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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number: WO 92/22285
A61K 9/70	A1	(43) International Publication Date: 23 December 1992 (23.12.92)

(21) International Application Number: PCT/US92/05124

(22) International Filing Date: 15 June 1992 (15.06.92)

(30) Priority data:
715,813 14 June 1991 (14.06.91) US

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(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ALGINATE WOUND DRESSINGS

(57) Abstract

The present invention provides materials suitable for use as a dressing in the care of wounds. The material is comprised of alginate fibers containing at least one biological agent that promotes the natural healing process of wounds. In addition, the present invention provides methods of preparing such materials useful as wound dressings.

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ALGINATE WOUND DRESSINGS

BACKGROUND OF THE INVENTION

This invention relates to wound care, and more specifically to alginate wound dressings containing biological agents and methods of making such dressings.

Wounds resulting from bodily injuries, whether traumatic or elective as in surgery, normally undergo a natural healing process. Depending on the nature and severity of the injury, wound dressings may be necessary to provide an environment that promotes healing. For example, dressings provide a barrier to bacterial and particulate contamination that may cause infection and other secondary complications.

Ideally, a dressing should not only protect the wound from contamination, but should also maintain a balance between absorbing excess exudate (fluids seeping from a wound) and preventing the wound from drying out too early in the healing process. Other desirable properties of an ideal dressing include: (1) gas permeability to provide the wound with adequate oxygen while allowing wound gases to escape; (2) insulating the wound from excessive temperature changes; (3) flexibility to conform to any irregular or difficult-to-dress areas; (4) being non-adherent so as to protect new tissue growth and minimize discomfort to the patient; (5) gentle application and removal; and (6) active intervention of the natural healing process by providing wounds with biological or therapeutic agents that promote a more rapid recovery. The ideal dressing would have several advantages including, among others, promoting faster recovery time, reducing the risks of secondary complications and re-injury to a wound during the healing process, requiring less nursing time and reducing discomfort to the patient, with an overall benefit of reducing health care costs.

Traditional dressings known in the health care industry have failed to satisfy all the requirements of the ideal dressing described above. For example, non-adherent dressings usually lack absorbency to control the level of exudate, whereas absorbent dressings tend to adhere to the wound causing considerable discomfort to the patient upon removal and disruption of newly formed tissue. Even known alginate dressings, such as those described in the International Patent Application Numbers PCT/GB80/00066 and PCT/GB84/00084 entitled "Man-Made Filaments and Wound Dressings Containing Them" and "Process for Treating Alginic Material," respectively, have not contained biological or therapeutic agents that actively promote the natural healing process. Currently, such agents are usually applied directly on a wound, thus subjecting the patient to additional discomfort.

There exists a need for wound dressings that possess the desirable properties of an ideal dressing described above. The present invention satisfies this need and provides related advantages as well.

SUMMARY OF THE INVENTION

The present invention provides materials suitable for use as a dressing in the care of wounds. The material is comprised of alginate fibers containing at least one biological agent that promotes the natural healing process of wounds. In addition, the present invention provides methods of preparing such materials useful as wound dressings.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides materials suitable for dressing wounds comprising alginate fibers, preferably calcium alginate fibers, having incorporated

therein at least one biological agent. The biological agent preferably promotes wound healing and is preferably selected from the group consisting of magnesium, calcium, zinc, and silver.

The alginate used to prepare the fibers of the present invention is obtained from commercial sources, such as Kelco, San Diego, CA. Figure I provides a flow chart showing a process for manufacturing sodium alginate.

Alginate fibers may be prepared according to any method known in the art and include, for example, the methods described in the patent applications published as International Publication Nos. WO 80/02300 and WO 84/03705, as well as British Patents 567,641, 568,177, 571,657 and 624,987. The alginate fibers useful for the present invention are the calcium alginate fibers as described, for example, in International Publication No. WO 80/02300. The reduced calcium alginate fibers as described, for example, in International Publication No. WO 84/03705 are preferred. The reduction of calcium in the alginate fibers can lessen the chance of soft tissue calcification. Briefly, calcium alginate tow is treated in a solution containing magnesium and zinc acetate in IMS. It is then washed in three changes of liquor containing increasing concentrations of IMS and then dried. The process is described further in Figure II.

As used herein, the term "fiber" is used interchangeably with the term "tow." Since the scope of the present invention encompasses the care of wounds for medical and veterinary purposes, whenever the term "patient" is used, it is meant to cover humans as well as other animals.

The biological agents of the present invention are substances capable of promoting the natural healing process. Such agents may, for example, provide chemical elements, hormones, minerals, nutrients, growth factors that promote healing by preventing or treating infections, by providing necessary substances for tissue proliferation and maturation, or by eliminating necrotic debris (such as eschar or devitalized tissue) or increasing oxygen supply. Any biological agent may be used as long as it can be incorporated into the alginate fibers and processed into a material that can be used for dressings such that the agent's biological utility is not substantially altered. Also, a biological agent may be incorporated into the alginate fibers alone or in combination with other biological agents.

For example, the preferred biological agents of the present invention for all types of wounds include magnesium and zinc. Magnesium is needed for many chemical activities of the body and is important for the effective functioning of nerves and muscles. Magnesium is required for nucleic acid and protein synthesis, both important for cell renewal. The effective range of magnesium is 1 to 10%. Preferably, the alginate fibers of the present invention contain magnesium in the range of about 2.8% to about 4.8% by weight, more preferably about 3.8% by weight. Likewise, a deficiency of zinc, which is an essential nutrient in the body, may result in prolonging the healing process. Preferably, the alginate fibers of the present invention contain zinc in the range of about 1 to 25%, preferably about 2.8% to about 7.2% by weight, and more preferably about 5.0% by weight.

The choice of biological agent or combination of agents to incorporate into the alginate fibers will depend on the nature of the wound. For example, silver, preferably in the form of silver sulfadiazine (AgSD), is

useful for wounds resulting from second or third degree burns. AgSD is known in the art to be useful for the prevention and treatment of infection involving such burns. Preferably, the alginate fibers of the present invention contain silver in the range of about 0.25% to 1%, preferably about 0.05% to about 0.25% by weight, and more preferably about 0.1% by weight.

The present invention additionally relates to methods of preparing alginate material suitable for use as wound dressings. First, the alginate fibers, preferably reduced calcium alginate fibers as discussed previously, are treated in a solution containing the desired biological agent or agents. The biological agent or agents may be added to a solution in any suitable solvent that does not substantially swell the treated alginate fibers, for example, an aqueous alcoholic solution. The preferred aqueous alcoholic solution is industrial methylated spirits (IMS) (Hays Chemicals, Leicester, England).

Next, the treated alginate fibers are then washed one or more times by alternately adding solution followed by the removal of excess fluid with a mangle. The treated fibers may then be converted to a fabric-like woven or preferably non-woven material. For example, the alginate tow is cut into a suitable length, opened and made into a lightweight web, which is in turn continuously cross-folded to form a non-woven fabric of the desired mass/unit area. The fabric is then moistened and dried by any means known in the art. For example, the moistened non-woven web may be dried by air, blow drying, heat drying and the like. Preferably, the non-woven fabric is dried over heated rollers as described in International Publication No. WO 80/02300.

The alginate material prepared according to the present invention is particularly useful as a dressing for the local management of dermal ulcers, pressure sores, secreting dermal lesions, superficial wounds and the like. Depending on the nature of the wound, the alginate material may be the only therapy required for the care of such wounds or may be used in combination with other methods of patient care known to trained health professionals.

The material forms a soft, moist, non-adherent, hydrocolloid gel upon contact with any fluid, for example, exudate from a wound. As a gel, the material provides conformability to all wound surfaces, including irregular or difficult-to-dress areas. In addition, the material is highly absorbent and is therefore particularly suitable for heavily and moderately exudating wounds. Since the material is hemostatic, it is also useful for heavily bleeding wounds such as skin graft donor sites. Of course, a secondary dressing made of gauze or other material may be used to absorb excess exudate to reduce the number of dressing changes required and to provide additional cushioning.

The material is also permeable to gases allowing sufficient oxygenation of tissues to promote natural healing while allowing wound gases to escape, thus preventing the wound from becoming malodorous.

Another important property of the alginate material is that it dissolves in physiological solutions such as, for example, saline and Ringer's solution. As such, the dressing may be removed by gentle irrigation with the physiological solution with little, if any, discomfort to the patient.

The incorporation of biological agents into the dressing provides a means for directly introducing such agents to the wound without a separate application and with no additional discomfort to the patient. In this regard, the material may be useful for other purposes in addition to wound dressings. For example, it may be used to introduce various therapeutic drugs for absorption through the skin or to diagnose topical skin reactivity to various agents.

The following examples are intended to illustrate but not limit the present invention.

EXAMPLE I

To produce alginate fibers containing calcium, magnesium and zinc, 1 kg calcium alginate tow (Focus Polymers, Courtaulds PLC Coventry) having a calcium content of 10 percent on dry weight was treated in 10 dm^3 of a conversion liquor containing 2 kg anhydrous magnesium acetate (Food Grade) supplied by Medex Packing & Chemicals Ltd, Market Harborough, England and 1 kg zinc acetate dihydrate (BP Grade) supplied by Rhone Poulenc Chemicals, Gloucester, England, in 20% IMS (IMS is supplied as a 99% spirit by Hays Chemicals, Leicester, England). The fiber is placed in a suitable clean plastic container and the conversion liquor poured on top. The fiber is then agitated to ensure complete wetting out of the fiber. The container is sealed and left for twelve hours to allow the conversion process to reach equilibrium. After converting the calcium alginate to calcium magnesium zinc alginate (CaMgZn alginate), the converted tow was fed through a mangle (manufactured by Mather Platt Ltd, Manchester, England) for removal of excess liquid, which was collected and discarded.

The mangle is run at ambient temperature at a speed of 5 m/min with a roller gap of zero.

After removing the excess liquid, the tow was washed three times. For each wash, 10 dm^3 of wash liquor was prepared as follows:

	IMS (liters)	"100% IMS recycle" (liters)	WATER (liters)	Tween 20 (ml)	IMS* (%)
Run 1 Wash 1	2	0	8	0	20
Run 1 Wash 2	2	0	8	0	29
Run 1 Wash 3	10	0	0	50	87

	IMS (liters)	"100% IMS recycle" (liters)	WATER (liters)	Tween 20 (ml)	IMS* (%)
Run 2 Wash 1	0	2.5	7.5	0	20
Run 2 Wash 2	0	2.5	7.5	0	32
Run 2 Wash 3	5	5.0	0	25	85

	IMS (liters)	"100% IMS recycle" (liters)	WATER (liters)	Tween 20 (ml)	IMS* (%)
Run 3 Wash 1	0	2.5	7.5	0	20
Run 1 Wash 2	0	2.5	7.5	0	31
Run 1 Wash 3	10	0	0	50	87

For all further even number production runs, use Run 2 solutions. For all further odd number production runs, use Run 3 solutions.

* Concentration of IMS in contact with the fiber during the washing stage.

The purified water used in this process is produced by deionization of mains water using an ion exchange process. The Tween 20 (Polyoxyethylene sorbitan monolaurate) used in the wash solution was obtained from ICI Speciality Chemicals (Leatherhead, Surrey, England).

The wash solution, which has been thoroughly mixed, is placed into a suitable container and the tow placed into the solution.

After each wash stage, the tow is fed through the mangle as described above. For wash 1 and 2, the spent wash solution is discarded; for wash 3, the spent solution is retained as "100% IMS for recycle."

The treated CaMgZn alginate tow was then dried. Drying is achieved by placing the tow underneath extraction hoods and allowing the IMS to evaporate from the tow. The drying process is carried out at ambient temperature with an air flow of approximately 150 m^3/min. The tow after drying will have a "Loss of Drying" value of between 10-25 percent.

The dried alginate tow was then formed into a nonwoven fabric. First, the tow was cut into 50 mm length staple (staple is defined as a tuft or lock of fibers with a predetermined property, usually length) and then opened (opening is defined as the action of separating closely packed fibers from each other at an early stage of production of a carded nonwoven). This is carried out by passing the staple fiber through an opener which is comprised of a rotating spiked roller with three spiked beater bars, the action of which teases the staple fiber into a loose ball of fibers.

TABLE 1

CHEMICAL PROPERTIES

	TYPICAL VALUE	MINIMUM VALUE	MAXIMUM VALUE	UNITS
CALCIUM	3.8	2.8	4.8	WEIGHT%
MAGNESIUM	2.1	1.2	3.0	WEIGHT%
ZINC	5.0	2.8	7.2	WEIGHT%
LEAD	3		5	PPM
CADMIUM	<1		2	PPM
ARSENIC	<1		3	PPM
IRON	100		500	PPM
LOSS ON DRYING	16.0	10.0	25.0	WEIGHT%

PHYSICAL PROPERTIES

FABRIC WEIGHT	130	110	150	GRAMS

EXAMPLE II

Calcium magnesium zinc alginate fabric containing silver is prepared in a similar method. First, 1 Kg of the calcium alginate tow is converted to CaMgZn alginate tow followed by two washings as described in Example I. After removal of the excess liquid from the second wash, 10 dm^3 of a silver solution comprised of the same solution as described in Example I but also containing 20 g of silver sulphadiazene is used for the final wash. Silver sulphadiazine is prepared on-site using the following materials: sulphadiazine (supplied by Aldrich Chemicals, Gillihgham, Dorset, England); sodium hydroxide (supplied by Aldrich Chemicals, Gillihgham, Dorset, England); and silver nitrate (supplied by Ubichem Chemicals, Eastliegh, Hampshire, England).

The washing stage is carried out by immersing the tow into the silver solution and agitating it for two minutes, after which the tow is fed through the mangle as previously described in Example I. After the final wash, the AgSD/IMS solution is filtered to remove the AgSD suspension, this is then dried and used in subsequent final washes. The AgSD "free" recycled IMS is reused as previously described in Example I.

The resulting fibers are then dried and processed following the procedure described in Example I. The chemical and physical properties of this fabric are provided in Table 2.

TABLE 2

CHEMICAL PROPERTIES

	TYPICAL VALUE	MINIMUM VALUE	MAXIMUM VALUE	UNITS
CALCIUM	3.8	2.8	4.8	WEIGHT%
MAGNESIUM	2.1	1.2	3.0	WEIGHT%
ZINC	5.0	2.8	7.2	WEIGHT%
LEAD	3		5	PPM
CADMIUM	<1		2	PPM
ARSENIC	<1		3	PPM
IRON	100		500	PPM
SILVER	0.1	0.05	0.25	WEIGHT%
LOSS ON DRYING	16.0	10.0	25.0	WEIGHT%

PHYSICAL PROPERTIES

FABRIC WEIGHT	130	110	150	GRAMS

EXAMPLE III

TREATMENT OF WOUNDS

Alginate dressings have been used in the treatment of a variety of wounds in human subjects.

WS is a 68 year old white male with a biopsy-proven basal cell carcinoma of the right nasal ala. The tumor was treated utilizing the Mohs' surgical technique. After the tumor was removed, a full thickness 10 x 9 mm defect remained. Treatment options for closure of the defect were reviewed in detail with the patient and he elected healing by secondary intention. Wound treatment care consisted of normal saline cleansing followed by an alginate dressing prepared as described in Example I. The alginate dressing was covered by a secondary gauze dressing and taped in place. Dressings were changed once daily or every other day. The defect granulated in and it had appeared to reduce in size by fifty percent by day seven. The patient noted no pain. Near the end of the second week, the dressing was discontinued because the wound was no longer exudative. Simple bacitracin ointment gauze dressings were then substituted until the wound had totally epithelialized (about Day 22).

EF is a 78 year old Mexican male who presented in September, 1990, with a three month history of a left lower extremity ulcer. His past medical history was notable for coronary artery disease, venous insufficiency, and lower extremity stasis dermatitis. Over the past several years, the patient had developed numerous other lower extremity ulcers which slowly healed with local care. The recent left leg ulcer developed soon after a coronary bypass procedure during which venous grafts had been harvested from both legs. The patient's past medical history also includes

hypertension, angina, and possible transient ischemic attack.

The patient's initial management included local care with Dakin's wet to dry dressings and oral antibiotics (ciprofloxacin). The ulcer did not improve so the patient was switched to alginate-based dressing material as prepared in Example I by an outside physician.

On the patient's initial visit to the University, examination revealed a 9 x 6 cm. left medial malleolar ulcer with a granulating base, but with peripheral crust and debris. By history, the ulcer had improved ten percent since initiation of the new dressing material six weeks prior and the base was "filling in." The leg was edematous (4+ pitting, knee level), ill-defined erythema surrounded the ulcer, old stasis dermatitis changes were evident bilaterally, and pulses were barely palpable secondary to edema. Soon after, the patient's course was complicated by cellulitis. There was no evidence for deep vein thrombosis or osteomyelitis. The patient was hospitalized and treated with intravenous antibiotics and recovered without complications. Ulcer management was changed to include whirlpool, debridement as needed, hyperbaric oxygen, and the alginate dressings were continued. Six weeks later, the ulcer was partially healed, having reduced in size by forty percent overall. After 15 weeks, whirlpool and hyperbaric oxygen therapy were discontinued because of transportation difficulties but local wound care with alginate dressings remained unchanged. Table 3 provides a summary of additional examples of treatment.

TABLE 3

Patient No.	Disease	Outcome
1	Epidermolysis bullosa	Patient felt dressing was too messy. Discontinued.
2	R Hip ulcer, ? origin	No healing benefit. Decreased pain.
3	Leg ulcer, lupus	Decrease in size by 50%, then exacerbation of disease, worsening of ulcer.
4	S/P trauma, R knee	Complete healing, decreased pain.
5	S/P Mohs, nose, surgical defect	Complete healing, no pain.
6	S/P Mohs, nose, surgical defect	Complete healing, no pain.
7	Leg ulcers, superficial	No benefit - even with saline moistening, dressing dried out.
8	Leg ulcer, venous stasis	Reduction in size by 70% on therapy, 5 months.
9	Leg ulcer, venous stasis	Reduction in size 5%, decreased pain, new granulating base on therapy, 1 month with Unna boot (no change with Unna boot only x 12 months).
10	Leg ulcer, venous stasis	Early granulation response. Patient discontinued self.

Although the invention has been described with reference to the presently preferred embodiments, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

We Claim:

1. A material useful for dressing wounds comprising alginate fibers having incorporated therein at least one biological agent.

2. The material of claim 1, wherein said alginate fibers are calcium alginate fibers.

3. The material of claim 1, wherein the biological agent is calcium in a concentration greater than 50% wt/wt.

4. The material of claim 1, wherein no single biological agent is present in a concentration greater than 49.9% of the total biological agents.

5. The material of claim 1, wherein said biological agent is selected from the group consisting of magnesium, zinc and silver.

6. The material of claim 5, wherein a weight percentage of magnesium is in the range of about 1.2 to about 3.0.

7. The material of claim 5, wherein a weight percentage of zinc is in the range of about 2.8 to about 4.8.

8. The material of claim 5, wherein a weight percentage of silver sulfadiazine is in the range of about 0.05 to about 0.25.

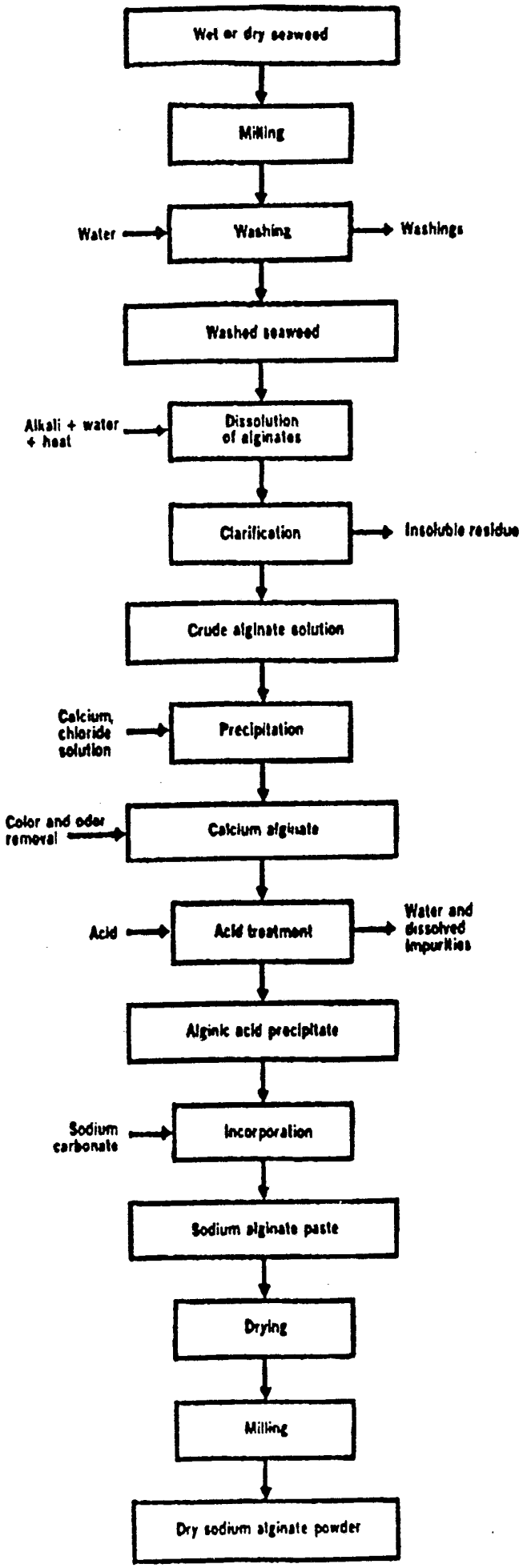
9. A method of preparing a material useful for dressing wounds comprising the steps of:

treating alginate fibers with a biological agent;

washing said fibers;

processing said fibers to form a fabric; and

drying said fabric to produce said material.


Wet or dry seaweed
Milling
Water
Washing
Washings
Washed seaweed
Alkali + water + heat
Dissolution of alginates
Clarification
Insoluble residue
Crude alginate solution
Calcium chloride solution
Precipitation
Color and oder removal
Calcium alginate
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Alginic acid precipitate
Sodium carbonate
Incorporation
Sodium alginate paste
Drying
Milling
Dry sodium alginate powder

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/05124

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/70
US CL :424/443
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. : NONE

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)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A, 4,837,024 (MICHACHLI) 06 JUNE 1989 Entire document	1-9
Y	The Merck Index, 1989, (BUDAVARI ET AL.) Pages 41-42.	1-9
Y	WO,A, WO 84/03705 (COURTAULDS PLC) 27 SEPTEMBER 1984 Entire document.	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
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Date of the actual completion of the international search
06 AUGUST 1992

Date of mailing of the international search report
12 AUG 1992

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