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STERILE GEL COMPOSITIONS FOR WOUND TREATMENT

The present invention relates to sterile gel compositions for application to the surface of wounds, such as decubitus ulcers and burns. The present invention also relates to a method of making such sterile gel compositions.

Aqueous gel compositions for application to the surface of wounds to assist healing are known. The purpose of applying the gels is to form a wound-friendly and humectant wound contact layer between the wound surface and conventional wound dressing layers. This also helps to reduce the adherence of conventional wound dressings, such as bandages or gauzes, to the wound surface. The aqueous gel can also serve as a vehicle for pharmaceutically active agents such as antiseptics or antibiotics.

US-A-4393048 describes protective gel compositions for wounds comprising about 0.5 to 3% by weight alkali metal alginate, about 8 to 12% by weight glycerol and about 82 to 90% by weight water. Medicaments in an amount of 0.01 to 10% by weight may optionally be included in the compositions. The resulting gel is brushed over the surface of the wound and dries in air to form a non-toxic, flexible and stretchable film covering the wound.

A drawback of the gel compositions described in US-A-4393048 is that they cannot readily be prepared in a sterile form suitable for medical applications. This is because the usual methods of sterilisation, namely gamma-ray irradiation or autoclaving, result in hydrolysis of the alginate and consequent drastic reduction in the gel viscosity. This rules out sterilisation of the alginate gel after it has been manufactured and filled into packages. In fact, the only way to manufacture an alginate gel of this type that is sterile would be to sterilise all the ingredients dry and then mix and package them under aseptic conditions. This method of manufacture would be prohibitively expensive for

the wound dressings market.

WO84/00111 describes heat sterilisable pharmaceutical gel compositions for the treatment of burns, cuts, wounds or abrasions. The gel compositions comprise a pharmaceutically acceptable glycol and a cellulose derivative which is heat sterilizable. The preferred glycol is propylene glycol, preferably in an amount of 20-30% w/v. The preferred cellulose derivative is hydroxy ethyl cellulose, preferably in an amount of 1-4% w/v. The gel compositions optionally contain medicaments and/or dissolved physiologically acceptable salts. The use of hydroxy ethyl cellulose gives a gel that is heat sterilisable. That is to say, the gel retains its consistency and does not break down into a liquid when it is sterilised in an autoclave.

A drawback of the gel compositions described in WO84/00111 is that the heat sterilisable cellulose derivatives are inherently less effective in promoting wound heating than natural biopolymers such as alginates.

Accordingly, it is an object of the present invention to provide a heat sterilisable alginate gel for use in the treatment of burns, cuts, wounds, ulcers or abrasions.

The present invention provides an aqueous gel composition for use as a wound dressing comprising from 2% to 10% w/v of alginate and from 15% to 40% w/v of polyhydric alcohol, said composition being substantially sterile.

Surprisingly, it has been found that the inclusion of relatively large amounts of polyhydric alcohol (more than 15% w/v) results in an alginate gel that is stabilised against hydrolysis and consequent loss of viscosity during sterilisation. Sterilisation can be carried out by autoclaving using standard conditions. Compositions containing more than 40% w/v of polyhydric alcohol tend to separate on autoclaving. Such compositions can also cause

discomfort or stinging when applied to a wound.

The alginate may consist of one or more of alginic acid and its salts. Preferably, a soluble alginate salt is used to produce a gel that is fully water soluble both before and after sterilization. Preferably, the alginate consists of sodium alginate and/or potassium alginate. Preferably, the gel compositions comprise 3% to 6% w/v of the alginate. Preferably, the molecular weight of the alginate is in the range of 50,000 to 500,000.

The polyhydric alcohol preferably comprises one or more C_3-C_6 dihydric or trihydric alcohols, more preferably C_3-C_6 dihydric alcohols and most preferably propylene glycol or hexylene glycol. Other preferred polyhydric alcohol include ethylene glycol, butylene glycol, glycerol, diethylene glycol, dipropylene glycol, polyethylene glycol and polypropylene glycol. Preferably, the composition contains a total of 20% to 35% w/v of the one or more polyhydric alcohols.

The entire balance of the gel compositions other than the alginate and polyhydric alcohol may consist of water. However, preferably, the gel compositions also contain 0.01% to 10% w/v of one or more pharmaceutically active compounds, more preferably 0.1% to 5% w/v of such compounds. Preferred pharmaceutically active compounds are selected from: antiseptics such as chlorhexidine or silver sulphadiazine; antibiotics such as pencillins or tetracyclines; analgesics such as aspirin, paracetamol, ibuprofen or naproxen; steroids; glycosaminoglycans such as hyaluronic acid and its salts, chondroitin sulfate or heparan sulfate; vitamins such as vitamins A and E; haemostats; cytokines; antibodies; enzymes; inflammatory agents; anti-inflammatory agents, and growth factors. Preferably, the total water content of the aqueous gel is from 55% to 79% w/v.

The alginate gel according to the present invention may also

contain up to 3% w/w, preferably less than 2% w/w of one or more cellulose derivatives, such as carboxymethyl cellulose or hydroxyethyl cellulose.

The aqueous gel preferably further comprises from 0.1% to 5% w/v of dissolved salts. The salts are preferably selected from the chlorides, iodides, sulfates, phosphates, bromides, carbonates, bicarbonates and hydroxides of sodium, potassium, ammonium, zinc, silver and calcium. The dissolved salts preferably comprise sodium chloride, since it has been found that the presence of small amounts of sodium chloride can significantly affect the change in viscosity of the gel on sterilisation. The sodium chloride content thus provides a further parameter with which to control the viscosity of the sterile gel compositions. Also preferably, the gel compositions comprise phosphate salts or other suitable buffers to regulate the pH of the gel.

As noted above, an advantageous feature of the gels according to the present invention is that they retain useful viscosity after sterilisation. Preferably, the sterile gel compositions have a viscosity in the range 5,000-100,000 cps at 20°C, more preferably 10,000-50,000 cps at 20°C. This allows the gels to be coated onto the wound site reasonably conveniently.

The present invention also provides a process to prepare a substantially sterile gel for application to burns, cuts, wounds, ulcers or grazes, the process comprising the steps of: providing an aqueous gel comprising from 2% to 10% w/v of alginate and from 15% to 40% w/v of polyhydric alcohol; and sterilising the aqueous gel.

Preferred compositions and constituents of the aqueous gel are the same as those described above for the gel compositions according to the present invention.

Preferably, the step of sterilizing is carried out by

heating at a temperature of for a period sufficient to give a sterility measure of FO_4, more preferably FO_8, and most preferably FO_{12}. These FO values are standard measurements of the cumulative lethal effect of heating at a specified temperature for a specified time. Heating at 121°C (250°F) for 2.45 minutes corresponds to FO_{12}, since it is understood to achieve a 10^{12} - fold reduction in viable *CL. Botulinum* spores in phosphate buffer. Details of the FO measurement may be found in Principles and Practice of Disinfection, Preservation and Sterilization, 2nd edition, edited by A.D. Russell, W.B. Hugo and G.A.J. Ayliffe (Blackwell Scientific Publications), pages 521-524. Preferably, this step of heat-sterilising is carried out under pressure in an autoclave.

Preferably, the process according to the present invention further comprises the step of inserting the aqueous gel into a package prior to carrying out the step of sterilising. Preferably, the package is a tube, can or sachet. This procedure is advantageous because it enables the aqueous gels to be made under non-sterile conditions, packaged and then sterilised, thereby providing a relatively low-cost route to packaged sterile alginate gels.

In order for the aqueous gel to be easily packaged prior to sterilisation, it is preferable for the viscosity of the aqueous gel (as determined by a spindle riscometer at ambient temperature) before sterilisation to be less than 150,000 cps, preferably less than 100,000 cps. After sterilization, the viscosity at ambient temperature is preferably in the range 70,000-180,000 cps. Preferably, the change in viscosity on autoclaving is no more than ± 20%.

Specific embodiments of the gel compositions and processes according to the present invention will now be described further in and by the following Examples:-

Example 1

The effect of propylene glycol (PG) content on the heat

sterilisability of aqueous alginate gels is determined as follows.

A number of aqueous alginate gels is made up according to the following proportions. The sodium alginate (Protanal LF 10/60) has a stated molecular weight in the range 70,000 to 200,000. The potassium alginate has a molecular weight range of 300,000 to 350,000. Each gel is then sterilised in an autoclave to give a sterility measure of FO_{12}.

The viscosity in centipoise (cps) at 20°C is measured before and after sterilisation for each of the gels. The viscosity measurements are carried out with a rotating spindle, dial reading mechanical viscometer manufactured by Brookfield Viscometers Ltd. Brookfield Spindle No. 7 is used at a speed of 10 revolutions per minute. The sample is held in a cylindrical container measuring at least 50mm in diameter and holding sample to a depth of at least 70mm.

The results are as follows (* denotes a comparative example).

a) 4% w/v Sodium Alginate

PG Conc. % w/v	Unsterile Viscosity (cps)	Sterile Viscosity (cps)
5*	2000	100
10*	2200	100
15	4300	130
20	9000	190
25	7480	270
30	2700	13600
35	200	30000
40	50	17600

b) 5% w/v Sodium Alginate

PG Conc. % w/v	Unsterile Viscosity (cps)	Sterile Viscosity (cps)

	5*	4000	200
	10*	6000	220
	15	12300	320
	20	19800	490
5	25	16200	21400
	30	5780	53000
	35	1400	34000
	40	50	Separated

c) 6% w/v Sodium Alginate

PG Conc. % w/v	Unsterile Viscosity (cps)	Sterile Viscosity (cps)
5*	7200	440
10*	17600	460
15	29920	740
20	38000	2200
25	28000	27000
30	10600	104000
35	4000	139000
40	70	Separated

d) 3% w/v Potassium Alginate

PG Conc. % w/v	Unsterile Viscosity (cps)	Sterile Viscosity (cps)
5*	8400	180
10*	12000	190
15	14000	400
20	24200	440
25	30200	700
30	44000	1100
35	35200	1760
40	12400	30000

e) 4% w/v Potassium Alginate

PG Conc. % w/v	Unsterile Viscosity (cps)	Sterile Viscosity (cps)
5*	33000	900
10*	32000	1200
15	42600	1700
20	61200	1940
25	78000	3460
30	87200	4100
35	67200	30000
40	28000	122000

f) 5% w/v Potassium Alginate

PG Conc. % w/v	Unsterile Viscosity (cps)	Sterile Viscosity (cps)
20	141000	5400
25	129000	7600
30	154000	36400
35	114000	172000
40	26400	126000

These results demonstrate clearly that, by optimising the level of alginate and propylene glycol, it is possible to produce an alginate gel which maintains, or even increases, its viscosity on autoclaving.

Example 2

The procedure of Example 1 is followed for the following compositions, in which the propylene glycol (PG) of Example 1 has been replaced by hexylene glycol (HG). The results are as follows (* denotes a comparative example).

a) 3% w/v Sodium Alginate

HG Conc. % w/v	Unsterile Viscosity (cps)	Sterile Viscosity (cps)
5*	400	4
10*	980	14
15	2900	40
20	1200	60
25	80	10000
30	20	Separated

b) 4% w/v Sodium Alginate

HG Conc. % w/v	Unsterile Viscosity (cps)	Sterile Viscosity (cps)
5*	2200	50
10*	4400	104
15	9700	156
20	2900	2100
25	25	10000
30	10	Separated

c) 5% w/v Sodium Alginate

HG Conc. % w/v	Unsterile Viscosity (cps)	Sterile Viscosity (cps)
5*	4980	190
10*	14200	236
15	17400	360
20	6600	32000
25	300	20600
30	20	Separated

d) 6% w/v Sodium Alginate

HG Conc. % w/v	Unsterile Viscosity (cps)	Sterile Viscosity (cps)
5*	9850	100
10*	28700	100
15	30300	24400
20	13400	39600
25	1000	78000
30	Separated	Separated

These results demonstrate that hexylene glycol can also be used to form autoclave-stable alginate gels. It appears that less hexylene glycol than propylene glycol is needed to achieve equivalent stabilisation.

Example 3

The effect of adding 0.6% w/v of sodium chloride to a 3% sodium alginate gel is illustrated by the following data (* denotes a comparative example)@

PG Conc. % w/v	Unsterile Viscosity (cps)	Sterile Viscosity (cps)
2.5*	1000	105
5.0*	1100	145
10.0*	4010	135
15.0	2950	170
20.0	584	2000
25.0	44	12000
40.0	13	260

It can be seen that the addition of 0.6% w/v sodium chloride to the aqueous alginate gel at 25% w/v PG content results in a gel having substantially increased viscosity after autoclaving.

Example 4

A heat-sterilizable alginate gel composition is manufactured as follows:-

Component	Trade Name	% w / w in Formulation
Sodium Alginate	Protanal ®LF 10/60	3.00
Carboxymethyl Cellulose	Aquasorb ® A250	7.00
Hydroxyethyl Cellulose	Natrosol ® 250HX	0.35
Sodium Chloride	-	0.30
Propylene Glycol	Mono-PG USP	25.00
Purified Water	-	70.35

The components are mixed thoroughly and then heat - sterilized to FO_{12}. The resulting clear, sterile gel has a dynamic viscosity at 21°C of 150,000 cps.

The above embodiments have been described by way of example only. Many other embodiments falling within the scope of the accompanying claims will be apparent to the skilled reader.

* C L M S *

CLAIMS

1. An aqueous gel composition for use as a wound dressing comprising from 2% to 10% w/v of alginate and from 15% to 40% w/v of polyhydric alcohol, said composition being substantially sterile.

2. An aqueous gel composition according to claim 1, wherein the composition comprises from 3% to 6% w/v of the alginate.

3. An aqueous gel composition according to claim 1 or 2, wherein the alginate is a water-soluble alginate salt.

4. An aqueous gel composition according to claim 1, 2 or 3, wherein the composition contains 20% to 35% w/v of the polyhydric alcohol.

5. An aqueous gel according to any preceding claim, wherein the polyhydric alcohol comprises one or more C_3-C_6 dihydric alcohols.

6. An aqueous gel according to claim 5, wherein the C_3-C_6 dihydric alcohols are selected from the group consisting of propylene glycol and hexylene glycol.

7. An aqueous gel according to any preceding claim, further comprising from 0.01% to 10% w/w of pharmaceutically active compounds, preferably 0.1% to 5% w/w of said compounds.

8. An aqueous gel according to claim 7, wherein the pharmaceutically active compounds comprise an antiseptic, an antibiotic, an analgesic, a glycosaminoglycan, a vitamin, an antibody, an enzyme, a haemostat, a cytokine, an inflammatory agent, an anti-inflammatory agent, a steroid or a growth factor.

9. An aqueous gel according to any preceding claim, further comprising from 0.1% to 5% w/v of dissolved salts.

10. An aqueous gel according to claim 9, wherein the dissolved salts comprise sodium chloride or phosphate salts.

11. A process to prepare a substantially sterile gel for use as a wound dressing, the process comprising the steps of:

providing an aqueous gel comprising from 2% to 10% w/v of alginate and from 15% 40% w/v of polyhydric alcohol; and

sterilising the aqueous gel.

12. A process according to claim 11, wherein the step of sterilising is carried out by heating at a temperature and for a time sufficient to give a sterility measure of FO_4.

13. A process according to claim 12, wherein the step of heat-sterilising is carried out under pressure in an autoclave.

14. A process according to claim 11, 12 or 13, wherein the aqueous gel has a composition as defined in any of claims 2 to 12.

15. A process according to any of claims 11 to 14, further comprising the step of inserting the aqueous gel into a sealed package prior to the step of sterilising.