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(21) International Application Number: PCT/GB98/02637 (22) International Filing Date: 2 September 1998 (02.09.98) (30) Priority Data: 9718568.0 3 September 1997 (03.09.97) GB (71) Applicant (for all designated States except US): CHAUVIN PHARMACEUTICALS LIMITED [GB/GB]; Ashton Road, Harold Hill, Romford, Essex RM3 8SL (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): RAO, Leburu, Seshagiri [GB/GB]; Flat 6, May Villa, 148 Belgrave Avenue, Rom- ford, Essex RM2 6PR (GB). (74) Agents: SANDERSON, Laurence, Andrew et al.; Sanderson & Co., 34 East Stockwell Street, Colchester, Essex CO1 1ST (GB).		(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, HR, 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, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: METHOD FOR PREPARING PHARMACEUTICAL FORMULATIONS (57) Abstract A pharmaceutical formulation may be prepared by a method comprising providing the active ingredient in solution in a pharmacologically-acceptable base and mixing the resulting solution with a pharmacologically-acceptable acid in an amount such that the formulation attains a pH in the range of from about 3.5 to about 8.5 to thereby precipitate out the active ingredients, a viscosity-enhancing agent having been incorporated in the formulation prior to or during the mixing with acid. The formulation is suitable for administration of a pharmacologically active ingredient which is sparingly soluble in water at a pH acceptable for administration, for example to the eye of the patient.		

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- 1 -

Method for Preparing Pharmaceutical Formulations

The present invention relates to a method of preparing pharmaceutical formulations and to pharmaceutical formulations, particularly for ophthalmic use, which may be prepared by that method. In particular, the present invention relates to a method of preparing
5 pharmaceutical formulations wherein the active ingredient is of sparing solubility in pharmaceutically-acceptable solvents.

There is a recurring problem of how to formulate pharmacologically active ingredients which exhibit low solubility in pharmacologically- and pharmaceutically-acceptable solvents at a pH
10 acceptable for the intended use. It is particularly difficult to solve when the formulation is to be administered to a sensitive organ such as the skin or the eye and is required to be at a pH acceptable to the eye. Such ingredients can often only be formulated as ointments in acceptable carriers for pharmaceutical use, such as paraffin or as
15 emulsions with suitable additives. In these instances it has not been found possible to formulate in aqueous and/or non aqueous formulations such as eye drops or gels of wider acceptability.

One such poorly-soluble, active ingredient is the drug aciclovir (formerly acyclovir; 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-
20 6H-purin-6-one or 9-(2-hydroxyethoxymethyl)guanine) which is well-known for its antiviral properties especially against several Herpes viruses. Due to its low lipid and water solubilities, aciclovir is also of low bioavailability, further compounding the formulation problems. It is sold, for topical ocular application, in the form of a paraffin-based ointment,
25 and, for dermal application, as a 5% aqueous emulsion incorporating a high content of propylene glycol.

However, to be of practical use for administration to the eye, an alternative formulation to such an ointment is required. Highly desirable

- 2 -

would be a form of eye drops for ease of administration and use, and to increase bioavailability. However, with aqueous solubility of less than 0.1% w/v, it has not been possible to incorporate aciclovir as the active ingredient in eye drop formulations. For an alternative formulation to be medically and commercially successful, it would have to comprise an aqueous carrier in which the aciclovir were bioavailable to a degree that 1% aciclovir by weight of the total formulation could be administered 2-3 times per day, rather than a paraffinic formulation which requires 5 applications per day of a formulation having a high concentration (say, 3% w/w) of aciclovir.

Similar problems exist with other low solubility, low bioavailability antiviral drugs such as ganciclovir (2-amino-1,9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]-6H-purin-6-one) which is especially effective in cases of cytomegalo virus retinitis. Penciclovir (9-[4-hydroxy-3-(hydroxymethyl) butyl] guanine) is another effective antiviral having low aqueous (and even lipid) solubility and low bioavailability.

If alternative formulations of these drugs were available which would be suitable, for example, for topical ocular administration, then they could also be modified (e.g. by increasing its viscosity) so as to be suitable for dermal application.

The present invention provides a method of preparing a pharmaceutical formulation suitable for administering to a patient in need thereof a pharmacologically active ingredient which is sparingly soluble in water at the pH acceptable for administration, comprising providing the active ingredient in solution in a pharmacologically-acceptable base and mixing the resulting solution with a pharmacologically-acceptable acid in an amount such that the formulation attains a pH in the range of from about 3.5 to about 8.5 to thereby precipitate out the active ingredients, a viscosity-enhancing agent having been incorporated in the formulation prior to or during the mixing with acid.

- 3 -

Preferably at least one ion-sensitive, hydrophilic polymer is also incorporated in the formulation prior to or during the mixing with acid, which polymer has been found to provide an additional viscosity-enhancer and enhance stability of the formulation.

5 It has been unexpectedly discovered that, by this method, formulations can be produced which are suspensions of appropriately-sized microparticles of active ingredient, suitably in an aqueous gel, and where the particle size is surprisingly evenly distributed throughout the suspension when compared to formulations prepared by suspending pre-
10 micronized drug in an aqueous gel.

Furthermore, the method has the advantage that sterile conditions are relatively easy to maintain throughout because the microparticles are generated in situ, in contrast to a process involving physical micronization of the active ingredient and subsequent suspension where
15 it is difficult to maintain sterility.

An example of an active ingredient suitable for formulation in accordance with the invention is aciclovir. In the case of aciclovir, using sodium hydroxide and hydrochloric acid as base and acid, on neutralization by the acid of the sodium aciclovir salt initially formed from
20 aciclovir plus base, a precipitate of aciclovir is produced which is suspended in a sodium chloride solution.

However, without the use of a viscosity-enhancing agent, the aciclovir precipitates out as needle-shaped crystals having a length greater than 30 μ m, and without the ion-sensitive polymer has an
25 unacceptable tendency to sedimentation. Particularly for ocular use, the crystals are too long by a factor of about six, and too sharp. It was surprisingly found that incorporating a viscosity-enhancing agent, particularly prior to neutralization, produced acceptable crystal morphology. Furthermore, a formulation having appropriate stability
30 (e.g. which does not sediment on standing to form a 'cake' which can not be resuspended or which has an unacceptable resuspension time), was

- 4 -

produced by incorporating the ion-sensitive, hydrophilic polymer component, especially a cross-linked polyacrylic acid (also acting as a viscosity-enhancing agent), also preferably prior to the neutralization step.

5 Therefore, a preferred method in accordance with the invention comprises:

- (i) dissolving the active ingredient in base to form a salt solution;
- (ii) forming an aqueous suspension or dispersion of the ion-sensitive, hydrophilic polymer(s) and the viscosity-enhancing agent; and
- 10 (iii) bringing the salt solution, the aqueous suspension or dispersion and the acid into admixture

whereby there is formed a precipitate of microparticles of the active ingredient wherein 90% of the microparticles are of a diameter less than about 10 μ m (number) when measured by a Coulter counter (100 μ m
15 tube).

Step (iii) may be undertaken by first bringing the salt solution into admixture with the aqueous suspension or dispersion followed by addition of the acid. However, preferably, the acid is added to the aqueous suspension/dispersion prior to addition thereto of the salt
20 solution. Preferably, more base is then added to the suspension to neutralize the hydrophilic polymer(s). The resulting formulation is an aqueous gel having fine particles of precipitated active ingredient in aqueous suspension. It has been found that the mean size of particles of active ingredient produced according to the process of the present
25 invention is of the order of 2-10 μ m (number) or 4-16 μ m (volume); preferably around 4 μ m (number) or 8 μ m (volume).

However, in contrast to when pre-micronized active ingredient is used, the process of the present invention whereby such fine particles are produced in situ by precipitation results in a better distribution of
30 particle size, with the D₉₀ at room temperature being of the order of 5-10 μ m (number), preferably 7-9 μ m (number) or 10-16 μ m (volume),

- 5 -

whereas for pre-micronized drug the D_{90} is of the order of 5-10 μ m (number) or 21-24 μ m (volume). The formulations of the present invention exhibit similar D_{90} values at room temperature for the initial formulation and also after storage for up to 18 months. The term " D_{90} "
5 as used herein with respect to particle size distribution means that 90% of the particles have a diameter, when measured by a Coulter counter (100 μ m tube), of less than the quoted figure. Unless otherwise stated, all measurements are taken at room/ambient temperature.

Therefore a further preferred method in accordance with the
10 invention, for preparing a suspension of microparticles of an active ingredient in an aqueous gel, comprises:

- (i) dissolving the active ingredient in base to form a salt solution;
- (ii) forming an acidic dispersion of an ion-sensitive, hydrophilic polymer and a viscosity-enhancing agent in an acid; and
15 (iii) mixing the salt solution with the acidic dispersion to produce a precipitate of particles of active ingredient having a particle size D_{90} less than about 16 μ m (volume); and
- (iv) adding sufficient base to produce an aqueous gel having a pH in the range of from about 3.5 to about 8.5.

20 Conveniently, the active ingredient used in step (i) is non-micronized but, especially if readily commercially available, pre-micronized powder may also be used.

When used, a non-ionic surfactant is preferably added in the acidic dispersion with the ion-sensitive, hydrophilic polymer. Other
25 ingredients such as a preservative or the like are preferably added after the mixing/neutralizing step.

The invention also includes pharmaceutical formulations when prepared by the method as described above.

The present invention also includes a pharmaceutical formulation
30 which may be prepared by the above method and suitable for

- 6 -

administering to a patient in need thereof a pharmacologically active ingredient which is sparingly soluble in water at the pH acceptable for administration, which formulation comprises:

- (a) 0.1 - 5% w/w of the active ingredient;
 - 5 (b) a viscosity-enhancing agent;
 - (c) a pharmacologically-acceptable base in which the active ingredient is soluble in an amount sufficient to dissolve substantially all of the active ingredient; and
 - (d) a pharmacologically-acceptable acid in an amount such that the
- 10 formulation has a pH in the range of from about 3.5 to about 8.5 and such that substantially all of the active ingredient precipitates out.

Preferably the formulation also includes 0.1 to 3% (preferably 0.05 to 3%) w/w of one or more ion-sensitive, hydrophilic polymer(s) and the base(c) is present in an amount sufficient both to dissolve substantially

15 all of the active ingredient and to neutralize the ion-sensitive hydrophilic polymer(s).

The present invention further provides a pharmaceutical formulation comprising a suspension of particles of the active ingredient having a mean particle size in the range of from 2-10 μm (number) or 4-

20 15 μm (volume) and a D_{90} (as hereinbefore defined) of the order of 5-10 μm (number), preferably 7-9 μm (number) or 10-16 μm (volume) in an aqueous gel having a pH in the range of from about 3.5 to about 8.5.

The amount and type of viscosity-enhancing agent is chosen such that the viscosity of the final formulation is suitable for its chosen

25 method of administration. For example, final viscosity may be in the range of from about 1000 to about 3500 cP, preferably about 2000-3000 cP, to enable, in the case of an ophthalmic formulation, administration in droplet form. On the other hand, for dermal application, a higher viscosity in the range of from about 5000 to about 10000 cP, preferably

30 about 7000 cP, would be suitable. Increasing the viscosity in this way generates the required particle size of active ingredient and helps to

- 7 -

maintain the stability of the particle size in the suspension. Suitable viscosity-enhancing agents include hydroxyalkylcelluloses (such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose), and also hyaluronic acid and
5 polyvinyl pyrrolidone, or mixtures thereof. A preferred viscosity-enhancing agent is sold under the tradename Natrosol, for example, Natrosol 250M Pharm. The viscosity enhancing agent is suitably present in the formulation in an amount in the range of from about 0.1 to about 3.0% w/w, preferably from about 0.3 to about 1.0% w/w, more
10 preferably 0.5 to 1.0% w/w.

Preferably, the ion-sensitive, hydrophilic polymer(s) is or are one(s) which is/are acidic and form(s) a gel on neutralisation. Some may act as a viscolising (viscosity-enhancing) agent as well as functioning as a suspending agent for the particles of active ingredient in the
15 formulation. The hydrophilic polymer thereby functions to prevent or substantially reduce sedimentation of the particles of active ingredient in the formulation. Particularly preferred ion-sensitive, hydrophilic polymers are therefore selected from those wherein the resulting gel has a yield value in excess of about 80 dynes/cm²; more preferably, >90
20 dynes/cm²; especially >100 dynes/cm² as measured at room/ambient temperature with a Brookfield viscometer (such as model no. RVTDV II) having a spindle speed of 20rpm.

Suitable polymers therefore include cross-linked polyacrylic acid(s). Particularly suitable cross-linked polyacrylic acids are
25 carbomers which are synthetic high molecular weight polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. Especially suitable are the Carbopol (registered trademark) resins, Pemulen (registered trademark) polymeric emulsifiers and Noveon (registered trademark) polycarbophils. Preferably, Carbopol polymers are used
30 which are polymers of acrylic acid cross-linked with either allylsucrose or alkyl ethers of pentaerythritol; they contain in the range of from 56 - 68%

- 8 -

of carboxylic acid groups (calculated on the dry basis). Especially preferred for use in the formulations of the present invention is Carbopol 974P, having a molecular weight of approximately 3m, being a high purity grade of resin having excellent stability at high viscosity; its
5 viscosity (0.5%, pH 7.5) is in the range of 29,400-39,400cP. Alternatively, however, other ion-sensitive, hydrophilic polymers such as those which function as pH-sensitive gelling polymers could be used instead. Preferably, such polymers are present in an amount in the range of from about 0.1 to about 3.0, preferably about 0.3 to about 1.0%
10 w/w, more preferably, about 0.4 to about 0.6% such as 0.45 or 0.55% w/w.

In the formulations of the present invention, the hydrophilic polymer(s), if present, is/are neutralized by the base to produce a highly viscous gel. For this purpose, the base may comprise amino acids;
15 borax; alkali metal hydroxides such as sodium or potassium hydroxide; and/or polar organic amines such as triethanolamine. One gram of carbomer, for example, is neutralized by about 0.4g sodium hydroxide. However, the other function of the base in these formulations is to form a soluble salt of the active ingredient. Preferred, therefore, are alkali
20 metal hydroxides and carbonates which are pharmacologically acceptable, particularly for use in the eye. Especially preferred is to use sodium hydroxide resulting, in the case of the active ingredient being aciclovir, in a solution of sodium aciclovir.

The amount of acid to be included in these formulations is
25 calculated both to ensure that a substantial portion of the active ingredient is precipitated out of the initially basic solution and in the light of the amount of base present, to ensure a final pH of the formulation in the range of 3.5 to 8.5, preferably about 7 (neutral). The term "neutralization" used herein is therefore to be construed accordingly.
30 The acid chosen must be pharmacologically acceptable and result in a pharmacologically acceptable salt which will be formed in situ from the

- 9 -

base. Suitable acids therefore include inorganic acids such as hydrochloric and phosphoric, and some organic acids such as acetic. Preferably, hydrochloric acid is used.

In addition to the above-mentioned ingredients, the formulations of
5 the present invention may further comprise other pharmacologically-acceptable excipients. Preferably, there is included a non-ionic surfactant which, suitably, has a hydrophile-lipophile balance (HLB) in the range of from about 12 to about 20, more preferably about 14 to about 16. In general, the polysorbates are suitable, such as polysorbate
10 80, or any other non-ionic surfactant capable of coating the particles of active ingredient precipitated so as to help both maintain the particles in suspension and hinder crystal growth. Particularly preferred are those surfactants which aid wetting of the hydrophilic polymer(s). Suitable surfactants are sold under the trade names Pluronic, Span and Tween,
15 such as Pluronic L64 and Tween 80, both having HLB = 15. Conveniently, the amount of non-ionic surfactant in the formulation is in the range of from about 0.05 to about 0.2% w/w.

A preservative is present typically in the range of from 0-0.02% w/w of the formulation, preferably about 0.01%, such as benzalkonium
20 chloride (for example, 0.02% of a 50% solution), chlorhexidine, cetrimide, disodium edetate (EDTA), the parabens, thiomersal, chlorbutanol or the like, or a mixture thereof. Other excipient(s) may be selected from buffering agents such as disodium hydrogen phosphate and/or sodium dihydrogen phosphate; tonicity-enhancing agents such as
25 sorbitol, mannitol, glycerin, dextrose and the like; permeation-enhancing agents such as propylene glycol; and other pharmaceutically- and pharmacologically-acceptable excipients available in the art.

The formulations of the present invention are suitable for treating any condition for which the active ingredient is pharmacologically
30 effective, in particular: ocular viral infections such as those instigated by Herpes simplex (epithelial and stromal keratitis; corneal ulcers; and

- 10 -

kerato-uveitis); Varicella zoster (dendritic keratitis, uveitis and retinopathy); cytomegaloviruses (retinopathy) and adenoviruses (kerato-conjunctivitis); and skin conditions such as those caused by Herpes simplex (genital herpes and cold sores) and Varicella zoster (shingles).

5 It will be appreciated that the pharmaceutical formulations, while primarily intended for human use, may also be suitable for veterinary use, so that the term "patient" is to be understood as including humans and animals.

While the invention has been found particularly effective for
10 formulation of aciclovir, it can also be used for formulation of low solubility, low bioavailability antiviral drugs such as ganciclovir and penciclovir. Additionally the method of the invention may be applied to drugs for treating allergic reactions such as sodium cromoglycate which is soluble in alkali but precipitates at acidic pH (about pH 4) to give a
15 fine insoluble material which can then be incorporated in formulations having a relatively prolonged action when used by the patient.

Similarly, a broad spectrum antibiotic such as cefuroxime the sodium salt of which is soluble at alkaline pH can be finely precipitated at a pH of about 5 for use in suspension formulations intended to give
20 prolonged effect when used, for example, in the eye. It will be appreciated that when using a salt as starting material the incorporation of additional base may not be necessary.

The formulations can be used for optical and/or dermal use and may also find application in other areas, such as in the preparation of
25 suppositories.

The method of the invention and pharmaceutical formulations in accordance with the invention will now be illustrated with reference to the following examples:

Example 1: Ophthalmic Suspension of Aciclovir (Multidose)

<u>Ingredient</u>	<u>Concentration, % w/w</u>
Aciclovir Ph. Eur.	1.00
Polysorbate 80 Ph. Eur	0.10
5 Hydrochloric Acid (1N)	4.55
Carbomer NF/BP (Carbopol 974P)	0.55
Hydroxyethylcellulose Ph. Eur (Natrosol 250M Pharm)	0.50
Sodium hydroxide Ph. Eur.	0.44
Benzalkonium chloride Ph. Eur (50% solution)	0.01
10 Purified water Ph. Eur	q.s. to 100

The polysorbate 80 is dissolved in water and stirred. The carbomer is added gradually with stirring continued. The cellulose is added and stirring continued. The resulting carbomer dispersion is autoclaved at 121°C for 15 minutes. The hydrochloric acid (1N) is filter
15 sterilised (0.2 µm), added aseptically to the carbomer dispersion and the acidic mixture homogenised.

About 40% of the sodium hydroxide is dissolved in water to which solution the aciclovir is added and stirred until dissolved. After filter
sterilising (0.2 µm), the aciclovir salt is added to the acidic mixture,
20 followed by homogenisation then deaeration. A 10% w/v solution of the remainder of the sodium hydroxide (filter sterilised to 0.2 µm) is then aseptically added with stirring. Finally, the benzalkonium chloride (also filter sterilised to 0.2 µm) is added aseptically with stirring.

Example 2: Unpreserved Ophthalmic Suspension (Unit Dose)

The following formulation was prepared in accordance with the method described with respect to Example 1, up to but excluding the final step (addition of benzalkonium chloride):

5	<u>Ingredient</u>	<u>Concentration, % w/w</u>
	Aciclovir	1.00
	Polysorbate 80	0.10
	Hydrochloric Acid (1N)	4.55
	Carbopol 974P	0.55
10	Natrosol 250M Pharm	0.50
	Sodium hydroxide	0.44
	Purified water	q.s. to 100

Example 3: Aciclovir Suspension vs. H. keratitis

The biological activity of an aciclovir suspension according to
 15 Example 1 of the present invention against Herpes keratitis was
 compared with that of placebo (formulated as for the aciclovir
 suspension in the absence of the aciclovir) and Zovirax (registered
 trademark, 3% aciclovir in paraffin-based ointment) using the rabbit eye
 model. A description of the model may be found in Bull. Soc. Belge
 20 Ophtalmol., 186, 109-118, (1979) and Antimicrob. Agents Chemother.,
17, 8-12, (1980), both of which are herein incorporated by reference in
 their entirety.

Ten rabbits were infected in both eyes with a 20 μ l inoculum
 containing 10 e4.5 pfu/ml of TK HSV-1 (McIntyre strain). Four days after
 25 infection, 50 μ l of placebo or aciclovir suspension, or a 1cm length of
 ointment was instilled into the lower fornix of each eye for 5 days. The
 severity of keratitis was assessed on a scale of 0-5 (0 = normal,

- 13 -

transparent cornea; 5 = total corneal ulceration). The mean keratitis score was recorded as an average daily score for all 20 eyes.

Two studies were undertaken: in the first, the aciclovir suspension was administered 5 and 3 times per day; and in the second, the aciclovir suspension was administered 3 and 1 time(s) per day. The results are shown in the tables below from which it can be seen that the aciclovir suspension administered 5x and 3x was generally superior or similar in performance to Zovirax 5x; and that it exhibited a similar order of efficiency when administered 1x.

10 Results (to one decimal place)

Study 1 Mean scores of keratitis (n=10)

DAY	PLACEBO	ZOVIRAX x5	SUSPENSION x5	SUSPENSION x3
0	0.55	0.65	0.49	0.49
1	1.26	0.53	0.26	0.31
2	2.02	0.64	0.21	0.19
3	2.32	0.54	0.09	0.12
4	2.15	0.39	0.10	0.05
5	2.20	0.48	0.04	0.04

- 14 -

Study 2 Mean scores of keratitis (n=10)

DAY	PLACEBO	ZOVIRAX x5	SUSPENSION x3	SUSPENSION x1
0	0.52	0.67	0.63	0.68
1	1.18	0.36	0.36	0.48
2	2.08	0.25	0.27	0.48
3	2.24	0.16	0.19	0.50
4	2.33	0.06	0.26	0.41
5	2.29	0.06	0.24	0.41

10 **Example 4: Aciclovir Multidose Formulation**

An alternative aciclovir formulation may be prepared using the method described in Example 1 containing the following ingredients in the given concentrations.

	Aciclovir	1.00% w/w
15	Polysorbate 80	0.10% w/w
	Hydrochloric Acid (1N)	4.55% w/w
	Carbopol 974	0.55% w/w
	Natrosol 250M	0.50% w/w
	Sodium Hydroxide	0.44% w/w
20	Benzalkonium Chloride	0.01% w/w
	Disodium Edetate	0.06% w/w
	Purified Water	to 100% w/w

Example 5: Ganciclovir Multidose Formulation

A multidose formulation containing ganciclovir may be prepared using the method described in Example 1 and containing the following ingredients in the given concentrations.

5	Ganciclovir	1.00% w/w
	Polysorbate 80	0.10% w/w
	Hydrochloric Acid (1N)	4.03% w/w
	Carbopol 974	0.55% w/w
	Natrosol 250M	0.50% w/w
10	Sodium Hydroxide	0.42% w/w
	Benzalkonium Chloride	0.01% w/w
	Disodium Edetate	0.06% w/w
	Purified Water	to 100% w/w

Example 6: Penciclovir Multidose Formulation

15 A multidose formulation containing penciclovir may be prepared using the method described in Example 1 and containing the following ingredients in the given concentrations.

	Penciclovir	1.00% w/w
	Polysorbate 80	0.10% w/w
20	Hydrochloric Acid (1N)	4.06% w/w
	Carbopol 974	0.55% w/w
	Natrosol 250M	0.50% w/w
	Sodium Hydroxide	0.42% w/w
	Benzalkonium Chloride	0.01% w/w
25	Disodium Edetate	0.06% w/w
	Purified Water	to 100% w/w

Example 7: Ganciclovir Unit Dose Formulation

A unit dose formulation containing ganciclovir may be prepared using the method described in Example 1 and containing the following ingredients in the given concentrations.

5	Ganciclovir	1.00% w/w
	Polysorbate 80	0.10% w/w
	Hydrochloric Acid (1N)	4.03% w/w
	Carbopol 974	0.55% w/w
	Natrosol 250M	0.50% w/w
10	Sodium Hydroxide	0.42% w/w
	Purified Water	to 100% w/w

Example 8: Penciclovir Unit Dose Formulation

A unit dose formulation containing penciclovir may be prepared using the method described in Example 1 and containing the following ingredients in the given concentrations.

	Penciclovir	1.00% w/w
	Polysorbate 80	0.10% w/w
	Hydrochloric Acid (1N)	4.06% w/w
	Carbopol 974	0.55% w/w
20	Natrosol 250M	0.50% w/w
	Sodium Hydroxide	0.42% w/w
	Purified Water	to 100% w/w

- 17 -

CLAIMS

1. A method of preparing a pharmaceutical formulation suitable for administering to a patient in need thereof a pharmacologically active ingredient which is sparingly soluble in water at the pH acceptable for administration, comprising providing the active ingredient in solution in a
5 pharmacologically-acceptable base and mixing the resulting solution with a pharmacologically-acceptable acid in an amount such that the formulation attains a pH in the range of from about 3.5 to about 8.5 to thereby precipitate out the active ingredients, a viscosity-enhancing agent having been incorporated in the formulation prior to or during the
10 mixing with acid.
2. A method according to claim 1 wherein at least one ion-sensitive, hydrophilic polymer is incorporated in the formulation prior to or during the mixing with acid.
3. A method according to claim 2 which comprises
15 (i) dissolving the active ingredient in base to form a salt solution;
(ii) forming an aqueous suspension or dispersion of the ion-sensitive, hydrophilic polymer(s) and the viscosity-enhancing agent; and
(iii) bringing the salt solution, the aqueous suspension or dispersion and the acid into admixture
20 whereby there is formed a precipitate of microparticles of the active ingredient wherein 90% of the microparticles are of a diameter less than about 10 μm (number) when measured by a Coulter counter (100 μm tube).
4. A method according to claim 3 which comprises
25 (i) dissolving the active ingredient in base to form a salt solution;
(ii) forming an acidic dispersion of an ion-sensitive, hydrophilic polymer and a viscosity-enhancing agent in an acid; and

- 18 -

(iii) mixing the salt solution with the acidic dispersion to produce a precipitate of particles of active ingredient having a particle size D_{90} less than about 16 μm (volume); and

(iv) adding sufficient base to produce an aqueous gel having a pH
5 in the range of from about 3.5 to about 8.5.

5. A method according to claim 2, 3 or 4, wherein the or at least one of the ion-sensitive hydrophilic polymers is a cross-linked polyacrylic acid.

6. A method according to any one of the claims 2 to 5 wherein the
10 ion-sensitive hydrophilic polymer component is present in an amount of from about 0.1 to about 3.0 % w/w.

7. A method according to any one of the preceding claims wherein the viscosity-enhancing agent is present in the formulation in an amount of from about 0.1 to about 3.0 % w/w.

15 8. A method according to any one of the preceding claims wherein the viscosity-enhancing agent is selected from hydroxyalkylcelluloses, hyaluronic acid, polyvinyl pyrrolidone or mixtures thereof.

9. A method according to any one of the preceding claims where the active ingredient is aciclovir.

20 10. A pharmaceutical formulation when prepared by the method of any one of the preceding claims.

11. A pharmaceutical formulation suitable for administering to a patient in need thereof a pharmacologically active ingredient which is sparingly soluble in water at the pH acceptable for administration, which
25 formulation comprises

(a) 0.1 - 5% w/w of the active ingredient;

(b) a viscosity-enhancing agent;

(c) a pharmacologically-acceptable base in which the active ingredient is soluble in an amount sufficient to dissolve substantially all of the active
30 ingredient; and

- 19 -

(d) a pharmacologically-acceptable acid in an amount such that the formulation has a pH in the range of from about 3.5 to about 8.5 and such that substantially all of the active ingredient precipitates out.

12. A formulation according to claim 11 which also includes 0.1 to 3%
5 w/w of one or more ion-sensitive hydrophilic polymer(s) and the base (c) is present in an amount sufficient both to dissolve substantially all the active ingredients and to neutralize the ion-sensitive hydrophilic polymer(s).

13. A pharmaceutical formulation suitable for administering to a
10 patient in need thereof a pharmacologically active ingredient which is sparingly soluble in water at the pH acceptable for administration, which formulation comprises a suspension of particles of the active ingredient having a mean particle size in the range of from 2-10 μm (number) or 4-15 μm (volume) and a D_{90} (as hereinbefore defined) of the order of 5-10
15 μm (number), preferably 7-9 μm (number) or 10-16 μm (volume) in an aqueous gel having a pH in the range of from about 3.5 to about 8.5.

14. A pharmaceutical formulation according to claim 11, 12 or 13 wherein the active ingredient is aciclovir.

15. The use of a pharmaceutical formulation according to any one of
20 claims 10 to 14 in the treatment of an organ of a patient which is sensitive to pH outside the range of 3.5 to 8.5.

16. The use of a pharmaceutical formulation according to any one of claims 10 to 14 in the treatment of the eye(s) or skin of a patient.

INTERNATIONAL SEARCH REPORT

Inter nal Application No

PCT/GB 98/02637

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/00 A61K31/52 A61K9/14 A61K9/16

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 6 A61K

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 practical, 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.
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E	WO 98 43643 A (TOA MEDICINE) 8 October 1998 see abstract ---	1-16
A	DATABASE WPI Section Ch, Week 9651 Derwent Publications Ltd., London, GB; Class A14, AN 96-514906 XP002086520 & JP 08 268892 A (YUWA SHOGI) , 15 October 1996 see abstract -----	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

2 December 1998

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14/12/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT

information on patent family members

Internal Application No

PCT/GB 98/02637

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9843643 A	08-10-1998	NONE	