

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
31 December 2003 (31.12.2003)

PCT

(10) International Publication Number
WO 2004/000910 A1

(51) International Patent Classification⁷: **C08G 63/91**,
C08F 8/00, A61F 2/00

(21) International Application Number:
PCT/US2003/010397

(22) International Filing Date: 4 April 2003 (04.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/177,995 21 June 2002 (21.06.2002) US

(71) Applicant: **ISP INVESTMENTS INC.** [US/US]; 300
Delaware Avenue, Wilmington, DE 19801 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors: **PLOCHOCKA, Krystyna**; 2305 Mountain Avenue, Scotch Plains, NJ 07076 (US). **LYNN, Jeffrey, A.**; 78 Overlook Road, West Milford, NJ 07480 (US).

Published:
— with international search report

(74) Agents: **MAUE, Marilyn, J.** et al.; Legal Department, Bldg. 10, International Specialty Products, 1361 Alps Road, Wayne, NJ 07470 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: POLYMERIC HYDROGELS

(57) Abstract: What is described is a polymeric hydrogel of a polymeric anhydride or acid, e.g. maleic anhydride or maleic acid polymer, or copolymer thereof, crosslinked with a crosslinking agent containing at least 2 crosslinkable groups, particularly, -OH or -NH₂, or both. The reaction product is a crosslinked polymeric ester or amide/imide, or both, suitably having a mole ratio of -OH, or -NH₂, to -COOH, of 1:10 to 10:1, preferably 2:10 to 7:1. The hydrogel is particularly swellable in water, e.g. > 100 % in 1 hour in aqueous media; and forms a thin, tacky layer on a substrate, which property is useful in bioadhesive products.

WO 2004/000910 A1

POLYMERIC HYDROGELS

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to hydrogels, and, more particularly, to polymeric hydrogels which are crosslinked polymeric esters or amides/imides, or both, of a polymeric anhydride or acid, or copolymers thereof, which are very swellable in water, and form thin, tacky layers on a substrate, and bioadhesive products thereof.

2. Description of the Prior Art

Hydrogels are polymeric materials which can swell appreciably in water. However, what is described as hydrogels can be viscous polymeric solutions without the swelling characteristic of a true hydrogel. Such hydrogels also are not tacky, a necessary property for making bioadhesive products. See U.S. Pats. 4,740,365; 4,990,551; 5,135,753; 5,336,501; and 5,846,214. Accordingly, it is desired to provide new and useful polymeric hydrogels having exceptional swelling properties in water, and which are tacky; and bioadhesive products of such hydrogels.

IN THE DRAWINGS

Figure 1 – Swelling of Gantrez AN 200 SF/PVOH hydrogel.

Figure 2 – Swelling of Gantrez S 97/glycerol hydrogel.

Figure 3 – Swelling of Gantrez S 97/sorbitol hydrogel.

Figure 4 – Swelling of Gantrez S 97/PVOH hydrogel.

Figure 5 – Swelling versus time in buffer pH 7.

Figure 6 – Swelling of S 97/Glycerol hydrogels in buffer pH 7.

Figure 7 – Weight loss at room temperature for S 97/glycerol hydrogels.

SUMMARY OF THE INVENTION

What is described herein is a polymeric hydrogel which is a polymeric anhydride or acid or copolymer thereof, e.g. maleic anhydride or maleic acid polymer, or copolymer thereof, preferably with an alkylvinylether; e.g. methylvinylether or isobutylvinylether; or an olefin, e.g. butylenes or isobutylene; crosslinked with a crosslinking agent having at least 2 crosslinkable groups; e.g. an alcohol, -OH, an amine, -NH₂, or alcohol-amine groups, e.g. polyols such as polyvinyl alcohol, glycerol, glucose, sorbitol, pentaerythritol, nonionic surfactants, alginates, starch, cellulose, ethylene glycol, diethylene glycol and ethoxylated/propoxylated derivatives thereof; or a polyamine or ethoxylated amine, e.g. an aminoalcohol, amino acid and the like.

The polymeric hydrogel of the invention preferably has a mole ratio of -OH or -NH₂:COOH of 1:10 to 10:1, most preferably 2:10 to 7:1.

The polymeric hydrogel herein is particularly characterized by its exceptional swelling properties and tackiness, which are useful for making bioadhesive products.

The polymeric hydrogels of the invention are made by reacting a maleic anhydride or maleic acid polymer, or copolymer, with a crosslinking agent having at least 2 crosslinkable groups, particularly a polyol or polyamine, or alcohol amine, unexpectedly, in water as solvent, in the presence of an esterification or amidation catalyst.

The reaction product is a crosslinked polymeric ester or amide/imide, or both.

Generally the polymer hydrogels of the invention contain a considerable amount of water, usually about 50 wt % or more.

DETAILED DESCRIPTION OF THE INVENTION

The polymeric hydrogel of the invention is made by a crosslinking reaction between an acidic polymer, particularly copolymers of maleic anhydride or maleic acid, or mixtures thereof, and a comonomer, e.g. an alkylvinylether, such as methylvinylether or isobutylvinylether, or olefin, e.g. butylenes or isobutylene; with a suitable crosslinking agent, i.e. a compound having at least 2 groups crosslinkable with such copolymers, such as present in polyols, diols, triols, etc. present in compounds such as glycerol, pentaerythritol, sorbitol, and nonionic surfactants; in polymers such as polyvinyl alcohol, (PVOH), sugars, e.g. glucose, saccharose, alginates, starch, cellulose, and its derivatives; or amines, or aminoalcohols, present and in polyamines, polyaminoalcohols, ethoxylated amines, amino acids, e.g. arginine, glutamine, lysine and gelatine.

The crosslinking reaction produces a crosslinked polymeric ester or amide/imide, or mixed ester-amide/imide. Unexpectedly this reaction suitably is carried out in an aqueous solution or slurry of polymer and crosslinking agent in the presence of an esterification or amidization catalyst, e.g. sulfuric acid, phosphoric acid or toluene sulfonic acid, at about 60-130°C, preferably 80-110°C.

Preferably the hydrogel is formed as continuous molds or sheets on a substrate, not as discrete particles in the bulk.

The polymeric hydrogel obtained has advantageous swelling properties in various solvent media e.g. water, base, salt, buffers, etc. When applied to a substrate, the polymeric hydrogel of the invention forms a thin, tacky layer suitable for use as a bioadhesive. The hydrogels also are useful in oral care, personal care, wound care and drug delivery systems.

The physical properties of the hydrogel, e.g. swelling/tack/solubility/rate of drying/dispersibility in water, and viscoelastic properties, and feel, etc. can be predetermined by the mole ratio of $-OH$ or $-NH_2:COOH$ in the hydrogel, as well as the reaction conditions employed, e.g. temperature, catalyst, reaction time, amount of water, etc.

Preferably the mole ratio of $-OH$ or $-NH_2:COOH$ in the hydrogel is 1:10 to 10:1, most preferably 2:10 to 7:1.

The invention will now be described in specific detail by the following examples.

EXAMPLE 1

Maleic anhydride/methylvinylether copolymer (MAN) (Gantrez[®] AN SF i.e. solvent free anhydride) powder (20 g) was slurried into 188 g of aqueous polyvinyl alcohol (PVOH) solution containing 20 wt % PVOH. The mole ratio of $-OH$ groups in the PVOH to the $-COOH$ groups in Gantrez[®] AN was 3.34. Then 2 g of p-toluenesulfonic acid was added to the slurry with agitation. The agitated slurry was poured into a section of flexible Tygon tubing which was sealed by clamping at both ends. The tubing served as a mold for making a rod-shaped pieces of hydrogel. The tubing with slurry inside then was placed in a 105°C oven and it was held at that temperature for 6 hrs. After cooling to room temperature, a rod-shaped, rubbery, slightly tacky, uniform, semi-transparent hydrogel was obtained. The tubing was cut into sections for swell testing in various media.

The sections of hydrogel were weighted and placed in DI water, buffered at pH levels of 4, 7 and 10, and in 0.1% NaOH and 0.1% NaCl aqueous solutions. The pieces were taken out, wiped dry and weighed again. The pieces retained their shape and integrity after soaking for 6 weeks.

EXAMPLE 2

Maleic acid/methylvinylether (MAA) (Gantrez[®] S-97, 16.78 % by wt in water) (120 g) was blended with 200 g PVOH (20% in water) and 4 g of sulfuric acid (50%) to yield a viscous solution. The mole ratio of -OH groups from PVOH to -COOH groups from Gantrez[®] S-97 was 3.95. The solution was poured into Tygon tubing and kept in a 105°C oven for 6 hrs. After cooling the tubing was removed to provide a rod-shaped, slightly tacky, uniform, transparent hydrogel, which was tested as in Example 1.

EXAMPLE 3

Gantrez[®] S-97 (16.78 % by wt in water) 240 g, glycerol 80 g and 8 g sulfuric acid (50%) were blended to yield a uniform solution. The mole ratio of -OH groups from glycerol to -COOH groups from Gantrez S-97 was 5.65. The solution was poured into several 8 oz jars to form about 10 mm thick layer. The jars were sealed and placed in a 105°C oven for 9 hrs. After cooling to room temperature, a flat, soft, smooth, colorless, transparent hydrogel molds were obtained. The hydrogels were very tacky, attached themselves lightly to skin, but could be easily removed without leaving any residue. Pieces cut from the molds were tested for swelling as described in the preceding examples. The tackiness vs. % swelling curves showed a diminishing relationship. After reaching 300 to 500% of swelling, the hydrogels became non-tacky.

EXAMPLE 4

Hydrogel molds were prepared as in Example 3; however, starting with a blend of Gantrez[®] S-97 120 g, sorbitol (70% aq.) 116 g and sulfuric acid (50%) 8 g. The mole ratio of -OH groups from sorbitol to -COOH groups from Gantrez S-97 was 5.8. The hydrogels obtained had an appearance, feel and swelling behavior very similar to those made with glycerol, and their tack behavior was also similar.

EXAMPLE 5

Blends of Gantrez[®] S-97 and glycerol, or sorbitol, or PVOH, as in Examples 2 through 4 containing sulfuric acid as a catalyst, were poured onto a polyester cloth placed at the bottom of glass trays to a thickness of about 3 mm. Then the trays were covered with a plastic wrap and placed in a 85°C oven for 6 hrs, and, thereafter, in a 105°C oven for 9 hrs. After cooling to room temperature, the products were recovered as tacky transparent thin sheets on the polyester backing. Tackiness was compared by touch:

TABLE 1
Tack of Thin Layer Hydrogels as Evaluated by Touch

Crosslinker	Tack
Glycerol	Very tacky
Sorbitol	Very tacky
PVOH	Slightly tacky
Band Aid [®] (J&J)	Very tacky
Scotch [®] tape	Tacky

EXAMPLE 6

A blend of Gantrez[®] S-97 (16.78% in water) 120 g, ethanolamine 14 g and p-toluenesulfonic acid 2 g, is molded in glass jars as in Example 3. The mole ratio of -OH or -NH₂ groups from ethanolamine to -COOH groups from Gantrez[®] S-97 is 2.0. Hydrogels recovered after molding have an appearance and feel similar to the products of Examples 3 and 4.

Figures 1-7 show the swelling characteristics of the hydrogels of the present invention in various aqueous media in graphical representation. In general, the swelling property and tack of the hydrogel product of the invention is predetermined by the following factors: (1) the particular crosslinker used, (2) the -OH or -NH₂/-COOH mole ratio, and (3) the aqueous solvent media used in its preparation. Usually, the order of swelling for a given crosslinker used, in a pH 7 buffer, was sorbitol > glycerol > PVA; with swelling ranging from 200% to 1200% over a soaking time of 1-25 hours; and in different solvent media it was 0.1% NaOH >> pH 7 ≥ pH 10 ≥ pH 4 > DI water ~ 0.1% NaCl: ranging from 100% to 3000% for a similar soaking period.

The hydrogels with glycerol and sorbitol were very tacky at time zero, but, after swelling to > 300%, they became only slightly tacky, and then were non-tacky at > 500% swelling; PVA crosslinked hydrogels were slightly tacky at time zero. A significant degree of swelling without loss of integrity is indicative of a crosslinked hydrogel.

Hydrogels with PVA as crosslinker retained their shape after soaking in water for several weeks.

The bioadhesive hydrogels of the invention find wide application in many products, such as topical drug and cosmetic delivery systems; e.g. skin and mucous membranes; personal care products such as skin care; an oral care, e.g. denture liners, flavor and drug delivery; wound care and in systems for drug delivery.

While the invention has been described with particular reference to certain embodiments thereof, it will be understood that changes and modifications may be made which are within the skill of the art. Accordingly, it is intended to be bound only by the following claims, in which:

WHAT IS CLAIMED IS:

1. A polymeric hydrogel comprising a polymeric anhydride or acid, or copolymer thereof, crosslinked with a crosslinking agent having at least 2 crosslinkable groups.
2. A polymeric hydrogel of claim 1 including maleic anhydride or maleic acid polymer, or copolymer thereof with an alkylvinylether or olefin.
3. A polymeric hydrogel according to claim 1 where the crosslinkable group is an alcohol (-OH), amine (-NH₂) or alcohol-amine (-OH) (-NH₂).
4. A polymeric hydrogel according to claim 3 wherein said crosslinking agent is a polyol.
5. A polymeric hydrogel according to claim 4 wherein said polyol is selected from polyvinyl alcohol, glycerol, glucose, sorbitol, pentaerythritol, nonionic surfactants, alginates, starch, cellulose.
6. A polymeric hydrogel according to claim 1 wherein said crosslinking agent is a polyamine or ethoxylated amine.
7. A polymeric hydrogel according to claim 1 wherein said crosslinking agent is an aminoalcohol.
8. A polymeric hydrogel according to claim 6 wherein said polyamine is an amino acid.

9. A polymeric hydrogel according to claim 1 wherein the mole ratio of said alcohol (-OH) or amine (-NH₂) groups in the crosslinking agent to carboxyl groups (-COOH) in the polymer or copolymer is 1:10 to 10:1.

10. A polymeric hydrogel according to claim 9 wherein said mole ratio of -OH or -NH₂:COOH is 2:10 to 7:1.

11. A polymeric hydrogel according to claim 1 in the form of a continuous sheet.

12. A method of making a polymeric hydrogel of claim 1 which comprises reacting a maleic anhydride or maleic acid polymer with a crosslinking agent having at least 2 crosslinkable groups in the presence of an esterification or amidation catalyst, in water as solvent.

13. A method according to claim 12 wherein said crosslinking agent is an alcohol, amine or alcohol-amine

14. A method according to claim 1 which is run at 60°-130°C.

15. A method according to claim 14 which is run at 80°-110°C.

16. The reaction product of claim 12 which is a crosslinked polymeric ester or amide/imide, or both.

17. A bioadhesive comprising the polymeric hydrogel of claim 1 on a substrate.

18. A composition including the polymeric hydrogel of claim 1.

1/4

FIG. 1

Swelling of Gantrez AN 200 SF/ PVOH hydrogel.
-OH/-COOH = 3.34

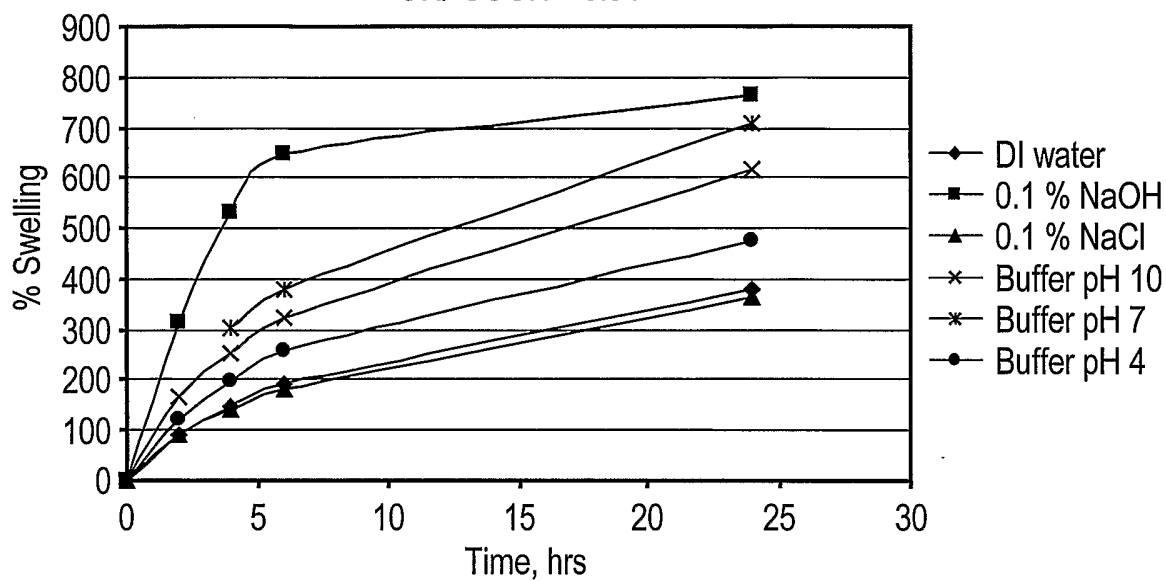
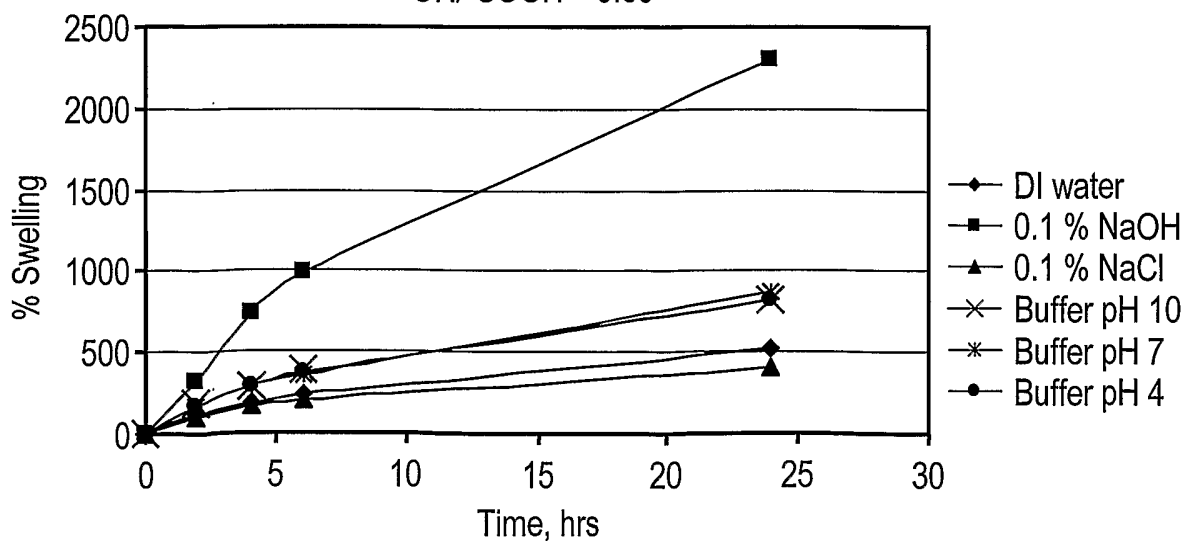


FIG. 2

Swelling of Gantrez S 97/glycerol hydrogel.
-OH/-COOH = 5.65



2/4

FIG. 3

Swelling of Gantrez S 97/ sorbitol hydrogel
-OH/-COOH = 5.8

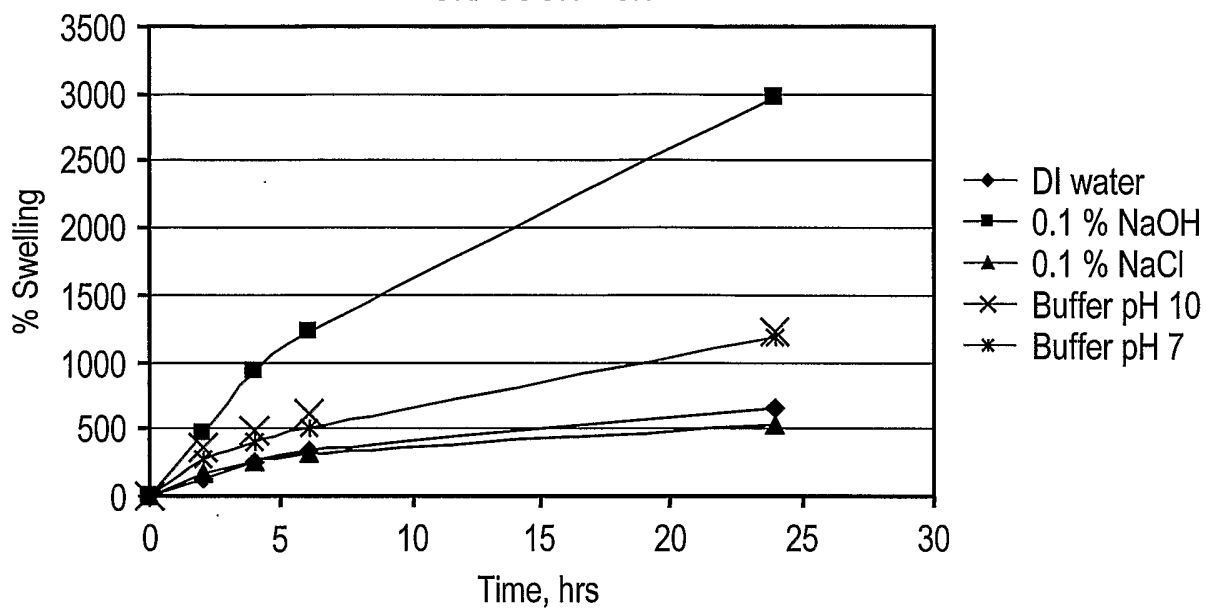
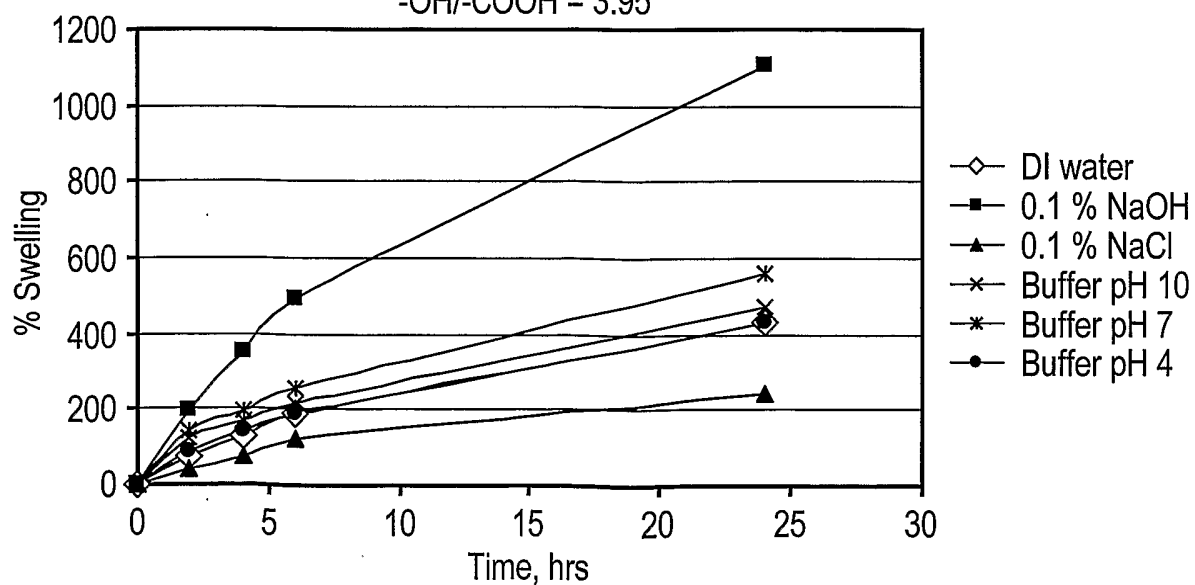


FIG. 4

Swelling of Gantrez S 97 / PVA hydrogel.
-OH/-COOH = 3.95



3/4

FIG. 5

Swelling versus time in buffer pH 7.
Different crosslinkers.

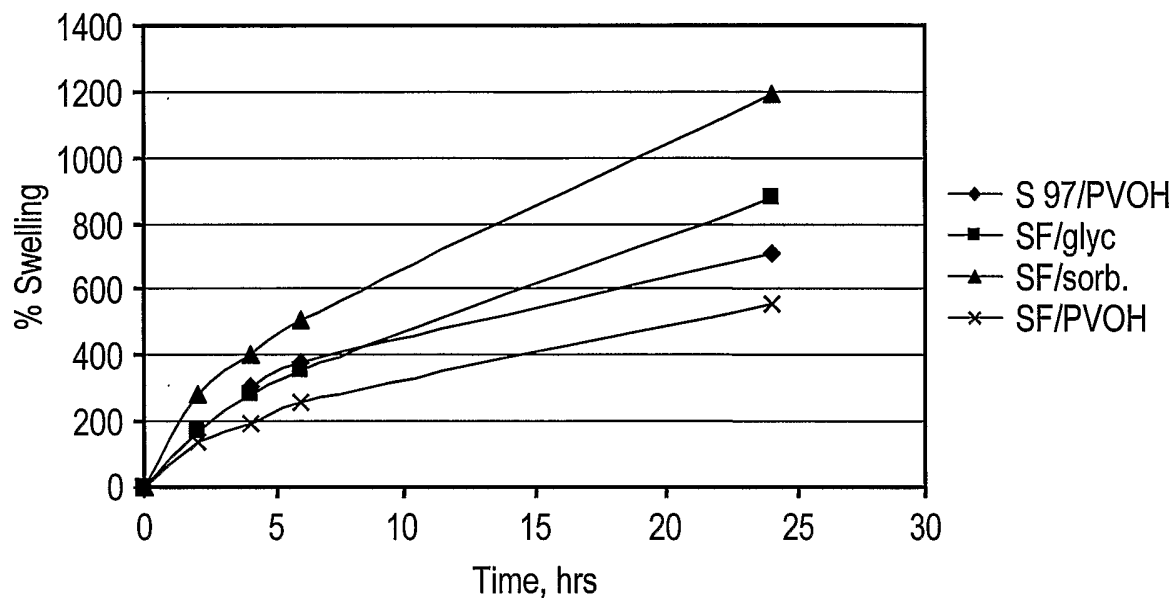
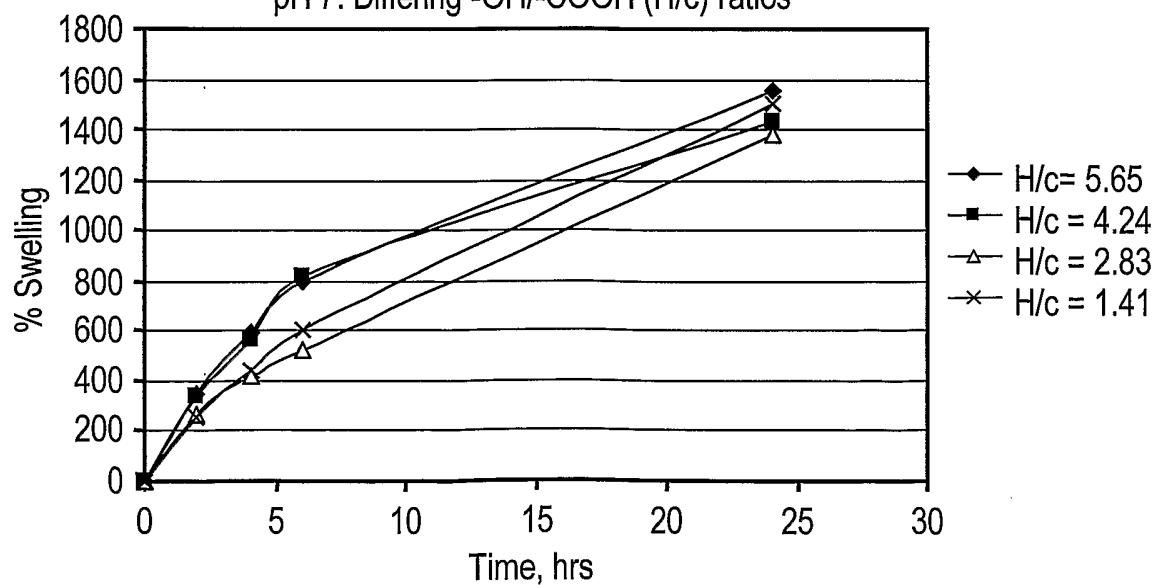


FIG. 6

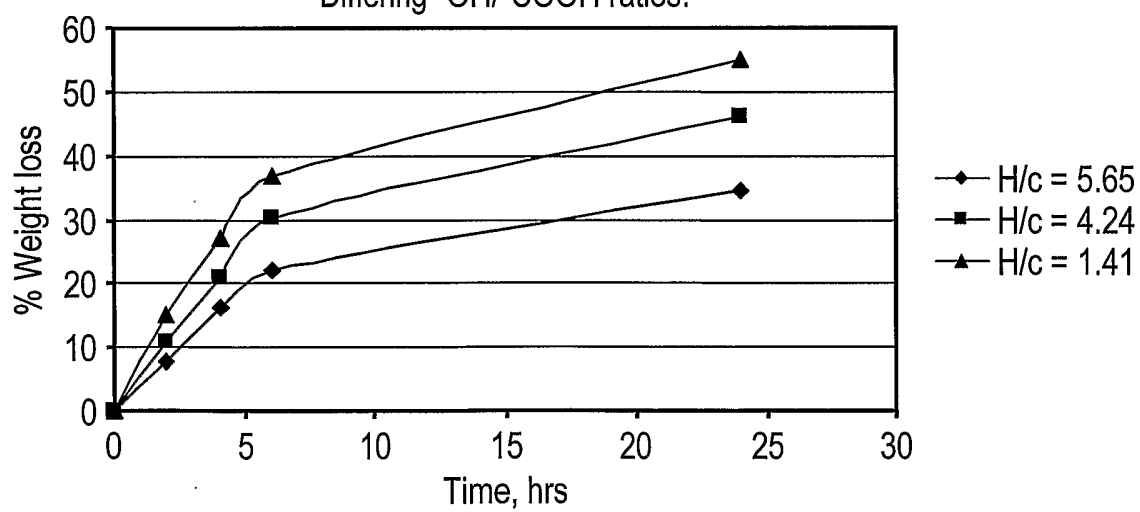
Swelling of S 97/glycerol hydrogels in buffer
pH 7. Differing -OH/-COOH (H/c) ratios



4/4

FIG. 7

Weight loss at room temperature for S 97/glycerol hydrogels.
Differing -OH/-COOH ratios.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/10397

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C08G 63/91; C08F 8/00; A61F 2/00

US CL : 525/54.2, 191; 424/426

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)

U.S. : 525/54.2, 191; 424/426

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 practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 3,989,586 A (BASHAW et al) 02 November 1976 (02.11.1976), column 3, lines 43-57, 66-67 col. 4, lines 30-34, col. 4, lines 59-62.	1-7, 11, 18 ----- 8-10, 12-17
X --- Y	US 5,614,578 A (DONG et al) 25 March 1997 (25.03.1997), col. 6, lines 15-63, col. 8, lines 12-15.	1-5, 11, 18 ----- 6-10, 12-17
X --- Y	US 6,072,005 A (KOBLYVKER et al) 06 June 2000 (06.06.2000), col. 6, lines 8-30, col. 7, lines 48-51.	1-5, 11, 17-18 ----- 6-10, 12-16



Further documents are listed in the continuation of Box C.



See patent family 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 application or patent 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

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

20 May 2003 (20.05.2003)

Date of mailing of the international search report

05 JUN 2003

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

THAO TRAN

Telephone No. 703-308-0661

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/10397

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.