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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 47/40, 47/48

A1

(11) International Publication Number: **WO 98/47536**

(43) International Publication Date: 29 October 1998 (29.10.98)

(21) International Application Number: PCT/NZ98/00051

(22) International Filing Date: 23 April 1998 (23.04.98)

(30) Priority Data:
314664 23 April 1997 (23.04.97) NZ

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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: CONTROLLED RELEASE OF OPHTHALMIC COMPOSITIONS

(57) Abstract

The invention provides ophthalmic compositions which deliver increased bioavailability of an ophthalmically acceptable drug to the eye of a patient. The compositions comprise a carboxylic acid containing polymer conjugated to a cyclodextrin, with the drug encapsulated in the cyclodextrin portion of the conjugate.

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CONTROLLED RELEASE OF OPHTHALMIC COMPOSITIONS

TECHNICAL FIELD

This invention relates to carboxylic acid containing polymer - cyclodextrin conjugates, the use of such conjugates in the preparation of ophthalmic compositions, and to methods of treating ophthalmic conditions using these ophthalmic compositions.

BACKGROUND

The desirability of being able to treat medical conditions, particularly ophthalmic medical conditions by administering therapeutic compositions directly to the eye has long been recognised. Localised delivery means that limited amounts of a therapeutic composition can be provided directly to the target site. Localised delivery therefore has significant benefits over systemic delivery which is untargeted, uses larger amounts of the therapeutic composition to be delivered, and results in lower levels of the therapeutic composition in the eye than is the case with localised delivery.

However, the delivery of a therapeutic composition to the eye has been attended by a number of problems. Most compositions administered show low bioavailability, commonly in the order of only one to two percent, and also exhibit considerable variability in the amount of composition delivered at any given time. Moreover, the residence time for compositions in the eye tends to be very short, and this is problematic especially for those compositions with a short half life. As a result of the short residence time for compositions in the eye frequent dosing is required which is generally inconvenient and undesirable from a patient's perspective.

Various attempts have been made to address these difficulties, and in particular to prolong residence time of a therapeutic composition in the eye. These attempts include:

- the use of viscosity enhancing agents including gels and ointments;
- inserts which are loaded with drug and placed in the cul-de-sac of the eye;
- particulate forms such as liposomes, nanoparticles and microparticles;

- gelling systems such as polymers which respond to changes in pH or temperature or ionic strength; and
- bioadhesive polymers.

These options have so far only provided a partial solution to the problems identified above.

In recent years there has been a growing interest in drug delivery and the design and evaluation of controlled release systems based on bioadhesive polymers. These bioadhesive polymers have been used as platforms for drug delivery to various mucosal membranes of the body including those of the eye, nose, mouth, vagina, rectum and gastro-intestinal tract.

Besides acting as platforms for drug delivery, bioadhesive polymers can exert some control over the rate and amount of drug being released. However, their ability to control drug release is limited and control is often more a function of the drug than the polymer. Consequently, for some drugs, enhanced retention of the delivery platform at the adsorption site is achieved but the drug is poorly retained.

Carboxylic acid containing polymers have been used as bioadhesive polymers. Examples of such carboxylic acid containing polymers include polyacrylic acid (PAA), carboxymethyl cellulose and hyaluronic acid. For example, polyacrylic acid polymers are described as having the ability to interact with mucous membranes and so form a drug delivery platform.

Cyclodextrin inclusion complexes have also been described. Cyclodextrins are cyclic oligosaccharides which have a hydrophobic core and a hydrophilic exterior. The hydrophobic core enables cyclodextrins to form inclusion complexes with a wide range of drug molecules. The inclusion complex formed is not permanent, rather, it is in equilibrium with the free drug. Thus, if the free drug is removed from the system, the complex will disassociate to re-establish the equilibrium. Additionally, cyclodextrins are not absorbed across biological membranes. These two properties render cyclodextrins particularly useful in drug delivery as they can act as a drug reservoir, continuously replenishing the supply of free drug.

Cyclodextrin polymers are disclosed in *Cyclodextrin Containing Polymers, Harada. A et al, Macromolecules* 5 (1976) 701-704. Conjugates of polyacrylic acid and cyclodextrin are also disclosed in *Sustained-Release of Drugs from Cyclodextrin-Containing Hydrogels, Chino.M et al; Proceed.Intern.Symp.Control.Rel.Bioact.Mater. 18 (1992), Controlled Release Society Inc.* at pages 98 and 99.

Carboxylic acid containing polymer-cyclodextrin conjugates (CACP-CD) and more particularly polyacrylic acid - cyclodextrin (PAA-CD) conjugates, can be used to enable the controlled release of drugs.

Surprisingly, the applicant has now found that CACP-CD conjugates when administered to the eye(s) of a patient can be used to increase bioavailability of an ophthalmically administrable drug encapsulated within the cyclodextrin portion of the CACP-CD conjugate. It is this general finding upon which the present invention is based.

The object of the present invention is therefore to provide a pharmaceutical composition comprising a carboxylic acid containing polymer - cyclodextrin drug encapsulating conjugate composition which is formulated for ophthalmic administration, or at least to provide the public with a useful choice.

SUMMARY OF THE INVENTION

Accordingly, in a first aspect the present invention can broadly be said to consist in an ophthalmically acceptable pharmaceutical composition comprising:

a carboxylic acid containing polymer - cyclodextrin conjugate with an ophthalmically administrable drug encapsulated within the cyclodextrin portion of the conjugate, and an ophthalmically acceptable liquid carrier or diluent.

Preferably the carboxylic acid containing polymer is a polyacrylic acid. Particularly preferred polyacrylic acids are Carbopol 934P, or polyacrylic acid having a molecular weight of 450,000.

A preferred cyclodextrin is β-cyclodextrin, or a derivative thereof, particularly a hydroxypropyl derivative of β-cyclodextrin.

In a further aspect, the present invention relates to the use of a carboxylic acid containing polymer - cyclodextrin conjugate in the preparation of an ophthalmic solution suitable for ophthalmic administration to treat a medical condition in a patient, said medicament being in a form such that an ophthalmically administrable drug is encapsulated within the cyclodextrin portion of the conjugate.

In a still further aspect, the present invention provides a method of treating a medical condition in a patient comprising the step of administering an ophthalmic composition as described above to the eye(s) of a patient in need thereof.

Most usually, the medical condition to be treated will be an ophthalmic medical condition.

The term patient as used herein refers to human and non-human animal patients.

DESCRIPTION OF THE DRAWINGS

Although the present invention is broadly as defined above, it will be appreciated by those persons skilled in the art that the invention is not limited thereto and that it also includes embodiments of which the following description gives examples. In particular preferred aspects of the invention will be described in relation to the accompanying drawings in which:

Figure 1 is a graph illustrating the comparative bioavailability of hydrocortisone in a suspension formulation and as encapsulated in a cyclodextrin-Carbopol 934P conjugate in the cornea following topical application of 25 µl of a hydrocortisone formulation.

Figure 2 is a graph illustrating the comparative bioavailability of hydrocortisone in a suspension formulation and as encapsulated in a cyclodextrin-Carbopol 934P

conjugate in the aqueous humor following topical application of 25 µl of a hydrocortisone formulation.

DESCRIPTION OF THE INVENTION

In a first aspect, the present invention provides an ophthalmically acceptable pharmaceutical liquid composition incorporating a carboxylic acid containing polymer - cyclodextrin (CACP-CD) conjugate.

The carboxylic acid containing polymer used in the formation of the conjugate may comprise any known carboxylic acid containing polymer. It is however currently preferred that the polymer be one already approved for human or animal uses and which is in the molecular weight range 1000 to 10 million.

Examples of suitable carboxylic acid containing polymers include hyaluronic acids, polyacrylic acids, polymethacrylic acids, polyethacrylic acids, carboxymethylcelluloses, and hydroxypropylmethylcellulose phthalate amongst others.

Particularly preferred are polyacrylic acids and especially Carbopol 934P, (available from B F Goodrich Co., Cleveland, Ohio, U.S.A.) and polyacrylic acid (Aldrich; MW 450,000 available from Aldrich Chemical Co., Milwaukee, Wisconsin, U.S.A.).

Carbopol is the Registered Trade Mark of the Goodrich Company.

Cyclodextrins used in the formation of the conjugate may comprise α-, β- or γ-cyclodextrin or functionally equivalent variants or derivatives thereof. Cyclodextrins useful in the present invention include hydroxypropyl, hydroxyethyl, glucosyl, multosyl and multotryosol derivatives amongst others. A particularly preferred cyclodextrin is β-cyclodextrin available from the American Maize Products Co., Hammond, Indianapolis, U.S.A. Also preferred is the hydroxypropyl derivative of β-cyclodextrin.

A preferred CACP-CD conjugate is a polyacrylic acid (PAA)- β-cyclodextrin conjugate, or a conjugate of a PAA and a hydroxypropyl derivative of β-cyclodextrin.

The CACP-CD conjugates used in the invention may be prepared by conjugating a selected CACP to a selected CD using any conventional method known in the art.

The reader will note that the following preparative methods refer to PAA-CD conjugates but are generally applicable to the preparation of CACP-CD conjugates, and pharmaceutical compositions containing same.

One method for preparing a PAA-CD conjugate is disclosed in the article *Influence of β-cyclodextrin concentration and polyacrylic acid molecular weight on swelling and release characteristics of metoclopramide-containing hydrogels N.García-González et al., International Journal of Pharmaceutics, 100(1993) 25-31* at page 26 (incorporated herein by reference).

However, a preferred preparative method is to add a predetermined amount of a selected polyacrylic acid to a solution of dimethyl formamide containing N,N'-carbonyldiimidazoyl and 4-pyrrolidinopyridine followed by the addition of a selected cyclodextrin in an appropriate ratio. The solution is then mixed for an extended period of time (in the order of two to five days). The PAA-CD conjugate is then isolated by standard precipitation techniques, followed by centrifugation. The conjugate produced is then purified.

The ratio of cyclodextrin to polyacrylic acid is based on the number of cyclodextrin molecules present relative to the carboxylic acid groups on the polyacrylic acid.

An appropriate ratio of the cyclodextrin to the carboxylic acids of the polyacrylic acid is from substantially 1:1 to 1:100. Preferred ratios of cyclodextrin to polyacrylic acid carboxylic acids are 1:50 and 1:60.

The degree of substitution of the cyclodextrin is the number of carboxylic acid groups reacted with each cyclodextrin molecule. An appropriate ratio is 1:1 to 1:14.

The solution is preferably mixed for approximately three days before precipitation. Generally, organic (e.g. ether) or acid precipitation is preferred.

The conjugate once precipitated may be purified either by repeated washings with an acid, or by standard dialysis, ion-exchange and ultra filtration procedures.

To provide the product in a form suitable for use in the ophthalmic composition of the invention, the product is additionally freeze-dried and ground prior to use.

As a next step, in preparing the sterile ophthalmic composition of the invention, an ophthalmically administrable drug is encapsulated within the cyclodextrin portion of the PAA-CD conjugate formed above. Encapsulation of the selected drug may be achieved using conventional encapsulation techniques.

A preferred encapsulation technique is to dissolve a selected PAA-CD conjugate in an appropriate solvent and to mix it with a selected ophthalmically acceptable drug. If the formulation is not to be used immediately it can optionally be freeze dried. If the formulation is freeze dried then the ophthalmic composition of the invention is subsequently prepared by dissolving the PAA-CD conjugate with encapsulated drug in an ophthalmically acceptable diluent or carrier such as water. Optionally, additional ophthalmically acceptable agents may be included in the formulation. Examples of such agents include buffers, salts to adjust tonicity, anti-microbial agents and chelating agents.

Preferably, the ophthalmic composition of the invention is prepared by mixing the PAA-CD conjugate with the drug to be encapsulated, a carrier or diluent, and optionally one or more ophthalmically acceptable agents as identified above, in a single process.

In a particularly preferred process the drug encapsulation step and preparation of the ophthalmic composition is accomplished by mixing a suspension of the PAA-CD conjugate with the drug to be encapsulated in water. The mixture is then probe sonicated for a short period (in order of 1 to 20 minutes) followed by a longer period of rotation (in the order of 12 to 36 hours) at a temperature of between substantially 25 to 45°C, and at a rotation rate of between about 15 and 75 rpm.

Most desirably the mixture is probe sonicated for approximately 2 minutes, followed by rotation end-over-end in a bottle for 24 hours at 33°C and at 45 rpm.

Because the composition is for administration to the eye it is important that it be provided in a sterile condition. This can be achieved by preparing the composition under aseptic conditions or alternatively by sterilising the composition once produced. Suitable sterilisation techniques include radiation treatment, autoclaving, and filtration (for low MW conjugates) amongst others. The composition may then be stored at room temperature until required.

The term "drug" is used in a broad sense to refer to compounds or compositions useful in methods of human and veterinary therapy. Examples of ophthalmically acceptable drugs for incorporation into the PAA-CD conjugate include antibacterials, antifungals, antivirals, anti-inflammatories, mydriatics, cycloplegics, miotics, beta-blockers, local anaesthetics, carbonic anhydrase inhibitors and immunosuppressants.

The amount of the drug present in the formulation can of course be varied on a percentage w/v basis as desired. Generally the drug will be present in the formulation in a range of from 0.01 % to 5 % w/v formulation.

In a further aspect, the present invention relates to the use of a CACP-CD conjugate as described above in the preparation of an ophthalmic medicament suitable for opthalmic administration to treat a medical condition in a patient.

In a still further aspect, the present invention relates to a method of treating a medical condition in a human or animal patient comprising the step of administering an ophthalmic composition of the invention to the eye(s) of a patient in need thereof.

The medical condition to be treated will most usually be an ophthalmic condition such as bacterial, fungal or viral eye infections or inflammatory states. Examples of conditions amenable to treat with the composition of the invention include glaucoma and conjunctivitis. The compositions may also be formatted as anaesthetics.

In the method of the invention, an ophthalmic composition prepared as described above is instilled into the eye(s) of the patient using any conventional means such as

an eye dropper, or squeeze bottle, or may be administered in the form of a gel, spray or insert.

The amount of composition administered may of course vary with the drug being administered and according to the condition to be treated. For a solution such as a spray or eye drop it is anticipated that the amount administered would not exceed 50µl (or 1 drop), for a gel it is anticipated that the amount administered would be in the order of 50-100 mg.

In use, the ophthalmic composition is administered to the eye(s) of a patient in need thereof. It has been found that some of the compositions of the invention when administered to the eye(s) surprisingly form a gel. This gel potentially assists in enhancing drug bioavailability.

More generally, it is believed that the enhanced bioavailability results from one or more of the following factors:

the enhanced retention of the drug within the eye due to the complexing and bioadhesive properties of the polymer conjugate; the drug being dispersed in a molecular form and in the presence of the bioadhesive polymer; or enhanced concentration of drug near the corneal membrane; or a combination of these factors together with the possibility that the drug may be displaced from the complex by endogenous materials leading to supersaturation of the solution adjacent to the corneal membrane.

Tests to date indicate that bioavailability of a drug from the PAA-CD conjugate may be increased from substantially 2 to substantially 10 times that of the availability of the drug from a suspension formulation of the drug alone. This increase in bioavailability was found to occur to varying degrees in all ocular tissues including the aqueous humour, cornea and iris/ciliary bodies.

Specific non-limiting examples of the invention will now be described.

Example 1 - Synthesis of a PAA-cyclodextrin Conjugate

1.2g of Carbopol 934P was dispersed in 60 mls dry dimethyl formamide. 0.36g of N,N'-carbonyldiimidazole was added to the mixture and stirred for 30 minutes. 0.6g of 4-pyrrolidinopyridine in 40 mls dry dimethyl formamide was then added together with 1.2g of β-cyclodextrin. The mixture was shaken for 3 days. After this time period, the reaction mixture was added to 800 mls dilute hydrochloric acid and then adjusted to pH3 with dilute hydrochloric acid (0.23M) to precipitate the cyclodextrin-polymer. The product was isolated by centrifugation and purified by repeated washings with dilute hydrochloric acid until the washings show no absorbance at 282 nm. The isolated, purified product was freeze dried and ground prior to use.

Approximately 1.2g of the cyclodextrin-Carbopol 934P polymer was recovered. The product was found to contain 20% w/w β-cyclodextrin. This composition was confirmed by elemental analysis. The analyses suggests that one cyclodextrin molecule interacts with an average of 3.5 carboxylic acid groups of the poly (acrylic acid). The binding of the cyclodextrin to the polymer backbone is stable as determined by ultrafiltration.

Example 2 - Synthesis of Medium Molecular Weight PAA-cyclodextrin Conjugate

1.2g of poly (acrylic acid) molecular weight 450,000 (Aldrich) was dispersed in 60 mls dry dimethyl formamide. 0.36g of N,N'-carbonyldiimidazole was added to the mixture and stirred for 30 minutes. 0.6g of 4-pyrrolidinopyridine in 40 mls dry dimethyl formamide was then added together with 1.2g of β-cyclodextrin. The mixture was shaken for 3 days. After this time period, the reaction mixture was added to 400mls dry ether to precipitate the cyclodextrin-polymer. The precipitate was subsequently isolated and vacuum dried to remove residual ether. The product was then dissolved in water to a concentration of 3.3% w/v and stirred over a cation-exchange resin (amberlite IR20) for 30 minutes. The solution was adjusted to pH 5 and decanted. The product was further purified by ultrafiltration through a 10,000 molecular weight cut-off membrane washing 5 times with purified water. The product was finally isolated by freeze-drying.

The product was found to contain 20% w/w ß-cyclodextrin and had an aqueous solubility in excess of 25mg/ml.

Example 3 - Preparation of Ophthalmic Composition

10 ml of a 5% suspension of the β-cyclodextrin-PAA(934P) of Example 1 in water was added to 30 mg of hydrocortisone and sonicated for two minutes. The solution was then placed in a bottle vortexed and rotated end-over-end for 24 hours at 33°C and at 45 rpm. All the hydrocortisone present was either complexed or in solution.

Example 4 - Comparison of Ocular Bioavailability of a Hydrocortisone Formulated as a Suspension and as a Complex with a Carbopol 934P-Cyclodextrin Conjugate

Ocular bioavailability of hydrocortisone formulated as a suspension and as a complex with the cyclodextrin-Carbopol 934P polymer.

The ocular bioavailability of a 0.3% w/v suspension formulation of hydrocortisone was compared to that of a 0.3% w/v hydrocortisone and 0.1% w/v hydrocortisone formulated using the cyclodextrin-Carbopol 934P polymer. 25 µl of each formulation was instilled into the eyes of rabbits. At various time intervals post-instillation, the rabbits were sacrificed and the concentration of hydrocortisone in various ocular tissues determined. The results are shown in the graphs in Figures 1 and 2.

RESULTS

The aqueous humour bioavailability (as determined by the area under the concentration time profile over the first 3 hours) of the 0.3% w/v formulation containing the cyclodextrin Carbopol 934P polymer was found to be 6-fold higher than that of the suspension formulation (see Figure 2). A similar increase in bioavailability was observed for the cornea (see Figure 1) and the iris/ciliary body. Bioavailabilities in all other ocular tissues were also increased to various magnitudes (at least 2-fold) by the cyclodextrin-Carbopol 934P polymer.

INDUSTRIAL APPLICATION

In accordance with the present invention there is provided an ophthalmic composition which enables the controlled release of an ophthalmically administrable drug and at bioavailability levels significantly enhanced from the bioavailability levels in cases where the drug is administered in a suspension or solution formulation by itself. The ophthalmic composition of the invention therefore provides advantages in treating medical and particularly ophthalmic conditions more effectively or at least provides an alternate and potentially superior mode of administration. With the ophthalmic compositions of the present invention targeted localised delivery is achieved with prolonged drug residence times, reducing the need for frequent dosing. It is believed that adverse reactions, side effects and variability in amount of drug delivered should be reduced using the ophthalmic composition of the invention. Cost reductions are also possible in the treatment of ophthalmic conditions by being able to produce more effective drug formulations.

It will be further appreciated by those persons skilled in the art that the present description is provided by way of example only and that the scope of the invention is limited only by the lawful scope of the appended claims. In particular, drugs other than hydrocortisone can be readily encapsulated in the composition for delivery to the eye.

CLAIMS

1. An ophthalmically acceptable pharmaceutical composition comprising:

a carboxylic acid containing polymer - cyclodextrin conjugate with an ophthalmically administrable drug encapsulated within the cyclodextrin portion of the conjugate, and an ophthalmically acceptable liquid carrier or diluent.

2. A composition according to claim 1 wherein the carboxylic acid containing polymer is a polyacrylic acid.

3. A composition according to claim 2 wherein the polyacrylic acid is Carbopol 934P.

4. A composition according to claim 2 wherein the polyacrylic acid is polyacrylic acid having a molecular weight of approximately 450,000.

5. A composition according to any one of claims 1 to 4 wherein cyclodextrin is β-cyclodextrin or a derivative thereof.

6. A composition according to claim 5 wherein the cyclodextrin is a hydroxypropyl derivative of β-cyclodextrin.

7. A composition according to any one of the preceding claims in which the drug is selected from an antibacterial, antifungal, antiviral, anti-inflammatory, mydriatic, cycloplegic, miotic, beta-blocking, anaesthetic or immunosuppressive drug.

8. The use of a carboxylic acid containing polymer - cyclodextrin conjugate in the preparation of an ophthalmic solution suitable for ophthalmic administration to treat a medical condition in a patient, said medicament being in a form such that an ophthamically acceptable drug is encapsulated within the cyclodextrin portion of the conjugate.

9. A method of treating a medical condition in a patient comprising the step of administering an ophthalmic composition according to any one of claims 1 to 7 to the eye(s) of a patient in need thereof.

10. A method according to claim 9 wherein the medical condition to be treated is an ophthalmic medical condition.

11. A method according to claim 9 or claim 10 wherein the patient is a human patient.

12. A method according to claim 9 or claim 10 wherein the patient is a non-human patient.

FIG 1

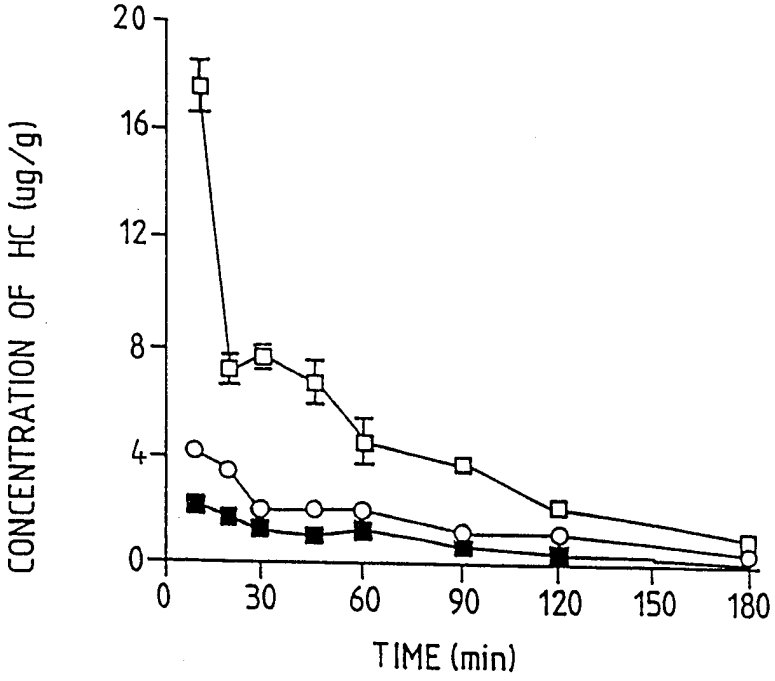
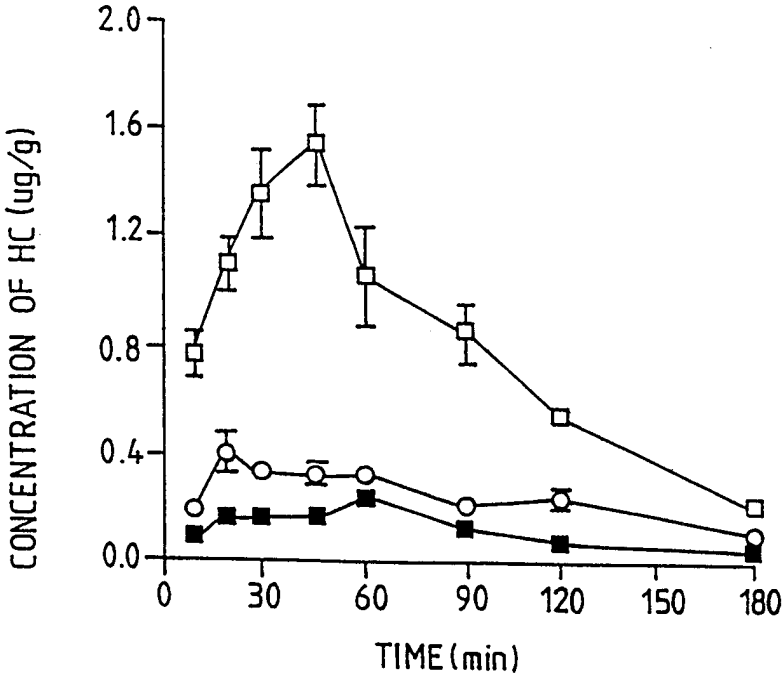


FIG 2



□ HC 0.3% w/v with CD-PAA polymer 5.0%w/v
○ HC 0.1% w/v with CD-PAA polymer 1.2% w/v
■ HC suspension 0.3% w/v

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/NZ 98/00051

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 47/40, 47/48

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A61K 47/40, 47/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT: polymer:or copolymer: or polyacrylic()acid: or carbopol or carboxymethyl cellulose or hyaluronic()acid and cyclodextrin: and A61K/IC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AU 71396/91 B (CHILDREN'S MEDICAL CENTRE) 12 September 1991	
A	JP 09216810 A (NOEVIR) 19 August 1997	

☐ Further documents are listed in the continuation of Box C

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7 September 1998	24 SEP 1998
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer **CEDRIC SCHAFFER** Telephone No.: (02) 6283 2277

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No.
PCT/NZ 98/00051

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AU	71396/91	AT	132741	CA	2037624	DE	69116186
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		US	5227372				

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