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(11) (C) **1,341,396**

(21) 586,611

(22) 1988/12/21

(45) 2002/11/05

(52) 530-7.64
C.L. CR 167-103.8

(51) Int.Cl. ^{7} C07K 7/64; A61K 38/13

(19) (CA) **CANADIAN PATENT** (12)

(54) Cyclosporin Crystal Form, Processes for Its Production Pharmaceutical Compositions Containing It and Its Use

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(30) (US) U.S.A. 136,230 1987/12/21
(US) U.S.A. 172,613 1988/03/24
(US) U.S.A. 212,548 1988/06/28

(57) 21 Claims

586, 611

1341396

100-7234

ABSTRACT

Novel pharmaceutical compositions, in particular topical forms, e.g. for dermal or topical ophthalmic use, and injectible forms, e.g. for intra-lesional or intra-articular injection, comprising Ciclosporin as active ingredient in orthorhombic crystal form. Ciclosporin in non-solvate orthorhombic crystal form is preferred for use in the compositions of the invention, is new and also part of the invention, together with its use and processes for its production.

NEW CICLOSPORIN CRYSTAL FORM, PROCESS FOR ITS PRODUCTION, PHARMACEUTICAL COMPOSITIONS CONTAINING IT AND ITS USE.

The present invention relates to novel pharmaceutical compositions comprising Ciclosporin as active ingredient.

Ciclosporin, or cyclosporin A, is a known fungal metabolite having valuable pharmaceutical utility. Ciclosporin is a cyclic poly-N-methylated endecapeptide of formula

-MeBmt-	αAbu-	Sar-	MeLeu-	Val-	MeLeu-	Ala-	(D)Ala-	MeLeu-	MeLeu-	MeVal-
1	2	3	4	5	6	7	8	9	10	11

in which -MeBmt- represents an N-methyl-(4R)-4-but-2E-en-1-yl-4-methyl-(L)threonyl residue.

Ciclosporin as well as methods for its production are, for example, described in US patent no. 4,117,118. The primary area of clinical investigation for ciclosporin has been as an immunosuppressive agent, in particular in relation to its application in treating recipients of organ transplants, e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, bone-marrow, skin and corneal transplants and, in particular, allogenic organ transplants. In this field Ciclosporin has achieved a remarkable success and reputation and is now widely employed in clinic and commercially available under the Registered Trade Mark SANDIMMUN^{R} or SANDIMMUNE^{R}, for example in the form of an infusion concentrate, of an oral solution and of a gelatin encapsulated solution, the latter two variants being described and claimed for example in US patent no. 4,388,307.

At the same time, investigation of the applicability of Ciclosporin to various autoimmune diseases and to inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, has been intensive and reports and results in vitro, in animal models and in clinical trials are wide-spread in the literature. Specific auto-immune diseases for which Ciclosporin therapy has been proposed or applied include, autoimmune hematological disorder (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopaenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease), pemphigus, endocrine opthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, primary juvenile diabetes (diabetes mellitus type I), Behcet's disease, uveitis (anterior and posterior), vernal conjunctivitis, keratoconjunctivits sicca, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

Further areas of investigation have included potential applicability as an anti-parasitic, in particular anti-protozoal agent, with possible uses suggested including treatment of malaria, coccidiomycosis and schistosomiasis, as well as use in reversing tumor resistance to chemotherapeutic, e.g. cytostatic, therapy and in promoting hair growth, e.g. for the treatment of alopecia.

In the solid state, Ciclosporin exists in both amorphous and crystalline form. In the crystalline state, both a tetragonal and an orthorhombic modification are known.

The tetragonal modification ($P4_1$), also referred to herein for convenience as "Cy-A/X-I", is described together with processes for its production, e.g. in Austrian patent specification No. 353,961. Cy-A/X-I has a latice a=b= 13.8 Å c= 41.2 Å, volume per asymmetric unit = 1974 $Å^3$, a melting point at ca. 140-150 °C and comprises ca. 2 molecules H_2O per Ciclosporin molecule.

A first orthorhombic modification ($P2_12_12_1$) is obtainable by recrystallisation from di-isopropyl ether as discussed in an article entitled "Total synthesis - change in molecular structure - biological effect: Ciclosporin as example" by R. Wenger, in "Sandorama" 1984/III. This particular modification comprises a Ciclosporin/di-isopropyl ether (ca. 1:2) solvate, with a crystal lattice of a = 12.5 Å, b = 22.9 Å, c = 28.4 Å, vol per asymmetric unit = 2027 $Å^3$, and a melting point at ca. 150 °C. Orthorhombic Ciclosporin solvate crystals are obtainable by recrystallisation of supersaturated Ciclosporin solutions in an appropriate solvent medium over prolonged periods of time. Thus the orthorhombic Ciclosporin/di-isopropyl ether solvate modification prepared by Wenger is obtained by addition of a concentrated solution of Ciclosporin in methylene chloride (in which Ciclosporin is rather readily soluble) to di-isopropyl ether (in which Ciclosporin is relatively less soluble) and evaporation of the methylene chloride. Crystallisation from the remaining di-isopropyl ether is then allowed to proceed over a period of ca. 7 days at ambient temperature. Orthorhombic crystal forms comprising such Ciclosporin solvates are also referred to, for convenience, herein generically as "CY-A/X-II".

A further orthorhombic ($P2_12_12_1$) modification has now been identifed, characterised by the absence or substantial absence of any solvent component, i.e. consisting substantially of, or essentially of, free Ciclosporin.

Brief Description of the Drawings

In the drawings which illustrate preferred embodiments of the invention:

Figs 1, 2 and 3 are plots of skin thickness v. test time for three different test materials, and

Fig 4 shows X-ray powder diffractions for three materials.

The dimensions of the crystal lattice for solvent free or non-solvate, orthorhombic Ciclosporin modification are a = 12.7 Å, b = 15.7 Å, c = 36.3 Å, vol. per asymmetric unit = 1804 $Å^3$. The melting point is of the order of from about 180 to about 190 °C up to about 195 °C, e.g.

depending on degree of purity/source as indicated in Examples 1 and 2 hereinafter, in which specific methods for the obtention of this modification are described. Ciclosporin in non-solvate (or solvent free) orthorhombic crystal form is also referred to herein for convenience as "CY-A/X-III". Further characterising (X-ray powder diffraction) data for CY-A/X-III are provided in Table III and Fig. IV hereinafter, together with corresponding data for CY-A/X-I and CY-A/X-II.

Despite the very considerable success and reputation which Ciclosporin has achieved and despite the major contribution to medical science, in particular to the art of organ transplant, which it has already made, its use in practice is still not ideal or problem free. A particular area of difficulty which has been encountered is in the provision of galenic forms permitting convenient or wholly satisfactory administration, or best suited for the treatment of specific diseases or conditions for which Ciclosporin has already been identified as a potential drug of choice.

These difficulties are in part attributable to the particular physical characteristics of Ciclosporin, for example its relatively limited solubility or (hitherto experienced) compatibility with available, pharmaceutically applicable carrier media. Such difficulties are compounded by the very nature of certain of the disease conditions for which Ciclosporin represents potential first line therapy as well as the occurrence of undesirable side effects which Ciclosporin may induce when administered orally. For example Ciclosporin has been identified as effective in the treatment of psoriasis following oral administration. Psoriasis is a wide-spread condition causing considerable patient suffering and for which there is at present no generally accepted, effective therapy. Sufferers from psoriasis clearly represent a patient population at need. While available evidence would suggest that Ciclosporin might meet this need it is improbable that oral Ciclosporin therapy could be justified as a conventional means of psoriasis treatment. Similar considerations apply to the treatment of e.g. eye diseases such as posterior uveitis and keratoconjunctivitis sicca.

Various systems have been proposed for the administration of Ciclosporin, including galenic forms intended for topical or dermal application or for ophthalmic application, i.e. topical application to the eye, e.g. for possible use in the treatment of psoriasis, of other dermatological diseases and conditions, for example atopic dermatosis and alopecia, or for the treatment of uveitis. Such systems have however hitherto not brought any notable benefit, or have not proven wholly satisfactory.

Thus variously reported attempts to treat psoriatic subjects by the application of the known oral solution directly at the superficial site of psoriatic lesion have met with minimal or no success and success in relation to subjects suffering from atopic dermatosis has been strictly limited. Similarly, while topical application to the eye has been found to be widely effective as a means of preventing e.g. corneal transplant rejection, or of treating disease in the anterior segment of the eye, no topical formulation has hitherto been reported which might permit ready, safe or effective treatment of diseases or conditions as they affect sites deeper within the eye, for example for the general treatment of uveitis, including posterior uveitis.

Comparable difficulties have been encountered in relation to the development of other ciclosporin drug delivery systems, for example injectible forms, e.g. suitable for intra-articular injection for the local treatment of arthritic diseases, e.g. as hereinbefore set forth, or for intra-lesional injection, e.g. for the treatment of severe psoriatic lesion, or alternative oral delivery systems, e.g. having modified bioavailability or drug-release characteristics.

Hitherto attempts to formulate Ciclosporin have made use of the compound in solution or, less commonly, in amorphous or Cy-A/X-I form, the latter being, for example, the crystal form identified e.g. for drug registration purposes. And despite the very considerable efforts expended in seeking new or improved alternatives, the oral solution and infusion concentrate already referred to remain the only widely applied delivery systems for Ciclosporin.

In accordance with the present invention, it has now surprisingly been found that orthorhombic crystalline forms of ciclosporin, for example Cy-A/X-II and, in particular, Cy-A/X-III, are of especial advantage and benefit in the preparation of ciclosporin galenic formulations of various and diverse kind.

In particular it has been found that such crystal modifications may be used to prepare galenic formulations comprising Ciclosporin in stable, fine particulate form and/or having enhanced stability or release characteristics. By this finding the way is opened to the production of novel and improved Ciclosporin drug delivery systems, e.g. possessing sustained or delayed Ciclosporin delivery characteristics and/or adapted to or suitable for the treatment of diseases or conditions hitherto refractory to Ciclosporin therapy or for which conventional Ciclosporin therapy has been inherently less suited. More especially, it has been found that by use of such crystal modifications, e.g. in fine particulate form as aforesaid, galenic forms may be obtained suitable for topical or dermal application or for topical ophthalmic application, for the treatment of diseases or conditions affecting the skin or eye, e.g. as hereinbefore set forth, in particular for the treatment of psoriasis, atopic dermatitis, contact dermatitis, occular symptoms of Behchet's disease, uveitis and keratoconjunctivitis sicca. Use of such crystal modifications also enables the preparation of injectible forms for Ciclosporin having sustained or delayed release characteristics and hence of particular utility, e.g. in the treatment of diseases or conditions for which required frequency of administration may otherwise impede utility, for example for the treatment of arthritic or similar disease of the joint by intra-articular injection or for the treatment of psoriasis or similar disease of the skin by intra-lesional injection.

For such purposes orthorhombic crystal forms, in particular CY-A/X-III, have been found to be inherently much better suited than other available forms, in particular amorphous Ciclosporin or CY-A/X-I, e.g. in terms of physico-chemical properties, especially stability, release characteristics, i.e. release of Ciclosporin from the crystal lattice, and susceptibility to the necessary procedures of galenic formulation. CY-A/X-III is new and the preferred orthorhombic crystal form for galenic and/or therapeutic use in accordance with the invention. In a first embodiment the present invention accordingly provides:

A CY-A/X-III, i.e. Ciclosporin in non-solvate orthorhombic crystal form;
in particular:

A^1 CY-A/X-III having a crystal lattice or other physical characteristic substantially as hereinbefore defined, and/or

A^2 CY-A/X-III having X-ray powder diffraction characteristics substantially as herein set forth in Table III or as represented in Fig. IV.

The present invention also provides:

B A process for the production of CY-A/X-III which process comprises crystallising Ciclosporin from a CY-A/X-III bearing medium and recovering CY-A/X-III thus obtained.

Suitable CY-A/X-III bearing media for use in the above process are, in particular, solvent media for Ciclosporin comprising higher molecular weight solvent components, e.g. having a molecular weight >200. Especially suitable are media comprising higher molecular weight ethers, in particular polymeric ethers, for example polyalkyl ethers, e.g. polyethylene-, and polypropylene-glycols. Examples of polymeric ethers which have been found to be appropriate are polyethylene and polypropylene glycols, e.g. having a molecular weight of >200; glycerin-polyethyleneglycol esters, e.g. glycerin-polyethyleneglycolricinoleates and glycerin-polyethyleneglycoloxystearates as, for example, available under the Trade Marks "Cremophor EL" and "Cremophor RH" (c.f. Fiedler, "Lexikon der Hilfstoffe" 2nd edition, Vol. 1, p.p. 257 and 258); polyoxyethylene-sorbitan esters, for example as available under the Trade Mark "Tween" (c.f. Fiedler, 2, p.p. 972-975); polyoxyethylene esters, e.g. polyoxyethylene-stearinic acid esters, for example as available under the Trade Mark "Myrj" (c.f. Fiedler, 2, p.p. 636); and trans-esterification products of natural oil triglycerides and polyalkylene polyols, including the trans-esterification products of maize oil, kernel oil, almond oil, ground nut oil, olive oil, palm oil and mixtures thereof with polyethylene-glycols, in particular polyethylene-glycols having a molecular weight of from 200 to 800, for example as available under the Registered Trade Mark "Labrafil" (c.f. Fiedler, p. 539). Especially suitable are media comprising polyethylene-glycols having a molecular weight of ca. 200 to ca. 600, in particular of ca. 300 to ca. 400.

As will be appreciated, the CY-A/X-III bearing medium may include one or more components in addition to those recited above, for example lower molecular weight alcohols and/or water, as a means of modifying solvent/crystallisation characterisitics. A particularly suitable CY-A/X-III bearing medium has been found to be one comprising ca. 0.5 parts by volume ethanol, ca. 8.0 parts by volume polyethylene-glycol (300) and ca. 1.0 parts by volume H_2O.

The process of the invention comprises first dissolving Ciclosporin, e.g. in amorphous or tetragonal form in the selected CY-A/X-III bearing medium at elevated temperature. The dissolution temperature will of course vary depending on the particular medium chosen but will generally be >40°C more especially >50°C. In the case of polyethylene-glycol based media the dissolution temperature will generally be >70°C, e.g ca. 75-130°C. Suitably the obtained solution will comprise >5%, preferably >10%, e.g. up to about 40-60%, preferably up to a maximum of 20% by weight Ciclosporin based on the total weight of the solution. Crystallisation of Ciclosporin is then allowed to proceed with cooling, suitably over a relatively prolonged period of time, e.g. of the order of 10-35 minutes or more depending on desired crystal growth.

If desired nucleation procedures may be commenced, e.g. by sonication or seeding. Where ethanol/polyethylene-glycol/H_2O crystal bearing media, e.g. as described above, are employed it has, for example, been found that nucleation can be readily initiated at temperatures of ca. 60-90°C, e.g. ca. 65-85°C. by application of sonic vibration at ca. 20,000 c.p.c. As indicated in example 2 hereinafter, by continuing sonication in this manner throughout the course of crystallisation, micro crystals may be obtained of very fine and relatively constant particle size.

The rate of crystal growth and the size of crystals obtained will of course, depend on the particular medium chosen and the conditions under which crystallisation is performed, for example on whether or not sonication is applied and at what frequency. For use in accordance with the present invention, e.g. for the preparation of galenic formulations as hereinafter described, CY-A/X-III will preferably be employed in fine particulate form, e.g. having an average particle size of <200µM, e.g. of from 0.5 to 200µM. Where initially obtained crystals are of relatively large size, particulate preparations having the desired size characteristics can, of course, be obtained by conventional comminution procedures, e.g. by grinding, milling, pulverising, micronising or otherwise fragmenting to reduce size. While particulate preparations obtained in this way may be entirely adequate for some purposes, for example in the preparation of topical compositions for application to the skin, use of grinding or milling or equivalent techniqes will in many cases not be preferred. Reasons for this are that the products of such procedures tend to exhibit relatively wide particle size distribution and to have a relatively coarse or abrasive structure as a consequence of crystal fracture. In addition comminution will tend to destroy physical characteristics at the natural crystal surface and is in any event difficult or costly to perform while maintaining required conditions of sterility, e.g. in the manufacture of galenic formulations for intra-articular administration. For such reasons it is commonly preferred to carry out the method of the invention in such a manner as to obtain crystals, e.g. microcrystals, of dimensions within the desired end particle size range. Thus for use in the manufacture of e.g. compositions for intra-articular or other parenteral application use of CY-A/X-III particle preparations in non-comminuted microcrystalline state (i.e. CY-A/X-III microcrystals in native or non-fractured condition, e.g. which have not been subjected to grinding, milling, micronization or other reductive procedures) will be preferred.

In order to obtain CY-A/X-III microcrystals which can be used directly in non-comminuted state in the above described manner, the process of the invention will suitably be carried out with agitation, for example by stirring, e.g. at 200-300 r.p.m. rising to e.g. 700 r.p.m. during crystallisation, and, especially, by application of ultra-sonic vibration, e.g. within the range of 10,000-30,000 cycles per sec, suitably of the order of about 20,000 cycles per sec.

By variation of the CY-A/X-III bearing medium and adjustment of the rate of cooling and degree of agitation during the recrystallisation procedures in accordance with techniques known in the art and as hereinafter exemplified, CY-A/X-III microcrystals may be produced of varying average particle size, e.g. as set forth above or as hereinafter described for use in relation to individual types of galenic formulation in accordance with the invention.

As previously indicated crystallisation in accordance with the process of the invention will suitably be performed under sterile conditions. Purification of the obtained CY-A/X-III may be carried out in conventional manner, e.g. by rinsing with poly ethylene glycol (300) : water e.g. in a ratio of 3-4:1 p.p.w./ washing with warm water, as described in the examples. The obtained CY-A/X-III will suitably be recovered free or substantially free of Ciclosporin in any other form, preferably in pure or substantially pure form. The rinsing step above assists prevention of the formation of amorphous Ciclosporin.

In accordance with the foregoing the present invention additionally provides: Ciclosporin producible by any of the above described procedures as well as:

A^3 CY-A/X-III according to any one of A to A^2 above, free or substantially free of Ciclosporin in any other form, e.g. free or substantially free of Ciclosporin in amorphous form, of CY-A/X-I or of CY-A/X-II;

A^4 CY-A/X-III according to any one of A to A^3 above in pure or substantially pure form;

A^5 CY-A/X-III according to any one of A to A^4 above in fine particulate form, e.g. having particle size characteristics as hereinbefore set forth or as hereinafter described, e.g. in relation to galenic forms comprising CY-A/X-III;

A^6 CY-A/X-III according to any one of A to A^5 above consisting predominantly, or consisting entirely or substantially entirely, of non-comminuted crystal material, e.g. CY-A/X-III according to A^5 above wherein the component particles are comprised predominantly, or comprised entirely or substantially entirely, of non-comminuted microcrystals; and

A^7 CY-A/X-III according to any one of A to A^6 above in sterile or substantially sterile condition, e.g. in a condition suitable for pharmaceutical use, in particular suitable for parenteral application, e.g. for administration by parenteral injection, e.g. intra-articular injection.

In addition the present invention also provides:

C A pharmaceutical composition comprising
a) Ciclosporin in orthorhombic crystal form as active ingredient, together with
b) a pharmaceutically acceptable diluent or carrier therefor.

Ciclosporin may be present in the compositions of the invention in any appropriate orthorhombic crystal form, e.g. as CY-A/X-II or CY-A/X-III. Use of CY-A/X-II will however generally be less preferred having regard to its physico-chemical properties which are less well suited for use both in terms of tolerability and useability for the manufacture of effective Ciclosporin-based pharmaceutical products. Most preferably Ciclosporin will be present in the compositions of the invention as CY-A/X-III, e.g. according to any one of A to A^7 above.

Though Ciclosporin is present in the compositions of the invention in solid (crystalline) form, the compositions themselves may be of any appropriate constitution. Compositions in accordance with the invention thus include solid forms, such as capsules, tablets, dragées, powders and granulates, semi-solid forms such as ointments, gels, creams and pastes, as well as liquid forms, e.g. comprising the defined Ciclosporin component in fine particulate form (for example micronised or microparticulate form) suspended or dispersed in a liquid pharmaceutical diluent or carrier, in which the chosen crystal form may be retained.

Compositions in accordance with the invention include both systems comprising a single Ciclosporin-containing phase or compartment, for example simple creams, gels, ointments etc... as aforesaid or simple one compartment capsules or ampoules, for example hard or soft gelatin capsules or ampoules for injection, as well as systems comprising a plurality of phases or compartments. Thus the invention is to be understood as embracing, e.g. compositions comprising a Ciclosporin-containing phase or compartment together with one or more non-Ciclosporin-containing phases or compartments, e.g. coating, carrier, retard or placebo phases, or phases or compartments comprising other drug substances or adjuvant materials. The invention is thus to be understood as embracing, for example: coated tablets having a core comprising Ciclosporin in orthorhombic crystal form, surrounded e.g. by other non-Ciclosporin-containing coating phases or the like; mantle tablets comprising a core or mantle comprising Ciclosporin in orthorhombic form and provided with a non-Ciclosporin-containing mantle or core; mixed granulates comprising a first granulate phase comprising Ciclosporin in orthorhombic crystal form and a second non-Ciclosporin-containing granulate phase; and split capsules having two or more compartments, e.g. divided by an internal wall, one of which contains Ciclosporin in orthorhombic form and one of which does not. Other alternatives and variants will be apparent to those skilled in the art.

Preferably Ciclosporin will be present on the compositions of the invention in a major proportion in orthorhombic crystal form, e.g. as CY-A/X-III. It is particularly preferred that the Ciclosporin be present entirely or substantially entirely in said orthorhombic crystal form.

The compositions of the invention will suitably comprise at least one phase or compartment comprising Ciclosporin in orthorhombic crystal form, e.g. CY-A/X-III, throughout which said crystal form is distributed or distributable uniformly. Such systems include for example homogeneous creams, ointments, gels and the like as well as liquid systems in which the contained crystalline Ciclosporin is or can be readily distributed homogenously, for example by hand agitation.

Compositions in accordance with the invention may include: forms suitable for topical administration e.g. dermal or topical ophthalmic administration; for parentaral administration, e.g. by infusion or injection, including sub-cutaneous or intramuscular injection and, in particular, intra-lesional or intra-articular injection; as well as forms for enteral administration, for example suppositories, pessaries and the like and oral dosage forms. Enteral forms, for example oral dosage forms will however generally be less preferred.

Preferably orthorhombic crystalline Ciclosporin, e.g. CY-A/X-III, will be present in the compositions of the invention in fine particulate form, e.g. micronised, microparticulate or non-comminuted microcrystalline form as hereinbefore described. Appropriate particle size will of course vary depending on the particular nature of the composition, its intended use and mode of application and the effect desired. In general however, average particle size will suitably be of

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the order of from 0.5-200µM. Particular ranges, e.g. in relation to the preparation of oral, topical or injectible forms are further discussed hereinafter.

TOPICAL FORMS e.g. for dermal or topical ophthalmic administration, e.g. for the treatment of psoriasis or atopic dermatosis or of diseases or conditions of the eye requiring immunosuppressive therapy, for example uveitis, conjunctivitis, including keratoconjunctivits sicca or vernal keratoconjunctivitis, or corneal transplant.

Gels, creams, ointments and the like for topical or dermal administration can be prepared in accordance with any of the techniques known and generally employed in the art, for example by compounding Ciclosporin in orthorhombic crystal form with an appropriate flowable base material, e.g. aqueous gel, for example aqueous cellulose-ether based gel, with the addition of appropriate tensides, thickeners etc. including e.g. aerosil.

The Ciclosporin component is preferably present in fine particulate form, e.g. having an average particle size of from 0.5-200µM. Preferably the average particle size is <60-80µM, more preferably <40µM, yet more preferably <30µM, most preferably <20µM. Advantageously the particles will have as narrow a particle size distribution as possible. Preferably substantially all particles present will be less than 60-80µM.

Compositions of the invention for topical ophthalmic use, i.e. application to the eye, may include, for example suitably thickened suspensions or dispersions presented e.g. in the form of viscous eye-drop preparations or creams or gels for occular application. In the case of compositions for administration to the eye, the average particle size for the crystalline Ciclosporin material present will suitably be <25µM. More preferably substantially all particles present will be less than 25µM. Average particle size for such eye drop preparations will suitably be in the range of from about 0.1, or preferably from about 0.5, to about 20µM or, preferably, to about 10µM.

The hydrophilic/lipophilic content of the carrier system for use in forms for dermal application or for use in preparations for application to the eye may vary, e.g. depending on the particular surface to which the composition is to be applied, e.g. depending on the characteristics of the particular skin area to be treated.

Compositions for topical, in particular dermal, application suitably comprise a carrier medium in which the active ingredient (Ciclosporin component) is only slightly soluble. Suitably the solubility of the Ciclosporin component (e.g. CY-A/X-III) in such compositions is <10%, preferably <1.0% by weight. More preferably solubility is <0.1%, most preferably <0.001% by weight.

Suitable carrier media include hydrophilic, water miscible carriers as well as hydrophobic carriers.

Hydrophilic, water miscible carrier components are suitably of relatively low volatility. Examples of appropriate carrier components belonging to this class include liquid polyalkylene glycols, propylene glycol, glycerol and ethylene glycol. Suitable polyalkylene glycols include in particular, liquid polyethylene glycols, e.g. having an average molecular weight up to about 600, e.g. having an average molecular weight from about 250 to 450, especially ca. 300.

Representative compositions in accordance with the invention, e.g. for topical application, accordingly comprise:

C^1 a) Ciclosporin in orthorhombic, preferably non-solvate orthorhombic, crystal form, e.g. Cy-A/X-III, e.g. as defined under any one of A to A^7 above;

b) A hydrophilic, water miscible carrier, e.g. as described above; and, optionally

c) Pharmaceutical grade water.

The amount of component (a) present will suitably be of the order of from about 0.1 to about 30.0%, especially about 0.5 or 1.0 to 20%, e.g. ca. 1.0, 2.0, 5.0 or 10.0% based on the total weight of the composition. Components (b) and (c) will suitably be present in a ratio of from 1:0 to 1:20 p.p.w. More suitably components (b) and (c) will be present in a ratio of from 1:0.5 to 1:5, e.g. from 1:1 to 1:3, most suitably 1:1.5 to 1:2.5 p.p.w.

Such compositions will suitably additionally comprise:

d) A surface active agent.

Suitable components (d) include, inter al.

d^1 Trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols.

Such trans-esterification products are known from the art and may be obtained e.g. in accordance with the general procedures described in US Patent No. 3 288 824. They include trans-esterification products of various natural (e.g. non-hydrogenated) vegetable oils for example, maize oil, kernel oil, almond oil, ground nut oil, olive oil and palm oil and mixtures thereof with polyethylene glycols, in particular polyethylene glycols having an average molecular weight of from 200 to 800. Preferred are products obtained by trans-esterification of 2 molar parts of a natural vegetable oil triglyceride with one molar part of polyethylene glycol (e.g. having an average molecular weight of from 200 to 800). Various forms of trans-esterification product of the class defined are known and commercially available under the Trade Mark Labrafil [see Fiedler, "Lexikon der Hilfstoffe", 2nd. revised and expanded edition (1981), Vol. 2, page 539]. Especially useful as components of the compositions of the invention are the products: Labrafil M 1944 CS, a trans-esterification product of kernel oil and polyethylene glycol having an acid number of ca. 2, a saponification number of 145- 175 and an iodine number of 60 - 90;

and Labrafil M 2130 CS, a trans-esterification product of a C_{12}- to C_{18}- glyceride and polyethylene glycol having a melting point of ca. 35 - 40°C., an acid number of <2, a saponification value of ca. 185 - 200 and an iodine number of <3.

d^2 Reaction products of a natural or hydrogenated castor oil and ethylene oxide. Such products may be obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil with ethylene oxide, e.g. in a molar ratio of from about 1:35 to about 1:60, with optional removal of the polyethyleneglycol component from the product, e.g. in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819. Especially suitable are the various tensides available under the Trade Mark Cremophor. Particularly suitable are the products Cremophor RH 40 having a saponification number of ca. 50-60, an acid number <1, an iodine number <1, a water content (Fischer) <2%, an n_D^{60} of ca. 1,453 - 1,4578 and an HLB of ca. 14 - 16; Cremophor RH60 having a saponification number of ca. 40 - 50, an acid number <1, an iodine number <1, a water content (Fischer) 4.5-5.5%, an n_D^{25} of ca. 1,453 - 1,57 and an HLB of ca. 15 - 17; and Cremophore EL having a molecular weight (by steam osmometry) of ca. 1630, a saponification number of ca. 65 - 70, an acid number of ca. 2, an iodine number ca. 28 - 32 and an n_d^{25} of ca. 1,471. Also suitable for use in this category are the various tensides available under the Trade Mark Nikkol, e.g. Nikkol HCO-60. The said product Nikkol HCO-60 is a reaction product of hydrogenated castor oil and ethylene oxide exhibiting the following characteristics: Acid number of 0.3; Saponification number of 47.4; Hydroxy value of 42.5; pH (5%) of 4.6; Color APHA = 40; m.p. = 36.0°C; Freezing point = 32.4°C; H_2O content (%, KF) = 0.03.

d^3 Polyoxyethylene-sorbitan-fatty acid esters or polysorbates e.g. of the type known and commercially available e.g. under the Trade Marks Tween and Armotan (c.f. Fiedler, 2, p.p. 745-746 and 972-975) including the products Tween

20 [polyoxyethylene(20)sorbitanmonolaurate],
40 [polyoxyethylene(20)sorbitanmonopalmitate],
60 [polyoxyethylene(20)sorbitanmonostearate],
65 [polyoxyethylene(20)sorbitantristearate],
80 [polyoxyethylene(20)sorbitanmonooleate],
85 [polyoxyethylene(20)sorbitantrioleate],
21 [polyoxyethylene(4)sorbitanmonolaurate],
61 [polyoxyethylene(4)sorbitanmonostearate], and
81 [polyoxyethylene(5)sorbitanmonooleate].

d^4 Polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters of the type known and commercially available under the Trade Mark Myrj (c.f. Fiedler, 2, p. 636) as well as polyoxyethylene fatty acid esters known and commercially available under the Trade Mark Cetiol HE. (c.f. Fiedler, 1, p. 228), and polyoxyethylene fatty alcohol ethers, for example polyoxyethylene stearylether, oleyl ether, or cetyl ether, e.g. of the type known under the Trade Mark Brij (c.f. Fiedler, 1, 184-186), e.g. Brij 78 and 96, and Cetomacrogel 1000 (c.f. Fiedler, 1, 229).

d^5 Polyoxyethylene-polyoxypropylene co-polymers e.g. of the type known and commercially available under the Trade Marks Pluronic and Emkalyx (c.f. Fiedler, 2, p.p. 720-722.

d^6 Sorbitan fatty acid esters e.g. of the type known and commercially available under the Trade Mark Span, for example including sorbitan-monolauryl, -monopalmityl, -monostearyl, -tristearyl, -monooleyl and -trioleyl esters - c.f. Fiedler, 2, p.p. 850-851.

d^7 Partial glycerides, e.g. products comprising mono- and/or di-glyceride components, for example mixed mono-/di-/tri-glyceride/free glycerol based surfactants as well as, e.g., glycerol monostearates and glycerol monooleates. Examples of such products include those known and commercially available under the Trade Marks Imwitor (c.f. Fiedler, 1, 491) for example Imwitor 191 and Imwitor 780< and Softigen (c.f. Fiedler, 2, 833) for example Softigen 701.

d8 Ionic surfactants or emulsifying agents such as sodium lauryl sulfate and sodium cetostearyl sulfate.

Components (d) when present are suitably present in an amount of up to maximally 30%, more preferably maximally 15%, based on the total weight of the composition. Most suitably components (d) are present in an amount of from about 0.5 to about 10%, e.g. about 1.0%, based on the total weight of the composition.

Such compositions will suitably also comprise:

e) A thickening agent.

Suitable components (e) include for example:

e1 Polymethylacrylate resins, e.g. of the type known and commercially available under the Trade Mark Eudispert (c.f. Fiedler, 1, 371-372).

e2 Cellulose derivatives including e.g. ethyl-, propyl-, methyl-, hydroxypropylmethyl- and carboxymethyl-celluloses.

e3 Polyvinyl resins, e.g. including polyvinylalcohols and polyvinylpyrrolidones, as well as other polymeric materials including gelatin, alginates, pectins, gum traganth, gum arabicum, gum xanthan, and polyacrylic acids such as known and commercially available under the Trade Mark Carbopol (c.f. Fiedler, 1, 206-207).

e4 Materials such as silica gel, bentonite, and magnesium-aluminium silicate.

Components (e) when present are suitably present in an amount of up to 20%, more preferably up to 10%, based on the total weight of the composition. Most suitably components (e) are present in an amount of from about 0.5 to about 15%, e.g. from about 1.0 to about 3.0% based on the total weight of the composition.

In addition such compositions also suitably comprise an anti-microbial agent such as methylparaben, propylparaben, benzalconium chloride or benzyl alcohol, e.g. in an amount of from 0.05 to 0.5% or, in the case of benzyl alcohol, up to 2.0%, e.g. ca. 0.1%, or, in the case of benzyl alcohol, ca. 1.0% by weight based on the total weight of the composition.

Alternative carrier media include hydrophobic materials, e.g. which meet the solubility criteria with respect to the active ingredient hereinbefore described. Further preferred compositions in accordance with the invention, e.g. for topical application, accordingly comprise

C^2 a) Ciclosporin in orthorhombic, preferably non-solvate orthorhombic, crystal form, e.g. Cy-A/X-III, e.g. as defined under anyone of A to A^7 above; and

f) A hydrophobic carrier, e.g. as set forth above.

The amount of component (a) present will suitably be as described above in relation to compositions as defined under C^1. Suitable components (f) include, for example, petroleum derivatives, including mineral oils, fats and jellys, as for example petrolatum (mineral fat or petroleum jelly) liquid petrolatum (white mineral oil or liquid paraffin), or any of the products known and commercially available under the Trade Mark Vaseline [c.f. Fiedler loc. cit. 2, 986], as well as non-ionic lanoline based derivatives such as available under the Trade Mark Amerchol, e.g. Amerchol CAB [Fiedler, 1, 119-120].

Further suitable components (f) include, for example natural or saturated vegetable oils and fats, e.g. fractionated coconut oils as known and commercially available under the Trade Mark Miglyol, e.g. Miglyol 812 (c.f. Fiedler, 2, 616) and peanut and saturated pea-nut oils, as well as higher fatty or branched chain alcohols and fatty esters, such as stearic alcohol, cetyl palmitate and 2-octyldodecanol which is known and commercially available under the Trade Mark Eutanol G (c.f. Fiedler, 1, 375).

Such compositions may also comprise one or more of any of components (d) and (e) hereinbefore described, as well as one or more anti-microbial agents, e.g. as hereinbefore described.

In particular such compositions may additionally comprise one or more components (d), suitably in an amount of up to at most 30%, more preferably at most 20%, suitably in an amount of from about 1 to about 15% by weight based on the total weight of the composition.

Hydrophobic based compositions in accordance with C^2 and comprising an emulsifier component (d), may also be prepared in the form of creams or emulsions by the further addition of water. The obtained creams or emulsions may be either of the oil-in-water or water-in-oil type. The amount of water present in such compositions may thus vary from e.g. 5 to 80% based on the total weight of the composition, suitably from 20 to 70%.

Amounts of components (e)/antimicrobial agent, when incorporated, will be of the same or similar order to those set forth in relation to compositions of the invention in accordance with C^1 above.

The amount of any topical form applied will, of course, vary depending on the concentration of the composition, the condition to be treated and the effect desired, as well , in the case of dermal application, the area to be covered. In the case of compositions for dermal application, e.g. in the treatment of psoriasis or atopic dermatosis, amounts applied will generally be sufficient to provide a Ciclosporin dosaging of the order of from about 0.1 to about 5mg/cm², e.g. ca. 0.5mg/cm², with administration e.g. 2x daily to the desired site. In the case of ophthalmic preparations, administration may suitably be performed employing preparations comprising about 0.1 to about 10%, e.g. 1.0

or 2.0% Ciclosporin by weight, applied in drop form to each eye 1 to 3x daily.

INJECTIBLE FORMS, e.g. for sub-cutaneous, intra-muscular or other parenteral injection, including, in particular, intra-articular injection, e.g. in the treatment of arthritic disease such as rheumatoid arthritis, or for intra-lesional injection, e.g. in the treatment of psoriasis.

Dispersions, suspensions, emulsions and like compositions suitable for injection can be prepared in accordance with any of the techniques known and generally employed in the art, for example by dispersing, suspending or otherwise distributing Ciclosporin in fine particulate orthorhombic crystal form in an appropriate liquid carrier medium with the addition of appropriate emulsifiers, sufactants, stabilizing or flocculating agents etc... Preferably the Ciclosporin component in such compositions will have an average particle size of <100µM, more preferably <50µM, most preferably <20µM. Suitably the average particle size will be of the order of from 0.1 or 0.5 up to the indicated 20, 50 or 100µM maxima.

Where injectible forms are intended e.g. for sub-cutaneous or intra-muscular injection, for example to achieve a depot affect, use of larger particle size will be possible. Where such forms are intended for intra-lesional application or, in particular, intra-articular injection, use of finer particule preparations will be indicated. For such uses a suitable average particle size is e.g. of the order of from about 0.1 or about 0.5 to about 20µM, e.g. ca. 5 to 15µM.
To achieve stability of particles in injectible forms, e.g. to avoid increase in size of larger crystalline particles at the expense of smaller particles, the particles will preferably be of as uniform a size as possible. Suitably variation between maximum and minimum particle size will not exceed about 50µM, more preferably about 20µM.

Although the desired particle size may be achieved by use of appropriate comminution procedures, e.g. micronisation, to minimize particle size variation, to avoid the presence of fragmented particles, to avoid modification of the crystal surface, e.g. to retain wettability characteristics, and to more easily meet required sterility requirements, it will generally be preferred to employ non-comminuted microcrystals, i.e. crystals grown to the desired size requirements as hereinbefore described.

Injectible compositions in accordance with the invention thus appropriately comprise:

C^3 a) Ciclosporin in fine particulate, orthorhombic, preferably non-solvate orthorhombic, crystal form, e.g. CY-A/X-III, e.g. as defined under any one of A to A^7, in particular A^6 and A^7, above, distributed or distributable within,

b) an injectible carrier medium.

Suitable carrier media include, in particular, pharmaceutical grade water.

In addition compositions as defined under C^3 will suitably, comprise

g) a sufactant as dispersant or emulsifying agent and/or a flocculating agent, to assist or maintain distribution of the particles throughout the carrier phase.

Suitable surfactant components (g) include polyoxyethylene--sorbitan fatty acid esters or polysorbates, e.g. as set forth under (d^3) above, e.g. Tween 80* or Polysorbate 80* (c.f. Fiedler, 2, p.p. 746). Suitable flocculating agents (g) include ethylene diamine tetra-acetate and salts thereof, for example Calcium EDTA and Sodium EDTA, as well as other equivalent chelating agents, and peptisating agents such as succinic or citric acid.

In order to maintain particle size distribution, a stabilizing agent is also suitably incorporated. Suitable stabilizing agents

*Trademark

include e.g. gelatins or modified gelatins such as the plasma expander known and commercially available under the Trade Mark Gelafundin and Haemaccel or cold-water soluble gelatins of highly purified collagen hydrolysates.

Compositions in accordance with C^3 above may also include one or more anti-microbial agents, e.g. as hereinbefore described, as well as peptisating agents such as succinic or citric acid.

The ratio of components (a):(b) in compositions as defined under C^3 is suitably of the order of 1:10 to 1:1,000, preferably of the order of from 1:50 to 1:200 e.g. about 1.100 p.p.w.

In order not to unduly disturb particle stability, surfactants present as component (g) will preferably be present in only minor concentrations, e.g. of the oder of from 0.1 to 2.0%, suitably ca. 1% by weight based on the weight of component (a). Where a flocculating agent is present the ratio of flocculating agent to component (a) is suitably of the order of from 1.3 to 1:8 p.p.w. e.g. ca. 1:5 p.p.w. When a stabilizing agent is present, the ratio of component (a):stabilizing agent is suitably of the order of from 1:5 to 1:30, more preferably 1:10 to 1:30, e.g. ca. 1:20 p.p.w. When a peptisating agent is present, the ratio of peptising agent to component (a) is suitably of the order of from 1:1 to 1:10, e.g. ca. 1:15 p.p.w.

The amount of Ciclosporin present in unit dosage forms for injection in accordance with the invention will of course vary depending on e.g. the condition to be treated, the site of injection and the effect desired, e.g. whether depot effect or relatively speedy release into the surrounding tissues is contemplated. Suitably individual unit dosage forms will comprise ca. 10 to 500 mg, especially from ca. 20 to 100mg Ciclosporin/dosage.

As will be appreciated, unit dosage forms in accordance with the invention also include more complex systems, e.g. double chambered syringes or syringe barrels in which the particulate Ciclosporin together with other appropriate components, e.g. stabilizer or anti-microbial agent, is retained in a first chamber and the carrier medium is retained in a second chamber, the components of the two chambers being brought into admixture, e.g. following actuation of the syringe plunger. Such double chamber syringe systems are well known in the art and unit dosage forms comprising them are to be understood as being within the purview of the present invention.

ORAL DOSAGE FORMS e.g. for the treatment of auto-immune and other diseases and conditions as hereinbefore set forth, e.g. for the prevention of transplant rejection.

Although, as previously indicated, oral dosage forms in accordance with the present invention are generally of lesser interest and hence less preferred, such forms are also within the purview of the invention.

Oral dosage forms in accordance with the invention may be prepared employing any appropriate carrier or carrier medium as known and practiced in the art. Liquid or semi-solid oral dosage forms may for example comprise Ciclosporin in orthorhombic crystal form, e.g. as CY-A/X-III, together with pharmaceutically acceptable diluents or carriers in which the crystal form is itself insoluble or substantially insoluble. Such carriers and diluents include for example trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols as hereinbefore described under (d^1) for example Labrafils as well as reaction products of natural or hydrogenated castor oil end ethylene oxide as hereinbefore described under (d^2), in particular liquid Cremophore products, for example Cremophore EL.

The Ciclosporin is preferably present in fine particulate form, e.g. having an average particle size of from 0.5 to 200µM, especially of the order of from e.g. 0.5. to 30µM, preferably less than 20µM, e.g. from 0.5 to 10µM.

For convenience of administration, compositions as aforesaid will suitably be filled into hard or soft-gelatin capsules.

Unit dosage forms in accordance with the invention for oral administration suitably comprise from about 25 to about 75, or up to 200, e.g. ca. 50 or 100mg Ciclosporin/unit dosage. Such forms are administered e.g. from 1 to 4x daily to achieve individual patient serum ciclosporin concentrations (e.g. as determined by RIA) of the same or equivalent order to those achieved employing conventional Ciclosporin therapy, e.g. employing the available Ciclosporin oral solution.

Ingredients referred to herein or defined as components of pharmaceutical compositions in accordance with the invention are to be understood as being suitable for pharmaceutical application as required, e.g. in the case of ingredients of compositions for oral administration, as being pharmaceutically acceptable or, in the case of ingredients of compositions for topical administration, as being topically, e.g. dermally or occulary, applicable, acceptable or tolerable.

Further galenic forms for administration by equivalent or alternative routes to those above described, will be apparent to the skilled worker.

The following examples are illustrative of the present invention in each of its various aspects.

EXAMPLE 1

PREPARATION OF Cy-A/X-III

a) 100 g of Ciclosporin in amorphous form are dissolved with stirring in 400g polyethylene glycol 300 at 50°C. CY-A/X-III development commences shortly after completion of dissolution. The solution is allowed to stand for 24-48 hrs. at ca. 35-40 °C to complete crystallisation and then diluted with 1000 ml water with vigorous stirring. The obtained precipitate is separated by filtration, washed with H_2O to remove remaining polyethylene glycol and dried to yield CY-A/X-III in substantially pure form: m.p. = 195 °C, particle size = ca. 100-200 µM.

CY-A/X-III forms may be prepared analogously to the above procedure but employing the following materials as solvent in place of polyethylene glycol 300.

	SOLVENT	M.P. FOR OBTAINED CY-A/X-III (°C)
b)	Polyethyleneglycol 300/ Cremophore RH 40 (1:1 by volume)	---
c)	Cremophore EL	190
d)	Solutol HS 15	188
e)	Gelucire 44/14 TM	180
f)	Myrj 52	184
g)	Tween 80	186
h)	Cremophor RH40	190

In each case the obtained average particle size is of the order of from about 50 to about 200 µM. Determined lattice structure is as hereinbefore defined. X-ray diffraction data are as hereinafter described with reference to Table III and Fig. IV.

EXAMPLE 2

PREPARATION OF CY-A/X-III

20g Ciclosporin as CY-A/X-I is dissolved in 60ml ethanol and condensed to 1/6th of the initial volume by distillation under reduced pressure at >60°C. 160ml polyethylene glycol (MW 300) + 20ml H_2O are then added slowly at 50-85°C. with stirring at 300 r.p.m.. An ultrasonic vibrator/mixer is installed operating at 20,000 c.p.c. Nucleation is initiated at 65-75°C. over 3 to 5 minutes. The obtained dispersion is then cooled linearly over 10-20 minutes to 40°C. with continued stirring at 700 r.p.m. and ultrasonic vibration. The obtained thick pasty mixture is filtered, rinsed with polyethyleneglycol (MW 300)/H_2O (3:1 p.p.vol), washed with warm water (30°C.) and dried at 50°C. under high vacuum, to yield CY-A/X-III in pure form : m.p. = 192°C. Particle size = 3-15μM. Determined lattice structure as hereinbefore defined. X-ray diffraction data as described hereinafter with reference to Table III and Fig. IV.

Repeat experiments indicate that crystal size is influence by nucleation temperature and rate of crystal growth rather than duration of processing. Thus by initiating nucleation at ca. 75°C. and continuing crystallisation at the same temperature, an average crystal particle size of ca. 50μM is obtained.

EXAMPLE 3

PREPARATION OF A GALENIC FORM FOR ORAL ADMINISTRATION

3.1 GELATIN ENCAPSULATED PREPARATIONS I

A suspension comprising 20 % by weight of Cy-A/X-III obtained in accordance with the procedures of Example 1 in Gelucire 44/14 is milled at elevated temperature employing a colloidal mill until the average Cy-A/X-III particle size is of the order of from 0.5 to 10 μM.

250 mg portions of the obtained milled suspension are filled into hard-gelatine capsules size 2, each comprising 50 mg Ciclosporin (as Cy-A/X-III) as active ingredient.

3.2 GELATIN ENCAPSULATED PREPARATION II

CY-A/X-III obtained in accordance with the procedures of Example 1 is milled in a colloidal mill until the average CY-A/X-III particle size is of the order of from 0.5 to 20μM. 50mg portions are then intimately admixed with 200g Cremophore EL and filled into hard gelatine capsules size 2, each comprising 50mg Ciclosporin (as CY-A/X-III) as active ingredient.

EXAMPLE 4

PREPARATION OF GALENIC FORMS FOR TOPICAL APPLICATION

4.1 GEL PREPARATION I

Cy-A/X-III obtained in accordance with the procedures of Example 1 is micronised employing an air-jet mill. Micronised product having a maximum particle size of 60-70μM and an average particle size of from 2-10μM is combined and mixed in conventional manner with the ingredients shown in the table below to provide an aqueous gel comprising 10 % by weight Ciclosporin (as Cy-A/X-III) and suitable for topical application, e.g. for the treatment of psoriasis.

INGREDIENT	% BY WEIGHT
a) CICLOSPORIN (micronised Cy-A/X-III)	10.0
b) Polyacrylic acid (Carbopol 934P)	0.5
c) NaOH-solution (5%)	3.0
d) Methylparaben	0.07
e) Propylparaben	0.03
f) H_2O (pharmaceutical grade)	to 100.0 %

4.2 GEL PREPARATION II

INGREDIENT	% BY WEIGHT Composition A	 Composition B
a) CICLOSPORIN (micronised Cy-A/X-III)	10.0	1.0
b) Polyethylenglycol 300	30.0	30.0
c) Labrafil M 2130 CS	1.0	1.0
d) Carbopol 934 P	1.0	1.0
e) Sodium hydroxide 5%	6.0	6.0
f) Methylparaben	0.07	0.07
g) Propylparaben	0.03	0.03
h) H_2O (p.g.)	51.9	60.9
	100.0 %	100.0 %

a) is prepared as for 4.1 above. c), f) and g) are dissolved in b) with warming and the obtained mix cooled to toom temperature. This solution is then dispersed in water h). d) is added and the whole homogenized to effect dispersion. a) is added and the mix again homogenized. e) is added to neutralise, with stirring, and the resulting gel filled into collapsible tubes for topical application, e.g. in the treatment of psoriasis.

4.3 OINTMENT PRAPARATION

INGREDIENT	% BY WEIGHT Composition A	 Composition B
a) CICLOSPORIN (micronised Cy-A/X-III)	1.0	10.0
b) Amerchol CAB	2.0	2.0
c) Liquid paraffin	42.0	37.5
d) White petrolatum	55.0	50.5
	100.0 %	100.0 %

a) is prepared as for 4.1 above. b), c) and d) are melted together and stirred and a) added at ca. 30°C, the particles being distributed employing an homogenizer. The obtained ointment is cooled and filled into collapsible tubes for topical application, e.g. in the treatment of psoriasis.

4.4 CREAM PREPARATION

INGREDIENT	% BY WEIGHT
a) CICLOSPORIN (micronised Cy-A/X-III)	1.0
b) Polysorbate 60	5.0
c) Cetylstearyl alcohol	10.0
d) Glycerol 85%	10.0
e) White petrolatum	24.0
f) Methylparaben	0.07
g) Propylparaben	0.03
h) H_2O (p.g.)	49.0
	100.0 %

a) is prepared as for 4.1 above, combined with components b) to h) analogously to 4.3 above and filled into collapsible tubes for topical application, e.g. in the treatment of psoriasis.

4.5 OINTMENT PREPARATION

A suspension comprising 20 % by weight of Cy-A/X-III (obtained in accordance with the procedures of example 1) in polyethyleneglycol 300 is wet-milled until the average Cy-A/X-III particle size is of the order of from 2 to 10 µM. 10g of the obtained milled product is mixed in conventional manner with 50g polyethyleneglycol 300 and 40g melted polyethyleneglycol 1500 to yield a flowable paste comprising 10 % by weight ciclosporin (as Cy-A/X-III) and suitable for topical application, e.g. for the treatment of psoriasis.

4.6 GEL PREPARATION

INGREDIENT	% BY WEIGHT
a) CICLOSPORIN (micronised CY-A/X-III)	1.0
b) Labrafil M 1944 CS	1.0
c) Polyethylene glycol 300	30.0
d) Benzyl alcohol	1.0
e) Hydroxypropylmethylcellulose (Methocel E4M)^{TM}	2.5
f) H_2O (p.g.)	64.5
	100.0 %

a) is prepared as for 4.1 above. b), c) and d) are mixed, and f) added and mixed. a) is then suspended in the resulting mixture by homogenisation. e) is then added slowly with stirring until gel formation is complete. The gel is then filled into collapsible tubes for topical application, e.g. in the treatment of psoriasis.

4.7 GEL PREPARATION

INGREDIENT	% BY WEIGHT
a) CICLOSPORIN (micronised CY-A/X-III)	5.0
b) Polyethyleneglycol 300	30.0
c) Glycerylmonostearate	5.0
d) Methylparaben	0.07
e) Propylparaben	0.03
f) Carbopol 934 P	1.0
g) Sodium hydroxide 5%	6.0
h) H_2O (p.g.)	52.9
	100.0 %

a) is prepared as for 4.1 above. c), d) and e) are dissolved in b) with warming. The warm mixture is dispersed in h) by homogenisation and cooled to room temperature. a) and f) are then added and the whole homogenised. g) is then added and gel formation completed. The obtained gel is filled into collapsible tubes for topical application, e.g. in the treatment of psoriasis.

4.8 CREAM PREPARATION (WATER IN OIL)

INGREDIENT	% BY WEIGHT
a) CICLOSPORIN (micronised CY-A/X-III)	2.0
b) Amerchol CAB	5.0
c) Miglyol 812	10.0
d) White petrolatum	53.0
e) H_2O (p.g.)	30.0
	100.0 %

a) is prepared as for 4.1 above and dispersed with b) in e) while warming and homogenising. c) and d) are molten together, mixed and the mixture added to the previously obtained dispersion with intensive homogenisation, and the whole cooled to provide a fatty white cream. This is filled into collabsible tubes for topical application, e.g. in the treatment of psoriasis.

4.9 GEL/CREAM PREPARATIONS

Examples 4.1 to 4.8 above are repeated but employing the crystalline product of example 2 directly as CICLOSPORIN component.

EXAMPLE 5

5.1 INJECTIBLE FORM, E.G. FOR PARENTERAL APPLICATION

A Cy-A/X-III suspension is prepared under sterile conditions, by conventional techniques and employing the following ingredients

INGREDIENT		WT (mg)
a) CICLOSPORIN (CY-A/X-III)		20.0
b) Polysorbate 80		4.0
c) Sodium carboxymethyl cellulose		5.0
d) NaCl		9.0
e) Benzyl alcohol		9.0
f) H_2O (injection grade)	to an end volume of	1.0 ml

The active ingredient release characteristics of the obtained formulation are dependent upon the average particle size of component a). Thus where activity over longer periods of time is required, Cy-A/X-III product of large average particle size (e.g. 100-200 µM as obtainable directly via the procedures of example 1) will be chosen. Where activity over relatively shorter periods of time is required, Cy-A/X-III product of relatively smaller average particle size (e.g. obtained by micronisation or milling of Example 1 product, e.g. to a particle size of from 0.5-10 µM) will be chosen. The obtained suspension is filled into injection ampoules for parenteral administration or for intra-lesional injection in the treatment of psoriasis, for example to provide a depot effect.

In an especially preferred embodiment the example is performed employing CY-A/X-III prepared in accordance with example 2 above, having a particle size of from 5-15µM, and prepared under sterile conditions.

5.2 INJECTIBLE FORMS, E.G. FOR INTRA-ARTICULAR INJECTION

Injectible forms suitable for intra-articular administration are prepared employing the following ingredients:

INGREDIENT		WT (mg)
Composition A		
a) CICLOSPORIN (CY-A/X-III)		10.0
b) Sodium carboxymethyl cellulose		10.0
c) Na EDTA		2.0
d) H_2O (injection grade)	to an end volume of	1.0 ml
Composition B		
a) CICLOSPORIN (CY-A/X-III)		10.0
b) Polysorbate 80		0.1
c) Citric acid		2.0
d) H_2O (injection grade)	to an end volume of	1.0 ml

Formulation is carried out in accordance with standard techniques under sterile conditions. Component (a) comprises non-comminuted micro-crystals, produced under sterile conditions in accordance with the procedures of example 2 and having a particle size of from 3-15μM. The obtained compositions are filled, again under sterile conditions, into ampoules for injection, e.g. intra-articular injection for the treatment of rheumatoid arthritis.

The advantageous properties of compositions in accordance with the invention may be demonstrated in animal test models as well as in clinic. Thus particular utility of compositions in accordance with the invention intended for dermal application, e.g. in the treatment of psoriasis or dermatosis, may be demonstrated in the following test model:

ALLERGIC CONTACT DERMATITIS IN THE GUINEA PIG (DTH-TEST)

Guinea pigs (Hartley, ♂, 400-500 g) are sensitized by application of 50 µl of 2 % dinitrofluorobenzene (DNFB) in acetone/olive oil (1:1) to the inner side of the right ear. 7 days later, the animals are re-treated with 20 µl, 0.5 % DNFB in acetone/olive oil (4:1) applied to marked areas on the shaven, left and right flank. This second challenge exposure induces an allergic inflammation, leading to reddening and cellular infiltration (thickening) of the skin. Test composition in an amount of from 200-250 mg is applied with a spatula to the DNFB treated area of the right flank. The left flank is similarly treated with placebo as control. Application of test composition/placebo is effected 5x at intervals of 20 mins, 8hrs., 24 hrs., 32 hrs., and 48 hrs., after the challenge. Skin thickness at the site of application is determined before each application, and again 8 hrs. after the last application, by raising the skin into a fold and measuring the thickness of this. Degree of reddening or inflammation is also estimated visually on a scale of from 0 to 4. Efficacy of test preparation in preventing inflammatory response is determined by comparison with results recorded for placebo treated flanks.

Results obtained in the above test model employing compositions in accordance with examples 4.1 and 4.5 above but comprising 0.1 % by weight Ciclosporin as CY-A/X-III, in comparison with placebo and with topically applied 0.1 % Ciclosporin in convention oral solution form are shown in Figs. I, II and III appendant to the present application. [A 0.1% CY-A/X-III concentration is employed in this test model in view of its extreme sensitivity. Test compositions are prepared entirely analogously to examples 4.1 and 4.5 but by reduction of the Ciclosporin component to 0.1g and compensation by addition of 9.9g water in the case of example 4.1 and polyethyleneglycol components in the case of example 4.5.)

In each figure, measured skin thickness is plotted against time. In Fig. I results employing 0.1% (by weight) Ciclosporin in conventional applied in the form of the conventional, commercial oral, drink solution form are compared with placebo. Slight but insignificant reduction in reaction as compared with placebo is evidenced for the oral solution. In Figs. II and

III, results employing 0.1% (by weight) Ciclosporin containing compositions in accordance with examples 4.1 and 4.5 respectively are compared with placebo. In both instances, substantial reduction in skin thickening as compared with placebo are achieved following first application and continuing through treatment as compared with placebo are achieved following first application and continuing through treatment until completion of the experiment.

Utility of compositions in accordance with the present invention may also be demonstrated in clinical trials e.g. performed as follows:

CLINICAL TRIAL: TREATMENT OF PSORIASIS BY TOPICAL (DERMAL) APPLICATION

The trial is performed in randomized, placebo controlled, double-blind design. Each patient receives active composition and placebo (vehicle alone) on two symmetrical lesions simultaneously. Allocation of active and placebo compositions is randomised to the left and right lesions.

Selected subjects are taken in groups of from 12 to 24 patients, aged 18-70 years including males and females who are postmenopausal, surgically sterile or using oral contraceptives with a negative pregnancy test.

Inclusion criteria include: a) written informed consent and b) clinically defined, stable, chronic plaque psoriasis. At least two moderate to severe bilateral symmetrical lesions, each having an area of 4 to 25cm^2 and a severity score >5 on a scale ranging from 0 to 9. This score is a composite of individual scores of 0 (least severe) to 3 (most severe) for each of three parameters: erythema, scaling and skin thickness. Lesions on both sides must be comparable within the same patient (i.e. not differing by more than 20% in severity score or area).

The following exclusion criteria are applied:

a) Any medical condition which, in the opinion of the investigator, would compromise the study.

b) Systemic psoriasis therapy. (PUVA, methotrexate, steroids, retinoids, ciclosporin) within the last 2 months.

c) Specific topical treatment - except indifferent substances (e.g. white vaselin) or formulations containing salicylic acid (not more than 10%) - on lesions selected for study within the last 2 weeks before entering the study. These emollients may however be used on lesions not selected for the study.

d) Patients whose psoriasis appears to be spontaneously improving, flaring without treatment, or rebounding from cessation of therapy.

e) Known hypersensitivity to any of the ingredients of the test medication.

f) Uncooperative patients who are unlikely to follow medical instructions exactly, patients not willing or not able to attend regular visits.

g) Treatment with an investigational drug within one month before study enrollment.

h) Severe concomitant disease, especially renal dysfunction with serum creatinine above 130µMol/l.

i) Hypertension (diastolic BP> 95mm Hg after 5 minutes in sitting position). Patients with drug controlled hypertension are included into the study.

j) Malignancy or history of malignancy, including skin cancer.

k) Acute bacterial, viral, or fungal associated skin lesions.

l) Pregnancy, lactation.

m) Patients with a history of alcoholism, drug abuse, psychosis, or emotional or intellectual problems.

n) Patients who need continuous concomitant therapy with other immunosuppressants, chemotherapeutic agents, compounds with a nephrotoxic potential (e.g. aminoglycosides) and drugs which are known to interact with the pharmacokinetics of Ciclosporin (ketoconazole, erythromycin, phenytoin, phenobarbitone, rifampicin, INH, carbamazepine, sodium valproate).

o) Patients with abnormal baseline laboratory values > 15% outside normal limits for the testing laboratory.

p) Patients with clinically significant findings in physical examination.

Trial compositions employed are in accordance with any one of examples 4.1 to 4.9 hereinbefore described, e.g.: the 1% composition B of example 4.2 or the 10% composition B of example 4.3.

Each patient receives a pair of 20g coded tubes bearing a two-panel label. The label is blue for the substance which has to be applied on the right side and red for the left side. Further, the side to be treated, left or right, the study code, the investigator name, the patient number, and the date of starting treatment, are written on each panel of the label. The tear-off panel of the label is affixed in the case report form.

Test medication is applied 2x daily, morning and evening, the amount applied depending on lesion size, to give a daily Ciclosporin dosaging of from 0.2 to 2.0mg Ciclosporin/cm^2, e.g. in one test series ca. 0.5mg Ciclosporin/cm^2. Placebo is applied in equivalent amount. Neither trial composition nor placebo is applied to a body surface >25cm^2 and no more than lg Ciclosporin is applied per week. At each clinic visit the medication/placebo tubes are weighed and the topically applied daily dose determined. Subjects may bathe shortly before application of medication. Disposable gloves are put on and changed to apply each trial composition and placebo to avoid cross contamination. At least three hours are allowed to elapse between administration and washing of the treated areas. The first application is supervised and a patient instruction sheet is provided. Duration of treatment is 4 weeks. If complete clearance of lesions occurs earlier, treatment is continued until week 4. Patients are investigated before trial commencement (week -1), at the beginning of the trial (week 0) and after 1, 2, 3 and 4 weeks.

Dermatological assessment (local psoriasis severity index or LPSI) is assessed by the same investigator, not involved in medication, using the following 0-3 numeric scales.

Erythema	Scaling	Skin Thickness
0 = None	0 = none	0 = none
1 = Minimal: faintly detectable erythema; very light pink	1 = Minimal: poorly defined scales	1 = Minimal: barely perceptible elevation
2 = Moderate dull red distinguishable	2 = Moderate: well-defined scales starting to pile up	2 = Moderate: elevation clearly perceptible
3 = Strong: deep/bright red	3= Severe: well defined scales; piled up to compact	3 = Severe: high elevation

The total LPSI range = value of erythema plus scaling plus thickness = 0 to 9 is evaluated. To enter into the study, at least 2 signs must be moderate to severe for both selected lesions (LPSI >5).

At entry and at each clinic visit, the area of the treated lesions is evaluated (Entry size: 4 to 25cm^2 for each plaque). Area refers to presence of one or more of the three criteria, erythema, scaling, thickening. Pigmentation within the lesion area is not considered in area estimation

The plaques are registered by photographs before (week -1) and after the treatment (week 4). Three pictures are taken: one showing both lesions together and one for each lesion.

Pruritus is evaluated from patient interview using the following scale:
0 = none
1 = minimal: occasionally has urge to scratch
2 = moderate: has urge to scratch frequently

3 = severe: has urge to scratch very frequently, may disturb sleep.

At end of the study, a global assessment of response to therapy is made in accordance to the following criteria:

- cleared = 100% resolution
- marked improvement = at least 66% reduction of LPSI, and/or at least 66% reduction of plaque area
- moderate improvement: between 65% and 33% reduction of LPSI, and/or between 65% and 33% reduction of plaque area
- poor: less than 32% reduction of LPSI and/or less than 32% reduction of plaque area
- worse: exacerbation of disease

Therapeutic success is defined as any lesion which has "cleared" or which exhibits "marked improvement".

Physician and patient also indicate their preference for left or right side medication in accordance with the following criteria:
. left side definitely better
. left side slightly better
. no difference detectable
. right side slightly better
. right side definitely better

To test efficacy at the end of treatment, subject LPSI scores and lesional areas are compared by means of the WILCOXON-Sign Rank test for paired treatments between Ciclosporin-treated sides and placebo treated sides with respect to change in score from baseline to after 4 weeks of treatment.

All further comparisons (at other time points and for the remaining parameters of efficacy), including the p-values attached to them, are taken as descriptive of progress in trial.

In the above trial, subjects exhibit marked improvement in psoriatic lesion, e.g. of LPSI scores for erythema, scaling and skin thickness, on sides to which test composition comprising Ciclosporin is applied as compared with side receiving placebo. Subjective improvement is also recorded, together with improvement in recorded values for pruritis on Ciclosporin treated as compared with placebo treated sides.

Positive results are also obtained in trials of parallel design for subjects exhibiting contact dermatitis as diagnosed via 3 or more of the following criteria:

- Pruritus
- Typical morphology and distribution:
  Flexural lichenification or linearity in adults
  Facial and extensor involvement in infants and children
- Chronic or chronically-relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis);

plus 3 or more minor features including:

Xerosis, ichthyosis/palmar hyperlinearity/keratosis pilaris, immediate (type I) skin test reactivity, elevated serum IgE, early age of onset(< 5 years), tendency toward cutaneous infections (esp. Staph. aureus and Herpes simplex)/ impaired cell-mediated immunity, tendency toward non-specific hand or foot dermatitis, nipple eczema, cheilitis, recurrent conjunctivitis, Dennie-Morgan infraorbital fold, keratoconus, anterior subcapsular cataracts, orbital darkening, facial pallor/facial erythema, pityriasis alba, anterior neck folds, itch when sweating, intolerance to wool and lipid solvents, perifollicular accentuation, food intolerance, course influenced by environmental/emotional factors and white dermographism/delayed blanch. The trial period is three weeks, with evaluation on a scale of 0 to 3 for the following parameters: pruritis, erythema, exudation, excoriation and lichenification.

Topical formulations as hereinbefore described in examples 4.1 to 4.9, containing 1-10% Ciclosporin, for example the 5.0% composition in accordance with example 4.7 are also found to be effective in the treatment of allergic contact dermatitis as well as of alopecia.

In accordance with the foregoing the present invention also provides:

D. A method of administering Ciclosporin to, or effecting Ciclosporin therapy in, a subject receiving or requiring such therapy, which method comprises administering to said subject an effective amount of Ciclosporin in orthorhombic crystal form, in particular non-solvate orthorhombic crystal form, e.g. as CY-A/X-III, e.g. as defined under any one of A to A^7 above.

In a more specific embodiment there is provided:

D^1 A method of effecting immunosuppressive or anti-inflammatory therapy in a subject in need thereof, which method comprises administering to said subject an effective amount of Ciclosporin in orthorhombic crystal form, in particular non-solvate orthorhombic crystal form, e.g. as CY-A/X-III, e.g. as defined under any one of A to A^7 above.

Purposes for which the above methods are applicable include treatment of any disease or condition as hereinbefore described in relation to use of Ciclosporin, e.g. prevention of transplant rejection, treatment of auto-immune or rheumatic disease, treatment of any other disease or condition involving undesirably high response of the immune system, treatment of parasitic infection, treatment of chemotherapeutic resistance, e.g. reversal of tumor resistance to anti-neoplastic chemotherapy, as well as the treatment of alopecia. The above methods are in particular applicable to the treatment of diseases or conditions of the skin or eye, e.g. psoriasis, atopic or contact dermatitis, corneal transplant, conjunctivitis and uveitis, by topical administration, as well as to the treatment of rheumatoid arthritis or other disease or condition of the joint, by intra-articular administration.

In the alternative the present invention provides:

E. Ciclosporin in non-solvate orthorhombic crystal form, e.g. as

CY-A/X-III, e.g. as defined under any one of A to A^7 above, for use as a pharmaceutical, e.g. for use in the treatment of any disease or condition as hereinabove set forth in relation to D or D^1 above, for example, for use as an immunosuppressive or anti-inflammatory agent; as well as

F. Ciclosporin in orthorhombic crystal form, e.g. as CY-A/X-III, e.g. as defined under any one of A to A^7 above, for use in the preparation of a pharmaceutical compostiion for use as defined under E above.

To assist identification of Cyclosporin in orthorhombic crystal form, in particular CY-A/X-III, X-ray powder diffraction data for CY-A/X-III and for the two forms CY-A/X-I and CY-A/X-II also referred to herein, are provided in the following Tables I to III. Fig. IV attached provides a representation of the X-ray powder diffraction diagram from which the data in Tables I to III were obtained. The diffraction diagram was obtained employing a Guinier-DeWolff II camera, using CuKα-radiation, λ = 1.542 Å

TABLE I

X-RAY DIAGRAM FOR CY-A/X-I

Line No.	d (Å)	Intensity
1.	13.0	VS
2.	11.4	VS
3.	10.3	VS
4.	9.7	VS
5.	9.4	VS
6.	8.25	VS
7.	7.1	S
8.	6.1	M
9.	5.85	S
10.	5.6	S
11.	5.25	VS
12.	4.81	S
13.	4.58	S
14.	4.25	M
15.	4.0	M
16.	3.67	M
17.	3.45	M

TABLE II

X-RAY DIAGRAM FOR CY-A/X-II

Line No.	d (Å)	Intensity
1.	17.9	S
2.	11.4	VS
3.	11.0	S
4.	10.6	M
5.	10.2	S
6.	8.9	M
7.	8.7	M
8.	8.1	M
9.	7.2	VS
10.	6.3	M
11.	5.95	M
12.	5.7	M
13.	5.35	M
14.	5.1	S
15.	4.85	S
16.	4.8	M
17.	4.55	M
18.	4.4	M

TABLE III

X-RAY DIAGRAM FOR CY-A/X-III

Line No.	d (Å)	Intensity
1.	12.0	M
2.	10.4	VS
3.	9.6	S
4.	8.7	S
5.	7.9	M
6.	7.7	S
7.	6.7	M
8.	6.0	M
9.	5.83	S
10.	5.3	M
11.	5.2	M
12.	4.92	S
13.	4.88	S
14.	4.58	M
15.	4.48	M
16.	4.0	M
17.	3.59	M
18.	3.38	M

VS = very strong
S = strong
M = medium

Claims:

1. Ciclosporin in non-solvate orthorhombic crystal form.
2. Ciclosporin in orthorhombic crystal form having a crystal lattice ≡ a= 12.7 Å, b=15.7 Å, c=36.3 Å, and a volume per asymmetric unit=1804 Å^3.
3. Ciclosporin in orthorhombic crystal form exhibiting the following X-ray diffraction characteristics:

Line Number	Distance (d) (Å)	Intensity
1.	12.0	M
2.	10.4	VS
3.	9.6	S
4.	8.7	S
5.	7.9	M
6.	7.7	S
7.	6.7	M
8.	6.0	M
9.	5.83	S
10.	5.3	M
11.	5.2	M
12.	4.92	S
13.	4.88	S
14.	4.58	M
15.	4.48	M
16.	4.0	M
17.	3.59	M
18.	3.38	M

wherein VS = very strong S = strong and M = medium

VS = very strong

S = strong

M = medium

4. Ciclosporin in orthorhombic crystal form according to claim 1, 2 or 3 free or substantially free of Ciclosporin in any other form.

5. Ciclosporin in orthorhombic crystal form according to claim 1, 2 or 3 in pure or substantially pure form.

6. Ciclosporin in orthorhombic crystal form according to claim 1 in fine particulate form.

7. Ciclosporin in orthorhombic crystal form according to claim 6 wherein the component particles have an average particle size of <200 μM.

8. Ciclosporin in orthorhombic crystal form according to claim 7 wherein the component particles have an average particle size of from 0.5 to 200 μM.

9. Ciclosporin in orthorhombic crystal form according to claim 7 wherein the component particles have an average particle size of <25 μM.

10. Ciclosporin in orthorhombic crystal form according to claim 1, 2 or 3, a major proportion of which consists of non-comminuted crystal material.

11. Ciclosporin in orthorhombic crystal form according to claim 6, 7 or 8, a major proportion of which consists of non-comminuted micro-crystalline material.

12. Ciclosporin in orthorhombic crystal form according to claim 1, 2 or 3 in sterile or substantially sterile condition.

13. Process for the production of Ciclosporin orthorhombic crystal form as defined in claim 1, 2 or 3 which process comprises crystallising Ciclosporin from a Ciclosporin non-solvate orthorhombic crystal bearing solvent medium and recovering Ciclosporin non-solvate orthorhombic crystals thus obtained.

14. A pharmaceutical composition comprising
a) Ciclosporin in orthorhombic crystal form as claimed in claim 1 as active ingredient, together with b) a pharmaceutically acceptable diluent or carrier therefor.

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15. A pharmaceutical composition comprising
a) Ciclosporin in orthorhombic crystal form as claimed in claim 2 as active ingredient, together with b) a pharmaceutically acceptable diluent or carrier therefor.

16. A pharmaceutical composition comprising
a) Ciclosporin in orthorhombic crystal form as claimed in claim 3 as active ingredient, together with b) a pharmaceutically acceptable diluent or carrier therefor.

17. A pharmaceutical composition according to claim 14, 15 or 16 wherein a major proportion of the Ciclosporin present in said composition is in orthorhombic crystal form.

18. A pharmaceutical composition according to claim 14, 15 or 16 having at least one compartment or phase comprising Ciclosporin in orthorhombic crystal form, said crystal form being distributed or distributable throughout said compartment or phase.

19. A pharmaceutical composition according to claim 14, 15 or 16 in flowable form permitting topical application or application by injection or infusion.

20. A pharmaceutical composition according to claim 14, 15 or 16 comprising from 0.05 to 30% by weight of Ciclosporin based on the total weight of the composition.

21. Use of Ciclosporin in orthorhombic crystal form as defined in claim 1, 2 or 3 for effecting Ciclosporin therapy.

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FIG. 1

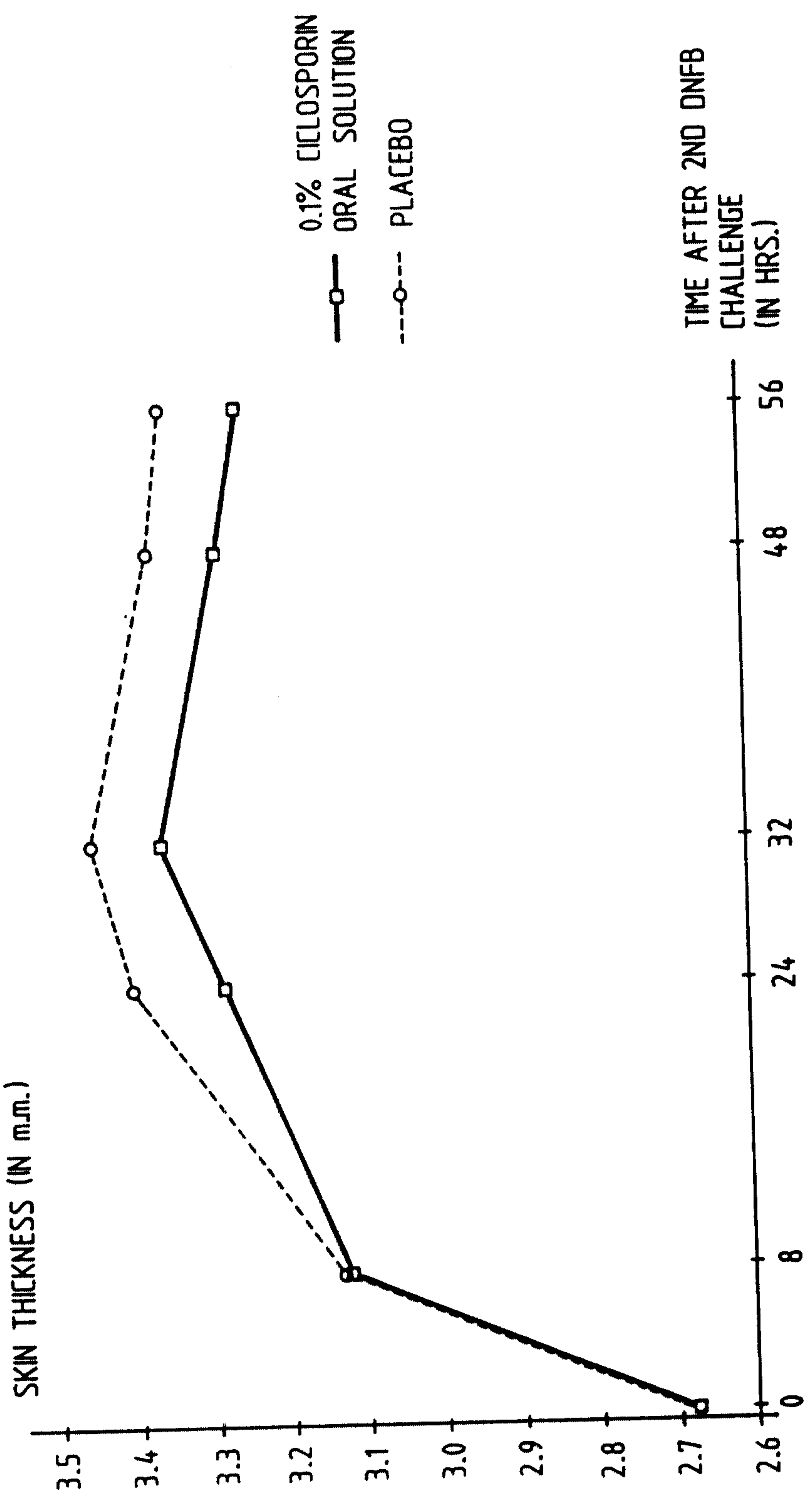

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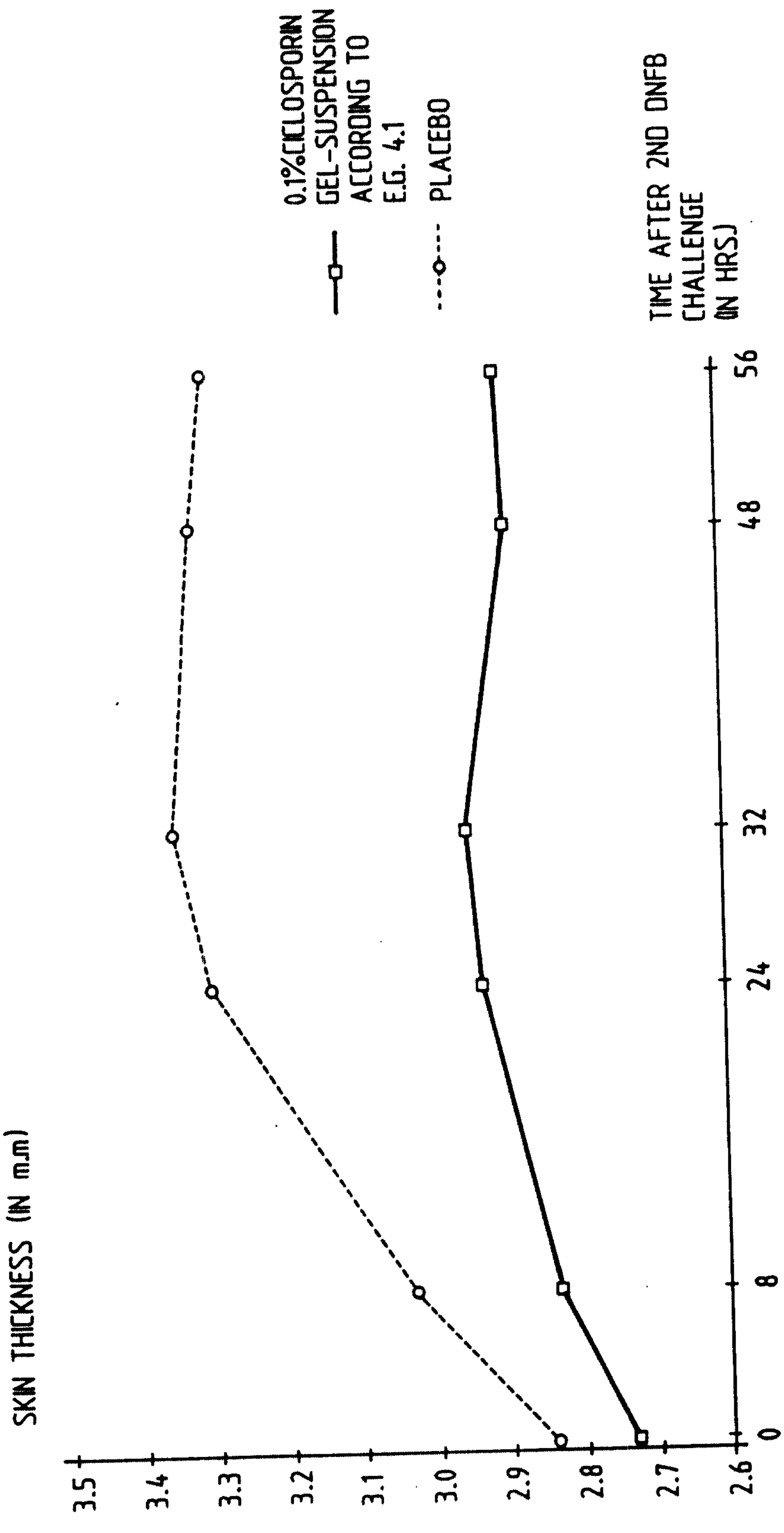
FIG. 2



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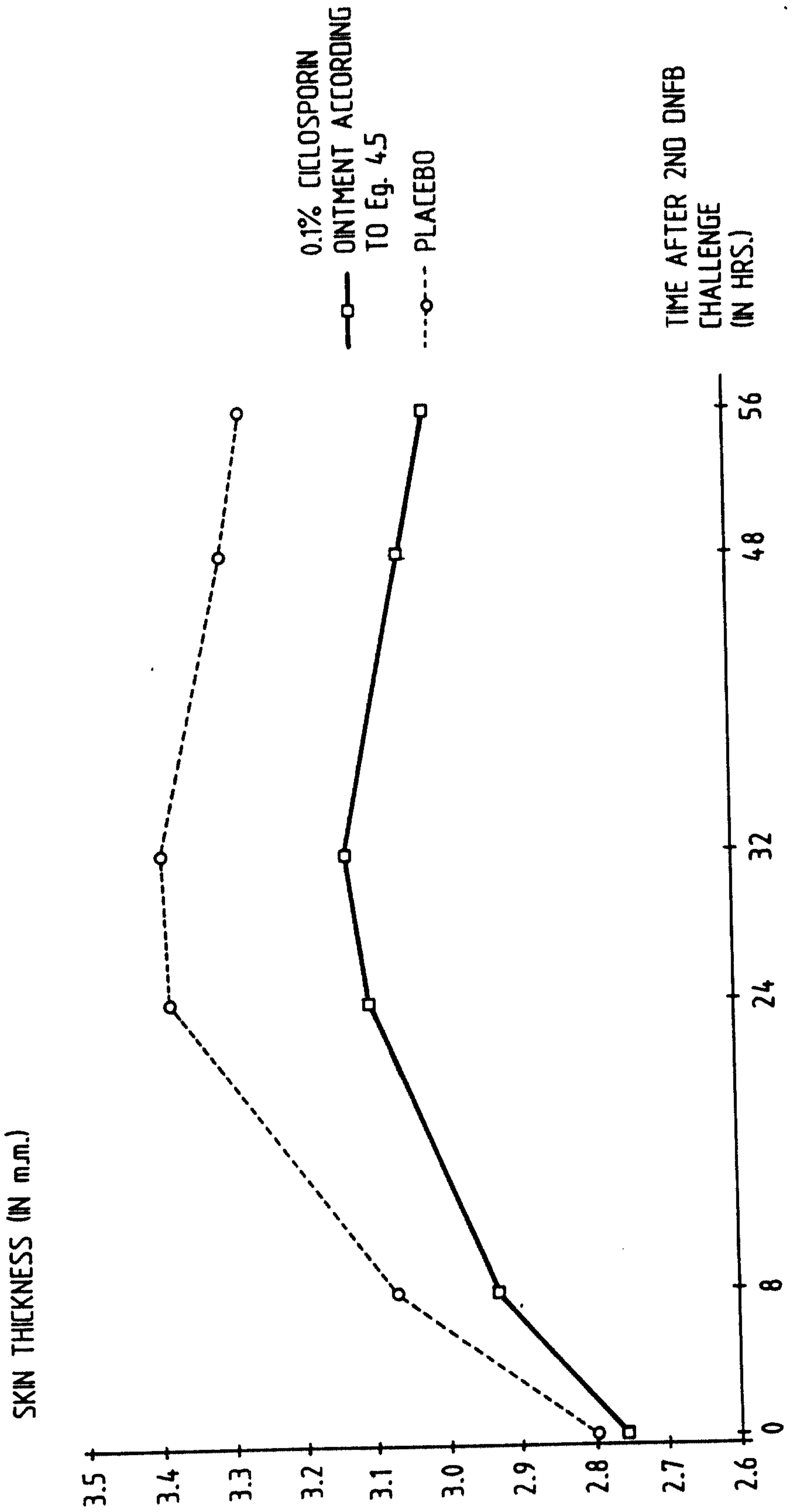
Gale, Baker

FIG. 3



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Application number / numéro de demande: 1341396

Figures: 4

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