(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.

## SUMMARY

**[0014]** According to aspects of the invention illustrated herein, there is provided a sustained release formulation of colchicine comprising: granules comprising colchicine or a pharmaceutically acceptable salt thereof in an amount of 0.5 mg to 0.6 mg; a first filing agent comprising lactose monohydrate in an amount of 10% to 80% (w/w) of the formulation, and a binder comprising hydroxypropyl methylcellulose (HPMC) 6 mPa•s in an amount of 1% to 30% (w/w) of the formulation, wherein the total amount of colchicine is between 0.25 wt % and 0.75 wt % of the sustained release formulation; a release retarding agent admixed or blended with said granules in an amount of about 20% to about 30% w/w of the formulation, said release retarding agent being approximately equal portions of HPMC having a viscosity of 4000 mPa•s and lactose monohydrate at least one pharmaceutically acceptable excipient admixed or blended with said granules, wherein the pharmaceutically acceptable excipient is a starch, gelatin, polyvinylpyrrolidone (PVP), microcrystalline cellulose, hydroxypropyl cellulose (HPC), polyvinyl alcohol, talc, or a mixture thereof; and a second filling agent admixed or blended with the granules comprising lactose monohydrate in an amount of 10% to 30% (w/w) of the formulation.

**[0015]** According to 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.

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% weight to about 0.75 % weight of the total composition of colchicine in an acceptable solvent; and adding a binder and a filling agent to Step A, and forming a wet granulate, wherein the binder comprises hypromellose having a viscosity rating of 6 mPa•s; drying the wet granulation of Step B; blending the dried granulation from Step C with a retarding agent, a filling agent, a glidant, and/or a lubricant, wherein the retarding agent is approximately equal portions of hypromellose and lactose monohydrate having a viscosity of 4000 mPa•s; and compressing the blended granulation from step D into a tablet or pill form.

**[0018]** According to examples of the present disclosure, 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 tablet produced by wet granulating a sufficient amount of colchicine to comprise from about 0.25 percent weight to about 0.75 percent weight of the total tablet 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, HPMC 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 to 0.6 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 ng/mL to 5 ng/mL, and a time after the first administration at

WHAT IS CLAIMED IS:

1. A sustained release formulation of colchicine comprising:

(a) granules comprising colchicine or a pharmaceutically acceptable salt thereof in an amount of 0.5 mg to 0.6 mg, a first filling agent comprising lactose monohydrate in an amount of 10% to 80% (w/w) of the formulation, and a binder comprising hydroxypropyl methylcellulose (HPMC) 6 mPa•s in an amount of 1% to 30% (w/w) of the formulation, wherein the total amount of colchicine is between 0.25 wt % and 0.75 wt % of the sustained release formulation;

(b) a release retarding agent admixed or blended with said granules in an amount of 20% to 30% w/w of the formulation, said release retarding agent being approximately equal portions of HPMC having a viscosity of 4000 mPa•s and lactose monohydrate;

(c) at least one pharmaceutically acceptable excipient admixed or blended with said granules, wherein the pharmaceutically acceptable excipient is a starch, gelatin, polyvinylpyrrolidone (PVP), microcrystalline cellulose, hydroxypropyl cellulose (HPC), polyvinyl alcohol, talc, or a mixture thereof; and

(d) a second filling agent admixed or blended with the granules comprising lactose monohydrate in an amount of 10% to 30% (w/w) of the formulation.

2. The formulation of claim 1, wherein the formulation releases no more than 30% of the colchicine *in vitro* within the first 30 minutes.

3. The formulation of any one of claim 1 or claim 2, wherein the release retarding agent further comprises one or more cellulose ethers, cellulose esters, acrylic acid copolymers, waxes, gums, glyceryl fatty acid esters, or sucrose fatty acid esters.

4. The formulation of any one of claims 1-3, further comprising a glidant or a lubricant.

5. The formulation of any one of claims 1-4, wherein the total amount of the first and second filling agents in the formulation is between 5.0 wt % and 80.0 wt % of the formulation.

6. The formulation of claim 4, wherein the glidant or lubricant is selected from one or more of colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, talc, or tribasic calcium phosphate.

7. The formulation of claim 4, wherein the lubricant is selected from one or more of glyceryl behenate, stearic acid, hydrogenated vegetable oils, stearyl alcohol, leucine, polyethylene glycol, magnesium stearate, glyceryl monostearate, polyethylene glycol, ethylene oxide polymers, sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, or colloidal silica.

8. The formulation of any one of claims 4-7, wherein the lubricant is included in an amount between 0.5 wt % to 5 wt % of the formulation.

9. The formulation of any one of claims 1-8, wherein the formulation is in the form of a tablet, a pill, a capsule, a caplet, a suppository, a dermal patch, a cream, a sublingual formulation, an eye drop, a gel, an ointment, a troche, a pouch, sprinkles, or in fixed combination with a surgically insertable medical device.

10. The formulation of any one of claims 1-9, wherein the dosage form is a tablet.

11. The formulation of claim 10, wherein the compression strength of the tablet is between 30N and 130N.

12. The formulation of any one of claims 1-11 for use in preventing and/or treating a cardiovascular disease.

13. The formulation for use according to claim 12, wherein the cardiovascular disease is one or more of acute pericarditis, recurrent pericarditis, post-pericardiotomy syndrome (PPS), or cardiovascular events in subjects with stable coronary disease.

14. The formulation of any one of claims 1-11, for use in combination with conventional therapy for the long-term prevention of an acute cardiovascular event in subjects with established stable coronary disease.

15. The formulation for use according to any one of claims 12-14, wherein the acute cardiovascular event is acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke.

16. The formulation for use according to claim 14, wherein the conventional therapy is a statin.

17. The formulation for use according to claim 16, wherein the statin is combined with colchicine.

18. The formulation for use according to claim 16 or claim 17, wherein the statin is one or more of atorvastatin, rosuvastatin, simvastatin, pravastatin, and a salt thereof.

19. The formulation of any one of claims 1-11 for use in preventing and/or treating an inflammatory disease.

20. The formulation for use according to claim 19, wherein the inflammatory disease is gout, familial Mediterranean fever, Behcet's disease, Age-related macular degeneration, or Alzheimer's disease.

21. Use of a sustained release formulation of colchicine according to any one of claims 1-11 in the manufacture of a medicament for treating and/or preventing a cardiovascular disease in a subject.

22. The use of claim 21, wherein the cardiovascular disease is acute pericarditis, recurrent pericarditis, post-pericardiotomy syndrome (PPS), or cardiovascular events in subjects with stable coronary disease.

23. The use of claim 21 or claim 22, wherein the sustained release formulation is to be combined with a conventional therapy for the long-term prevention of an acute cardiovascular event in subjects with established stable coronary disease.

24. The use of any one of claims 21-23, wherein the acute cardiovascular event is acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke.

25. The use of claim 23, wherein the conventional therapy comprises a statin.

26. The use of claim 25, wherein the statin is one or more of atorvastatin, rosuvastatin, simvastatin, pravastatin, and a salt thereof.

27. Use of a sustained release formulation of colchicine according to any one of claims 1-11 in the manufacture of a medicament for treating and/or preventing an inflammatory disease in a subject.

28. The use of claim 27, wherein the inflammatory disease is gout, familial Mediterranean fever, Behcet's disease, Age-related macular degeneration, or Alzheimer's disease.

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

(A) forming a granulate by dissolving 0.25 % weight to 0.75 % weight of the total composition of colchicine in an acceptable solvent;

(B) adding a binder and a filling agent to Step A, and forming a wet granulate, wherein the binder comprises hypromellose having a viscosity rating of 6 mPa•s;

(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/or a lubricant, wherein the retarding agent is approximately equal portions of hypromellose and lactose monohydrate having a viscosity of 4000 mPa•s; and

(E) compressing the blended granulation from step D into a tablet or pill form.

30. The process of claim 29 wherein:

in Step B the filling agent is lactose monohydrate and pregelatinized starch; and

in Step D the filing agent is lactose monohydrate, the glidant is talc, and the lubricant is stearic acid.

31. The process of claim 29 or claim 30, wherein the tablet or pill comprises:

| **Ingredient** | **mg / Tablet** | **Tablet %** |
|---|---|---|
| Colchicine | 0.500 | 0.5 |
| Lactose monohydrate | 59.00 | 59.0 |
| Pregelatinized Starch | 7.50 | 7.5 |
| Hydroxypropyl Methylcellulose (HPMC) 6mPa•s | 1.000 | 1.0 |
| Purified water | q.s. | q.s. |
| Retalac (lactose monohydrate and hydroxypropyl methylcellulose (HPMC) 4000mPa•s, 50/50 w/w %) | 5.0 - 40.00 | 5.0 - 40.0 |

| | | |
|---|---|---|
| Talc | 1.00 | 1.0 |
| Stearic acid 50 | 1.00 | 1.0 |
| ***Total tablet weight [mg]:*** | **100.00** | |

32. A shaped and compressed colchicine tablet produced by wet granulating a sufficient amount of colchicine to comprise from 0.25 percent weight to 0.75 percent weight of the total tablet with the excipients, wherein the excipients comprise the following:

| **Ingredient** | **% Range** |
|---|---|
| Lactose monohydrate | 10-80 |
| Pregelatinized Starch | 5-50 |
| HPMC 6mPa•s | 1-30 |
| Purified water[1] | q.s. |
| Retalac (lactose monohydrate and hydroxypropyl methylcellulose (HPMC) 4000mPa•s, 50/50 w/w %) | 5-40 |
| Talc | 0.5-5 |
| Stearic acid 50 | 0.5-5 |

33. The composition of claim 32, wherein the total amount of excipients is at least 99 percent of the total weight of said shaped and compressed composition.

34. Use of 0.5 mg to 0.6 mg colchicine in the manufacture of a medicament for treating a patient having a cardiovascular disease, wherein the medicament is to be administered orally to a human patient, wherein the use provides a maximum colchicine blood plasma concentration (Cmax) in a range of 0.5 ng/mL to 5 ng/mL, and a time after the first administration at which Cmax is reached (Tmax) of 1.5 hr to 8 hr.

35. The use of claim 34, wherein the use further provides an area under the curve of colchicine plasma concentration versus time from time 0 to time t ($AUC_{0-t}$), wherein t is the last time point with a measurable colchicine plasma concentration, in a range of from 4 ng-hr/mL to 20 ng-hr/mL.

36. The use of claims 34 or claim 35, wherein the use further provides an area under the curve of colchicine plasma concentration versus time from time 0 to time infinity (AUC0-∞) in a range of from 4 ng-hr/mL to 20 ng-hr/mL.

37. The use of any one of claims 34-35, wherein the use further provides an area under the curve of colchicine plasma concentration versus time from time 0 to time t (AUC0-t), wherein t is the last time point with a measurable colchicine plasma concentration, in a range of 4 ng-hr/mL 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 from 4 ng-hr/mL to 20 ng-hr/mL.

38. The use of any one of claims 34-37, wherein in medicament comprises 0.5 mg to 0.6 mg of colchicine.

39. The use of any one of claims 34-38, wherein the dosage form is a tablet.