similar efficacy to treatment with high doses of the drug. Generally, these studies have shown that maintaining a febuxostat plasma concentration of 100 ng/ml is required to provide 95% or greater inhibition of xanthine oxidase. Currently, there the only commercially available formulations of febuxostat are immediate release formulations. There are no currently commercially available extended or delayed release formulations of febuxostat. Therefore, a formulation of febuxostat that maintains the drug concentration above the critical concentration of 100 ng/ml for an extended period of time is expected to result in higher efficacy of the drug, and would be a desirable treatment option for the control of hyperuricemia, gout, and many other disease states.

Summary of the Invention

In one aspect, there is provided a modified release pharmaceutical composition comprising immediate release febuxostat beads in an amount ranging from approximately 20% to approximately 40% (w/w) of the total composition weight and delayed release febuxostat beads having a solubility at pH levels greater than or equal to 6.8 in an amount ranging from approximately 60% to approximately 80% (w/w) of the total composition weight,

wherein said immediate release beads comprise

(a) an inert core in an amount ranging from about 50% to about 55% (w/w) of the weight of the immediate release bead, and

(b) an immediate release layer that encapsulates the inert core comprising a mixture of febuxostat and hydroxypropyl methylcellulose in an amount ranging from about 45% to about 50% (w/w) of the weight of the immediate release bead, the ratio of febuxostat to hydroxypropyl methylcellulose ranging from about 1.5 to about 3; and

wherein said delayed release beads comprise

(a) an inert core in an amount ranging from about 40.5% to about 43% (w/w) of the weight of the delayed release bead,

(b) an immediate release layer encapsulating the inert core comprising a mixture of febuxostat and hydroxypropyl methylcellulose in an amount ranging from about 35% to about 40% (w/w) of the weight of the delayed release bead, the ratio of febuxostat to hydroxypropyl methylcellulose ranging from about 1.5 to about 3,

(c) a delayed release enteric polymer layer encapsulating the immediate release layer comprising a delayed release enteric polymer in an amount ranging from about 17% to about 20% (w/w) of the delayed release bead, said delayed release enteric polymer comprising a mixture of methacrylic acid copolymer type A and methacrylic acid copolymer type B in a ratio ranging from approximately 0.1 to approximately 0.5, and

(d) a plasticizer in an amount ranging from about 1% to about 3% (w/w) of the weight of the delayed-controlled release bead, said plasticizer comprising triethyl citrate.

In one aspect, there is provided a modified release pharmaceutical composition comprising immediate release febuxostat beads in an amount ranging from approximately 20% to approximately 40% (w/w) of the total composition weight and delayed-controlled release febuxostat beads having a solubility at pH levels greater than or equal to 6.8 and providing prolonged release of febuxostat over a period of about 4 hours to about 6 hours, in an amount ranging from approximately 60% to approximately 80% (w/w) of the total composition weight,

wherein said immediate release beads comprise

(a) an inert core in an amount ranging from about 50% to about 55% (w/w) of the weight of the immediate release bead, and

(b) an immediate release layer that encapsulates the inert core comprising a mixture of febuxostat and hydroxypropyl methylcellulose in an amount ranging from about 45% to about 50% (w/w) of the weight of the immediate release bead, the ratio of febuxostat to hydroxypropyl methylcellulose ranging from about 1.5 to about 3; and

wherein said delayed-controlled release beads comprise

(a) an inert core in an amount ranging from about 34% to about 37% (w/w) of the weight of the delayed-controlled release bead,

(b) an immediate release layer that encapsulates the inert core comprising a mixture of febuxostat and hydroxypropyl methylcellulose in an amount ranging from about 31% to about 34% (w/w) of the weight of the delayed-controlled release bead, the ratio of febuxostat to hydroxypropyl methylcellulose ranging from about 1.5 to about 2.5,

(c) a controlled release layer that encapsulates the immediate release layer comprising a controlled release polymer in an amount ranging from about 10% to about 14% (w/w) of the weight of the delayed-controlled release bead, said controlled release polymer comprising a mixture of ethylcellulose aqueous dispersion and hydroxypropyl methylcellulose, the ratio of ethylcellulose aqueous dispersion to hydroxypropyl methylcellulose ranging from about 1.5 to about 3,

(d) a delayed release pH 6.8 layer that encapsulates the controlled release layer comprising a delayed release pH 6.8 polymer in an amount ranging from about 17.5% to about 20% (w/w) of the weight of the delayed-controlled release bead, said delayed release pH 6.8 polymer comprising a mixture of methacrylic acid copolymer type A and methacrylic acid copolymer type B, the ratio of copolymer type A to copolymer type B ranging from about 0.1 to about 0.5, and

(e) a plasticizer in an amount ranging from about 1% to about 3% (w/w) of the weight of the delayed-controlled release bead, said plasticizer comprising triethyl citrate.

In one aspect, there is provided a modified release pharmaceutical composition comprising immediate release febuxostat beads in an amount ranging from approximately 10% to approximately 30% (w/w) of the total composition weight and controlled release febuxostat beads providing prolonged release of febuxostat over a period of about 10 hours to about 12 hours, in an amount ranging from approximately 70% to approximately 90% (w/w) of the total composition weight,

wherein said immediate release beads comprise

(a) an inert core in an amount ranging from about 50% to about 55% (w/w) of the weight of the immediate release bead, and

(b) an immediate release layer that encapsulates the inert core comprising a mixture of febuxostat and hydroxypropyl methylcellulose in an amount ranging from about 45% to about 50% (w/w) of the weight of the immediate release bead, the ratio of febuxostat to hydroxypropyl methylcellulose ranging from about 1.5 to about 3; and

wherein said controlled release beads comprise

(a) an inert core in an amount ranging from about 47% to about 51% (w/w) of the weight of the controlled release bead,

(b) an immediate release layer that encapsulates the inert core comprising a mixture of febuxostat and hydroxypropyl methylcellulose in an amount ranging from about 42% to about 48% (w/w) of the weight of the controlled release bead, the ratio of febuxostat to hydroxypropyl methylcellulose ranging from about 1.5 to about 2.5, and

(c) a controlled release layer that encapsulates the immediate release layer comprising a controlled release polymer, said controlled release polymer comprising a mixture of ethylcellulose and hydroxypropyl methylcellulose in an amount ranging from about 4% to about 8% (w/w) of the weight of the controlled release bead, the ratio of ethylcellulose to hydroxypropyl methylcellulose ranging from about 1 to about 2.

In one aspect, there is provided the use of a therapeutically effective amount of the modified release pharmaceutical composition as defined above, in the manufacture of a medicament for treating a patient suffering from gout, hyperuricemia, prostatitis, inflammatory bowel disease, QT interval prolongation, myocardial infarction, cardiac hypertrophy, hypertension, nephrolithiasis, chronic kidney disease, metabolic syndrome, diabetes, diabetic nephropathy, congestive heart failure.

In one embodiment, the present disclosure relates to modified release dosage forms. The modified release dosage forms can comprise at least one xanthine oxidoreductase inhibitor or at least one xanthine oxidase inhibitor.

In another embodiment, the modified release dosage forms of the present disclosure comprise: a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof, wherein said dosage form, after oral administration to a subject in need of treatment thereof exhibits at least one of the following:

(a) maintains in the subject a plasma concentration of xanthine oxidoreductase inhibitor or pharmaceutically acceptable salt thereof greater than about 0.1 μg/mL for a period of from about 5 hours to about 24 hours; and

(b) produces in the subject a maximum plasma concentration (C_{max}) of a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof in an amount between about 2.5 μg/mL to about 0.5 μg/mL.

Alternatively, the modified release dosage form, after oral administration to a subject in need of treatment thereof, exhibits the following:

(a) maintains in the subject a plasma concentration of xanthine oxidoreductase inhibitor or pharmaceutically acceptable salt thereof greater than about 0.1 μg/mL for a period of from about 5 hours to about 24 hours; and