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(54) Title: METHYL CELLULOSE PHARMACEUTICAL COMPOSITION

(57) Abstract

A pharmaceutical composition comprising methyl cellulose and an immunomodulator such as interleukin providing prolonged elaboration of the immunomodulator in a subject animal, and method of preparation and use.

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METHYL CELLULOSE PHARMACEUTICAL COMPOSITION

Field of the Invention

This invention concerns a pharmaceutical composition comprising methyl cellulose and an immunomodulator (such as interleukin) providing prolonged elaboration of the immunomodulator in a subject animal, and method of preparation and use.

Background of the Invention

A number of peptide immunomodulators ("immunomodulators") such as colony stimulating factor (e.g., granulocytic CSF and monocytic CSF), interferons (currently including alpha through gamma) and interleukins have recently been identified as clinically useful and are now available in commercial quantities.

The family of interleukins, currently comprising the IL1, IL2, IL3 and IL4 peptides, has recently become the object of therapeutic interest as a result of advances in the techniques of isolation and production of peptides.

Interleukin, particularly IL2, is thought to be of therapeutic effect in the treatment of certain pathologies such as neoplasms and immunodeficiencies (e.g. AIDS) in animals, including humans. Among the problems associated with the therapeutic use of interleukin (and other peptide immunomodulators) are maintenance of therapeutically effective blood levels of immunomodulators in the subject animal being treated, toxicity of the imminomodulator, and the interrelated problem of short half-life of immunomodulator (possibly as a result of the action of proteolytic enzymes) in requiring large and relatively toxic amounts of immunomodulator per dose to yield

suitable duration of therapeutically effective plasma levels. Interleukin is a labile peptide subject to breakdown in and excretion from the in vivo physiological environment. Some investigators have reported that 95% of free interleukin administered to an animal is lost within 1 hour after administration. Donohue, J.H. and Rosenberg, S.A., "The Fate of Interleukin-2 after in vivo Administration", Journal of Immunology, 130:2203 (1983); Chang, A.E., Hyatt, C.L., and Rosenberg, S.A., "Systemic Administration of Recombinant Human Interleukin-2 in Mice", Journal of Biological Response Modifiers, 3:561 (1984).

The general use of gels including methyl cellulose in the administration of therapeutic agents has been reported in U.S. Patent Ser. No. 4,708,861 issued November 24, 1987 to Popescu et al.

It has now been discovered that immunomodulators like interleukin dispersed specifically in methyl cellulose suprisingly remains present and biologically active for up to 12 days or longer subsequent to administration. This effect is not found with other cellulosic materials.

Summary of the Invention

This invention will be understood to include a pharmaceutical composition of prolonged elaboration comprising methyl cellulose and an immunomodulator. In some embodiments the immunomodulator is encapsulated in a liposome, such as an SPLV, a FATMLV, an SUV, a LUVET, an MPV, or an MLV.

In particular embodiments the immunomodulator is a colony stimulating factor, an interferon, or an interleukin, particularly an interleukin such as IL2. In some applications IL2 is present in from about 0.5ug/mg to about 600ug/mg methyl cellulose.

Further included is methyl cellulose from about 1,000 to about 10,000cp, particularly from about 1,000 to about 4,000cp, and further wherein the methyl cellulose is a gel. Preferred gel is from about 1% to about 15% (w/v) methyl cellulose, and more preferred from about 3% to about 12% w/v (particularly 6% w/v), and yet further preferred wherein the methyl cellulose is about 1,500cp and also about 6% w/v. Methyl cellulose of 1.500cp and 6% w/v is preferred for IL2.

This invention also includes a method of treating an animal, including a human, in need of such treatment by the method of administering to said animal a pharmaceutical composition of prolonged elaboration comprising methyl cellulose and an immunomodulator. This method is preferred wherein the immunomodulator is a colony stimulating factor, an interferon, or an interleukin, particularly an interleukin.

This invention includes a method of preparing a pharmaceutical composition of prolonged elaboration comprising admixing methyl cellulose and an immunomodulator, and further includes forming a gel of methyl cellulose. In one embodiment the admixing is performed at a temperature at least below about 10°C. In some embodiments of this method the immunomodulator is encapsulated in a liposome, such as by forming an SPLV, a FATMLV, an SUV, a LUVET, an MPV, or an MLV.

This invention yet further includes a method of prolonged administration of an immunomodulator to an animal comprising administering said immunomodulator in methyl cellulose. In some embodiments the administration is parenteral such as subcutaneous, intramuscular or intraperitoneal, and particularly intramuscular.

Included in the method is methyl cellulose from about 1,000 to about 10,000cp, and particularly from about 1,000 to about 4,000cp, and most particularly about 1,500cp.

Also included in the is wherein the methyl cellulose being a gel.

This includes the methyl cellulose being from about 1% to about 15% w/v (particularly at 1,500cp), and wherein the methyl cellulose being from about 3% to about 12% w/v and particularly wherein the gel is about 6% w/v.

Further included in this invention is the method of prolonged administration of an immunomodulator to an animal comprising administering said immunomodulator in methyl cellulose includes wherein the immunomodulator is a colony stimulating factor, an interferon, or an interleukin, and particularly interleukin such as IL2. Also included is wherein the immunomodulator is encapsulated in a liposome. Included as to IL2 in the practice of this method of is IL2 administered from about 0.25ug to about 2ug/kg animal weight or wherein IL2 is present in from about 0.5ug to about 600ug/mg methyl cellulose. In a particular embodiment of this method is the methyl cellulose being about 1,500cp and about 6% (w/v).

Detailed Description of the Invention

Immunomodulator (in some citations "immunomoderator") will be understood to mean peptides or proteins which posotively or negatively regulates the immune response of an animal to foreign antigens, such as cells, bacteria, viri and parisites. Exemplary of such immunomodulators are colony stimulating factor, interferon, and interleukin as well as analogues and derivatives thereof.

Interleukin shall be understood to include all interleukins such as IL1, ILla, IL2, IL3, IL4, and analogues and derivatives thereof.

Interleukin is available from several sources such as ICN Biochemical, Cleveland, Ohio (IL1, IL2, IL3) and Amgen Biologicals, Thousand Oaks, California (IL2).

Methyl cellulose shall be understood to mean a methyl ether of

cellulose (long chain substituted cellulose ether of about 50-1500 anhydrous units containing about 26-32% methoxyl groups).

Methyl cellulose is available from many sources and in many forms and at viscosities of from about 10 to about 10,000cp (e.g., powdered methyl cellulose is available from Sigma Chemical Co., St. Louis, MO.). Preferred in this invention is are the viscosities in about the 1,500 to 4,000cp range, with about 1,500cp most preferred.

Methyl cellulose in powdered form is suitable to form a gel composition of this invention. This is conveniently accomplished in boiling water or buffer however lower temperatures may be used with vigorous mixing. Gel concentrations of about 1% to about 15% (w/v) are useful. With 1,500cp methyl cellulose from about 3% to about 12% concentrations are preferred. To avoid methyl cellulose accumulation at the site of injection, the lowest concentration offering adequate immunomodulator retention is preferred.

Mixing of the immunomodulator and the methyl cellulose in the form of a gel is suitable to form the composition of this invention. This is conveniently accomplished at a reduced temperature, below about 10°c and above the freezing point if the gel (at least as low as 0°C), and preferably about 4°C. Lower nonfreezing temperatures are preferred to minimize loss of immunomodulator activity. Care must be taken so that the immunomodulator is not denatured or deactivated by the process.

When a powdered methyl cellulose was used, the powder was first hydrated by adding it to boiling water, stirring to moisten and immediately cooling the reaction vessel in a heat sink such as ice. After cooling the immunomodulators such as interleukin, conviently in solution, may be combined with the methyl cellulose, conveniently with thorough mixing, such as by paddle mixer or vortexing.

In practice it was convenient to add higher concentration interleukin solution than that anticipated for the final composition

to allow for dilution of the final product with the methyl cellulose.

In one embodiment the immunomodulator may be liposomally encapsulated prior to admixture with methyl cellulose. Long term elaboration of immunomodulator is provided by this embodiment, but the initial plasma level profile is somewhat reduced, as compared to free immunomodulator in methyl cellulose.

Liposomes are completely closed lipid bilayer membranes containing an entrapped aqueous volume. Liposomes may be unilamellar vesicles (possessing a single bilayer membrane) or multilameller vesicles (onion-like structures characterized by multiple membrane bilayers, each separated from the next by an aqueous layer). The bilayer is composed of two lipid monolayers having a hydrophobic "tail" region and a hydrophilic "head" region. The structure of the membrane bilayer is such that the hydrophobic (nonpolar) "tails" of the lipid monolayers orient toward the center of the bilayer while the hydrophilic "head" orient towards the aqueous phase.

The original liposome preparation of Bangham, et al. (J. Mol. Biol., 1965, 12:238-252) involves suspending phospholipids in an organic solvent which is then evaporated to dryness leaving a phospholipid film on the reaction vessel. Next, and appropriate amount of aqueous phase is added, the mixture is allowed to "swell," and the resulting liposomes which consist of multilamellar vesicles (MLVs) are dispersed by mechanical means. This technique provides the basis for the development of the small sonicated unilamellar vesicles (SUVs) described by Papahadjopoulos et al. (Biochim. Biophys. Acta., 1968, 135:624-638), and large unilamellar vesicles.

Unilamellar vesicles may be produced using an extrusion apparatus by a method described in Cullis et al., PCT Application No. WO 87/00238, published January 16, 1986, entitled "Extrusion Technique for Producing Unilamellar Vesicles" incorporated herein by reference. Vesicles made by this technique, called LUVETS, are extruded under pressure through a membrane filter.

Monophasic vesicles (MPVs) are a particularly stable type of liposome described in U.S. Patent Ser. No. 4,588,578 to Fountain et al. the teachings of which are incorporated herein by reference.

Another class of liposomes are those characterized as having substantially equal lamellar solute distribution. This class of liposomes is denominated as stable plurilamellar vesicles (SPLV) as defined in U.S. Patent No. 4,522,803 to Lenk, et al., monophasic vesicles as described in U.S. Patent No. 4558,579 to Fountain, et al. and frozen and thawed multilamellar vesicles (FATMLV) wherein the vesicles are exposed to at least one freeze and thaw cycle; this procedure is described in Bally et al., PCT Publication No. 87/00043, January 15, 1987, entitled "Multilamellar Liposomes Having Improved Trapping Efficiencies" and each of which is incorporated herein by reference.

A variety of sterols and their water soluble derivatives have been used to form liposomes; see specifically Janoff et al., PCT Publication No. WO 85/04578, published October 24, 1985, entitled "Steroidal Liposomes." Mayhew et al., PCT Publication No. WO 85/00968, published March 14, 1985, described a method for reducing the toxicity of drugs by encapsulating them in liposomes comprising alpha-tocopherol and certain derivatives thereof. Also, a variety of tocopherols and their water soluble derivatives have been used to form liposomes, see Janoff et al., PCT Publication No. WO 87/02219, published April 23, 1987, entitled "Alpha Tocopherol-Based Vesicles."

The best results of admixing interleukin with methyl cellulose were obtained with about 6% w/v and 1,500cp methyl cellulose exhibiting retention/elaboration through over 10 days after intramuscular injection.

Liposomal encapsulation did not reduce the retention and release of the immunomodulator interleukin in various gels The most prolonged elaboration of interleukin was provided by methyl cellulose, particularly 1,500cp, and most particularly of about 6% to about

12%. These formulations substantially exceded the elaboration of interleukin from ultra-high viscosity carboxyvinyl polymers (HIVIS-A is the polymer suspended in 5mM ammonium acetate, approximately 200,000cp; HIVIS-G is the polymer suspended in glycerol approximately 1,500,000cp), or any other known method.

The term prolonged elaboration as used herein is understood to mean the release of therapeutic agents from liposomal encapsulation over a period in excess of about 24 hours, preferably at least about 3 days, and in some embodiments as long as about 2 weeks.

Methly cellulose substantially extended the elaboration of interleukin, and did so at elevated plasma levels, beyond the 3 day level seen for free interleukin or 7 day elaboration for liposomal interleukin without methyl cellulose.

The composition of the present invention can be used therapeutically in animals such as mammals, including man, in the treatment of infections or conditions which require the sustained delivery of immunomodulators in bioactive form. Such conditions include but are not limited to disease states such as cancer, AIDS and other immunodeficiencies. Each immunomodulator will exhibit prolonged therapeutic activity consonant with the particular immunomodulator.

The mode of administration of the preparation may determine the sites and cells in the organism to which the compound will be delivered. The composition of the present invention can be administered alone but may be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. The preparations may be injected parenterally, for example, or intra-arterially or intravenously (if not too viscous). The preparations may also be administered via intraperitoneal, subcutaneous, or intramuscular routes. For parenteral administration, they can be used, for example, in the form of a sterile aqueous solution which may contain other solutes, for

example, enough salts or glucose to make the solution isotonic. Other uses, depending upon the particular properties of the preparation, may be envisioned by those skilled in the art.

For administration to humans in the curative treatment of disease states responding to immunomodulator therapy, the prescribing physician will ultimately determine the appropriate dosage for a given human subject, and this can be expected to vary according to the age, weight, and response of the individual as well as the nature and severity of the subject's disease. The dosage of the immunomodulator in liposomal form will generally be about that employed for the free immunomodulator. In some cases, however, it may be necessary to administer dosages outside these limits.

Dosage and administration of immumomodulator, in this invention, presumes therapeutically effective amounts. Therapeutically effective amounts of immunomodulator as used herein will mean that amount of immunomodulator that produces therapeutic action. This amount will be understood to vary with the particular immunomodulator or analog or derivative thereof, the condition being treated, the site, manner and duration of administration and other considerations known to those skilled in the art.

The compositions of this invention possess valuable pharmacological properties. They afford prolonged elaboration of immunomodulators including interleukins in a subject animal and provide antiviral, anticancer and antiAIDs efficacy in human and veterinary medicine. Effectiveness as to IL2 can be demonstrated, for example, using the the composition of this invention in a chemotherapy regimen, such as by weekly intramuscular injection at a concentration of about 5ug to about 60ug of interleukin/mg methyl cellulose in a dosage of from about 0.25 to about 2ug/kg subject weight.

Thus, depending on the immunomodulator, these compositions can be used in both antiviral and anticancer applications.

For interleukin the compositions are particularly useful as antitumor agents.

The compositions of this invention are generally administered to mammals, including but not limited to humans.

The pharmacologically active compositions of this invention can be processed in accordance with conventional methods of galenic pharmacy to produce medicinal agents for administration to sublects, e.g., mammals including humans in need of such treatment.

The compositions of this invention can be employed in admixture with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral (e.g., oral or inhalation) or topical application which do not deleteriously react with the active compositions. Suitable pharmaceutically acceptable carriers include but are not limited to water and salt solutions etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers and the like which do not deleteriously react with the active compounds. They can also be combined where desired with other active agents, e.g., chemotherapeutics.

Generally, the compositions of this invention are dispensed in unit dosage form. For IL2 unit dosage form comprises about 5 to 60ug interleukin in methyl cellulose carrier per unit dosage.

As to interleukin, the dosage of the compositions according to this invention generally are 0.25 to 2ug/kg/wk, preferably 0.5 to lug/kg/wk, when administered to subjects, e.g., humans to treat (e.g., cancer or viral infection) analogously to the known agent IL2.

It will be appreciated that the actual preferred amounts of active compositions in a specific case will vary according to the specific

compositions being utilized, the particular compositions formulated, the mode of application, and the particular situs and organism being treated. Dosages for a given host can be determined using conventional considerations, e.g., by customary comparison of the differential activities of the subject compositions and of a known agent, e.g., by means of an appropriate, conventional pharmacological protocol.

Example 1

Free IL2 in Methyl Cellulose

Powdered methyl cellulose (1500cp), 60mg, was weighed into a 1.4ml eppendorf tube. To this was added 0.6ml of boiling 5mM ammonium acetate, pH 5.0, and the resulting mixture stirred. After stirring the mixture was placed on ice and cooled to 4°C or until the mixture appeared transparent.

To the cooled mixture 133ul of IL2 at 3mg/ml was added and the mixture stirred. The volume was then brought up to 1.0ml with buffer.

For administration, the mixture, a methyl cellulose gel containing IL2 was loaded into a 1ml syringe which was centrifuged to remove bubbles. The loaded syringe was placed at 45°C for 1 hour prior to injection.

Example 2

Liposomal IL2 in Methyl Cellulose

Methyl cellulose was prepared according to the procedure of Example 1. Powdered methyl cellulose (1500cp), 60mg, was weighed into a

1.4ml eppendorf tube. To this was added 0.6ml of boiling 5mM ammonium acetate, pH 5.0, and the resulting mixture stirred. After stirring the mixture was placed on ice and cooled to 4°C or until the mixture appeared transparent.

To the cooled mixture of methyl cellulose and water, 0.4mg IL2 encapsulated in LUVETS (by the method described in Cullis et al., PCT Application No. WO 87/00238, published January 16, 1986, entitled "Extrusion Technique for Producing Unilamellar Vesicles") at a concentration of 25ug IL2/mg of lipid (egg phosphatidylcholine) was added and the mixture stirred. Specifically, the LUVETS were prepared from SPLVs by first drying down the lipid (egg phosphatidylcholine) in a round bottom flask, resuspending in ether and IL2 at a ratio of 12:1 lipid to IL2 (200mg EPC: 17mg IL2), and sonicating the mixture while evaporating off the ether with nitrogen gas. The SPLVs, resuspended in in a minimal volume of buffer to form a paste, were then passed through successively smaller filters in a LUVET apparatus (Lipex Biomembrane, Vancouver, B.C.) starting at 0.4um and ending with 10 passes through a 0.1um filter. The resulting LUVETs were washed by centrifugation over a ficoll hypaque gel cushion. The volume was then brought up to 1.0ml with buffer. Sufficient LUVET material was used to add 0.4mg of IL2/ml of methyl cellulose.

For administration, the mixture, the methyl cellulose gel containing IL2 was loaded into a 1ml syringe which was centrifuged to remove bubbles. The loaded syringe was placed at 45°C for 1 hour prior to injection.

The results of admixing interleukin with methyl cellulose are shown in TABLE I. In this table injections were intramuscular. The best results were obtained with about 6% w/v 1,500cp methyl cellulose exhibiting retention/elaboration through over 10 days. In this table "K" represents hydroxypropyl methyl cellulose of 4,000, 15,000 and 100,000cp, "MC" represents methyl cellulose followed by the centipoise number.

Table II examines the retention and release of free interleukin in various gels. Liposomal encapsulation did not reduce retention and elaboration as compared to free interleukin in similar gels. In Table II the most prolonged elaboration of interleukin was provided by methyl cellulose, particularly 1,500cp, and most particularly of about 6% to 12%. These formulations suprisingly substantially exceded the elaboration of interleukin from ultra-high viscosity carboxyvinyl polymers (HIVIS-A is the polymer suspended in 5mM ammonium acetate, approximately 200,000cp; HIVIS-G is the polymer suspended in glycerol approximately 1,500,000cp), or any other known method.

TABLE I

SUMMARY OF MOUSE STUDIES

Frequency of Positive Responses 1/

Study	Formulation	1h	4h	7h	1d	2d	3d	5d	7d	10d
1	Free IL2	6/6	5/5	5/5	5/5	2/5	0/5	-	-	-
2	Free/3% MC 1500	6/6	6/6	6/6	6/6	6/6	6/6	1/6	0/6	-
3	Free/6% MC 1500	6/6	6/6	5/5	5/5	5/5	5/5	3/5	1/5	-
4	Free/6% MC 1500	6/6	6/6	6/6	6/6	6/6	6/6	6/6	4/4	2/4
5	LUVET/6% MC 1500	10/10	10/10	10/10	10/10	10/10	9/9	9/9	6/9	2/9
6	LUVET/6% MC 1500	6/6	6/6	6/6	6/6	6/6	6/6	6/6	3/6	-
7	LUVET/1.5% MC 4000	6/6	6/6	6/6	6/6	5/6	6/6	3/6	1/6	-
8	LUVET/3.0% MC 4000	6/6	6/6	6/6	6/6	6/6	6/6	6/6	0/6	-
9	LUVET/2.0% K4M	6/6	NT	NT	5/5	NT	5/5	2/5	0/5	-
10	LUVET/2.0% K15M	6/6	NT	NT	5/5	NT	4/5	2/5	0/5	-
11	LUVET/2.0% K100M	6/6	NT	NT	6/6	NT	6/6	3/5	0/6	-

Average Normalized Blood Levels 2/

Study	Formulation	1h	4h	7h	1d	2d	3d	5d	7d	10d
1	Free IL2	1027	109.3	16.9	1.45	0.39	-	-	-	-
2	Free/3% MC 1500	976	127	30.7	1.97	1.8	.67	-	-	-
3	Free/6% MC 1500	720	104	53	3.87	1.73	.67	0.17	-	-
4	Free/6% MC 1500	1006	307	108	15.6	10	4.0	1.07	.56	.17
5	LUVET/6% MC 1500	142	93	58	12	4.4	1.64	0.41	.29	.17
6	LUVET/6% MC 1500	34	28	12.8	3.7	1.14	.96	0.22	.20	-
7	LUVET/1.5% MC 4000	66	27	12	2.31	0.41	.33	0.28	-	-
8	LUVET/3.0% MC 4000	71	42	18.3	3.43	0.79	.99	0.48	-	-
9	LUVET/2.0% K4M	163	NT	NT	7.03	NT	1.04	0.26	-	-
10	LUVET/2.0% K15M	225	NT	NT	5.24	NT	1.11	0.41	-	-
11	LUVET/2.0% K100M	167	NT	NT	6.02	NT	1.06	0.51	-	-

1/ Number of mice in each study that had a measurable IL2 blood level at a given time point.

2/ Average normalized blood levels were calculated for positive animals only (minimum n = 2) by the formula $\frac{\text{ng/ml}}{\text{dose/animal}} \times 100$

TABLE II

SUMMARY OF FREE IL-2/GEL FORMULATIONS IN MICE

FORMULATION	GEL	1h	4h	7h	1d	2d	3d	5d	7d	10d
1	-	1027	109	17	1.5^{5}	$.39^{2}$	- 2/	-	NT 3/	NT
2	3.0% MC1500	976	31	31	2.0	1.8^{6}	$.7^{6}$	-	-	NT
3	6.0% MC1500	1006	307	108	16.0	10.0^{6}	4.0^{6}	1.1^{6}	$.56^{6}$	$.17^{2}$
4	6.0% MC1500	720	104	53	4.0	1.7^{5}	$.7^{5}$	$.17^{3}$	-	NT
5	9.0% MC1500	356	NT	NT	12.0	NT	1.8^{6}	$.24^{3}$	$.17^{3}$	NT
6	12.0% MC1500	361	NT	NT	11.0	NT	2.4^{6}	$.46^{3}$	$.22^{2}$	$.28^{3}$
7	9.0% MC4000	372	NT	NT	8.0	NT	2.2^{6}	$.27^{2}$	-	NT
8	0.5% HIVIS-G	504	NT	NT	1.5	NT	$.14^{4}$	-	-	NT
9	1.0% HIVIS-A	518	NT	NT	2.0	NT	-	-	NT	NT

1/ Table entries are blood levels normalized by the formula $\frac{\text{ng/ml}}{\text{dose/mouse}} \times 100$. Superscripts refer to the number of responding animals at that time point. In most studies six animals were tested per formulation.

2/ Below sensitivity of detection in the assay.

3/ Not tested

Claims

1. A pharmaceutical composition of prolonged elaboration comprising methyl cellulose and an immunomodulator.

2. The composition of Claim 1 wherein the immunomodulator is encapsulated in a liposome, optionally an SPLV, a FATMLV, an SUV, a LUVET, an MPV, or an MLV.

3. The composition of Claim 1 wherein the immunomodulator is a colony stimulating factor, an interferon, or an interleukin.

4. The composition of Claim 4 wherein the immunomodulator is interleukin, optionally IL2.

5. The composition of Claim 4 wherein IL2 is present in from about 0.5ug/mg to about 600ug/mg methyl cellulose.

6. The composition of Claim 1 wherein the methyl cellulose is from about 1,000 to about 10,000cp, optionally from about 1,000 to about 4,000cp.

7. The composition of Claim 1 wherein the methyl cellulose is a gel, optionally from about 1% to about 15% w/v and particularly from about 3% to about 12% w/v.

8. The composition of Claim 7 wherein the methyl cellulose is about 1,500cp.

9. The composition of Claim 7 wherein the methyl cellulose is about 6% w/v, optionally wherein the methyl cellulose is about 1,500cp.

10. The composition of Claim 9 wherein the immunomodulator is IL2.

11. A method of treating an animal, including a human, in need of such treatment by the method of administering to said animal the composition of any of Claims 1 through 10.

12. A method of preparing a pharmaceutical composition of prolonged elaboration comprising admixing methyl cellulose and an immunomodulator.

13. The method of Claim 12 comprising forming a gel of methyl cellulose, optionally wherein the admixing is performed at a temperature at least below about 10°C.

14. The method of Claim 12 or 13 further comprising encapsulating said immunomodulator in a liposome, optionally an SPLV, a FATMLV, an SUV, a LUVET, an MPV, or an MLV.

15. A method of manufacture of methyl cellulose and immunomodulator for the prolonged administration of an immunomodulator to an animal comprising admixing said immunomodulator in methyl cellulose.

16. The method of Claim 15 wherein administration is parenteral, optionally subcutaneous, intramuscular or intraperitoneal.

17. The method of Claim 16 wherein the administration is intramuscular.

18. The method of Claim 15, 16 or 17 wherein the methyl cellulose is from about 1,000 to about 10,000cp, optionally from about 1,000 to about 4,000cp.

19. The method of Claim 18 wherein the methyl cellulose is about 1,500cp.

20. The method of any of Claims 15, 16, 17 or 19 wherein the methyl cellulose is a gel, optionally wherein the methyl cellulose is from about 1% to about 15% w/v, or from about 3% to about 12% w/v or about 6% w/v.

21. The method of Claim 20 wherein the methyl cellulose is about 1,500cp.

22. The method of Claim 15, 16, 17, 19 or 21 wherein the immunomodulator is a colony stimulating factor, an interferon, or an interleukin.

23. The method of Claim 22 wherein the immunomodulator is encapsulated in a liposome.

24. The method of Claim 22 wherein the immunomodulator is an interleukin, optionally IL2.

25. The method of Claim 24 wherein IL2 is administered in from about 0.25ug to about 2ug/kg animal weight.

26. The method of Claim 24 wherein IL2 is present in from about 0.5ug to about 600ug/mg methyl cellulose.

27. The method of Claim 24 wherein the methyl cellulose is about 1,500cp and about 6% (w/v).

INTERNATIONAL SEARCH REPORT

International Application No PCT/US88/04267

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.(4):A61K 37/02, 45/02,31/70

U.S. CL.424/85.2,85.3,85.4,85.5,85.6,85.7,450; 514/2,8,23,57

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/85.1,85.2,85.3,85.4,85.5,85.6,85.7,450; 514/2,8,23,57 970,963,964

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

Search on CAS and Dialog; Files: CA,BIOSIS, 155,350,351, For: Methyl-Cellulose and (Interleukin or Interferon or Colony Stimulating Factor) and Liposome and Stabilize.

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X / Y	US, A, 4,708,861 (POPESCU), 24 November 1987, See Col. 7-8.	1-2,6-9,11-21 / 3-5,10,22-27
Y	US, A, 4,359,483 (KAETSU), 16 November 1987, See Col. 2-3.	1-27
Y	US, A, 4,680,175, (ESTIS), 14 July 1987, See Col. 5-6	1-27
Y	PCT,A, 83/01198, (OSTHER), 14 April 1983, See pages 8-9.	1-27
Y,P	US, A, 4,717,717, (FINKENAUR), 5 January 1988, See Col. 2.	1-27
Y,P	US, A, 4,762,720, (JIZOMOTO), 9 August 1988, See Col. 2.	1-27
Y	Science, Vol. 236, Issued June 1987; "The Human Hematopoietic Colony-Stimulating Factors," (CLARK), pages 1229-37, See pages 1235-36.	3,11,22-24

* Special categories of cited documents: [15]

"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

"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
27 February 1989	03 APR 1989
International Searching Authority [1]	**Signature of Authorized Officer** [20]
ISA/US	GARNETTE D. DRAPER

Form PCT/ISA/210 (second sheet) (May 1986)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	Blood, Vol. 67, Issued February 1986, "The Molecular Biology and Functions of the Granulocyte-Macrophage Colony-Stimulating Factors," (METCALF), pages 257-67, See pages 259, 262-64.	3, 11,22-24
Y	Seminars in Oncology, Vol. 13, Issued June 1986, "Future Perspectives for Biological Response Modifiers," (MIHICH), pages 234-54, See all.	1-27
A	US, A, 4,609,546, (HIRATANI), 2 September 1986.	1-27
A,P	US, A, 4,762,915, (KUNG), 9 August 1988.	1-27