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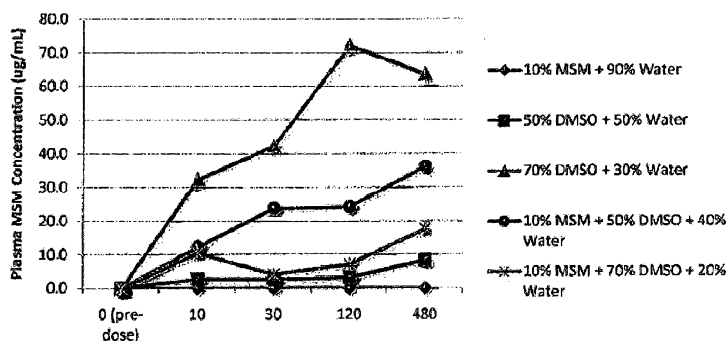
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(54) Title: DIMETHYL SULFOXIDE (DMSO) AND METHYLSULFONYLMETHANE (MSM) FORMULATIONS TO TREAT OSTEOARTHRITIS

Figure 2



(57) Abstract: Embodiments of the invention relate generally to the use of formulations comprising DMSO and MSM to treat arthritis (such as osteoarthritis), pain, inflammation, and/or degeneration. DMSO and MSM formulations are administered orally and/or topically in several embodiments and provide effective treatment of both chronic and acute symptoms of arthritis (e.g., osteoarthritis), pain, inflammation, and/or degeneration. Solid forms of DMSO are provided in several embodiments.

**DIMETHYL SULFOXIDE (DMSO) AND METHYLSULFONYLMETHANE
(MSM) FORMULATIONS TO TREAT OSTEOARTHRITIS**

RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Application Nos. 61/256,935, filed October 30, 2009; and 61/319,203, filed March 30, 2010, the disclosure of each of which is expressly incorporated by reference herein

BACKGROUND

Field of the Invention

[0002] Embodiments of the invention relate generally to formulations comprising dimethyl sulfoxide (DMSO) and/or methylsulfonylmethane (MSM) and the use of those compounds for the treatment of arthritis (such as osteoarthritis) and other conditions. Solid formulations comprising DMSO, alone or in combination with MSM, are provided in several embodiments.

Description of the Related Art

[0003] Cartilage is a protein matrix which functions to lubricate and cushion the joints. Osteoarthritis, or degenerative arthritis, refers to a class of diseases and mechanical abnormalities that result in degradation of joints, structurally and therefore, functionally. The articular cartilage of joints and the juxtaposed subchondral bone (e.g., the ends of the bone) are frequently affected.

[0004] Clinically, osteoarthritis may present with symptoms such as joint pain or minor tenderness of load bearing joints. Symptoms range from this level of “everyday aches and pains” to severe sensitivity of joints, stiffness, inflammation, creaking, and locking of joints.

[0005] Osteoarthritis is the most common form of arthritis in the United States, affecting nearly 27 million people, and is the leading cause of chronic disability. Osteoarthritis is linked to approximately 25% of visits to primary care physicians, and about 50% of non-steroidal anti-inflammatory prescriptions. Thus, in its various stages, osteoarthritis accounts for an enormous burden on those who suffer from the disease, their family and caretakers, as well as the medical community.

[0006] Severe cases of osteoarthritis may require surgery to replace joints, remove bone fragments, reposition and/or fuse bones to increase stability and reduce

pain. However, these surgeries are costly, are associated with long recovery times, and in some cases do not lead to significant alleviation of symptoms.

[0007] Dimethyl sulfoxide (DMSO; $(\text{CH}_3)_2(\text{SO})$) is a polar, aprotic solvent widely used as a solvent. It is frequently used in various chemical and biological reactions and as a cryoprotectant for cell storage. The strong unpleasant odor of DMSO, along with several undesired side effects, have adversely impacted the use of DMSO in medical applications.

[0008] Methylsulfonylmethane (MSM; $(\text{CH}_3)_2\text{SO}_2$), also known as dimethyl sulfone, is an organosulfur compound that is a metabolite of DMSO and certain sulfur-containing amino acids. MSM has been marketed primarily as a dietary supplement.

[0008A] Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed
5 before the priority date of each claim of this application.

[0008B] Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

SUMMARY

[0009] The etiology of osteoarthritis is varied, and includes hereditary, developmental, metabolic, and mechanical aspects that may lead to loss of cartilage. Ironically, the responses generated by the body (e.g., immune and regrowth processes) may accelerate damage to the cartilage. For example, when bone surfaces lose cartilage, subchondral bone may be exposed, damaged, and regrown. However, regrowth may lead to excessive proliferation of dense bone in central areas of cartilage loss, further exacerbating the cartilage loss. As a result, a person suffering from progressive osteoarthritis may experience increasing pain upon weight bearing, including walking and standing. Additionally, the decreased movement because of the pain may cause regional muscles to atrophy and reduce tension on ligaments, further compromising the functionality of the joint.

[0010] Several options for therapy are available currently for those afflicted with osteoarthritis. Paracetamol (Tylenol®/acetaminophen) is commonly used to treat osteoarthritis pain and has demonstrated roughly equivalent benefit to ibuprofen. However, doses demonstrating effective pain relief (~ 4g/day) have been associated

with alterations in liver function as well as gastrointestinal bleeding or renal damage when used chronically.

[0011] Non-steroidal anti-inflammatory (NSAID) drugs may be prescribed for more severe cases of osteoarthritis. This class of drugs acts by inhibiting the formation of prostaglandins and may reduce both the pain and inflammation associated with osteoarthritis. These drugs, however, are also associated with adverse events including increased gastrointestinal bleeding, stomach upset, cramping, diarrhea, and peptic ulcer. Some of these drugs, namely the cyclooxygenase-2 inhibitors, have been withdrawn from the market due to their elevated risk for cardiovascular disease. Several NSAIDs are available for topical use, though the therapeutic effect is generally minimal and short lived.

[0012] Oral corticosteroids carry a high rate of adverse side effects and produce limited symptomatic improvement, and therefore are not typically recommended for osteoarthritis treatment. Injections of corticosteroids into the intra-articular space may provide acute (e.g., several weeks) relief of pain, but do not generally offer a long term therapeutic effect.

[0013] Thus, there remains a need in the art for an effective treatment for osteoarthritis, particularly one that addresses both the chronic condition of osteoarthritis as well as the acute symptoms associated with the illness. Accordingly, in several embodiments, formulations comprising MSM and DMSO, individually or combined, are provided for either oral or topical use, either alone or in combination, to provide efficacious relief of both chronic and acute symptoms of osteoarthritis, while inducing minimal, reduced, or no, side effects.

[0013A] Accordingly, in a first aspect of the invention, there is provided an oral and topical dual formulation system for improving the symptoms of osteoarthritis, the system comprising:

an oral formulation comprising dimethylsulfoxide (DMSO) and methylsulfonylmethane (MSM),

wherein said oral formulation is suitable for oral administration,

wherein said oral formulation comprises about 300 mg to about 750 mg MSM,

5 and

wherein said oral formulation comprises about 10 mg to about 50 mg DMSO,

when used for oral administration to improve the symptoms of osteoarthritis, the DMSO in the oral formulation enhances the efficacy of MSM in the oral formulation and the DMSO reduces the amount of MSM in the oral formulation

10 required to achieve a comparable therapeutic result; and

a topical formulation comprising dimethylsulfoxide (DMSO) and methylsulfonylmethane (MSM),

wherein said topical formulation is suitable for topical administration,

wherein said topical formulation comprises about 10% to about 15% MSM,

5 wherein said topical formulation comprises about 40% to about 90% DMSO,

when used for topical administration to improve the symptoms of osteoarthritis, the MSM in the topical formulation reduces an odor and reduces at least one undesired side-effect of the DMSO in the topical formulation, and

wherein the oral formulation and topical formulation are used concurrently or sequentially to improve chronic and acute symptoms of osteoarthritis.

[0013B] In a second aspect of the invention, there is provided a method for producing the oral formulation according to the first aspect in a solid form, the method comprising: providing DMSO in a liquid form; combining said liquid DMSO with hydrogen peroxide; heating the liquid DMSO and the hydrogen peroxide to obtain a combination of DMSO and MSM; and cooling the DMSO and MSM combination into a solid formulation, wherein said solid formulation is solid at temperatures between 20 degrees Celsius and 30 degrees Celsius.

[0013C] In a third aspect of the invention, there is provided a use of the dual formulation system according to the first aspect in the preparation of a medicament for the treatment of one or more symptoms of osteoarthritis.

[0013D] In a fourth aspect of the invention, there is provided a kit comprising the dual formulation system according to the first aspect with instructions to administer the oral formulation orally 3 times daily and instructions to administer the topical formulation topically 3 times daily.

[0013E] In a fifth aspect of the invention, there is provided a method for treating at least one symptom of osteoarthritis, the method comprising: providing the dual formulation system according to the first aspect; orally administering or instructing oral administration of the oral formulation to a subject 1-4 times daily; topically administering or instructing topical administration of the topical formulation to said subject 1-4 times daily.

[0013F] In a sixth aspect of the invention, there is provided an oral and topical dual formulation system for treating at least one of joint pain and inflammation, the system comprising:

a first formulation comprising dimethylsulfoxide (DMSO) and methylsulfonylmethane (MSM),

wherein said first formulation is suitable for oral administration,

wherein said first formulation comprises about 300 mg to about 800 mg MSM,
and

wherein said first formulation comprises about 5 mg to about 50 mg DMSO,

when used for oral administration to treat at least one of joint pain and
5 inflammation, the DMSO in the first formulation enhances the efficacy of the MSM in
the first formulation and the DMSO reduces the amount of MSM in the first
formulation required to achieve a comparable therapeutic result; and

a second formulation comprising dimethylsulfoxide (DMSO) and
methylsulfonylmethane (MSM),

10 wherein said second formulation is suitable for topical administration,

wherein said second formulation comprises about 1% to about 15% MSM, and

wherein said second formulation comprises about 30% to about 90% DMSO,

when used for topical administration to treat at least one of joint pain and
inflammation, the MSM in the second formulation reduces an odor and reduces at least
15 one undesired side-effect of the DMSO in the second formulation, and wherein the first
formulation and second formulation are used concurrently or sequentially to treat at
least one of joint pain and inflammation on a chronic and/or acute basis.

[0013G] In a seventh aspect of the invention, there is provided the use of the
dual formulation system of the sixth aspect in the preparation of a medicament for the
treatment of joint pain and inflammation, joint pain or inflammation from arthritis, joint
pain or inflammation from rheumatoid arthritis, or joint pain or inflammation from
osteoarthritis.

[0013H] In an eighth aspect of the invention, there is provided a topical
formulation for treating joint pain and inflammation, the formulation comprising:

dimethylsulfoxide (DMSO) between about 40% to about 90% per dose,

methylsulfonylmethane (MSM) between about 5% and about 15% per dose, and

20 wherein said DMSO and MSM are suitable for topical administration to a
subject to treat one or more of joint disorders, inflammation, degeneration, and/or pain,
and

when used for topical administration to treat joint pain and inflammation, the MSM in
the topical formulation reduces odor associated with topical application of DMSO and
reduces at least one undesired side-effect of the DMSO in the topical formulation.

[0013I] In a ninth aspect of the invention, there is provided an oral formulation
for improving the symptoms of osteoarthritis, the formulation comprising:

dimethylsulfoxide (DMSO) in an amount of about 10 mg to about 50 mg
DMSO;

methylsulfonylmethane (MSM);

wherein said DMSO and MSM are provided in a solid form capable of encapsulation;

wherein said oral formulation is encapsulated in a capsule;

wherein said capsule delivers said DMSO and MSM in a time-released manner;

when used for oral administration to improve the symptoms of osteoarthritis said oral formulation is analgesic and said oral formulation is anti-inflammatory;

wherein said MSM reduces an odor associated with DMSO; and

wherein said MSM reduces one or more side effects associated with DMSO.

[0013J] In a tenth aspect of the invention, there is provided an oral formulation for improving the joint pain and inflammation, the formulation comprising:

dimethylsulfoxide (DMSO) in an amount of about 10 mg to about 50 mg DMSO;

methylsulfonylmethane (MSM);

5 when used for oral administration to improve joint pain and inflammation said oral formulation is analgesic and said oral formulation is anti-inflammatory;

wherein said MSM reduces an odor associated with DMSO; and

wherein said MSM reduces one or more side effects associated with DMSO.

[0013K] In a eleventh aspect of the invention, there is provided an oral and topical system for improving the symptoms of osteoarthritis, the system comprising:

10 a first formulation comprising dimethylsulfoxide (DMSO) and methylsulfonylmethane (MSM),

wherein said first formulation is suitable for oral administration,

wherein said first formulation comprises about 60-70% MSM, and

wherein said first formulation comprises about 0.1-3% DMSO,

15 when used for oral administration to improve the symptoms of osteoarthritis, the DMSO in the first formulation enhances the efficacy of MSM in the first formulation and the DMSO reduces the amount of MSM in the first formulation required to achieve a comparable therapeutic result, and

a second formulation comprising dimethylsulfoxide (DMSO) and methylsulfonylmethane (MSM),

20 wherein said second formulation is suitable for topical administration,

wherein said second formulation comprises about 10%-15% MSM, and

wherein said second formulation comprises about 50%-90% DMSO,

when used for topical administration to improve the symptoms of osteoarthritis, the MSM in the second formulation reduces an odor and reduces at least one undesired side-effect of the DMSO in the second formulation, wherein the first formulation and second formulation are used concurrently or sequentially to improve chronic and acute symptoms of osteoarthritis.

[0013L] In a twelfth aspect of the invention, there is provided a formulation comprising: dimethyl sulfoxide (DMSO) and MSM, wherein the formulation is in a solid phase at temperatures between about 20 degrees Celsius and about 30 degrees Celsius, wherein the formulation comprises about 10 mg to about 50 mg DMSO, and wherein the MSM in the formulation reduces an odor associated with the DMSO.

5 [0013M] In a thirteenth aspect of the invention, there is provided a method for producing a formulation according to the twelfth aspect in a form that is solid at temperatures between about 20 degrees Celsius and about 30 degrees Celsius, said method comprising: providing DMSO in a liquid form; combining said liquid DMSO with hydrogen peroxide; heating the liquid DMSO and the hydrogen peroxide to obtain a combination of DMSO and methylsulfonylmethane (MSM); and cooling the DMSO
10 and MSM combination into a solid formulation, wherein said solid formulation is solid at temperatures between about 20 degrees Celsius and about 30 degrees Celsius.

[0013N] In a fourteen aspect of the invention, there is provided a treatment system, comprising:

15 an oral formulation comprising about 0.045g/day dimethylsulfoxide (DMSO) and about 1.85g/day methylsulfonylmethane (MSM), and optionally

a topical formulation comprising 40%-90% dimethylsulfoxide (DMSO) and 10%-15% methylsulfonylmethane (MSM),

20 wherein the DMSO in the oral formulation enhances the efficacy of MSM in the oral formulation and the DMSO reduces the amount of MSM in the oral formulation required to achieve a comparable therapeutic result, wherein the MSM in the topical formulation reduces an odor and reduces at least one undesired side-effect of the DMSO in the topical formulation.

[0014] In several embodiments, formulations comprising DMSO and MSM, individually or combined, are formulated as solids. A solid form of DMSO, alone or in combination with MSM is particularly surprising and beneficial because, in some embodiments, the solid form is associated with less odor than the liquid form. In several embodiments, the solid form stays solid at room temperature (e.g., about 20°C - 23°C). In other embodiments, the solid form stays solid at temperatures up to 30°C, 45°C, 60°C, 75°C, 100°C, or higher. In some embodiments, the solid form does not

crystallize and/or lose its texture at temperatures below room temperature, 25°C, 15°C, 10°C, 5°C, or lower. In several embodiments, the solid form maintains its chemical stability and/or integrity (e.g., phase integrity) at a wide range of temperatures, including but not limited to ranges between about 0°C to about 100°C, about 5°C to about 50°C, about 10°C to about 40°C, about 20°C and about 30°C, and overlapping ranges thereof. In several embodiments, the solid form maintains a similar consistency, e.g., maintains one or more

of a hardness, firmness, density, texture, and/or viscosity that is at least 75%, 85%, 95% or 100% the same, over a range of temperatures from about 0°C to about 100°C, about 5°C to about 50°C, about 10°C to about 40°C, about 20°C and about 30°C, and overlapping ranges thereof. In several embodiments, the addition of a coating to the solid form and/or a stabilizer increases the stability temperature stability range by at least 10%, 25%, 50% or more. In one embodiment, the solid form maintains its chemical stability and/or integrity (e.g., phase integrity) in a range from about 10°C to about 40°C without a coating and about 0°C to about 50°C with a coating. Coatings include, but are not limited to, vegetable-based coatings, biopolymers, colloidal particles, multilayer emulsions, colloidosomes, or combinations thereof.

[0015] In several embodiments, solid forms of DMSO, alone or in combination with MSM, are provided in the form of a capsule. In one embodiment, the use of solidified DMSO reduces the odor typically associated with DMSO. In another embodiment, the use of solidified DMSO reduces the physiological side effects typically associated with DMSO. In some embodiments, the formulations are consumed orally to treat osteoarthritis, while in some other embodiments, the formulations are applied topically. In still other embodiments, both oral and topical formulations are used. In several other embodiments, formulations comprising DMSO and MSM, individually or combined, are formulated as liquids.

[0016] As used herein, the phrase “symptoms of osteoarthritis” shall be given its ordinary meaning and shall include, but not be limited to, one or more of the following: cartilage degeneration, degeneration of subchondral bone, joint pain, tenderness, stiffness, creaking, locking of joints, inflammation, structural changes in the joint, swelling, diminished grip strength, bony enlargement, diminished range of motion, osteophyte (or spur) formation, and synovial irritation. Symptoms of osteoarthritis can occur, for example, in the knee, toe, thumb, finger, ankle, spine, hip, shoulder or other joint.

[0017] In several embodiments, formulations comprising MSM, DMSO and/or a combination of MSM and DMSO, alone or with other colors, flavorings, additives, fillers, carriers, excipients, and/or therapeutics are used to prevent and/or treat

osteoarthritis and/or symptoms thereof, arthritis and/or symptoms thereof, inflammation, joint pain, and/or structural changes of the joint.

[0018] In several embodiments, formulations comprising MSM, DMSO and/or a combination of MSM and DMSO, alone or with other carriers, flavorings, additives, fillers, carriers, excipients, and/or therapeutics are used to prevent and/or treat the following conditions that are unrelated to an osteoarthritic etiology: tissue degeneration, pain (e.g., joint pain), and/or inflammation.

[0019] Due to its physical properties, DMSO exists as a liquid at room temperature, and is therefore typically utilized as a liquid. However, there is a long felt and as yet unmet need for a solid form of DMSO at room temperature. For example, a solid form of DMSO is particularly advantageous because, in some embodiments, it can be provided as a pill, tablet or capsule, is suitable for concentrated dosages, and exhibits reduced side effects as compared to a liquid form (e.g., less irritation, sensitivities, gastrointestinal effects, etc.). In several embodiments, solid forms offer controlled release in the body, and in some embodiments, are more slowly released and/or more effectively absorbed. In one embodiment, a solid form that dissolves in a desired area (e.g., small intestine) is provided, thereby offering enhanced bioavailability based on targeted delivery. Further, solid forms of DMSO exhibit reduced or no odor as compared to the liquid form in some embodiments. Thus, several embodiments of the present invention provide a formulation comprising DMSO that is solid at room temperature, and methods of making same.

[0020] In several embodiments, formulations comprising DMSO and MSM (and/or a compound related to MSM) exhibit reduced odor than formulations comprising DMSO alone. Formulations in liquid, gel, solid, and/or gaseous forms exhibit reduced odor when DMSO is combined with MSM (and/or a compound related to MSM) in some embodiments.

[0021] In several embodiments, the invention comprises an oral and topical system for improving the symptoms of arthritis (e.g., osteoarthritis), including, but not limited to, pain, osteophytes, stiffness, grip strength, limited range of motion, tissue enlargement in joints, inflammation (specific to a joint or localized to a general region of the body), swollen joints, joint deformity, and combinations thereof. In one embodiment,

the system comprises a first formulation comprising DMSO and MSM, wherein said first formulation is suitable for oral administration. In some embodiments, the first formulation comprises about 300 mg to about 750 mg MSM and about 10 mg to about 50 mg DMSO. In some embodiments, the first formulation comprises about 300 mg to about 700 mg MSM and about 10 mg to about 50 mg DMSO. The second formulation comprises DMSO and MSM, and is suitable for topical administration. In some embodiments, the second formulation comprises between about 100 mg and about 1500 mg MSM and between about 500 mg and about 5000 mg DMSO, depending on the volume applied. The second formulation, in some embodiments, comprises about 900 mg to about 1200 mg MSM and about 3000 mg to about 5000 mg DMSO. In some embodiments, the second formulation comprises about 10% to about 15% MSM and about 40% to about 70% DMSO, or higher (e.g., up to 90% or more DMSO).

[0022] In one embodiment, the first formulation (e.g., oral) comprises 650 mg MSM and 15 mg DMSO and the second formulation (e.g., topical) comprises 10% MSM and 50% DMSO. In one embodiment, the first formulation comprises 500 mg MSM and 15 mg DMSO and the second formulation comprises 917 mg MSM and 4585 mg DMSO. In one embodiment, an oral formulation comprises 400-600 mg MSM and 10-20 mg DMSO and a topical formulation comprises 800-1000 mg MSM and 3500-5000 mg DMSO.

[0023] In one embodiment, the first formulation comprises about 900 mg to about 2100 mg MSM and about 30 mg to about 150 mg DMSO and the second formulation comprises about 10% to about 15% MSM, and about 50% to about 90% DMSO. In one embodiment, the first formulation comprises about 900 mg to about 2100 mg MSM and about 30 mg to about 150 mg DMSO and the second formulation comprises about 2700 mg to about 3600 mg MSM, and about 9000 mg to about 15,000 mg DMSO.

[0024] In one embodiment, the first formulation comprises about 1500 mg MSM and about 45 mg DMSO and the second formulation comprises about 10% MSM and about 50% DMSO. In one embodiment, the first formulation comprises about 1500 mg MSM and about 45 mg DMSO and the second formulation comprises about 2751 mg MSM and about 10,800 mg DMSO.

[0025] In one embodiment, the first formulation comprises about 60-99% MSM, and about 0.1-3% DMSO and the second formulation comprises about 10-15% MSM, and about 50-70% DMSO, or higher (e.g., up to 90% or more DMSO).

[0026] In one embodiment, the first formulation comprises about 60-70% MSM and about 0.1-3% DMSO and the second formulation comprises about 10%-15% MSM and about 40%-90% (e.g., 50%-70%) DMSO.

[0027] In one embodiment, the first formulation comprises about 0.045g/day DMSO and about 1.85g/day MSM and the second formulation comprises about 50%-70% DMSO and about 10%-15% MSM. In one embodiment, an oral formulation comprises about 0.045g/day DMSO and about 1.85g/day MSM and a topical formulation comprises about 40%-90% DMSO and about 10%-15% MSM.

[0028] In several embodiments herein, only the first formulation (e.g., oral) is used (alone or combined with other compounds). In other embodiments, only the second formulation (e.g., topical) is used (alone or combined with other compounds). In yet other embodiments, a dual treatment approach is employed. In some embodiments, the dual treatment approach comprises an oral and topical therapy comprising DMSO, MSM and one or more additional compounds.

[0029] In one embodiment, the therapeutic system is suitable for treating a subject, and is administered (or is suitable for administration) in the following doses: the first formulation comprises about 10-30 mg MSM per kg body weight of the subject and about .1-1 mg DMSO per kg body weight and the second formulation comprises about 30-50 mg MSM per kg body weight and about 125-175 mg DMSO per kg body weight. In one embodiment, the second formulation comprises about 30-70 mg MSM per kg body weight and about 125-225 mg DMSO per kg body weight

[0030] In one embodiment, the first formulation and/or the second formulation are administered (or are suitable for administration) at least once, twice or thrice daily.

[0031] In several embodiments, the MSM reduces an odor or other side-effect of the DMSO. In some embodiments, MSM reduces dermal irritation that may be caused by administration of DMSO. In some embodiments, DMSO reduces a side-effect of the MSM. In some embodiments, DMSO enhances the efficacy of the MSM. In some

embodiments, the enhanced efficacy of the MSM is due to the DMSO in the oral formulation. In some embodiments, DMSO in the oral formulation reduces the amount of MSM that is required to achieve a given therapeutic result. MSM used according to any of the embodiments provided herein may be isolated, purified or processed. MSM that has been granted a GRAS (Generally Recognized As Safe) designation is used for several embodiments described herein.

[0032] In some embodiments, the first formulation is in a capsule, tablet, oral suspension, liquid, inhalant, and/or effervescent form, wherein said forms are optionally coated and/or flavored. The second formulation, according to some embodiments, is in a gel, cream, serum, liquid, spray, ointment, and/or patch form. Heat or cold therapy may be additionally provided in conjunction with the second formulation.

[0033] In several embodiments, the first oral formulation treats the chronic symptoms of osteoarthritis and/or generalized pain and/or injury and the second topical formulation treats the acute symptoms of osteoarthritis and/or localized pain and/or injury. The first and/or the second formulations are optionally provided in time-released formulations.

[0034] In one embodiment, the invention comprises the use of the formulations described herein in the preparation of a medicament for the treatment of osteoarthritis and/or symptoms of osteoarthritis. In one embodiment, the invention comprises a kit comprising one or more formulations according to any one of the preceding claims with instructions to administer the first formulation orally 1-4 times daily and/or instructions to administer the second formulation topically 1-4 times daily. In one embodiment, the instructions instruct the administration of the first formulation orally 3 times daily. The instructions may also instruct administration of the second formulation topically 1-4 times daily for up to two weeks. In one embodiment, the instructions instruct the administration of the second formulation topically 3 times daily for up to two weeks.

[0035] In several embodiments, the invention comprises a method for treating the symptoms of arthritis (e.g., osteoarthritis). Symptoms that are treated in some embodiments include one or more of pain, osteophytes, stiffness, grip strength, limited range of motion, tissue enlargement in joints, swollen joints, and joint deformity. In

some embodiments, the invention comprises a method for treating the symptoms other types of arthritis, such as, for example, adult onset rheumatoid arthritis. In some embodiments, the invention is used to treat and/or improve the symptoms of juvenile rheumatoid arthritis. In one embodiment, the method comprises providing the first and second formulation as disclosed herein, orally administering or instructing oral administration of the first formulation to a subject 1-4 times daily; and topically administering or instructing topical administration of the second formulation to said subject 1-4 times daily.

[0036] In several embodiments of the invention, a topical formulation for improving the symptoms of osteoarthritis is provided. In one embodiment, the formulation comprises DMSO in an amount between about 2000 mg to about 5000 mg DMSO per dose (e.g., a 5mL dose) and MSM in an amount between about 300 mg to about 1200 mg MSM per dose (e.g., a 5mL dose). In one embodiment, the formulation comprises DMSO in an amount between about 3000 mg to about 5000 mg DMSO per dose and MSM in an amount between about 900 mg to about 1200 mg MSM per dose. In one embodiment, the DMSO and MSM are suitable for topical administration to a subject to improve the symptoms of osteoarthritis. In one embodiment, the DMSO and MSM are suitable for topical administration to a subject to treat one or more of joint disorders, inflammation, degeneration, and/or pain. Optionally, an oral formulation comprises about 300 mg to about 700 mg MSM and about 10 mg to about 50 mg DMSO per dose is provided.

[0037] In one embodiment, MSM is configured to act as a lubricant to reduce irritation associated with topical application of DMSO. In one embodiment, MSM reduces the odor associated with topical application of DMSO.

[0038] In one embodiment, the invention comprises a method of reducing the amount oral DMSO to achieve a therapeutic effect comprising: providing the oral or topical formulation as described herein to reduce the amount of DMSO needed to achieve a therapeutic effect, thereby reducing the side effects of DMSO.

[0039] In several embodiments, the invention comprises an oral formulation for improving the symptoms of arthritis (e.g., osteoarthritis). In one embodiment, the formulation comprises DMSO and at least one second compound in a solid form that is

encapsulated in a capsule or other encapsulation format. In one embodiment, the capsule delivers said DMSO and at least one second compound in a time-released manner. In some embodiments, the oral formulation is analgesic and anti-inflammatory. The second compound reduces an odor associated with DMSO and reduces one or more side effects associated with DMSO. In one embodiment, the second compound is MSM, urea, a sulfur-binding agent, or combinations thereof. In one embodiment, the second compound comprises a nutrient (e.g., an amino acid). In one embodiment, the second compound comprises a carbonyl group attached to two organic amine residues. In one embodiment, the second compound includes carbamide peroxide, allantoin, and hydantoin, biurets, amides, carbamates, diimides, carbodiimides, thiocarbamides, or combinations thereof. Preferably, one or more of MSM, urea and/or a sulfur-binding compound are used, although other compounds are provided in several embodiments to reduce an odor or side-effect of DMSO.

[0040] In one embodiment, the encapsulated oral formulation is provided in a dosage of about 1 gram or less. In one embodiment, the formulation is suitable for administration 1-4 times per day with or without food. In some embodiments, the synergistic effects of DMSO and MSM do not require the formulation to be ingested with food. In several embodiments, the use of MSM permits higher concentrations of DMSO to be used and tolerated, by for example, reducing the side-effects of DMSO and/or reducing the odor associated with DMSO. In one embodiment, the use of MSM in amounts greater than 800 mg (e.g., in a single or daily dose) increase the tolerability of DMSO in amounts greater than 200 mg (e.g., in a single or daily dose).

[0041] In several embodiments of the invention, a formulation comprising DMSO in a solid form is provided. In some embodiments, the DMSO is in a solid phase at room temperature. The DMSO in solid formulation is suitable for the treatment of several disorders, including arthritis (e.g., osteoarthritis, rheumatoid arthritis), and other disorders that would benefit from DMSO treatment (e.g., osteophyte formation). In some embodiments, the solid formulation is used for the treatment of inflammation, pain, or a combination thereof. In several embodiments, DMSO and MSM are combined to form a solid, wherein the solid remains a solid at room temperature. The solid formulation includes, but is not limited to, a capsule, a gel-cap, a tablet, an oral suspension, a powder,

an effervescent, or combinations thereof. A coating is provided in some embodiments. The coating provides sustained-release, sustained-action, extended-release, controlled-release, or continuous-release of the formulation according to several embodiments. In some embodiments, the coating further provides a flavorant. In one embodiment, DMSO is between about 0.01% to about 10% by weight of the formulation. In another embodiment, DMSO is between about 45% to about 55% by weight of the formulation. In one embodiment, the formulation is provided in a capsule comprising about 100 mg to about 1000 mg of said DMSO, wherein said capsule is suitable for delivery 1-4 times daily.

[0042] In several embodiments, the invention comprises a method for producing DMSO in a form that is solid at room temperature. In one embodiment, the method comprises providing DMSO in a liquid form, combining said liquid DMSO with hydrogen peroxide, heating the liquid DMSO and the hydrogen peroxide to obtain a combination of DMSO and MSM, cooling the DMSO and MSM combination into a solid formulation, wherein said solid formulation is solid at room temperature. Flaking, prilling and/or freezing is performed according to some embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0043] Figure 1 depicts plasma concentrations of MSM after a 5 minute topical exposure to 10% MSM and varied concentrations of DMSO.

[0044] Figure 2 depicts the change from baseline of the MSM plasma concentrations.

DETAILED DESCRIPTION

[0045] The invention, in some embodiments, comprises a formulation comprising DMSO and MSM, individually or combined, to treat the chronic effects of osteoarthritis as well the acute symptoms associated with osteoarthritis. In several embodiments, the invention comprises a therapeutic system comprising DMSO and MSM, individually or combined, to treat generalized pervasive pain via an oral formulation and localized pain via a topical formulation. In one embodiment, topical formulations of DMSO and/or MSM are also effective for generalized pain. In several embodiments, formulations comprising DMSO and MSM, individually or combined, are multifunctional in that the formulations not only treat the symptoms of an illness (such as

osteoarthritis), but also confer unrelated benefits (e.g., improvements in skin and other aesthetic benefits, cardiovascular health, neurological health, immunity, vision, etc.).

[0046] As discussed herein, in several embodiments, there is provided an oral and topical dual formulation system for improving the symptoms of arthritis (including but not limited to osteoarthritis), the system comprising a first formulation comprising DMSO and a sulfur-binding and/or sulfur-based agent (including but not limited to MSM), wherein the first formulation is suitable for oral administration, wherein the first formulation comprises about 300 mg to about 750 mg MSM (or other agent) and about 10 mg to about 50 mg DMSO (e.g., about 650 mg MSM, or other agent, and about 15 mg DMSO) and a second formulation comprising DMSO and MSM (or other agent), wherein the second formulation is suitable for topical administration, wherein the second formulation comprises about 10% to about 15% MSM (or other agent) about 40% to about 70% DMSO, or higher (e.g., about 10% MSM, or other agent, and about 50% DMSO).

[0047] Unless stated otherwise, percentages of MSM, DMSO or other compounds provided herein are provided as % by weight.

[0048] In one embodiment, a dual formulation system comprising an oral dosage of 500 mg MSM and 15 mg DMSO together with a topical dosage of 50% DMSO and 10% MSM is provided. The oral dosage may be in the form of a tablet, capsule, powder, liquid, oral suspension, effervescent, or any other form suitable for oral delivery. The topical dosage may be in the form of a spray, gel, cream, lotion, patch, or any other form suitable for topical delivery. In some embodiments, the formulation is administered intravenously or via inhalation in addition to, or instead of, oral administration.

[0049] In several embodiments, the combined use of MSM reduces or eliminates the odor normally associated with DMSO. In some embodiments, the use of solid DMSO reduces or eliminates the odor normally associated with DMSO. The odor reduction is surprising, and beneficial in several embodiments because practitioners have avoided using DMSO in high concentrations (or in any amount) because of its unpleasant odor.

[0050] In some embodiments, the invention comprises an oral formulation of DMSO and MSM. In other embodiments, the invention comprises a topical formulation

of DMSO and MSM. According to one embodiment, the topical formulation is particularly advantageous because MSM reduces or eliminates the skin irritation that can result from that topical application of DMSO. For example, in some embodiments, MSM acts as a lubricant and/or barrier that shields the skin from DMSO while still permitting penetration. In one embodiment, topical DMSO in concentrations greater than 25% (e.g., 50%, 70%, or more) are tolerated because of the presence of MSM. In one embodiment, the presence of MSM reduces the formation of rash, redness, dryness of skin, itching, and/or combinations thereof. In one embodiment, MSM reduces the occurrence, probability or symptoms associated with a generalized allergic reaction to DMSO, including heart arrhythmias and breathing difficulties. Because higher concentrations of DMSO can be administered topically in certain embodiments, the oral dose of DMSO can be reduced, thereby reducing the gastrointestinal side effects that can result from the topical administration of DMSO.

[0051] In several embodiments, the amount of DMSO is reduced when combined with MSM because of additive or synergistic effects between DMSO and MSM. In several embodiments, the amount of MSM is reduced when combined with DMSO because of additive or synergistic effects between DMSO and MSM. In several embodiments, MSM is provided in solution in a concentration of less than about 15%. In some embodiments, oral doses of MSM of less than about 2 grams per day are administered (e.g., 1g, 1.5g, 1.75g and 1.85g) to reduce gastrointestinal side effects in certain applications. In several embodiments, DMSO increases the penetration of MSM into tissue (e.g., skin).

[0052] In another embodiment, a formulation comprises, consists or consists essentially of an oral dosage (e.g., a solid form) of about 200 mg to about 2000 mg MSM and about 1 mg to about 100 mg DMSO together with a topical dosage of about 5% to about 90% DMSO and about 1% to about 50% MSM. In some such embodiments, MSM in the oral dosage ranges from about 200 to 500 mg, 500 to 800 mg, 800 to 1100 mg, 1100 to 1400 mg, 1400 to 1700 mg, 1700 to 2000 mg, and overlapping ranges thereof. In some such embodiments, DMSO in the oral dosage ranges from about 10 to 30 mg, 30 to 50 mg, 50 to 70 mg, 70 to 90 mg, 80 to 100 mg, and overlapping ranges thereof. In one embodiment, the invention comprises, consists or consists essentially of about 200 mg to

about 2000 mg MSM and about 1 mg to about 100 mg DMSO, e.g., 400-600 mg MSM and 10-20 mg DMSO, 500 mg MSM and 15 mg DMSO, or 650 mg MSM and 15 mg DMSO.

[0053] In several embodiments, the invention comprises an oral formulation (e.g., a solid form) comprising a ratio of MSM to DMSO of 33:1, and optionally, a topical formulation comprising a ratio of MSM to DMSO of 1:5. In other embodiments, the invention comprises an oral formulation having a ratio of MSM to DMSO of 30-50:1, and optionally, a topical formulation having a ratio of MSM to DMSO of 1:2-10. In yet other embodiments, the invention comprises an oral formulation having a ratio of MSM to DMSO of 25-35:1, and optionally, a topical formulation having a ratio of MSM to DMSO of 1:3-7. The ratio of MSM to DMSO in several embodiments is surprisingly advantageous because the MSM synergistically improves the efficacy of DMSO. Thus, DMSO, which may have side effects when administered at certain concentrations, may be provided at lower concentrations to offer the same or better therapeutic efficacy. As discussed herein, the presence of MSM in certain embodiments functions as an emollient. In some embodiments, MSM reduces the odor normally associated with DMSO.

[0054] In some embodiments, the invention comprises a method of managing the symptoms of osteoarthritis by administering an oral dosage of MSM and DMSO daily for at least 1 month, together with a topical dosage of DMSO and MSM daily for about two weeks. Certain embodiments are particularly advantageous because they permit fast-acting symptom relief with the topical dosage, while allowing the oral dosage to gradually provide long-term relief. In some embodiments, relief is provided for extended periods of time, e.g., a week or more, several weeks, about a month, two months or more. At the point when the oral dosage becomes effective, patients can discontinue repetitive use of the topical formulation, thus reducing the risk of skin irritation and/or localized bioaccumulation. In still other embodiments, once the oral dosage has reduced pain and/or symptoms, the topical formulation is not necessary. In some embodiments, the dosage of the oral or the topical formulations is adjusted to personalize the therapy for a particular individual. For example, if an individual normally has limited chronic symptoms, but severe acute symptoms, a lower dose oral formulation with a higher dose topical formulation may be used. In other embodiments, an individual with more severe

chronic symptoms, and few acute symptomatic episodes may benefit from a higher dose oral formulation and a less concentrated topical formulation. Thus, a dual formulation comprising both oral and topical routes of administration are surprisingly advantageous in several embodiments.

[0055] Oral formulations comprising MSM and DMSO, individually or combined, are administered multiple times per day in certain embodiments. In some embodiments, dosing occurs two, three, four or more times daily, depending on the severity of the osteoarthritis symptoms. In other embodiments, oral formulations are taken once per day. Topical formulations, in certain embodiments, are used multiple times daily, for example two, three, four or more times. In other embodiments, topical formulations are used only for treatment of acute exacerbation of symptoms. In some embodiments, oral formulations are used in conjunction with topical formulations, while in other embodiments, only oral formulations are administered.

[0056] In certain embodiments, formulations comprising MSM and DMSO, individually or combined, (oral, topical, or combinations thereof) are efficacious in ameliorating one or more symptoms of osteoarthritis. In some embodiments, formulations comprising MSM and DMSO, individually or combined, reduce or prevent pain or stiffness in one or more joints during periods of rest. In some embodiments, formulations comprising MSM and DMSO, individually or combined, reduce or prevent pain or stiffness in one or more joints during periods of light or moderate activity. In still other embodiments, formulations comprising MSM and DMSO, individually or combined, reduce or prevent pain or stiffness in one or more joints during periods of strenuous activity. In several embodiments, formulations comprising MSM and DMSO, individually or combined, reduce pain, stiffness and/or inflammation at rest, during activity, and/or post-activity.

[0057] In several embodiments, the combination of DMSO and MSM in a single formulation results in a synergistic effect, thereby lowering the concentration of DMSO, MSM, or both DMSO and MSM needed to effectively reduce one or more symptoms of osteoarthritis. Toxicology studies have established that DMSO can be chronically administered at 5 g/kg daily without any serious adverse effects. In certain embodiments, the dosage of oral DMSO ranges from about 0.003 to 0.06 g per day. In

some embodiments, the dosage of oral DMSO is about 0.045 g per day. Assuming an average of 50 kg per subject, these dosages equate to a range of about 0.00006 to about 0.0012 g/Kg daily (0.0012 to 0.024% of the dose given in the toxicology studies without serious adverse effect).

[0058] Oral toxicity of MSM has been previously determined through standard methods in rats. The LD₅₀ value was approximately 17 g/kg, which corresponds to an oral dose of 2.6 pounds per day for a 150 pound human. In certain embodiments, the dosage of oral MSM ranges from about 1.0 to 2.5 g per day. In some embodiments, the dosage of oral MSM is 1.95 g per day. In other embodiments, MSM is administered (e.g., orally) in a dosage of up to about 6 g/day. These doses are well below the range of toxicity determined for MSM. At this dosage level, MSM reduces inflammation and radiological changes in the joint in several embodiments.

[0059] In certain embodiments, the synergistic effects between DMSO and MSM reduce the concentration of DMSO and/or MSM required to function as an effective anti-inflammatory or to generate analgesic effects. In certain embodiments, the synergy reduces the concentration of DMSO and/or MSM required to prevent structural changes to affected joints, the articular cartilage of joints and the juxtaposed subchondral bone. In several embodiments, DMSO functions to facilitate the activity of MSM (e.g., analgesia, anti-inflammatory effects, and the like). In some embodiments, DMSO provides further positive effects on the same aspects of a disease or condition that MSM positively impacts. Thus, in some embodiments, DMSO supplements and also facilitates the actions of MSM.

[0060] Further, the synergistic effects of certain embodiments reduce the amount of time from inception of treatment to amelioration of osteoarthritis symptoms. In some embodiments, this time period is reduced several fold, for example from the order of several months down to the order of several weeks. In certain embodiments, the synergistic effects result in symptomatic improvement within about 2 to 6 weeks.

[0061] In several embodiments, a formulation comprising DMSO and MSM lowers the amount of MSM required orally. In one embodiment, DMSO allows MSM to penetrate skin more effectively. According to some embodiments, the combination permits lower amounts of both DMSO and MSM to be used therapeutically, and

optionally lowers odor, gastrointestinal symptoms, and/or the size of the capsule (or pill, tablet, or other dosage format). In one embodiment, MSM binds with DMSO metabolites for further odor reduction. In some embodiments (e.g., liquid forms for children), a flavor is added to DMSO and MSM to improve taste. Formulations comprising DMSO and/or MSM may also be added to therapeutic confectionaries, such as chews and gummies.

[0062] The synergism of DMSO and MSM according to several embodiments, allows reductions in the concentrations needed to effectively reduce osteoarthritis symptoms. In certain embodiments, the MSM functions as a skin protectant and unexpectedly protects the skin from the adverse effects of DMSO exposure. In some embodiments, topical MSM functions primarily as an inactive ingredient, e.g., it functions primarily to minimize dermal irritation that may otherwise be induced by topical DMSO administration. In some embodiments, MSM functions as a lubricant for the skin (e.g., to prevent excessive drying of the skin). In certain embodiments, the efficacious concentration of DMSO for lower limb joint treatment is reduced to 50% DMSO, or lower. In certain embodiments, the efficacious concentration of DMSO for upper limb joint treatment is reduced to 25-50% DMSO. In some embodiments, the duration that the skin is exposed to DMSO is reduced, because the DMSO/MSM formulation is more efficacious than DMSO alone. Thus, in certain embodiments, the DMSO/MSM topical formulation is left on the skin for 2-15 minutes and then removed (e.g., washed off). In other embodiments, DMSO/MSM topical formulation is left on the skin for about 5-10 minutes and then removed (e.g., washed off). In such embodiments, the possibility of side effects from DMSO exposure is reduced due to the reduction in exposure time and the protectant effects of MSM. However, in further embodiments, DMSO/MSM topical formulation is left on the skin and not removed. In some embodiments, DMSO and/or MSM act as antioxidants.

[0063] In several embodiments, the penetrant effect of DMSO allows MSM to achieve greater skin penetration and absorption, allowing enhanced anti-inflammatory effects. In some embodiments, the DMSO/MSM topical formulation unexpectedly provides analgesic effects. Further, the synergism exhibited by DMSO and MSM in the topical formulations can improve osteoarthritis symptoms in as little as about ½ a day to

about 3 days, according to several embodiments. In some embodiments, DMSO and/or MSM are analgesic when provided in an oral dosage form.

[0064] In some embodiments, the synergism of DMSO and MSM, and the associated reduction in doses of both compounds, enables the simultaneous use of both oral and topical formulations. The reduced concentrations of DMSO and MSM (as compared to therapies of either DMSO or MSM alone), according to several embodiments described herein, reduce the overall occurrence of side effects and thereby enable simultaneous use of oral and topical formulations. Such embodiments therefore allow use of a topical formulation to ameliorate any acute joint pain, while the oral formulation serves to lower inflammation and pain on a chronic basis with minimal complications.

[0065] In some embodiments, the combination of DMSO and MSM and/or the use of solidified DMSO unexpectedly reduces the unpleasant odor normally experienced with DMSO use. For example, in certain embodiments, formulations comprising DMSO and MSM produce no perceptible odor after use. In some embodiments, a formulation comprising 10%-50% MSM reduces or eliminates the odor of DMSO provided at a concentration of 50%-90%. Previously, DMSO used at concentrations approaching 50% (or more) were associated with a strong unpleasant odor that could be detected through the skin or on the breath of a patient. Thus, several embodiments of the compositions described herein are unexpectedly advantageous because they reduce or eliminate the odor-related side effect.

[0066] According to any of the embodiments disclosed herein, a therapeutic system comprising MSM and DMSO, individually or combined, also includes one or more of the following compounds: ibuprofen, fenoprofen, indomethacin, naproxen, tolmetin, salicylic acid, and sulindac. In other embodiments, a therapeutic system comprising DMSO and/or MSM also includes one or more of the following compounds: antioxidants, glucosamine, chondroitin, niacinamide, S-adenosylmethionine, curcumin, quercetin, omega-3 fatty acids, papain, hyaluronic acid, and bromelain. In several embodiments, a formulation comprising DMSO and/or MSM and about 500-2500 mg glucosamine is provided. One or more of the following compounds may be used in addition to, or in place of, glucosamine: about 500-5000 mg fish oil, about 500-5000 IU

Vitamin D, about 500-2500 mg chondroitin, 500-5000 mg or IU antioxidants (such as vitamin C, E or beta-carotene), about 500-2500 mg curcumin, and about 50-2500 mg hyaluronic acid. In some embodiments, formulations comprising DMSO and/or MSM inhibit the secretion of pro-inflammatory enzymes that contribute to the breakdown of cartilage, including collagenase, hyaluronidase, and elastase. In some embodiments, formulations consisting or consisting essentially of DMSO and/or MSM inhibit the secretion of pro-inflammatory enzymes that contribute to the breakdown of cartilage.

[0067] In several embodiments, a formulation comprising DMSO and/or MSM without a gastroprotectant is provided. Thus, several embodiments of the invention are particularly advantageous because it is estimated that many severe arthritic patients who are receiving NSAIDs are also co-prescribed a gastroprotectant.

[0068] In certain embodiments, the amount of DMSO in a topical formulation ranges from about 0.01% by weight to about 70% by weight. In other embodiments, the formulation comprises between about 0.01% and 10% DMSO by weight, and overlapping ranges thereof. Other embodiments comprise between about 10% and 20% DMSO, about 20-30% DMSO, about 30-40% DMSO, about 40-50% DMSO, about 50-60%, or about 60-70% DMSO, and overlapping ranges thereof. Still other embodiments comprise a formulation comprising between about 7% and 15% DMSO, about 15-25% DMSO, about 25-35% DMSO, about 35-45% DMSO, about 45-55% DMSO, about 55-60%, about 60-65%, or about 65-70%, and overlapping ranges thereof. In certain embodiments, DMSO is present in a range between about 45-55% by weight, including 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, and 55%, and overlapping ranges thereof. In some embodiments, DMSO is provided in a range from about 70% to about 90%. Higher concentrations of DMSO may also be used in other embodiments.

[0069] In certain embodiments, the amount of MSM in a topical formulation ranges from about 0.01% by weight to about 70% by weight. In some embodiments, the formulation comprises between about 0.01% and 10% MSM by weight, and overlapping ranges thereof. Other embodiments comprise a formulation comprising between about 10% and 20% MSM, about 20-30% MSM, about 30-40% MSM, about 40-50% MSM, about 50-60%, or about 60-70% MSM, and overlapping ranges thereof. Still other embodiments comprise between about 7% and 15% MSM, about 15-25% MSM, about

25-35% MSM, about 35-45% MSM, or about 45-55% MSM, and overlapping ranges thereof. In certain other embodiments, MSM is present in a range between about 5-15% by weight, including 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15%, and overlapping ranges thereof. In some embodiments, MSM is provided in a range from about 70% to about 90%. Higher concentrations of MSM may also be used in other embodiments. In several embodiments, the percentages above are based on the volume of MSM used in an embodiment.

[0070] In several embodiments, a topical formulation MSM and DMSO, individually or combined, is provided in a concentration sufficient for application to the body in a thin layer. In one embodiment, the DMSO/MSM formulation is wiped across the surface of a joint in a thin layer and removed about five to ten minutes later with, for example, a wet wash cloth. In one embodiment, the target tissue (e.g., skin of the knee or other joint) is cleaned to deter the penetration of contaminants by DMSO. In some embodiments, volumes of the topical formulation applied range from about 0.5 mL to about 10mL, depending on the tissue to which the formulation is applied. Thus, in some embodiments, the amount of the topical formulation applied in one use is between about 0.5mL to about 1mL, about 1mL to about 3mL, about 3mL to about 5mL, about 5mL to about 7mL, about 7mL to about 10mL, about 10mL to about 20mL, and overlapping ranges thereof. In some embodiments, a formulation comprising MSM, DMSO, or a combination of MSM and DMSO is provided in a topical formulation and a user is instructed to apply about 3mL to about 15mL per application per body part (e.g., knee).

[0071] In several embodiments, the topical formulation comprising MSM and DMSO, individually or combined, further comprises one or more inactive ingredients including, among others, de-ionized water and various polymers (for example, carbopol 974 NF). Active ingredients may also be provided. In some embodiments, a formulation consisting or consisting essentially of MSM and DMSO, individually or combined, is provided.

[0072] In some embodiments, formulations comprising DMSO and urea, and optionally MSM are provided to reduce odor. In some embodiments, formulations comprising DMSO and sulfur-binding compounds are used to reduce odor. In some embodiments, formulations comprising DMSO and at least one odor-reducing nutrient

are used to reduce odor. In several embodiments in which odor is reduced, odors associated with the oxidation, metabolism, degradation or other conversion of DMSO are reduced. For example, in one embodiment, odors associated with methylthiomethane (DMS) are reduced. In some embodiments, MSM is used to reduce the odor of DMS that is produced by bacterial transformation of DMSO waste that is disposed (e.g., into sewage systems).

[0073] In several embodiments in which odor is reduced, odors associated with the oxidation, metabolism, degradation or other conversion of DMSO are reduced. In some embodiments, odors are reduced through the binding of odiferous compounds. In some embodiments, odors are reduced by reducing the production of odor-causing compounds. In some embodiments, odors are reduced by increasing the degradation of odor-causing compounds. According to one embodiment, compounds such as MSM are provided to reduce the odor associated with DMSO use by reducing the formation of DMSO metabolites or by binding to DMSO metabolites (e.g., DMS).

[0074] In several embodiments, a combined topical and oral DMSO/MSM formulation is used to treat osteoarthritis of the knee. In some embodiments, the formulation is used to treat a condition in which the patient has both knee pain and osteophytes (bone spurs) visualized on radiographs or when the patient is 40 years of age (or older), has morning knee stiffness lasting 30 minutes or less, and crepitus (grating, crackling or popping sounds) is detectable on motion of the knee.

[0075] In several embodiments, a combined topical and oral DMSO/MSM formulation is used to treat osteoarthritis of the hand. In some embodiments, the formulation is used to treat a condition in which a patient has hand pain, aching or stiffness, hard tissue enlargement of two or more of 10 selected joints, fewer than three swollen metacarpophalangeal joints, and hard tissue enlargement of two or more distal interphalangeal joints. In other embodiments, the formulation is used to treat a condition in which a patient has deformity of two or more of 10 selected joints (second and third distal interphalangeal joints, the second and third proximal interphalangeal joints and the first carpometacarpal joints (of both hands)).

[0076] In several embodiments, a formulation comprising DMSO and MSM, alone or combined, is used to treat one or more joints of a patient, including but not

limited to the knee, toe, thumb, finger, ankle, spine, hip, shoulder or other joint. In some embodiments, a formulation comprising DMSO and MSM, alone or combined, is used to treat lower back pain (e.g., pain in or associated with spinal column).

[0077] According to any of the embodiments disclosed herein, a combined topical and oral formulation comprising MSM and DMSO, individually or combined, is used to treat cartilage degeneration and/or degeneration of subchondral bone. In some embodiments, the formulation prevents, halts or treats bone spur formations, calcified areas and/or other undesired formations. A combined topical and oral DMSO/MSM formulation may also be used to treat joint pain, tenderness, stiffness, creaking, locking of joints, and/or local inflammation. In several embodiments, a combined topical and oral DMSO/MSM formulation is used to positively affect one or more of the following measures: (i) Radiological testing for both the knee and hand; (ii) Likert pain index on resting for both the knee and hand; (iii) Fuchs swelling index for both the knee and hand; (iv) Range of motion for both the knee and hand (or other joint); (v) Visual analog scale - pain intensity (VAS-PI) with loading for both the knee and hand and VAS Patient global assessment; (vi) The Lequesne index for the knee; (vii) WOMAC (Western Ontario and McMaster Osteoarthritis) physical stiffness and pain scale for the knee; (viii) Functional Index for Hand Osteoarthritis; (ix) Grip strength measurement; and (x) Rescue medication usage. Improvements of about 5%-100% in the identified measures are provided according to several embodiments (e.g., improvements of about 10-25%, 25-50%, 50-75%, 75-100%, and overlapping ranges thereof). Improvements in pain and inflammation may also be accompanied by increased range of motion, grip strength and general ability to perform daily activities according to several embodiments.

[0078] In several embodiments, a formulation comprising MSM and DMSO, individually or combined, is used to treat weakness, inflammation and/or pain in the hand, knee, or other joint. The formulation can be administered orally, topically, orally, or both orally and topically.

[0079] According to any of the embodiments disclosed herein, an oral formulation comprising MSM and DMSO, individually or combined, is used exclusively (without the topical treatment). According to any of the embodiments disclosed herein, a formulation comprising MSM and DMSO, individually or combined, is provided in a

form suitable for administration intravenously, intra-articularly, and/or via inhalation in addition to or instead of oral administration. In some embodiments, the formulation is administration intravenously, intra-articularly, and/or via inhalation in addition to or instead of topical administration.

[0080] In several embodiments, subjects treated with a formulation comprising MSM and DMSO, individually or combined, include humans, non-human mammals, domesticated animals and livestock. In some embodiments, a formulation comprising MSM and DMSO, individually or combined, is used to not only treat undesired symptoms and illnesses, but can also act as a preventative. For example, an oral and/or topical formulation comprising MSM and DMSO, individually or combined, may be taken on a regular basis to prevent the onset of illness. Reversal of osteoarthritis is provided in several embodiments, while in other embodiments, formulations comprising MSM and DMSO, individually or combined, prevent the onset or progression of the disease.

Formulations Comprising Solid DMSO

[0081] In several embodiments, a formulation comprising solid DMSO, alone or in combination with MSM, is provided. Pure DMSO is typically a clear and colorless dipolar liquid at room temperature with a melting point of 18.4°C (or 65°F), a flash point of 95°C, and a boiling point of 189°C at sea level. It is an aprotic and very hygroscopic chemical with a molecular weight of 78.13. However, application or ingestion of DMSO often yields an unpleasant odor, which “tastes” like garlic shortly after it contacts the skin. In addition, irritation, dryness, redness and/or itching of the skin can develop where DMSO is applied topically in repeated doses or in high concentrations. Other side effects of DMSO can include sensitivity to light, visual disturbances, headache, nausea, upset stomach, and diarrhea. Side effects, such as allergic reactions to DMSO, can occur in certain cases, e.g., palpitations, arrhythmias, and/or respiratory issues. Undesired effects of DMSO may be caused by DMSO, its metabolism, catalysis, oxidation, degradation, and/or other conversion. Due to its physical properties, DMSO is typically utilized in its liquid form.

[0082] MSM is an organosulfur compound that is a metabolite of DMSO and certain sulfur-containing amino acids. It is a white, water-soluble powder with a melting

point of 109 °C, a flash point of 143 °C, and a boiling point of 248 °C. It has a molecular weight of 94.13.

[0083] Due to its physical properties, DMSO exists as a liquid at room temperature, and is therefore typically utilized as a liquid. However, there is a long felt and as yet unmet need for a solid form of DMSO at room temperature. For example, solid forms of DMSO are particularly advantageous because they (i) are able to be manufactured or packaged into pill, tablet or capsule form; (ii) are able to achieve concentrated forms (about 2-50 fold more concentrated than liquid forms per dose size); (iii) exhibit reduced side effects as compared to the liquid form (e.g., less irritation, sensitivities, gastrointestinal effects, etc.); and (iv) exhibit reduced or no odor as compared to the liquid form. In some embodiments, the use of DMSO that stays solid at room temperature is particularly advantageous because it permits the inclusion of DMSO into capsules (or other packaging) that would normally be degraded by liquid DMSO.

[0084] In some embodiments, DMSO that is solid at room temperature is provided. In some embodiments, DMSO that is solid at temperatures between 70-80°F, 80-90°F, 90-100°F, 100-125°F, and higher than 125°F is provided. In other embodiments, DMSO that is solid at room temperature is provided, wherein said DMSO liquefies at about 65°F.

[0085] In accordance with certain embodiments, surprisingly, the combination of DMSO and MSM yields a solid form of DMSO at room temperature. In some embodiments, DMSO and MSM are combined by mixing hydrogen peroxide with a liquid form of DMSO. In these embodiments, the hydrogen peroxide and DMSO are heated. In some embodiments, MSM is formed, but not all of the DMSO is removed. In certain other embodiments, DMSO and MSM are combined by mixing a liquid form of DMSO in a MSM solution. In these embodiments, the solution can be heated and agitated. In some embodiments, DMSO and MSM are combined by mixing a solid form of MSM in a liquid form of DMSO. In other embodiments, DMSO and MSM are combined by mixing a liquid form of DMSO with a molten form of MSM.

[0086] In one embodiment, liquid DMSO is used as a starting material. The liquid form of DMSO is mixed with hydrogen peroxide (H₂O₂) at a temperature and time sufficient for substantially all of the hydrogen peroxide to be consumed and for MSM and

water by-product to form. In certain embodiments, not all of the DMSO is removed, thereby yielding a molten DMSO/MSM combination that may subsequently be cooled. For example, in one embodiment, liquid DMSO at a concentration of about 90-100% is combined with 30% to 51% H_2O_2 at stoichiometric ratio and a temperature of about 230-250°F until at least 90% of the H_2O_2 is consumed, and a product containing about 0.1%-15% DMSO and 85%-99.9% MSM is produced. Extreme caution must be maintained as this is an extremely exothermic reaction.

[0087] In several embodiments, the preparation of MSM involves a high temperature distillation step which results in molten MSM. In such embodiments, DMSO may be added back into the molten MSM in known quantities under agitation. In some embodiments, the DMSO added back is in liquid form, while in other embodiments, the DMSO is in solid form. The resultant DMSO/MSM combination is further agitated and then rapidly cooled in one embodiment.

[0088] In one embodiment, the molten DMSO/MSM combination is sent to a spray cooler/prilling chamber to form solid prills or microprills (microspherical pellets). In certain embodiments, the molten DMSO/MSM combination is fed into the prilling chamber where the molten DMSO/MSM combination enters a droplet generator to discharge the material in the form of droplets. As the droplets fall freely, they are cooled and solidify into spheres or prills. The spheres or prills have a diameter in the range of about 75 microns to 840 microns (e.g., about 75-150 microns, about 150-300 microns, about 300-450 microns, about 450-600 microns, about 600-840 microns, and overlapping ranges therein).

[0089] In certain embodiments, the droplets are cooled with a flow of cold gas, such as but not limited to air, nitrogen gas, or carbon dioxide. In certain other embodiments, the droplets are cooled with a spray of cold water or cold liquid nitrogen. In other embodiments, the droplets are cooled by dry ice. In accordance with certain embodiments described herein, after the droplets are cooled, since the exteriors of the droplets cool first, the prills can remain in the cool temperature to solidify the interiors of the prills.

[0090] In certain other embodiments, the molten DMSO/MSM combination (e.g., mixture) is sent to a flaking system to form solid flakes. For example, in one

embodiment, the molten DMSO/MSM combination is sent to a drum flaker, where a thin warm layer of the molten DMSO/MSM combination is applied to the outside of a rotating drum. As the drum rotates, a cooling agent housed within the rotating drum cools and solidifies the layer of material on the exterior of the drum, and a knife scraper removes the material in the shape of flakes. Various cooling agents can be used, for example, liquid nitrogen, liquid oxygen, cooled water, or cooled water containing polypropylene glycol.

[0091] In accordance with several embodiments described herein, MSM can be purified prior to combining it with DMSO. In some embodiments, purification is accomplished by distillation, among other methods. In certain embodiments, DMSO powders or flakes are combined with MSM prill. In other embodiments, DMSO powders or flakes are combined with MSM flakes. In other embodiments, DMSO powders or flakes are combined with MSM powder. In certain embodiments, a homogenous mixture of DMSO/MSM is produced, while in other embodiments, a non-homogenous mixture results.

[0092] In accordance with several embodiments described herein, MSM may be combined with DMSO to form a DMSO/MSM solution, and the resultant mixed solution is subsequently frozen and ground into powder. In some embodiments, the liquid phase of the DMSO/MSM solution is water. In some embodiments, distilled, deionized, or distilled-deionized water is used. In other embodiments, other liquids may be used. For example, the DMSO/MSM solution may contain normal saline, or another acceptable solvent. In certain embodiments, the ionic characteristics of the liquid may be adjusted to affect the resultant DMSO/MSM product. In some embodiments, other ingredients are added into the solution, with the solution heated and agitated to facilitate mixing. The DMSO/MSM solution can be cooled and frozen. For example, the liquid DMSO can be cooled in a cooling chamber containing cold gas, such as but not limited to air, nitrogen gas, or carbon dioxide. The DMSO/MSM combination is then ground by any grinding or milling technique well known in the art or yet to be devised.

[0093] In other embodiments, DMSO is added to molten MSM. In certain embodiments, the DMSO/MSM combination is formed into a solid by a spray

cooler/prilling chamber as described above. In other embodiments, the DMSO/MSM combination is formed into a solid by a flaking system as described herein.

[0094] In some embodiments, the purity of the starting raw materials can be altered to adjust the purity of the end product. Depending on the level of purity required, one or more purification processes may be employed. For example, in some embodiments where DMSO is the starting material, impurities can exist because DMSO is a strong solvent. Thus, the starting MSM and/or DMSO may be purified prior to the manufacture of the DMSO/MSM combination. In some embodiments, the synthesis of MSM from DMSO yields side reactions and compounds. In some embodiments, additional purification can be performed after the DMSO/MSM product is formed.

[0095] In one embodiment, distillation is employed as the purification process. Other contaminant/by-product removing procedures may be used instead of, or in addition to, distillation. Distillation removes the water and contaminants from the raw materials and from side reactions. In accordance with some embodiments described herein, distillation can form a molten MSM into which DMSO may be added. In some embodiments, the DMSO/MSM combination is tested after production to reduce potential hazardous heavy metals, such as lead, mercury, cadmium, and arsenic, to levels below specified standards.

[0096] In some embodiments, gelatin and/or hydroxypropyl methylcellulose (HPMC) is used with the organic based solvent system to form a gel-cap. In other embodiments, the organic based solvent system is used to form a tablet. In some embodiments, the tablet is uncoated. In some embodiments, the tablet is coated. In certain embodiments, the coating is pH stable and provides a time-release effect, such that the tablet is positioned in a portion of the gastrointestinal tract that is highly absorptive, such as the ileum.

[0097] In several embodiments, the organic based solvent system is used to formulate an orally consumable effervescent DMSO/MSM formulation, allowing for enhanced absorption of DMSO and MSM. For example, in certain embodiments, a DMSO/MSM powder is produced that when added to a consumable liquid, dissolves and yields an effervescent beverage for consumption. In certain embodiments, the DMSO/MSM powder is pre-packaged into single-dose serving sizes. In other

embodiments, formulations comprising DMSO and MSM, alone or combined, are formulated into a tablet that can similarly be dissolved to produce an effervescent beverage. Any consumable liquid may be used to dissolve, the powder or tablet, with the taste of the liquid being driven by the choice of the consumer. In other embodiments, flavors may be added to the DMSO and/or MSM powder or tablet, such that, when combined with water, a flavored effervescent beverage results.

[0098] In accordance with some embodiments described herein, a DMSO/MSM active capsule is produced. In one non-limiting example, prior to or during the process to form the DMSO/MSM combination into a solid, vegetable coating, amorphous silicon dioxide, and magnesium stearate are blended and added into the DMSO/MSM combination to produce a formulation comprising 650 mg of MSM, 15 mg of DMSO, 285 mg of Dritex-S Flake coating, 4.75 mg of silicon dioxide, and 4.75 mg of magnesium stearate. The vegetable coating may be fully hydrogenated soybean oil that has been further processed into flake form such as Dritex-S flakes and used as an encapsulating agent. A placebo capsule can also be produced with a formulation consisting of 1 mg of DMSO, 950 mg of Pac-Gel 70, 4.75 mg of silicon dioxide, and 4.75 mg of magnesium stearate. In several embodiments, as discussed herein, greater or lesser percentages of MSM and/or DMSO are used for active oral formulations. Placebos are also adjusted accordingly. In some embodiments, multilayer emulsions are provided as coating materials. In one embodiment, nano-laminated lipids are used as coating materials. Polymers are used in some embodiments. In some embodiments, coatings comprise hydrogels, gelatins, soybean oil, malitol, or combination thereof.

[0099] In accordance with certain embodiments described herein, topical formulations, e.g., gels, lotions, and creams, can be produced by mixing DMSO into a MSM solution. In some embodiments, distilled, deionized, or distilled-deionized water is used. In other embodiments, other liquids may be used. For example, the MSM solution may contain normal saline, or another acceptable solvent. In certain embodiments, other ingredients such as thickening agents, emulsifiers, and fragrances, used in topical formulations which are well known in the art or yet to be devised can be mixed into the solution. In certain embodiments, the solution is heated and agitated to facilitate

dissolution. Once mixed, the solution is allowed to cool to form a gel, lotion or cream in some embodiments.

[0100] In one embodiment, an active topical gel is produced. In one non-limiting example, 50 ml of de-ionized water is warmed on a hot plate. MSM (12 g) is added to the warm water and dissolved. After complete dissolution of the MSM, DMSO (60 g) is added to the MSM solution. Crosslinked acrylic acid polymer (Carbopol 974 NF) is added to the solution with constant agitation, which serves to wet the polymer as it is being added. The temperature of the solution is brought to between about 50-60°C and agitation is continued until the polymer is completely dissolved. Sodium carbonate (Na_2CO_3 , 0.02 g) is dissolved in an additional 10 mL of deionized water. Once the Na_2CO_3 is completely dissolved, it is added to the DMSO/MSM/polymer solution with simultaneous stirring by hand. Once thoroughly mixed, the solution is allowed to cool, resulting in a viscous gel of containing 50% DMSO/10% MSM with 1% Carbopol 974 NF and 39% de-ionized water. Viscosity is measured at approximately 300,000cPs at 23°C (73°F). In several embodiments, as discussed herein, greater or lesser percentages of MSM and/or DMSO are used for topical formulations. In several embodiments, percentages of DMSO and/or MSM are by volume, as stated, rather than by weight.

[0101] In certain embodiments described herein, formulations comprising DMSO and MSM, alone or in combination, are provided the form of a capsule, a gel-cap, a tablet, oral suspension, a powder, or an effervescent. Gels, slurries, particles, powders and other dehydrated forms are also provided in some embodiments. In certain embodiments, a formulation comprising DMSO and MSM that is not liquid (e.g., a solid) at room temperature is provided. In some embodiments, solid formulations are advantageous in that they maintain their consistency, e.g., maintain one or more of a hardness, firmness, density, texture, and/or viscosity that is at least 75%, 85%, 95% or 100% the same, over a wide range of temperatures (e.g., from about 0°C to about 100°C, about 5°C to about 50°C, about 10°C to about 40°C, about 20°C and about 30°C, and overlapping ranges thereof). Certain embodiments are covered with a coating while other embodiments are not coated. Where a coating is provided, the coating may render a time-release effect. In certain embodiments, DMSO is between about 0.01% to about

10% by weight of the formulation. In several embodiments, the percentages above are based on the volume of DMSO used in an embodiment.

[0102] In several embodiments, a solid formulation comprising DMSO is used in several industrial and medical applications. In some embodiments, solid DMSO is used for storing and transporting DMSO.

[0103] In several embodiments, the amount of DMSO in a solid formulation comprising DMSO and MSM (and optionally other ingredients) ranges from about 0.01% by weight to about 90% by weight. In other embodiments, the formulation comprises between about 0.01% and 10% DMSO by weight. In certain embodiments DMSO is present in about 0.01% to about 5%, about 0.01% to about 2.5%, or 0.01% to about 2.0%. In some embodiments, DMSO is present in about 0.5% to about 1.75%, including 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.55, 1.6, 1.65, 1.7, and 1.75%, and overlapping ranges thereof. Other embodiments comprise a formulation comprising between about 10 and 20% DMSO, about 20-30% DMSO, about 30-40% DMSO, about 40-50% DMSO, about 50-60% DMSO, about 60-70% DMSO, about 70-80% DMSO, about 80-90% DMSO. Still other embodiments comprise from about 7 to about 15% DMSO, about 15-25% DMSO, about 25-35% DMSO, about 35-45% DMSO, about 45-55% DMSO, about 55-65% DMSO, about 65-75% DMSO, or about 75-85% DMSO, and overlapping ranges thereof. Several embodiments for capsules, gel-caps, powders, and effervescent tablets comprise between about 0.01-10% DMSO, including 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 9% DMSO. Several embodiments for gels, lotions, and creams comprise DMSO at a concentration of between 30% and 90%, for example, about 45-55%.

[0104] In several embodiments, the amount of MSM in a solid formulation comprising DMSO and MSM (and optionally other ingredients) ranges from about 0.01% by weight to about 70% by weight. In other embodiments, the formulation comprises between about 0.01% and 10% MSM by weight. Other embodiments comprise between about 10 and 20% MSM, about 20-30% MSM, about 30-40% MSM, about 40-50% MSM, about 50-60% MSM, or about 60-70% MSM including 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, and 70% MSM, and overlapping ranges thereof. Still other embodiments comprise a formulation comprising about 7 and 15% MSM, about 15-25% MSM, about 25-35% MSM, about 35-45% MSM, about 55-60% MSM, about 60-65% MSM, or about

65-70% MSM, and overlapping ranges thereof. Some embodiments for capsules, gel-caps, powders, and effervescent tablets comprise between about 90-99% MSM, including 91, 92, 93, 94, 95, 96, 97, and 98% MSM. Several embodiments for gels, lotions, and creams comprise between about 5 to 15% MSM.

[0105] In some embodiments, the solid formulation is uncoated. In other embodiments, the solid formulation is covered with a coating. In some embodiments, the coating provides a time-release effect (e.g., sustained-release, sustained-action, extended-release, controlled-release, or continuous-release). Coatings, in some embodiments, incorporate a flavor additive, such that there is no chalky or medicinal-tasting residue remaining after consuming the solid formulation. As used herein, "solid" shall be given its ordinary meaning and shall additionally refer to semi-solids, gels, viscous solutions, and other compounds that are not in liquid or gaseous phases. Solidified DMSO, alone or in combination with MSM, may be provided in the form of oral capsules, gel-caps, tablets, powders, and effervescent tablets, or topical gels, lotions, and creams. Other forms may also be manufactured. As used herein, "compound" shall be given its ordinary meaning and shall include, but not be limited to, molecules, ingredients, atoms, substances and elements.

[0106] In some embodiments, one or more additional agents are added into the DMSO/MSM combination. In certain embodiments, pharmaceuticals, including but not limited to analgesics and anti-inflammatory agents, are employed with the DMSO/MSM combination. In certain embodiments, antimicrobials, such as penicillin and antibiotics, can be employed with the DMSO/MSM combination. In certain embodiments, vitamins and supplements are added.

[0107] In several embodiments, a solid formulation comprising MSM and DMSO, individually or combined, is provided that optionally comprises one or more inactive ingredients including, among others, microencapsulating agents (for example Dritex-S Flake coating), silicon dioxide, and magnesium stearate. In several embodiments, a solid formulation comprising MSM and DMSO, alone or in combination, is encapsulated to, for example, facilitate delivery, bioactivity, absorption, time-release, and/or palatability. In several embodiments, non-encapsulated powders facilitate delivery, bioactivity, absorption, time-release, and/or palatability.

EXAMPLE

[0108] The following example is provided to further illustrate certain embodiments within the scope of the invention. The example is not to be construed as a limitation of any embodiments, since numerous modifications and variations are possible without departing from the spirit and scope of the invention.

Example 1Absorption of MSM in Topical Formulation is Within Recognized Safe Levels

[0109] Approximately 17% of DMSO is metabolized into MSM in the body. DMSO has been established to function as a penetration enhancer (among other functions). This study investigated the circulating concentrations of MSM when MSM is topically applied in combination with one of two concentrations of DMSO. According to the study, in some embodiments, MSM is not a pharmacologically active ingredient when applied topically. Rather, in some embodiments, topical MSM works synergistically with DMSO to reduce one or more side effects of DMSO. Thus, higher concentrations of DMSO (which would otherwise be prohibitive because of the undesired side effects) are able to be used to treat subjects.

[0110] New Zealand White rabbits, which are an accepted animal model for dermal absorption studies, were used to assess the absorption and resultant blood levels of MSM. Rabbits were obtained from Charles River Canada (Saint-Constant, Quebec). Five male rabbits, ages 12-13 weeks (and ranging in weight from 2.6kg to 2.7kg) were used for the dermal absorption studies. Rabbits were used because of their greater skin permeability as compared to rats, pigs or humans. Thus, testing on rabbits is a more conservative approach for the safety of topical products for human use. The size of rabbit was based on the ethical restriction of collecting greater than 6 mL/kg body weight of blood within a two week period. The total volume of blood to be removed during this study was 10mL on a single day. One animal per group was used to minimize the number of animals required. Animals were housed individually in stainless steel cages with 12 hours light/dark cycles. The animal room environment was monitored daily (targeted ranges: 18-26°C and relative humidity 25-50%). Fresh air was supplied to the room at a

sufficient rate to provide approximately 15 to 17 changes of room air per hour. Clinical observations were conducted for all animals to ensure animals were in good health prior to dosing. Morbidity and mortality observations were also conducted during the study period.

[0111] Treatment groups were as shown in Table 1:

Table 1 : Study 1 Design

Group	Test Article	Surface Area Exposed	Volume Applied	Number of Animals	Blood Collection Times (min)
A	10% MSM + 90% Water	6cm ²	0.5mL	1	0 (pre-dose), 10, 30, 120, 480 minutes
B	50% DMSO + 50% Water	6cm ²	0.5mL	1	0 (pre-dose), 10, 30, 120, 480 minutes
C	70% DMSO + 30% Water	6cm ²	0.5mL	1	0 (pre-dose), 10, 30, 120, 480 minute
D	10% MSM + 50% DMSO + 40% Water	6cm ²	0.5mL	1	0 (pre-dose), 10, 30, 120, 480 minutes
E	10% MSM + 70% DMSO + 20% Water	6cm ²	0.5mL	1	0 (pre-dose), 10, 30, 120, 480 minutes

[0112] One day prior to the experiment, the rump of each rabbit was closely clipped using hair clippers. An area of 6 cm² was measured and marked to ensure equivalence in the application of the various compositions. Each product was applied by pipetting 0.5mL of each composition into the center of the test area and spread to cover the entire test area. After the 5 minute exposure period, the compositions were removed by wiping, rinsing and drying the test area.

[0113] Prior to blood collection, animals were tranquilized with Acepromazine (1 mg/kg) by intramuscular injection in the right hind leg muscle, after which EMLA cream (lidocaine/prilocaine) was applied to both ears along the ear artery. Blood was collected by insertion of a 21G needle (hub removed) into the ear artery. Approximately 2mL of whole blood was collected into 4mL vacutainer™ tubes (Becton Dickinson, Mississauga, ON) containing K₂EDTA. Tubes were inverted to mix with the anticoagulant and stored refrigerated until plasma was separated by centrifugation. Plasma was separated from whole blood by centrifugation at 3000 x g for 10 minutes.

Plasma was collected, transferred and stored in a cryovial at -70°C until further processing for MSM analysis.

[0114] Following the 5 minute exposure period to the various test products (see Table 1), blood was collected after 10 minutes, 30 minutes, 2 hours and 8 hours. Prior to the 2 and 8 hour blood collections, EMLA cream was applied to the ears (approximately 30 minutes prior to each of these blood draws) as the anesthetic effects of the EMLA cream lasts approximately 1-2 hours. Both EMLA cream and Acepromazine were used due to ethical considerations and to provide for the well being of the animals used in this project.

[0115] The concentrations of MSM in plasma were quantified by Gas Chromatography-Mass Spectrometry (GC/MS) based on established methods. Briefly, 450µL of plasma sample was mixed with 50µL of physiological saline and vortexed for 30 seconds. Following this 1 mL of Acetonitrile (Fisher, HPLC grade) was added to the mixture. The solution was vortexed vigorously for 60 seconds and centrifuged at 2000 rpm for 5 minutes. 1 µL of the clear supernatant was introduced to the GC/MS system (GC/MS QP20108 EI, Shimadzu, Kyoto, Japan). The analysis was performed on a Shimadzu SHR5XLB column (0.25mm ID X length 30m, film 0.25um, Kyoto, Japan). The retention time of MSM was 6.1-6.3 minutes. MSM was detected with MS and m/z 79 (M+-15) was used for monitoring MSM ion SIM profiles. Helium gas was used as the carrier gas, head pressure was 0.25kg/cm², make-up gas was 30 ml/min, column temperature was 80°C, injector temperature 120°C, separator temperature 200°C and ion source temperature 250°C. The ionization energy was 70eV. An external standard graph was prepared with MSM dissolved in acetonitrile at the following concentrations: 62.5 µg/ml, 31.3 µg/ml, 15.6 µg/ml, 7.8 µg/ml, 3.9 µg/ml, 1.9 µg/ml, 0.98 µg/ml and 0.49 µg/ml. The MSM concentration in plasma samples was calculated from the slope of the standard curve. The best fitted graph was linear with a R² value of 0.998.

[0116] All animals were observed prior to the start of the experiment and all demonstrated good health. During the course of the experiment and subsequent to the experiment, all animals demonstrated good health. Morbidity, mortality and injury were assessed twice daily. No animals demonstrated any morbidity, mortality or injury.

[0117] The results of the absorption study are summarized in Table 2 and graphically depicted in Figures 1 and 2. Baseline plasma concentrations of MSM (prior to exposure to test articles) ranged between 4.2 µg/mL and 104.2 µg/mL (see Figure 1). The variation in baseline is within the normal range of variation of natural MSM concentrations that have been established in prior studies. Following exposure to the various test articles, the highest plasma concentrations of MSM measured were less than or equal to approximately 140 µg/mL (see Figure 1). This peak concentration results from exposure to 10% MSM + 70% DMSO + 20% water. When corrected for natural variation in baseline MSM concentrations, the largest change in plasma MSM was detected in the 70% DMSO + 30% water group. These data suggest that variations in MSM, either due to absorption or due to metabolism of DMSO, are within the natural range of MSM concentrations.

[0118] As such, in several embodiments, MSM is an inert ingredient in topical applications, with respect to analgesic function. However, as discussed herein, MSM does provide several beneficial effects. In several embodiments, MSM functions to reduce the side effects normally associated with DMSO (skin effects, odor, etc.). In several embodiments, MSM functions as an emollient, which also may aid in reducing irritation of the skin by DMSO. As such, the combination of MSM with DMSO in the topical formulation embodiments described herein allow for the use of concentrations of DMSO that function to reduce one or more symptoms of osteoarthritis without the normal array of DMSO-associated side effects. Thus, in certain embodiments, the presence of MSM advantageously allows for the unexpected use of higher (and more efficacious) concentrations of DMSO without the side effects.

Table 2: Concentration of MSM in Plasma After Exposure to MSM and DMSO

Treatment	Time point (minute)	MSM Concentration ($\mu\text{g/mL}$)
10% MSM + 90% water	0	25.6
	10	17.6
	30	16.3
	120	14.0
	480	15.4
50% DMSO + 50% water	0	4.2
	10	6.9
	30	6.9
	120	7.4
	480	12.6
70% DMSO + 30% water	0	56.7
	10	89.0
	30	98.9
	120	128.7
	480	120.2
10% MS M + 50% DMSO + 40% water	0	104.2
	10	116.5
	30	127.9
	120	128.4
	480	140.4
10% MSM + 70% DMSO + 20% water	0	26.8
	10	37.3
	30	30.9
	120	33.9
	480	44.4

[0119] It will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the embodiments of the present invention. Method steps described herein need not be performed in the order set forth. It should be clearly understood that embodiments disclosed herein are illustrative only and are not intended to limit the scope of the present invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An oral and topical dual formulation system for improving the symptoms of osteoarthritis, the system comprising:

5 an oral formulation comprising dimethylsulfoxide (DMSO) and methylsulfonylmethane (MSM),

wherein said oral formulation is suitable for oral administration,

wherein said oral formulation comprises about 300 mg to about 750 mg MSM, and

10 wherein said oral formulation comprises about 10 mg to about 50 mg DMSO, when used for oral administration to improve the symptoms of osteoarthritis, the DMSO in the oral formulation enhances the efficacy of MSM in the oral formulation and the DMSO reduces the amount of MSM in the oral formulation required to achieve a comparable therapeutic result; and

15 a topical formulation comprising dimethylsulfoxide (DMSO) and methylsulfonylmethane (MSM),

wherein said topical formulation is suitable for topical administration,

wherein said topical formulation comprises about 10% to about 15% MSM,

wherein said topical formulation comprises about 40% to about 90% DMSO,

20 when used for topical administration to improve the symptoms of osteoarthritis, the MSM in the topical formulation reduces an odor and reduces at least one undesired side-effect of the DMSO in the topical formulation, and

wherein the oral formulation and topical formulation are used concurrently or sequentially to improve chronic and acute symptoms of osteoarthritis.

25 2. The dual formulation system of Claim 1, wherein the oral formulation is provided in solid form, wherein said solid form remains solid at room temperature.

30 3. The dual formulation system of Claim 2, wherein the solid form maintains a similar consistency over a temperature range of about 10°C to about 40°C.

4. The dual formulation system according to Claim 1 or 2, wherein the oral formulation comprises 650 mg MSM and 15 mg DMSO and wherein the topical formulation comprises 10% MSM and 50% DMSO.

5. The dual formulation system according to any one of claims 1 to 4, wherein the undesired side-effect is dermal irritation.

6. The dual formulation system according to any one of claims 1 to 5, wherein both the oral and topical formulation are suitable for administration at least three times daily.

7. The dual formulation system according to any one of claims 1 to 6, wherein the symptoms of osteoarthritis comprise one or more of the following symptoms: pain, osteophytes, stiffness, grip strength, limited range of motion, tissue enlargement in joints, swollen joints, and joint deformity.

8. The dual formulation system according to any one of claims 1 to 7, wherein the oral formulation is in one or more forms selected from the group consisting of: a capsule, a tablet, oral suspension, a liquid, and an effervescent, wherein said forms are optionally coated and/or flavored.

9. The dual formulation system according to any one of claims 1 to 8, wherein the topical formulation is in one or more forms selected from the group consisting of: a gel, a cream, a serum, a liquid, a spray, an ointment, and a patch.

10. The dual formulation system according to any one of claims 1 to 9: wherein the oral formulation treats the chronic symptoms of osteoarthritis, wherein the topical formulation treats the acute symptoms of osteoarthritis, and wherein at least one of the oral and topical formulation are optionally provided in time-released formulations.

11. The dual formulation system according to any one of claims 1 to 10, wherein the oral formulation is provided in a solid form, wherein the solid oral formulation is produced by a method comprising:

providing DMSO in a liquid form;
combining said liquid DMSO with hydrogen peroxide;
heating the liquid DMSO and the hydrogen peroxide to obtain a combination of
DMSO and MSM; and

5 cooling the DMSO and MSM combination into a solid formulation, wherein
said solid formulation is solid at temperatures between 20 degrees Celsius and 30
degrees Celsius.

12. A use of the dual formulation system according to any one of claims 1 to
10 10 in the preparation of a medicament for the treatment of one or more symptoms of
osteoarthritis.

13. A kit comprising the dual formulation system according to any one of
claims 1 to 10 with instructions to administer the oral formulation orally 3 times daily
15 and instructions to administer the topical formulation topically 3 times daily.

14. A kit comprising the system according to Claim 13, with instructions to
administer the topical formulation topically 3 times daily for up to two weeks.

20 15. A method for treating at least one symptom of osteoarthritis, the method
comprising:

providing the dual formulation system according to any one of claims 1 to 10;
orally administering or instructing oral administration of the oral formulation to
a subject 1-4 times daily;

25 topically administering or instructing topical administration of the topical
formulation to said subject 1-4 times daily.

16. An oral and topical dual formulation system for treating at least one of
joint pain and inflammation, the system comprising:

30 a first formulation comprising dimethylsulfoxide (DMSO) and
methylsulfonylmethane (MSM),

wherein said first formulation is suitable for oral administration,

wherein said first formulation comprises about 300 mg to about 800 mg MSM,
and

wherein said first formulation comprises about 5 mg to about 50 mg DMSO,

when used for oral administration to treat at least one of joint pain and
5 inflammation, the DMSO in the first formulation enhances the efficacy of the MSM in
the first formulation and the DMSO reduces the amount of MSM in the first
formulation required to achieve a comparable therapeutic result; and

a second formulation comprising dimethylsulfoxide (DMSO) and
methylsulfonylmethane (MSM),

10 wherein said second formulation is suitable for topical administration,

wherein said second formulation comprises about 1% to about 15% MSM, and

wherein said second formulation comprises about 30% to about 90% DMSO,

when used for topical administration to treat at least one of joint pain and
inflammation, the MSM in the second formulation reduces an odor and reduces at least
15 one undesired side-effect of the DMSO in the second formulation, and wherein the first
formulation and second formulation are used concurrently or sequentially to treat at
least one of joint pain and inflammation on a chronic and/or acute basis.

17. The use of the dual formulation system of claim 16 in the preparation of
20 a medicament for the treatment of joint pain and inflammation, joint pain or
inflammation from arthritis, joint pain or inflammation from rheumatoid arthritis, or
joint pain or inflammation from osteoarthritis.

18. A dual approach therapeutic system comprising:
25 a topical formulation comprising dimethylsulfoxide (DMSO) between about
40% to about 90% per dose,

methylsulfonylmethane (MSM) between about 5% and about 15% per dose,

wherein said DMSO and MSM are suitable for topical administration to a
subject to treat one or more of joint disorders, inflammation, degeneration, and/or pain,

30 when used for topical administration to treat joint pain and inflammation, the
MSM in the topical formulation reduces odor associated with topical application of

DMSO and reduces an undesired side-effect of the DMSO in the topical formulation;
and

an oral formulation comprising about 300 mg to about 700 mg MSM and about
10 mg to about 50 mg DMSO per dose.

5

19. A method of reducing the amount of oral DMSO to achieve a
therapeutic effect comprising:

providing the topical formulation according to Claim 18 for topical
administration,

10

thereby reducing the amount of oral DMSO needed to achieve a therapeutic
effect,

thereby reducing the side effects of oral DMSO.

15

20. An oral and topical system for improving the symptoms of osteoarthritis,
the system comprising:

a first formulation comprising dimethylsulfoxide (DMSO) and
methylsulfonylmethane (MSM),

wherein said first formulation is suitable for oral administration,

wherein said first formulation comprises about 60-70% MSM, and

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wherein said first formulation comprises about 0.1-3% DMSO,

when used for oral administration to improve the symptoms of osteoarthritis,
the DMSO in the first formulation enhances the efficacy of MSM in the first
formulation and the DMSO reduces the amount of MSM in the first formulation
required to achieve a comparable therapeutic result, and

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a second formulation comprising dimethylsulfoxide (DMSO) and
methylsulfonylmethane (MSM),

wherein said second formulation is suitable for topical administration,

wherein said second formulation comprises about 10%-15% MSM, and

wherein said second formulation comprises about 50%-90% DMSO,

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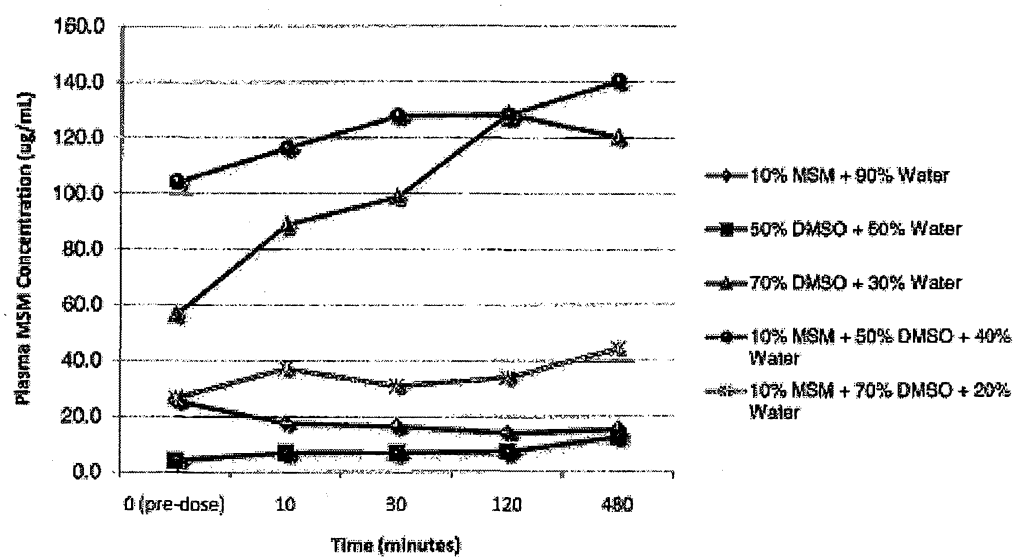
when used for topical administration to improve the symptoms of osteoarthritis,
the MSM in the second formulation reduces an odor and reduces at least one undesired
side-effect of the DMSO in the second formulation,

wherein the first formulation and second formulation are used concurrently or sequentially to improve chronic and acute symptoms of osteoarthritis.

21. A treatment system, comprising:
- 5 an oral formulation comprising about 0.045g/day dimethylsulfoxide (DMSO) and about 1.85g/day methylsulfonylmethane (MSM), and optionally
- a topical formulation comprising 40%-90% dimethylsulfoxide (DMSO) and 10%-15% methylsulfonylmethane (MSM),
- 10 wherein the DMSO in the oral formulation enhances the efficacy of MSM in the oral formulation and the DMSO reduces the amount of MSM in the oral formulation required to achieve a comparable therapeutic result,
- wherein the MSM in the topical formulation reduces an odor and reduces at least one undesired side-effect of the DMSO in the topical formulation.
- 15 22. The dual approach therapeutic system of claim 18, wherein said MSM in the topical formulation is configured to act as a lubricant to reduce irritation typically associated with topical application of DMSO.
23. The dual formulation system according to any one of claims 1 to 12,
- 20 wherein said oral formulation is encapsulated and wherein said encapsulated oral formulation is administered 1-4 times per day.
24. The dual formulation system of claim 23, wherein said encapsulated oral formulation is administered with food.
- 25 25. The dual formulation system of claim 23, wherein said encapsulated oral formulation is administered without food.

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Figure 1



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Figure 2

