

FORM 1
REGULATION 9

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1973

APPLICATION FOR A PATENT

We NIPPON SHINYAKU COMPANY LIMITED

of 14, Kisshoin Nishinosho Monguchicho, Minami-ku, Kyoto 601, Japan

hereby apply for the grant of a Patent for an invention entitled:

DRUG CARRIERS

which is described in the accompanying complete specification. This Application is a Convention Application and is based on the Application numbered: Sho-62-272770 for a Patent or similar protection made in Japan on 28 October 1987.

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DATED this 28th day of October, 1988.

NIPPON SHINYAKU COMPANY LIMITED
By their Patent Attorneys



GRIFFITH HACK & CO.

TO: THE COMMISSIONER OF PATENTS
COMMONWEALTH OF AUSTRALIA

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Section 29(1)
Regulation 3.1(2)

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Patents Act 1990

NOTICE OF ENTITLEMENT

We NIPPON SHINYAKU COMPANY LIMITED

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being the applicant and nominated person in respect of Application No. 24472/88,
state the following:

The person nominated for the grant of the patent:

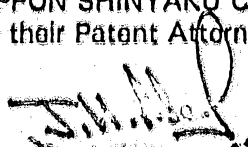
1. Has, for the following reasons, gained entitlement from the actual inventors:

The applicant/nominated person is the assignee of the invention from the inventors.
2. Is the applicant of the basic application listed on the patent request form.
3. The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

The actual inventors are Makoto SUGIYAMA, Atsuhiko OKITA and Junzo SEKI.

DATED this 6th day of February 1992

NIPPON SHINYAKU COMPANY LIMITED
By their Patent Attorney



GRIFFITH HACK & CO

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(86) Prior Art Documents
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(57) Claim

1. A parenteral drug carrier system in the form of a conventional synthetic surfactant free fatty emulsion of particles having a mean particle diameter of 10 to 70nm and each comprising a core and a surface layer in which the substance constituting the core is a simple lipid, a derived lipid, a drug itself or a mixture thereof and the core forms 30 to 85% of the carrier, and the substance constituting the surface layer is different from that comprising the core and is a complex lipid, a derived lipid, a drug itself or a mixture thereof and the surface layer forms 15 to 70% of the carrier.

2. A drug carrier system as claimed in claim 1 in which the simple lipid is a neutral lipid and/or a cholesterol ester.

3. A drug carrier system as claimed in claim 1 or claim 2 in which the complex lipid is a phospholipid and/or a glycolipid.

4. A drug carrier system as claimed in any one of the claims 1 to 3 in which the derived lipid is a fatty acid and/or a higher alcohol and/or a hydrocarbon.

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PATENTS ACT 1952

Form 10

COMPLETE SPECIFICATION

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TO BE COMPLETED BY APPLICANT

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Complete Specification for the invention entitled:
DRUG CARRIERS

The following statement is a full description of this invention,
including the best method of performing it known to us:-

Drug Carrier

The present invention relates to improved drug carriers for delivery of a drug contained therein from the blood stream or the site of application into lesional tissue.

Various investigations have been made into drug carriers for improving the delivery of a drug from the blood stream or the site of application into lesional tissue. For example, there has been proposed the use of a liposome prepared from a phospholipid ("Drug Carriers in Biology and Medicine"), G. Gregoriadis Ed., Academic Press, 1979). However this approach gives drawbacks in that (1) there are problems in stability of the liposome during storage, and (2) in the case of administration into blood, almost all the liposomes are taken up into tissue with a developed reticulo-endothelial system (RES), such as the liver or spleen, so that they are only difficultly distributed to other cells or tissues. The reason for this is believed to be that the liposome has a structure wherein the inner and outer aqueous phases are separated from each other by a phospholipid bilayer and the liposome is thus unstable to various forces. Further, during storage, an increase in particle diameter due to aggregation may occur.

It is known to dissolve various drugs in a fat emulsion having a particle diameter of 0.2 μ m, composed of soybean oil and yolk lecithin heretofore used clinically as a fluid nutrient supplement.

Good results are thereby obtained [SAISHIN IGAKU (Latest Medicine), 40, 1806-1813 (1980)]. This carrier is characterized in that it has no internal aqueous phase and it is storage stable as compared to liposomes. However, the carrier is readily taken up into reticulo-endothelial system tissue. Such rapid metabolism is desirable for a high calorie fluid supplement but gives poor distribution of a drug into other tissues.

It is also known (see JP-A-63/500456) to use, as a drug carrier, a fat emulsion in which 90% of the particles are 100 + 30 nm. However, this system also gives preferential accumulation in reticulo-endothelial tissue.

In order to overcome the above problems, there has been proposed a technique of applying serum lipoproteins composed of a simple lipid (including sterols), a complex lipid and an apolipoprotein as a drug carrier (JP-A-60-163824). However, this carrier serves to introduce a drug into cells by physiological and specific recognition of the lipoprotein. Thus, the carrier is rapidly transferred into tissue via its receptors so that disappearance from the blood is relatively rapid. For this reason, transfer into tissue having poor receptor activity is not always adequate. Furthermore, apolipoprotein is an essential constituent so that the technique involves high production costs.

It has been proposed to reduce the size of a fat emulsion of 200nm particle size (JP-A-62/29511). However, in this proposed system only a small amount of yolk lecithin is employed so that the resulting microparticles re-coagulate with lapse of time giving rise to storage stability problems.

5 In general, a drug administered moves and is distributed in the body due to the inherent properties of the drug. Then the drug reaches the site of action to exhibit its pharmacological effects. Whilst it would be desirable for the drug to be concentrated only at the site necessary for it to exhibit its pharmacological effects, the drug is, however, generally distributed over the entire body and is present at
10 sites that do not require the drug. This is sometimes a cause of side effects. Thus, it becomes desirable to improve disposition of a drug in the body.

The present invention therefore relates to a parenteral drug carrier system in the form of a conventional synthetic surfactant free fatty emulsion of particles having a mean particle diameter of 10 to 70nm and each comprising a core and a
15 surface layer in which the substance constituting the core is a simple lipid, a derived lipid, a drug itself or a mixture thereof and the core forms 30 to 85% of the carrier, and the substance constituting the surface layer is different from that comprising the core and is a complex lipid, a derived lipid, a drug itself or a mixture thereof and the surface layer forms 15 to 70% of the carrier.

20 Basically, the present invention is concerned with a drug carrier which is a fat emulsion containing the drug and having a mean particle size of less than 200nm.

Suitably, the drug carrier is a fat emulsion constituted by two components, namely a lipophilic substance forming the core and a lipophilic substance covering
25 the core surface, the carrier is not in a form, such as in a liposome, wherein there is an internal aqueous phase present; the drug may be present in the same carrier in dispersal or dissolved form, or may form of mixed micelles with or chemically bind with the lipid. The carrier particle diameter is suitably not less than 5nm and is less than 200nm.

The drug carrier of the invention takes the form of a stable fatty emulsion. Its particle diameter is preferably from not less than 5 nm to less than 200 nm, in order to avoid uptake into the reticulo-endothelial system. By dividing the drug carrier very finely, blood concentration can be maintained at a higher level than for a fat emulsion having a diameter of about 0.2 μ m. Particularly preferred is a particle diameter of 100 nm or less so that the carrier can easily exude from a blood vessel through a region in which vasopermeability is accentuated.

It is known that various regions called pore systems or other slits between cells are present in blood vessels and vasopermeability is accentuated in various focal regions including sites of inflammation, tumours and atherosclerosis (it is considered that a small pore system having a diameter up to 9 nm and a large pore system having a diameter of 25 to 70 nm are present and it is known that the vasopermeability is further increased in various focal regions including neoplastic vessels). In such a region, the drug carrier of the present invention is selectively exuded from blood vessels in large amounts and transferred into the focal tissue. At the same time, the drug contained in the drug carrier is also delivered into the lesion. Thus, the drug can be selected and delivered to the focal region so that a drug concentration at the focal region increases and its effect can be enhanced. Further

by using the drug carrier of the invention, a drug can be administered together with a lipid so that sustained release of the drug and lymphotropic properties of the drug can be improved. The drug carrier of the invention also subjects to phagocytosis properties to phagocyte.

An important feature of the invention is the use of a very finely divided lipid as a drug carrier. As a result not only is selection delivery obtained but also uptake by the reticulo-endothelial system is reduced.

The maintenance of drug concentration in blood can also be achieved.

The drug carrier of the invention is characterized by using larger amounts of the surface layer (e.g. a compound lipid) in proportion to the core (e.g. simple lipid), as compared to the conventional high calorie fluid supplements comprising soybean oil and yolk lecithin. Thus, the surface layer preferably formed is 70% of the total of core and surface layer.

Since the surface area of the core in the drug carrier is increased by very fine division it is necessary to increase the amount of surface layer to cover the core and stabilize the emulsion. If less than 15% of complex lipid is used particles having a diameter of 0.2 μ m or more will be present. If more than 70% of complex lipid is used, liposome particles will be present.

The drug carrier of the invention thus suitably takes the form of a fat emulsion composed of a core and a surface layer, wherein (1) the substance constituting the core is a simple lipid, a derived lipid, a drug itself or a mixture thereof and the core forms 30 to 85% of the carrier and (2) the substance constituting the surface layer is a complex lipid, a derived lipid, a drug itself or a mixture thereof and the surface layer forms 15 to 70% of the carrier.

The drug may be dispersed or dissolved in the drug carrier, may form a mixed micelle with one or more constituents of the carrier or may be chemically based with one constituent(s) of the carrier so that the drug is not readily released from the drug carrier.

The lipid used in the drug carrier of the invention, may be a simple lipid, derived lipid or a complex lipid derived from natural animal, vegetable or mineral sources or a mixture thereof. Examples include simple lipids, derived lipids or complex lipids derived from yolk, soybean, cotton, linseed, corn, sesame, peanut, safflower, bovine tissue, hog tissue, sheep tissue, etc. or a wholly synthetic simple lipid, derived lipid or complex lipid.

Examples of simple lipids include neutral lipids such as refined soybean oil, cotton seed oil, linseed oil, sesame oil, corn oil, peanut oil, safflower oil, triolein, trilinolein, tripalmitin, tristearin, trimyristin and triarachidonin. Simple lipids also

include cholesterol derivatives such as cholesteryl oleate, cholesteryl linoleate, cholesteryl myristate, cholesteryl palmitate and cholesteryl arachidonate. This is because neutral lipids are relatively easily decomposed by various lipases present in, for example, blood vessel endothelium, whereas cholesterol derivatives are only decomposed with difficulty by these enzymes.

Examples of derived lipids include cholesterol, fatty acids such as stearic acid, palmitic acid, oleic acid, linoleic acid, linolenic acid and eicosapentaenoic acid, and derivatives thereof and squalene. They may also be used as emulsification aids.

Furthermore, oily compounds such as azone, etc. may be exemplified.

Examples of complex lipids include phospholipids derived from yolk, soybean, bovine tissue and hog tissue, synthetic phospholipids and glycolipids purely synthetically produced. Specific examples of phospholipids include phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol, etc., which are exemplified by yolk phosphatidyl choline, soybean phosphatidyl choline, dipalmitoyl phosphatidyl choline, dimyristoyl phosphatidyl choline, distearoyl phosphatidyl choline, dioleoyl phosphatidyl choline, dipalmitoyl phosphatidyl inositol, etc. Products obtained by hydrogenation of these phospholipids may also be used. Among them, a representative preferred example is yolk phosphatidyl choline. As glycolipids, mention may be made of cerebroside, etc. Steryl glucosides, e.g., B-sitosterol-B-D-glucoside, can also be

used. Furthermore, changed lipids such as stearylamine, dicetyl phosphate and phosphatidic acid, may also be used to impart a surface charge to the drug carrier.

The drug may be pharmaceutically acceptable any drug. Even a drug that is insoluble or sparingly soluble can also be used. In the present invention, the drug readily forms a complex with the carrier.

In the case of a water-soluble drug, the drug carrier of the invention can be formed by using the drug chemically bound to a constituent (for example, lipid, etc.) of the carrier.

Even though a drug is unstable in the body and thus is so far incapable of administration, such a drug can also be readily administered by using the carrier of the invention. The drug contained in the carrier is present in oil droplets of lipids so that it is shielded from the surrounding environment and enzymatic or non-enzymatic decomposition can be inhibited.

Examples of drugs include antiinflammatory agents, analgesics, anti-allergic agents, antibiotics, chemotherapeutic agents, anti-cancer agents, antiviral agents, anti-atherosclerosis agents, anti-lipemic agents, antiulcer agents, immunoregulators, vaccines, radical scavengers, bronchodilators, hypnotics, tranquilizers, topical anesthetics and diagnostics. Specific examples of such drugs are anticancer agents such as Ancitabine, fluorouracil, mitomycin C, mitomycin C farnesylamide, mitomycin C

farnesylacetic amide, Carmofur, Futraful palmitate, 5-fluorouracil myristate, Adriamycin, Daunomycin, Aclarubicin, Maclarubicin, Vinblastine, Vincristine, Cytarabine fatty acid esters, Mitotane and Estramustine; antiviral agents such as Dichloroflavan; steroidal agents (for example, Dexamethasone palmitate, hydrocortisone palmitate, Prednisolone palmitate, Dexamethasone Stearate, Methylprednisolone, Paramethasone, Fluocinolone acetonide, Vectamethasone propionate, Hydrocortisone fatty acid

esters, Aldosterone, Spironolactone, etc.) and non-steroidal agents (for example, Ibuprofen, Flufenamic acid, Ketoprofen, Phenacetin, Antipyrine, Aminopyrine, Phenylbutazone indoleacetate, Biphenylpropionic acid derivatives, Indometacin, Indometacin ethoxycarbonylmethyl ester, Indometacin stearyl ester, Sodium aurothiomalate cetyl ester, 'Diclofenac, acetylsalicylic acid and derivatives thereof, etc.).

Antiallergic agents such as Tranylast, Ketotifen, Azelastine, etc. may also be used. As antibiotics and chemotherapeutic agents, mention may be made of, for example, tetracyclines, Erythromycin, Midecamycin, Amphotericin, Nalidixic acid, Griseofulvin, Minocyclin, etc. As examples of prostaglandines, there may be used PGE1, PGA1, PGA1 alkyl esters, PGE1 alkyl esters, PGE1 derivatives, PGI2 derivatives, PGD2 derivatives, etc. Antihistaminic agents such as Diphenhydramine, Orphenadrine, Chlorphenoxamine, Chlorpheniramine, Promethazine, Mecridine, Cyproheptadine, Loxatidine acetate, etc. are mentioned. Furthermore, as topical anaesthesia, mention may be made of Lidocaine, Benzocaine, Dantrolene, Cocaine, Tetracaine, Piperocaine, Mepyracaine, and derivatives thereof, etc. There are also mentioned hepatic disorder improving agents (for example, Marotirate, Glycyrrhetic acid, ethyl acetyl-glycyrretinate, methyl glycyrretinate, etc.), antiulcer agents (for example, Farnesol, Geraniol, Gefarnate, Teprenone, Plaunotol, Safarceen, etc.). There are also agents acting on

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central nerves (for example, Phenobarbital, , Methaqualon, Heroin, Diazepam, Medazepam, Frazepam, Clotiazepam, Etizolam, Mecridine, Bucridine, Adiphenine, Methamphetamine, Imipramine, Chlorimipramine, Amitriptyline, Mianserin, Trimethadione, Phensuximide, Tetrabenzamide, Benzquinamide, Camphor, Dimorphoramine, Strychnine, Chlorpromazine, Promethazine, Prochlorperazine, Mequitazine, Triflupromazine, Levomepromazine, Difenidol, etc. and derivatives thereof). Also cerebrovasodilators (for example, Cinnarizine, etc.) may be mentioned. As bronchodilators, mention may be made of Vestphyllin and other theophylline derivatives, methylephedrine, etc. Anticholinergic agents (for example, Benztropine, Physostigmine, Atropine, Scopolamine, etc.), parasympathetic blockers (for example, Oxyphenycyclimine, Pirenzamine, Etomidrine, etc.), calcium blockers (for example, Diltiazem, Nifedipine, Verapamil, etc.), α -blockers (for example, Dibenzamine, Phenoxybenzamine, etc.), antitussive agents (for example, Noscapine, Dextromethorphan, Pentoxyverine, Benproperine, etc.), agents for treating prostatic hypertrophy (for example, Gastron, Oxendolone, etc.), agents for treating glaucoma (for example, Pilocarpine, etc.), agents acting on smooth muscle (for example, Sparteine, Papaverine, etc.), agents for treating hyperlipemia (for example, Chlorfibrate, Cimfibrate, Probucol, etc.) and the like. In addition, mention may be made of, for example, amino acids, vitamins, Dilazep, Ubidecarenone, Flavoxate, Cyclosporin, vaccines for influenza,

etc., Dibenzthione, Diphenylpyraline, Phenovalinium, Metadione, Tofiaopam, Limonen, etc.).

Antioxidants (for example, tocopherol, flavone derivatives, gallic acid derivatives, coffee acid derivatives, Goshipol, Sesamol, oxyfatty acid, camphene, Cineol, Rosmanol, Eugenols, Filozurucine, catechins, lignan homologues, p-coumaric acid, sterols, terpenes or bromophenol) can also form the drug carrier of the present invention as one of the constituents.

Further, gualazulene, essential oil type crude drugs (for example, apricot kernel oil, fennel oil, thyme oil, turpentine oil, eucalyptus oil, palm oil, poppy seed oil, saubaki oil, peppermint oil, clove oil, mint oil, sage oil and other components for spicy crude drugs, etc.) and the like can also form the drug carrier of the invention as one of the constituent factors of the carrier.

As diagnostics, mention may be made of, for example, a compound labelled with radiolabels, radioactive drugs or iodated poppy oil fatty acid esters as X-ray contrast materials, etc.

The carrier of the invention is particularly suitable for the administration of drugs for the treatment of inflammation, tumour, blood vessel or immune or lymphoid systems.

The drug concentration in the carrier of the invention is suitably such that the content does not exceed 85% in the drug carrier, according to the biological activity of the drug. Further the concentration of the drug carrier of the invention in medical preparations obtained using the carrier can be varied as desired.

The drug carrier and medical preparations using it, may be prepared by methods hitherto used for preparing emulsions. For example, they can be prepared by sufficiently finely dividing all the constituents including the drug by means of a homogenizer of the Manton-Gaurin type, a microfluidizer or an ultrasonic wave homogenizer. They can be also prepared by solubilizing the constituents using a surface active agent (for example, bile acid) or a water-micelle solvent (for example, ethanol, polyethylene glycol), and then removing the surface activity agent or water-micelle solvent, by dialysis or gel filtration. Fatty acids or derivatives thereof may also be added as emulsification aids. Furthermore, the drug carrier and its medical preparations may be obtained by adding a drug to a previously prepared fat emulsion free from particles having a diameter of 200 nm or more.

The shape and particle diameter of the drug carrier of the present invention can easily be confirmed by electron microscopy, by means of particle diameter analyzer of the light scattering type, or by filtration through a membrane filter. As optional components for medical preparations using the drug carrier of the invention, mention may be made of additives and auxiliary substances used for ordinary injections, etc. Examples include antioxidants, preservatives, stabilizers, isotonic agents, and buffers. Required and optimum amounts of these additives, or auxiliary substances can be varied depending upon their purposes.

The carrier can be sterilized (for example by filtration or with steam under high pressure in an autoclave, if necessary, and sealed in an ampoule together with nitrogen gas. Also if necessary, the carrier may be freeze dried. The freeze dried drug carrier can be restored by adding an appropriate solution thereto.

The drug carrier is generally administered intravenously to humans and animals but if necessary, can also be administered intraarterially, intramuscularly, subcutaneously and the like.

Furthermore, the drug carrier of the present invention can also be used as an eye drop, a nose drop, an oral agent, a suppository or the like. In this case, additives such as pharmaceutically accepted bases, excipients and the like can be mentioned as optional components.

The carrier of the invention makes it possible to markedly enhance drug availability. The effects of the carrier of the invention can be summarized as follows: (1) delivery of a drug into the focal lesion is improved; (2) uptake by the reticulo-endothelial system is inhibited; (3) blood concentration of the drug can be maintained; (4) storage stability can be obtained; and (5) production costs are reduced.

The major constituents of the carrier of the invention are therapeutically acceptable lipids conventionally used for therapy in the clinical field so that they can be used with safety.

In order that the invention may be well understood, the following Examples are given by way of illustration.

Example 1

To 27 mg of triolein were added 38 mg of yolk lecithin and 10mg of gualazulen (antiinflammatory agent) and, 10 ml of physiological saline was added to the mixture. Using a probe type ultrasonic wave homogenizer (Branson Sonifier Model 185),

the mixture was subjected to a ultrasonic wave treatment for 60 minutes under ice cooling. The formed drug carrier containing guaiazulene was blue and clear. A mean particle diameter of the drug carrier was 26.4 nm when measured by a light scattering particle diameter measurement device. Further in observation by an electron microscope, the drug carrier was recognized to be uniform, spherical ultra finely divided particles. Any lipid bilayer membrane as in liposome was not noted. It was also noted that the drug carrier passed by 100% through a filtering membrane of 0.2 μm and did not contain particles of 0.2 μm or more.

Example 2

Yolk lecithin, 2.5 mg and 10 mg of guaiazulene were added and, 10 ml of physiological saline was added to the mixture. Using a probe type ultrasonic wave homogenizer (Branson Sonifier Model 185), the mixture was subjected to a ultrasonic wave treatment for 60 minutes under ice cooling. The formed drug carrier containing guaiazulene had a mean particle diameter of 48.4 nm according to an apparatus for measuring optical scattering particles. It was also noted that the drug carrier passed by 100% through a filtering membrane of 0.2 μm and did not contain particles of 0.2 μm or more.

Example 3

To 100 mg of triolein were added 100 mg of yolk lecithin and 4 mg of a compound (Dexamethasone palmitate) obtained by chemically binding a fatty acid with Dexamethasone

(antiinflammatory agent) and, 10 ml of 0.24 M glycerin aqueous solution was added to the mixture. Using a probe type ultrasonic wave homogenizer (Branson Sonifier Model 185), the mixture was subjected to a ultrasonic wave treatment for 60 minutes under ice cooling. The formed drug carrier containing Dexamethasone palmitate was slightly bluish white and clear. A mean particle diameter of the drug carrier was 29.9 nm when measured by a light scattering particle diameter measurement device.

It was also noted that the drug carrier passed by 100% through a filtering membrane of 0.2 μm and did not contain particles of 0.2 μm or more.

Example 4

To 80 mg of triolein were added 20 mg of cholesteryl linoleate, 100 mg of yolk lecithin and 4 mg of Dexamethasone palmitate. Then, 10 ml of 0.24 M glycerin aqueous solution was added to the mixture. Using a probe type ultrasonic wave homogenizer (Branson Sonifier Model 185), the mixture was subjected to a ultrasonic wave treatment for 60 minutes under ice cooling. The formed drug carrier containing Dexamethasone palmitate was slightly bluish white and clear. A mean particle diameter of the drug carrier was 30.6 nm when measured by a light scattering particle diameter measurement device. It was also noted that the drug carrier passed by 100% through a filtering membrane of 0.2 μm and did not contain particles of 0.2 μm or more.

Example 5

To 100 mg of cholesteryl linolate were added 100 mg of yolk lecithin and 4 mg of Dexamethasone palmitate. Then, 10 ml of 0.24 M glycerin aqueous solution was added to the mixture. Using a probe type ultrasonic wave homogenizer (Branson Sonifier Model 185), the mixture was subjected to a ultrasonic wave treatment for 60 minutes under ice cooling. The formed drug carrier containing Dexamethasone palmitate was slightly bluish white and clear. A mean particle diameter of the drug carrier was 22.7 nm when measured by a light scattering particle diameter measurement device. It was also noted that the drug carrier passed by 100% through a filtering membrane of 0.2 μm and did not contain particles of 0.2 μm or more.

Example 6

To 100 mg of triolein were added 100 mg of yolk lecithin and 10 mg of Diphenhydramine (antihistaminic agent). Then, 10 ml of 0.24 M glycerin aqueous solution was added to the mixture. Using a probe type ultrasonic wave homogenizer (Branson Sonifier Model 185), the mixture was subjected to a ultrasonic wave treatment for 60 minutes under ice cooling. The formed drug carrier containing Diphenhydramine was slightly bluish white and clear. A mean particle diameter of the drug carrier was 31.6 nm when measured by a light scattering particle diameter measurement device. It was also noted that the drug carrier passed by 100% through a filtering membrane of 0.2 μm and did not contain particles of 0.2 μm or more.

Example 7

To 100 mg of triolein was added 100 mg of yolk lecithin. Then, 10 ml of 0.24 M glycerin aqueous solution was added to the mixture. Using a probe type ultrasonic wave homogenizer (Branson Sonifier Model 185), the mixture was subjected to a ultrasonic wave treatment for 60 minutes under ice cooling. The formed drug carrier was slightly bluish white and clear. A mean particle diameter of the drug carrier was 47.2 nm when measured by a light scattering particle diameter measurement device. It was also noted that the drug carrier passed by 100% through a filtering membrane of 0.2 μ m and did not contain particles of 0.2 μ m or more.

A compound (Vinblastine palmitate), 500 μ g, obtained by chemically binding a fatty acid with Vinblastine (anticancer agent) was added to the drug carrier obtained above. The mixture was gently mixed and stirred for 6 hours to take the drug up into the drug carrier. Thus, the drug carrier containing the drug was obtained.

A compound (5-Fluorouracil palmitate), 500 μ g, obtained by chemically binding a fatty acid with 5-Fluorouracil (anticancer agent) was added to the drug carrier obtained above. The mixture was gently mixed and stirred for 6 hours to take the drug up into the drug carrier. Thus, the drug carrier containing the drug was obtained.

A compound (Cytarabine levulinate), 500 μ g, obtained by

chemically binding a fatty acid with Cytarabine (anticancer agent) was added to the drug carrier obtained above. The mixture was gently mixed and stirred for 6 hours to take the drug up into the drug carrier. Thus, the drug carrier containing the drug was obtained.

Example 8

To 80 mg of triolein were added 20 mg of cholesteryl linoleate and 100 mg of yolk lecithin. Then, 10 ml of 0.24 M glycerin aqueous solution was added to the mixture. Using a probe type ultrasonic wave homogenizer (Branson Sonifier Model 185), the mixture was subjected to a ultrasonic wave treatment for 60 minutes under ice cooling. The formed drug carrier was slightly bluish white and clear. A mean particle diameter of the drug carrier was 19.1 nm when measured by a light scattering particle diameter measurement device. The analytical results are shown in Fig. 1. It was also noted that the drug carrier passed by 100% through a filtering membrane of 0.2 μm and did not contain particles of 0.2 μm or more.

Example 9

To 20 mg of refined soybean oil was added 20 mg of yolk lecithin. Then, 10 ml of 0.24 M glycerin aqueous solution was added to the mixture. Using a probe type ultrasonic wave homogenizer (Branson Sonifier Model 185), the mixture was subjected to a ultrasonic wave treatment for 60 minutes under ice cooling. The formed drug carrier was slightly bluish white and

clear. A mean particle diameter of the drug carrier was 16.1 nm when measured by a light scattering particle diameter measurement device. It was also noted that the drug carrier passed by 100% through a filtering membrane of 0.2 μ m and did not contain particles of 0.2 μ m or more.

Furthermore, a drug carrier was prepared in a manner similar to above, except for using 40 mg of refined soybean oil. The formed drug carrier was slightly bluish white and clear. A mean particle diameter of the drug carrier was 37.7 nm when measured by a light scattering particle diameter measurement device. It was also noted that the drug carrier passed by 100% through a filtering membrane of 0.2 μ m and did not contain particles of 0.2 μ m or more.

Example 10

To 10 g of soybean oil was added 10 g of yolk lecithin. Then, 1 liter of 0.24 M glycerine aqueous solution was added to the mixture. Using a microfluidizer, the mixture was emulsified. It was noted that the formed drug carrier passed by 100% through a filtering membrane of 0.2 μ m and did not contain particles of 0.2 μ m or more.

[Test on stability of the drug carrier of the present invention]

Test Example 1-1

The sample obtained in Example 1 was sealed in a brown ampoule of 1 ml volume together with nitrogen gas. A forced deterioration test was performed at 60°C for 4 weeks in a

conventional manner. The residual rate of guiazulene was 98.3% more and it was confirmed that the drug carrier of the present invention had effects in stability of the drug.

Test Example 1-2

The samples obtained in Examples 1, 3 and 4 described above were sealed, respectively in a brown ampoule of 1 ml volume together with nitrogen gas. After a sterilizing treatment of the ampoules with steam under high pressure in an autoclave, a particle diameter of each sample was measured by a light scattering particle diameter measurement device. There was no significant difference between prior to and after the treatment. Neither aggregation nor increase in the particle diameter was noted. Further they were stored at 4 °C for 6 months but no change such as aggregation, etc. was noted.

Test Example 1-3

The sample obtained in Example 3 described above was freeze dried in a conventional manner. Thereafter, distilled water for injection was added to the sample followed by stirring to restore. Then a particle diameter of the sample was measured by a light scattering particle diameter measurement device. A mean particle diameter was 28.3 nm. There was neither significant aggregation nor increase in the particle diameter was noted but the sample was uniformly dispersed.

[Test on utility of the present invention]

Test Example 2-1

The drug carrier of the present invention containing ^3H -labeled Dexamethasone palmitate prepared in a manner similar to Example 3 was used as a test sample. As a comparative sample, a fat emulsion having a diameter of $0.2\ \mu\text{m}$ as the prior art was used. This comparative sample was obtained by adding 10 ml of 0.24 M glycerin aqueous solution to 4 mg of ^3H -labeled Dexamethasone palmitate, 100 mg of refined soybean oil and 12 mg of yolk lecithin.

The test sample and the comparative sample were intravenously administered to rats. Then, a change in blood concentration was examined.

Change in the total radioactivity in plasma when the test sample and the comparative sample were intravenously administered to the tail vein of SD strain male rats (weighing about 210 g) in a dose of 0.05 mg/kg calculated as Dexamethasone is shown in Fig. 2, by calculating into Dexamethasone. The comparative sample rapidly disappeared from plasma but disappearance of the test sample was gentle. Half life periods in the distribution phases were 10.5 minutes and 5.5 minutes, respectively.

Test Example 2-2

Delivery of the drug into an inflammatory region induced by carrageenin edema was compared between the test sample and the comparative sample, using the drug carrier of the present invention ^3H -labeled Dexamethasone palmitate prepared in a manner similar to Example 4 as a test sample and the same comparative

sample as used in Test Example 2-1.

Table 1 Delivery of Drug into Carrageenin Inflammatory Region

	<u>Test Sample</u>	<u>Comparative Sample</u>
Paw with inflammation (ng)	475 $\pm$ 175	154 $\pm$ 17
(ng/g)	204 $\pm$ 53	64 $\pm$ 8
Control paw (ng)	164 $\pm$ 19	89 $\pm$ 24
(ng/g)	94 $\pm$ 8	52 $\pm$ 14
Edema region	(ng/g) 538 $\pm$ 142	94 $\pm$ 42
Plasma	(ng/g) 448 $\pm$ 38	122 $\pm$ 12

Indication is (mean $\pm$ standard deviation)

Carrageenin edema was induced by subcutaneously administering 0.1 ml of 0.5% λ -carrageenin to SD strain male rats (weighing about 195 g) at one paw heel. Two hours after the administration of carrageenin, the test sample and the comparative sample were intravenously administered in the tail vein in a dose of 0.5 mg/kg when calculated as Dexamethasone. Sixty minutes after the intravenous administration, blood was collected from the aorta in the abdomen to obtain plasma. At the same time, the paw with inflammation and the opposite paw (control paw) were cut off from the ankle joint. Each radioactivity was measured after treating with a sample oxidizer.

In Table 1, with respect to the test sample, large amounts

of the drug were transferred into the inflammatory region (edema region) and strong accumulation onto the inflammatory region was noted, as compared to the comparative sample. A drug concentration of 5.7 times that of the comparative sample was noted in the edema region induced by inflammation.

Test Example 2-3

Table 2 indicates the results of comparison in delivery of a drug into the hydrothorax and the major organs in rats with pleurisy model, using the same test sample and comparative sample as used in Test Example 2-2 described above.

2% λ -Carrageenin, 0.1 ml, was administered to SD strain male rats (weighing about 300 g) at the thoracic cavity. Two and half hours after the administration of carrageenin, the test sample and the comparative sample were intravenously administered in the tail vein in a dose of 1.25 mg/kg when calculated as Dexamethasone. Thirty minutes after the intravenous administration, blood was collected from the aorta in the abdomen and fluid in the thoracic cavity was washed out with physiological saline to make 10 ml. Its radioactivity was determined. At the same time, the major organs were ectomized. Each radioactivity was measured after treating with a sample oxidizer.

Table 2 Transfer into Inflammatory Region and Major Tissues

		<u>Test Sample</u>	<u>Comparative Sample</u>
Fluid in the thoracic cavity	(μg)	2.65	0.68
Diaphragm	($\mu\text{g}/\text{g}$)	1.06	0.68
Spleen	($\mu\text{g}/\text{g}$)	3.05	27.34
Liver	($\mu\text{g}/\text{g}$)	7.71	17.84
Heart	($\mu\text{g}/\text{g}$)	1.53	1.53
Lung	($\mu\text{g}/\text{g}$)	2.36	1.93
Kidney	($\mu\text{g}/\text{g}$)	2.66	1.37
Plasma	($\mu\text{g}/\text{ml}$)	10.07	2.37

Indication is a mean value when converted into Dexamethasone.

In Table 2, with respect to the test sample, large amounts of the drug were delivered into the inflammatory region (hydrothoracic region) and strong accumulation onto the inflammatory region was noted, as compared to the comparative sample. A drug concentration of 3.9 times that of the comparative sample was noted in the fluid in the thoracic cavity. In distribution into the major organs, the test sample showed extremely low transfer in transfer into organs having developed reticulo- endothelial system such as liver and spleen.

Test Example 2-4

The same test sample and comparative sample as used in Test Example 2-2 described above were intravenously administered to BALB/C male mice (weighing about 25 g). Thirty minutes after the administration, a concentration of the unchanged drug and a concentration of Dexamethasone as its metabolite were determined in plasma and liver. The dose was made 5 mg/kg when calculated as Dexamethasone.

Table 3 shows each concentration of the unchanged drug (Dexamethasone palmitate, its concentration was converted into Dexamethasone) and its metabolite (Dexamethasone) separately determined quantitatively.

In the case of the test sample, a concentration in plasma was high and distribution in the liver was low. Further the test sample was mostly present in plasma as the unchanged drug. In the case of using the drug carrier of the present invention, maintenance of blood concentration of the drug and a preventing effect in uptake into the reticulo-endothelial system are obviously noted.

Table 3

	Test Sample ($\mu\text{g/ml}$, g)	Comparative Sample ($\mu\text{g/ml}$, g)
Unchanged drug in plasma	36.3 ± 2.2	7.7 ± 1.6
Dexamethasone in plasma	4.6 ± 0.5	5.2 ± 0.9
Unchanged drug in Liver	not detectable	not detectable
Dexamethasone in Liver	24.0 ± 1.2	41.0 ± 1.3
Liver/Plasma ratio in concentration (total amount)	0.6 ± 0.0	3.0 ± 0.5

Indication is (mean $\pm$ standard deviation)

Test Example 5

With respect to the same test sample and comparative sample as used in Test Example 2-2 and a physiological saline solution of Dexamethasone phosphate, their pharmacological effects were examined using carrageenin edema inhibition as the index.

λ -Carrageenin (0.5%, 1 ml) was subcutaneously administered to SD strain male rats (weighing about 160 g) at one paw heel. Thirty minutes after, the test sample, the comparative sample and Dexamethasone phosphate were intravenously administered in the tail vein. For the control group, physiological saline was administered. A volume of the paw was measured prior to the administration of carrageenin and 5 hours after the administration in a conventional manner to determine an edema inhibition ratio.

Fig. 3 shows its dose-response curve (indicated as

Dexamethasone calculated). Fig. 4 shows a 50% edema inhibition dose (ED_{50}).

It is apparent that the test sample had an antiinflammatory activity by about twice that of the other two samples, even in inflammation of this kind which was not improved with the comparative sample as the prior art. That is, the effect of the drug carrier of the present invention was confirmed as an effect of enhancing the drug effect. It is thus clear that this is because the drug is efficiently delivered to the focal lesion by using the drug carrier of the present invention.

Table 4 50% Edema Inhibition Dose

	<u>ED_{50} (mg/kg)</u>
Test Sample	0.012
Comparative Sample	0.031
Dexamethasone phosphate	0.023
(Indication is made by conversion into Dexamethasone)	

Test Example 2-6

With respect to the same test sample and comparative sample as used in Test Example 2-2 and a physiological saline solution of Dexamethasone phosphate, their pharmacological effects were examined by the inhibition of carrageenin granuloma as the index. Further, weights of thymus and adrenals were examined.

λ -Carrageenin (2.0%, 4.0 ml) was subcutaneously administered

to SD strain male rats (weighing about 160 g) at the back. From on Day 5, each sample was intravenously administered to the tail vein once daily for 3 days 3 times in total. A dose of the drug administered was made 0.05 mg/kg/once. For the control group, physiological saline was administered. Eight days after, granuloma, thymus and adrenal were ectomized and their weights were measured.

It is noted from Fig. 5 that the test sample showed obviously strong granuloma formation inhibition activity as compared to the comparative sample and dexamethasone phosphate and also showed less atrophy in the thymus and the adrenals. That is, it is shown that the test sample had a strong pharmacological effect but less side effects.

Table 5 Weights of granuloma, thymus and adrenal

	<u>granuloma</u>	<u>Thymus</u>	<u>Adrenal</u>
Control	20.5 $\pm$ 5.4 g	416.0 $\pm$ 63.3 mg	55.2 $\pm$ 9.6 mg
Test Sample	10.9 $\pm$ 1.4 g	205.0 $\pm$ 57.2 mg	44.5 $\pm$ 7.2 mg
Comparative Sample	15.5 $\pm$ 2.6 g	149.8 $\pm$ 31.3 mg	39.6 $\pm$ 2.7 mg

Indication is (mean $\pm$ standard deviation)

Test Example 2-7

In order to confirm deliverability to the tumor region, a test was performed.

P388 leukemia cells, 10^6 cells, were subcutaneously transplanted to CDF1 male mice (weighing about 25 g) at the right front limb. Six days after, the right front limb was cut out and provided for the experiment 5 days after. By this treatment, metastatic cancer model into the right upper arm and the right axilla lymph nodes was obtained. As the test sample, the drug carrier of the present invention prepared in Example 8 using ^3H -labeled cholesteryl linoleate was used. As the comparative sample, a fat emulsion having a diameter of $0.2\ \mu\text{m}$, composed of refined soybean oil and yolk lecithin hitherto known in which ^3H -labeled cholesteryl linoleate had been incorporated was used. The test sample and the comparative sample were intravenously administered into the tail vein and 60 minutes after, the right upper arm and the right axilla lymph nodes in which tumor metastasis was noted were ectomized. Further as a non-metastatic lymph node, the left upper arm and the left axilla lymph nodes were simultaneously ectomized. Each radioactivity was measured.

As shown in Table 6, the drug carrier of the present invention was transferred to the tumor region in a concentration as high as twice or more. In the comparative sample, such a selective delivery in a high concentration was not noted.

Table 6 Delivery to Metastatic Lymph Node Tumor

	<u>Test Sample</u>	<u>Comparative Sample</u>
Metastatic lymph nodes	2.60 $\pm$ 0.87	0.91 $\pm$ 0.27
Non-metastatic lymph nodes	1.04 $\pm$ 0.27	0.86 $\pm$ 0.39

Indication is (% of dose/g, mean $\pm$ standard deviation)

Test Example 2-8

For purposes of confirming stability of the drug carrier of the present invention in the body in which cholesteryl linoleate was the core, the drug carrier of the present invention obtained in Example 3 was used as a test sample and as a comparative sample, the drug carrier of the present invention obtained in Example 4 was used. These samples were intravenously administered to rats, respectively. Change in blood concentration was determined. Samples prepared using ^3H -labeled Dexamethasone palmitate were used as the respective samples.

Change in total radioactivity in plasma when the test sample and the comparative sample were intravenously administered to SD male rats (weighing about 250 g) in tail vein in a dose of 0.05 mg/kg when calculated as Dexamethasone is shown in Fig. 4, by converting into Dexamethasone. The test sample disappeared from plasma more gently than the comparative sample. Half lives for the disappearance in the distribution phase were 21.6 minutes and 11.5 minutes, respectively.

Test Example 2-9

The test samples obtained in Examples 3, 4 and 5 and the comparative sample used in Test Example 2-1 were mixed with rat plasma, respectively to examine the stability. A concentration of the sample in plasma was made 23 µg/ml when calculated as Dexamethasone. As shown in Table 7, the amount of the unchanged drug (Dexamethasone palmitate) remained after incubation at 37°C for 90 minutes, namely, stability in plasma, was obviously superior in the drug carrier of the present invention to the comparative sample.

In addition, it was also confirmed that the use of cholesteryl linoleate the core of the drug carrier of the present invention increased the stability depending upon its content.

Table 7 Stability in Plasma

	<u>Remaining amount of Unchanged Drug</u>
Test Sample obtained in Example 3	39.8%
Test Sample obtained in Example 4	47.5%
Test Sample obtained in Example 5	68.1%
Comparative Sample of Test Example 2-1	20.1%

Test Example 2-10

After applying an eye drop of test preparation to the eye of ddY mice (weighing about 30 g) under anesthesia with

pentobarbital, a drug concentration in the eyeball was measured and deliverability of the drug into the eyeball was examined.

Test preparations are four below.

Test sample - (1) drug carrier of the present invention containing antiinflammatory guaiazulene obtained in Example 1

Test sample - (2) drug carrier of the present invention containing antiinflammatory guaiazulene obtained in Example 2

Comparative sample - (1) fat emulsion having a diameter of 0.2 μ m composed of soybean oil and yolk lecithin as the prior art in which guaiazulene had been incorporated

Comparative sample - (2) fat emulsion having a diameter of 0.2 μ m composed of soybean oil and yolk lecithin as the prior art in which sodium guaiazulene-3-sulfonate as a water soluble derivative of guaiazulene had been mixed and dissolved.

A dose was made 5 μ g/eye when calculated as guaiazulene. After applying to the eye, the eyeball was ectomized in a definite time. After immediately washing with physiological saline, the eyeball was homogenized and the drug was determined by high performance liquid

chromatography.

Change in drug concentration in the eyeball is shown in Fig. 5. The test samples all showed better deliverability to the eyeball than the comparative samples. It is evident that delivery of the drug into the eyeball was improved in the case of using the drug carriers of the present invention.

Test Example 2-11

Using the drug carrier containing guaiazulene obtained in Example 1 as a test sample and water soluble derivative of guaiazulene, sodium guaiazulene-3-sulfonate as a comparative sample, these samples were applied to the eye of Japanese white rabbits (weighing about 3 kg) to examine delivery of the drug to the aqueous humor. Thirty minutes after the eyedropping, the aqueous humor was collected and a drug concentration was measured. The results are shown in Table 8. Only in the case of using the drug carrier of the present invention, delivery of the drug to the aqueous humor was noted.

Table 8 Delivery of Drug to Aqueous Humor
after Application to the Eye

Test Sample	3.47 ± 3.31
Comparative Sample	not detectable
Indication is (mean $\pm$ standard deviation)	

Test Example 2-12

Using the drug carrier of the present invention containing antihistaminic Diphenhydramine obtained in Example 6 as a test sample and a Diphenhydramine hydrochloride solution in physiological saline as a comparative sample, a preventive action against accentuation of vasopermeability¹ induced by intracutaneous administration of histamine was examined.

The test sample or the comparative sample were intravenously administered to SD strain male rats (weighing about 300 g). After a definite time period, 10 mg of Evans Blue was intravenously administered and at the same time, histamine hydrochloride (1 μ g/50 μ l) was intracutaneously injected to the abdominal skin. Further 30 minutes after, The skin was peeled apart to quantitatively determine Evans Blue exudated into the skin. After the skin was solubilized with 3 ml of conc. hydrochloric acid, 3 ml of 10% benzarconium chloride was added to the solution, Evans Blue was extracted with 5 ml of chloroform. An amount of Evans Blue exudated into the skin ^{was determined} by absorbance at 620 nm in the chloroform layer.

Fig. 6 shows time-dependent change of the inhibition of the vasopermeability induced by intracutaneously injecting histamine 15, 30 and 120 minutes after administration of both samples, doses of which were made 2 mg/kg when calculated as Diphenhydramine. The test sample showed the maximum effect already 15 minutes after the administration. The effect was

continued up to 2 hours. On the other hand, in the comparative sample, its inhibition rate was lower than the test sample. The comparative sample showed the maximum effect 30 minutes after the administration and the effect was then decreased. The test sample showed the inhibition of the vasopermeability by 3 times or more than the comparative sample 2 hours after the administration. By the results, it is shown that the test sample not only enhances the drug effects but also has an effect of duration in the drug action.

Fig. 7 shows a dose-response curve showing the inhibition of vasopermeability obtained 30 minutes after administration of the samples. It is evident that the test sample are excellent in the inhibition of the vasopermeability as compared to the comparative sample.

4. Brief Description of the Drawings

Fig. 1 shows results of a particle diameter of the drug carrier of the present invention prepared in Example 8 measured with a light scattering particle diameter measurement device, wherein the vertical axis represents the number of particles and the abscissa represents a particle diameter with a logarithmic scale.

Fig. 2 shows change of the total radioactivity in plasma when the test sample and the comparative sample examined in Test Example 2-1 were intravenously administered to rats, wherein the vertical axis represents a concentration of the drug calculated

as Dexamethasone (ng/ml) and the abscissa represents a time passage (hour) after administration; a curve connected with • and a curve connected with o represent the test sample and the comparative sample, respectively.

Fig. 3 is a dose-response curve of antiinflammatory activity obtained using a carrageenin edema inhibition rate as the index, when the test sample and the comparative sample examined in Test Example 2-2 were intravenously administered to rats, wherein the vertical axis represents a inhibitory rate of carrageenin edema by % and the abscissa represents a dose of the drug calculated as Dexamethasone with a logarithmic scale; a curve connected with •, a curve connected with Δ and a curve connected with o represent the test sample, Dexamethasone phosphate and the comparative sample, respectively.

Fig. 4 represents change of the total radioactivity in plasma when the test sample and the comparative sample examined in Test Example 2-8 were intravenously administered to rats, wherein the vertical axis represents a concentration (ng/ml) of Dexamethasone calculated from the radioactivity and the abscissa represents passage of time (hour) after administration; a curve connected with Δ and a curve connected with • represent the test sample and the comparative sample, respectively.

Fig. 5 represents amount of the drug delivered to the eyeball after applying the two test samples and the two comparative samples examined in Test Example 2-10, wherein the

vertical axis represents a concentration (ng/ml, calculated as guaiazulene) of the drug in the eyeball and the abscissa represents passage of time (hour) after application to the eye; a curve connected with ▲, a curve connected with △, a curve connected with ■ and a curve connected with ○ represent Test Sample - (1), Test Sample - (2), Comparative Sample - (1) and Comparative Sample - (2), respectively.

Fig. 6 represents the time courses of the inhibition of the vasopermeability when the test sample and the comparative sample examined in Test Example 2-12 were intravenously administered to rats, wherein the vertical axis represents the inhibition of the vasopermeability by per cent and the abscissa represents passage of time (hour) after administration of sample.

A curve connected with ● and a curve connected with ○ represent the test sample and the comparative sample, respectively.

Fig. 7 represents a dose-response curve in the inhibition of the vasopermeability when the test sample and the comparative sample examined in Test Example 2-12 were intravenously administered to rats, wherein the vertical axis represents the inhibition of the vasopermeability by per cent and the abscissa represents dose of the drug calculated as Diphenhydramine hydrochloride with a logarithmic scale.

A curve connected with ● and a curve connected with ○ represent the test sample and the comparative sample,

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respectively.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A parenteral drug carrier system in the form of a conventional synthetic surfactant free fatty emulsion of particles having a mean particle diameter of 10 to 70nm and each comprising a core and a surface layer in which the substance constituting the core is a simple lipid, a derived lipid, a drug itself or a mixture thereof and the core forms 30 to 85% of the carrier, and the substance constituting the surface layer is different from that comprising the core and is a complex lipid, a derived lipid, a drug itself or a mixture thereof and the surface layer forms 15 to 70% of the carrier.

2. A drug carrier system as claimed in claim 1 in which the simple lipid is a neutral lipid and/or a cholesterol ester.

3. A drug carrier system as claimed in claim 1 or claim 2 in which the complex lipid is a phospholipid and/or a glycolipid.

4. A drug carrier system as claimed in any one of the claims 1 to 3 in which the derived lipid is a fatty acid and/or a higher alcohol and/or a hydrocarbon.

5. A drug carrier system as claimed in any one of claims 1 to 4, in which the drug is dispersed or dissolved in the drug carrier, forms a mixed micelle with one or more constituent(s) of the carrier or is chemically bound with a constituent of the carrier.

6. A drug carrier system substantially as herein described with reference to any one of the Examples and excluding any comparative Examples.

DATED this 15th day of January 1992.

NIPPON SHINYAKU COMPANY LIMITED

By their Patent Attorneys

GRIFFITH HACK & CO.

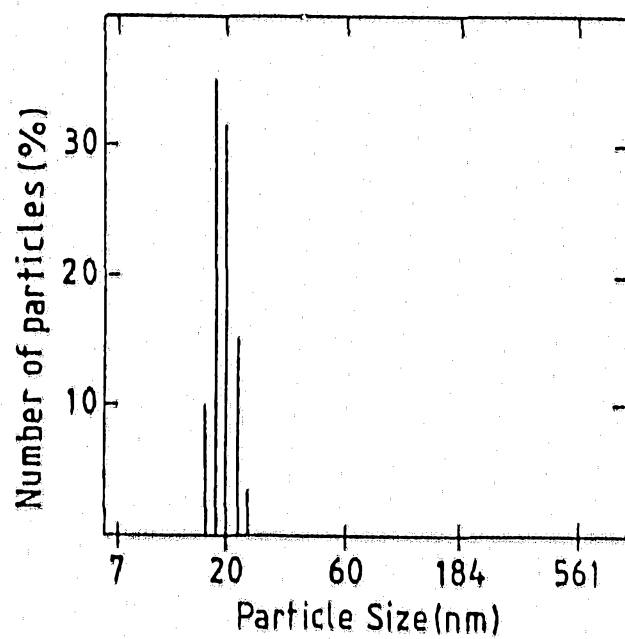


FIG.1.

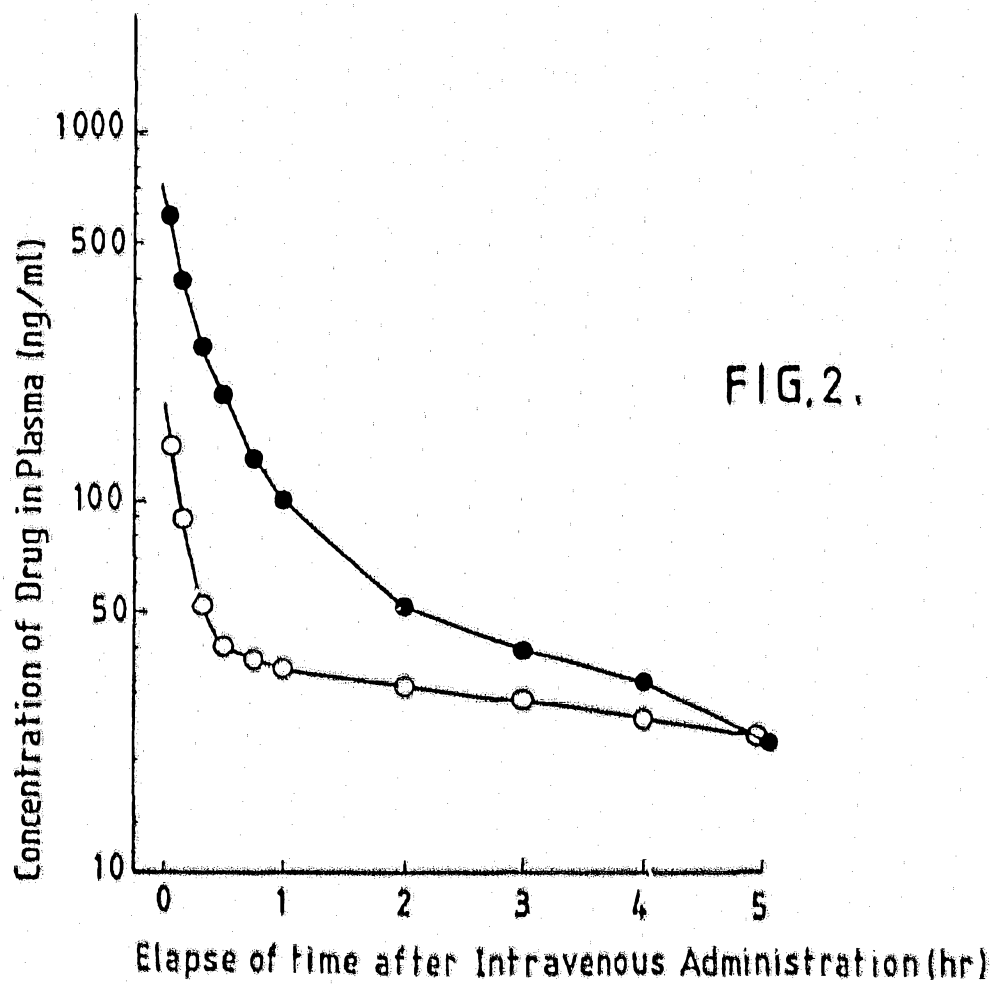


FIG.2.

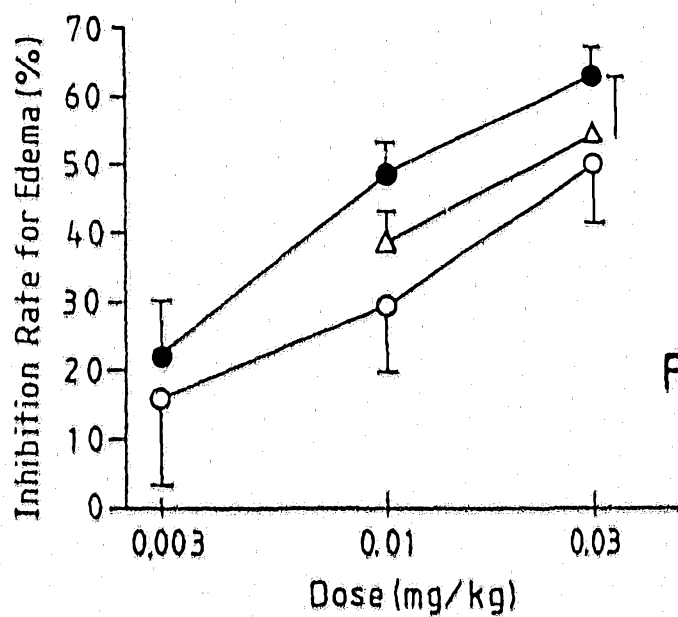


FIG.3.

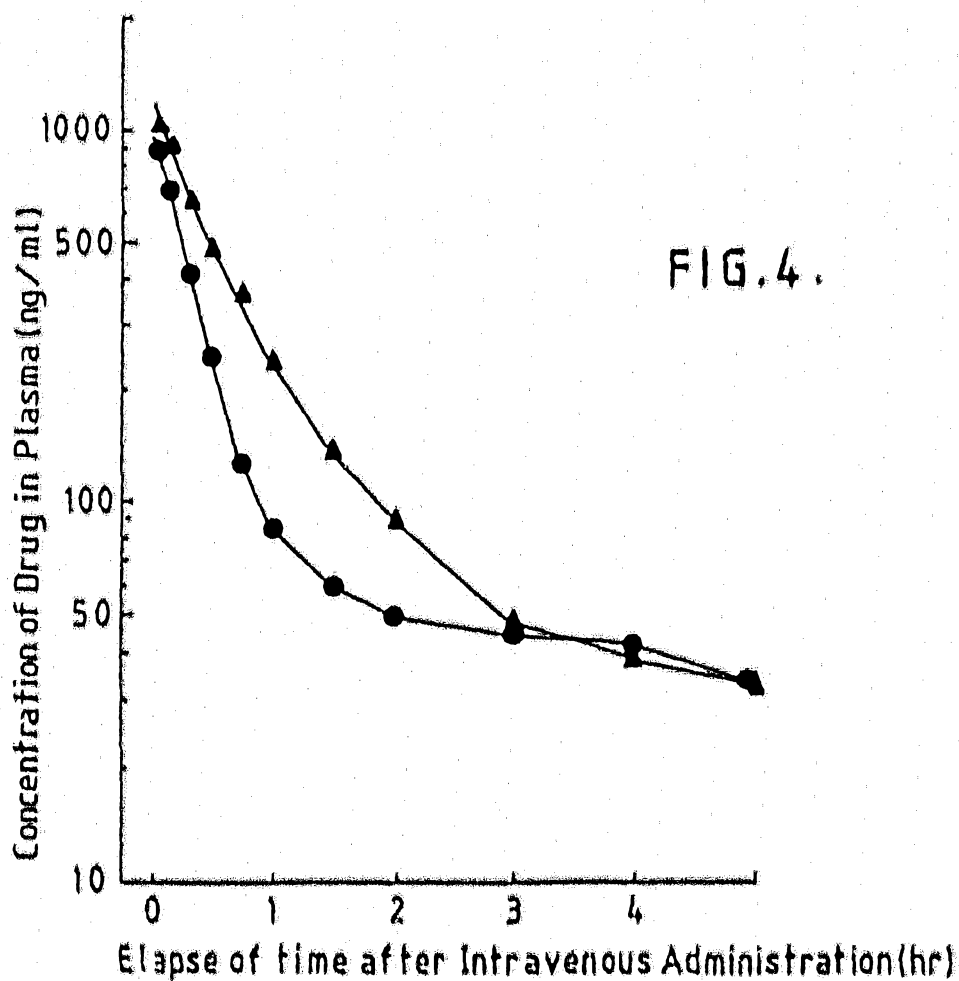
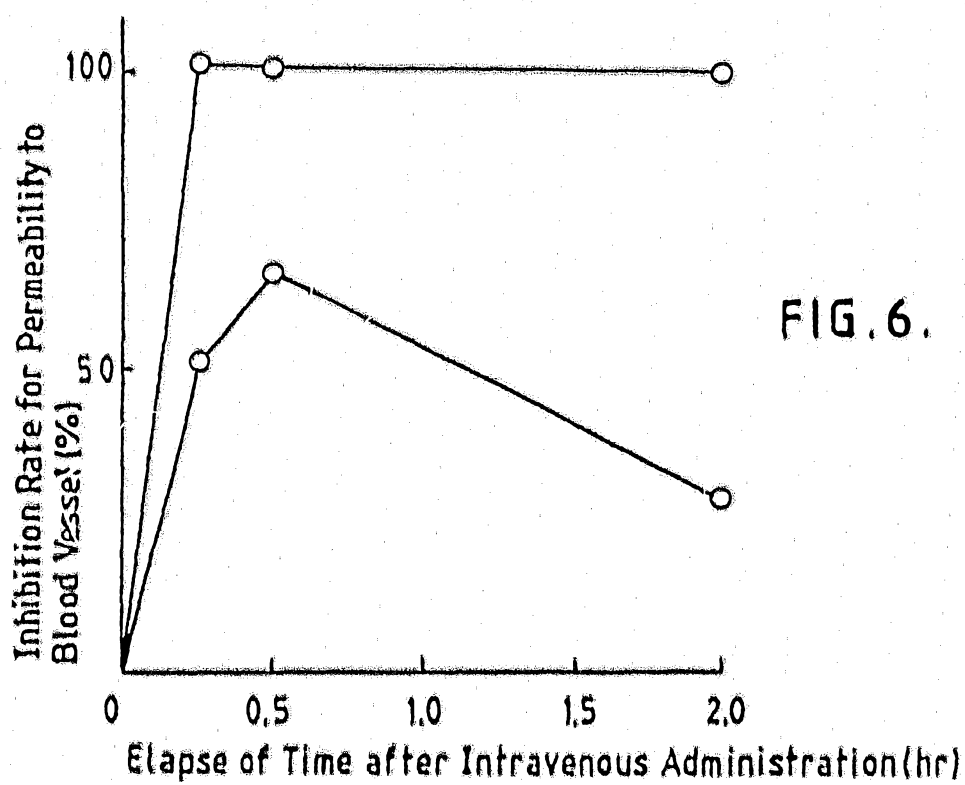
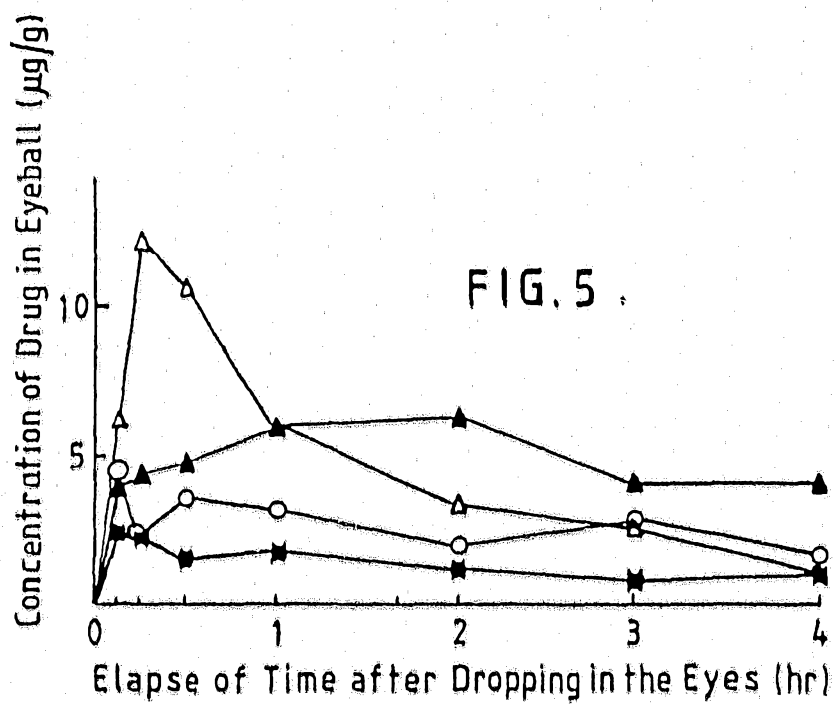


FIG.4.



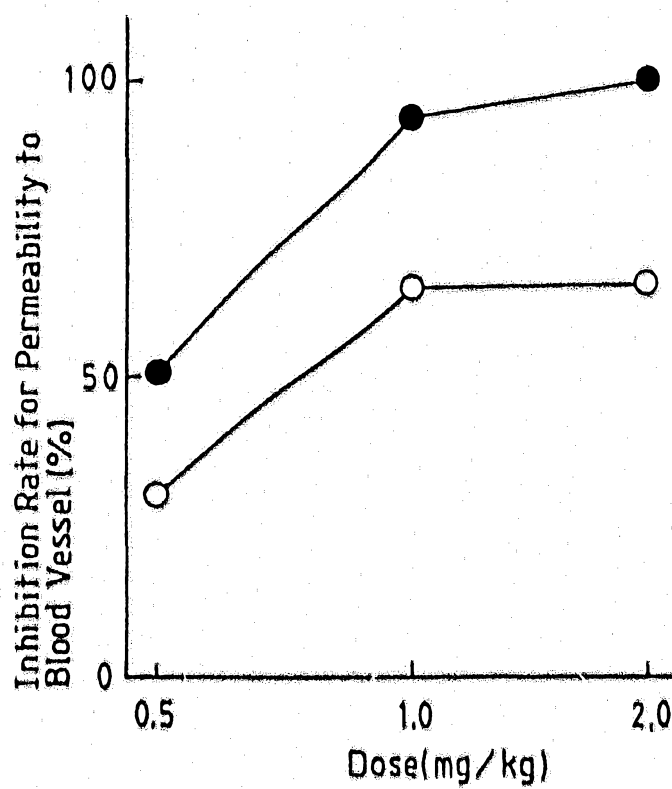


FIG.7.