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(74) Agent: **RENZONI, George, E.**; Christensen O'Connor
Johnson Kindness PLLC, Suite 2800, 1420 Fifth Avenue,
Seattle, WA 98101 (US).

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(71) Applicant (for all designated States except US): **SONUS
PHARMACEUTICALS, INC.** [US/US]; 22026 20th Av-
enue, S.E., Bothell, WA 98021 (US).

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(72) Inventors; and

(75) Inventors/Applicants (for US only): **LAMBERT, Karel,
J.** [US/US]; P.O. Box 971, Woodinville, WA 98071 (US).
KESSLER, Dean, R. [US/US]; 17170 Sealawn Drive,
Edmonds, WA 98026 (US). **NIENSTEDT, Andrew, M.**
[US/US]; 3038 N.W. 61st Street, Seattle, WA 98107 (US).
HARTGRAVES, Greg, A. [US/US]; 21924 - 49th Avenue
S.E., Bothell, WA 98021 (US). **CONSTANTINIDES,
Panayiotis, P.** [US/US]; 95 Berkshire Court, Gurnee, IL
60031 (US).

(54) Title: TOCOL-BASED COMPOSITIONS CONTAINING AMIODARONE

(57) Abstract: Pharmaceutical compositions comprise amiodarone or one of its prodrugs or analogs and one or more tocols.



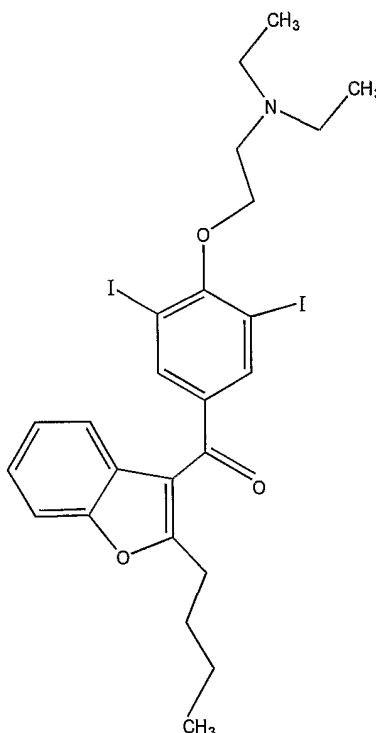
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TOCOL-BASED COMPOSITIONS CONTAINING AMIODARONE

BACKGROUND OF THE INVENTION

This application relates to pharmaceutical compositions containing the therapeutic
5 agent amiodarone or an analog or prodrug of amiodarone, and to methods for preparing such compositions.

Amiodarone (Scheme I), (2-butyl-3-benzofuranyl)[4-[2-(diethylamino)-ethoxy]-
3,5-diiodophenyl]methanone, is a Class III anti-arrhythmic for care of patients suffering
from, or at risk of, heart attack. It is generally made available in the form of the
10 hydrochloride salt, and is usually administered as an aqueous solution of that salt.



(I)

The marketed drug formulation is a preconcentrate solution of amiodarone in 10%
15 Tween 80 (sorbitan mono-oleate) and 2% benzyl alcohol and is available in sealed glass ampules. It must be administered with caution because of the observed acute hypotensive effects. To avoid these complications it is first diluted with a 5% dextrose solution and administered slowly by intravenous drip. Cumulative therapeutic effects appear over several days of therapy.

Toxicity of the formulation could be ameliorated by an alternative drug vehicle using emulsion or microemulsion technology. The general benefits of emulsions are several. Emulsification can lead to reduced toxicity, improved biocompatibility and pharmacokinetic profile (e.g. less inpatient variability) when compared to aqueous solutions of the drug. Extreme conditions of pH or ionic strength can be required to solubilize some drugs in aqueous solutions. Also, sustained release has been observed from emulsions formed as a blood pool or intra-tissue depot, from which the active agent is progressively released with desirable increased efficacy or duration of treatment. In other cases, a high plasma peak concentration (C_{max}) can be obtained by administration of an emulsion without undue risk to the patient. Finally, the stability of selected drugs in the oil phase may be improved when compared to aqueous solutions of the same drug at the desired pH.

The use of α -tocopherol or other tocopherols, tocotrienols or derivatives thereof as a solvent to dissolve certain drugs at high enough concentrations to be therapeutically useful has been described, primarily in certain patents and/or patent applications such as US patents 4,439,432 (Peat), 5,041,278 (Liposome Co.) and 5,583,105 (Biogal), and PCT published applications WO 95/11039 (Hexal Pharma), WO/95,31217 (A/S Dumex), WO 98/30205 (Sonus Pharmaceuticals), WO 97/22358 and WO 98/30204 (Sherman); and WO 97/03651 and WO 99/04787 (Danbiosyst UK Ltd.). These include the use of additional ingredients such as TPGS (α -tocopherol polyethyleneglycol 1000 succinate), phospholipids, and certain co-solvents and emulsifiers. Emulsions of pharmaceutically active ingredients in tocopherols, tocotrienols or derivatives thereof have the added advantage that the emulsion itself may be therapeutic for certain conditions, particularly for cardiovascular drugs, both as intravenous and oral preparations.

None of the patents or patent applications cited above discloses pharmaceutical compositions in which a tocopherol or tocotrienol is used as a solvent for amiodarone.

SUMMARY OF THE INVENTION

This invention comprises pharmaceutical compositions comprising amiodarone, or one of its prodrugs or analogs and a solvent comprising one or more tocopherols.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Surprisingly, it has been found that amiodarone, both the HCl salt and free base are soluble in tocopherols (a class of compounds defined below) and that pharmaceutically

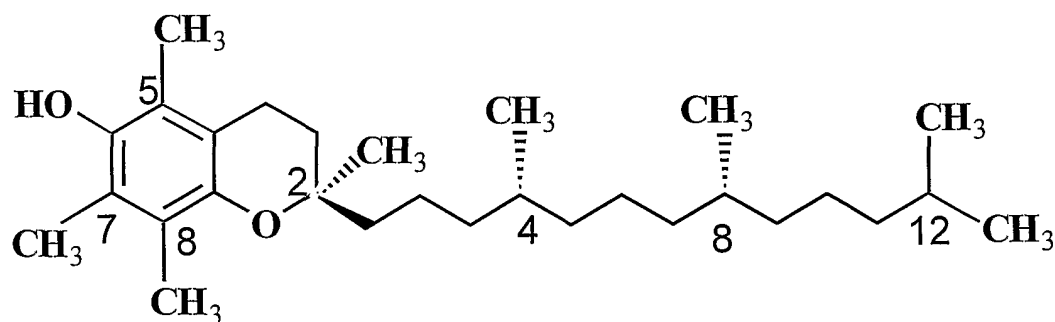
useful compositions including emulsions can be prepared that comprise amiodarone and a tocol as a solvent.

Amiodarone has intrinsic surfactant properties and is capable of forming micelles in solution. It has a surface tension of 15 dynes/cm at the air/water interface and its
5 octanol/buffer partition coefficient is reported to be 6.6 (Amiodarone, Harris and Roncucci, eds, MEDSI, Paris, 1986). Due to its planar hydrophobic ring structure it can easily penetrate through lipid bilayers and cellular membranes.

In addition to the parent compound, amiodarone, various prodrugs and analogs have been reported in the literature. Among the prodrugs, N-
10 phosphonooxymethylamiodarone has been shown to be active (J. Med. Chem. 42: 3094-3100, 1999). In addition, several amiodarone analogs resulting from dealkylation, deamination and deiodination reactions have been reported (Eur. J. Clin. Pharmacol. 55: 807-814, 2000).

To aid in understanding the invention the following definitions are provided.

15 Tocopherols: tocopherols are a family of natural and synthetic compounds. d- α -Tocopherol, also known as Vitamin E, is the most familiar member of this class of compounds and has the following chemical structure (Scheme II):



20

II

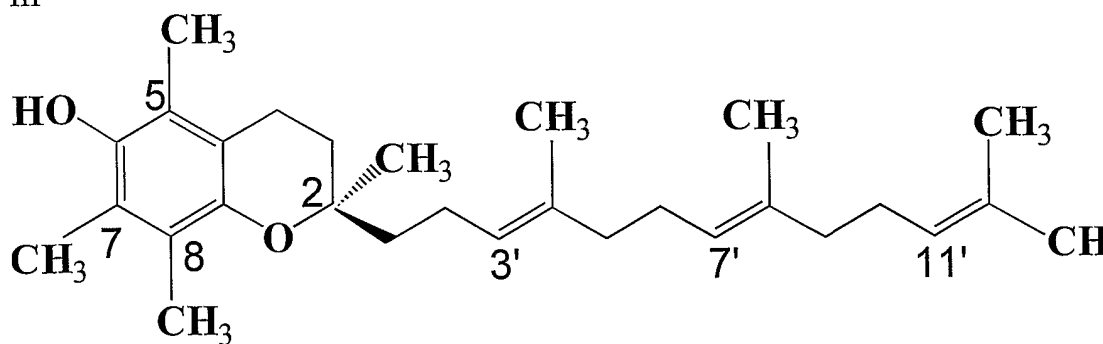
The molecule contains three structural elements, a chroman head with a phenolic alcohol and a phytyl tail. Not all tocopherols have three methyl groups on the chroman head. The simplest member of this group, 6-hydroxy-2-methyl-2-phytylchroman
25 contains no methyl groups on the chroman ring, and is sometimes simply referred to as "tocol". However, the terms "tocols" and "tocol" is used herein to represent a broader class of compounds. Other members of the tocopherol class include α -, β -, γ -, and δ -

tocopherols and Trolox[®] (6-hydroxy, 2,5,7,8-tetramethylchroman-2-carboxylic acid) and its desmethyl analogs. In addition to their use as a primary solvent, some tocopherols and their derivatives are useful as therapeutic agents. d- α -Tocopherol most commonly is sold as a mixture of tocopherols and often contains a substantial amount of a triglyceride oil or mixtures thereof. Synthetic d,l- α -tocopherol is sold as mixture of isomers and is available in highly purified form.

Tocotrienols: tocotrienols have structures related to the tocopherols but possess a 3', 7', 11' triene "tail". The structure of d- α -tocotrienol is shown in Scheme III.

10

III



Like tocopherols, not all tocotrienols have three methyl groups on the chroman head. There are four major tocotrienols, α -, β -, γ -, and δ -tocotrienols. Most commonly, tocotrienols are available as mixtures. Purified tocotrienols have only recently become available.

Tocols: "Tocols" is used herein in a broad sense to indicate the family of tocopherols and tocotrienols and derivatives thereof, including those common derivatives esterified at the 6-hydroxyl on the chroman ring. This use of the term "TOCOLS" is appropriate since all tocopherols and tocotrienols are fundamentally derivatives of the simplest tocopherol, 6-hydroxy-2-methyl-2-phytylchroman (sometimes referred to as "tocol").

Multiphase System: As used herein, this term refers to a system where one or more phases is (are) dispersed throughout another phase, which is usually referred to as the continuous phase or vehicle, or a precursor thereof. Emulsions, microemulsions and other nanoparticulates, including liposomes and niosomes, are examples of multiphase systems.

Liposome: A lipid bilayer vesicle formed spontaneously upon dispersion of lipids/phospholipids in water. "Liposome" is also defined as a vesicular structure consisting of hydrated bilayers.

Niosome: In analogy to a liposome, a niosome is a nonionic surfactant vesicle.
5 Classes of commonly used non-ionic surfactants include polyglycerol alkylethers, glucosyl dialkylethers, crown ethers and polyoxyethylene alkyl ethers and esters.

Micelle: Organized aggregates of one or more surfactants that exist at a concentration above the critical micellar concentration (CMC) in water or buffer. These molecular aggregates typically have a diameter of less than 10 nm to perhaps 20 or 25 nm
10 in some systems.

Emulsion: A colloidal dispersion of two immiscible liquids, such as oil and water, in the form of droplets. The internal phase is also termed the dispersed phase and the external phase is termed the continuous phase. The mean diameter of the dispersed phase, in general, is between about 0.1 and about 5.0 microns, as is commonly measured
15 by particle sizing methods. Emulsions in which the dispersed phase and continuous phase have different refractive indexes are typically optically opaque. Emulsions possess a finite or limited stability over time, and can be stabilized by the incorporation of amphiphilic excipients known as surfactants and by viscosity modifiers.

Microemulsion: A thermodynamically stable, isotropically clear dispersion of
20 two immiscible liquids, stabilized by an interfacial film of surfactant molecules. Microemulsions have a mean droplet diameter of less than about 200 nm, in general between about 10 – 100 nm and are typically self-assembling.

Tocol microemulsion: A thermodynamically stable, translucent or clear dispersion of a tocol in water, stabilized by an interfacial film of surfactant molecules.
25 Tocol microemulsions have a mean droplet diameter of less than about 200 nm, in general between about 50 and about 100 nm, and typically are not self-assembling, but require heat or increased shear to assemble due to the high viscosity of the tocol oil.

Self-Emulsifying Drug Delivery Systems (SEDDS):

In the absence of an aqueous phase, mixtures of oil(s) and non-ionic surfactant(s)
30 form clear and isotropic solutions that are known as self-emulsifying drug delivery systems (SEDDS). They have successfully been used to improve lipophilic drug

dissolution and oral absorption. Such systems are essentially precursors of emulsion-type multiphasic systems.

The compositions of the current invention may be emulsions, microemulsions, self-emulsifying systems, liposomal and niosomal dispersions, gels or liquid crystalline mesophases or their precursors, using one or more tocols as a solvent for the amiodarone. The preferred forms of the invention are oil-in-water emulsions, microemulsions and self-emulsifying drug delivery systems (SEDDS or SMEDDS) for oral administration of an active agent. Examples of multiphasic systems having two or more phases include oil-in-water and water-in-oil emulsions and microemulsions, and multiple emulsions of the oil-in-water-in-oil and water-in-oil-in-water structure.

A highly preferred form of the invention for drug delivery is a tocol microemulsion as defined above. These vehicles for drug delivery are translucent and isotropic, and are of small mean droplet diameter, preferably less than about 150 nm, even more preferably less than about 100 nm, and most preferably from about 30 to 90 nm. In general they possess high drug solubilization capacity (a relative measure for each individual drug), and most characteristically have extended stability on storage, which is preferably greater than 1 year, even more preferably greater than two years. The microemulsions of the current invention have a surfactant to oil ratio of about 1:1 to 1:5, preferably from about 1:1 to 1:2 and are frequently formulated with one or more co-solvents or co-surfactants to improve processing. Unlike vegetable oil microemulsions, which form spontaneously, tocol microemulsions are formed by homogenization in a high-shear device. However, once formed, they are essentially transparent or translucent and stable. They preferably exhibit no particle size growth over a typical pharmaceutical shelf life of one year or more.

Compositions of this invention including amiodarone in tocol-based emulsions and microemulsions may be useful for bolus or IV drip infusion as a vascular tonic in the treatment of myocardial infarction or for oral administration. By delivering the amiodarone in the form of an emulsion or microemulsion, its release time in the blood or tissue can be extended. Reducing the peak concentration (C_{max}) in plasma can minimize or modulate systemic or non-specific toxic or adverse events.

Relatively volatile co-solvents such as monohydric alcohols (e.g., ethanol, butanol, or isopropanol) may be used to prepare compositions of this invention if desired.

However, if a co-solvent is to be used, such co-solvent should preferably be a relatively non-volatile co-solvent. Examples of the latter are polyethylene glycols (for example, PEG-400), benzyl benzoate, benzyl alcohol, glycerol, glycerol-, propylene glycol- and polyethylene glycol-based esters (oils) that are commercially available under different trade names such as Capmul® MCM (glyceryl mono-/di-caprylate/caprate), Captex® 355 (caprylic/capric triglycerides from coconut oil), Captex® 200 (propylene glycol dicaprylate/ dicaprate), Labrafil® M1944 (primarily oleic acid polyglycolized glycerides from apricot kernel oil), Labrasol® (caprylate/caprate polyglycolized glycerides from coconut oil), Myvacet® (distilled acetylated monoglycerides), Lauroglycol® (propylene glycol mono-/di-laurate), propylene glycol and Transcutol® (diethylene glycol monoethyl ether). Also useful are essential lipids (as in US 5,716,928) such as allspice berry, fennel, amber essence, anise seed, arnica, balsam of Peru, basil, bay leaf, parsley, peanut, benzoin gum, bergamot, rosewood, cajeput, marigold, camphor, caraway, cardamon, carrot, cedarwood, celery, chamomile, cinnamon, citronella, palm oils, sage, clove, coriander, cumin, cypress, eucalyptus, aloe, fennel, fir, frankincense, garlic, geranium, rose, ginger, lime, grapefruit, orange, hyssop, jasmine, jojoba, juniper, lavender, lemon, lemongrass, marjoram, mugwort, watercress, mullen, myrrh, bigarde neroli, nutmeg, bitter orange, oregano, patchouli, pennyroyal, primrose, retinols, papaya, pepper, peppermint, poppyseed, petitegrain, pine, poke root, rosehip, rosemary, sandalwood, sassafras, spearmint, spikenard, hemlock, tangerine, tea tree, thyme, vanilla, banana, coconut, vetivert, wintergreen, witch hazel, ylang ylang extract, or synthetic analogs, also β -carotene, carotenoids, quinones, menadiones, lycopene, crown ethers, tributyrin, 1-methyl-2-pyrrolidinone, dimethylsulfoxide, polyvinylalcohol, polyvinylpyrrolidinone, phenol, cholesterol, astaxanthins, phospholipids, polyoxyethylated phospholipids, secondary tocots, Amifat® P30 (glyceryl monopyroglutamate monooleate), and mixtures thereof.

Compositions of the invention may also include one or more surfactants such as Cremophor® EL (polyoxyethylated castor oil), Solutol-HS-15 (polyethylene glycol 660-12-hydroxystearate) polyoxyethylene/polyoxypropylene block copolymers (poloxamers) such as Poloxamer 407 (Pluronic® F-127) and others of the Pluronic® line (available from BASF), phospholipids such as lecithin, fatty acids, fatty acid esters such as palmitoyl carnitine, bile acids, tocol esters, such as tocopherol succinate-PEG1000

(TPGS), tocopherol succinyl-aspartate, tocopherol succinyl glutamate, tocopherol succinyl polygulatamate, and mixtures thereof.

Other tocopherol succinyl derivatives useful in the composition include tocopherol succinyl amino acid derivatives and tocopherol succinyl peptide derivatives.

- 5 These derivatives can be prepared by coupling a suitable tocopherol succinyl derivative with a suitable amino acid or peptide derivative.

Other additives, such as antioxidants, may be included in the compositions.

- 10 The compositions may also include other pharmaceutically active compounds, such as other cardiovascular drugs and anti-oxidants (either in the tocol phase or in an aqueous phase of a biphasic system) that are synergistic with, or suitable for administration with, amiodarone.

- The following examples are presented to illustrate the invention. However, the invention is not to be regarded as limited by these examples, as it is directed broadly to the provision of pharmaceutical compositions that comprise amiodarone and one or more
15 tocols as a solvent for it.

EXAMPLES

EXAMPLE 1

Preparation of Amiodarone Free Base

- Amiodarone was purchased as the HCl salt (Sigma Chemicals, St. Louis MO).
20 The free base was prepared by dissolving the drug in chloroform and washing the organic phase with 1% NaOH in saturated brine. The organic layer was collected and dried under vacuum. A pale yellow oil was obtained with a yield of 98% and was chromatographically pure.

EXAMPLE 2

- 25 Amiodarone/Tocol Microemulsion with TPGS

An emulsion containing 12 mg/mL amiodarone as the free base was then formulated as follows:

	Amiodarone (free base)	0.6 gm
	d,l- α -tocopherol	1.0 gm
30	TPGS	1.0 gm
	Poloxamer P-407	0.5 gm
	PEG-400	3.0 gm
	Buffer	to 50 mL

Following homogenization in an Avestin C5 (Ottawa, CANADA) at 47 °C for 5 min, a transparent microemulsion was obtained with a mean droplet diameter of 24 nm as measured by photon correlation spectroscopy (PCS, Nicomp 370, Particle Sizing Systems, Santa Barbara CA). Formulations of amiodarone as the HCl salt in tocol emulsions are also anticipated.

EXAMPLE 3

Amiodarone/Tocol Emulsion with POLOXAMER

An emulsion containing 10 mg/mL amiodarone was prepared as follows:

	Amiodarone (free base)	1.0 gm
10	d- α -Tocopherol	2.0 gm
	Poloxamer P-407	3.0 gm
	Glucose	5.0 gm
	Buffer	to 100 mL

Following homogenization in an Avestin C5 at 75 °C for 5 min, an emulsion was obtained with a mean droplet diameter of 47 nm as measured by PCS.

EXAMPLE 4

Amiodarone/Tocol Emulsion with POLOXAMER and Sodium Laurel Sulfate

An emulsion containing 1.2 g/ml amiodarone was prepared as follows:

	Amiodarone hydrochloride	3.6 gm
20	Poloxamer P-407	9.0 gm
	d- α -Tocopherol	18.0 gm
	Sodium laurel sulfate	3.0 eq
	Water	to 300 mL

Following homogenization in an Avestin C5 at 60 °C for at least 15 minutes, an emulsion was obtained with a mean droplet diameter of 44 nm at 25 °C and 40 °C as measured by PCS.

EXAMPLE 5

Amiodarone/Tocal Emulsion with POLOXAMER and Lactic Acid

An emulsion containing 1.2 g/ml amiodarone was prepared as follows:

30	Amiodarone hydrochloride	3.6 gm
	Poloxamer P-407	9.0 gm
	d- α -Tocopherol	6.0 gm
	Lactic acid	6.0 eq

Water to 300 mL

Following homogenization in an Avestin C5 at 60 °C for at least 15 minutes, an emulsion was obtained with a mean droplet diameter of 36 nm at 25 °C and 40 °C as measured by PCS.

5

EXAMPLE 6

Amiodarone/Tocol Emulsion with POLOXAMER

An emulsion containing 1.0 g/ml amiodarone was prepared as follows:

	Amiodarone hydrochloride	3.0 gm
	Poloxamer P-407	3.0 gm
10	d- α -Tocopherol	6.0 gm
	PEG-400	3.0 gm
	Buffer	to 300 mL
	pH adjusted to 3.0 with tartaric acid	

Following homogenization in an Avestin C5 at 60 °C for at least 15 minutes, an emulsion was obtained with a mean droplet diameter of 50 nm at 25 °C and 40 °C as measured by PCS.

15

EXAMPLE 7

Amiodarone/Tocol Emulsion with Tocopherol Acetate

An emulsion containing 10 mg/mL amiodarone was then formulated as follows:

20	Amiodarone (free base)	1.0 gm
	d- α -Tocopherol	2.0 gm
	Tocopherol acetate	0.7 gm
	Poloxamer P-407	3.0 gm
	PEG-400	5.0 gm
25	Buffer	to 100 mL

Following homogenization in an Avestin C5 at 75 °C for 5 min, an emulsion was obtained with a mean particle size of 127 nm as measured by PCS.

EXAMPLE 8

Tocopherol Succinyl Aspartate

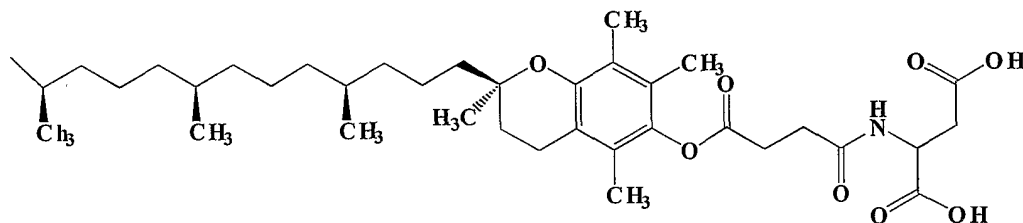
Synthesis of the tocopherol succinyl aspartate conjugate was carried out via the use of mixed anhydride chemistry. D- α -tocopherol succinate was activated by adding 1.2 equivalents of isobutylchloroformate (IBCF) and 1.4 equivalents of N-methylmorpholine (NMM) in a tetrahydrofuran (THF) medium at -5 °C. To insure complete conversion to the mixed anhydride the reaction was stirred for 1 hour allowing the mixture to slowly

30

warm to room temperature. The mixed anhydride was filtered to remove the N-methylmorpholine hydrochloride salt (NMMâHCl). The resulting filtrate was added drop-wise over 45 minutes to a -5 °C solution of 1.0 equivalence of L-aspartic acid dibenzyl ester p-toluenesulfonate salt and 1.5 equivalence of triethylamine (TEA) in THF. The reaction was allowed to warm to room temperature and was stirred for an additional 15 hours before isolating the product.

Once the reaction was complete the THF was removed in a vacuo to yield a crude yellow sticky solid. The product was dissolved in dichloromethane (DCM) and washed with 2X 0.1 N HCl, 1X Sat. NaHCO₃, and 1X Sat. NaCl. The resulting organic mixture was dried over MgSO₄ and the solvent removed under vacuum. An off-white solid was obtained.

The tocopherol succinyl-aspartate dibenzyl ester was deprotected by hydrogenation to yield the free diacid product. Total yield = 72%. Purity = 95%+ by HPLC analysis. FT-IR: amide, ester, amide, and ether (N-H, C=O, C=O, and C-O stretch) are 3336, 1736, 1645, 1153 cm⁻¹ respectively. The structure was confirmed by LC mass spectroscopy and is shown below.



Tocopherol succinyl mono- and polyglutamates similarly can be made by this chemistry. Our work shows that compounds can be anticipated to have utility as surfactants (detergents) and bioavailability enhancers for use in pharmaceutical emulsions, microemulsions and SEDDS, cosmetic lotions and the like.

EXAMPLE 9

Amiodarone/Tocol Self-Emulsifying System

A SEDDS emulsion containing 20 mg/mL amiodarone was then formulated as follows:

Amiodarone (free base)	0.20 gm
Tocotrienols	0.10 gm

Acetylated monoglycerides	0.10 gm
Tocopherol succinyl aspartate	0.30 gm
PEG-300	0.50 gm

Purified mixed tocotrienols were obtained from InCon Processing (Batavia IL),
5 and acetylated monoglycerides from Eastman (Kingsport TN). Tocopherol succinyl
aspartate was synthesized as described in Example 5. Earlier work had demonstrated that
tocopherol succinyl aspartate has good properties as a surfactant. Amiodarone and
tocopherol succinyl aspartate were readily soluble in the tocotrienol oil and did not
precipitate when Labrasol and PEG-300 were added. The formulation was warmed to
10 ensure complete dissolution and then cooled to room temperature.

Following this procedure, 0.1 gm of the SEDDS was added to 10 mL of buffer
(NaPO_4 5 mM, pH 7.4). An emulsion with a particle size of 177 nm by PCS was
obtained. SEDDS typically are useful for oral drug delivery. Use of tocotrienols as an
oral supplement provides added benefit to patients receiving cardiovascular medications.

15

EXAMPLE 10

Single Dose Acute Intravenous Toxicity

A single dose acute intravenous toxicity in mice was conducted using the
emulsion of Example 4. The marketed formulation, Cordarone[®] IV diluted 1:5 with
D5W, was used for comparison. Both formulations contained amiodarone at a
20 concentration of 10 mg/mL. At a dose of 160 mg/kg, 66% of the mice receiving
Cordarone died, and death was preceded by prostration, spasms and deep respiratory
depression. In the case of emulsion at an equal dose, no deaths were recorded, and
adverse reactions were limited to decreased activity and poor grooming.

EXAMPLE 11

25

Biodistribution

Sprague-Dawley rats were administered Cordarone[®] IV by tailvein injection, or
an equivalent dose of amiodarone as the drug emulsion of Example 3. A liposomal
formulation of amiodarone was used for reference. Cordarone IV was diluted 1:10 with
D5W before administration. After about 5 hr, the rats from each group were sacrificed
30 and necropsied (n=5). Harvested blood and organs were assayed for amiodarone.
Tissues were first homogenized in acidic methanol and the extracts were taken to dryness
and reconstituted in methanolic buffer prior to extraction on an SPE reverse phase
disposable column. Amiodarone was selectively eluted with 85% recovery and

quantitated by HPLC. The tissue distribution data are reported below for blood, heart and lungs.

Tissue	Cordarone® IV (ug/gm)	Emulsion of Example 3 (ug/gm)	Liposomal Preparation (ug/gm)
Blood	1.35 ± 0.41	3.74 ± 1.79	2.29 ± 1.32
Heart	12.13 ± 4.54	16.67 ± 4.87	17.16 ± 4.32
Lungs	62.86 ± 27.40	85.39 ± 18.12	113.66 ± 28.88

- 5 Riva et al, (Riva E et al. 1982. Pharmacokinetics of amiodarone in rats. J. Cardiovasc. Pharm. 4:270-275.) have reported on the biodistribution of amiodarone following administration of Cordarone IV and the results for cardiac muscle are in excellent agreement. Riva obtained drug loading of 13.4 ug/gm in heart at 6 hours and 0.05 ug/gm in plasma, suggesting rapid clearance of the soluble form from the plasma
- 10 compartment. Unlike the emulsified form of Example 3, with Cordarone IV we noted high plasma levels of desethylamiodarone, the major metabolite, increasing rapidly after 1 hour, as would be consistent with rapid liver metabolism of the drug.

EXAMPLE 12

Drug Stability in Emulsion

- 15 The microemulsion of Example 3 was re-assayed for drug potency 40 days post preparation and the following data was obtained.

Day	Amiodarone Concentration (mg/g)
1	9.3
40	9.6

- 20 These data are within experimental sampling error and are consistent with acceptable pharmaceutical stability. No significant degradants of amiodarone were detected. Desethylamiodarone was not detected.

EXAMPLE 13

Emulsion pH

The pH of the microemulsion of Example 4 was obtained at 25 °C and 40°C.

Week	pH at 25°C	pH at 40 °C
1	6.91	6.89
2	6.95	6.88
3	6.99	6.77
4	6.91	6.82
8	6.98	6.67
12	6.96	6.61

5

EXAMPLE 14

Emulsion pH

The pH of the microemulsion of Example 5 was obtained at 25 °C and 40°C.

Week	pH at 25°C	pH at 40 °C
1	7.77	7.58
3	7.58	7.39
4	7.78	7.63
8	7.69	7.27

10

EXAMPLE 15

Emulsion pH

The pH of the microemulsion of Example 6 was obtained at 25 °C and 40°C.

Week	pH at 25°C	pH at 40 °C
2	2.99	3.00
4	3.04	3.06
6	3.00	3.01

EXAMPLE 16

Drug Stability in Emulsion

The microemulsion of Example 4 was re-assayed for drug potency post
 5 preparation and the following data was obtained.

Week	Amiodarone Concentration (mg/g) at 25°C	Amiodarone Concentration (mg/g) at 40 °C
1	11.1	11.4
2	11.0	10.9
3	11.2	11.2
4	11.6	11.5
8	11.2	10.9
12	11.7	10.3

EXAMPLE 17

Drug Stability in Emulsion

10 The microemulsion of Example 5 was re-assayed for drug potency post
 preparation and the following data was obtained.

Week	Amiodarone Concentration (mg/g) at 25°C	Amiodarone Concentration (mg/g) at 40 °C
1	11.4	11.4
3	10.6	10.4
4	10.7	10.6
8	11.1	10.9

EXAMPLE 18

Drug Stability in Emulsion

The microemulsion of Example 6 was re-assayed for drug potency post preparation and the following data was obtained.

5

Week	Amiodarone Concentration (mg/g) at 25°C	Amiodarone Concentration (mg/g) at 40 °C
2	9.7	9.6
4	9.9	9.7
6		9.8

EXAMPLE 19

Volume Weighted Particle Size (nm)

The mean droplet diameter of the emulsion of Example 4 at 25 °C and 40 °C was
10 measured by PCS.

Week	nm at 25°C	nm at 40 °C
1	44	43
2	40	49
3	49	43
4	48	45
8	48	44
12	44	42

EXAMPLE 20

Volume Weighted Particle Size (nm)

The mean droplet diameter of the emulsion of Example 5 at 25 °C and 40 °C was measured by PCS.

5

Week	nm at 25°C	nm at 40 °C
1	35	38
3	35	40
4	40	44
8	45	46

EXAMPLE 21

Volume Weighted Particle Size (nm)

The mean droplet diameter of the emulsion of Example 6 at 25 °C and 40 °C was measured by PCS.

10

Week	Nm at 25°C	nm at 40 °C
2	50	54
4	53	51
6	50	48

While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A pharmaceutical composition, comprising amiodarone or a prodrug or analog thereof, and one or more tocals.
2. The composition of Claim 1, wherein amiodarone comprises amiodarone free base.
3. The composition of Claim 1, wherein the prodrug comprises N-phosphono-oxymethyl amiodarone.
4. The composition of Claim 1, wherein the prodrug is an ester of the acidic metabolite of amiodarone.
5. The composition of Claim 4, wherein the ester is at least one of an isopropyl ester, a sec-butyl ester, and a neopentyl ester.
6. The composition of Claim 1, wherein the analog comprises at least one of a dealkylated analog, a deaminated analog, and a deiodinated analog.
7. The composition of Claim 1, wherein the composition comprises a multiphase system.
8. The composition of Claim 7, wherein the multiphase system comprises at least one of an emulsion and a microemulsion.
9. The composition of Claim 7, wherein the multiphase system comprises a biphasic emulsion.
10. The composition of Claim 7, wherein the multiphase system comprises at least one of an oil-in-water emulsion and a water-in-oil emulsion.
11. The composition of Claim 1, wherein the composition comprises a self-emulsifying drug delivery system.
12. The composition of Claim 1 further comprising one or more surfactants.

13. The composition of Claim 1 further comprising one or more co-solvents.
14. The composition of Claim 1, wherein the tocol comprises a tocopherol.
15. The composition of Claim 1, wherein the tocol comprises a tocotrienol.
16. The composition of Claim 1, wherein the tocol comprises d- α -tocopherol.
17. The composition of Claim 1 further comprising one or more therapeutic agents.
18. The composition of Claim 17, wherein the therapeutic agent acts synergistically with amiodarone.
19. The composition of Claim 1 further comprising an antioxidant.
20. A pharmaceutical composition, comprising amiodarone, one or more tocols, and tocopherol succinyl aspartate.
21. A pharmaceutical composition, comprising amiodarone, one or more tocols, and tocopherol succinyl glutamate.
22. A pharmaceutical composition, comprising amiodarone, one or more tocols, and tocopherol succinyl polyglutamate.
23. A pharmaceutical composition, comprising one or more tocols and tocopherol succinyl aspartate.
24. A pharmaceutical composition, comprising one or more tocols and tocopherol succinyl glutamate.
25. A pharmaceutical composition, comprising one or more tocols and tocopherol succinyl polyglutamate.
26. A pharmaceutical composition, comprising one or more tocols and a tocopherol succinyl derivative, wherein the derivative comprises an amino acid or peptide.

27. The composition of any one of Claims 20 to 26, wherein the tocol comprises a tocopherol.

28. The composition of any one of Claims 20 to 26, wherein the tocol comprises a tocotrienol.

29. The composition of any one of Claims 20 to 26, wherein the tocol comprises d- α -tocopherol.

30. A pharmaceutical composition, comprising at least one of tocopherol succinyl asparate, tocopherol succinyl glutamate, and tocopherol succinyl polyglutamate.