(12)   Patent Application

(54) **Title:**
COMPOSITIONS OF SMALL MOLECULE THERAPEUTICS

(57) **Abstract:**
Compositions containing a small molecule therapeutic and an
alkyl N, N-disubstituted amino acetate are disclosed. Inclusion
of the alkyl N, N-disubstituted amino acetate enhances the
pharmacokinetic properties of the small molecule therapeutic.

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(54) Title: COMPOSITIONS OF SMALL MOLECULE THERAPEUTICS

(57) Abstract: Compositions containing a small molecule therapeutic and an alkyl N, N-disubstituted amino acetate are disclosed.
Inclusion of the alkyl N, N-disubstituted amino acetate enhances the pharmacokinetic properties of the small molecule therapeutic.

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COMPOSITIONS OF SMALL MOLECULE THERAPEUTICS

Cross-Reference to Related Application

This application claims the priority of U.S. Provisional Application Serial No. 61/343,781, filed May 4, 2010, the
5   disclosures of which are incorporated in their entirety herein by reference.

Field of Invention

This invention relates to compositions of small molecule therapeutics with enhanced pharmacokinetic properties.

10 ### Background of Invention

Small molecule drug discovery is actively pursued by biotech companies to complement the therapeutic advances made with protein based drugs such as recombinant proteins and monoclonal antibodies. Moreover, small molecule drug treatments often may
15   enjoy cost benefits. Patients are also more likely to accept orally available small molecule treatments than the typical injectable protein based drug. It has now been found that the pharmacokinetic properties of small molecule therapeutics can be improved by the co-administration of certain enhancers.

20 ### Summary of the Invention

Pharmacokinetic properties of small molecule therapeutics such as the taxanes and small molecule drug substances classified according to the Biopharmaceutics Classification System (BCS) as Class 2-4 compounds are enhanced by the addition of an
25   alkyl N,N-disubstituted-amino acetate in free base or salt form. A greater systemic exposure, higher peak plasma levels, and longer mean residence time can be achieved.

Particularly preferred are compositions comprising paclitaxel and dodecyl 2-(N,N-dimethylamino) propionate (DDAIP) in
30   free base or salt form.

The solubility and absorption of small molecule drug substances classified as BCS 2 and BCS 4 compounds, are particularly enhanced by dodecyl 2-(N,N-dimethylamino) propionate in free base or salt form. Particularly preferred are the BCS Class 2 compounds,
35   lansoprazole, haloperidol and sulfasalazine, the BCS Class 3

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compounds, atenolol and glucosamine; and the BCS Class 4 compounds, furosemide and chlorothiazide.

Preferred routes of administration are oral and subcutaneous.

5   **Brief Description of Drawings**

FIGURE 1 is a graphical representation of paclitaxel concentrations in rat plasma samples after oral (PO) dosing (5 mg/kg); data points represent mean values and error bars represent standard errors of the mean values.

10   FIGURE 2 is a graphical representation of paclitaxel concentrations in rat plasma samples after subcutaneous (SC) dosing (5 mg/kg); data points represent mean values and error bars represent standard errors of the mean values.

FIGURE 3 is another graphical representation of
15   paclitaxel concentrations in rat plasma samples after oral (PO) dosing (5 mg/kg); data points represent mean values and error bars represent standard errors of the mean values.

FIGURE 4 is a graphical representation of lansoprazole and DDAIP effects on gastric emptying in mice.

20   FIGURE 5 is a graphical representation of pharmacokinetic profile of lansoprazole in dog plasma samples after oral administration with and without DDAIP.

Detailed Description of Preferred Embodiments

As used herein, the term "small molecule therapeutic"
25   denotes a low molecular weight organic compound which is not a polymer but binds with relatively high affinity to a biopolymer such as a protein, a nucleic acid, or polysaccharide and also alters the activity or function of the biopolymer. The upper molecular weight limit for a small molecule therapeutic is about 1000 Daltons which
30   allows for diffusion across all membranes so that intracellular sites of action can be reached. Very small oligomers are also considered small molecules, e.g., dinucleotides, disaccharides, and the like. Illustrative are paclitaxel, DHA-paclitaxel, mesalamine (Pentasa®), motexafin gadolinium, temozolomide, erlotinib (Tarceva®),
35   cinacalcet (Sensipar®), safinamide, simvastatin (Zocor®), pravastatin

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(Pravachol®), sildenafil, peptide mimetics, the siRNAs, and the like.

Taxanes are diterpenes utilized in cancer chemotherapy. Particularly well suited for purposes of the present invention are paclitaxel, docetaxel, tesetaxel, and mixture thereof.

Also suited for purposes of the present invention are small molecule therapeutic compounds that are potent and pharmaceutically relevant but usually poorly soluble or insoluble compounds. A Biopharmaceutics Classification System (BCS) is a guide provided by the U.S. Food and Drug Administration for predicting the intestinal drug absorption. The system correlates *in vitro* drug product dissolution and *in vivo* bioavailability based on recognition that drug dissolution and gastrointestinal permeability are fundamental parameters controlling rate and extent of drug absorption. Four drug classes are defined in an article by Amidon G.L, et al., "*A theoretical basis for a biopharmaceutic drug classification: the correlation of* in vitro *product dissolution and* in vivo *bioavailability.*" Pharm. Res.,12(3), 413-20 (1995).

According to the Biopharmaceutics Classification System, drug substances are classified as follows:

Class 1 - High permeability, High solubility drugs. Those compounds are well absorbed and their absorption rate is usually higher than excretion. An example compound is metoprolol.

Class 2 - High permeability, Low solubility drugs. The bioavailability of those products is limited by their solvation rate. A correlation between the *in vivo* bioavailability and the *in vitro* solvation can be found. Example compounds are lansoprazole, haloperidol, sulfasalazine, and glibenclamide.

Class 3 - Low permeability, High solubility drugs. The, absorption is limited by the permeation rate but the drug is solvated very fast. Example compounds are atenolol, glucosamine (or salts thereof), and cimetidine.

Class 4 - Low permeability, Low solubility drugs. Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is

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expected. Example compounds are furosemide, chlorothiazide, and
hydrochlorothiazide.

The drugs are classified in BCS on the basis of the
following parameters: 1. solubility; 2. permeability; and 3.
5   dissolution. The class boundaries for solubility are based on the
highest dose strength of an immediate release product. A drug is
considered highly soluble when the highest dose strength is soluble
in 250 milliliters (ml) or less of aqueous media over the pH range
of 1 to 7.5. The class boundaries for permeability are based
10   indirectly on the extent of absorption of a drug substance in humans
and directly on the measurement of rates of mass transfer across
human intestinal membrane. Alternative non-human systems capable of
predicting the drug absorption in humans can be used (such as *in
vitro* culture methods). A drug substance is considered highly
15   permeable when the extent of absorption in humans is determined to
be 90% or more of the administered dose based on a mass-balance
determination or in comparison to an intravenous dose. The class
boundaries for dissolution for an immediate release product to be
considered rapidly dissolving is when no less than 85% of the
20   labeled amount of the drug substance dissolves within 30 minutes
using a USP Dissolution Apparatus 1 at 100 RPM or Apparatus 2 at 50
RPM in a volume of 900ml or less in a media of 0.1N HCl or simulated
gastric fluid or pH 4.5 buffer and pH 6.8 buffer or simulated
intestinal fluid.
25   Class 2-4 compounds are particularly well suited for
compositions embodying this invention. Preferred are small molecule
therapeutic compounds appearing in the *WHO List of Essential Drugs,*
16th Ed., revised March 2010. Particularly preferred small molecule
therapeutic compounds are lansoprazole, haloperidol, and
30   sulfasalazine in Class 2; atenolol, and glucosamine in Class 3; and
furosemide and chlorothiazide in Class 4.

The alkyl N,N-disubstituted amino acetates suitable for
purposes of the present invention are represented by the formula:

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$$CH_3-(CH_2)_n-\overset{\overset{\displaystyle R_3}{\vert}}{\underset{\underset{\displaystyle R_4}{\vert}}{C}}-O-\overset{\overset{\displaystyle O}{\vert\vert}}{C}-\overset{\overset{\displaystyle H}{\vert}}{\underset{\underset{\displaystyle R}{\vert}}{C}}-N\overset{\displaystyle R_1}{\underset{\displaystyle R_2}{}}$$
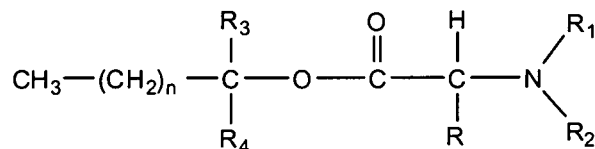
wherein n is an integer having a value in the range of about 4 to
about 18; R is a member of the group consisting of hydrogen, C_1 to C_7
5   alkyl, benzyl and phenyl; R_1 and R_2 are members of the group
consisting of hydrogen and C_1 to C_7 alkyl; R_3 and R_4 are members of
the group consisting of hydrogen, methyl and ethyl.

Preferred alkyl (N,N-disubstituted amino)-acetates are C_4
to C_{18} alkyl (N,N-disubstituted amino)-acetates and C_4 to C_{18} alkyl
10   (N,N-disubstituted amino)-propionates as well as pharmaceutically
acceptable salts and derivatives thereof. Exemplary specific alkyl-
2-(N,N-disubstituted amino)-acetates include

$$CH_3-(CH_2)_{10}-\overset{\overset{\displaystyle H}{\vert}}{\underset{\underset{\displaystyle H}{\vert}}{C}}-O-\overset{\overset{\displaystyle O}{\vert\vert}}{C}-\overset{\overset{\displaystyle H}{\vert}}{\underset{\underset{\displaystyle CH_3}{\vert}}{C}}-N\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{}}$$
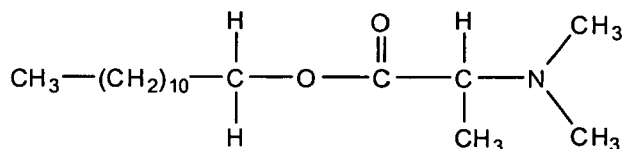
15

dodecyl 2-(dimethylamino)-propionate (DDAIP) and

$$CH_3-(CH_2)_{10}-\overset{\overset{\displaystyle H}{\vert}}{\underset{\underset{\displaystyle H}{\vert}}{C}}-O-\overset{\overset{\displaystyle O}{\vert\vert}}{C}-\overset{\overset{\displaystyle H}{\vert}}{\underset{\underset{\displaystyle H}{\vert}}{C}}-N\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{}}$$
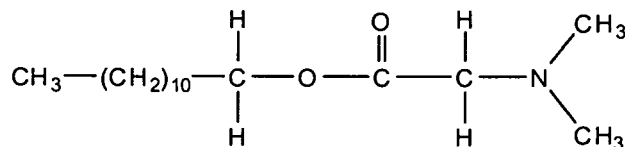
dodecyl 2-(N,N-dimethylamino)-acetate (DDAA)

20

Alkyl-2-(N,N-disubstituted amino) acetates are known.
For example, dodecyl 2-(N,N-dimethylamino)-propionate (DDAIP) is
available from Steroids, Ltd. (Chicago, Ill). In addition, alkyl-2-

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(N,N-disubstituted amino) alkanoates can be synthesized from more readily available compounds as described in U.S. Patent No. 4,980,378 to Wong et al., which is incorporated herein by reference to the extent that it is not inconsistent. As described therein,

5   alkyl-2-(N,N-disubstituted amino) acetates are readily prepared via a two-step synthesis. In the first step, long chain alkyl chloroacetates are prepared by reaction of the corresponding long chain alkanols with chloromethyl chloroformate or the like in the presence of an appropriate base such as triethylamine, typically in

10   suitable solvent such as chloroform. The reaction can be depicted as follows:

$$CH_3-(CH_2)_n-\underset{\underset{R_4}{|}}{\overset{\overset{R_3}{|}}{C}}-OH \ + \ Cl-\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{\overset{\overset{H}{|}}{C}}-Cl \ \longrightarrow$$

$$CH_3-(CH_2)_n-\underset{\underset{R_4}{|}}{\overset{\overset{R_3}{|}}{C}}-O-\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{\overset{\overset{H}{|}}{C}}-Cl$$
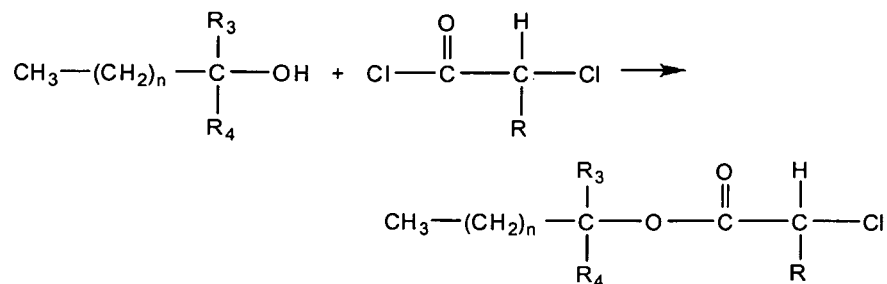
wherein n, R, R_1, R_2, R_3 and R_4 are defined as above. The reaction temperature may be selected from about 10 degrees Celsius to about 200 degrees Celsius or reflux, with room temperature being

15   preferred. The use of a solvent is optional. If a solvent is used, a wide variety of organic solvents may be selected. Choice of a base is likewise not critical. Preferred bases include tertiary amines such as triethylamine, pyridine and the like. Reaction time generally extends from about one hour to three days.

20   In the second step, the long chain alkyl haloacetate such as chloroacetate is condensed with an appropriate amine according to the scheme:

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$$CH_3\text{—}(CH_2)_n \text{—} \underset{\underset{R_4}{|}}{\overset{\overset{R_3}{|}}{C}} \text{—} O \text{—} \overset{\overset{O}{\|}}{C} \text{—} \underset{\underset{R}{|}}{\overset{\overset{H}{|}}{C}} \text{—} Cl \quad + \quad HNR_1R_2 \quad \longrightarrow$$

$$CH_3\text{—}(CH_2)_n \text{—} \underset{\underset{R_4}{|}}{\overset{\overset{R_3}{|}}{C}} \text{—} O \text{—} \overset{\overset{O}{\|}}{C} \text{—} \underset{\underset{R}{|}}{\overset{\overset{H}{|}}{C}} \text{—} NR_1R_2$$
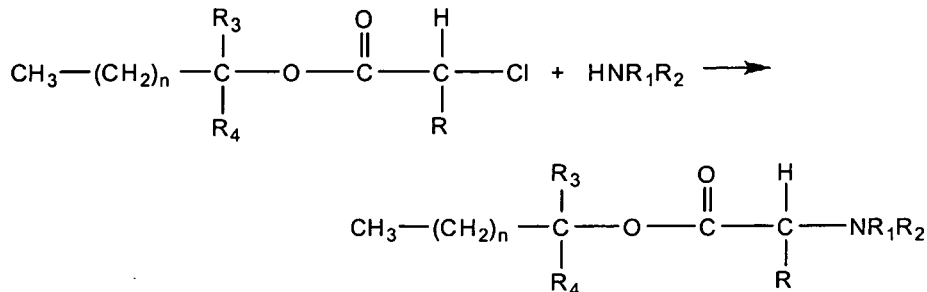
wherein n, R, R_1, R_2, R_3 and R_4 are defined as before. Excess amine
reactant is typically used as the base and the reaction is
conveniently conducted in a suitable solvent such as ether. This
second step is preferably run at room temperature, although

5   temperature may vary. Reaction time usually varies from about one
hour to several days. Conventional purification techniques can be
applied to ready the resulting ester for use in a pharmaceutical
composition.

The free base forms of the foregoing compounds are

10   liquids at ambient temperature. The salt forms, on the other hand,
are solids.For administration to a patient, both forms can be
combined with the small molecule therapeutic in a physiologically
acceptable carrier such as water or water-solvent admixture
depending upon the solubility of the small molecule therapeutic. A

15   pharmacologically acceptable carrier for the active ingredient and
the alkyl N,N-disubstituted amino acetate can be a liquid or a
solid. The choice of the particular carrier is dictated usually by
the active ingredient. The term "pharmaceutically acceptable
carrier" is art-recognized and refers to a pharmaceutically-

20   acceptable material, composition or vehicle, such as a liquid or
solid filler, diluent, excipient, solvent or encapsulating material,
involved in carrying or transporting the active ingredient from one,
organ, or portion of the body, to another organ, or portion of the
body. Each carrier must be "acceptable" in the sense of being

25   compatible with the active ingredient and not injurious to the
patient. Some examples of materials which may serve as
pharmaceutically acceptable carriers include: (1) sugars, such as
lactose, glucose and sucrose; (2) starches, such as corn starch and

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potato starch; (3) cellulose, and its derivatives, such as sodium
carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4)
powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8)
excipients, such as cocoa butter and suppository waxes; (9) oils,

5   such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive
oil, corn oil and soybean oil; (10) glycols, such as propylene
glycol; (11) polyols, such as glycerin, sorbitol, mannitol and
polyethylene glycol; (12) esters, such as ethyl oleate and ethyl
laurate; (13) agar; (14) buffering agents, such as magnesium

10   hydroxide and aluminum hydroxide; (15) alginic acid; (16) pryogen-
free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl
alcohol; (20) phosphate buffer solutions; and (21) other non-toxic
compatible substances employed in pharmaceutical formulations.

              An illustrative water-solvent carrier for taxanes that

15   is physiologically acceptable is a water-polyethylene glycol (PEG)
admixture containing about 10 to about 20 percent (v/v) polyethylene
glycol 300 (PEG 300) or polyethylene glycol 400 (PEG 400).

              The amount of taxane administered to a patient can vary,
but usually is in the range of about 200 to 250 mg/m^2. In one

20   embodiment, paclitaxel (Taxol$^®$) was formulated in either 10%
polyethylene glycol 400 (PEG 400) in water, or in aqueous solutions
of DDAIP, or its hydrochloric salt, DDAIP·HCL (40%).

Example I

              Using Sprague Dawley rats as an animal model, the body

25   weights of the animals were measured prior to dosing to determine
the appropriate amount of test article to deliver. Animals were
dosed (5 mg/kg) by oral gavage (PO) or subcutaneously (SC) with the
test composition in the different formulations as a single bolus.
Then blood samples were taken via the lateral tail vein at 0.5, 1, ,

30   2, 4, 8 and 24 hours following the dose.

              Blood samples were collected into blood collection tubes
containing Na$_2$EDTA, placed on ice and within 30 minutes of sampling
the blood samples were centrifuged to obtain plasma. The plasma was
separated from the cellular component and placed in microcentrifuge

35   tubes and frozen, then stored at -80°C until processed for analysis

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by LC-MS/MS (liquid chromatography-mass spectrometry with peptide mass fingerprinting). Standard samples were created by adding known amounts of paclitaxel to blank rat plasma. Standard curves were created by analyzing the standard samples by LC-MS/MS and using the

5   resultant areas under the chromatographic peaks in conjunction with the known concentration of the samples.

The experimental samples were analyzed using the same method and the areas under the chromatographic peaks were used in conjunction with the standard curves to calculate the concentration

10   of paclitaxel in the samples. The peak plasma concentrations (C_{max}) of paclitaxel were increased 10-fold after oral dosing and 2-fold after subcutaneous dosing in DDAIP·HCL formulation as compared to the PEG formulation. Use of the DDAIP·HCL formulation resulted in longer absorption phases and later onset of T_{max} times when dosed

15   both orally and subcutaneously compared to the use of the PEG formulation.

The overall systemic exposure (AUC) and bioequivalence were increased with the DDAIP·HCL formulation as compared to when the PEG 400 formulation was used. After oral administration with

20   the DDAIP·HCL formulation, the overall systemic exposure of paclitaxel was increased approximately 75 times and after subcutaneous dosing approximately 20 times compared to the PEG formulations via the same administration routes. The mean residence time (MRT) increased to 9.8 hours after oral dosing and 11.5 hours

25   after subcutaneous dosing when the DDAIP·HCL formulation was used compared to the PEG 400 formulation (3.8 hours PO and 8.5 hours SC). Additionally, dosing with DDAIP·HCL, the hydrochloride salt of DDAIP, resulted in greater systemic exposure, higher peak plasma levels and longer MRT compared to DDAIP alone. The experimental

30   results are graphically presented in FIGURES 1 and 2.

It can be concluded from these results that the formulation DDAIP·HCL provides superior pharmacokinetic properties to paclitaxel compared to the polyethylene glycol (PEG 400) formulation. Additionally, the DDAIP·HCL formulation provided

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superior pharmacokinetic properties to paclitaxel compared to DDAIP alone.

Standard samples for PO delivery of paclitaxel (Taxol®) formulated in 10% PEG 400, DDAIP and 40% DDAIP·HCL were created by adding known amounts of paclitaxel to blank rat plasma. The Standard samples were analyzed by LC-MC/MS and the resultant areas under the chromatographic peaks were used to construct a standard curve. The results are shown in Tables I-III for the PO delivery.

Table I. Results of the LC-MS/MS Analysis of the Standard Samples.

Actual Conc.	Mean Area Ratio	First Injection	Second Injection	Mean Measured Conc.	Accuracy
0.5	0.00365	0.55	0.448	0.449	99.80
1	0.0061	1.045	1.274	1.1595	115.95
5	0.0215	4.475	4.565	4.52	90.40
10	0.0454	9.915	9.876	9.8955	98.96
25	0.1144	24.346	26.561	25.4535	101.81
50	0.2218	47.726	51.603	49.6645	99.33
75	0.33305	70.706	78.75	74.728	99.64
100	0.4797	102.494	113.091	107.7925	107.79

The best fit straight line by least squares linear regression is represented by the formula:

Area Ratio = 4.66E-3 (conc'n in ng/ml) - 2.19E-03

R^2 - 9.97 E-01

Table II. Results of the LC-MS/MS Analysis of the PO Samples.

Formula	Time (Hr.)	R-1	R-2	Mean	SEM
10% PEG400	0	0.232	0	0.1	0.1
	0.5	0.325	0.351	0.3	0.0
	1	0.48	0	0.0	0.0
	2	0	1.137	0.8	0.3
	4	0	0.369	0.2	0.2
	8	0	0.481	0.2	0.2
	24	0	0	0.0	0.0
DDAIP	0	0	0	0.0	0.0
	0.5	2.963	3.215	3.1	0.1
	1	3.32	3.092	3.2	0.1
	2	4.539	5.306	4.9	0.4
	4	2.679	2.376	2.5	0.2
	8	1.459	1.331	1.4	0.1
	24	0.487	0.556	0.5	0.0
40% DDAIP HCl	0	0	0	0.0	0.0
	0.5	1.401	1.159	1.3	0.1
	1	4.168	3.652	3.9	0.3
	2	5.169	4.872	5.0	0.1
	4	9.699	8.008	8.9	0.8
	8	6.009	5.124	5.6	0.4
	24	3.012	3.057	3.0	0.0

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Table III.   Derivation of Pharmacokinetic Parameters from the PO
Data.

Formulation	Parameter (units)	R-1	R-2	Mean	SEM
10% PEG400	C_{max} (ng/mL)	0.5	1.1	0.8	0.46
	T_{max} (hr.)	2	2	2.0	0.00
	AUC (ng* hr/mL)	0.9	7.8	4.4	4.85
	Mean Residence Time (MRT, hr.)	1.6	6.0	3.8	3.06
	$T1/2_{MRT}$ (hr.)	1.1	4.1	2.6	2.12
DDAIP	C_{max} (ng/mL)	4.5	5.3	4.9	0.54
	T_{max} (hr.)	2	2	2.0	0.00
	AUC (ng* hr/mL)	37.3	36.8	37.0	0.38
	Mean Residence Time (MRT, hr.)	6.9	7.1	7.0	0.10
	$T1/2_{MRT}$ (hr.)	4.8	4.9	4.9	0.07
40% DDAIP HCl	C_{max} (ng/mL)	9.7	8.0	8.9	1.20
	T_{max} (hr.)	4	4	4.0	0.00
	AUC (ng* hr/mL)	124.9	110.3	117.6	10.26
	Mean Residence Time (MRT, hr.)	9.6	10.1	9.8	0.35
	$T1/2_{MRT}$ (hr.)	6.6	7.0	6.8	0.24

Bioequivalence ($AUC_{DDAIP}/AUC_{10\% PEG}$)	39.7	4.7	22.2	24.71
Bioequivalence ($AUC_{40\% DDAIP\cdot HCL}/AUC_{10\% PEG}$)	132.8	41.2	73.5	83.87

$T_{1/2}$ MRT = 0.693 * MRT

        Standard samples for SC delivery of paclitaxel
formulated in 10% PEG 400 and 40% DDAIP·HCL were created by adding
known amounts of paclitaxel to blank rat plasma. The Standard
samples were analyzed by LC-MS/MS, and the resultant areas under the
chromatographic peaks were used to construct a standard curve. and'
in Table IV and VI for the SC delivery.

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Table IV.   Results of the LC-MS/MS analysis of the Standard Samples.

Actual Conc.	Mean Area Ratio	First Injection	Second Injection	Mean Measured Conc.	Accuracy
0.2	0.0008	N/A	0.211	0.211	105.50
0.5	0.00135	0.426	0.463	0.4445	88.90
1	0.00285	1.063	1.114	1.0885	108.85
5	0.01185	4.876	5.066	4.971	99.42
10	0.02335	9.705	10.103	9.904	99.04
25	0.0617	26.224	26.661	26.4425	105.77
50	0.1092	46.623	47.127	46.875	93.75
75	0.1765	75.029	76.672	75.8505	101.13
100	0.2335	101.111	99.734	100.4225	100.42

5   The best fit straight line by least squares linear
regression is represented by the formula:

Area Ratio = 2.32E-03 (conc'n in ng/ml) + 1.98 E-04

R^2 = 9.99E-01

Table V. Results of the LC-MS/MS Analysis of the Experimental SC
Samples.

Formula	Time (Hr.)	R-1	R-2	R-3	Mean	SEM
10% PEG 400	0	0	0	0	0.0	0.0
	0.5	10.913	12.249	12.774	11.6	0.7
	1	3.167	3.094	4.223	3.1	0.0
	2	1.667	1.829	1.942	1.7	0.1
	4	1.617	1.667	1.578	1.6	0.0
	8	2.763	1.882	2.062	2.3	0.4
	24	0.755	1.175	0.906	1.0	0.2
DDAIP	0	0	0	0	0.0	0.0
	0.5	13.017	11.983	10.804	12.5	0.5
	1	12.399	10.938	11.891	11.7	0.7
	2	17.564	22.256	20.427	19.9	2.3
	4	17.55	19.542	20.66	18.5	1.0
	8	23.776	25.873	25.143	24.8	1.0
	24	15.818	14.976	21.433	15.4	0.4

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Table VI.   Derivation of Pharmacokinetic Parameters from the SC Data

Formulation	Parameter (units)	R-1	R-2	R-3	Mean	SEM
10% PEG 400	C_{max} (ng/mL)	10.9	12.2	12.8	12.0	0.68
	T_{max} (hr.)	0.5	0.5	0.5	0.5	0.00
	AUC (ng* hr/mL)	48.9	44.4	45.1	46.1	1.70
	Mean Residence Time (MRT, hr.)	8.1	9.2	8.2	8.5	0.42
	$T1/2_{MRT}$ (hr.)	5.6	6.4	5.7	5.9	0.29
40% DDAIP HCl	C_{max} (ng/mL)	23.8	25.9	25.1	24.9	0.75
	T_{max} (hr.)	8	8	8	8.0	0.00
	AUC (ng* hr/mL)	459.1	484.7	529.8	491.2	25.32
	Mean Residence Time (MRT, hr.)	11.4	10.8	12.2	11.5	0.47
	$T1/2_{MRT}$ (hr.)	7.9	7.5	8.4	7.9	0.33

Bioequivalence ($AUC_{40\% DDAIP \cdot HCL}/AUC_{20\% PEG}$)	9.4	10.9	11.8	10.7	0.85

$T_{1/2MRT} = 0.693 * MRT$

5

       In another embodiment, paclitaxel (Taxol®) was formulated
in either 10% polyethylene glycol 300 (PEG 300) in water, or in
aqueous solution of DDAIP·HCL (40%). Rats were dosed (5 mg/kg) by
oral gavage (PO), as above, with the test composition in the
10   different formulations as a single bolus and blood plasma levels
were determined. A 30-fold increase in AUC was achieved with the
aqueous solution of DDAIP·HCL over that achieved with the PEG 300
formulation, with no inhibition of P-glycoprotein (P-gp) up to 10mM.
The results are graphically represented in Figure 3.

15   **EXAMPLE II**

       Two small molecule therapeutic compounds were selected
from each of BCS Class 2, BCS Class 3, and BCS Class 4 for oral
delivery (PO) to jugular vein cannulated (JVC) male Sprague Dawley
rats (200-250 gram weight). The BCS Class 2 compounds were
20   haloperidol and sulfasalazine. Haloperidol is an antipsychotic
butyrophenone sold under the brand name Haldol® and sufasalazine is
an anti-inflammatory sulfa drug derivative of mesalazine sold under

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the brand name Azulfidine®. The BCS Class 3 compounds were
atenolol, and glucosamine (in the salt form glucosamine sulfate).
Atenolol is in the class of beta blocker drugs and is sold under the
brand names Senormin® and Tenomin®. The BCS Class 4 compounds were

5   furosemide (Lasix®) and chlorothiazide (Diuril®), both of which are
diuretics.

The compounds from BCS Class 2, 3 and 4 were each
formulated at 5 mg/ml in a liquid carrier of either an aqueous
solution of polyethylene glycol 400 (20% PEG 400), or an aqueous

10 solution of DDAIP·HCL (20%). The BCS Class 2 compounds, haloperidol
and sulfasalazine, formed suspensions in either liquid vehicle. The
BCS Class 3 compounds, atenolol and glucosamine sulfate formed
suspensions in the PEG 400 vehicle and solutions in the water
vehicle. The BCS Class 4 compounds, furosemide and chlorothiazide

15 formed suspensions in the PEG400 vehicle and solutions in the water
vehicle.

Cohorts of three animals per group were placed in the
study. On day 1, animals from each group were dosed at 30 mg/kg (6
ml/kg) by oral gavage (PO). Animals were fed at the time of dosing.

20 Serial blood samples were collected at pre-dose, and after post-dose
intervals of 30 minutes, 1 hour, 2 hours and 4 hours. The blood
samples were collected into lithium heparin-coated tubes. At each
time point, 0.15 ml of blood was collected via left jugular vein
cannulae and processed for collection of plasma by centrifuging at

25 approximately 2,000 rpm for approximately 10 minutes. The cellular
fraction of the blood was discarded. Collection times and volume of
plasma samples were recorded and tabulated. Plasma samples were
transferred into clean tubes and snap frozen onto dry ice. Samples
were stored at -80 °C until ready for bio-analysis by LC/MS/MS. The

30 results are tabulated in Table VII. The drug concentration was
measured from supernatant after centrifugation of the dosing
solution

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Table VII.   Oral Formulations - Solubility and AUC

BCSCl	Compound 5 mg/ml	Aqueous Dosing solution (20%)	Drug Conc. mg/ml	Sol.* over PEG	AUC 0-24h **	Sol.*** H$_2$O mg/ml	Sol. Over H$_2$O
2	Haloperidol	PEG 400	1.43				1430
		DDAIP·HCL	1.73	---	1.3	0.001	1730
2	Sulfasalazine	PEG400	<0.01				0
		DDAIP·HCL	4.46	>446	24	0.010	446
3	Glucosamine	PEG 400	4.52				---
		DDAIP·HCL	4.42	---	2.5	551.000	---
3	Atenolol	PEG 400	2.74				---
		DDAIP·HCL	6.28	2.300	2.1	13.500	---
4	Furosemide	PEG 400	<0.01				0
		DDAIP·HCL	4.00	>400	9.1	0.006	667
4	Chlorothiazide	PEG 400	<0.01				0
		DDAIP·HCL	3.63	>363	18	0.300	12

Notes to Table VII.

    *Solubility improvement fold over PEG 400
    **AUC-improvement fold for hourly period
    ***Reported solubility from the literature
    ****Solubility improvement fold over water.
  *****Pharmacokinetic parameters were calculated
        with PK Solutions 2.0 software
        (Summit Research Services, Montrose, CO)

    The results show that the DDAIP·HCL improves the
solubility of the compounds when compared to water or PEG vehicle.
This improvement is also reflected in the enhanced blood levels of ,
drug in the rat plasma. In particular, the Class 2 and 4 compounds,
where solubility is a determining factor, displayed over a 400-fold
solubility improvement and over a 20-fold AUC improvement. The data
show that formulations with DDAIP·HCL significantly improve the oral
delivery of difficult-to-absorb small molecule therapeutic compounds
by improving their solubility and, hence, their absorption.

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EXAMPLE III

Male CD1 mice were used (Harlan, USA) in this study and weighed 20-24 grams at the time of use. A 1.5% aqueous methylcellulose solution was made overnight with continuous heating and stirring. To this, 50 mg Phenol Red was added to 100 ml of 1.5% aqueous methylcellulose. Mice were pre-treated with saline or 20% DDAIP free base (5 ml/kg) with and without lansoprazole (10 mg/kg) 15 minutes before challenge with Phenol Red at T_0 (150 µl/mouse). Ten and thirty minutes after Phenol Red challenge, mice were euthanized with isoflurane and the stomachs rapidly excised (clamping the pyloric and cardiac sphincters to avoid loss of contents). Stomachs were then cut into several pieces and placed in 15 ml tubes containing 2 ml water prior to processing for A_{558} nm measurements. Several mice were sacrificed immediately after gavage with dye to act as an indicator of maximum dye retrieval (75 µg dye was dosed to each mouse).

Data (n=3) for stomach emptying (i.e., the amount of dye remaining in the stomach) 10 and 30 minutes after challenge are shown in FIG. 4. Pre-treatment with DDAIP slowed stomach emptying compared to pre-treatment with saline at both time points. The same pattern was observed when lansoprazole was administered in either vehicle. Mice that were challenged with dye and immediately sacrificed had stomachs that contained virtually all the administered amount of dye (75 µg). This experiment shows that increased absorption is not due to faster gastric emptying so that, in addition to improvement in solubility, protection of API in stomach and/or increased absorption in the stomach and intestine are other likely mechanisms.

EXAMPLE IV

A total of nine male Beagle dogs (three groups of n = 3 with body weights ranging from 9.4 - 10.6 kg) were used from Bio-Quant's colony (originally sourced from Marshall Farms, North Rose, New York, USA) and fasted overnight prior to an intramuscular injection of pentagastrin (6 µg/kg at 0.03 ml/kg) one hour before treatment with lansoprazole (15 mg per animal). Pre-treatment blood

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samples were taken prior to intramuscular injection with
pentagastrin (-60 minutes) and treatment with lansoprazole (time 0).
Dogs were then treated with lansoprazole as detailed in Table VIII
below.

5

TABLE VIII: Experimental Grouping Table

Group (n = 3)	Pre-Treatment	Dose	Route	Regimen	Bleeds	Overnight Fasting
1,2.3	Pentagastrin	60 µg/kg at 0.03 ml/kg	I.M.	Single (-60')	Predose (-60')	Yes
	Treatment	**Dose per Dog**	**Route**	**Regimen**	**Bleeds**	**Overnight Fasting**
1	Lansoprazole powder in 1 gelatin capsule	15 mg	Oral gavage with Petfiller followed by 50 ml H$_2$O	1 capsule per dog	Pre-dose, 30 min, 1 hr, 2 hr. 4 hr, 8 hr, 24 hr. post-dosing	Yes
2	Lansoprazole powder in 1 gelatin capsule containing 0.625g of 100% DDAIP•base	15 mg		1 capsule per dog		
3	Lansoprazole powder in 5 gelatin capsules, each containing 0.625g of 100% DDAIP•base	15 mg		5 capsules per dog		

Formulations:

Group 1: Dosed with 15 mg lansoprazole powder in a single gelatin

10   capsule (size 00).

Group 2: 700 µl (0.625g) DDAIP•base was mixed with 15 mg of
             lansoprazole powder in a single gelatin capsule (size 00).

15   Group 3: 700 µl (0.625g) DDAIP•base was mixed with 3 mg of
             lansoprazole powder in *each of 5 gelatin capsules* (size
             00).

Blood Collection:

             At each time point shown in Table VIII above, 0.5 ml
20   whole blood samples were collected from the saphenous vein into
heparinized blood collection tubes. Following centrifugation at

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10,000 rpm at 4 °C for 10 minutes, plasma samples were collected and stored at -80 °C until analysis by LCMS-MS.

Results and Conclusion

FIGURE 5 shows the pharmacokinetic profiles after oral
5   treatment with lansoprazole in all groups. Table IX details
individual parameters, such as T_{max}, C_{max} and T½. In comparison to
treatment with lansoprazole powder alone, the addition of DDAIP
(0.625 g in 12 capsule or 3.125 g in a total of capsules) resulted
in higher C_{max}, longer T½ (Table IX) and significantly increased AUC
10   values. T_{max} occurred at 1 hour in all groups. Furthermore, AUC
values were also significantly different in both DDAIP-treated
groups.

This study illustrates that the pharmacokinetic profile
of orally-administered lansoprazole is significantly improved in
15   dogs by the addition of DDAIP to the formulation. In addition, the
group treated with 3.125 g DDAIP in five gelatin capsules exhibited
significantly improved pharmacokinetic properties when compared to
groups treated with control formulation or 0.625 g DDAIP in one
gelatin capsule. These improvements are representative of human
20   subjects' dosing since this experiment was performed at
physiological pH of the human stomach.

Table IX: Pharmacokinetic Properties in all Groups

Group	C_{max} (ng/ml)	T_{max} (hr.)	T½ (hr.)
1	260		0.61
2	369	1	1.78
3	445		1.78

25   The foregoing discussion and the examples are
illustrative, but are not to be taken as limiting. Still other
variants within the spirit and scope of this invention are possible
and will readily present themselves to those skilled in the art.

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Claims

     1. A composition which comprises a small molecule therapeutic and an alkyl N, N-disubstituted-amino acetate.

     2. The composition in accordance with claim 1 wherein the small molecule therapeutic is selected from the group consisting of a taxane, and a compound classified under the Biopharmaceutics Classification System (BCS) in at least one of Class 2, Class 3 or Class 4.

     3. The composition in accordance with claim 2 wherein the taxane is a member of the group consisting of paclitaxel, docetaxel, tesetaxel, and mixtures thereof.

     4. The composition in accordance with claim 2 wherein the compound is a member of BCS Class 2.

     5. The composition in accordance with claim 4 wherein the compound is selected from the group consisting of lansoprazole, haloperidol, sulfasalazine, and glibenclamide.

     6. The composition in accordance with claim 2 wherein the compound is a member of BCS Class 3.

     7. The composition in accordance with claim 6 wherein the compound is selected from the group consisting of atenolol, glucosamine or salt thereof, and cimetidine.

     8. The composition in accordance with claim 2 wherein the compound is a member of BCS Class 4.

     9. The composition in accordance with claim 8 wherein the compound is selected from the group consisting of furosemide, chlorothiazide, and hydrochlorothiazide.

     10. The composition in accordance with claim 1 further including a physiologically tolerable carrier.

     11. The composition in accordance with claim 1 wherein, the alkyl N,N-disubstituted-amino acetate is dodecyl 2-(N,N-dimethylamino) propionate.

     12. The composition in accordance with claim 1 wherein the alkyl N,N-disubstituted-amino acetate is dodecyl 2-(N,N-dimethylamino) propionate hydrochloride.

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13. The composition in accordance with claim 1 wherein the small molecule therapeutic is a taxane and the alkyl N,N-disubstituted amino acetate is dodecyl 2-(N,N-dimethylamino) propionate.

14. The composition in accordance with claim 1 wherein the small molecule therapeutic is a taxane and the alkyl N,N-disubstituted amino acetate is dodecyl 2-(N,N-dimethylamino) propionate hydrochloride.

15. The composition in accordance with claim 1 wherein the small molecule therapeutic is paclitaxel and the alkyl N,N-disubstituted amino acetate is dodecyl 2-(N,N-dimethylamino) propionate.

16. The composition in accordance with claim 1 wherein the small molecule therapeutic is a paclitaxel and the alkyl N,N-disubstituted amino acetate is dodecyl 2-(N,N-dimethylamino) propionate hydrochloride.

17. A composition which comprises a taxane and an alkyl N,N-disubstituted-amino acetate.

18. The composition in accordance with claim 17 wherein the taxane is a member of the group consisting of paclitaxel, docetaxel, tesetaxel, and mixtures thereof.

19. The composition in accordance with claim 17 wherein the alkyl N,N-disubstituted amino acetate is dodecyl 2-(N,N-dimethylamino) propionate.

20. The composition in accordance with claim 17 wherein the alkyl N,N-disubstituted amino acetate is dodecyl 2-(N,N-dimethylamino) propionate hydrochloride.

21. The composition in accordance with claim 17 wherein the taxane is paclitaxel and the alkyl N,N-disubstituted-amino acetate is dodecyl 2-(N,N-dimethylamino) propionate.

22. The composition in accordance with claim 17 wherein the taxane is paclitaxel and the alkyl N,N-disubstituted-amino acetate is dodecyl 2-(N,N-dimethylamino) propionate hydrochloride.

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    23.   The composition in accordance with claim 4 wherein
the alkyl N,N-disubstituted-amino acetate is dodecyl 2-(N,N-
dimethylamino) propionate.

    24.   The composition in accordance with claim 5 wherein
5   the alkyl N,N-disubstituted-amino acetate is dodecyl 2-(N,N-
dimethylamino) propionate.

    25.   The composition in accordance with claim 6 wherein
the alkyl N,N-disubstituted-amino acetate is dodecyl 2-(N,N-
dimethylamino) propionate hydrochloride.

10   26.   The composition in accordance with claim 7 wherein
the alkyl N,N-disubstituted-amino acetate is dodecyl 2-(N,N-
dimethylamino) propionate.

    27.   The composition in accordance with claim 8 wherein
the alkyl N,N-disubstituted-amino acetate is dodecyl 2-(N,N-
15 dimethylamino) propionate hydrochloride.

    28.   The composition in accordance with claim 7 wherein
the alkyl N,N-disubstituted-amino acetate is dodecyl 2-(N,N-
dimethylamino) propionate hydrochloride.

    29.   The composition in accordance with claim 9 wherein
20 the alkyl N,N-disubstituted-amino acetate is dodecyl 2-(N,N-
dimethylamino) propionate.

    30 The composition in accordance with claim 9 wherein
the alkyl N,N-disubstituted-amino acetate is dodecyl 2-(N,N-
dimethylamino) propionate hydrochloride.

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