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(54) **FORMULATIONS A BASE DE PHOSPHOLIPIDES**

(54) **PHOSPHOLIPID FORMULATIONS**

(57) A medicinally active formulation contains i) at least three compounds selected from the group consisting of egg phosphatidylcholine, dilauryl phosphatidylcholine, dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, dioleoyl phosphatidylcholine, dimyristoyl phosphatidylglycerol, dipalmitoyl phosphatidylglycerol, dimyristoyl phosphatidic acid, dipalmitoyl phosphatidic acid, dipalmitoyl phosphatidylethanolamine, distearoyl phosphatidylcholine, brain phosphatidylserine, brain sphingomyelin, cholesterol, cardiolipin, trioctanoin, triolein, soy phosphatidylcholine, poly(adenylic acid), phosphatidylethanolamine, phosphatidyl glycerol, phosphatidyl inositol, sphingosine, cerebroside (glycolipid), and ii) at least one biodegradable polymer selected from the group consisting of copolymers of sucrose and epichlorohydrin having molecular weights of from 70 000 to 400 000, glucose polymers having molecular weights of from 10 000 to 300 000, polyethylene glycols having molecular weights of from 1000 to 100 000, polyvinyl alcohols having molecular weights of from 70 000 to 110 000, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-methyl cellulose, hydroxypropyl-ethyl cellulose, sodium carboxymethyl cellulose, , starch, crosslinked starch, polyethyleneimine, methoxypolyethylene glycol, ethoxypolyethylene glycol, polyethylene oxide, polyoxyethylene, polyoxypropylene, cellulose acetate, sodium alginate, N,N-diethylaminoacetate, block copolymers of polyoxyethylene and polyoxypropylene, polyvinyl pyrrolidone, polyoxyethylene X-lauryl ether wherein X is from 9 to 20, and polyoxyethylene sorbitan esters. The formulation is useful for the production of stable liposomes for delivery of cosmetics, drugs, enzymes, growth factors, hormones, interferons, interleukins, moisturizers, peptides, proteins, and steroids. A variety of administration techniques, e.g. oral, injection, topical, may be used, depending on the medicinally active ingredient.

ABSTRACT OF THE DISCLOSURE

A medicinally active formulation contains i) at least three compounds selected from the group consisting of egg phosphatidylcholine, dilauryl phosphatidylcholine, 5 dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, dioleoyl phosphatidylcholine, dimyristoyl phosphatidylglycerol, dipalmitoyl phosphatidylglycerol, dimyristoyl phosphatidic acid, dipalmitoyl phosphatidic acid, dipalmitoyl 10 phosphatidylethanolamine, distearoyl phosphatidylcholine, brain phosphatidylserine, brain sphingomyelin, cholesterol, cardiolipin, trioctanoin, triolein, soy phosphatidylcholine, poly(adenylic acid), phosphatidylethanolamine, phosphatidyl glycerol, 15 phosphatidyl inositol, sphingosine, cerebroside (glycolipid), and ii) at least one biodegradable polymer selected from the group consisting of copolymers of sucrose and epichlorohydrin having molecular weights of from 70 000 to 400 000, glucose polymers having 20 molecular weights of from 10 000 to 300 000, polyethylene glycols having molecular weights of from 1000 to 100 000, polyvinyl alcohols having molecular weights of from 70 000 to 110 000, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl 25 cellulose, hydroxypropyl-methyl cellulose, hydroxypropyl-ethyl cellulose, sodium carboxymethyl cellulose, , starch, crosslinked starch, polyethyleneimine, methoxypolyethylene glycol, ethoxypolyethylene glycol, polyethylene oxide, 30 polyoxyethylene, polyoxypropylene, cellulose acetate, sodium alginate, N,N-diethylaminoacetate, block

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copolymers of polyoxyethylene and polyoxypropylene, polyvinyl pyrrolidone, polyoxyethylene X-lauryl ether wherein X is from 9 to 20, and polyoxyethylene sorbitan esters.

5       The formulation is useful for the production of stable liposomes for delivery of cosmetics, drugs, enzymes, growth factors, hormones, interferons, interleukins, moisturizers, peptides, proteins, and steroids. A variety of administration techniques, e.g.  
10 oral, injection, topical, may be used, depending on the medicinally active ingredient.

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CLAIMS:

1. A liposomal formulation comprising i) at least one  
medicinally active ingredient, ii) at least three  
phospholipids selected from the group consisting of egg  
5 phosphatidylcholine, dilauryl phosphatidylcholine,  
dimyristoyl phosphatidylcholine, dipalmitoyl  
phosphatidylcholine, dioleoyl phosphatidylcholine,  
dimyristoyl phosphatidylglycerol, dimyristoyl  
phosphatidylglycerol, dipalmitoyl phosphatidic acid,  
10 dipalmitoyl phosphatidic acid, dipalmitoyl  
phosphatidylethanolamine, distearoyl  
phosphatidylcholine, brain phosphatidylserine, brain  
sphingomyelin, cholesterol, cardiolipin, trioctanoin,  
triolin, soy phosphatidylcholine, poly(adenylic acid),  
15 phosphatidylethanolamine, phosphatidyl glycerol,  
phosphatidyl inositol, sphingosine, cerebroside  
(glycolipid), and iii) at least two biodegradable  
polymers selected from the group consisting of ficolls  
having molecular weights of from 70 000 to 400 000,  
20 glucose polymers having molecular weights of from 10 000  
to 300 000, polyethylene glycols having molecular  
weights of from 1000 to 100 000, polyvinyl alcohols  
having molecular weights of from 70 000 to 110 000,  
hydroxymethyl cellulose, hydroxyethyl cellulose,  
25 hydroxypropyl cellulose, hydroxypropyl-methyl cellulose,  
hydroxypropyl-ethyl cellulose, sodium carboxymethyl  
cellulose, starch, crosslinked starch,  
polyethyleneimine, methoxypolyethylene glycol,  
ethoxypolyethylene glycol, polyethylene oxide,  
30 polyoxyethylene, polyoxypropylene, cellulose acetate,

sodium alginate, N,N-diethylaminoacetate, block  
copolymers of polyoxyethylene and polyoxypropylene,  
polyvinyl pyrrolidone, polyoxyethylene X-lauryl ether  
wherein X is from 9 to 20, and polyoxyethylene sorbitan  
5 esters.

2. A formulation according to Claim 1 wherein there  
are at least three biodegradable polymers in the  
formulation.

3. A liposomal formulation according to Claim 1,  
10 wherein the at least 3 phospholipids are selected from  
the group consisting of the following combinations of  
compounds:

- i) brain phosphatidylserine, cholesterol, triolin and  
phosphatidylethanolamine, ii) egg phosphatidylcholine,  
15 distearoyl phosphatidylcholine, cholesterol and triolin,  
iii) cholesterol, cardiolipin, poly(adenylic acid) and  
triolin, iv) egg phosphatidylcholine, distearoyl  
phosphatidylcholine, cholesterol and trioctanoin, v) egg  
phosphatidylcholine, cholesterol, trioctanoin and  
20 phosphatidyl glycerol, vi) egg phosphatidylcholine,  
cholesterol, cardiolipin and triolin, vii) dioleoyl  
phosphatidylcholine, cholesterol, cardiolipin and  
triolin, viii) egg phosphatidylcholine, cholesterol,  
brain phosphatidylserine and triolin, ix) dioleoyl  
25 phosphatidylcholine, brain phosphatidylserine,  
cholesterol and triolin, x) egg phosphatidylcholine,  
dipalmitoyl phosphatidylglycerol, cholesterol and  
trioctanoin, xi) dimyristoyl phosphatidylcholine,  
dipalmitoyl phosphatidylcholine, distearoyl  
30 phosphatidylcholine and triolin, xii) egg  
phosphatidylcholine, dipalmitoyl phosphatidylcholine,

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distearoyl phosphatidylcholine and trioctanoin, xiii)  
phosphatidylcholine, cholesterol, brain  
phosphatidylserine and triolin, xiv)  
phosphatidylethanolamine, cholesterol cardiolipin and  
5 triolin, xv) phosphatidylcholine, cholesterol,  
trioctanoin and dipalmitoyl phosphatidylethanolamine,  
xvi) dimyristoyl phosphatidylcholine, dipalmitoyl  
phosphatidylcholine, distearoyl phosphatidylcholine and  
triolin, xvii) phosphatidylcholine,  
10 phosphatidylethanolamine, cholesterol, brain  
phosphatidylserine and triolin, xviii)  
phosphatidylcholine, phosphatidylethanolamine,  
cholesterol, cardiolipin and triolin, xix)  
phosphatidylcholine, dioleoyl phosphatidylcholine,  
15 cholesterol, cardiolipin and triolin, xx)  
phosphatidylcholine, dioleoyl phosphatidylcholine,  
cholesterol, brain phosphatidylserine and triolin, xxi)  
phosphatidylcholine, dimyristoyl phosphatidylcholine,  
dipalmitoyl phosphatidylcholine, distearoyl  
20 phosphatidylcholine and triolin and xxii)  
phosphatidylcholine, cholesterol, phosphatidylcholine  
ethanolamine and triolin.

4. A liposomal formulation according to Claim 1 having  
liposomes, said liposomes being coated with a coating  
25 comprising at least one biodegradable polymer selected  
from the group consisting of ficolls having molecular  
weights of from 70 000 to 400 000, glucose polymers  
having molecular weights of from 10 000 to 300 000,  
polyethylene glycols having molecular weights of from  
30 1000 to 100 000, polyvinyl alcohols having molecular

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weights of from 70 000 to 110 000, hydroxymethyl  
cellulose, hydroxyethyl cellulose, hydroxypropyl  
cellulose, hydroxypropyl-methyl cellulose,  
hydroxypropyl-ethyl cellulose, sodium carboxymethyl  
5 cellulose, starch, crosslinked starch,  
polyethyleneimine, methoxypolyethylene glycol,  
ethoxypolyethylene glycol, polyethylene oxide,  
polyoxyethylene, polyoxypropylene, cellulose acetate,  
sodium alginate, N,N-diethylaminoacetate, block  
10 copolymers of polyoxyethylene and polyoxypropylene,  
polyvinyl pyrrolidone, polyoxyethylene X-lauryl ether  
wherein X is from 9 to 20, and polyoxyethylene sorbitan  
esters.

5. A formulation according to any one of Claims 1, 3  
15 or 4 wherein the medicinally active ingredient is  
selected from the group consisting of insulin, heparin,  
hirugen, hirulos, hirudin, influenza virus vaccine,  
pneumonia vaccine, hepatitis A vaccine, hepatitis B  
vaccine, and hepatitis C vaccine, cholera toxin B-  
20 subunit, influenza vaccine virus, typhoid vaccine,  
plasmodium falciparum vaccine, diphtheria vaccine,  
tetanus vaccine, herpes simplex virus vaccine,  
tuberculosis vaccine, HIV vaccine, bordetella pertussis  
vaccine, measles vaccine, mumps vaccine and rubella  
25 vaccine (MMR), bacterial toxoids, vaccinia virus,  
adenovirus vaccine, canary pox vaccine, polio vaccine  
virus, bacillus calmette guerin (BCG) vaccine,  
klebsiella pneumonia vaccine, HIV envelope  
glycoproteins, bovine somatropin, oestrogen, androgens,  
30 prostaglandins, somatotropins, thyroid enzyme, pituitary

enzyme, digestive enzyme,  $\alpha$ -,  $\beta$ - and  $\gamma$ interferons, tuftsin, interleukins, insulin and insulin like growth factors, cytokines, steroids, terpenoids, triterpenes, retinoids, anti-ulcer  $H_2$  receptor antagonists, anti-  
5 ulcer drugs, hypoglycaemic agents, moisturizers, cosmetics, drugs, tetanus toxoid, diphtheria toxoid, pseudomonas A toxoid and, mycobacterium tuberculosis toxoid.

CLAIMS:

1. A formulation comprising i) at least one medicinally active ingredient, ii) at least three phospholipids selected from the group consisting of egg
- 5 phosphatidylcholin, dilauryl phosphatidylcholin, dimyristoyl phosphatidylcholin, dipalmitoyl phosphatidylcholin, dioleoyl phosphatidylcholin, dimyristoyl phosphatidylglycerol, dimyristoyl phosphatidylglycerol, dipalmitoyl phosphatidic acid,
- 10 dipalmitoyl phosphatidic acid, dipalmitoyl phosphatidylethanolamine, distearoyl phosphatidylcholin, brain phosphatidylserine, brain sphingomyelin, cholesterol, cardiolipin, trioctanoin, triolin, soy phosphatidylcholin, poly(adenylic acid),
- 15 phosphatidylethanolamine, phosphatidyl glycerol, phosphatidyl inositol, sphingosine, cerebroside (glycolipid), and iii) at least two biodegradable polymer selected from the group consisting of ficolls having molecular weights of from 70 000 to 400 000,
- 20 glucose polymers having molecular weights of from 10 000 to 300'000, polyethylene glycols having molecular weights of from 1000 to 100 000, polyvinyl alcohols having molecular weights of from 70 000 to 110 000, hydroxymethyl cellulose, hydroxyethyl cellulose,
- 25 hydroxypropyl cellulose, hydroxypropyl-methyl cellulose, hydroxypropyl-ethyl cellulose, sodium carboxymethyl cellulose, gelatine, starch, crosslinked starch, polyethyleneimine, methoxypolyethylene glycol, ethoxypolyethylene glycol, polyethylene oxide,
- 30 polyoxyethylene, polyoxypropylene, cellulose acetate, sodium alginate, N,N-diethylaminoacetate, block copolymers of polyoxyethylene and polyoxypropylene, polyvinyl pyrrolidone, polyoxyethylene X-lauryl ether wherein X is from 9 to 20, and polyoxyethylene sorbitan
- 35 esters.
2. A formulation according to Claim 1 wherein there are at least three biodegradable polymers in the

formulation.

3. A formulation according to Claim 1 wherein the phospholipid combinations are selected from the group consisting of:

- 5 i) brain phosphatidylserine, cholesterol, triolin and phosphatidylethanolamine, ii) egg phosphatidylcholin, distearoyl phosphatidylcholin, cholesterol and triolin, iii) cholesterol, cardiolipin, poly(adenylic acid) and triolin, iv) egg phosphatidylcholin, distearoyl
- 10 phosphatidylcholin, cholesterol and trioctanoin, v) egg phosphatidylcholin, cholesterol, trioctanoin and phosphatidyl glycerol, vi) egg phosphatidylcholin, cholesterol, cardiolipin and triolin, vii) dioleoyl phosphatidylcholin, cholesterol, cardiolipin and
- 15 triolin, viii) egg phosphatidylcholin, cholesterol, brain phosphatidylserine and triolin, ix) dioleoyl phosphatidylcholin, brain phosphatidylserine, cholesterol and triolin, x) egg phosphatidylcholin, dipalmitoyl phosphatidylglycerol, cholesterol and
- 20 trioctanoin, xi) dimyristoyl phosphatidylcholin, dipalmitoyl phosphatidylcholin, distearoyl phosphatidylcholin and triolin, xii) egg phosphatidylcholin, dipalmitoyl phosphatidylcholin, distearoyl phosphatidylcholin and trioctanoin, xiii)
- 25 phosphatidylcholin, cholesterol, brain phosphatidylserine and triolin, xiv) phosphatidylethanolamine, cholesterol cardiolipin and triolin, xv) phosphatidylcholin, cholesterol, trioctanoin and dipalmitoyl phosphatidylethanolamine,
- 30 xvi) dimyristoyl phosphatidylcholin, dipalmitoyl phosphatidylcholin, distearoyl phosphatidylcholin and triolin, xvii) phosphatidylcholin, phosphatidylethanolamine, cholesterol, brain phosphatidylserine and triolin, xviii)
- 35 phosphatidylcholin, phosphatidylthanolamine, cholesterol, cardiolipin and triolin, xix) phosphatidylcholin, dioleoyl phosphatidylcholin,

cholesterol, cardiolipin and triolin, xx)  
phosphatidylcholin, dioleoyl phosphatidylcholin,  
cholesterol, brain phosphatidylserine and triolin, xxi)  
phosphatidylcholin, dimyristoyl phosphatidylcholin,  
5 dipalmitoyl phosphatidylcholin, distearoyl  
phosphatidylcholin and triolin and xxii)  
phosphatidylcholin, cholesterol, phosphatidylcholin  
ethanolamine and triolin.

4. A formulation according to Claim 1 wherein the  
10 liposome is coated with a coating comprising at least  
one biodegradable polymer selected from the group  
consisting of ficolls having molecular weights of from  
70 000 to 400 000, glucose polymers having molecular  
weights of from 10 000 to 300 000, polyethylene glycols  
15 having molecular weights of from 1000 to 100 000,  
polyvinyl alcohols having molecular weights of from  
70 000 to 110 000, hydroxymethyl cellulose,  
hydroxyethyl cellulose, hydroxypropyl cellulose,  
hydroxypropyl-methyl cellulose, hydroxypropyl-ethyl  
20 cellulose, sodium carboxymethyl cellulose, gelatine,  
starch, crosslinked starch, polyethyleneimine,  
methoxypolyethylene glycol, ethoxypolyethylene glycol,  
polyethylene oxide, polyoxyethylene, polyoxypropylene,  
cellulose acetate, sodium alginate, N,N-  
25 diethylaminoacetate, block copolymers of polyoxyethylene  
and polyoxypropylene, polyvinyl pyrrolidone,  
polyoxyethylene X-lauryl ether wherein X is from 9 to  
20, and polyoxyethylene sorbitan esters.

5. A formulation according to any one of Claims 1, 3  
30 or 4 wherein the medicinally active ingredient is  
selected from the group consisting of insulin, heparin,  
hirugen, hirulos, huridine, influenza virus vaccine,  
pneumonia vaccine, hepatitis A vaccine, hepatitis B  
vaccine, and hepatitis C vaccine, cholera toxin B-  
35 subunit, influenza vaccine virus, typhoid vaccine,  
plasmodium falciparum, diphtheria, tetanus, herpes  
simplex virus, tuberculosis, HIV, bordetala pertussis,

measles, mumps and rubella vaccine (MMR), bacterial  
toxoids, vaccinia virus, adenovirus, canary pox, polio  
vaccine virus, bacillus calmette geurin (BCG),  
klebsiella pneumonia, HIV envelop glycoproteins, bovine  
5 somatropine, oestrogen, androgens, prostaglandins,  
somatotropins, thyroid enzyme, pituitary enzyme,  
digestive enzyme,  $\alpha$ -,  $\beta$ - and  $\gamma$ interferons, tuftsin,  
interleukins, insulin and insulin like growth factors,  
cytokins, steroids, terpenoids, triterpenes, retenoids,  
10 anti-ulcer H<sub>2</sub> receptor antagonists, anti-ulcer drugs,  
hypoglycaemic agents, moisturizers, cosmetics, drugs,  
tetanus toxoid, diphtheria toxoid, pseudomonas A toxoid,  
mycobacterium tuberculosis toxoid, HIV envelop  
glycoproteins.