(93%) and statins (95%) were randomly assigned colchicine 0.5 mg/day or no colchicine and followed for a median of 3 years (Nidorf *et al.*, *JACC*, 2013, 61 (4), 404-410). This study showed that colchicine 0.5 mg/day administered in addition to statins and other standard secondary prevention therapies appeared effective for the prevention of cardiovascular events in patients with stable coronary disease.

[0011] For the treatment of gout, the recommended dose of colchcine (COLCRYS®) is 1.8 mg/day in one or multiple doses in one hour For adults with gout, treatment is initiated with a dose of 1.2 mg at the first sign of symptoms followed by 0.6 mg one hour later. (Physician's Desk Reference, 68th ed., (2014)).

[0012] COLCRYS® is an immediate release formulation. Adverse effects associated with the administration of COLCRYS® include, but are not limited to, nausea, vomiting, abdominal pain, diarrhea, hair loss, weakness, nerve irritation, severe anemia, low white blood counts, and low platelets (Physician's Desk Reference, 68th ed., (2014)).

[0013] The instant invention addresses these and other needs by providing a modified formulation of colchicine characterized by a sustained release of an active ingredient. This invention additionally provides an effective, once-daily dosage form of colchicine or salts thereof, which may improve patient compliance and also may reduce some of the side effects of colchicine compared to the current or higher daily doses of immediate release colchicine formulations.

BRIEF SUMMARY OF THE INVENTION

[0014] According to aspects of the invention illustrated herein, there is provided a sustained release formulation of colchicine as an active ingredient, the formulation comprising colchicine or a pharmaceutically acceptable salt thereof; a retarding agent; and at least one pharmaceutically acceptable excipient.

[0015] According to ~~aspects of the invention~~an example illustrated herein, there is provided a method for treating and/or preventing a cardiovascular disease in a subject, comprising administering to the subject a therapeutically effective amount of a sustained release formulation of colchicine. In one other aspect, the present invention refers to the use of a sustained release formulation of colchicine according to the present invention in the manufacture of a medicament for treating and/or preventing a cardiovascular disease in a subject.

[0016] According to ~~aspects of the invention~~another example illustrated herein, there is provided a method for treating and/or preventing an inflammatory disease in a subject, comprising administering

to the subject a therapeutically effective amount of a sustained release formulation of colchicine. In another aspect, the present invention refers to the use of a sustained release formulation of colchicine according to the present invention in the manufacture of a medicament for treating and/or preventing an inflammatory disease in a subject.

[0017] According to aspects of the invention illustrated herein, there is provided a process of preparing a colchicine-sustained release tablet comprising forming a granulating agent by dissolving 0.25-0.75 % weight of the total composition of colchicine; adding a filling agent and a binder to Step A, and forming a wet granulation; drying the wet granulation of Step B; blending the dried granulation from Step C with a retarding agent, a filling agent, a glidant and a lubricant; and compressing the final granulation from step D into a tablet.

[0018] According to aspects of the invention illustrated herein, there is provided a shaped and compressed sustained release therapeutic composition comprising colchicine and excipients combined into a matrix, characterized by a long-lasting, slow and relatively regular incremental release of the colchicine upon administration, wherein the excipients include Hypromellose, and wherein the total amount of excipients is effective to bind the colchicine in a sustained release solid matrix and is no less than 99 percent of the weight of said shaped and compressed composition.

[0019] According to aspects of the invention illustrated herein, there is provided a shaped and compressed colchicine sustained release tablet made by wet granulating a sufficient amount of colchicine to comprise from about 0.25 to about 0.75 percent of the total composition with the excipients wherein the excipients comprise the following: lactose monohydrate from about 10 to about 80 percent of the total composition, pregelatinized starch from about 5 to about 50 percent of the total composition, Hypromellose 6mPa*s from about 1 to about 30 percent of the total composition, purified water (q.s.), Retalac from about 5 to about 40 percent of the total composition, talc from about 0.5 to about 5 percent of the total composition, and stearic acid from about 0.5 to about 5 percent of the total composition. In still another aspect, the present invention refers to the use of 0.5 mg colchicine in the manufacture of a medicament for treating a patient having a cardiovascular disease, wherein the medicament is to be administered orallyto a human patient, wherein the use provides a maximum colchicine blood plasma concentration (Cmax) in a range of about 0.5 to 5 ng/mL, and a time after the first administration at

which Cmax is reached (Tmax) of about 1.5 to 8 hr. In another aspect, the present invention refers to the use of an adjusted daily dosage amount of colchicine in the manufacture of a medicament for treating a patient with a cardiovascular disease, wherein the use comprises administration to the patient the adjusted daily dosage amount of colchicine, wherein the adjusted dialy dosage amount of colchicine is based on the weight of the patient, wherein the adjusted daily dosage amount of colchicine is about 50% to about 300% of 0.5 mg per day, which is suitable for the patient if the patient weighs about 70kg.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0020] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

33. Use of a sustained release formulation of colchicine according to any one of claims 1-22 in the manufacture of a medicamentA ~~method~~ for treating and/or preventing a cardiovascular disease in a subject~~, comprising administering to the subject a therapeutically effective amount of a sustained release formulation of colchicine according to any one of claims 1-22~~.

34. The ~~method~~ use of claim 33, wherein the cardiovascular disease is selected from the group consisting of acute pericarditis, recurrent pericarditis, post-pericardiotomy syndrome (PPS) and cardiovascular events in patients with stable coronary disease.

35. The ~~method~~ use of claims 33 and 34, wherein the total amount of colchicine in the formulation is from about 0.1 to about 5.0mg per dose.

36. The ~~method~~ use of any one of claims 33-35, wherein the amount of colchicine per dose is between 0.1 mg to 2.0 mg, 0.1 mg to 1.75 mg, 0.1 mg to 1.5 mg, 0.1 mg to 1.25 mg, 0.1 mg to 1.0 mg, 0.1 mg to 0.75 mg, 0.1mg to 0.6mg, 0.1 mg to 0.5 mg or more than 0.25 mg and less than 0.5 mg.

37. The ~~method~~ use of any one of claims 33-36, wherein the total daily dose of colchicine to be administered to the subject is no more than about 0.75mg.

38. The ~~method~~ use of any one of claims 33-37, further comprising ~~administering~~ administration to the subject a conventional therapy for the long-term prevention of an acute cardiovascular event in patients with established stable coronary disease.

39. The ~~method~~ use of any one of claims 33-38, wherein the acute cardiovascular event is acute coronary syndrome, out-of-hospital cardiac arrest or noncardioembolic ischemic stroke.

40. The ~~method~~ use of any one of claims 33-39, wherein the conventional therapy includes the administration of a colchicine-compatible statin.

41. The ~~method~~ use of any one of claims 33-40, wherein the colchicine-compatible statin is selected from the group consisting of atorvastatin, rosuvastatin, simvastatin and pravastatin, a derivative or a salt thereof.

42. Use of a sustained release formulation of colchicine according to any one of claims 1-22 in the manufacture of a medicament~~A method~~ for treating and/or preventing an inflammatory disease in a subject~~, comprising administering to the subject a therapeutically effective amount of a sustained release formulation of colchicine according to any one of claims 1-22~~.

43. The ~~method~~ use of claim 42, wherein the inflammatory disease is selected from the group consisting of gout, familial Mediterranean fever, Behcet's disease, Age-related macular degeneration and Alzheimer's disease.

44. The ~~method~~ use of claims 42 and 43, wherein the total amount of colchicine in the formulation is from about 0.1 to about 5.0mg per dose.

45. The ~~method~~ use of any one of claims 42-44, wherein the amount of colchicine per dose is between 0.1 mg to 2.0 mg, 0.1 mg to 1.75 mg, 0.1 mg to 1.5 mg, 0.1 mg to 1.25 mg, 0.1 mg to 1.0 mg, 0.1 mg to 0.75 mg, 0.1mg to 0.6mg, 0.1 mg to 0.5 mg or more than 0.25 mg and less than 0.5 mg..

46. The ~~method~~ use of any one of claims 42-45, wherein the total daily dose of colchicine to be administered to the subject is no more than about 0.75mg.

47. A process of preparing a colchicine-sustained release tablet comprising:

(A) forming a granuate by dissolving about 0.25 to about 0.75 % weight of the total composition of colchicine in an acceptable solvent, water and

(B) adding a binder and a filling agent to Step A, and forming a wet granulate;

(C) drying the wet granulate of Step B;

(D) blending the dried granulate from Step C with a retarding agent, a filling agent, a glidant and a lubricant; and

(E) compressing the final granulation from step D into a tablet.

48. The process of claim 47 wherein:

in Step A the binder is Hypromellose;

in Step B the filling agent used is lactose monohydrate and Pregelatinized Starch; and

53. A shaped and compressed colchicine sustained release tablet made by wet granulating a sufficient amount of colchicine to comprise from about 0.25 to about 0.75 percent weight of the total composition with the excipients wherein the excipients comprise the following:

Ingredient	**% Range**
Lactose monohydrate	10-80
Pregelatinized Starch	5-50
Hypromellose 6mPa*s	1-30
Purified water[1]	q.s.
Retalac (Compound of Lactose monohydrate and Hypromellose 4000mPa*s 50/50 w/w %)	5-40
Talc	0.5-5
Stearic acid 50	0.5-5

54. A composition of claim 53 wherein the total amount of excipients is at least about 99 percent of the total weight of said shaped and compressed composition.

55. Use of 0.5 mg colchicine in the manufacture of a medicament for~~A method of~~ treating a patient having a cardiovascular disease, ~~the method consisting of:~~wherein the medicament is to be administered orally ~~administering 0.5 mg colchicine~~ to a human patient, wherein the ~~method~~ use provides~~ing~~ a maximum colchicine blood plasma concentration (Cmax) in a range of about 0.5 to 5 ng/mL, and a time after the first administration at which Cmax is reached (Tmax) of about 1.5 to 8 hr.

56. The ~~method~~ use of claim 55, the ~~method~~ use further ~~providing~~ provides an area under the curve of colchicine plasma concentration versus time from time 0 to time t (AUC0-t), where t is the last time point with a measurable colchicine plasma concentration, in a range of about 4 to 20 ng-hr/mL.

57. The ~~method~~ use of claims 55 and 56, the ~~method~~ use further ~~providing~~ provides an area under the curve of colchicine plasma concentration versus time from time 0 to time infinity (AUC0-∞) in a range of 4 to 20 ng-hr/mL.

58. The ~~method~~ use of any one of claims 55-57, the ~~method~~ use further ~~providing~~ provides an area under the curve of colchicine plasma concentration versus time from time 0 to time t (AUC0-t), where t is the last time point with a measurable colchicine plasma concentration, in a range of about 4 to 20 ng-hr/mL and an area under the curve of colchicine plasma concentration versus time from time 0 to time infinity (AUC0-∞) in a range of about 4 to 20 ng-hr/mL.

59. The ~~method~~ use of any one of claims 55-58, wherein each said oral~~ly administering~~ administration comprises ~~administering~~ that one or more dosage forms each containing 0.5 mg colchicine are to be adminstered.

60. The ~~method~~ use of any one of claims 55-59, wherein the dosage form is a tablet.

61. The ~~method~~ use of any one of claims 55-60, wherein the tablet is a sustained release tablet.

62. Use of an adjusted daily dosage amount of colchicine in the manufacture of a medicament for~~A method of~~ treating a patient with a cardiovascular disease, ~~comprising administering~~wherein the use comprises administration to the patient ~~an~~ the adjusted daily dosage amount of colchicine, wherein the adjusted dialy dosage amount of colchicine is ~~-~~based on the weight of the patient, wherein the adjusted daily dosage amount of colchicine is about 50% to about 300% of 0.5 mg per day, which is suitable for the patient if the patient weighs about 70kg.

63. The formulation of claims 1 or 2, wherein the formulation releases at least about 80% of the colchicine in vitro in between about 1.5 and about 3.5 hours.