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(54) Title: PHARMACEUTICAL COMPOSITIONS AND METHODS

(57) Abstract: Disclosed, inter alia, is a pharmaceutical composition in the form of a tablet comprising an effective amount of Compound A, a swelling polymer, a matrix polymer, a floating agent, and optionally further comprising a diluent, a binder, a glidant, and/or a lubricant. Also disclosed is a method of treating or preventing thromboembolic disorders comprising administering an effective amount of the composition to a patient in need thereof.

WO 2006/089215 A2

PHARMACEUTICAL COMPOSITIONS AND METHODS

The present invention relates to improved pharmaceutical compositions comprising 4-methyl-2-oxo-2H-1-benzopyran-7-yl-5-thio-β-D-xylopyranoside ("Compound A").

The invention also relates to methods of delivering Compound A to a patient suffering from a thromboembolic disorder, comprising administering a pharmaceutical composition of the invention. The invention also relates to methods of treating or preventing thromboembolic disorders comprising administering a pharmaceutical composition of the invention.

Article I. Background of the Invention

Many medical problems relate to thromboses. For example, atrial fibrillation (AF), myocardial infarction (MI), heart failure, surgery (especially major orthopedic surgery, including knee or hip replacement surgery), valvular heart disease, coronary artery disease, peripheral arterial occlusive disease, cerebrovascular disease, various cancers, and diabetes are associated with thrombogenesis and/or embolism, which can result in stroke or myocardial infarction.

In particular, patients undergoing major orthopedic surgery such as total hip arthroplasty (THA) have a high risk of developing thromboembolic complications in the immediate post-operative period. In addition, atrial fibrillation is a common cardiac arrhythmia, and stroke is its most devastating complication.

Most ischemic strokes associated with atrial fibrillation are probably due to embolism of stasis-associated thrombi forming in the left atrium and particularly its appendage. See, e.g., Fuster, V. et al., 1997. Hemostasis, thrombosis, fibrinolysis, and cardiovascular disease. Heart Disease, Braunwald E 1809-1842. Philadelphia, PA: WB Saunders Company. Similarly, thrombosis within the venous system is mostly related to blood stasis and endothelial damage, leading to activation of the clotting system.

As thromboses consist of platelets, fibrin (and often erythrocytes), various approaches have been taken for the prevention and/or treatment of thromboses, including the use of antiplatelet drugs, anticoagulant drugs, and thrombolytic agents. See A.D. Blann et al., BMJ Vol. 325, Oct 5, 2002, 762-765.

Anticoagulants are designed to inhibit or antagonize one or more aspects of the coagulation cascade, in order to ultimately inhibit the formation of fibrin. These effects may be achieved by targeting thrombin, which acts on fibrinogen and factor XIII to form fibrin and crosslinked fibrin polymer, respectively. For example, an anticoagulant may be designed to limit functional prothrombin synthesis, attenuate thrombin generation, or inhibit formed thrombin. For example, warfarin inhibits the synthesis of factors dependent on vitamin K, i.e.,

prothrombin, factors VII, IX and X, protein C, and protein S. Heparin binds to antithrombin III thereby inactivating thrombin IIa, factor IXa, and factor Xa (unfractionated heparin having action against XIIa, XIa, IXa, VIIa and thrombin; low molecular weight heparin (LMWH) having action primarily against Xa). Direct thrombin inhibitors like melagatran, argatroban, and hirudin bind directly in the thrombin active site and thereby inhibit its formation.

One thrombin inhibitor that is present endogenously in the circulation is Heparin Cofactor II ("HCII"). HCII is Serpin (serine protease inhibitor) activated by glycosaminoglycans (GAGs), including heparin, heparin sulfate, and dermatan sulfate. It has been reported that HCII is capable of inhibiting both fibrin-bound and clot-bound thrombin. See J. A. Huntington et al., TRENDS in Pharmacological Sciences, Vol 24, No 11, Nov 2003 589-595; G. Mascellani et al., Thrombosis Research. 84(1): 21-32, Oct 1, 1996.

Available anti-thrombotic therapies for stroke prevention in AF include aspirin and warfarin. Anti-thrombotic therapy for DVT prophylaxis includes primarily LMWH, with some usage of warfarin. Post-MI patients have been treated primarily with aspirin, and also with clopidogrel, ticlopidine, LMWH and warfarin. See, e.g., R.G. Hart et al., Atrial Fibrillation and Stroke, Stroke 2001; 32:803-808 2001; P. Petersen et al., Ximelagatran Versus Warfarin for Stroke Prevention in Patients with Nonvalvular Atrial Fibrillation, Jnl of the Amer College of Cardiology, Vol 41, No. 9, 1445-1451, 2003; R.D. Hull et al., Extended Out-of-Hospital Low-Molecular-Weight Heparin Prophylaxis against Deep Venous Thrombosis In Patients after Elective Hip Arthoplasty: A Systematic Review, Ann Intern Med 2001; 135:858-869 2001; and the Physician's Desk Reference.

Additional background relating to antithrombotic prophylaxis, including in patients undergoing orthopedic surgery and for the prevention of stroke in chronic atrial fibrillation is provided by:

Article II. Agnelli G, Sonaglia F. Prevention of venous thromboembolism in high risk patients.. Haematologica, 1997;82:496-502;

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Hirsh J, Dalen JE, Guyatt G. The Sixth (2001) ACCP Guidelines for Antithrombotic Therapy for Prevention and Treatment of Thrombosis. Chest, 2001;119:1S-2S;

Hull, R.D. et al., Extended Out-of-Hospital Low-Molecular-Weight Heparin Prophylaxis against Deep Venous Thrombosis In Patients after Elective Hip Arthoplasty: A Systematic Review, Ann Intern Med 2001; 135:858-869 2001;

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Leclerc JR, Gent M, Hirsh J, ET AL. The incidence of venographic venous thromboembolism during and after prophylaxis with enoxaparin: A multi-institutional cohort study in patients who underwent hip or knee arthroplasty. Arch Intern Med, 1998;158:873-8;

Petersen P, Godtfredsen J, Boysen G, Andersen ED, Andersen B. Placebo-controlled, randomised trail of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation - The Copenhagen AFASAF Study. The Lancet. 1989;1:175-179;

Physician's Desk Reference;

Planes A, Vochelle N, Darmon J-Y, et al. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomized comparison of enoxaparin versus placebo. Lancet, 1996;348:224-8;

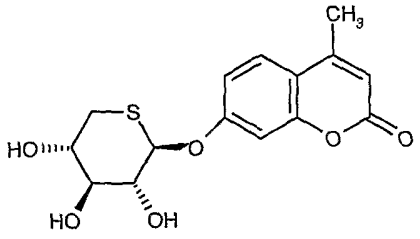
Planes A, Samama MM, Lensing AWA, et al. Prevention of deep vein thrombosis after hip replacement. Comparison between two low-molecular-weight heparins, tinzaparin and enoxaparin. Thromb Haemost, 1999;81:22-5;

Robinson KS, Anderson DR, Gross M, ET AL. Ultrasonic screening before hospital discharge for deep vein thrombosis after arthroplasty. Ann Intern Med, 1997;127:439-45;

Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study. Circulation. 1991;84:527.

Orally active β-D-thioxylosides have been proposed as anticoagulants. See Millet J, Theveniaux J, Brown NL. The Venous Antithrombotic Effect of LF 1351 in the rat following oral administration. Thromb & Haemost 1992;67:176-179; Millet J, Theveniaux J, Brown NL. The Venous Antithrombotic profile of Naroparcil in the rabbit. Thromb & Haemost 1994;72:874-879; Bellamy F, Horton D, Millet J, Picart F, Samreth S, Chazan JB. Glycosylated derivatives of benzophenone, benzhydrol, and benzhydril as potential venous antithrombotic agents. J Med Chem 1993;36:898-903; Masson PJ, Coup D, Millet J, Brown NL. The effect of the b-D-Xyloside Naroparcil on circulating plasma glycosaminoglycans. J Biol Chem 1995;270:2662-2668; Lohmander S, Madsen K, Hinek A. Secretion of proteoglycans by chondrocytes. Archives of Biochemistry and Biophysics 1979;192:148-157; Masson P, Theveniaux J, Coup D,Grégoire T, Vaillot M, Dupouy D, Sié P, Boneu B, Millet J. Further studies on the mechanism for the antithrombotic effects of naroparcil, an orally active thioxyloside compound. Thromb & Haemost 1999;81:945-950; Martin NB, Masson P, Sepulchre C, Theveniaux J, Millet J, Bellamy F. Pharmacologic and biochemical profiles of new venous antithrombotic b-D-Xyloside derivatives: Potential antiathero/thrombotic drugs. Seminars in Thrombosis and Hemostasis 1996;22:247-253. See also WO 2004/043983, WO2002/092614 and WO2001/036437 (each V. Barberousse et al.)

The compound, 4-methyl-2-oxo-2H-1-benzopyran-7-yl-5-thio-β-D-xylopyranoside is depicted by the following chemical structure:



and is alternatively referred to herein as "Compound A". Compound A and its preparation is disclosed in U.S. Patent No. 5,169,838, issued to Samreth et al. on Dec 8, 1992. This patent discloses, inter alia, the use of the disclosed benzopyranone-β-D-thioxyloside compounds in the treatment of venous and arterial thrombosis, and treatment and prevention of diseases associated with circulatory disorders.

Without intending to be limited or bound by theory, Compound A is believed to induce glycosaminoglycan (GAG) production and subsequent elevation of anti-IIa activity via heparin cofactor II (HCII), leading to prevention of thrombosis. Anti-IIa activity, expressed in dermatan sulfate units, may serve as a pharmacodynamic marker of the antithrombotic effect of Compound A. See, e.g., JA Huntington, Journal of Thrombosis & Haemostasis. 1(7):1535-49, Jul 2003, and Masson, PJ et al., The effect of the β-D-xyloside naroparcil on circulating plasma glycosaminoglycans, J. Biol Chem 1995; 270:2662-2668.

Compound A has exhibited pronounced oral efficacy in experimental animal models of venous and arterial thrombosis, and limited effects on coagulation parameters and bleeding times in animals. In animal thrombosis models using Compound A, anti-thrombotic activity has been correlated with anti-thrombin (anti-IIa) activity expressed in dermatan sulfate units. Based on preclinical studies in the rabbit and rat, it is estimated that steady state, anti-IIa trough levels of ≥0.5 μg (e.g., 0.5 to about 6, 0.5 to about 4, 0.5 to 3.5, 0.5 to about 2 μg) dermatan sulfate units/mL plasma may correlate with significant benefits in treating and/or preventing thromboembolism. For example, ID_{50}s in these animal models (e.g., 0.75-2.2μg/mL) provide a target anti-IIa activity for clinical development. It is especially predicted that an anti-IIa trough level of ≥1 ug, more especially ≥2 ug, dermatan sulfate units/mL plasma, may correlate with significant benefits in treating and/or preventing thromboembolism. Pharmacokinetic (PK)-pharmacodynamic (PD) modeling suggests that mean trough concentrations of at least about 0.25-0.4 (including 0.25-0.4, at least about 0.25, and at least about 0.4) ug Compound A/mL plasma may produce an anti-IIa trough level of ≥1 ug dermatan sulfate units/mL plasma, and that mean trough concentrations of at least about 0.5-0.8 (including 0.5-0.8, at least about 0.5, and at least about 0.8) ug Compound A/mL plasma may produce an anti-IIa trough level of ≥2 ug dermatan sulfate units/mL plasma.

The specific antithrombotic activity of Compound A, which is similar to the selective inhibition of thrombin observed with dermatan sulfate that also activates HCII (see Ofosu FA, Modi GJ, Smith LM, et al. Heparin sulphate and dermatan sulphate inhibit the generation of thrombin activity in plasma by complementary pathways. Blood, 1984;64:742-7) may result in a reduced bleeding risk compared with vitamin A antagonists, unfractionated, low molecular

weight heparins (LMWHs) and direct thrombin inhibitors, while providing anti-thrombotic efficacy.

Therefore, Compound A may be useful in the treatment and/or prevention of thromboembolism, e.g., associated with prothrombotic or hypercoagulable states. Accordingly, Compound A may be useful in the treatment and/or prevention of venous thromboembolism (such as associated with orthopedic surgery, e.g., deep vein thromboses [DVT]), or thromboembolism/stroke associated with atrial fibrillation or other systemic embolic events.

In the prophylaxis or treatment of thromboses or hypercoagulability, it is desirable to achieve and maintain a substantially constant, therapeutically effective concentration of the compound (or its active metabolite) within the blood stream of the patient. Drug delivery systems are generally designed to provide such blood concentrations, delivering the drug at a particular rate taking into consideration the rate of drug clearance from the body.

For ease of patient use and compliance, it is often desirable to provide a dosage form which can maintain a controlled concentration of the active drug for an extended period of time. The use of modified release technology may allow for release of a drug at a substantially constant rate at a desired concentration into a patient's system for many hours. For example, if a modified release tablet possesses release properties and sufficient drug to maintain a desired drug concentration for twelve or more hours, that would desirably enable dosing twice daily, or less frequently each day. Modified release systems may provide other potential benefits.

It is also desirable to provide a therapeutic dose with minimum pill burden, in order to promote treatment compliance and ease of taking the medication. Preferably, an effective dose is provided with a single dosage unit at each dosing interval. Furthermore, it is desirable that oral dosage forms for single dosage unit administration are in a form that is easy to administer.

The present invention relates in part to the finding that Compound A has a relatively narrow absorption window, i.e., it is absorbed primarily in the upper gastro-intestinal (GI) tract (i.e., the stomach and upper small intestine or duodenum). Therefore, it may be desirable to provide a formulation which tends to increase residence time or release in the upper GI tract so as to potentially provide optimum absorption, exposure, bioavailability and/or efficacy of Compound A.

It is also desirable to provide a pharmaceutical formulation comprising Compound A, which is capable of providing steady-state, therapeutically effective and safe levels of Compound A over extended periods of time after oral administration, e.g., for at least about 8, 10 or 12 hours, in an oral dosage form which is convenient for patients (e.g., permitting

twice or less frequent daily dosing). In particular, it is desirable to provide a pharmaceutical formulation comprising Compound A, which is capable of providing an effective anti-IIa steady state level over an extended period of time after oral administration, e.g., at least about 8, 10 or 12 hours. More particularly, it is desirable to provide a pharmaceutical formulation comprising Compound A, which is capable of providing a steady state dermatan sulphate concentration of at least 0.5, 1, or 2 dermatan sulphate units µg/mL plasma, and/or a steady state Compound A concentration of at least about 0.25-0.4, or 0.5-0.8 µg/mL plasma, over an extended period after oral administration (e.g., at least about 8, 10 or 12 hours). It is desirable to provide a formulation which is capable of providing a steady state, mean drug concentration of at least about 0.25 (also at least about 0.4, 0.5 and/or 0.8) µg Compound A/mL plasma over a period of at least 8 hours, moreso at least 10 hours, especially at least 12 hours following oral administration.

It is also desirable to provide a pharmaceutical composition of Compound A which can be dosed with a minimal number of dosage units per day in order to achieve a daily clinical dose. For example, administration of a clinical dose via, e.g., one tablet twice a day, may promote treatment compliance and ease of taking the medication to the patient population.

However, the properties of Compound A make it difficult to achieve a formulation having one or more of such properties. It has been found that Compound A has a short half life of about 2-3 hours. The narrow absorption window of Compound A imparts additional constraints. Compound A also has low aqueous solubility, and is less likely to be absorbed through the GI tract than more soluble drugs with a wider absorption window. Additionally, the pharmacodynamic effects of Compound A lags the pharmacokinetic properties by several hours.

Furthermore, oral dosage forms having higher drug concentrations tend to be more difficult to formulate in a manner which provides both ease of use and desired therapeutic properties.

The present inventors have now found a modified release tablet formulation comprising Compound A, which may be capable of providing steady-state, therapeutically effective and safe levels of Compound A over extended periods of time after oral administration, e.g., for at least about 8, 10 or 12 hours, in an oral dosage form which tends to be convenient for patients (e.g., permitting twice or less frequent daily dosing). The formulation is believed to increase residence time or release in the upper GI tract, to provide improved absorption, exposure, bioavailability, and/or efficacy.

In one aspect, the present invention provides tablets comprising Compound A, which can be administered as a single tablet to provide an effective dose of Compound A, for

example, with twice daily dosing. Single tablet dosing may promote treatment compliance and ease of taking the medication.

Article III. Summary of the Invention

In one aspect, the present invention relates to a pharmaceutical tablet comprising a therapeutically effective amount of Compound A, a swelling polymer, a matrix polymer, and a floating agent, and optionally further comprising a diluent, a binder, a glidant and/or a lubricant. In some embodiments, the the swelling polymer is sodium carboxy methyl cellulose, the matrix polymer is hypromellose, the floating agent is Na bicarbonate, the optional diluent is microcrystalline cellulose, the optional binder is povidone, the optional glidant is colloidal silica, and the optional lubricant is magnesium stearate.

In another aspect, the present invention relates to methods of preparing such tablets.

In yet another aspect, the invention relates to a pharmaceutical tablet comprising an effective amount of Compound A, which is characterized by one or more of a defined steady state anti-IIa activity, steady state Compound A level, and/or dissolution profile.

The invention also relates to a method of treating or preventing thromboembolic disorders comprising administering an effective amount of a composition of the invention to a patient in need thereof.

In other aspects the invention relates to methods of providing a defined steady state anti-II level and/or steady state Compound A level comprising administering a composition of the invention to a patient in need thereof.

Other aspects of the invention will be apparent to those skilled in the art.

Article IV. Brief Description of the Figures

Figure 1 represents the chemical structure of Compound A and a labelled standard.

Figure 2 represents positive ion spray mass spectra of Compound A and its labelled standard.

Figure 3 represents product ion mass spectra of Compound A and its labelled standard.

Figure 4 represents a typical MRM chromatogram of drug-free human plasma.

Figure 5 represents a typical chromatogram of human plasma samples containing 5.00 ng/mL Compound A.

Figure 6 represents a typical calibration plot for Compound A in human plasma.

Figure 7 represents a dermatan sulphate assay standard curve.

Figure 8 represents a plot of the median Compound A plasma concentration vs time profiles for 3 modified release tablets of the present invention, following single dosing.

Figure 9 represents a plot of the mean (+/- standard errors) for Anti-IIa activity via HCII vs time profiles for 3 modified release tablets of the present invention, following single dosing and following repeat dosing.

Figure 10 represents a plot of the median Compound A plasma concentration vs time profiles for 3 modified release tablets of the present invention, following repeat dosing.

Figure 11 represents the dissolution profile for 3 modified release Compound A formulations of the present invention.

Detailed Description of the Invention

The present invention relates to modified release formulations comprising Compound A, in the form of tablets. The modified release formulations of the invention comprise an effective amount of Compound A, a swelling polymer, a matrix polymer and a floating agent, and preferably further comprise a diluent, a binder, a glidant, and a lubricant (one or more of each such components may be utilized).

Tablets of the present invention suitably comprise from about 5 to about 60% of Compound A, based on the total weight of the tablet. (Unless otherwise stated, % compositions herein are based on the total weight of the composition, in uncoated form. Also, unless otherwise stated, the term "about" includes the number expressly set forth, e.g., "about 1" includes 1.) In some embodiments, the composition comprises from about 30 to about 50% Compound A. In some embodiments, the composition comprises from about 35 to about 50%, e.g., about 37 to about 48%, Compound A. In other embodiments, the composition comprises from about 30 to about 45%, e.g., from about 30 to about 40%, of Compound A. In some embodiments, tablets of the invention comprise from about 125, to about 1000 mg or to about 500 mg (e.g., about 250mg to about 500 mg), Compound A. For example, tablets of the invention may comprise about 125, 150, 200, 250, 300, 375, 400, or 500 mg Compound A, more particularly about 250, 375, or 500 mg Compound A.

The swelling polymer is capable of swelling to greater than its original volume when in contact with aqueous fluid, such as gastric fluid. Suitable swelling polymers include sodium carboxymethylcellulose. Compositions of the invention suitably comprise from about 5 to about 30% swelling polymer. In some embodiments the composition comprises about 5 to about 25% swelling polymer. In some embodiments, the composition comprises about 5 to about 15%, e.g., about 8 to about 13%, swelling polymer. In other embodiments, the composition comprises about 10 to about 25% swelling polymer.

In some embodiments the swelling polymer is sodium carboxymethyl cellulose having a degree of substitution of from 0.65-0.95 (e.g., 0.65-0.90, 0.65-0.95, or 0.80-0.95) and a sodium content of from 7.0-9.2 (e.g., 7.0-8.8, 7.0-9.2, 8.1-9.2), such as commercially available from Aqualon Div., Hercules Inc., Wilmington, Delaware ("Aqualon") (e.g., type 7, 7S, 7O, 9 or 12).

In some embodiments the swelling polymer is sodium carboxymethyl cellulose having a degree of substitution of from 0.80-0.95 (e.g., about 0.9) and a viscosity of 2,500-6,000 (e.g., 2,500-4,500) cps (1 wt% aqueous solution, Brookfield LVF viscometer, spindle no. 4, speed 30 rpm, 25C), such as commercially available from Aqualon. In some embodiments such a polymer has a sodium content of from 8.1 to 9.2.

In other embodiments the swelling polymer is sodium carboxymethyl cellulose having a degree of substitution of from 0.65 to 0.95 (e.g., about 0.7) and a viscosity of 1,000 to 2,800 cps (1 wt% aqueous solution, Brookfield LVF viscometer, spindle no. 3, speed 30 rpm, 25C), such as commercially available from Aqualon. In some embodiments such a polymer has a sodium content of from 7.0 to 9.2.

In some embodiments, the swelling polymer is sodium carboxymethylcellulose grade 9H4F, commercially available from Aqualon. In other embodiments, the swelling polymer is sodium carboxymethylcellulose grade 7H3SF, also available from Aqualon. In other embodiments, the swelling polymer is carboxymethylcellulose Walocel® CRT, including Walocel 30000 and 40000, available from Wolff Cellulosics GmbH & Co KG, Walsrode, Germany.

In some embodiments, the carboxy methyl cellulose has an average particle size which is less than 325 mesh, as determined by sieve analysis through standard U.S. sieves. In some embodiments the carboxy methyl cellulose has a fine particle size, e.g., the following particle size characteristics: a maximum of 0.1% remains on a U.S. 30 mesh sieve; a maximum of 0.5% remains on a U.S. 60 and above mesh sieve; and a minimum of 80.0% passes through a U.S. 200 mesh sieve.

The matrix polymer interacts with the swelling polymer to provide a matrix to the tablet, contribute to tablet integrity, and control the compound A release rate. Suitable matrix

polymers include hydrophilic water soluble polymers such as hydroxypropylmethyl cellulose, hydroxypropyl ethyl cellulose, hydroxypropyl cellulose, ethyl cellulose, polyethylene glycols, starches, and alginates. Compositions of the invention suitably comprise from about 0.1 to about 7%, e.g., from about 0.1 to about 5%, matrix polymer. In some embodiments the composition comprises from about 0.1 to about 2% matrix polymer. In other embodiments the composition comprises about 2 to about 5% matrix polymer.

In some embodiments, the matrix polymer is hydroxypropyl methyl cellulose ("HPMC"). For example, the HPMC controlled release Methocel® series available from Dow Chemical Company, Midland MI (e.g., Methocel® K100LV, K4M, K15M, K100M, E4M or E10M Premium may be used.

In some embodiments, the matrix polymer is hydroxypropyl methyl cellulose having a methoxyl content of about 19-24%, a hydroxypropoxyl content of about 7-12%, an apparent viscosity of about 80,000-120,000 cP (nominal value 100,000) by Ubbelhode, a maximum loss on drying of about 5%, and a particle size of about 99% minimum through No. 40 US standard sieve. In some embodiments, the matrix polymer is hydroxypropyl methyl cellulose Methocel K100M Premium, available from Colorcon, West Point PA and Dow Chemical Company.

In some embodiments, the weight ratio of the swelling polymer to matrix polymer is from about 95:25 to about 95:5, especially from 95:15 to about 95:5, more especially from about 95:15 to about 95:10.

The floating agent is suitably a material which promotes flotation of the tablet in the stomach. Floating agents may suitably be a substance which generates gas upon contact with gastric fluid. Suitable floating agents include bicarbonates such as sodium bicarbonate and potassium bicarbonate, carbonates such as calcium carbonate or sodium glycine carbonate, and sulfites such as sodium sulfite, bisulfite or metabisulfite. In some embodiments the floating agent is sodium bicarbonate. In other embodiments the floating agent is calcium carbonate. Compositions of the invention suitably comprise from about 5 to about 15% of the floating agent. In some embodiments the composition comprises about 9 to about 13% of the floating agent. In other embodiments the composition comprises about 8 to about 10% of the floating agent.

A diluent is suitably employed to increase the bulk of the tablet such that it is a practical size for compression and/or to provide bulk in a granulation process. Suitable diluents include microcrystalline cellulose, lactose, and calcium phosphate. In some embodiments the diluent is microcrystalline cellulose (e.g., commercially available from FMC Biopolymer, Philadelphia, PA). Compositions of the invention suitably comprise about 20 to about 40%, e.g., about 20 to about 35%, diluent, based on the total weight of the

composition. In some embodiments the composition comprises from about 22 to about 33% diluent. In other embodiments the composition comprises from about 25 to about 35% diluent.

A binder is suitably used to impart cohesive properties to the powdered components of the composition, to assist tablet integrity after compression and/or to control granule hardness and size so as to improve flow. In one aspect of the present invention a binder is used in the preparation of active granules which are in turn used to prepare tablets of the invention. Suitable binders include povidone and hydroxypropyl methyl cellulose (for example, the Methocel® E5LV, E15LV, A15LV or K3 Premium HPMC available from Dow Chemical Company). In some embodiments the binder is povidone (nonlimiting examples being povidone K30). Compositions of the invention suitably comprise from 0.1 to about 5% of the binder, based on the total weight of the composition. In some embodiments, the composition comprises from about 0.1 to about 3% or from about 1 to about 2% binder.

A glidant is suitably used to improve the flow properties of the powdery mixture during preparation of the tablet. Suitable glidants include colloidal silicon dioxide and talc. In some embodiments the glidant is colloidal silicon dioxide. Compositions of the invention suitably comprise from 0.1 to about 5% glidant, based on the total weight of the composition. In some embodiments the composition comprises from 0.1 to about 1% or about 2% glidant.

A lubricant is suitably used, e.g., to prevent adhesion, reduce friction, enhance ejection, and/or improve flow. Suitable lubricants include magnesium stearate, talc, stearic acid, and stearic acid salts. In some embodiments the lubricant is magnesium stearate. Compositions of the invention suitably comprise from about 0.1 to about 5% lubricant, based on the total weight of the composition. In some embodiments the composition comprises from 0.1 to about 1% lubricant.

Various swelling polymers, matrix polymers, floating agents, binders, glidants, and lubricants are described in Handbook of Pharmaceutical Excipients, 2nd Edition, Editors A. Wade and P.J. Weller, American Pharmaceutical Association, 1994; Handbook of Pharmaceutical Additives, M. and I. Ash, Gower, 1995; and Remington, The Science and Practice of Pharmacy, 20th Edition, Editor A. Gennaro et al., Lippincott Williams & Wilkins, 2000.

The tablets of the invention may optionally comprise a coloring agent, e.g., pigments, such as are known in the art. In some embodiments the composition comprises from about 0.1 to about 5% coloring agent. For example, from about 0.1 to about 5 or 6 parts by weight coloring agent per 100 parts by weight of the compositions described herein may be used.

The compositions of the invention are suitably prepared by, in one or more steps, combining the components, blending the components together until appropriately

homogeneous, and compressing the mixture into tablets. In some embodiments, the compositions are prepared using a wet granulation method, such as are well known in the art. See, e.g., Remington, The Science and Practice of Pharmacy, supra. For example, the compound A, a portion of the diluent, binder, and sufficient amounts of a granulating fluid such as water are combined, granulated, dried and milled to form granules. The granules are then combined with the remaining components and the mixture is compressed into tablets.

In some embodiments of a wet granulated tablet of the invention, the diluent is present in both the granules (i.e., intragranular) and in the compression mixture (i.e., extragranular). In some embodiments, both the intragranular and extragranular diluent is microcrystalline cellulose. In some embodiments, the intragranular diluent is Avicel® PH 102 and the extragranular diluent is Avicel® PH 200.

In one aspect, the present invention relates to a method of preparing a pharmaceutical tablet comprising Compound A, comprising:

a) forming a dry mixture comprising Compound A, a diluent, and a binder; b) wet granulating the dry mixture with a suitable granulating fluid; c) drying the wet granules to substantially remove the granulating fluid; d) forming a compression mixture comprising mixing the dried granules with a matrix polymer, a swelling polymer, a floating agent, and optionally a diluent, lubricant and/or glidant; e) compressing the mixture to form a tablet; and f) optionally coating the tablet.

The diluent, binder, matrix polymer, swelling polymer, floating agent, lubricant and glidant may be as described herein. In some embodiments the granulating fluid is water.

In some embodiments, the tablets are compressed to a hardness (crushing strength) of about 7 to about 32 kp, including but not limited to about 7 to about 17kp, about 16 to about 25 kp, and about 24 to about 32 kp. Harder tablets are generally better suited for coating processes. Hardness may be determined using methods known in the art, using for example a Schleuniger 2E hardness tester.

The tablets may also be characterized by their friability (e.g., Roche-type friabilator such as Van Kel or Erweka friabilator, at 25 rpm, 4 min). Preferably the tablets have a friability of $\leq$1.0% weight loss after 4 minutes at 25 rpm.

In some embodiments, the tablets are round. In other embodiments, the tablets are elongated, i.e., oblong (e.g., in the form of caplets). Caplets tend to promote ease of taking the medication and treatment compliance, and are particularly useful for dosage units containing higher active concentrations.

The uncoated tablets may be described as a matrix tablet, e.g., the components are generally uniformly dispersed throughout the tablet, rather than in layers.

The tablets of the present invention may be coated with a suitable coating such as are known in the art. Suitable coatings include hydrophilic, water soluble, non-enteric coatings. The coating is typically applied in an amount of from about 0.5 to about 4% (dry coating) of the tablet, based on the weight of the uncoated tablet. In some embodiments, the coating is applied so as to coat essentially all of the tablet.

In some embodiments, the tablet comprises, based on its uncoated weight, 21-49% diluent, 7-15% floating agent, 7-24% swelling polymer, 0.1-6% matrix polymer, and 23-57% Compound A. In some embodiments, such a tablet is prepared by wet granulation and comprises 1-5% intragranular diluent and 18-46% extragranular diluent. These tablets optionally comprise 0.1-2% binder, 0.1-2% (e.g., 0.1-1%) glidant, and/or 0.1-1% lubricant.

In some embodiments, the tablet comprises, based on its uncoated weight, 23-47% diluent, 7-14% floating agent, 7-23% swelling polymer, 0.1-6% matrix polymer, and 24-55% Compound A. In some embodiments, such a tablet is prepared by wet granulation and comprises 1-5% intragranular diluent and 20-45% extragranular diluent. These tablets optionally comprise 0.1-2% binder, 0.1-2% (e.g., 0.1-1%) glidant, and/or 0.1-1% lubricant.

In some embodiments, the tablet comprises, based on its uncoated weight, 24-45% diluent, 8-14% floating agent, 8-22% swelling polymer, 0.1-6% matrix polymer, and 26-53% Compound A. In some embodiments, such a tablet is prepared by wet granulation and comprises 2-5% intragranular diluent and 21-43% extragranular diluent. These tablets optionally comprise 0.1-2% binder, 0.1-1% glidant, and/or 0.1-1% lubricant.

In some embodiments, the tablet comprises, based on its uncoated weight, 21-42% diluent, 8-15% floating agent, 7-15% swelling polymer, 0.1-2% matrix polymer, and 31-57% Compound A. In some embodiments, such a tablet is prepared by wet granulation and comprises 2-5% intragranular diluent and 18-38% extragranular diluent. These tablets optionally comprise 1-2% binder, 0.1-2% (e.g., 0.1-1%) glidant, and/or 0.1-1% lubricant.

In some embodiments, the tablet comprises, based on its uncoated weight, 23-40% diluent, 8-14% floating agent, 7-15% swelling polymer, 1-2% matrix polymer, and 33-55% Compound A. In some embodiments, such a tablet is prepared by wet granulation and comprises 2-5% intragranular diluent and 20-36% extragranular diluent. These tablets optionally comprise 1-2% binder, 0.1-2% (e.g., 0.1-1%) glidant, and/or 0.1-1% lubricant.

In some embodiments, the tablet comprises, based on its uncoated weight, 24-38% diluent, 9-14% floating agent, 8-14% swelling polymer, 1-2% matrix polymer, and 35-52% Compound A. In some embodiments, such a tablet is prepared by wet granulation and comprises 2-5% intragranular diluent and 21-35% extragranular diluent. These tablets optionally comprise 1-2% binder, 0.1-1% glidant, and/or 0.1-1% lubricant.

Without intending to be bound or limited by theory, it is believed that the compositions of the present invention tend to be gastro-retentive, i.e., the tablets tend to be retained in the stomach such that a significant portion of the Compound A tends to be released in the stomach and/or upper duodenum, in either the fed or fasted state. Thus, absorption, exposure, bioavailability and/or efficacy tends to be improved. Gastro-retention may be determined by imaging methods such as are known in the art, e.g., by magnetic resonance imaging, or by x-ray analysis of barium-spiked formulations (e.g., barium sulfate). Gastro-retention is also suggested by flotation of the tablet during in vitro dissolution testing such as described herein (e.g., at a pH similar to the stomach in the fed state (pH 4.9), the tablets rise from the bottom toward the top of the vessel, generally within about 2-3 hours after test start). Gastro-retention may in some instances also be evidenced by extended Compound A T_{max} values relative to a desired control.

Preferred compositions of the invention can be characterized as providing one or more of the following properties:

a) a steady state anti-IIa activity level of at least 1 µg dermatan sulphate units/mL plasma over an extended period of time, e.g., at least about 8, 10 or 12 hours, after oral administration; and/or

b) a steady state Compound A level of at least about 0.25 or 0.4 (including 0.25-0.4) µg Compound A /mL plasma over an extended period of time, e.g., at least about 8, 10 or 12 hours, after oral administration; and/or

c) an in-vitro dissolution profile wherein:

from about 5 to about 65% of the Compound A is released after 2 hours;

from about 35 to about 85% of the Compound A is released after 4 hours; and

not less than about 75% of the Compound A is released after 8 hours;

e.g., wherein the dissolution is measured using a type 2 dissolution apparatus (paddle) under the following conditions: at 100 +/- 4rpm, at a temperature of 37+/- 0.5C, in 1L +/- 5 ml of 0.05M acetate buffer in 0.05M sodium dodecyl sulfate, pH 4.9 +/- 0.05, for at least 8 hours.

In some embodiments, not less than about 75% of Compound A is released after 6 hours.

In some such embodiments, the tablet comprises, based on its uncoated weight, 21-49% diluent, 7-15% floating agent, 7-24% swelling polymer, 0.1-6% matrix polymer, and 23-57% Compound A. In some embodiments, such a tablet is prepared by wet granulation and comprises 1-5% intragranular diluent and 18-46% extragranular diluent. These tablets optionally comprise 0.1-2% binder, 0.1-2% (e.g., 0.1-1%) glidant, and/or 0.1-1% lubricant. In some embodiments, the tablets have an average hardness of 7-17 kp. In other

embodiments, the tablets have an average hardness of 16-25 kp. In other embodiments, the tablets have an average hardness of 24-32 kp.

In some embodiments, about 5 to about 55% Compound A is released after 2 hours, about 35 to about 85% Compound A is released after 4 hours, and at least 75% Compound A is released after 6 or after 8 hours.

In some such embodiments, about 10 to about 55% Compound A is released after 2 hours, about 40 to about 85% Compound A is released after 4 hours, and at least 75% Compound A is released after 6 hours. In some embodiments, tablets having this profile have an average hardness of 7-17 kp. In some such embodiments, tablets having this profile comprise, based on uncoated weight, 22-40% (e.g., 26-40%) diluent, 7-12% floating agent, 10-24% (e.g., 10-17%) swelling polymer, 2-6% (e.g., 2-4%) matrix polymer, 28-46% (e.g., 30-46%) Compound A, and optionally 0.1-2% (e.g., 1-2%) binder, 0.1-1% glidant, and/or 0.1-1% lubricant. In some embodiments, such a tablet is prepared by wet granulation and comprises 2-4% intragranular diluent and 20-37% (e.g., 24-37%) extragranular diluent.

In some such embodiments, about 10% to about 50% Compound A is released after 2 hours, about 45 to about 85%, or about 40% to about 80% Compound A is released after 4 hours, and at least 75% Compound A is released after 6 hours.

In some such other embodiments, about 15 to about 55% Compound A is released after 2 hours, about 45 to about 85% Compound A is released after about 4 hours, and at least 75% Compound A is released after 6 hours. In some such embodiments, tablets having this profile have an average hardness of 7-17 kp. In some such embodiments, tablets having this profile comprise, based on uncoated weight, 26-40% diluent, 7-12% floating agent, 10-17% swelling polymer, 2-4% matrix polymer, 30-46% Compound A, and optionally 1-2% binder, 0.1-1% glidant, and/or 0.1-1% lubricant. In some embodiments, such a tablet is prepared by wet granulation and comprises 2-4% intragranular diluent and 24-37% extragranular diluent.

In some embodiments, about 25 to about 65% Compound A is released after 2 hours, about 45 to about 85% Compound A is released after 4 hours, and at least 75% Compound A is released after 8 hours. In some embodiments, tablets having this profile have an average hardness of 7-17 kp. In other embodiments, the tablets have an average hardness of 16-25 kp. In other embodiments, the tablets have an average hardness of 24-32 kp.

In some such embodiments the tablet comprises, based on its uncoated weight, 21-42% diluent, 8-15% floating agent, 7-15% swelling polymer, 0.1-2% matrix polymer, 31-57% Compound A, and optionally 1-2% binder, 0.1-2% glidant (e.g., 0.1-1%), and/or 0.1-1% lubricant. In some embodiments, such a tablet is prepared by wet granulation and comprises 2-5% intragranular diluent and 18-38% extragranular diluent.

In some embodiments, tablets of the invention have a dissolution profile as follows: about 5 to about 40% Compound A is released after 2 hours, about 35 to about 75% Compound A is released after 4 hours, and at least 75% Compound A is released after 8 hours. In some embodiments, tablets having this profile have an average hardness of 7-17 kp. In some embodiments, tablets having this profile have an average hardness of 16-25 kp. In some embodiments, the tablets have an average hardness of 24-32 kp.

In some such embodiments the tablet comprises, based on its uncoated weight, 21-42% diluent, 8-15% floating agent, 7-15% swelling polymer, 0.1-2% matrix polymer, 31-57% Compound A, and optionally 1-2% binder, 0.1-2% (e.g., 0.1-1%) glidant, and/or 0.1-1% lubricant. In some embodiments, such a tablet is prepared by wet granulation and comprises 2-5% intragranular diluent and 18-38% extragranular diluent.

In some embodiments the formulations provide:

a) a steady state anti-IIa activity level of at least 2 μg dermatan sulphate units/mL plasma over an extended period of time, e.g., at least about 8, 10 or 12 hours, after oral administration; and/or

b) a steady state Compound A level of at least about 0.5 or 0.8 (including 0.5-0.8) μg Compound A /mL plasma over an extended period of time, e.g., at least about 8, 10 or 12 hours, after oral administration; and/or

c) the above-stated dissolution profile(s).

Steady-state anti-IIa activity, compound A plasma level, and dissolution profiles are determined in accordance with the methods described herein.

The present invention relates to a method of treating and/or preventing thromboembolic disorders comprising administration of an effective amount of a composition of the invention (and thus Compound A) to a patient in need thereof.

The term "thromboembolic disorder" refers to disorders associated with inappropriate or undesired thromboses formation, resulting in undesired venous or arterial blockages or constriction of blood flow at the primary site of thrombosis and/or, in the case of embolisms, a more remote site. In the case of an embolism, the initial thrombus which is formed, fragments at least partially and the part to fragment off (embolus) is transported in the plasma where it can sometimes occlude a remote blood vessel, often resulting in serious or even fatal consequences.

In one aspect, the thromboembolic disorder is thromboses associated with atrial fibrillation, including NVAF.

In another aspect, the thromboembolic disorder is thromboses following surgery, e.g., orthopedic surgery, including VTE, such as but not limited to deep vein thrombosis ("DVT"),

symptomatic VTE, and pulmonary embolism ("PE"). In some embodiments, the surgery is total or partial hip or knee replacement surgery.

By "administered", "administration" and the like is meant administration of a therapeutically effective dose of the composition (or Compound A) to a patient in need thereof.

By "therapeutically effective dose" herein is meant a dose that produces the effects for which it is administered.

By "effective amount" is meant that amount of Compound A or the composition thereof, which upon administration to a patient in need thereof provides a clinically desirable result in the treatment and/or prevention of a thromboembolic disorder. For example, an effective amount may inhibit partially or completely the formation of thromboses, including decreasing the size, weight and/or occurrence of thromboses.

"Patient" includes both mammals and other animals. Thus the methods are applicable to both human therapy and veterinary applications. In one embodiment the patient is a mammal, and in a particular embodiment the patient is a human.

In some embodiments, the method is for the treatment and/or prevention of thromboses or hypercoagulability, comprising administering a composition of the invention in an effective amount to a patient in need thereof.

In some embodiments the method is for the treatment and/or prevention of thromboses following orthopedic surgery, including VTE (e.g., deep vein thrombosis [DVT], symptomatic VTE, pulmonary embolism [PE]). In some embodiments, the surgery is total or partial hip or knee replacement surgery.

In other embodiments the method is for the treatment and/or prevention of thromboses associated with atrial fibrillation, particularly NVAF. In some embodiments, the method is for the prevention of stroke in atrial fibrillation.

In some embodiments the patient is one with chronic atrial fibrillation at high risk for stroke. This may include patients who have had a previous ischemic stroke, transient ischemic attack (TIA), or systemic embolism; patients greater than 75 years of age; patients with moderately or severely impaired left ventricular function and/or chronic heart failure; and patients with a history of hypertension or diabetes.

In other embodiments, the patient is one with chronic atrial fibrillation at low or intermediate risk for stroke. This may include patients $\leq$60 years of age with no heart disease, patients <60 years of age with heart disease but no risk factors (i.e., heart failure, LVEF <35%, diabetes, history of hypertension, and prior embolic event); and patients $\geq$60 years of age and $\leq$ 75 years of age with no risk factors (see above) and no heart disease.

It will be appreciated that the methods apply, e.g., to acute treatment or prophylaxis as well as the alleviation of established symptoms or conditions (e.g., a chronic disorder).

The composition is administered in an amount effective to treat and/or prevent a thromboembolic disorder (e.g., thromboses or hypercoagulability). As will be appreciated, the optimal amount to be administered depends upon the particular composition contemplated, the particular thromboembolic disorder being treated and its severity, relevant patient characteristics (sex, weight, age, general health including the presence or absence of other conditions, diet, etc), the time of administration, any drug or food interactions, etc.

In some embodiments, from about 125 mg to about 1000 mg of Compound A is administered per day (e.g., post-surgery). For example, about 125, 250, 300, 400, 500, 750, 800 or 1000 mg of Compound A is administered per day. In some embodiments, about 250, 300, 375, 400, 500, 750 or 800 mg to about 1000 mg of Compound A is administered daily.

For example, at least about 0.1 mg, to about 50 mg of Compound A per kilogram patient body weight may be administered per day. In some embodiments, at least about 1 or 2 mg, to about 5, 10, 15, 20, 25, 30 or 35 mg Compound A per kilogram patient body weight is administered per day.

In some embodiments, the composition is administered once or twice a day (e.g., about every 8-16, 10-14, or 12 hours). For example, the above-mentioned daily doses are split for twice daily administration (e.g., 1000 mg per day administered as a 500 mg dose twice a day, or as two 250 mg dosage units twice a day, and the like).

In some embodiments, each dose is administered in 1-4 dosage units. In some embodiments, each dose is administered as a single dosage unit. For example, each dosage unit may comprise about 250, about 375, about 400, or about 500 mg Compound A.

In some embodiments, about 250, 375, 400, or 500 mg Compound A is administered twice daily (for a total daily dose of about 500, 750, 800 or 1000 mg Compound A).

In some embodiments, the composition is administered at least once a day, including a morning dose.

Notwithstanding the particular dosages herein, it may nevertheless be advisable to use other dosages due to patient weight or physiological function, severity of disorder, etc. Accordingly, it might in some cases be preferred to use an amount of the composition (Compound A) which may fall outside these particular embodiments.

In some embodiments, treatment with the composition is preceded by an initial treatment with an anticoagulant at standard regimen, e.g., low molecular weight heparin or unfractionated heparin (e.g., tinzaparin, enoxaparin, dalteparin, ardeparin). Initial treatment with an anticoagulant is suitably utilized for acute VTE (e.g., DVT) therapy, e.g., in orthopaedic surgeries. For example, initial treatment with anticoagulant is suitably started

post-surgery, suitably once adequate hemostasis is achieved (generally within 12-24 hours). Such initial treatment may be continued as needed, for example, for about 24 hours or for several days, e.g., up to 2 or 3 weeks, including 6-10 or 7-10 days, post-surgery. In some embodiments, initial treatment is started before surgery, e.g., about 9-24 hours prior.

The composition is administered for a period sufficient to treat and/or prevent a thromboembolic disorder (e.g., thromboses including VTE), including acute and extended treatment. Duration of treatment will vary depending upon the particular thromboembolic disorder being treated, the patient being treated, the treatment setting, etc. In some cases, treatment might consist of a single administration. In some embodiments, the composition will be administered multiple times over a period of time sufficient to meet the needs of the particular situation.

In some embodiments, the composition is administered for a period of from about 1 to 60 days, e.g., 1 to 30 or 35 days. In some embodiments the composition is administered for a period of from between 6, 7, or 8 days to 10, 11, or 12 days (e.g., 6-10, 7-10 or 8-12 days). Such treatment may be after an initial treatment with anticoagulant such as described herein. In some embodiments, the Compound A is administered as soon as possible after surgery, i.e., dependent upon the ability of the patient to tolerate oral medication. For example, the Compound A is administered for a period of 6-12 or 7-12 days after surgery, or for a period of 6-12 or 7-12 days after an initial treatment with anticoagulant (e.g., LMWH) (e.g., for about 24 hours). Such methods may be particularly useful for acute treatment and/or prevention of thromboses (e.g., VTE such as in DVT).

In some extended treatment regimens, the composition is given regularly or fairly regularly, for the entire duration of the patient's need, without limit. In some embodiments, the period of treatment is for more than one year. In other embodiments, the composition is given regularly or fairly regularly for a period of from about 1 to 365 days; from about 1 and 180 days; from about 1 to 120 days; from about 1 to 90 days; from about 1 to 60 days; or from about 1 to 30 days (e.g., up to and including about 2, 4, 5, 6, 7 or 8 weeks). Treatment for months or years may be particularly suitable for thromboembolic disorders which are typically chronic, such as those associated with atrial fibrillation. Treatment in the order of days to about 2 or 3 months may be particularly suitable for thromboembolic disorders following orthopedic surgery.

In some embodiments, Compound A is administered for about 2-8 weeks, especially 3-6 weeks, including for about 4 weeks (such as 28 +/- 3 days). In other embodiments, Compound A is administered for about 4 weeks following initial anticoagulant therapy such as described herein. In other embodiments, Compound A is administered chronically (e.g., for

one or more months or years)(e.g., for 3 months or 6 months)(e.g., for the prevention or treatment of thromboses associated with atrial fibrillation).

According to some embodiments of the treatment and/or prevention of thromboses following surgery such as orthopaedic surgery (e.g., for prevention of DVT following surgery, e.g., in total knee or hip replacement), administration of the composition is suitably initiated as soon as possible after surgery (e.g., once adequate hemostasis is achieved, generally within about 24 hours, e.g., about 12 hours or about 6 hours after surgery). In some embodiments administration is initiated no later than 12 hours following completion of surgery.

In some embodiments, a composition of the invention is administered on a need to treat basis. Accordingly, under such a regimen, the composition may not be administered regularly, but rather may be administered according to the need of the particular individual. In such a scenario, the individual being treated might be treated once, or a number of times and the effect of the treatment monitored, measured or otherwise diagnosed, and if necessary, additional treatment undertaken as needed or desired.

In some embodiments, the composition is administered in the fasted state, i.e., on an empty stomach, e.g., at least one hour before eating or about 2 or more hours after eating.

In other embodiments, the composition is administered with food ("in the fed state"), e.g., concurrently with or shortly before or after eating a meal (e.g., within about 20-30 minutes after eating, e.g., within about 5 minutes of completing a meal). Administering Compound A with food tends to increase systemic exposure and the maximum plasma concentration.

In one embodiment, the composition is administered to a mammal, more particularly a human, in need thereof.

Non-limiting examples of compositions according to the present invention are described below.

EXPERIMENTAL

Example 1 - Tablet formulations

Tablets according to the present invention, comprising 150, 200 or 250 mg Compound A, are prepared as follows.

A granulation is prepared from the following nominal composition:

Component	%
Compound A	90.0
microcrystalline cellulose Avicel PH102 (NF)	7.0
Povidone K30 (USP)	3.0
Purified water (USP)	qs*

* purified water is used as a granulating liquid and is removed during drying of the granulation

Granules are prepared using a high-shear granulator (e.g., 25L T.K. Fielder) followed by fluid bed drying (e.g., Glatt GPCG 5/9) and milling (e.g., Co-Mil Quadro).

Screen the solid materials (nominal 20 mesh using vibratory sieve if necessary) and transfer to the granulator in the following order: about half the Compound A, Avicel PH102, povidone K30, and remainder of Compound A. Blend the mix using low main impeller speed (e.g., 1.2-2.0 KW, 220 rpm) and chopper setting (e.g., about 0.6 amps) for about 2 minutes. Slowly add water sufficient for granulation (e.g., about 800 g for a 5 kg total batch including water, i.e., about 16wt% water) (e.g., added over about 25 sec). Mix the mass (e.g., about 4 min 5 sec), scraping the mixer as necessary. Dry the granules (about 40-60C inlet temperature, particularly about 40C; about 25% inlet air flow), e.g. to a moisture content of <5% (by weight loss at 105C, about 7g sample) (e.g. dry time about 30-50 min). Mill and screen through the mill using a 039 screen and washer (spacer) size 250+200. Using a Fitsch sieve shaker (e.g., amplitude 8, 5 min), not more than 5% should be retained on a 20 mesh screen and not less than 20% should pass through a 100 mesh screen (2 different composite samples, each about 100 g). Screen the milled granulation through a 20 mesh screen (remainder on screen is waste).

Round uncoated tablets are then prepared according to the following nominal compositions:

Formulation:	1A	1B	1C
Tablet strength (mg)	250	200	150
Total tablet weight (mg)	660	560	425
	%	%	%
Granulation	42.09	39.64	39.22
Sodium carboxymethylcellulose 9H4F (Aqualon) (FCC, tested to USP)	13.64	17.86	20
hydroxypropyl methylcellulose 2208 Methocel K100M Premium (USP)("hypromellose")	3.03	3.57	4.71
Sodium bicarbonate (USP)	9.67	9.11	8.99
microcrystalline cellulose ("MCC") Avicel PH 200(NF)	30.29	28.61	25.88
colloidal silicon dioxide Cab-O-Sil (NF)	0.68	0.64	0.56
magnesium stearate (vegetable grade) (NF)	0.61	0.57	0.64

Combine the microcrystalline cellulose and colloidal silicon dioxide. Separately screen the NaCMC, MCC/colloidal silicon dioxide blend, Na bicarbonate and hypromellose through a nominal 30 mesh screen. To a suitable blender (e.g., a PK blender 8qt) add in the following order: about half the granules, the NaCMC, microcrystalline cellulose/colloidal silicon dioxide, Na bicarbonate, hypromellose, and the remaining granules. Blend the mix e.g., for 10 min at 25 RPM, until uniform (e.g., to meet USP 26 <905> requirements (within 85-115% of Compound A target and %RSD ≤ 6.0% for all)). Pass the magnesium stearate through a 30 mesh screen and blend into the mixture, e.g., for 3 min at 25 RPM. Compress the mixture into 1/2" round tablets using a tablet press (e.g., Stokes B2 fit with a 1/2" round standard concavity tooling) to provide tablets with the target unit weight, average hardness of 7-17 kp (e.g., about 12kp) (n=3-5) and ≤1.0% weight loss on friabilation (n=20 tablets or 6g) (Erweka, at 25 rpm, 4 min).

In this manner are prepared: Formula A tablets having a mean unit weight 661.3 mg; % target Compound A by HPLC 96.2 (RSD 0.1% n=3); Formula B tablets having a mean unit weight mg 562.5 mg; % target Compound A by HPLC 95.7 (RSD 0.6% n=3); and Formula C tablets having a mean unit weight 426.8 mg; % target Compound A by HPLC 95.9 (RSD 0.3% n=3).

Example 2 – Tablet formulations

A granulation is prepared in a manner similar to Example 1. A slightly shorter granulation time after fluid addition is used (2min 45sec).

Tablets in accordance with the present invention are prepared according to the following nominal compositions:

Example	2A	2B	2C	2D	2E	2F
Tablet strength (mg)	500	500	250	400	375	125
Total tablet weight (mg, uncoated)	1060	1055	640	910	850	425
	%	%	%	%	%	%
Granulation	52.4	52.7	43.4	48.8	49	32.7
Sodium carboxymethylcellulose 7H3SF (Aqualon) (USP)	9	9.5	12.5	9.9	10.6	16.5
hydroxypropyl methylcellulose 2208 (Methocel K100M Premium) (USP)("hypromellose")	1.4	0.5	1.6	1.1	1.2	2.3
sodium bicarbonate (USP)	12	12.1	10	11.2	11.2	9
microcrystalline cellulose Avicel PH 200(NF)	23.6	23.7	31.2	27.8	26.7	38.3
colloidal silicon dioxide Cab-O-Sil (NF)	0.8	0.8	0.7	0.7	0.7	0.6
magnesium stearate vegetable grade (NF)	0.8	0.7	0.6	0.5	0.6	0.6

Example 2A-1

Combine the microcrystalline cellulose (Avicel PH200) and colloidal silicon dioxide. Separately screen this blend, the NaCMC, Na bicarbonate, hypromellose, and magnesium stearate through a nominal 30 mesh screen. To a suitable blender (e.g., a PK blender 12-16qt), add in the following order about half the granules, the NaCMC, the microcrystalline cellulose/colloidal silicon dioxide, the Na bicarbonate, the hypromellose, and the remainder of the granules. Blend the mix until sufficiently uniform, e.g., for 10 min at 25 RPM (e.g., to meet USP <905> % target Compound A by HPLC). Pass the magnesium stearate through a 30 mesh screen and blend into the mixture until sufficiently uniform, e.g., for 3 min at 25 RPM. Compress the mixture into biconvex caplets using a suitable press (e.g., Stokes Tripact) with 0.3819" x 0.7238" punches and dies, to provide a target unit weight of 1060 mg, average hardness of 7-17 kp (e.g., about 12 kp) (n=3-5) and $\leq$1.0% average weight loss on friabilation (n=20 tablets or 6g) (Van Kel, 25 rpm 4 min). In this manner, tablets having a mean unit weight 1064.1 mg (n=20); % target Compound A content by HPLC 97% (RSD 0.5% n=3) are prepared.

Example 2A-2

In one embodiment, caplets nominally of percentage composition 2A are prepared, e.g., in a like manner as described above, and coated with Opadry White YS-1-7706-G (Colorcon, West Point PA), in an amount of about 1.8-1.9% (dry weight), based on the weight of the uncoated tablet.

For example, granules are prepared by adding the Compound A, Avicel PH102 and povidone to a suitable granulator in that order (solids pre-screened if necessary, e.g. 30 mesh screen). Blend the dry mix for about 2 minutes. Slowly add water sufficient for granulation over about 5 minutes with low speed granulation (e.g., about 12 wt% of the total mix, delivery rate about 4 kg/min). Granulate the wet mass for about 3 more minutes at low speed. Additional water may be added and/or granulation may be continued, e.g., for about 6 minutes. Screen the granules (0.5") and then dry them (e.g., Glatt dryer, inlet temperature about 40-60C, e.g, about 48-52C; initial air volume about 1800 m3/hr, then adjusted for adequate fluidization). Dry the granules, e.g. to a product bed temperature of about 33C or a moisture content of between 0.5-2.0% (by loss at 105C) (e.g., about 20-30 min dry time). Screen the dried granules (0.039").

Blend part of the Avicel PH200 with the Cabosil (e.g., about 5.6 Avicel:1 Cabosil). Separately pass this blend, the CMC, the remaining Avicel PH200, sodium bicarbonate, hypromellose, and magnesium stearate through a 30 mesh screen. Add all the MCC/Cabosil blend, all the hypromellose, about 10% of the CMC and about 10% of the sodium

bicarbonate to the mixer and blend at a suitable speed (e.g., about 10 minutes at about 17 rpm). Add about 50% of the remaining CMC, 50% of the remaining MCC and 50% of the remaining sodium bicarbonate to the mixer in that order and blend at a suitable speed (e.g., as above). Add about ½ of the granules, and then each of the remaining CMC, MCC, sodium bicarbonate and granules to the mixer in that order and blend at a suitable speed until uniform (e.g., as above)(e.g., passes USP <905> % target Compound A by HPLC). Add the magnesium stearate and blend at a suitable speed (e.g., for about 3 min at about 17 rpm). Compress the mixture into tablets using about 19.0 x 9.2 mm caplet shaped tooling, having a target unit weight of 1060 mg, average hardness of 24-32 kp (e.g. about 26 kp) (n=5); ≤1.0% weight loss on friabilation (n=20 tablets)(25 rpm 4 min). In this manner tablets having a mean unit weight of 1066.2 mg (n=20) are prepared.

Coat the tablets with about 1.85wt% Opadry white YS-1-7706G (dry coating weight, based on the weight of the uncoated core). Prepare an aqueous solution (about 10wt% Opadry in water) by adding the Opadry to at least a portion of the water and stirring gently until dispersed and dissolved (no lumps), then adding any remaining water. Use the solution within 24 hrs and stir for at least 1hr before use. Coat the cores using suitable equipment (e.g., Manesty 75), e.g., at a rate of about (0.3) x (weight of the cores), and dry.

Example 2B-1

Tablets nominally of percentage composition 2B are prepared and optionally coated as for Example 2A.

For example, uncoated tablets are prepared in the manner described in Example 2A-1 having a target unit weight of 1055 mg, average hardness of 7-17 kp (e.g., about 12 kp) (n=3-5), and ≤1.0% weight loss on friabilation (Van Kel, 25 rpm 4 min, n=20 tablets or 6g). In this manner tablets having a mean unit weight 1057.8 mg (n=20); % target Compound A by HPLC 97.7 (RSD 0.3% n=3) are prepared.

Example 2C-1

Combine about 1199 g of the microcrystalline cellulose Avicel PH200 and about 27 g of the colloidal silicon dioxide. Separately screen about 480 g NaCMC, the MCC/SiO2 blend, 383 g Na bicarbonate and 60 g hypromellose through a #30 mesh screen in that order. Add the following components to a PK crossflow blender: about 833.5 g of the granules, the NaCMC, microcrystalline cellulose/colloidal silicon dioxide, Na bicarbonate, hypromellose, and about another 833.5 g of the granulation (to total about 1667 g), in that order. Blend the mix for 10 min at 25 RPM until uniform (e.g., to comply with USP<905>, % target Compound A by HPLC). Screen about 24 g of magnesium stearate through a #30 mesh screen, add to

the blender and mix for 3 min at 25 RPM. Compress the mixture into ½" round, biconvex tablets using a Stokes B2 press with ½" standard punches and dies to provide tablets having a target unit weight of 640 mg; average hardness of 7-17 kp (e.g., 12) (n=3-5), and ≤1.0% weight loss on friabilation (n=20 tablets or 6g)(Van Kel, 25 rpm 4 min). In this manner tablets having a mean unit weight 646 mg (n=20); % Compound A by HPLC 97.3 (RSD 0.3% n=3) are prepared.

Example 2C-2

In one embodiment, tablets nominally of percentage composition 2C are prepared, e.g., in a like manner as described above, and coated with Opadry White YS-1-7706-G, in an amount of about 3% (dry weight) based on the uncoated tablet weight.

For example, granules and tablets are prepared in a manner similar to Example 2A-2, with the following modifications. During granulation, sufficient water is slowly added over about 165-300 sec with low speed granulation (e.g., about 12% water in total mix, delivery rate about 4kg/min). The wet mass is granulated for about 2-3 more minutes at low speed. Additional water may be added and/or granulation may be continued, e.g., for about 2-6 min. The tablets are compressed using ½" round tooling, to a target unit weight of 640 mg, average hardness of 24-32 kp (e.g., about 26 kp) (n=5) and ≤1.0% weight loss on friabilation (n=20 tablets, 25 rpm 4 min). In this manner tablets having a mean core weight 641.2 mg (n=20) are prepared. The tablets are coated with the Opadry at about 3wt% Opadry based on the uncoated tablet weight. In this manner coated tablets having mean unit weight 660.92 mg are prepared.

Example 2D-1

Combine about 1263 g of the microcrystalline cellulose Avicel PH200 and about 30 g of the colloidal silicon dioxide. Pass the CMC, the MCC/silicon dioxide mixture, Na bicarbonate, and hypromellose through a #30 mesh screen. Add to a suitable blender (e.g., 8 qt PK) about 50 g hypromellose, 45 g NaCMC, 129.3 g of the MCC/SiO2 blend and 51 g Na bicarbonate in that order and mix for 10 minutes at 24 +/- 3 rpm. Add about 202.5 g NaCMC, 581.9 g of the MCC/SiO2 blend and 229.5 g of Na bicarbonate in that order and mix for 10 minutes at 24 +/- 3 rpm. Add about 1111 g of granules prepared in a like manner to Example 2A-1, 202.5 g NaCMC, 581.8 g of the microcrystalline cellulose/colloidal silicon dioxide blend, 229.5 g Na bicarbonate and another 1111 g of the granulation in that order to the blender and mix until uniform (to comply with USP <905>, % target Compound A by HPLC)(e.g., 10 minutes at 24 +/- 3 rpm). Screen about 25 g magnesium stearate through a #30 mesh, add to the blender and mix for 3 min at 24 +/- 3 rpm. Compress the mixture into

tablets using a Stokes Tripact press with about 0.3819" X 0.7238" punches and dies to provide tablets having a target unit weight of 910 mg, average hardness of 16-25kp (e.g., about 20 kp) (n=3-5), ≤1.0% weight loss on friabilation (n=20 tablets or 6g, Van Kel, 25 rpm 4 min). In this manner tablets having mean unit weight 910.8 mg; % Compound A by HPLC 99.2 (RSD 0.1 n=3) are prepared.

Example 2E-1

Caplets nominally of percentage composition 2E are prepared, e.g., in a like manner as described in Examples 2A or 2D, and coated with Opadry White YS-1-7706-G, in an amount of about 2% (dry weight) based on the uncoated tablet weight.

For example, tablets are prepared in a manner similar to Example 2A-2, with the following modifications. During granulation, water sufficient for granulation (e.g., about 12 wt% of the total mix) is slowly added over about 3 minutes with low speed granulation (e.g., delivery rate 2.82-2.84 kg/min). The wet mass is granulated for about 2 more minutes at low speed. The compression mixture is compressed into tablets using about 19.0 x 9.2 mm caplet shaped tooling, to provide tablets having a target unit weight of 850 mg, average hardness of 24-32 kp (e.g., about 28 kp) (n=5) and ≤1.0% weight loss on friabilation (n=20, 25 rpm 4 min). In this manner tablets having mean core weight 853 mg are prepared. The tablets are coated with about 2wt% Opadry white YS-1-7706G (dry coating weight, based on the weight of the uncoated core). An aqueous solution (about 15wt% Opadry in water) is prepared by adding the Opadry to at least a portion of the water and stirring gently until dispersed and dissolved (no lumps), then adding any remaining water. The solution is used within 24 hrs and should be stirred for at least 1hr before use. The cores are coated using suitable equipment (e.g., Manesty 75), e.g., at a rate of about (0.133) x (weight of the cores), and dried. In this manner, coated tablets having mean unit weight of 874.3 mg are prepared.

Example 2F-1

Combine about 814g of the microcrystalline cellulose Avicel PH200 and about 14 g of the colloidal silicon dioxide. Pass the CMC, the MCC/silicon dioxide blend, the Na bicarbonate and the hypromellose through a #30 mesh screen. Add about 50 g hypromellose, 35 g NaCMC, 82.8 g of the MCC/SiO2 blend and 19.1 g Na bicarbonate in that order to a suitable blender (e.g., 8qt PK) and mix for 10 minutes at 24 +/- 3 rpm. Add about 157.5 g NaCMC, 372.6 g of the MCC/SiO2 blend, and 85.95 g of Na bicarbonate in that order to the blender and mix for 10 minutes at 24 +/- 3 rpm. Add about 347.5 g of granules prepared in a like manner to Example 2A-1, 157.5 g NaCMC, 372.6 g of the microcrystalline cellulose/colloidal silicon dioxide blend, 85.95 g Na bicarbonate and another 347.5 g of the

granulation in that order to the blender and mix until uniform (e.g., passes USP <905> % target Compound A by HPLC) (e.g., 10 minutes at 24 +/- 3 rpm). Screen about 12 g magnesium stearate through a #30 mesh screen, add to the blender and mix for 3 min at 24 +/- 3 rpm. Compress the mixture into round tablets using a Stokes Tripact press with ½" standard cup punches and dies, to provide tablets having a target unit weight of 425 mg; hardness of 16-25kp (e.g., about 20 kp) (n=3-5), ≤1.0% weight loss on friabilation (n=20 tablets or 6g)(Van Kel, 25 rpm, 4 min). In this manner, tablets having mean unit weight 424.1mg; % target Compound A by HPLC 97.2 (RSD 0.7 n=3) are prepared.

Example 3 – Pharmacokinetics/Pharmacodynamics

Methodology:

The pharmacokinetics and pharmacodynamics of compositions of the invention can be evaluated as described herein.

The following definitions apply herein:

AUC(0-∞) – area under the plasma concentration-time curve for the 0-infinity interval

AUC(0-τ) - area under the plasma concentration-time curve from 0 to the time of the next dose ($_\tau$)

Clast – the last quantifiable plasma concentration

Cmax – peak total plasma concentration

Cminss – trough Compound A plasma concentration

C12 – the quantifiable plasma concentration at 12 hours post-dose

CVb – between subject coefficients of variation

λz – elimination rate constant

n = number

NQ – non-quantifiable

PTF – peak-to-trough ratio at steady state

Relative bioavailability (RB) – the rate and extent (amount) of therapeutically active drug which reaches the systemic circulation, measured, e.g., in terms of Cmax and/or AUC. For example, the relative bioavailability of a drug product ("A") as compared to that of another drug product ("B"), based on AUC, is defined as follows:

For two drug products given at the same dosage level and by the same route of administration: $RB = (AUC)_A/(AUC)_B$

For two drug products given at different dosage levels by the same route of administration: $RB = (AUC)_A/\text{Dose A} \,//\, (AUC)_B/\text{Dose B}$

(Relative bioavailability based on Cmax can be similarly defined by corresponding formulas where Cmax replaces AUC.)

Steady state – the plateau concentration where the rate of drug leaving the body and the rate of drug entering the body are the same. Steady-state can be estimated as the concentration at (t1/2 x 5), e.g., for a t1/2 of 3 hours, steady state is estimated to be at 15 hours. Steady-state can also be determined by assaying plasma concentrations. As used herein, steady-state is determined by assaying plasma concentrations, and is achieved when plasma concentrations are essentially at plateau, under a constant regimen.

tmax – time of peak total plasma concentration

t1/2 – elimination half life

trough – refers to a value just prior to administration of the next dose

PK Methodology:

Blood samples (2mL) for PK analysis are collected into EDTA-containing tubes prior to dosing (time 0) and at nominal times as set forth above. The tubes are immediately chilled on ice, and plasma are separated by refrigerated centrifugation (i.e., 3000 rpm for approximately 10 minutes) within 30 minutes. Plasma are then transferred to polypropylene specimen containers and frozen at approximately -20C.

Plasma samples are assayed for Compound A using a protein precipitation method followed by LC/MS/MS analysis (lower limit of quantification 5.00 ng/mL for a 50 µL aliquot plasma). The Compound A is isolated from human plasma by protein precipitation with acetonitrile and quantified by LC/MS/MS using a Turbo IonSpray interface. Positive ion multiple reaction monitoring (MRM) is employed for the MS/MS detection of Compound A and the internal standard, Compound A [$^{13}C_4$] (Figure 1).

The following materials, methods and equipment, or suitable equivalents, are utilized.

Human plasma (EDTA as anticoagulant) - Biological Specialty Corporation (Colmar, PA)

Formic Acid, (88%)

Acetonitrile, HPLC grade ;Water, HPLC grade, Milli-Q System, Millipore Co. (Bedford, MA) ("Millipore water")

Ammonium Formate (reagent grade)

Dimethyl Sulfoxide (DMSO)

Ammonium formate buffer - 0.631 g Ammonium formate is dissolved in about 800 mL Millipore water. The pH is adjusted to 3.0 with formic acid and the final volume is brought to 1 liter with water. This solution is filtered through a 0.20 um Nylon 66 filter.

For HPLC, a Rheos 4000, quaternary pumping system with degasser, (Flux Instruments AB (Karlskoga, Sweden)) is used to deliver mobile phase to a 3 x 100 mm, 3 um Genesis C18 column (Jones Chromotography, Lakewood, Colorado) preceded by a 0.5 um

pre-column filter. Injections are made by a Perkin Elmer Series 200 autosampler (Concord, Ontario, Canada). The mobile phase is composed of a 40/50/10 (v/v) mixture of acetonitrile, Millipore water and 10 mM ammonium formate buffer (pH 3.0). The flow rate is set at 400 uL/min and is introduced into the source of a mass spectrometer without any post column split.

An API 3000 triple quadrupole mass spectrometer (Perkin Elmer Sciex Instruments (Concord, Ontario, Canada)) is coupled to the HPLC via a Turbo IonSpray interface. The mass spectrometer is set in positive ion mode to select the protonated molecules $[M+H]^+$ at m/z 325 (Compound A) and m/z 329 (internal standard) by the first quadrupole filter (Q1). These selected ions (precursor ions) are collided with nitrogen gas in the second quadrupole (collision cell, Q2) to generate product ions at m/z 177 (Compound A) and m/z 181 (internal standard). The product ions are monitored through the third quadrupole (Q3) before being detected by the electron multiplier (the product ions are only be detected as chromatographic signals if they are generated from their corresponding precursor ions in the collision cell). All masses in this method are nominal.

Sample Control (version 1.3, PE/Sciex) is used for data acquisition and MacQuan (version 1.4, PE/Sciex) is used for automatic data processing (including integration of chromatographic peaks and calibration).

Primary Stock of Compound A - At least 2 mg of Compound A dissolved in DMSO to give a standard stock solution of 1.0 mg/mL Compound A.

Working Standard Solutions - Serial dilutions of the Compound A calibration and validation primary stock solutions are prepared in acetonitrile/water (50/50, v/v) to give working solution concentrations of 100 ug/mL, 10 ug/mL, 1.0 ug/mL, and 0.1 ug/mL.

Calibration Stock Solutions – prepared as outlined in Table 1.

Table 1: - Preparation of Human Plasma Calibration Standards for Compound A

Plasma Std. Conc. (ng/mL)	Std. Solution Used (ug/mL)	Volume of Std. Sol. Used (uL)	Volume of Blank Human Plasma Added (uL)
5	0.1	25	475
10	0.1	50	450
20	1	10	490
50	1	25	475
100	1	50	450
200	10	10	490
500	10	25	475
1000	10	50	450
2000	100	10	490
5000	100	25	475

Validation /QC stock solutions - Validation samples are prepared as outlined in Table 2 and are pipetted in 0.5 mL aliquots into 1.5 mL Eppendorf polypropylene tubes and stored at approximately –20°C.

Table 2 – Preparation of Human Plasma Validation Samples for Compound A

QC Conc. (ng/mL)	QC Stock Solutions Used (ug/mL)	Volume of QC Stock Solution Used (uL)	Volume of Blank Human Plasma Added (mL)
5	0.1	150	2.850
20	1	60	2.940
500	10	150	2.850
5000	100	150	2.850

It has been found that the stability of compound A is acceptable through three freeze-thaw cycles at approximately -20C.

Internal Standard Stock: 1.0 mg/mL stock solution of Compound A - At least 2 mg of Compound A [$^{13}C_4$] in DMSO to give a solution of 1.0 mg/mL compound A [$^{13}C_4$].

Working compound A [$^{13}C_4$] solutions - stock solution of Compound A [$^{13}C_4$] is diluted with acetonitrile to give a solution of 10 ug/mL, which is used to make a final solution of 250 ng/mL in acetonitrile.

A 50 uL aliquot of the plasma blank, calibration standard or validation sample is added to a 1.5 mL Eppendorf tube. Internal standard (100 uL of 250 ng/mL Compound A [$^{13}C_4$] in acetonitrile) is added to the Eppendorf tubes (100 uL of acetonitrile is added to the "Blank" tubes). The tubes are capped and vortex mixed for 2 minutes, followed by centrifugation for 10 minutes (approximately 15,000 x g) in an Eppendorf 5403 centrifuge. Ammonium formate buffer, 10 mM, pH 3.0, (50 uL) is added to the autosampler vials and 125 uL of the supernatant is transferred to the autosampler vials. The vials are capped, vortex mixed and the samples are injected (0.5-2.5 uL) onto the LC/MS/MS system.

For calibration, a duplicate set of calibration standards is analyzed for each determination. A weighted (1/x) linear-regression method is used to construct a calibration curve for the peak area ratio of analyte to internal standard versus analyte concentration. The concentration of analyte in plasma is calculated using the equation,

$$\text{Concentration of analyte} = ((c)/(d)- a)/ b$$

Where b =slope of the regression line, a=y intercept of the regression line; c=peak area of analyte; d=peak area of internal standard.

For validation, six replicate samples from each pool of validation samples (5, 20, 500 and 5000 ng/mL) are extracted and analyzed. Concentrations are determined by comparison with a calibration curve prepared on the day of analysis. Validation statistics are determined from the data obtained, as follows:

Within-run precision: [S.D. x 100] / Mean measured concentration

Average within-run precision: [^{CV} run1 + ^{CV} run2 + ^{CV} run3] / Number of runs

Bias: [(Mean concentration x 100) / Nominal concentration] - 100

Between run precision: [S.D. determined from the within-run means x 100] / Average of within-run means

Average Bias: [Bias $_{run1}$ + Bias $_{run2}$ + Bias $_{run3}$]/ Number of runs

Assay Validation Data Analysis Program (ASVAL), Version 2.4a, (1) is used to generate bias and precision data.

Both $[M+H]^+$ ions (m/z 325 for Compound A and m/z 329 for Compound A [$^{13}C_4$]) are of base intensities (Figure 2 - positive ion, IonSpray mass spectra of Compound A and Compound A [$^{13}C_4$] (I.S.)). The product ion spectra of the two precursor ions produced by CID (collision induced dissociation) are shown in Figure 3. In order to maximize the

sensitivity of the method, base peaks in both precursor and product spectra are chosen for multiple reaction monitoring (MRM) detection, that is 325→177 for Compound A and 329→181 for the internal standard.

Typical chromatograms obtained from an extract from drug-free human plasma and a plasma sample spiked with 5.00 ng/mL (LLQ) of Compound A, are shown in Figures 4 and 5, respectively. Based on the analysis of drug free plasma samples (n=6), endogenous components do not interfere with the drug or the internal standard over the concentration range described in this method. Using 50 µL of plasma, the LLQ for Compound A is 5.00 ng/mL. A representative calibration plot for Compound A is shown in Figure 6. Linear responses in the analyte/internal standard peak area ratios are observed for analyte concentrations ranging from 5.00 ng/mL to 5000 ng/mL. Correlation coefficients obtained using weighted (1/x)) linear regression analysis of calibration curves are typically 0.998. Table 3 summarizes the calibration data (slope and intercept) obtained from a validation analyses.

Table 3 – Slope and Intercept Data for compound A in human plasma

	Run 1	Run 2	Run 3
Intercept	0.00236	0.000905	0.00055
Slope	0.00221	0.00199	0.00199
Correlation Coeff.	0.9997	0.99838	0.99968

The precision and bias results for a validation study for Compound A in human plasma are shown below:

COMPOUND A in Human Plasma

	Nominal Conc. (ng/mL)			
	5	20	500	5000
Average Within-run Precision (%)	6.07	3.47	2.90	2.38
Between-run Precision (%)	9.64	4.15	2.06	1.25
Average Bias (%)	-2.75	1.30	-0.52	-2.14

Using 50 uL of plasma, the lower limit of quantification (LLQ) for Compound A is 5.00 ng/mL. Linear responses in analyte/internal standard peak area ratios are observed for analyte concentrations ranging from 5.00 ng/mL to 5000 ng/mL. Chromatograms of drug-free plasma show no interfering peaks with retention times similar to those for Compound A or Compound A [$^{13}C_4$].

Compound A plasma concentration-time data are analyzed by noncompartmental methods using the computer program WinNonlin Professional, version 4.01 [WinNonlin User's Guide]. Calculations are based on actual collection times recorded during the study. The following pharmacokinetic parameters are estimated: AUC(0-∞), AUC(0-t), AUC(0-τ), Cmax, Cminss, C12, λz, t1/2, and tmax. PTF is calculated.

Area under the plasma concentration-time curve for Compound A is calculated using the linear trapezoidal rule for each incremental trapezoid resulting from an increase in concentration and log-trapezoidal rule for increments showing a decrease in concentration. AUC(0-∞) is estimated as the sum of AUC(0-t) and Clast divided by λz. λ_z is derived from the log-linear disposition phase of the concentration-time curve using least-squares regression analysis with visual inspection of the data to determine the appropriate number of terminal data points for regression analysis. t1/2 is calculated as ln 2/λ_z. Cminss is obtained by averaging the trough Compound A plasma concentrations from Days 2, 3, and 4 in Part II of the study. Cmax, C12 and tmax are obtained directly from the data.

PTF is calculated to assess the degree of fluctuation for Compound A plasma concentration at steady state:

PTF = Cmax Day 5 of Session 5/Cminss Day 5 of Session 5

where Cmin is the lowest observed Compound A plasma concentration from 0 to 24 hours postdose on Day 5, Session 5.

For descriptive statistics and summary graphs, NQ values are set to zero except when an individual NQ falls between two quantifiable values, in which case it is omitted. Mean and median Compound A plasma concentrations are generated and plotted against nominal sampling times.

PD Methodology:

Blood samples for PD analysis (anti-IIa activity via HCII) are collected into 4.5 mL 3.8% sodium citrate tubes (Becton Dickonson 366419) prior to dosing (time 0) and at nominal times as set forth above. Within 30 minutes of collection, the samples are centrifuged at 3000 x g for 10 minutes, immediately transferred into transfer tubes, and stored at -70C to -80C until PD analysis. The samples are assayed for dermatan sulfate concentration equivalents using a chromogenic assay technique, based on modifications of a method reported in the publication "A Simple Method to Measure Dermatan Sulfate at Sub-Microgram Concentrations in Plasma" by D. Dupouy, P. Sie, F. Dol and B Boneu in Thrombosis and Haemostasis, 1988, 60:236-239.

Dermatan sulfate is a glycosaminoglycan found in abundance in human tissues, especially in skin, blood vessels and heart valves. Dermatan sulfate exhibits anticoagulant

activity by indirectly inhibiting thrombin as it is formed in plasma. Dermatan sulfate activates heparin cofactor II (HCII), a plasma protease inhibitor which specifically inhibits thrombin but not other proteases involved in hemostasis. Plasma levels of dermatan sulfate may increase in response to the administration of β-D-xylosides under investigation for use as anti-thrombotics. Therefore, plasma dermatan sulfate concentration may prove to be a useful biomarker for measuring anti-thrombotic activity after administration of such potential therapeutic agents.

The following materials, methods and equipment or suitable equivalents are utilized.

Tris-HCl - Sigma Chemical Co.(Cat.# T-3253), St. Louis, MO

Dermatan sulfate - Celsus Laboratories, Inc. (Cat.# DS-03122) Cincinnati, OH

Bentonite - Sigma Chemical Co.(Cat.# T-3253), St. Louis, MO

Stachrom HCII Assay Kit - American Bioproducts Co. (Cat. # 851), Parsippany, NJ

Heparin Cofactor II - Haematologic Technologies, Inc.(Cat.# HCII-0190) Essex Junction, VT

HPLC Water - Sigma Chemical Co.(Cat.# 27,073-3), St. Louis, MO

1N NaOH - Sigma Chemical Co.(Cat.# 930-65), St. Louis, MO

Combi-tips – Eppendorf (Brinkman), (Cat. #22-49-510-1), Westbury, NY

Safe-Lock 0.5 mL centrifuge tubes - Eppendorf (Brinkman), (Cat. #22-36-361-1), Westbury, NY

Microplate reader - Dynex technologies (MRX), Chantilly, VA.

Titer Plate Shaker, Model 4625 - Lab-Line Instruments, Inc., Melrose Park, IL

Multichannel pipette, pipettors – Eppendorf (Brinkman), Westbury, CT

EDOS 5221 Automatic Pipetter - Eppendorf (Brinkman), Westbury, CT

Rotating Incubator, Model 4628GM - Lab-Line Instruments, Inc., Melrose Park, IL

Microtiter plates - Nunc (Cat.# 439454) Nalge NUNC International, Naperville, IL

Microtiter plate covers – Becton Dickonson (Falcon 3073), Oxnard, CA

Microcentrifuge - Jouan (Model A-14),Winchester, VA

Reagent Preparation:

0.02 M Tris, pH 7.4 - 3.15 g Tris-HCl is dissolved in 900 mL of deionized H2O. The pH is adjusted to 7.4 with 1N NaOH and the solution is diluted to a final volume of 1L with deionized H2O.

10 % Bentonite Suspension - 10 g of Bentonite is added to 80 mL of 0.02 M Tris, pH 7.4, mixed, diluted to a final volume of 100 mL and stored at 4-8°C.

Heparin Cofactor II, 10 ug/mL- 492 uL of HPLC water is added to a vial containing 8 uL of Heparin Cofactor II stock to give a concentration of 200 ug/mL. 50 uL of this HCII

solution is added to 950 uL HPLC water and vortexed (remaining 200 ug/mL solution is stored at 4-8°C).

Thrombin- 2 mL of HPLC water is added to a vial of thrombin from the Stachrom HCII kit and mixed well, to give a final concentration of 2.75 Units/mL.

Substrate- 2 mL of HPLC water is added to a vial of Thrombin Substrate from the Stachrom HCII kit and mixed well, to give a final concentration of 1.25 umol/mL.

Dermatan Sulfate - Dermatan sulfate is prepared to a concentration of 100 ug/mL in HPLC water.

Plasma Standards

Normal plasma contains endogenous low levels of dermatan sulfate. In order to construct a standard curve, dermatan sulfate is added to pooled plasma (equal volumes of plasma from 4 normal volunteers) to give a concentration of 16.00 ug/mL above the endogenous level. Serial dilutions of the 16.00 ug/mL standard are prepared to yield concentrations of 8.00, 4.00, 2.00, 1.00, 0.50, 0.25 ug/mL above endogenous level. The plasma pool without addition of dermatan sulfate is used for the 0.00 ug/mL standard. The standards are dispensed in 200 uL aliquots in 0.5 mL Safe-Lock Eppendorf tubes and placed at -80ºC for storage.

Assay procedure & Data Analysis:

The Bentonite suspension is removed from the refrigerator and mixed on a stir plate for 30 min. A set of standards is removed from the freezer and thawed at room temperature. 200 uL of each plasma sample to be analyzed is dispensed into a 0.5 mL Safe-Lock Eppendorf tube. 200 uL of Bentonite suspension is added to each sample and standard tube. The tubes are vortexed for 15 seconds, incubated for 5 minutes at room temperature, then centrifuged at 14,000 rpm for 2 min. 25 uL of HPLC water, 25 uL of Bentonite treated plasma or standard, and 50 uL of Heparin Cofactor II is added in that order to appropriate wells in the microtiter plate. Standards and samples are assayed in duplicate. The plate is covered, mixed for 15 – 30 seconds on the Titer-Tek rotator at 500 rpm at room temperature, then incubated for 10 min. at 150 rpm at 37ºC using the Rotating Incubator. 25 uL of Thrombin is added per well. The plate is covered, mixed and incubated for 10 min. at 150 rpm at 37ºC using the Rotating Incubator. 50 uL of substrate is added per well, then the plate is incubated at room temperature for 20-30 min. The plate is read using the DS-EP.asy program on the plate reader with the absorbance measured at 405 nm.

Using the Revelation software version 3.04 in the microplate reader, the standard curve values are plotted using a sigmoidal fit. Sample values are obtained by software analysis and interpolation from the standard curve.

A typical standard curve for optical density at 405 nm versus dermatan sulfate concentration, as well as the data used to generate the curve, are shown in Figure 7.

To estimate the limit of quantification (LOQ) above endogenous plasma levels, 10 determinations (20 blank wells) with 0 ug/mL plasma standard are assayed. This estimate for LOQ is probably higher than the actual LOQ because the pooled normal plasma contains some small amount of naturally occurring dermatan sulfate. For example, the average concentration is 0.04 ug/mL with a standard deviation (SD) of 0.03. The LOQ above endogenous plasma levels is calculated as the "mean + (6xSD)", or 0.22 ug/mL.

Inter-subject variability is assessed by assaying plasma from 20 normal volunteers. For example, most samples have values <LOQ. The mean is <LOQ and the range is <LOQ to 0.62 ug/mL.

To assess inter-assay variability, 2 normal plasma samples are spiked at 3 concentrations within the standard range. These 6 samples are assayed in 3 separate assays on three separate days. For example, the inter-assay variability is 8.09%.

Intra-assay variability is assessed using a plasma sample spiked at 3 concentrations of dermatan sulfate. Each sample is assayed 6 times on the same plate. Intra-assay variability is determined by averaging the variation of all 3 samples. For example, the intra-assay variability is 7.23 %.

It has been found that the samples may be frozen and thawed an additional 3 times if repeat analysis is needed, without significant loss of activity.

Recovery data is obtained from a plasma sample spiked at 0.50, 1.00, 2.00 and 3.00 ug/mL with dermatan sulfate above the endogenous level. Unspiked plasma is used as the 0.00 ug/mL control. The spiked samples are assayed for recovery. For example, the average recovery above endogenous levels is 88.60 %; the percent recovery of the various dermatan sulfate concentrations ranges from 78.00 % to 99.60 %.
Plasma samples with replicate CVs > 20 % are preferably reassayed.

Pharmacokinetic (PK)/Pharmacodynamic (PD) Study – Example 1 Tablets:

The PK/PD properties of the formulations according to Example 1, and an immediate-release capsule formulation were evaluated in a randomized, open label, 2-part, period balanced study with 5 sessions in healthy human volunteers.

In the first part of the study, a single dose of a Compound A formulation was administered. The first part of the study had 4 sessions. A different Compound A formulation was administered in each session.

In the second part of the study (consisting of session 5), repeat doses of a Compound A formulation were administered. In this part, subjects received a Compound A formulation

every 12 hours ("BID"; in the morning and evening) on days 1-4, and once in the morning on day 5. Subjects in this part received the same dose and formulation received in session 4 of the first study part. A minimum of 3 days separated study sessions.

The subjects were randomized to one of four treatment sequences which included the following regimens:

Regimen	Study Part 1 Single oral dose	Study Part 2 Repeat oral dose
A	500 mg Compound A formulation 1A (2X250 mg tablets)	--
B	400 mg Compound A formulation 1B (2X200 mg tablets)	--
C	300 mg Compound A formulation 1C (2X150 mg tablets)	--
D	--	500 mg Compound A formulation 1A (2X250 mg tablets)
E	--	400 mg Compound A formulation 1B (2X200 mg tablets)
F	--	300 mg Compound A formulation 1C (2X150 mg tablets)
G	Single oral dose immediate release (2x250 mg capsules)	
H		Repeat oral dose immediate release (2x250 mg capsules)

The immediate release capsules contained 250mg of uniform, white to off-white granules comprising Compound A. The granules were prepared using a high-shear granulator followed by fluid bed drying and milling nominally according to the following composition (%w/w): 90% Compound A, 7% Microcrystalline cellulose (Avicel PH102), 3% Povidone K30, and qs purified water (used as a granulating liquid and removed during processing). The granules were blended with magnesium stearate (lubricant; passed through a nominal 20-40 mesh screen using a vibratory sieve if required to de-aggregate), e.g., for 3 minutes at 24.4 RPM, or sufficient speed and/or time to achieve 60 +/- 10 revolutions, and filled into No. 0 opaque-white (white #9) capsules according to the following target formulation: 277.8 mg granules, 2.8 mg magnesium stearate (nominal dosage unit weight 280.6 mg, providing 250 mg Compound A).

In Part 1 of the study, subjects were dosed in the morning within 5 minutes of consuming a light breakfast, which was consumed within about 20 minutes [For example, a light breakfast may have about 500 calories, e.g., about 80 g carbohydrate, 30 g protein, and 10-15 g fat. The light breakfast may consist of cereal such as Cornflakes or Special K, 200 mL skim milk, one grilled strip of bacon, one egg scrambled with skim milk, 2 slices toast, 1 tsp butter, 4 oz apple or orange juice, which will be about 488 calories (approximately 77 g carbohydrate, 28 g protein, 12 g fat)]. Additional meals were provided at given times post-dose: lunch after 4 hours, optional snack after 8 hours, dinner after 11.5 hours.

In Part 2 of the study, subjects were dosed in the morning with a light breakfast such as described for Part 1, and provided additional meals as described for Part 1. Dinner was light, consisting of about 80 g carbohydrate, 30 g protein, and 12 g fat (consumed within about 20 minutes, with dosing within about 5 minutes after completing the meal).

Study formulations were administered with 240mL water.

Blood samples for PK/PD analysis were collected predose and serially to 24 hours postdose for each study period:

Part 1, sessions 1-4 and Part 2 (session 5), day 5:

For PK analysis - predose, and 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 18.0, 20.0, 24.0 hrs post-dose

For PD analysis - predose, and 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 18.0, 20.0, 24.0 hrs post-dose

Part 2 (session 5), days 2-4:

For PK and PD analysis - predose

Single dose pharmacokinetics:

The pharmacokinetic results after single dosing are shown in Table 4 below, and in Figure 8 (Regimens A-C). Data is based on plasma concentrations of Compound A and is presented as the geometric mean (range) unless otherwise stated.

Table 4:

Part I	Regimen A (n=27)	Regimen B (n=28)	Regimen C (n=28)	Regimen G (n=27)
AUC(0-∞) (ng*hr/mL)	12932[c] (7264 – 28178)	9910[d] (4951 – 14564)	7111[e] (3466 – 13048)	10276[f] (5747 – 32060)
DN***	25.8	24.7	23.7	20.5
AUC(0-τ) (ng*hr/mL)	11891 (7171 – 27707)	8649 (4848 – 19400)	6120 (2929 – 12877)	9489 (5170 – 31592)
DN	23.7	21.6	20.4	18.9
Cmax (ng/mL)	2292 (1065 – 6524)	1783 (755 – 4200)	1216 (686 – 3112)	1942 (1132 – 8008)
DN	4.5	4.4	4	3.8
T1/2 (hr)	2.36[c] (1.52 – 3.98)	2.20[d] (1.38 – 3.88)	1.92[e] (1.32 – 3.37)	2.28[f] (1.48 – 3.99)
tmax (hr)[a]	5.00 (2.02 – 10.00)	6.00 (3.00 – 12.00)	5.00 (3.00 – 18.00)	5.00 (2.00 – 8.00)
Average absorption**	5.64	5.55	5.84	5.29
DN	11.28	13.87	19.46	10.58
C12 mean (ng/mL) (SD)*	492[b] (454)	594[d] (609)	365 (324)	326[b] (410)
DN	984	1485	1216	652

[a] Presented as median (range)
[b] n=28 [c] n=26, [d] n=27, [e] n=23, [f] n=25
* SD not reported if more than 30% of values were imputed
** average absorption = $AUC_{(0-\infty)}$ / C_{max}
*** DN = Dose normalized values, = the parameter value/dose of Compound A.

All the formulations having a composition according to the invention provided, after single dosing (Regimens A-C), an average Cmax and C12 of > 0.25 µg/mL.

Single dose pharmacodynamics:

The pharmacodynamic results are shown in Table 5 below, and in Figure 9 (Regimens A-C). Data is based on plasma levels of dermatan sulfate units and is presented as the geometric mean (range) and/or [CVb%] unless otherwise stated.

Table 5:

Regimen	A N=26	B N=26	C N=20	G N=24
Parameter				
AUEC* (µg*hr/mL)	35.32 (11.1-81.25) [50.43]	31.69 (13.15-62.16) [39.1]	23.73 (11.95-45.48) [40.17]	27.74 (9.01-105.02) [60.16]
DN***	70.6	79.2	79.1	55.4
AUEC (0-24) (µg*hr/mL)	31.73 (6.41-78.44) [60.27]	28.6 (12.11-56.45) [43.42]	21.3 (9.23-44.25) [43.69]	24.48 (6.13-50.86) [58.56]

DN	63.4	71.5	71	48.9
C_{max} (µg/mL)	3.27 (1.23-6.02) [44.95]	3.01 (1.5-4.86) [27.66]	2.37 (1.39-3.79) [31.7]	2.72 (1.54-4.52) [37.0]
DN	6.54	7.52	7.9	5.44
$t_{1/2}$ (hr)	3.51 (1.98-10.1) [41.15]	3.02 (1.71-18.31) [52.03]	2.97 (1.39-13.33) [50.73]	3.07 (1.29-22.84) [65.02]
t_{max} median (hr)	8.01 (6-16)	10 (6-16)	8.03 (6-16)	8.02 (4-18)
C_{12} mean (µg/mL)	2.29[a] (0.13-5.4)	2.03[b] (0-3.83)	1.3[a] (0-3.55)	1.8[a] (0-4.18)
DN	4.58	5.07	4.33	3.6
Average effect (AUEC $_{0-24}$/Cmax)	9.7	9.5	8.9	9

* AUEC = area under the effect curve ($AUC_{(0-\infty)}$).
[a] n=28, [b] n=27
*** DN = Dose normalized values = the parameter value/dose of Compound A.

All the formulations having compositions according to the invention provided, after single dosing (Regimens A-C), an average Cmax and C12 of >1 µg dermatan sulfate units/mL plasma.

Repeat dose pharmacokinetics:

The pharmacokinetic results after repeat dosing are shown in Table 6 below, and in Figure 10 (Regimens D-F). Unless otherwise stated data is for day 5, session 5 and is representative of steady-state. Data is based on Compound A plasma levels and is presented as the geometric mean (range) unless otherwise stated.

Table 6:

Part II	Regimen D (n=5)	Regimen E (n=6)	Regimen F (n=7)	Regimen H (n=7)
AUC(0-∞) (ng*hr/mL)	16529[g] (13312 – 20862)	7850[g] (4898 – 13473)	6711[h] (4447 – 12396)	11735 (8593 – 14595)
DN***	33	19.6	22.3	23.4
AUC(0-τ) (ng*hr/mL)	12632 (8710 – 19014)	7946 (4805 – 17535)	5899 (4157 – 11205)	11183 (7901 – 14128)
DN	25.2	19.8	19.6	22.3
Cmax (ng/mL)	2375 (1177 – 3296)	1511 (617 – 3993)	1181 (884 – 2574)	2066 (1051 – 2822)
DN	4.7	3.7	3.9	4.1
Cminss (ng/mL)[b]	588 (202 – 1289)	516 (42.0 – 1149)	223 (101 – 293)	834 (568 – 1135)
DN	1.17	1.29	0.74	1.66
t1/2 (hr)	2.11[g] (1.71 – 3.19)	1.88[g] (1.75 – 2.00)	1.99[h] (1.26 – 3.85)	2.47 (2.07 – 3.32)
tmax (hr)[a]	8.00 (3.00 – 12.00)	4.50 (4.00 – 5.10)	5.00 (2.00 – 8.00)	5.00 (1.00 – 6.00)
PTF (%)[b]	210 (131 – 364)	222 (99.4 – 280)	231 (158 – 312)	208 (133 – 255)
DN	.42	.55	.77	.41
C_{12} mean (ng/mL) (SD*)	1180 (1247)	260 (445)	232 (158)	205 (105)
DN	2.36	.65	.77	.41
Average Absorption**	6.95	5.19	5.68	5.68
DN	13.9	12.9	18.9	11.3

PTF - peak-to-trough ratio at steady state
[a] Presented as median (range)
[b] Presented as arithmetic mean (range)
[d] n=27, [g] n=4, [h] n=6
* SD not reported if more than 30% of values were imputed
** average absorption = $AUC_{(0-\infty)}$ / C_{max}
*** DN = Dose normalized values = the parameter value/dose of Compound A.

All the formulations having compositions according to the invention provided, after repeat dosing (Regimens D-F), a steady-state average Cmax of > 0.25 µg/mL.

Formulas A and B provided a steady-state average Cminss of greater than 0.25 µg/mL.

Formulas A and B provided a steady-state average C12 of > 0.25 µg/mL.

Repeat dose pharmacodynamics:

The pharmacodynamic results are shown in Table 7 below, and in Figure 9 (Regimens D-F). Unless otherwise stated data is for day 5, session 5 and is representative of steady-state. Data is based on dermatan sulfate units in plasma and are presented as geometric mean (range) and/or [CVb%] unless otherwise stated.

Table 7:

Regimen:	D N=5	E N=6	F N=6	H N=7
Parameter:				
AUEC* (µg*hr/mL)	74.68 (47.03-103.3) [31.73]	50.76 (30.74-72.51) [33.85]	44.75 (30.94-60.43) [22.78]	65.21 (38.88-130.36) [44.52]
DN***	149.3	126.9	149.1	130.4
AUC (0-24) (µg*hr/mL)	69.08 (42.1-99.18) [34.12]	47.43 (28.69-68.98) [33.87]	39.92 (29.28-58.45) [27.09]	61.8 (38.23-122.25) [41.77]
DN	138.1	118.5	133	123.6
C_{max} (µg/mL)	5.25 (4.06-7.54) [23.43]	3.96 (2.25-6.51) [37.59]	3.05 (1.89-4.83) [30.01]	4.52 (3.11-7.42) [31.31]
DN	10.5	9.9	10.16	9.04
t_{max} median (hr)	12 (8-12)	8.02 (6-12)	10 (8-10)	8.02 (4-10)
$t_{1/2}$ (hr)	3.91 (2.83-4.81) [22.84]	3.63 (2.47-4.45) [22.72]	4.46 (2.4-12.61) [56.07]	3.23 (1.1-7.59) [69.08]
C12 mean (µg/mL)	4.27 (1.12-7.54)	2.97 (1.38-4.46)	2.4[a] (1.41-3.93)	3.42 (1.62-6.45)
DN	8.54	7.42	8	6.84

* AUEC = area under the effect curve ($AUC_{(0-\infty)}$).

[a] n=7

*** DN = Dose normalized values = the parameter value/dose of Compound A.

All the formulations having compositions according to the invention provided, after repeat dosing (Regimens D-F), a steady state average Cmax and C12 of >1 µg dermatan sulfate units/mL plasma.

In addition, in some subjects Regimen D (250 mg tablets BID) provided >1 (in some cases > 2) µg dermatan sulfate units/mL plasma for about 20 hours. This extended period of effective concentration may be useful, e.g., for maintaining effective drug levels in the event of missed or late dosing. This regimen may also provide effective drug concentrations at once-daily dosing.

Pharmacokinetic (PK)/Pharmacodynamic (PD) Study - Example 2 tablets:

Pharmacokinetic and pharmacodynamic properties of uncoated tablets according to examples 2A-1, 2B-1 and 2C-1, and an uncoated tablet made in the manner of Example 1A were evaluated in healthy human volunteers in a randomized, open-label, period-balanced, 4-period crossover study. Each subject received 4 dose regimens in 4 study sessions, with a minimum washout period between study sessions of 5 days.

Study subjects received a single oral dose of the test formulation after a light meal in the morning. A light meal consists of about 80 g carbohydrate, about 30 g protein, and about 12 g fat. At least 80% of the meal is consumed within 20 minutes, and subjects are dosed within 5 minutes of completing the meal. Lunch is provided about 4 hours post-dosing, and dinner about 11.5 hours post-dosing. An optional snack is provided about 8 hours post-dosing.

Dosage regimens were as follows: for Example 2A-1 and 2B-1 formulas – single dose 1x 500 mg tablet; Example 2C-1 and Example 1A formulas - single dose 2x 250 mg tablets.

The tablets according to the Example 1A formula (nominally 250 mg strength/660 mg, uncoated ½" round tablets) were prepared using granules made in the manner of Example 2 (2'45" post fluid addition mix time) and had a mean unit weight 661.6 mg, % target compound A by HPLC 97.4 (RSD 0.3% n=3), average hardness of 7-17 kp (e.g., about 12 kp) (n=3-5), ≤ 1.0% wt loss on friabilation (Van Kel, 25 rpm 4 min) (n=20 or 6 g).

Blood samples (about 2mL EDTA) are taken for determining Compound A plasma concentrations predose (within 15 minutes of dose), and at the following nominal intervals post-dose: 0.5, 2, 3, 4, 6, 8, 10, 12, 16, 18, 20, 22, and 24 hours. Blood samples (about 3mL Na citrate) are taken for determining anti-IIa activity via HCII predose (within 15 minutes of dose), and at the following nominal intervals post-dose: 4, 6, 8, 10, 12, 16, 18, 20, 22, and 24 hours.

Plasma samples were analyzed for compound A using a validated method based on protein precipitation followed by HPLC-MS/MS in accordance with the method described herein. The lower limit of quantification of the assay for Compound A was 5ng/mL (50 µL aliquot human plasma). Log_e –transformed AUC(0-t), $AUC_{(0-\infty)}$, Cmax and T1/2 were separately analyzed by a mixed effects model. Tmax was analyzed nonparametrically using the Wilcoxon's Matched Pairs Method. Descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum, 95% confidence intervals about the arithmetic mean and %CVb) were calculated for all PK parameters by regimen. For log_e-transformed endpoints, geometric means, 95% confidence intervals about the geometric mean, SD of the log_e-transformed data and between subject CVs were calculated. Homogeneity of variance was assessed by plotting the residuals against predicted values from the model, while normality was assessed by the use of normal probability plots. Within Subject coefficients of variation (CVw) were calculated based on the log-normal distribution.

The pharmacokinetic results after single dosing are shown in Table 8 below. Data is based on plasma concentrations of Compound A and is presented as the geometric mean [CVb%] or median (range) unless otherwise stated.

Table 8: PK values after single dosing

Formula:	Ex 1A	EX 2A-1	EX 2B-1	EX 2C-1
	N=39	N=38	N=37	N=39
Parameter:				
$AUC_{(0-t)}$ (ng*hr/mL)	11215 [43.9]	12588 [43.9]	12482 [38.1]	12165 [38.7]
$AUC_{(0-\infty)}$ (ng*hr/mL)	11103[c] [46.2]	12543[a] [44.2]	12422[b] [37.9]	12196 [38.7]
C_{max} (ng/mL)	2495 [40.0]	2813 [39.5]	2862 [42.1]	2746 [35.7]
$t_{1/2}$ (hr)	2.91[c] [37.7]	2.72[a] [34.6]	2.92[b] [32.1]	2.90 [33.2]
t_{max} median (hr)	3.00 (0.500, 12.0)	4.00 (0.500, 8.00)	3.00 (2.00, 6.03)	4.00 (1.98, 8.00)
C_{12} arithmetic mean (ng/mL)	141.86 [166.9]	203.68 [180.3]	152.94 [101.1]	192.53[d] [149.4]

[a] n=37, [b] n=36, [c] n=35, [d] n=40

The pharmacodynamic results are shown in Table 9. Data is based on plasma levels of dermatan sulfate units and is presented as the geometric mean (range) [CVb%] or median (range) unless otherwise stated.

Table 9: PD values after single dosing

Formula:	Ex 1A	EX 2A-1	EX 2B-1	EX 2C-1
	N=39	N=38	N=37	N=38
AUEC* (µg*hr/mL)	20.48 (9.08-47.72) [41.53]	21.74 (6.84-52.09) [43.8]	22.41 (8.02-54.36) [37.80]	22.4 (8.29-51.66) [44.13]
C_{max} (µg/mL)	2.09 (1.2-4.51) [34.06]	2.25 (1.04-6.12) [35.82]	2.25 (1.2-5.84) [30.43]	2.20[a] (1.07-5.42) [39.90]
$t_{1/2}$ (hr)	3.17 (1.96-5.18) [23.61]	2.97 (2.06-4.46) [17.98]	3.05 (1.52-7.1) [26.87]	3.1 (2-6.65) [28.16]
t_{max} median (hr) (Range)	8 (4-16)	8[a] (4-12)	8 (4-10)	8 (4-12)
C12 mean (µg/mL) (range)	1.04 (0.13-2.66)	1.31[a] (0.13-3.33)	1.28 (0.13-2.81)	1.36 (0.13-4.20)

AUEC = area under the effect curve ($AUC_{(0-\infty)}$).
[a] n=39

Uncoated tablets according to Examples 2A-1, 2B-1, 2C-1, and Ex 1A exhibited PK/PD which, based on PK/PD modeling, may provide antithrombotic efficacy in mammals. The PK/PD also suggests that the tablets are gastro-retentive. Surprisingly, caplets according to Examples 2A-1 and 2B-1 exhibit a Tmax similar to round tablets according to Example 2C-1, suggesting that each form has similar gastric retention.

Example 4 - Dissolution Profile

Dissolution is determined in accordance with USP <711> and <724>. Dissolution is determined utilizing a USP Dissolution Apparatus 2 equipped with 1L vessels and covers, a Distek Model 2230 autosampler, and a Hewlett Packard 8452 UV Spectrophotometer equipped with an autosampler and a peristaltic pump (wavelength range 220-450nm, analytical wavelength 319nm, integration time 5 sec, an appropriate cell length , background correction – subtract absorbance at 380nm).

Testing is conducted at 100 rpm (+/- 4rpm). The medium is 1 L (+/- 5 mL or 2.5 mL) of 0.05M acetate buffer (glacial acetic acid and sodium acetate) in 0.05M sodium dodecyl sulphate (SDS), pH 4.9 +/- 0.05, at 37C (+/- 0.5C). For 20L of medium: dissolve 52.4g Na acetate in 400 mL degassed water while stirring. Dissolve 288 g SDS in 3000mL degassed water while stirring. Add both solutions to a carboy containing 20L of degassed water, rinsing the solution containers with the carboy contents. Add 20.9 mL acetic acid and stir gently about 30 min. Adjust pH to 4.9 +/- 0.05.

Working standard/stock solutions of Compound A in the test medium are as follows: 125 mg tablets – 0.1 mg/mL solution; 150, 200, and 250 mg tablets - 0.2 mg/mL solution; 375, 400, and 500 mg tablets– 0.5 mg/mL solution. A few drops of MeOH can be used in the solutions to avoid foaming.

The absorptivity for the standard solution at 319 nm corrected for baseline at 380 nm should be between 44.0 -48.6 absorbance $(g/L)^{-1}$ cm^{-1}. The relative standard deviation of the response factors for absorbance measurements of standard solutions should not be more than 2%.

Each sample is done in replicate. For each sample replicate, a single tablet is placed into each of the dissolution vessels containing 1L medium according to USP<711> and <724>, and paddle rotation is started immediately (tablets should be freely moving in the vessel and ensured against sticking to the vessel during testing).

Automated sampling is conducted, with 12 mL pull at specified timepoints (consisting of 4.5 mL sample flush, 7.5 mL collection, 3-4 mL purge). Media is not replaced and any solids should be settled before analysis.

The absorbance of sample and standard solutions is determined. The absorbance of the dissolution medium is used as blank.

Calculations are as follows:

Response Factor (K) (mg/Absorbance unit) = $Ws/\Delta A_s$

where

ΔA_S = absorbance of a single standard at 319 nm minus 380 nm

W_S = weight of a standard (mg)

Absorptivity (a) $[(g/L)^{-1} cm^{-1}]$

$= \Delta A_S/Cs \times b$ OR $1/K_{av} \times b \times P \times D_s$

where:

ΔA_S = absorbance of a single standard at 319 nm minus 380 nm

C_S = concentration of the standard solution (wt/vol) in g/L

b = UV cell path length in cm (0.2 cm for 125 mg tablet; 0.1 cm for 150, 200, 250 mg tablet; 0.05 for 375, 400, or 500 mg tablet)

K_{av} = Average Response Factor

D_S = Dilution factor for standard solution (0.002 for 125 mg tablet; 0.004 for 150, 200, 250 mg tablet; 0.01 for 375, 400 or 500 mg tablet)

P = Purity of Standard (decimal)

Quantitation of Compound A in solution:

% Compound A dissolved per tablet = $(Y/L) \times K_{av} \times (D_s/D_u) \times P \times 100$

where:

Y = The appropriate expression for the sampling time. When a single sampling time is requested, only the first expression is used.

Time Y:

t_1 $(A_u \text{ at } t_1)(V \text{ at } t_1)$

t_2 $(A_u \text{ at } t_2)(V \text{ at } t_2) + (A_u \text{ at } t_1)(V_{rem}\ mL)$

t_3 $(A_u \text{ at } t_3)(V \text{ at } t_3) + [(A_u \text{ at } t_1) + (A_u \text{ at } t_2)](V_{rem}\ mL)$

t_4 $(A_u \text{ at } t_4)(V \text{ at } t_4) + [(A_u \text{ at } t_1) + (A_u \text{ at } t_2) + (A_u \text{ at } t_3)](V_{rem}\ mL)$

etc.

A_u = Absorbance for Compound A of a sample (319 nm minus 380 nm)

K_{av} = Average response factor for Compound A for all standards

D_S = Dilution factor for the standards (see above)

D_u = Dilution factor for a sample (1.00)

L = Label claim of the sample (e.g., 250 mg for a 250 mg tablet, 500 mg for a 500 mg tablet, etc.)

P = Purity of standard (decimal)

V = Volume of media in vessel at time point (mL)

V_{rem} = Volume removed at time point (mL)

Several tablets (e.g., n=6) from a given batch of each dosage formula are tested and the average value reported.

In some embodiments, tablets of the invention have an in-vitro dissolution profile wherein from about 5 to about 65% of the Compound A is released after 2 hours; from about 35 to about 85% of the Compound A is released after 4 hours; and not less than about 75% of the Compound A is released after 8 hours; wherein the dissolution is measured using a type 2 dissolution apparatus (paddle) at 100 +/- 4rpm, at a temperature of 37+/- 0.5C, in 1L +/- 5 ml of 0.05M acetate buffer in 0.05M sodium dodecyl sulfate, pH 4.9 +/- 0.05, for at least 8 hours. In some embodiments, not less than about 75% of Compound A is released after 6 hours. In other embodiments, the tablets have a release profile(s) as described herein.

Several tablets from one batch of each formula prepared as set forth in Example 1 were tested for dissolution (release of Compound A) and exhibited the following properties:

Time (hrs):	Ex 1A (250 mg) (n=6)		
	Avg (%)	RSD (%)	Range (%)
2	39	3.8	36-40
4	69	10.7	61-80
6	94	5.9	87-101
Time (hrs):	Ex 1B (200 mg) (n=6)		
	Avg (%)	RSD (%)	Range (%)
2	33	9.5	29-37
4	61	1.1	60-62
6	85	1.4	83-86
Time (hrs):	Ex 1C (150 mg) (n=6)		
	Avg (%)	RSD (%)	Range (%)
2	30	8.6	27-35
4	69	9.0	64-80
6	96	3.8	91-100

Test media 1L +/- 2.5 mL

The dissolution profiles of tablets according to Example 1 above are shown in Figure 11.

Another batch of formula A tablets made generally in accordance with Example 1 formula A (described in Example 3) exhibited the following dissolution properties (n=6):

Time (hrs)	Avg (%)	Range (%)
2	48	45-50
4	75	72-77
6	101	100-101

Several tablets from one batch of Example 2 formulas prepared as above were tested for dissolution (release of Compound A) and exhibited the following properties (average % release, range % release, n=6):

Time (hrs)	Ex 2A-1	Ex 2B-1	Ex 2C-1	Ex 2D-1	Ex 2F-1	Ex 2A-2	Ex 2C-2	Ex 2E-1
2	51, 47-57	46, 45-50	42, 36-48	48, 45-52	16, 15-17	23, 21-24	16, 14-16	21, 19-21
4	65, 60-70	60, 58-63	64, 61-65	70, 68-77	54, 46-62	51, 48-53	45, 43-46	52, 48-54
8	90, 85-97	88, 84-96	98, 95-101	96, 90-101	100, 98-102	81, 77-85	94, 88-101	91, 87-98

It is to be understood that the invention is not limited to the embodiments illustrated hereinabove and the right is reserved to the illustrated embodiments and all modifications coming within the scope of the following claims.

The various references to journals, patents, and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

It is to be understood that the present invention covers all combinations of particular and preferred groups described herein above. A given embodiment includes but is not limited to all disclosed embodiments encompassed thereby.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

What is claimed is:

1. A pharmaceutical composition in the form of a tablet comprising an effective amount of Compound A, wherein the composition is characterized by one or more of the following properties:

a) a steady state anti-IIa activity level of at least 1 µg (including, e.g., at least 2 µg) dermatan sulphate units/mL plasma over an extended period of time after oral administration; and/or

b) a steady state Compound A level of at least about 0.25-4 µg (including, e.g., at least 0.5-8 µg) Compound A/mL plasma over an extended period of time after oral administration; and/or

c) an in-vitro dissolution profile wherein:
from about 5 to about 65% of the Compound A is released after 2 hours;
from about 35 to about 85% of the Compound A is released after 4 hours; and
not less than about 75% of the Compound A is released after 8 hours;
wherein the dissolution is measured using a type 2 dissolution apparatus (paddle) under the following conditions: at 100 +/- 4rpm, at a temperature of 37+/- 0.5C, in 1L +/- 5 ml of 0.05M acetate buffer in 0.05M sodium dodecyl sulfate, pH 4.9 +/- 0.05, for at least 8 hours.

2. A composition of claim 1 wherein the steady state anti-IIa level and/or Compound A plasma level is exhibited for at least about 8 hours, at least about 10 hours, or at least about 12 hours, after oral administration.

3. A composition of claim 1 wherein from about 10 to about 55% of the Compound A is released after 2 hours; from about 40 to about 85% of the Compound A is released after 4 hours; and not less than about 75% of the Compound A is released after 6 hours.

4. A composition of claim 1 wherein from about 5 to about 40% of the Compound A is released after 2 hours; from about 35 to about 75% of the Compound A is released after 4 hours; and not less than about 75% of the Compound A is released after 8 hours.

5. A composition of claim 1 wherein the oral administration occurs in the fed state.

6. A pharmaceutical composition in the form of a tablet comprising an effective amount of Compound A, wherein the composition is capable of providing a steady state, mean Compound A concentration of at least about 0.25-0.4 (including, e.g., at least about 0.5-0.8) µg Compound A/mL plasma over a period of at least about 12 hours following oral administration.

7. A pharmaceutical composition comprising an effective amount of Compound A in the form of a tablet, characterized in that the tablet is gastro-retentive.

8. A pharmaceutical composition in the form of a tablet comprising a therapeutically effective amount of Compound A, a swelling polymer, a matrix polymer, and floating agent, and optionally further comprising a diluent, a binder, a glidant and/or a lubricant.

9. A pharmaceutical composition of claim 8 wherein the tablet comprises: from about 5 to about 60% Compound A, from about 5 to about 30% swelling polymer, from about 0.1 to about 7% matrix polymer, and from about 5 to about 15% floating agent, and optionally further comprises from about 20 to about 40% diluent, from about 0.1 to about 5% binder, from about 0.1 to about 5% glidant, and/or from about 0.1 to about 5% lubricant.

10. A composition of claim 9 wherein the tablet comprises:
from about 35 to about 50% Compound A, from about 5 to about 25% (e.g., about 5 to about 15%) swelling polymer, from about 0.1 to about 5% (e.g. about 0.1 to about 2%) matrix polymer, from about 5 to about 15% (e.g., about 9 to about 13%) floating agent, and optionally from about 20 to about 40% (e.g., about 20 to about 35%) diluent, from about 0.1 to about 3% (e.g., about 1 to about 2%) binder, from about 0.1 to about 5% (e.g., about 0.1 to about 1%) glidant, and from about 0.1 to about 5% (e.g., about 0.1 to about 1%) lubricant.

11. A composition of claim 9 wherein the tablet comprises:
from about 30-45% (e.g., about 30-40%) Compound A, from about 5-25% (e.g., about 10-25%) swelling polymer, from about 0.1-5% (e.g., about 2-5%) matrix polymer, from about 5-15% (e.g., about 8-10%) floating agent, and optionally from about 20-40% (e.g., about 25-35%) diluent, from about 0.1-3% (e.g., about 0.1-2%) binder, from about 0.1-5% (e.g., about 0.1-1%) glidant, and from about 0.1-5% (e.g., about 0.1-1%) lubricant.

12. A composition of claim 9 wherein the tablet comprises, based on its uncoated weight, 21-49% diluent, 7-15% floating agent, 7-24% swelling polymer, 0.1-6% matrix polymer, and

23-57% Compound A; and optionally further comprises 0.1-2% binder, 0.1-2% glidant, and/or 0.1-1% lubricant.

13. A composition of claim 12 wherein the tablet is prepared by wet granulation and comprises 1-5% intragranular diluent and 18-46% extragranular diluent.

14. A composition of claim 9 wherein the tablet comprises, based on its uncoated weight, 21-42% diluent, 8-15% floating agent, 7-15% swelling polymer, 0.1-2% matrix polymer, and 31-57% Compound A; and optionally further comprises 1-2% binder, 0.1-2% glidant, and/or 0.1-1% lubricant.

15. A composition of claim 14 wherein the tablet is prepared by wet granulation and comprises 2-5% intragranular diluent and 18-38% extragranular diluent.

16. A composition of any of claims 8-15 wherein the weight ratio of the swelling polymer to matrix polymer is from about 95:25 to about 95:5 (e.g., from 95:15 to about 95:5, e.g., from about 95:15 to about 95:10).

17. A composition of any of claims 8-16 wherein the components are independently selected as follows: the diluent is microcrystalline cellulose, the binder is povidone, the swelling polymer is sodium carboxy methyl cellulose (e.g., Aqualon 9H4F, Aqualon 7H3SF), the matrix polymer is hypromellose (e.g., Methocel K100M), the floating agent is Na bicarbonate, the glidant is colloidal silica, and the lubricant is magnesium stearate.

18. A composition of claim 17 wherein the sodium carboxy methyl cellulose has an average particle size of less than 325 mesh.

19. A composition of any of claims 8-18, comprising about 250, 375 or 500 mg Compound A.

20. A composition of any of claims 8-19, wherein the tablet is a caplet.

21. A method of providing a mean steady state anti-IIa level of at least 1 μg (including, e.g., at least 2μg) dermatan sulphate units/mL plasma in a mammal in need thereof comprising administering the composition according to any of the preceding claims to the mammal.

22. A method of providing a mean steady state Compound A plasma level of at least 0.25-0.4 µg (including, e.g., at least about 0.5-0.8 µg) Compound A/mL plasma in a mammal in need thereof comprising administering the composition according to any of claims 1-20 to the mammal.

23. A method of treating or preventing thromboembolic disorders (including thromboses or hypercoagulability) comprising administering an effective amount of the composition according to any of claims 1-20 to a patient in need thereof.

24. A method of claim 23 wherein the patient is a human.

25. A method of claim 23 wherein from about 125 to about 1000 mg (e.g., about 500, 750 or 1000 mg) Compound A is administered daily.

26. A method of claim 23 wherein from about 62.5 to about 500 mg (e.g, about 250, 375 or 500 mg) Compound A is administered every 8-16 hours (e.g., about every 10-14 or about every 12 hours).

27. A method of claim 23 wherein the Compound A is administered in the fed state.

28. A method of preparing a tablet comprising an effective amount of Compound A, wherein the method comprises:

a) forming a dry mixture comprising Compound A, a diluent, and a binder;

b) wet granulating the dry mixture with a suitable granulating fluid;

c) drying the wet granules to substantially remove the granulating fluid;

d) forming a compression mixture comprising mixing the dried granules with a matrix polymer, a swelling polymer, a floating agent, and optionally a diluent, lubricant and/or glidant;

e) compressing the mixture to form a tablet; and

f) optionally coating the tablet.

29. A method of claim 28 wherein step (a) the diluent is microcrystalline cellulose and the binder is povidone.

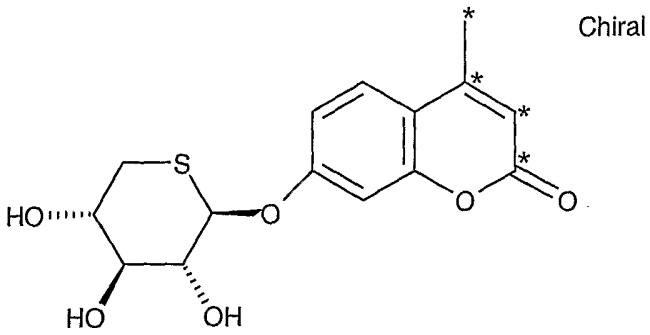
30. A method of claim 28 or 29 wherein step (b) the granulating fluid is water.

31. A method of any of claims 28-30 wherein step (c) the matrix polymer is hydroxypropylmethylcellulose, the swelling polymer is carboxy methyl cellulose, the floating agent is sodium bicarbonate, and the optional diluent is microcrystalline cellulose, the optional glidant is colloidal silica, and the optional lubricant is magnesium stearate.

32. A method of any of claims 28-31 wherein step (d) the tablet is compressed to a hardness of about 7 to about 32 kp (e.g., about 7 to about 17kp, about 16 to about 25 kp, or about 24 to about 32 kp).

33. A pharmaceutical tablet prepared by the method of any of Claims 28-32.

Figure 1 – chemical structure of compound A [$^{13}C_4$] (internal standard)



* Indicates position of ^{13}C.

Figure 2 – positive ion, ion spray mass spectra of compound A and compound A [13C4]

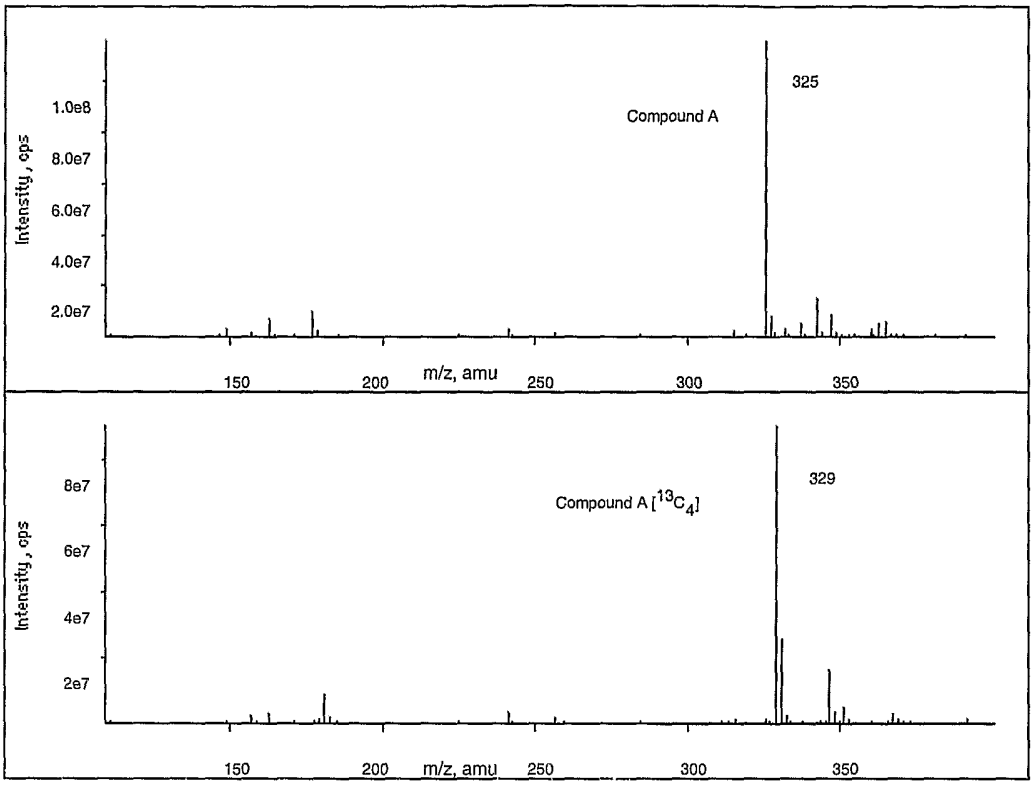


Figure 3 - product ion mass spectra of Compound A and Compound A [$^{13}C_4$]

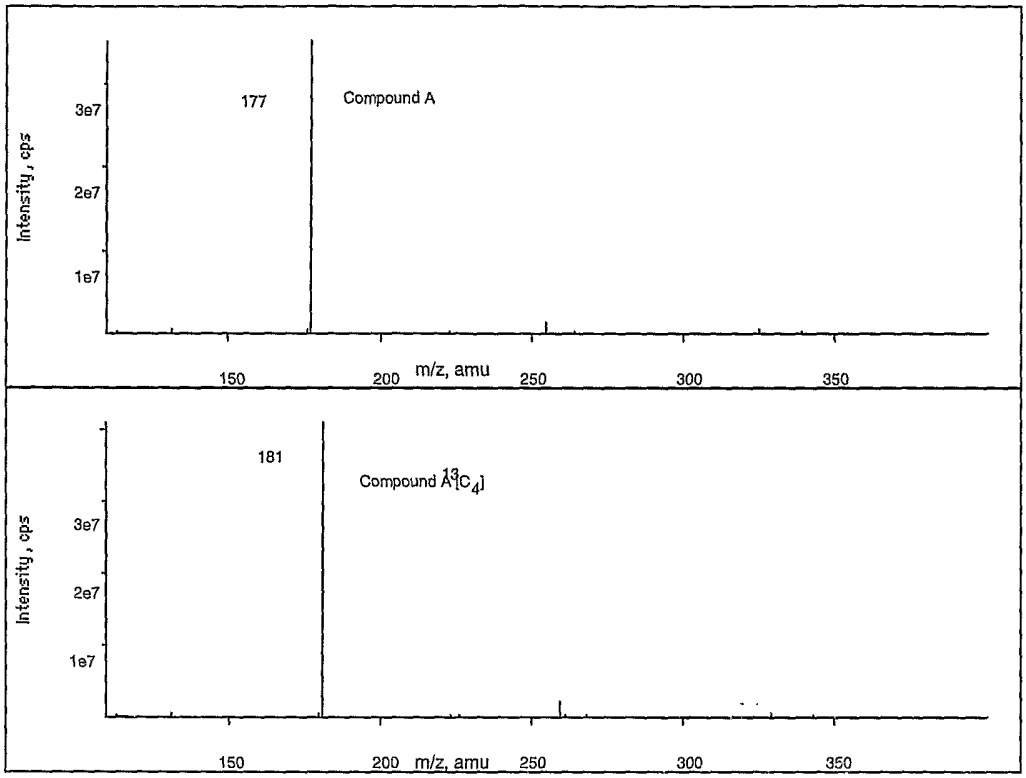


Figure 4 - Typical MRM Chromatograms of Drug Free Human Plasma

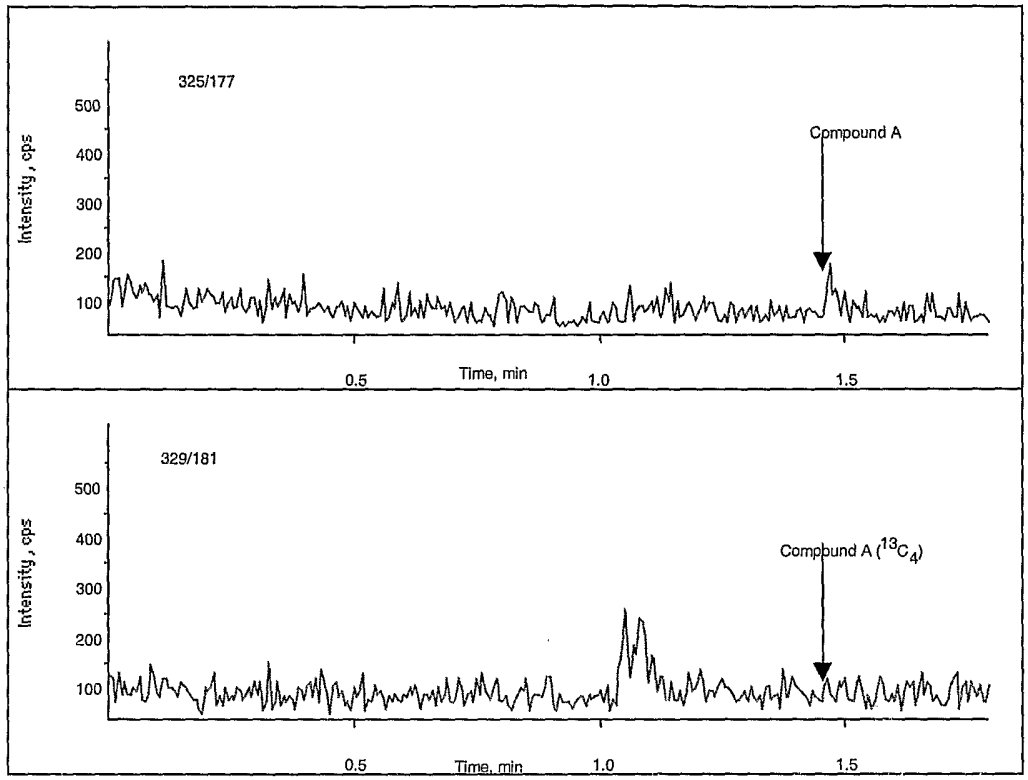


Figure 5 - Typical Chromatograms of Human Plasma Sample Containing 5.00 ng/mL of compound A (LLQ)

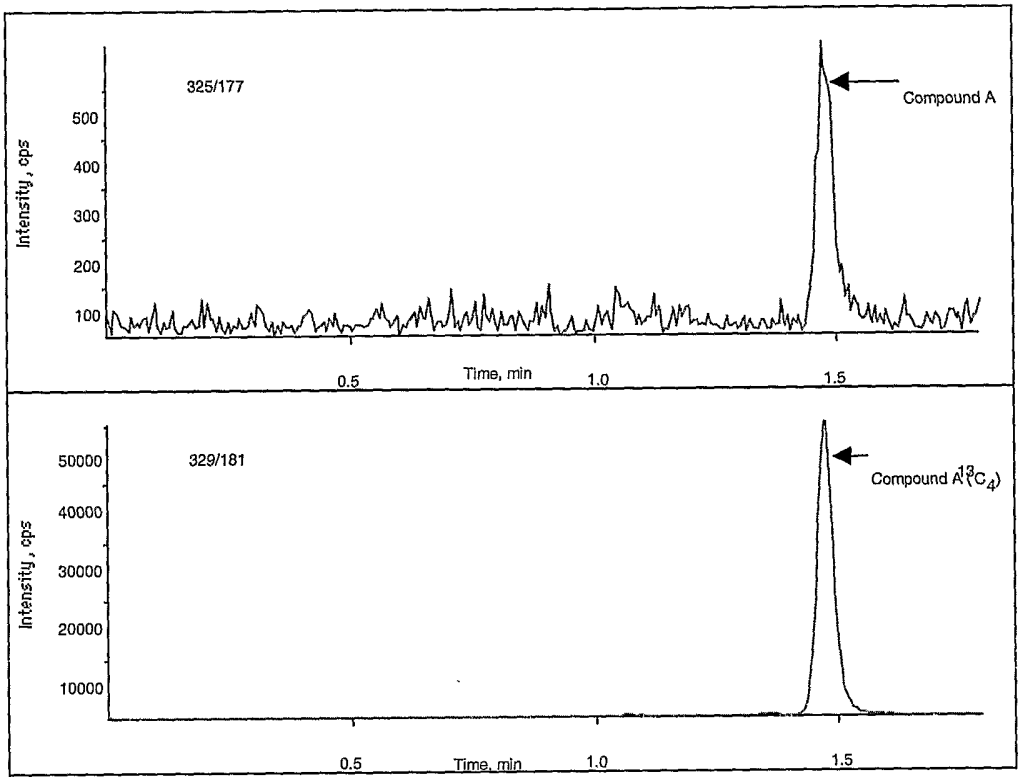


Figure 6 - Typical Calibration Plot for Compound A in Human Plasma

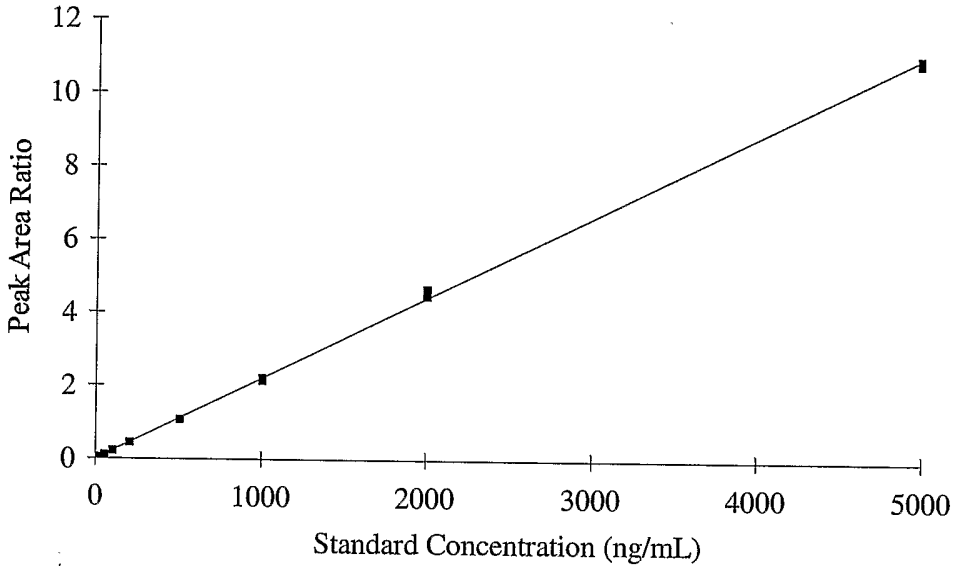
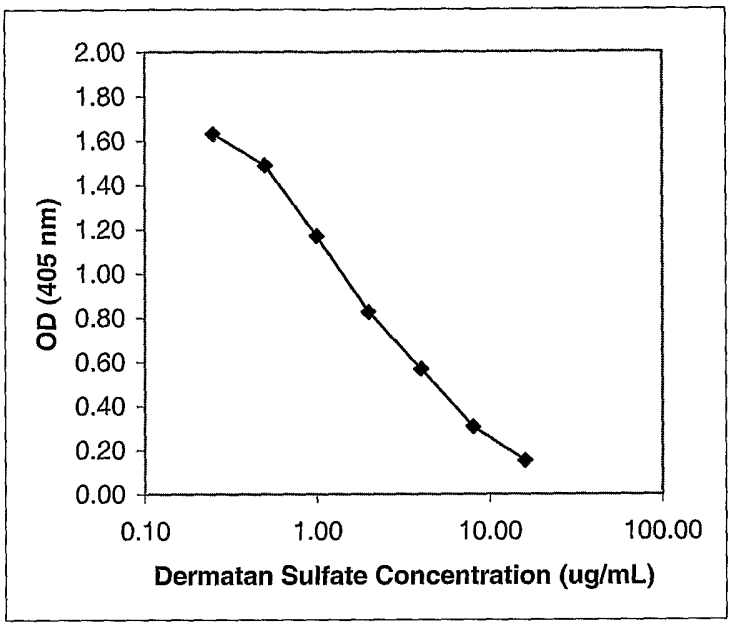


Figure 7 - Dermatan Sulfate Assay Standard Curve



Dermatan Sulfate Standards	
Conc. (ug/mL)	OD (405 nm)
16.00	0.15
8.00	0.31
4.00	0.57
2.00	0.83
1.00	1.17
0.50	1.49
0.25	1.63
0.00	1.76

Figure 8 - Median Compound A Plasma Concentration-Time Profiles Following a Single Dose Administration – Regimens A, B, C

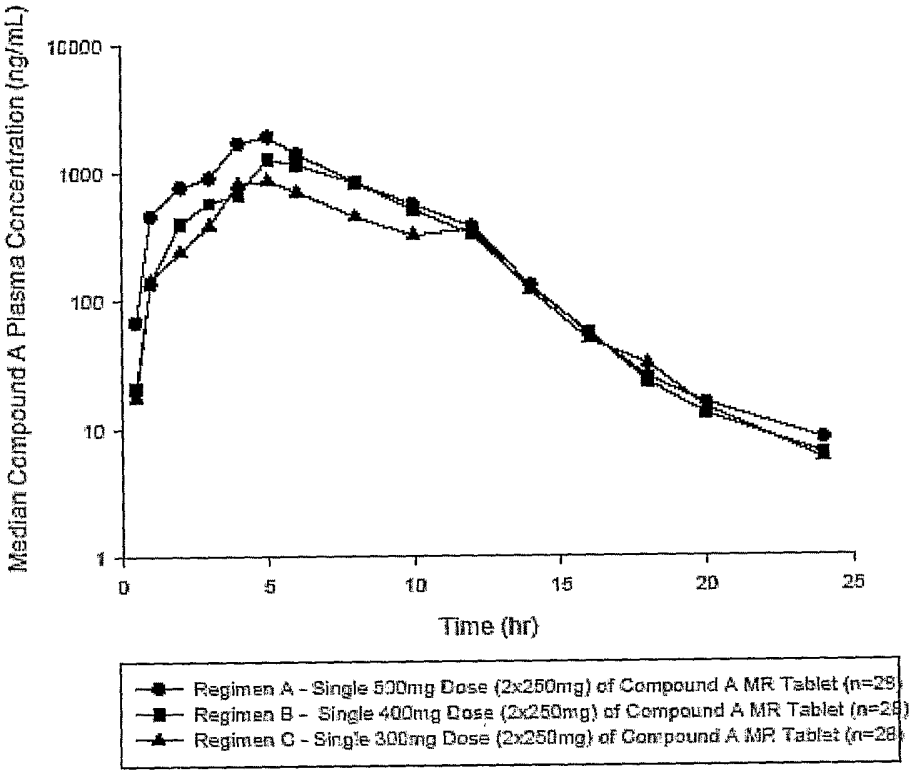
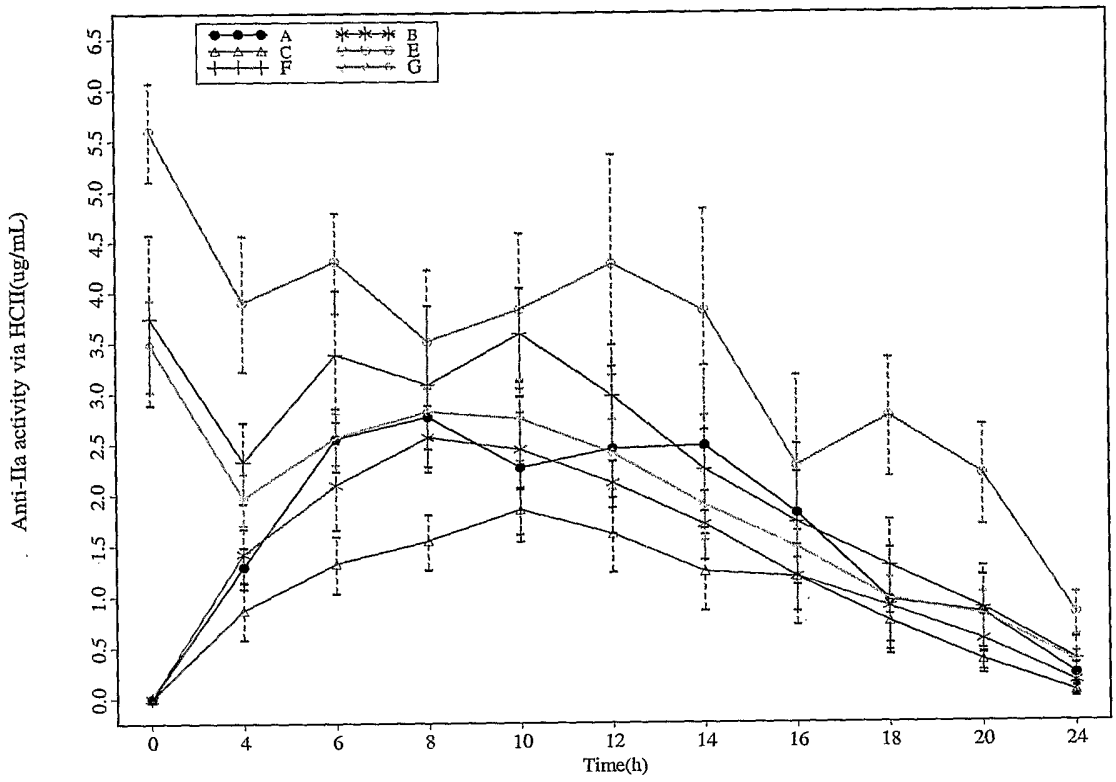


Figure 9 - Mean (+/-SE) Plot for Anti-IIa via HCII (in ug dermatan sulfate units/mL plasma) vs Time by Regimen



Regimen Key

A – single oral dose of Formula A

B – single oral dose of Formula B

C – single oral dose of Formula C

D – repeat oral dose of Formula A (BID) Days 1-4 followed by single oral dose on Day 5

E– repeat oral dose of Formula B (BID) Days 1-4 followed by single oral dose on Day 5

F– repeat oral dose of Formula C (BID) Days 1-4 followed by single oral dose on Day 5

Figure 10 - Median Compound A Plasma Concentration-Time Profiles Following Repeat Dosing on Days 2, 3, and 4, followed by a Single Dose of Compound A on Day 5 – Regimens D, E, F

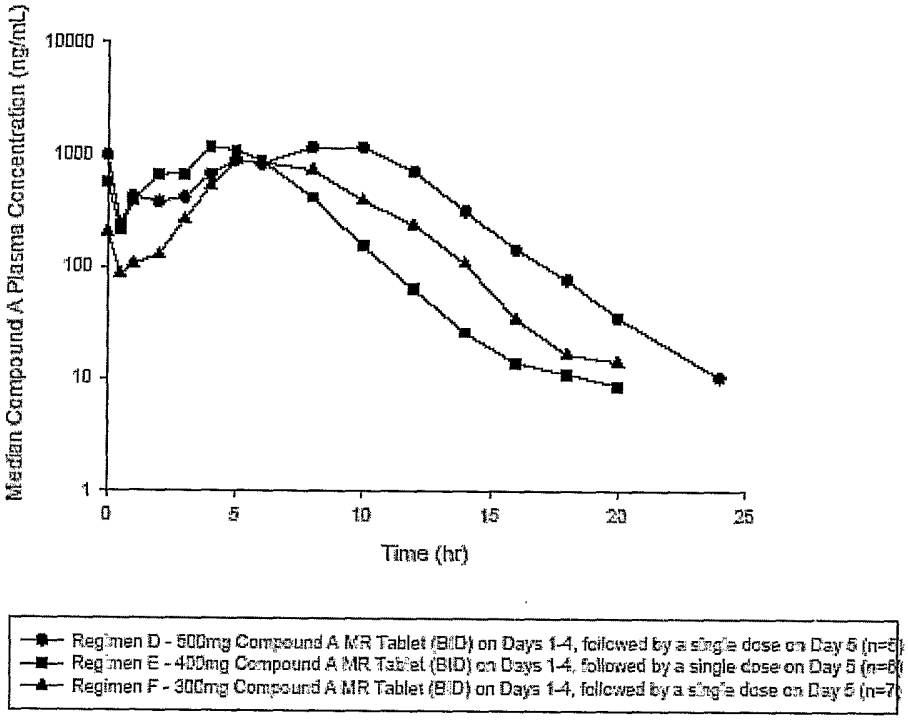


Figure 11 – Dissolution profiles Example 1 formulas A,B,C