characteristics. The level of acetyl groups in PVA also modifies characteristics of the hydrogel in terms of its transparency and strength which is related to basic network structure.

Hydrogel dressings are gaining widespread acceptance in recent times for burns and injury treatment. Different types of gels are either available in market abroad or under clinical trials. These Hydrogels are based on different formulations and production processes.

Some known commercial hydrogels dressings use multi layer/laminates (US Pat appln. 824564, 1997), foams dipped in gel like substance (Burn Free, USA), hydrogel (Geliperm, Switzerland), porous hydrogel and sheets (US Pat. 4663358, 1987), US Pat. 5076,265/19, 1991) gauze based hydrogel would dressing (US Pat. 5076,265, 1995) etc. Some gels have antibiotics in the dressing (US pat. 4646730/19 1987). Johnson and Johnson manufactures "Therapeutic Gell Dressing", which is a clear, semi firm, cross-linked PVP/water gel, supported by an internal non-woven web and a polyethylene backing, whose active surface is protected by a removable polyethylene release film. It is packaged in a shallow tray inside a foil peel-open pouch. (see US Pat. 4646730(1987)].

Most of the patented/reported processes generally consist of distinct and separate steps for gel formation, gel washing and gel sterilization. Moreover, these formulations include addition of number of synthetic chemical ingredients and the production processes are usually multistage ones. Manufacture of such hydrogels increases cost of the ingredients and multistage process invariably requires greater control of production parameters thereby substantially enhancing the cost of production.

The development work in this field in recent times is concentrated on using PVA as a base material. This is due to its greater and proven biocompatibility as compared to other materials used in past for such applications (F. Yoshii et.al., Radiat. Phys. Chem., Vol 46, No. 2, 169-174, 1995). One of the base material used namely PVP has been described as suspected carcinogen in its non-irradiated form (See Dangerous properties of industrial materials, "polyvinyl pyrrolidone" Irving N. Sax, VIth edition, Van Nostrand Reinhold, New York).

PVA hydrogels are normally mechanically weak. The high water content in the PVA hydrogel usually results in poor mechanical strength. A variety of methods have been reported to enhance the strength. Among them are use of chemical cross-linkers like formaldehyde, glutaraldehyde, boric acid, Borax etc., providing co-ordinate bonding by using metal ions like Ti, Cu, and Co and irradiation. These hydrogels require further extensive processing to impart desirable handlability, tackiness and sterilization (US Pat. Application No. 824564, March 26, 1997). The resultant hydrogels which have high mechanical strength have normally low water content and conversely hydrogels with high water content are mechanically very weak. Manufacturers have to provide additional physical support to impart mechanical strength to such weak hydrogels. All these steps result in expensive, complicated, and multistage process for manufacture of PVA based mechanically handlable hydrogel burn dressings (US pat. Application No. 824564, March 26, 1997).

Of these various patents the most relevant prior art patents are described below :

Polish Patent Specification No. 128,392 describes a method for manufacturing dressings including drugs, involving applying a layer of a hydrophilic gel obtained by the radiation polymerization of synthetic polymers, such as polyacrylamide, polyvinylpyrolidone, polyvinyl alcohol, polyethylene oxide, their monomers or their mixtures on the mechanical base of a dressing after or before impregnating it with a drug, thereafter the dressing is dried and sterilized. Although these dressings, are characterized by a relatively long drug releasing time and the gel used to obtain them does not contain admixtures of any catalysts nor chemical substances, but they do not provide sufficient protection against a loss of water and penetration of bacteria to the would, are opaque which prevents the observation of

the would healing process and, besides, the process of their manufacture is long and complicated.

United States Patent 4,871,490 (Rosiak, et al. October 3, 1989) describe a method of manufacturing hydrogel dressings from synthetic and natural polymers by polymerization and cross-linking involves pouring aqueous solutions of synthetic polymers, such as polyacrylamide and polyvinylpyrolidone, their monomers or their mixtures, natural polymers, such as gelatin or agar, or their mixtures and, possibly, plasticizing agents, such as poly/ethylene glycol, poly/propylene glycol and silicone oils, of the following composition. 2-20 percent by weight of synthetic polymers, not more than 5 percent by weight of natural polymers, not less than 75 percent by weight of distilled water and 1-3 percent by weight of plasticizing agent, into a mould imparting a shape to the dressing, tightly closing in the mould and subjecting to an ionizing radiation does not less than 25 kGy.

United States Patent Appln. 824564 (Makuuchi et al., March 26, 1997) discloses a PV hydrogel which comprises being obtained by irradiating a polyvinyl alcohol aqueous solution containing a polymer selected from the group consisting of polyvinyl pyrrolidone, a methyl vinyl ether-maleic anhydride copolymer and an isobutylene-maleic anhydride copolymer, with ionizing radiations, a process for preparing the PVA hydrogel, a hydrogel laminate using the PVA hydrogel, a process for preparing the hydrogel laminate, and a hydrogel wound-dressing material using the PVA hydrogel.

Functions of the hydrogel as a dressing for burn or other skin injuries would be :-

to protect the damaged skin surface from bacterial contact or prevent bacterial penetration of the wound,

to permit passage of oxygen to the skin to allow natural respiration and healing of wound,

to absorb exudates from the skin surface, it should have sufficient water absorption capacity,

to provide humid environment, cool the surface, to heal burn and other injuries faster,

to provide gentle adhesion to the injured/burnt skin, without causing any health hazard,

to remove necrotic tissue along with the hydrogel dressing when the dressing is removed,

to remain stable adhering to the skin at body temperature,

to remain transparent to allow observation of the status of the burn or injured surface,

to be easy to apply to the skin, i.e., it should be flexible and mechanically handlable, transparent, self adhesive, easy to peel off.

Although prior art processes and compositions are suitable for their intended purposes, a need continues to exist for process for preparing a hydrogel dressing that would satisfy these above functional requirements.

There is also exists a long felt need to produce a cheap and simple curative hydrogel dressing for burn and other injuries for poor people.

Object :

The main object of the present invention is to develop a process for manufacturing hydrogel dressings for burn or other skin injuries, satisfying the above functional requirements.

Another object of the invention is to obtain a hydrogel having stable, mechanically strong, physical structure, so that it can be used directly as a dressing for burn healing.

Another object of the invention is to develop one step irradiation process for formation of hydrogel and sterilization with a view to make it into simple, cheap burn dressing.

The production process should eliminate post irradiation treatment, like washing, annealing, use of secondary support, sterilization etc.

The process should fit into the normal commercial irradiation plant operation cycle give more that 95% yield and should be adaptable for automated large scale production of hydrogels. To make the hydrogel dressing economical, the process should be simple and use minimum and locally available ingredients.

Our approach is to develop a one stage irradiation process based on the excellent biocompatible synthetic polymer -PVA, supplementing it, if necessary, with different natural polymers, avoiding other extraneous chemicals, or mechanical

supports to obtain preferably 3-5 mm thick plain hydrogel dressing satisfying all functional requirements.

Summary of the invention :

According this invention relates to a process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, comprising :

(i) preparing an aqueous solution of polyvinyl alcohol, agar-agar and one or more natural polymers and/or their derivatives chosen from agar-agar, gelatin, carageenan, sodium alginate, carboxy methyl cellulose, guar gum, gum acacia etc. ;

(ii) putting the solution at 70-80°C in disposable plastic trays and sealing them ;

(iii) subjecting the said aqueous solution in the sealed trays obtained at the end of step (ii), to irradiation at room temperature to form the sterile ready to use hydrogel dressing.

Detail Description of the Invention :

In this invention polyvinyl alcohol used has average molecular wt. in the range 27,000 - 1,25,000 and its acetate content is less than 18% by wt. but preferably it is 6 - 12%.

The components of the aqueous solution is generally :

polyvinyl alcohol : 5-15% by wt.,

agar-agar and other natural polymers and their derivatives : 0.5-5% by wt. of which the said other natural polymer and/or its derivative form 0 - 4.5% by wt. of the aqueous solution.

Ingredients used for the gel production :

1. Polyvinyl alcohol : 5-15% (w/w)
Average Molecular weight : 25000 - 125000

Acetate contents = 0-12%, desirable 6-12%

2. Water : Distilled/deionized water, not less that 80% (w/w)

3. Natural polymers : 0.4 to 5% (w/w), from gelatin, agar-agar, carageenan, sodium alginate, sodium carboxymethyl cellulose, gum acacia etc. of high purity or pharmaceutical grade.

4. Containers : Disposable trays made up of PET (polyethylene terephthalate, HDPE (high density polyethylene) and PVC (polyvinyl chloride) of medical or food grade quality.

Note : All the materials described above are available locally.

5. Irradiation : Gamma or electron beam irradiation can be carried out for gel production.

6. Radiation Dose : 25-60 kGy

Irradiation facility : Commercial facility for gamma irradiation, available at ISOMED, BARC, MUMBAI - 400 085 was used for the process in the following Examples.

The hydrogel manufacturing process of the present invention, in general, is as follows :

PVA and natural polymers are dissolved in a suitable glass container. The solution is poured in plastic trays and cooled to room temperature for setting. The trays are sealed in polyethylene or laminate pouches made of PET/aluminium/PE. Number of such sealed trays are placed in card board carton and are irradiated by either gamma irradiation or electron beam at 25-60 kGy dose. Due to inherent production parameters the filled and sealed trays need not be irradiated immediately and this factor helps to accommodate delays (about one week) between production and irradiation. This factor is important to enable manufactures who use contract radiation sterilization services.

Polyvinyl alcohol chosen has any average molecular wt. covering the entire range 35,000 - 146,000 ; OR in the range 80,000 - 125,000 OR 90,000 - 100,000, OR 30,000 - 45,000, preferably 80,000 - 125,000.

The polyvinyl alcohol chosen of different molecular wt., has acetate content up to 18% by wt. OR 6 - 12% by wt. OR 8 -12% by wt. OR 0 - 1% by wt.

The radiation dose applied to the said aqueous solution to form the hydrogel is 25 - 60 kGy OR 35 - 50 kGy OR 25 - 30 kGy OR 30 kGy.

Hydrogels of this process of invention made with components such as in following quantities are found to have good water absorption and gel qualities.

a) Polyvinyl alcohol 14% by wt., agar-agar 3% by wt. of the aqueous solution and no other natural polymers and/or their derivatives are used.

b) Polyvinyl alcohol 6% by wt., agar-agar 1% by wt. of the aqueous solution and no other natural polymers and/or their derivatives are used.

c) Polyvinyl alcohol 8% by wt., agar-agar 1.5% by wt. and the other natural polymers and/or their derivatives is sodium alginate 0.5% by wt., of the aqueous solution.

d) Polyvinyl alcohol 8% by wt., agar-agar 1% by wt. and the other natural polymers and/or its derivative from 1.5% by wt., of the aqueous solution. The other natural polymers chosen is a combination of sodium alginate and gum acacia in 1:2 proportion.

Hydrogels of any desired thickness or shape are made by this process of invention but those in the 3-5 mm thickness are preferred.

Appropriate plastic mould can be selected for required gel dimensions.

Advantages of the Invention :

Polyvinyl alcohol solution in water, containing natural polymers, can be cross-linked using radiation to form mechanically handlable, flexible, transparent, self adhesive and water absorbing hydrogels of desirable thickness and shape. The gel formation and sterilization occurs simultaneously which has economic advantage as well as the product has very high degree of sterility assurance level. The gel so produced is in final, ready to use pack and does not require further treatment like washing, annealing etc. These gels have tendency to adhere to healthy skin only and

not to wet surface like that of a burn wound. This property allows gel dressing to be peeled off painlessly from the wound. Due to transparency, healing of the wound can be observed without removing the gel. The water absorption characteristics of the gel dressing can be controlled by varying concentrations of PVA and natural polymers in the basic formulation. The potential applications of these gels include efficient treatment of burn and injuries due to their excellent cooling effect, biocompatibility, oxygen permeability, absorption, sterility and humid environment which accelerate healing process of the wound. Scar formation is also reduced. These gels can also be used for treatment of trophic ulcers, bed sores, skin contractures, use on donor areas in plastic surgery eczema etc.

Examples :

The objects of the invention, its advantages and means for attaining the same are disclosed hereunder in greater details with reference to non-limiting embodiments of the same by way of Examples. The Examples are by way of illustration only and in no way restrict the scope of the invention.

Example I :

140 gm of PVA (Mol. Wt 35000, acetate content 10%) and 30 gm of agar was taken in 1000 ml of distilled water and dissolved at elevated temperature. The hot solution (70°C) was poured in plastic trays to fill up to 4 mm height. The trays were cooled to room temperature (25°C) and sealed in polyethylene pouches. Number of such sealed trays were placed in card board carton and irradiated at 50 kGy.

The hydrogel formed was elastic, mechanically handlable, kin adherent and showed water-absorbing capacity as 125% w/w when measured by method given at the end of the Examples.

Example II :

The PVA and Agar solution was made as in Example I, using 60 gm of PVA of 90,000 molecular weight, acetate content, 0-1% and 10 gm of agar. The solution was irradiated in the trays at 30 kGy.

The hydrogels produced were like those obtained in Example I, but their water-absorbing capacity in different batches was found 20-30% w/w only.

Example III :

The solution was made as in Example I, using 80 gm of PVA of 1,25,000 molecular weight 12% acetate content, 5 gm of agar and 5 gm of sodium alginate, and irradiated at 25 kGy.

The hydrogels produced were similar to those of Example I, but their water-absorbing capacity in different batches was found to be in the range 60-70% w/w only.

Example IV :

The hydrogel solution was made as in Example III, using 80 gm of PVA of 1,25,000 molecular weight, 12% acetate content, 10 gm of agar, 5 gm of sodium alginate, 10 gm of gum acacia and irradiated at 27 kGy.

The hydrogels produced were similar to those of Example I, but their water-absorbing capacity in different batches was found to be in the range 125-150% w/w only.

Characteristics of the Hydrogel obtained in the Examples :

In general, the hydrogels obtained in these examples are

3-5 mm thick, contain above 80% water and have following characteristics :-

i. Soft and flexible
ii. Elastic in nature (0% elongation more that 200%)
iii. Mechanically handlable (Tensile strength more than 300 gm/cm^2)
iv. Shape and thickness as desired
v. Good transparency.
vi. Heat Resistant (retains its characteristics in boiling water for 10 minutes)
vii. Contains above 80% water of its weight and has capacity to further absorb significant quantity of water 30-150% of its weight.
viii. Self adhesive.

It will be seen from these examples that the process is simple, low cost, and gives hydrogels in ready to use sterile form.

Method used for determining water absorption capacity of the hydrogels:

The water absorption capacity is determined by removing the hydrogel from its packing and putting into distilled water. The increase in weight is recorded at definite interval of time. The % increase in weight is given by (((Wt - Wo)/Wo)x100) where Wt is the weight of the hydrogel at time t and Wo the weight of the gel before putting it into water. This water absorption is over and above the water originally present in the hydrogel. The absorption values given in the examples are after 12 hours.

CLAIMS

1. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, comprising :

i) preparing an aqueous solution of polyvinyl alcohol, agar-agar and one or more natural polymers and/or their derivatives chosen from agar-agar, gelatin, carageenan, sodium alginate, carboxy methyl cellulose, guar gum, gum acacia etc. ;

ii) putting the solution at 70-80°C in disposable plastic containers and sealing them ;

iii) subjecting the said aqueous solution in the sealed containers obtained at the end of step (ii), to irradiation at room temperature to form the sterile ready to use hydrogel dressing.

2. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in Claim 1, wherein acetate content of polyvinyl alcohol is less than 18% by wt.

3. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1 or 2, wherein polyvinyl alcohol has molecular wt. in the range 27,000 - 1,46000.

4. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-3, wherein the said polyvinyl alcohol forms 5-15% by wt., the said agar-agar and other natural polymers and/or their derivatives form 0.5-5% by wt. of which the said other natural polymer and/or its derivative form 0 - 4.5% by wt. of the said aqueous solution.

5. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-4, wherein polyvinyl alcohol has molecular wt. in the range 35,000-146,000.

6. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-5, wherein the said polyvinyl alcohol has mol. Wt. 80,000 - 125,000.

7. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-6, wherein the said polyvinyl alcohol has mol. Wt. 90,000-100,000.

8. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-7, wherein the said polyvinyl alcohol has mol. Wt. 30,000-45,000.

9. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-8, wherein the polyvinyl alcohol has acetate content up to 12% by wt.

10. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-9, wherein the polyvinyl alcohol has acetate content 6-12% by wt.

11. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-10, wherein the polyvinyl alcohol has acetate content 8-12% by wt.

12. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in claim 1-11, wherein the polyvinyl alcohol has acetate content 0-1% by wt.

13. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in claim 1-12, wherein the radiation dose applied to the said aqueous solution to form the hydrogel is 25-60 kGy.

14. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in claim 1-13, wherein the radiation dose applied to the said aqueous solution to form the hydrogel is 35-50 kGy.

15. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in claim 1-14, wherein the radiation dose applied to the said aqueous solution to form the hydrogel is 25-30 kGy.

16. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in claim 1-15, wherein the radiation dose applied to the said aqueous solution to form the hydrogel is 30 kGy.

17. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-16, wherein the said polyvinyl alcohol forms 14% by wt., the said agar-agar forms 3% by wt. and the said other natural polymers and/or their derivatives form 0% by wt., of the said aqueous solution.

18. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-17, wherein the said polyvinyl alcohol forms 6% by wt., the said agar-agar forms 1% by wt. and the said other natural polymers and/or their derivatives form 0% by wt., of the said aqueous solution.

19. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-18, wherein the said polyvinyl alcohol forms 8% by wt., the said agar-agar forms 1.5% by wt. and the said other natural polymers and/or their derivatives form 0.5% by wt., of the said aqueous solution.

20. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-19, wherein the said polyvinyl alcohol forms 8% by wt., the said agar-agar forms 1% by wt. and the said other natural polymers and/or its derivative form 1.5% by wt., of the said aqueous solution.

21. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-20, wherein the said other natural polymers chosen is a combination of sodium alginate and gum acacia in 1:2 proportion.

22. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-21, wherein the said hydrogel dressing is 3-5 mm thick.

23. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, substantially as herein described in the text and in the examples.

AMENDED CLAIMS

[received by the International Bureau on 26 August 2000 (26.08.00);
original claim 1 amended; remaining claims unchanged (1 page)]

1. A one stage irradiation process for manufacture of hydrogel dressing free of synthetic plasticizers for treatment of burn and other skin injuries, comprising :

   i) preparing an aqueous solution of polyvinyl alcohol, agar-agar and one or more natural polymers and/or their derivatives chosen from agar-agar, gelatin, carageenan, sodium alginate, carboxy methyl cellulose, guar gum, gum acacia, chitosan and other similar natural viscosity modifiers and radical scavengers ;

   ii) putting the solution at 70-80°C in disposable plastic containers and sealing them ;

   iii) subjecting the said aqueous solution in the sealed containers obtained at the end of step (ii), to irradiation at room temperature to form the sterile ready to use hydrogel dressing.

2. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in Claim 1, wherein acetate content of polyvinyl alcohol is less than 18% by wt.

3. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1 or 2, wherein polyvinyl alcohol has molecular wt. in the range 27,000 - 1,46000.

4. A process for manufacture of hydrogel dressing for treatment of burn and other skin injuries, as claimed in any claim 1-3, wherein the said polyvinyl alcohol forms 5-15% by wt., the said agar-agar and other natural polymers and/or their derivatives form 0.5-5% by wt. of which the said other natural polymer and/or its derivative form 0 - 4.5% by wt. of the said aqueous solution.

STATEMENT UNDER ARTICLE 19(1)

The subject international application relates to a process of manufacture of hydrogel dressing for treatment of burn and other skin injuries. In the International Search Report (date of mailing 28th June 2000) issued on the above prior dated document ROSIAK J M Et Al. "Radiation formation of hydrogels for biomedical purposes. Some remarks and comments" RADIATION PHYSICS AND CHEMISTRY, NL, ELSEVIER SCIENCE PUBLISHERS BV., AMSTERDAM, Vol. 46, no. 2 and US Patent 4,871,490 A, have been cited as documents of particular relevance (X-category). It is important to note that while the above documents may also relate to hydrogel dressing, the process of the present invention is distinguished from the cited prior art revealed by the PCT International Search Report by way of the following distinguishing features :

i) One stage irradiation process ;
ii) Use of PVA (biocompatible) and natural polymer agar ;
iii) No use of toxic chemicals/plasticizers such as polyethylene glycol/silicone oil and/or separate mechanical supports ;
iv) No post irradiation treatment ;
v) The hydrogel dressing produced is biocompatible and of superior quality in terms transparency, handleability, flexibility and mechanical strength than PVP based gel.

To clearly and sufficiently bring out such inventive features of the invention vis-a-vis the prior art cited and to make the claims more clear and definitive vis-a-vis the prior art the following amendments have been made in replacement sheet 15.

i) Preamble of claim 1 amended to read :
"A one stage irradiation process for manufacture of hydrogel dressing free of synthetic plasticizers for treatment of burn and other skin injuries comprising : ....."

ii) In clause (i) of claim 1 –
The term "etc." after "..... guar gum, gum acacia **etc.**" was not definitive. The relevant portion has been amended by inclusion of name of a preferred natural polymer and/or their derivatives "Chitosan" and qualifying the selected natural polymer and/or their derivatives and clause (i) of claim 1 reworded to read :

"i) preparing an aqueous solution of polyvinyl alcohol, agar-agar and one or more natural polymer and/or their derivatives chosen from agar-agar, gelatin, carageenan, sodium alginate, carboxy methyl cellulose, guar gum, gum acacia, chitosan and other similar natural viscosity modifiers and radical scavengers ;"

The above amendments in the claims are well supported by the text and exemplary illustrations and do not go beyond the disclosure in the international application as filed.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 99/00068

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L15/60 A61L15/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, FSTA, INSPEC, COMPENDEX, MEDLINE, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROSIAK J M ET AL: "Radiation formation of hydrogels for biomedical purposes. Some remarks and comments" RADIATION PHYSICS AND CHEMISTRY,NL,ELSEVIER SCIENCE PUBLISHERS BV., AMSTERDAM, vol. 46, no. 2, 1 August 1995 (1995-08-01), pages 161-168, XP004051385 ISSN: 0969-806X	1,3,5-8, 12-16, 22,23
Y	page 164, right-hand column, paragraph 2 - paragraph 3 page 167, left-hand column, paragraph 2 -page 168, left-hand column, paragraph 1 table 1	1-3,9-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2000	28/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Menidjel, R

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INTERNATIONAL SEARCH REPORT

Inte ,onal Application No
PCT/IN 99/00068

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 871 490 A (ROSIAK JANUSZ ET AL) 3 October 1989 (1989-10-03) abstract column 1, line 43 - line 68	1,3,5-8, 13-16, 21-23
Y	MONDINO A V ET AL: "Physical properties of gamma irradiated poly(vinyl alcohol) hydrogel preparations" RADIATION PHYSICS AND CHEMISTRY,NL,ELSEVIER SCIENCE PUBLISHERS BV., AMSTERDAM, vol. 55, no. 5-6, 1 August 1999 (1999-08-01), pages 723-726, XP004172427 ISSN: 0969-806X page 723, left-hand column, paragraph 1 -right-hand column, paragraph 1 page 724, left-hand column, paragraph 2 -page 725, right-hand column, paragraph 1 page 726, left-hand column, paragraph 1	1-3,9-16
A	FR 2 596 404 A (LHD LAB HYGIENE DIETETIQUE) 2 October 1987 (1987-10-02) abstract page 3, line 10 -page 4, line 34 page 10, line 26 -page 11, line 33 page 14, line 2 - line 12	1,4, 17-23

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INTERNATIONAL SEARCH REPORT

International Application No. PCT/IN 99 /00068

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The claim 23 fails to comply with Rule 6.2(a) PCT such an extent that a meaningful search for the whole scope of the claim could not be carried out.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. ional Application No
PCT/IN 99/00068

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4871490 A	03-10-1989	DD 273200 A	08-11-1989
		DE 3744289 A	14-07-1988
		GB 2200643 A,B	10-08-1988
		HU 46050 A,B	28-09-1988
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