DESCRIPTION

TITLE OF INVENTION:

PHARMACEUTICAL COMPOSITIONS COMPRISING MELOXICAM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Pat. App. Nos. 62/693,871, filed July 3, 2018; 62/860,705, filed June 12, 2019; 62/846,311, filed May 10, 2019; 62/835,613, filed April 18, 2019; 62/803,756, filed February 11, 2019; and 62/802,198, filed February 6, 2019; all of which are incorporated by reference in their entirety.

BACKGROUND

There continues to be a need for therapies with improved efficacy in treating pain, inflammation, migraine, and related conditions.

SUMMARY

This disclosure relates to the use of a bicarbonate and/or a cyclodextrin, such as sulfobutylether β-cyclodextrin (SBEβCD), to improve the pharmacokinetics or bioavailability of a drug, such as a nonsteroidal anti-inflammatory drug (NSAID), e.g. meloxicam, a triptan, e.g. rizatriptan, or a combination thereof.

For example, some embodiments include dosage forms comprising a triptan (such as rizatriptan or frovatriptan), in combination with a cyclodextrin (optionally as an inclusion complex of the triptan and the cyclodextrin), and/or a bicarbonate, and methods of treatment using the dosage form.

Some embodiments include a dosage form comprising: meloxicam; a sulfobutyl ether β-cyclodextrin (SBEβCD); a bicarbonate; and a triptan wherein the dosage form is an oral dosage form having a shorter T_{max} of meloxicam than a reference dosage form that: 1)

contains the same amount of meloxicam, 2) does not contain an SBEβCD, and 3) does not contain a bicarbonate.

Some embodiments include an inclusion complex of a triptan such as rizatriptan or frovatriptan in a cyclodextrin.

Some embodiments include a dosage form comprising: 1) an inclusion complex of a triptan, such as rizatriptan or frovatriptan, and a cyclodextrin, or 2) a triptan, such as rizatriptan or frovatriptan, and a carbonate or a bicarbonate.

Some methods include administration of a product that contains a combination of a triptan with: 1) a cyclodextrin and/or 2) a buffering agent. In some embodiments, the method involves treating a patient with a pharmaceutical formulation comprising a triptan, such as rizatriptan or frovatriptan, and a cyclodextrin and/or a carbonate/bicarbonate. Some embodiments may also include increasing the bioavailability of a triptan, such as rizatriptan or frovatriptan, or increasing the rate at which the triptan becomes bioavailable in a subject in need thereof as compared to a formulation without a cyclodextrin or carbonate/bicarbonate.

Some embodiments include a method of improving the pharmacokinetics of a triptan or an NSAID, comprising orally administering a dosage form described herein to a mammal or human being in need of treatment with the triptan or the NSAID.

Some embodiments include a method of treating pain, comprising orally administering a dosage form described herein to a mammal or human being in need thereof.

Some embodiments include methods of treating pain, such as migraine, comprising administering meloxicam and rizatriptan to a human being suffering from pain, such as migraine. For migraine, these methods may be particularly useful when the meloxicam and rizatriptan are administered while the human being is suffering from an acute attack of migraine pain or migraine aura. In some embodiments, about 8-13 mg of rizatriptan is administered to the human being. In some embodiments, the combination of meloxicam and rizatriptan (e.g. 8-13 mg of rizatriptan) may be administered in a manner that results in a T_{max} of meloxicam of 3 hours or less, 2 hours or less, 110 minutes or less, and/or an AUC_{0-24} of meloxicam of about 30-50 µg·hr/mL.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 (denoted as FIG. 1) is a depiction of the results described in Example 2 and contained in Table 6.

Figure 2 (denoted as FIG. 2) is another depiction of the results described in Example 2 and contained in Table 6.

Figure 3 (denoted as FIG. 3) is another depiction of the results described in Example 2 and contained in Table 6.

Figure 4 (denoted as FIG. 4) is another depiction of the results described in Example 2 and contained in Table 6.

Figure 5 (denoted as FIG. 5) is another depiction of the results described in Example 2 and contained in Table 6.

Figure 6 (denoted as FIG. 6) is another depiction of the results described in Example 2 and contained in Table 6.

Figure 7 (denoted as FIG. 7) is another depiction of the results described in Example 2 and contained in Table 6.

Figure 8 (denoted as FIG. 8) is another depiction of the results described in Example 2 and contained in Table 6.

Figure 9 (denoted as FIG. 9) is another depiction of the results described in Example 2 and contained in Table 6.

Figure 10 (denoted as FIG. 10) is another depiction of the results described in Example 2 and contained in Table 6.

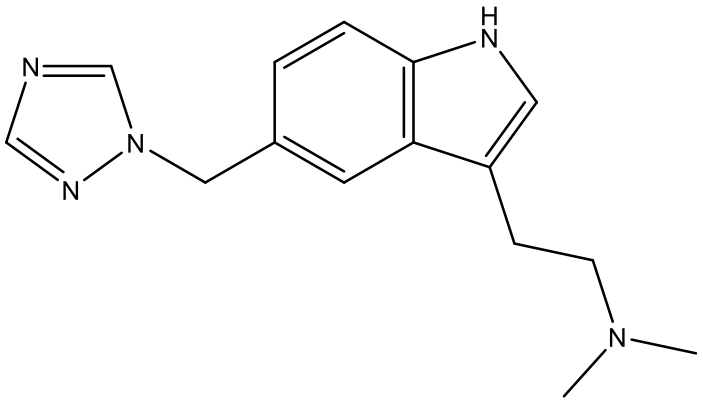
Figure 11 (denoted as FIG. 11) is a plot of meloxicam plasma concentration at various time points over the first 24 hours for an embodiment of a dosage form described herein and a commercially available meloxicam dosage form.

DETAILED DESCRIPTION

Meloxicam and some other NSAIDs, and other drugs, have poor aqueous solubility which may reduce bioavailability and slow the onset of pain relief. One method of increasing the solubility and bioavailability of meloxicam or another drug is through the use of cyclodextrins in combination with meloxicam.

Generally, this may be accomplished using a dosage form, such as an oral dosage form, containing a triptan (such as rizatriptan), optionally in combination with an NSAID (such as meloxicam), and 1) a cyclodextrin (optionally in an inclusion complex), and/or 2) a buffering agent, such as a bicarbonate. Administering this type of dosage form to a patient may increase the bioavailability of the triptan (e.g. rizatriptan) or the NSAID (e.g. meloxicam) in the patient or increase the rate at which the triptan (e.g. rizatriptan) or the NSAID (e.g. meloxicam) becomes bioavailable, or increase the rate at which the plasma concentration of the triptan or the NSAID increases. For example, the triptan or the NSAID may have a shorter T_{max}, or may have an increased C_{max} or area under the plasma concentration curve (AUC) as a result of the administration of this type of dosage form.

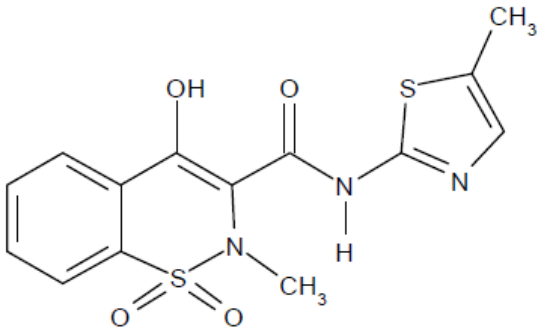
Any suitable triptan may be used, such as sumatriptan, rizatriptan, naratriptan, eletriptan, donitriptan, almotriptan, frovatriptan, alvitriptan, zolmatriptan, etc., including combinations or salts thereof. In some embodiments, the triptan comprises rizatriptan, which has the structure as shown below.



Rizatriptan

The NSAID may include, but is not limited to, celecoxib, rofecoxib, lumiracoxib, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337, NS398, aspirin, acetaminophen (considered to be an NSAID for the purposes of the present disclosure), ibuprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketorolac, lornoxicam, meloxicam, piroxicam, droxicam, tenoxicam, nabumetone, diclofenac, meclofenamate, mefenamic acid, diflunisal, sulindac, tolmetin, fenoprofen, suprofen, benoxaprofen, aceclofenac, tolfenamic acid, oxyphenbutazone, azapropazone, phenylbutazone, or combinations thereof.

In some embodiments, the NSAID is meloxicam, which has the structure:



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Meloxicam exhibits anti-inflammatory, analgesic, and antipyretic activities. The meloxicam mechanism of action may be related to the inhibition of prostaglandin synthetase (cyclo-oxygenase, COX) which is involved in the initial steps of the arachidonic acid cascade, resulting in the reduced formation of prostaglandins, thromboxanes and prostacylin.

A combination of rizatriptan and meloxicam (referred to herein for convenience as a "subject combination") may be used to treat a variety of pain conditions.

Unless otherwise indicated, any reference to a compound herein, such as meloxicam or rizatriptan, by structure, name, or any other means, includes pharmaceutically acceptable salts, alternate solid forms, such as polymorphs, solvates, hydrates, enantiomers, tautomers, deuterium-modified forms, or any other chemical species, such as precursors, prodrugs, or any other chemical species that may rapidly convert to a compound described herein under conditions in which the compounds are used as described herein.

A dosage form or a subject combination may be given enterally including, but not limited to, oral, sublingual, or rectal delivery, or parenterally including, but not limited to, intravenous, intramuscular, intranasal, or subcutaneous delivery. In some embodiments, both meloxicam and rizatriptan are administered orally. In some embodiments, meloxicam is administered intravenously and rizatriptan is administered orally. In some embodiments, meloxicam is administered intramuscularly and rizatriptan is administered orally.

Normally, the combination of meloxicam and rizatriptan is administered so that the human being receives the meloxicam and rizatriptan within a short period of time with respect to one another. For example, the meloxicam and rizatriptan may be administered within about 2 hours, within about 1 hour, within about 30 minutes, within about 20 minutes, within about 15 minutes, within about 10 minutes, within about 5 minutes, or within about 1 minute

of one another. In some embodiments, the meloxicam and rizatriptan are administered simultaneously, which for the purpose of this disclosure includes administration within about 5 minutes. In some embodiments, the meloxicam and rizatriptan are administered in a single dosage form.

The term "treating" or "treatment" broadly includes any kind of treatment activity, including the diagnosis, cure, mitigation, or prevention of disease in man or other animals, or any activity that otherwise affects the structure or any function of the body of man or other animals.

The dosage form or a subject combination may be used to treat, or provide relief of, any type of pain including, but not limited to, migraine and other types of headache, inflammatory pain, musculoskeletal pain, neuropathic pain, chronic pain, acute pain, localized pain, systemic pain, cancer-related pain, acute pain, pain due to injury, pain due to illness (e.g., fever), post-operative pain, etc. In some instances, pain relief may be palliative, or pain relief may be provided independent of improvement of the disease or condition or the underlying cause of the disease or condition. For example, although the underlying disease may not improve, or may continue to progress, an individual suffering from the disease may experience pain relief. In some embodiments, the pain affects a muscle, nerve, cartilage, bone, ligament, tendon, tendon sheaths, bursae, or joint.

Migraine is a headache disorder characterized by recurrent headaches that may be moderate to severe. The headaches may affect one half of the head, may be pulsating in nature, and may last from 2 to 72 hours. Associated symptoms may include nausea, vomiting, and sensitivity to light (photophobia), sound (phonophobia), or smell. The pain can be made worse by physical activity. Migraines may be associated with an aura, which may be a short period of visual disturbance which signals that the headache will soon occur.

Administering a subject combination to a human being suffering from migraine, such as an acute attack of migraine pain or aura, may quickly result in a reduction in a migraine symptom, such as pain, nausea, vomiting, photophobia, or phonophobia, such as at or within about 5 minutes (intended as a shorthand for "at about 5 minutes, or within about 5 minutes"), at or within about 10 minutes, at or within about 30 minutes, at or within about 1 hour, at or within about 90 minutes, at or within about 2 hours, at or within about 2.5 hours, or at or within about 3 hours. In some embodiments, a human being experiences a reduction

of, or complete relief from, pain, such as headache pain or migraine pain, allodynia, nausea, vomiting, photophobia, and/or phonophobia, at or within about 1 hour, at or within about 90 minutes, at or within about 2 hours, at or within about 2.5 hours, or at or within about 3 hours. In some embodiments, the relief experienced, is greater than would be experienced by receiving the same amount of rizatriptan without meloxicam. In some embodiments, the relief experienced, is greater than would be experienced by receiving the same amount of meloxicam without rizatriptan.

Observation of relief or reduction in a symptom at a specific period of time, such as "at 2 hours," is useful because it allows the effectiveness of the treatment to be evaluated at a specific or consistent time point, which facilitates comparison between patients. Observation of relief or reduction in a symptom within a specific period of time, such as "within about 2 hours," is useful because it may be desirable for relief or reduction of a symptom to occur as early as possible, and specifying that relief occur within a specified time sets a guideline in which it is desirable that relief occur.

For some methods, administration of the subject combination may achieve a reduction in migraine pain, allodynia, nausea, vomiting, photophobia, or phonophobia that lasts at least about one hour, at least about two hours, at least about three hours, at least about four hours, at least about six hours, at least about eight hours, about 8-24 hours, about 24 hours, or more than 24 hours.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and two hours after the meloxicam and the rizatriptan are administered, the human being experiences greater pain relief than the human being would have experienced two hours after receiving the same amount of meloxicam without the rizatriptan.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and twenty-four hours after the meloxicam and the rizatriptan are administered, the human being experiences greater pain relief than the human being would have experienced twenty-four hours after receiving the same amount of meloxicam without the rizatriptan.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and two hours

after the meloxicam and the rizatriptan are administered, the human being experiences greater pain relief than the human being would have experienced two hours after receiving the same amount of rizatriptan without the meloxicam.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and twenty-four hours after the meloxicam and the rizatriptan are administered, the human being experiences greater pain relief than the human being would have experienced twenty-four hours after receiving the same amount of rizatriptan without the meloxicam.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and two hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from allodynia than the human being would have experienced two hours after receiving the same amount of meloxicam without the rizatriptan.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and twenty-four hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from allodynia than the human being would have experienced twenty-four hours after receiving the same amount of meloxicam without the rizatriptan.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and two hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from allodynia than the human being would have experienced two hours after receiving the same amount of rizatriptan without the meloxicam.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and twenty-four hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from allodynia than the human being would have experienced twenty-four hours after receiving the same amount of rizatriptan without the meloxicam.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and two hours after the meloxicam and the rizatriptan are administered, the human being experiences

greater relief from nausea than the human being would have experienced two hours after receiving the same amount of meloxicam without the rizatriptan.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and twenty-four hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from nausea than the human being would have experienced twenty-four hours after receiving the same amount of meloxicam without the rizatriptan.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and two hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from nausea than the human being would have experienced two hours after receiving the same amount of rizatriptan without the meloxicam.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and twenty-four hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from nausea than the human being would have experienced twenty-four hours after receiving the same amount of rizatriptan without the meloxicam.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and two hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from vomiting than the human being would have experienced two hours after receiving the same amount of meloxicam without the rizatriptan.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and twenty-four hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from vomiting than the human being would have experienced twenty-four hours after receiving the same amount of meloxicam without the rizatriptan.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and two hours after the meloxicam and the rizatriptan are administered, the human being experiences

greater relief from vomiting than the human being would have experienced two hours after receiving the same amount of rizatriptan without the meloxicam.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and twenty-four hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from vomiting than the human being would have experienced twenty-four hours after receiving the same amount of rizatriptan without the meloxicam.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and two hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from photophobia than the human being would have experienced two hours after receiving the same amount of meloxicam without the rizatriptan.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and twenty-four hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from photophobia than the human being would have experienced twenty-four hours after receiving the same amount of meloxicam without the rizatriptan.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and two hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from photophobia than the human being would have experienced two hours after receiving the same amount of rizatriptan without the meloxicam.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and twenty-four hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from photophobia than the human being would have experienced twenty-four hours after receiving the same amount of rizatriptan without the meloxicam.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and two hours after the meloxicam and the rizatriptan are administered, the human being experiences

greater relief from phonophobia than the human being would have experienced two hours after receiving the same amount of meloxicam without the rizatriptan.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and twenty-four hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from phonophobia than the human being would have experienced twenty-four hours after receiving the same amount of meloxicam without the rizatriptan.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and two hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from phonophobia than the human being would have experienced two hours after receiving the same amount of rizatriptan without the meloxicam.

In some embodiments, the meloxicam and the rizatriptan are administered simultaneously (e.g. in a single dosage form, such as a single oral dosage form), and twenty-four hours after the meloxicam and the rizatriptan are administered, the human being experiences greater relief from phonophobia than the human being would have experienced twenty-four hours after receiving the same amount of rizatriptan without the meloxicam.

In some embodiments, the human being receiving the subject combination has a history of inadequate response to prior migraine treatments. For example, if the human being is asked whether he or she was pain-free within two hours of treatment for most attacks, and given the option of answering “never,” “rarely,” “less than half the time,” or “half the time or more;” and the human being answers “never,” “rarely,” or “less than half the time,” then the human being has had an inadequate response to the treatment. Similarly, if the human being is asked whether one dose of medication usually relieved the human being’s headache and kept it away for at least 24 hours, and given the option of answering “never,” “rarely,” “less than half the time,” or “half the time or more;” and the human being answers “never,” “rarely,” or “less than half the time,” then the human being has had an inadequate response to the treatment.

In some embodiments, the human being receiving the subject combination has indicated that he or she was “never” pain-free within two hours of treatment for most attacks. In some embodiments, the human being receiving the subject combination has indicated that

he or she was “rarely” pain-free within two hours of treatment for most attacks. In some embodiments, the human being receiving the subject combination has indicated that he or she was pain-free within two hours of treatment for most attacks “less than half the time.”

In some embodiments, the human being receiving the subject combination has indicated that one dose of medication “never” relieved the respondent’s headache and kept it away for at least 24 hours. In some embodiments, the human being receiving the subject combination has indicated that one dose of medication “rarely” relieved the respondent’s headache and kept it away for at least 24 hours. In some embodiments, the human being receiving the subject combination has indicated that one dose of medication relieved the respondent’s headache and kept it away for at least 24 hours “less than half the time.”

In some methods, the dosage form or the subject combination may be administered to relieve inflammatory pain, including inflammatory musculoskeletal pain, pain due to injury, arthritis pain, and complex regional pain syndrome. In other embodiments, the inflammatory pain may be chronic or acute.

In some embodiments, the dosage form (e.g. a dosage form containing a triptan such as rizatriptan or frovatriptan, and/or an NSAID such as meloxicam) or the subject combination may be administered to relieve arthritis pain, or other signs and/or symptoms of arthritis. Arthritis refers to inflammatory joint diseases that can be associated with pain. Examples of arthritis include, but are not limited to, rheumatoid arthritis, juvenile rheumatoid arthritis (pauciarticular and polyarticular course), osteoarthritis, erosive osteoarthritis, sero-negative (non-rheumatoid), arthropathies, non-articular rheumatism, peri-articular disorders, axial spondyloarthritis, transient osteoarthritis of the hip, vertebral crush fractures, arthritis associated with osteoporosis, and neuropathic arthropathies including Charcot’s foot, axial spondyloarthritis including ankylosing spondylitis, and SAPHO syndrome. In other embodiments, the arthritis pain may be chronic or acute. In some embodiments the dosage form or the subject combination may be administered to relief the signs and/or symptoms of an arthritis including but not limited to osteoarthritis.

In some embodiments, the dosage form (e.g. a dosage form containing a triptan such as rizatriptan or frovatriptan, and/or an NSAID such as meloxicam) or the subject combination may be administered to relieve neuropathic pain, including diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, monoradiculopathies, phantom limb pain,

sciatica, pudendal neuralgia, and central pain. Other causes of neuropathic pain may include, but are not limited to, cancer-related pain, lumbar nerve root compression, spinal cord injury, post-stroke pain, central multiple sclerosis pain, HIV-associated neuropathy, and radio-therapy or chemo-therapy associated neuropathy. The neuropathic pain may be chronic or acute.

For some methods, the dosage form (e.g. a dosage form containing a triptan such as rizatriptan or frovatriptan, and/or an NSAID such as meloxicam) or the subject combination may be administered to relieve musculoskeletal pain. Examples of musculoskeletal pain may include, but are not limited to, back pain, low back pain (e.g., lumbosacral pain), neck pain, infection, cramps, tendonitis, epidondylitis, carpal tunnel syndrome, joint pain, fibromyalgia, pain due to injury, Tunnel syndromes, pain associated with bone fractures, sprains, fibrous dysplasia, osteogenesis imperfecta, Paget's disease of bone, transient osteoporosis, and transient osteoporosis of the hip. In other embodiments, the musculoskeletal pain may be chronic or acute.

For some methods, administration of the dosage form (e.g. a dosage form containing a triptan such as rizatriptan or frovatriptan, and/or an NSAID such as meloxicam) or the subject combination may achieve a reduction in pain that lasts at least about one hour, at least about two hours, at least about three hours, at least about four hours, at least about six hours, at least about eight hours, about 8 to about 24 hours, or about 24 hours. In other embodiments, administration of the dosage form or the subject combination may achieve a reduction in pain that is observed at about 10 minutes, at about 30 minutes, at about one hour, at about two hours, at about three hours, at about four hours, at about five hours, at about six hours, at or within about 5 minutes, at or within about 10 minutes, at or within about 15 minutes, at or within about 20 minutes, at or within about 25 minutes, at or within about 30 minutes, at or within about 35 minutes, at or within about 40 minutes, at or within about 45 minutes, at or within about 50 minutes, or at or within about 60 minutes, at two hours or less, at three hours or less, or other time period bound by these ranges, after administration of the dosage form or the subject combination.

A human being that is treated for a disease or condition, such as migraine, with any of the dosage forms or the subject combination described herein (e.g. a dosage form containing a triptan such as rizatriptan or frovatriptan, and/or an NSAID such as meloxicam) may be of

any age. For example the person may have an age of about 0.1-10 years, about 10-90 years, about 20-80 years, about 30-75 years, about 40-70 years, about 1-16 years, about 80-95 years, about 18 years or more, about 20 years or more, about 25 years or more, about 30 years or more, about 40 years or more, about 45 years or more, about 50 years or more, about 55 years or more, about 60 years or more, about 65 years or more, or any other age in a range bounded by, or between, any of these values.

In some embodiments, a human being that is treated for a disease or condition, such as migraine, with a subject combination or a dosage form (e.g. a dosage form containing a triptan such as rizatriptan or frovatriptan, and/or an NSAID such as meloxicam) has suffered from the condition for at least 1 day, at least one week, at least 2 weeks, at least 1 month, at least 6 weeks, at least 2 months, at least 3 months, at least 6 months, at least 1 year, at least 5 years, at least 10 years, at least 15 years, at least 20 years, at least 30 years, at least 40 years, at least 50 years or any duration in a range bounded by, or between, any of these values.

A cyclodextrin used in a dosage form with a drug (including meloxicam or another NSAID, rizatriptan, frovatriptan, or another triptan) could include a cyclodextrin, a cyclodextrin derivative, and/or a salt thereof. Cyclodextrins (also known as cycloamyloses) are generally cyclic polysaccharides which form a bucket-like shape. Cyclodextrins help to increase bioavailability of other molecules because cyclodextrins are hydrophobic on the inside and hydrophilic on the outside which helps to facilitate the transport of hydrophobic molecules to a hydrophilic medium. The naturally occurring cyclodextrins include six, seven, and eight glucose units (α, β, and γ-cyclodextrin, respectively). However, synthetic cyclodextrins containing more or less glucose units are possible. In aqueous solutions, cyclodextrins can form complexes (i.e., an inclusion complex) with drugs by incorporating the drug into the center/hydrophobic portion of the cyclodextrin ring; although cyclodextrins are also known to aggregate around a drug in a micelle-type structure. This ability of cyclodextrins may allow them to act as carriers of less soluble drugs to increase the drugs' bioavailability.

An inclusion complex of drug (including meloxicam or another NSAID, rizatriptan, frovatriptan, or another triptan) and cyclodextrin may be more water-soluble relative to the non-complexed drug. The cyclodextrin may be a naturally-occurring cyclodextrin (e.g., α, β, or γ-cyclodextrins) or a synthetic cyclodextrin. In some embodiments, α-cyclodextrins, derivatives, or salts thereof may be used. α-Cyclodextrins may include, but are not limited to,

(2,3,6-tri-O-acetyl)-α-cyclodextrin, (2,3,6-tri-O-methyl)-α-cyclodextrin, (2,3,6-tri-O-octyl)-α-cyclodextrin, 6-bromo-6-deoxy-α-cyclodextrin, 6-iodo-6-deoxy-α-cyclodextrin, (6-O-tertbutyl-dimethylsilyl)-α-cyclodextrin, butyl-α-cyclodextrin, succinyl-α-cyclodextrin, (2-hydroxypropyl)-α-cyclodextrin, or combinations thereof.

In some embodiments, β-cyclodextrins, derivatives, or salts thereof may be used. β-cyclodextrins may include, but are not limited to, hydroxypropyl-β-cyclodextrin, 6-monodeoxy-6-monoamino-β-cyclodextrin, glucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin, 6-O-α-D-glucosyl-β-cyclodextrin, 6-O-α-maltosyl-β-cyclodextrin, 6-azido-6-deoxy-β-cyclodextrin, (2,3-di-O-acetyl-6-O-sulfo)-β-cyclodextrin, methyl-β-cyclodextrin, dimethyl-β-cyclodextrin (DMβCD), trimethyl-β-cyclodextrin (TMβCD), (2,3-di-O-methyl-6-O-sulfo)-β-cyclodextrin, (2,6-di-O-methyl)-β-cyclodextrin, (2,6-di-O-ethyl)-β-cyclodextrin, (2,3,6-tri-O-methyl)-β-cyclodextrin, (2,3,6-tri-O-acetyl)-β-cyclodextrin, (2,3,6-tri-O-benzoyl)-β-cyclodextrin, (2,3,6-tri-O-ethyl)-β-cyclodextrin, 6-iodo-6-deoxy-β-cyclodextrin, 6-(dimethyl-tert-butylsilyl)-6-deoxy-β-cyclodextrin, 6-bromo-6-deoxy-β-cyclodextrin, monoacetyl-β-cyclodextrin, diacetyl-β-cyclodextrin, triacetyl-β-cyclodextrin, (3-O-acetyl-2,6-di-O-methyl)-β-cyclodextrin, (6-O-maltosyl)-β-cyclodextrin, (6-O-sulfo)-β-cyclodextrin, (6-O-t-butyldimethylsilyl-2,3-di-O-acetyl)-β-cyclodextrin, succinyl-(2-hydroxypropyl)-β-cyclodextrin, (2,6-di-O-)ethyl-β-cyclodextrin, (2-carboxyethyl)-β-cyclodextrin (CMEβCD), hydroxyethyl-β-cyclodextrin (HEβCD), (2-hydroxypropyl)-β-cyclodextrin, (2-hydroxypropyl)-β-cyclodextrin (HPβCD), (3-hydroxypropyl)-β-cyclodextrin (3HPβCD), (2,3-hydroxypropyl)-β-cyclodextrin (DHPβCD), butyl-β-cyclodextrin, methyl-β-cyclodextrin, silyl((6-O-tert-butyldimethyl)-2,3,-di-O-acetyl)-β-cyclodextrin, succinyl-β-cyclodextrin, (2-hydroxyisobutyl)-β-cyclodextrin, randomly methylated-β-cyclodextrin, branched-β-cyclodextrin, or combinations thereof.

In other embodiments, a β-cyclodextrin may be a sulfoalkyl ether cyclodextrin, derivative, or salt thereof. Examples of sulfoalkyl ether cyclodextrin derivatives may include, but are not limited to, sulfobutyl ether-β-cyclodextrin (e.g., SBEβCD, betadex, CAPTISOL®). In some embodiments, a SBEβCD may have about 4-8, about 5-8, about 4-7, about 6-7, or about 6.5 sulfobutyl ether groups per cyclodextrin molecule.

In some embodiments, γ-cyclodextrins, derivatives, or salts thereof may be used. γ-cyclodextrins may include carboxymethyl-γ-cyclodextrin, (2,3,6-tri-O-acetyl)-γ-cyclodextrin, (2,3,6-tri-O-methyl)-γ-cyclodextrin, (2,6-di-O-pentyl)-γ-cyclodextrin, 6-(dimethyl-tert-

butylsilyl)-6-deoxy-γ-cyclodextrin, 6-bromo-6-deoxy-γ-cyclodextrin, 6-iodo-6-deoxy-γ-cyclodextrin, (6-O-t-butyldimethylsilyl)-γ-cyclodextrin, succinyl-γ-cyclodextrin, hydroxypropyl-γ-cyclodextrin, (2-hydroxypropyl)-γ-cyclodextrin, acetyl-γ-cyclodextrin, butyl-γ-cyclodextrin, or combinations thereof.

In some embodiments, the dosage form may include a bicarbonate, such as sodium bicarbonate, potassium bicarbonate, etc. A bicarbonate may help to increase the pharmacokinetics or bioavailability of meloxicam or another drug, such as rizatriptan.

In some embodiments, enhanced bioavailability of a drug, such as meloxicam or a triptan (e.g. rizatriptan) in the dosage form may be achieved by administering a dosage form comprising a salt form of the drug, by generating an inclusion complex of the drug with cyclodextrin, and/or by including a bicarbonate. This may allow a reduced molar amount of the drug to be used as compared to other dosage forms containing the drug in treating diseases or disorders.

Unless otherwise indicated, any reference to a compound herein, such as meloxicam, an NSAID, a triptan, rizatriptan, or a cyclodextrin, by structure, name, or any other means, includes pharmaceutically acceptable salts, alternate solid forms, such as polymorphs, solvates, hydrates, enantiomers, tautomers, deuterium-modified forms, or any other chemical species, such as precursors, prodrugs, or any other chemical species that may rapidly convert to a compound described herein under conditions in which the compounds are used as described herein.

In some embodiments, use of a cyclodextrin or a bicarbonate may improve the solubility or oral bioavailability (e.g. a higher C_{max} and/or higher AUC) of meloxicam in a subject (human or animal) by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, up to about 100%, up to about 200%, or any amount in a range bounded by, or between, any of these values as compared to administration of meloxicam alone.

In some embodiments, use of a cyclodextrin or a bicarbonate may improve the solubility or oral bioavailability (e.g. a higher C_{max} and/or higher AUC) of a triptan such as rizatriptan or frovatriptan in subject (human or animal) by at least about 10%, at least about 20**%**, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, up to about 100%, up to about 200%, or

any amount in a range bounded by, or between, any of these values as compared to administration of the triptan alone.

Due to the improved bioavailability as described above, the dosage form may contain, or a subject may receive, on a molar basis, less of the drug, such as a triptan (e.g. rizatriptan or frovatriptan) or an NSAID (e.g. meloxicam) than would otherwise be administered of the drug alone. For example, a dosage form may contain, or a mammal may receive, at least about 10 mole% less, at least about 20 mole% less, at least about 30 mole% less, at least about 40 mole% less, at least about 50 mole% less, at least about 60 mole% less, at least about 70 mole% less, at least about 80 mole% less, at least about 85 mole% less, and/or up to about 90 mole% less, 95 mole% less, 98 mole% less, or any amount in a range bounded by, or between, any of these values of meloxicam as that would otherwise be administered of meloxicam alone.

In other embodiments, use of other NSAIDs, opioids, or other pain medications may be reduced by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%, up to about 100%, or any amount in a range bounded by, or between, any of these values when administered with a drug such as an triptan (e.g. rizatriptan) or an NSAID (e.g. meloxicam), with a cyclodextrin and/or a bicarbonate, as compared to administration of the NSAID, the opioid or the other pain medication alone.

In some embodiments, a dosage form may contain an NSAID, such as celecoxib, rofecoxib, lumiracoxib, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337, NS398, aspirin, acetaminophen (considered to be an NSAID for the purposes of the present disclosure), ibuprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketorolac, lornoxicam, piroxicam, droxicam, tenoxicam, nabumetone, diclofenac, meclofenamate, mefenamic acid, diflunisal, sulindac, tolmetin, fenoprofen, suprofen, benoxaprofen, aceclofenac, tolfenamic acid, oxyphenbutazone, azapropazone, phenylbutazone, in an amount of about 1-1000 mg, about 1-500 mg, about 1-400 mg, about 1-300 mg, about 1-200 mg, about 1-100 mg, about 1-50 mg, about 1-10 mg, about 1-5 mg, about 2-6 mg, about 3-7 mg, about 4-8 mg, about 5-10 mg, about 7-12 mg, about 5-15 mg, about 10-20 mg, about 15-25 mg, about 20-30 mg, about 25-35 mg, about 30-40 mg, about

35-45 mg, about 40-50 mg, about 50-150 mg, about 50-100 mg, about 100-200 mg, about 150-250 mg, about 200-300 mg, about 250-350 mg, about 300-400 mg, about 350-450 mg, about 400-500 mg, about 100 mg, about 200 mg, about 325 mg, or any amount in a range bounded by, or between, any of these values. These doses may be a safe dose for repeated administration, such as 1, 2, 3, or 4 times a day, or repeated at an interval of 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, about 1 week, about 4 weeks, about 6 weeks, about 1-2 months, about 6 weeks, about 2-3 months, about 3-4 months, about 4-5 months, about 5-6 months, about 6-7 months, about 7-8 months, about 8-9 months, about 9-10 months, about 10-11 months, about 11-12 months, about 2 years, etc.

In some embodiments, a dosage form comprising meloxicam, or a subject combination in a dosage form, including an oral, intravenous, or intramuscular dosage form, may contain meloxicam in an amount of about 1-50 mg; about 1-10 mg; about 1-5 mg; about 10-40 mg; about 1-35 mg; about 2-6 mg, about 3-7 mg, about 4-8 mg, about 5-10 mg, about 7-12 mg, about 5-15 mg, about 10-20 mg, about 10-30 mg, about 18-22 mg, about 19-21 mg, about 15-25 mg, about 20-30 mg, about 25-35 mg, about 30-40 mg, about 35-45 mg, about 40-50 mg, about 1-25 mg; about 1-15 mg; about 5-20 mg; about 5 mg; about 7.5 mg; about 10 mg; about 15 mg; about 20 mg; about 30 mg; or any amount in a range bounded by, or between, any of these values. For any amounts of meloxicam (or any other compound) described herein, salt forms of meloxicam (or another compound) may be present in the amounts recited above, or amounts that are molar equivalents to these amounts for the non-salt form of meloxicam (or another compound). These doses may be safe for repeated administration, such as 1, 2, 3, or 4 times a day, or may be repeated at an interval of about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 15 days, about 16 days, about 17 days, about 18 days, about 19 days, about 20 days, about 21 days, about 22 days, about 23 days, about 24 days, about 25 days, about 26 days, about 27 days, about 28 days, about 29 days, about 30 days, about 31 days, about 1-2 months, about 4 weeks, about 6 weeks, about 2-3 months, about 3-4 months, about 4-5 months, about 5-6 months, about 6-7 months, about

7-8 months, about 8-9 months, about 9-10 months, about 10-11 months, about 11-12 months, about 1-2 years, about 2 years, etc.

For some dosage forms, a drug (such as meloxicam, frovatriptan, or rizatriptan) forms a complex with the substituted-β-cyclodextrin or other cyclodextrin which may be formulated into a solid dosage form. Such a dosage form may be suitable for oral administration. A drug-cyclodextrin inclusion complex may also be dissolved in water or another solvent to form a parenteral formulation. However, physical mixtures of drug and the substituted-β-cyclodextrin or other cyclodextrins that are not inclusion complexes may also be used in oral or parenteral dosage forms.

Formation of an inclusion complex of a drug (such as meloxicam, frovatriptan, or rizatriptan) and a cyclodextrin may help to improve the properties of a dosage form. For some inclusion complexes, the drug and the cyclodextrin (e.g., SBEβCD) may have a molar ratio of about 0.5-2 (a molar ratio of 0.5 is 0.5 moles of the drug to 1 mole of cyclodextrin), about 0.5-0.7, about 0.6-0.8, about 0.7-0.9, about 0.8-1, about 0.9-1.1, about 1-1.2, about 1.1-1.3, about 1.2-1.4, about 1.3-1.5, about 1.4-1.6, about 1.5-1.7, about 1.6-1.8, about 1.7-1.9, about 1.8-2, about 1.9-2.1, about 2-2.2, about 0.8-1.2, about 1, or any ratio in a range bounded by any of these values.

In some embodiments, an inclusion complex is formed by (1) mixing a homogeneous solution of a drug such as meloxicam or a triptan with a homogeneous solution of the cyclodextrin to form a homogeneous solution of the drug and the cyclodextrin, and (2) removing or evaporating the solvent of the homogeneous solution of the drug and the cyclodextrin to form the complex comprising the inclusion complex of the drug in a cyclodextrin. In some embodiments, the solutions can be pH-adjusted aqueous solutions. The pH can be adjusted using a buffering agent. In some embodiments, the solvent can be removed or evaporated by lyophilization, spray drying, or any other means that is suitable. In some embodiments, the solvent can be removed by vacuum drying, etc.

For some dosage forms, a cyclodextrin (e.g., SBEβCD) may be employed in a weight ratio to the meloxicam within the range of about 1-1000 (e.g. 1 g of cyclodextrin per 1 g of meloxicam is a weight ratio of 1); about 1-500, about 1-5, about 1-20; about 1-10; about 1-15; about 2-4, about 3-5, about 4-6, about 5-7, about 6-8, about 7-9, about 8-10, about 0.01-1; about 0.05-1; about 0.1-1; about 0.2-1; about 0.3-1, about 0.4-1, about 0.5-1, about 0.6-1,

about 0.7-1, about 0.8-1, or any weight ratio in a range bounded by, or between, any of these values. Each type of cyclodextrin employed may have a different weight ratio to the meloxicam in the dosage form.

For some dosage forms, a cyclodextrin (e.g., SBEβCD) may be employed in a weight ratio to the triptan, e.g. rizatriptan or frovatriptan, within the range of about 1-1000 (e.g. 10 g of cyclodextrin per 1 g of rizatriptan or frovatriptan is a weight ratio of 10); about 1-500; about 1-100; about 1-50; about 1-20; about 1-10; about 1-15; about 1-5, about 2-4, about 3-5, about 4-6, about 5-7, about 6-8, about 7-9, about 8-10, about 0.01-1; about 0.05-1; about 0.1-1; about 0.2-1; about 0.3-1; about 0.4-1; about 0.5-1; about 0.6-1; about 0.7-1; about 0.8-1; or any weight ratio in a range bounded by, or between, any of these values. Each type of cyclodextrin employed may have a different weight ratio to the triptan in the dosage form.

For some dosage forms, a cyclodextrin (e.g., SBEβCD) may be employed in a weight ratio to rizatriptan within the range of about 1-1000 (e.g. 10 g of cyclodextrin per 1 g of rizatriptan is a weight ratio of 10); about 1-500; about 1-100; about 1-50; about 1-20; about 1-10; about 1-15; about 2-4, about 3-5, about 4-6, about 5-7, about 6-8, about 7-9, about 8-10, about 9-11, about 10-12, about 11-13, about 12-14, about 13-15, about 14-16, about 15-17, about 16-18, about 17-19, about 18-20, about 19-21, about 0.001-1; about 0.01-1; about 0.05-1; about 0.1-1; about 0.2-1; about 0.3-1, about 0.4-1, about 0.5-1, about 0.6-1, about 0.7-1, about 0.8-1, or any weight ratio in a range bounded by, or between, any of these values. Each type of cyclodextrin employed may have a different weight ratio to rizatriptan in the dosage form.

In some embodiments; a dosage form or a subject combination may contain rizatriptan in an amount of about 1-50 mg; about 1-10 mg; 10-20 mg; about 20-30 mg; about 30-40 mg; or about 40-50 mg; about 10-40 mg; about 1-35 mg; about 1-25 mg; about 1-15 mg; about 1-10 mg; about 5-20 mg; about 1-5 mg; about 2-6 mg; about 3-7 mg; about 4-8 mg; about 5-10 mg; about 6-11 mg; about 7-12 mg; about 8-13 mg; about 9-11 mg; about 9-14 mg; about 10-15 mg; about 11-16 mg; about 12-17 mg; about 13-18 mg; about 14-19 mg; about 15-20 mg; about 5-15 mg; about 0.5 mg; about 1 mg; about 1.5 mg; about 2 mg; about 2.5 mg; about 3 mg; about 3.5 mg; about 4 mg; about 4.5 mg; about 5 mg; about 6 mg; about 7 mg; about 7.5 mg; about 8 mg, about 9 mg, about 10 mg; about 15 mg; about 20 mg, about 25 mg, about 30 mg; or any amount in a range bounded by, or between, any of these values.

For acute migraines, the amount of meloxicam and/or rizatriptan in a single dose, or the AUC of the meloxicam and/or rizatriptan associated with a single dose, is of particular interest. For example, after a single dose, the symptoms may be relieved for an extended period of time, such that, in the short term, repeated doses may not be needed. For more continuous conditions, including more chronic, continuous, or frequent migraine symptoms, daily, weekly, or monthly doses may be of particular interest.

For any amounts of rizatriptan described herein, salt forms of rizatriptan may be present in the amounts recited above, or amounts that are molar equivalents to these amounts for the rizatriptan free base. For example, assuming that the molecular weight of rizatriptan free base is 269.3 g/mol, 10 mg of rizatriptan is 37.1 mmol of rizatriptan. Thus, a molar equivalent of 10 mg of rizatriptan free base would be the mass of 37.1 mmol of that salt form. For example, for the benzoate salt (mw = 391.2 g/mol), the molar equivalent of 10 mg of the free base (or 37.1 mmol), would be 14.5 mg. These doses may be safe for repeated administration, such as 1, 2, 3, or 4 times a day, or repeated at an interval of 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, 4 weeks, 4-6 weeks, about 1-2 months, about 6 weeks, about 2-3 months, about 3-4 months, about 4-5 months, about 5-6 months, about 6-7 months, about 7-8 months, about 8-9 months, about 9-10 months, about 10-11 months, about 11-12 months, etc.

The other triptans may be administered to patients at any dosages effective at relieving pain. In some embodiments, the dosage form may contain the triptan in any amount in a range bounded by any of the values described above.

In some embodiments, a dosage form may contain frovatriptan or another triptan in an amount of about 1-50 mg; about 1-10 mg; about 20-30 mg; about 30-40 mg; or about 40-50 mg; about 10-40 mg; about 1-35 mg; about 1-25 mg; about 1-15 mg; about 5-20 mg; about 1-5 mg; about 2-6 mg; about 3-7 mg; about 4-8 mg; about 5-10 mg; about 6-11 mg; about 7-12 mg; about 8-13 mg; about 9-11 mg; about 9-14 mg; about 10-15 mg; about 11-16 mg; about 12-17 mg; about 13-18 mg; about 14-19 mg; about 15-20 mg; about 5-15 mg; about 10-20 mg; about 0.5 mg; about 1 mg; about 1.5 mg; about 2 mg; about 2.5 mg; about 3 mg; about 3.5 mg; about 4 mg; about 4.5 mg; about 5 mg; about 6 mg; about 7 mg; about 7.5 mg; about 10

mg; about 15 mg; about 30 mg; or any amount in a range bounded by, or between, any of these values. These doses may be a safe dose for repeated administration, such as 1, 2, 3, or 4 times a day, or repeated at an interval of 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, about 4 weeks, about 4-6 weeks, about 1-2 months, about 6 weeks, about 2-3 months, about 3-4 months, about 4-5 months, about 5-6 months, about 6-7 months, about 7-8 months, about 8-9 months, about 9-10 months, about 10-11 months, about 11-12 months, about 2 years, etc.

For some dosage forms, a cyclodextrin (such as SBEβCD) may be present in an amount of about 1-200 mg; about 1-100 mg; about 25-175 mg; about 50-150 mg; about 50-100 mg; about 50-200 mg; about 25-100 mg; about 75-150 mg; about 100-175 mg; about 20-80 mg; about 25-50 mg; about 60-100 mg; about 80-100 mg; about 100 mg; about 80-120 mg; about 100-120 mg; about 100-140 mg; about 120-160 mg; about 140-180 mg; about 150-200 mg, about 100-150 mg; about 30-90 mg; about 40-60 mg; about 40-80 mg; about 50-70 mg, about 55-65 mg, about 60-62 mg, or any amount in a range bounded by, or between, any of these values. A cyclodextrin may be effective in decreasing T_{max} and/or increasing AUC of meloxicam and/or rizatriptan.

For some dosage forms, an inclusion complex of a drug (such as meloxicam or another NSAID, or rizatriptan, frovatriptan or another triptan) and cyclodextrin is about 1-10%, about 5-20%, about 5-15%, about 6-16%, about 7-17%, about 8-18%, about 9-19%, about 10-20%, about 15-30%, about 30-40%, about 40-50%, about 50-70%, or about 70-90% of the total weight of the dosage form, or any percentage in a range bounded by any of these values.

Some dosage forms contain a bicarbonate (e.g., sodium bicarbonate) in amount of about 1-2000 mg; about 1-1000 mg; about 100-1000 mg; about 200-800 mg; about 1-500 mg; about 1-200 mg; about 1-100 mg; about 50-750 mg; about 500-1000 mg; about 100-500 mg; about 100-300 mg; about 500-1000 mg; about 300-700 mg; about 400-600 mg; about 50-250 mg; about 50-100 mg; about 250-750 mg; about 100-200 mg; about 200-300 mg; about 300-400 mg; about 400-500 mg; about 410-510 mg; about 420-520 mg; about 430-530 mg; about 440-540 mg; about 450-550 mg; about 460-560 mg; about 470-570 mg; about 480-580 mg; about 490-590 mg; about 500-600 mg; about 600-700 mg; about 700-800 mg; about 800-900

mg; about 900-1,000 mg; about 150-650 mg; about 350-850 mg; about 400 mg; about 450 mg; about 500 mg, about 550 mg; about 600 mg; or any amount in a range bounded by, or between, any of these values.

A bicarbonate, such as sodium bicarbonate, may be at least about 10%, at least about 15%, at least about 20%, about 20-40%, about 30-50%, about 40-60%, about 50-70%, about 60-80%, or about 70-90%, or any percentage in a range bounded by any of these values, of the total weight of the dosage form.

In some embodiments, the daily dose of meloxicam, or the amount of meloxicam administered in a single day (either in one administration, or by two or more divided doses adding up to the daily dose) is about 2-5 mg, about 2-6 mg, about 2-7 mg, about 2-8 mg, about 2-9 mg, about 2-10 mg, about 2-11 mg, about 2-12 mg, about 2-13 mg, about 2-14 mg, about 2-15 mg, about 2-16 mg, about 2-17 mg, about 2-18 mg, about 2-19 mg, about 2-20 mg, about 2-21 mg, about 2-22 mg, about 2-23 mg, about 2-24 mg, about 2-25 mg, about 2-26 mg, about 2-27 mg, about 2-28 mg, about 2-29 mg, about 2-30 mg, about 2-35 mg, about 2-40 mg, about 2-45 mg, about 2-50 mg, about 2-55 mg, about 2-60 mg, about 2-65 mg, about 2-70 mg, about 2-75 mg, about 3-8 mg, about 4-9 mg, about 5-10 mg, about 6-11 mg, about 7-12 mg, about 8-13 mg, about 9-14 mg, about 10-15 mg, about 11-16 mg, about 12-17 mg, about 13-18 mg, about 14-19 mg, about 15-20 mg, about 16-21 mg, about 17-22 mg, about 18-23 mg, about 19-24 mg, about 20-25 mg, about 21-26 mg, about 22-27 mg, about 23-28 mg, about 24-29 mg, about 25-30 mg, about 26-31 mg, about 27-32 mg, about 28-33 mg, about 29-34 mg, about 30-35 mg, about 31-36 mg, about 32-37 mg, about 33-38 mg, about 34-39 mg, about 35-40 mg, about 36-41 mg, about 37-42 mg, about 38-43 mg, about 39-44 mg, about 40-45 mg, about 41-46 mg, about 42-47 mg, about 43-48 mg, about 44-49 mg, about 45-50 mg, about 46-51 mg, about 47-52 mg, about 48-53 mg, about 49-54 mg, about 50-55 mg, about 51-56 mg, about 52-57 mg, about 53-58 mg, about 54-59 mg, about 55-60 mg, about 56-61 mg, about 57-62 mg, about 58-63 mg, about 59-64 mg, about 60-65 mg, about 61-66 mg, about 62-67 mg, about 63-68 mg, about 64-69 mg, about 65-70 mg, about 66-71 mg, about 67-72 mg, about 68-73 mg, about 69-74 mg, about 70-75 mg, or any amount in a range bounded by any of these values. The daily dose may be given as a single dose, given once a day, or may be given in 2, 3, 4, or more divided doses during a day.

In some embodiments, the weekly dose of meloxicam or the amount of meloxicam administered in a week (either in one administration, or by two or more divided doses adding up to the weekly dose) is about 1-1000 mg; about 1-500 mg; about 10-250 mg; about 100-300 mg; about 10-100 mg; about 10-150 mg; about 10-300 mg; about 20-150 mg; about 20-60 mg; about 30-70 mg; about 40-60 mg; about 50-70 mg; about 70-90 mg; about 90-110 mg; about 80-450 mg; about 80-100 mg; about 90-110 mg; about 100-120 mg; about 110-130 mg; about 120-140 mg; about 130-150 mg; about 140-160 mg; about 150-170 mg; about 160-180 mg; about 170-190 mg; about 180-200 mg; about 190-210 mg; about 200-220 mg; about 210-230 mg; about 220-240 mg; about 230-250 mg; about 240-260 mg; about 250-270 mg; about 260-280 mg; about 270-290 mg; about 280-300 mg; about 290-310 mg; about 300-320 mg; about 310-330 mg; about 320-340 mg; about 330-350 mg; about 340-360 mg; about 350-370 mg; about 360-380 mg; about 370-390 mg; about 380-400 mg; about 390-410 mg; about 400-420 mg; about 410-430 mg; about 420-440 mg; about 430-450 mg; about 50 mg; about 55 mg; about 100-150 mg; about 30-100 mg; or any amount in a range bounded by, or between, any of these values. The weekly dose may be given as a single dose, given once a week, or may be given in 2, 3, 4, 5, 6, or 7 individual doses during a week.

In some embodiments, the monthly dose of meloxicam (e.g., an oral dose), or a dose administered over a period of a month, is about 5000 mg or less; about 4000 mg or less; about 3000 mg or less; about 2000 mg or less; about 1000 mg or less; about 700 mg or less; about 600 mg or less; about 300-2400 mg; about 300-350 mg; about 310-360 mg; about 320-370 mg; about 330-380 mg; about 340-390 mg; about 350-400 mg; about 360-410 mg; about 370-420 mg; about 380-430 mg; about 390-440 mg; about 400-450 mg; about 410-460 mg; about 420-470 mg; about 430-480 mg; about 440-490 mg; about 450-500 mg; about 460-510 mg; about 470-520 mg; about 480–530 mg; about 490–540 mg; about 500–550 mg; about 510–560 mg; about 520–570 mg; about 530-580 mg; about 540-590 mg; about 550-600 mg; about 560-610 mg; about 570-620 mg; about 580-630 mg; about 590-640 mg; about 600-650 mg; about 610-660 mg; about 620-670 mg; about 630-680 mg; about 640-690 mg; about 650-700 mg; about 660-710 mg; about 670-720 mg; about 680-730 mg; about 690-740 mg; about 700-750 mg; about 710-760 mg; about 720-770 mg; about 730-780 mg; about 740-790 mg; about 750-800 mg; about 760-810 mg; about 770-820 mg; about 780-830 mg; about 790-840 mg; about 800-850 mg; about 810-860 mg; about 820-870 mg; about 830-880 mg; about 840-890

mg; about 850-900 mg; about 860-910 mg; about 870-920 mg; about 880-930 mg; about 890-940 mg; about 900-950 mg; about 910-960 mg; about 920-970 mg; about 930-980 mg; about 940-990 mg; about 950-1000 mg; about 960-1010 mg; about 970-1020 mg; about 980-1030 mg; about 990-1040 mg; about 1000-1050 mg; about 1010-1060 mg; about 1020-1070 mg; about 1030-1080 mg; about 1040-1090 mg; about 1050-1100 mg; about 1060-1110 mg; about 1070-1120 mg; about 1080-1130 mg; about 1090-1140 mg; about 1100-1150 mg; about 1110-1160 mg; about 1120-1170 mg; about 1130-1180 mg; about 1140-1190 mg; about 1150-1200 mg; about 1160-1210 mg; about 1170-1220 mg; about 1180-1230 mg; about 1190-1240 mg; about 1200-1250 mg; about 1210-1260 mg; about 1220-1270 mg; about 1230-1280 mg; about 1240-1290 mg; about 1250-1300 mg; about 1260-1310 mg; about 1270-1320 mg; about 1280-1330 mg; about 1290-1340 mg; about 1300-1350 mg; about 1310-1360 mg; about 1320-1370 mg; about 1330-1380 mg; about 1340-1390 mg; about 1350-1400 mg; about 1360-1410 mg; about 1370-1420 mg; about 1380-1430 mg; about 1390-1440 mg; about 1400-1450 mg; about 1410-1460 mg; about 1420-1470 mg; about 1430-1480 mg; about 1440-1490 mg; about 1450-1500 mg; about 1460-1510 mg; about 1470-1520 mg; about 1480-1530 mg; about 1490-1540 mg; about 1500-1550 mg; about 1510-1560 mg; about 1520-1570 mg; about 1530-1580 mg; about 1540-1590 mg; about 1550-1600 mg; about 1560-1610 mg; about 1570-1620 mg; about 1580-1630 mg; about 1590-1640 mg; about 1600-1650 mg; about 1610-1660 mg; about 1620-1670 mg; about 1630-1680 mg; about 1640-1690 mg; about 1650-1700 mg; about 1660-1710 mg; about 1670-1720 mg; about 1680-1730 mg; about 1690-1740 mg; about 1700-1750 mg; about 1710-1760 mg; about 1720-1770 mg; about 1730-1780 mg; about 1740-1790 mg; about 1750-1800 mg; about 1760-1810 mg; about 1770-1820 mg; about 1780-1830 mg; about 1790-1840 mg; about 1800-1850 mg; about 1810-1860 mg; about 1820-1870 mg; about 1830-1880 mg; about 1840-1890 mg; about 1850-1900 mg; about 1860-1910 mg; about 1870-1920 mg; about 1880-1930 mg; about 1890-1940 mg; about 1900-1950 mg; about 1910-1960 mg; about 1920-1970 mg; about 1930-1980 mg; about 1940-1990 mg; about 1950-2000 mg; about 1960-2010 mg; about 1970-2020 mg; about 1980-2030 mg; about 1990-2040 mg; about 2000-2050 mg; about 2010-2060 mg; about 2020-2070 mg; about 2030-2080 mg; about 2040-2090 mg; about 2050-2100 mg; about 2060-2110 mg; about 2070-2120 mg; about 2080-2130 mg; about 2090-2140 mg; about 2100-2150 mg; about 2110-2160 mg; about 2120-2170 mg; about 2130-2180 mg; about 2140-2190 mg; about 2150-2200 mg; about 2160-2210 mg; about 2170-2220

mg; about 2180-2230 mg; about 2190-2240 mg; about 2200-2250 mg; about 2210-2260 mg; about 2220-2270 mg; about 2230-2280 mg; about 2240-2290 mg; about 2250-2300 mg; about 2260-2310 mg; about 2270-2320 mg; about 2280-2330 mg; about 2290-2340 mg; about 2300-2350 mg; about 2310-2360 mg; about 2320-2370 mg; about 2330-2380 mg; about 2340-2390 mg; about 2350-2400 mg; about 1-4000 mg; about 1-1000 mg; about 10-1000 mg; about 50-1000 mg; about 10-600 mg; about 40-600 mg; about 50-600 mg; about 40-400 mg; about 50-200 mg; about 200-240 mg; about 240-280 mg; about 280-320 mg; about 320-360 mg; about 360-400 mg; about 400-450 mg; about 450-500 mg; about 500-600 mg; about 250-350 mg; about 100-600 mg; about 40-2000 mg; about 40-800 mg; about 100-900 mg; about 100-800 mg; about 40-1000 mg; about 50-1000 mg; about 100-1000 mg; or any monthly dose in a range bounded by, or between, any of these values. A monthly dose may be given as a single dose, or as two or more individual doses administered during the month. In some embodiments, the monthly dose is administered bi-weekly in 2 or 3 divided doses. In some embodiments, the monthly dose is administered weekly in 4 or 5 divided doses. In some embodiments, the monthly dose is administered daily in 28 to 31 divided doses, or in 56 to 62 divided doses or more. In some embodiments, the monthly dose is administered in 5 to 15 individual doses during the month. The monthly dose may be administered for only 1 month, or may be repeatedly administered for 2, 3, 4, 5, 6, or more months.

In some embodiments, the daily dose of frovatriptan or another triptan (e.g., an oral dose, a parenteral dose, etc.) is about 0.5-1 mg, about 1-2 mg, about 2-3 mg, about 3-4 mg, about 2-5 mg, about 2-6 mg, about 2-7 mg, about 2-8 mg, about 2-9 mg, about 2-10 mg, about 2-11 mg, about 2-12 mg, about 2-13 mg, about 2-14 mg, about 2-15 mg, about 2-16 mg, about 2-17 mg, about 2-18 mg, about 2-19 mg, about 2-20 mg, about 2-21 mg, about 2-22 mg, about 2-23 mg, about 2-24 mg, about 2-25 mg, about 2-26 mg, about 2-27 mg, about 2-28 mg, about 2-29 mg, about 2-30 mg, about 2-35 mg, about 2-40 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, or any amount in a range bounded by any of these values.

In some embodiments, the daily dose of rizatriptan is about 0.5-100 mg, about 5-50 mg, about 1-10 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-50 mg, about 1-5 mg, about 1-6 mg, about 2-7 mg, about 3-8 mg, about 4-9 mg, about 5-10 mg, about 6-11 mg, about 7-12 mg, about 8-13 mg, about 9-14 mg, about 10-15 mg, about 11-16 mg, about

12-17 mg, about 13-18 mg, about 14-19 mg, about 15-20 mg, about 16-21 mg, about 17-22 mg, about 18-23 mg, about 19-24 mg, about 20-25 mg, about 21-26 mg, about 22-27 mg, about 23-28 mg, about 24-29 mg, about 25-30 mg, about 26-31 mg, about 27-32 mg, about 28-33 mg, about 29-34 mg, about 30-35 mg, about 31-36 mg, about 32-37 mg, about 33-38 mg, about 34-39 mg, about 35-40 mg, about 36-41 mg, about 37-42 mg, about 38-43 mg, about 39-44 mg, about 40-45 mg, about 41-46 mg, about 42-47 mg, about 43-48 mg, about 44-49 mg, about 45-50 mg, about 46-51 mg, about 47-52 mg, about 48-53 mg, about 49-54 mg, about 50-55 mg, or any amount in a range bounded by any of these values. The daily dose may be given as a single dose, given once a day, or may be given in 2, 3, 4, or more divided doses during a day.

In some embodiments, the weekly dose of frovatriptan or another triptan (e.g., an oral dose) is about 1-1000 mg; about 1-500 mg; about 10-250 mg; about 100-300 mg; about 10-100 mg; about 10-150 mg; about 10-300 mg; about 20-150 mg; about 20-60 mg; about 30-70 mg; about 40-60 mg; about 50-70 mg; about 70-90 mg; about 90-110 mg; about 50 mg; about 55 mg; about 100-150 mg; about 30-100 mg; about 1-20 mg; about 1-10 mg; about 2-10 mg; about 2-5 mg; about 5-10 mg; about 2.5 mg; about 5 mg; about 7.5 mg; or any amount in a range bounded by, or between, any of these values. The weekly dose may be given as a single dose, given once a week, or may be given in 2, 3, 4, 5, 6, or 7 individual doses during a week.

In some embodiments, the weekly dose of rizatriptan is about 1-1000 mg; about 10-400 mg, about 50-250 mg, about 1-500 mg; about 10-250 mg; about 100-300 mg; about 10-100 mg; about 10-150 mg; about 10-300 mg; about 20-150 mg; about 20-60 mg; about 30-70 mg; about 40-60 mg; about 50-70 mg; about 70-90 mg; about 90-110 mg; about 50 mg; about 55 mg; about 100-150 mg; about 30-100 mg; about 1-20 mg; about 1-10 mg; about 2-10 mg; about 2-5 mg; about 5-10 mg; about 1-50 mg; about 10-60 mg; about 20-70 mg; about 30-80 mg; how about 40-90 mg; about 50-100 mg; about 60-110 mg; about 70-120 mg; about 80-130 mg; about 90-140 mg; about 100-150 mg; about 110-160 mg; about 120-170 mg; about 130-180 mg; about 140-190 mg; about 150-200 mg; about 160-210 mg; about 170-220 mg; about 180-230 mg; about 190-240 mg; about 200-250 mg; about 210-260 mg; about 220-270 mg; about 230-280 mg; about 240-290 mg; about 250-300 mg; about 260-310 mg; about 270-320 mg; about 280-330 mg; about 290-340 mg; about 300-350 mg; about 310-360 mg; about 320-370 mg; about 330-380 mg; about 340-390 mg; about 350-400 mg; or any amount in a

range bounded by, or between, any of these values. The weekly dose may be given as a single dose, given once a week, or may be given in 2, 3, 4, 5, 6, or 7 individual doses during a week.

In some embodiments, the monthly dose of frovatriptan or another triptan (e.g., an oral dose), or a dose administered over a period of a month, is about 5000 mg or less; about 4000 mg or less; about 3000 mg or less; about 2000 mg or less; about 1000 mg or less; about 700 mg or less; about 600 mg or less; about 1-4000 mg; about 1-1000 mg; about 10-1000 mg; about 50-1000 mg; about 10-600 mg; about 40-600 mg; about 50-600 mg; about 40-400 mg; about 50-200 mg; about 200-240 mg; about 240-280 mg; about 280-320 mg; about 320-360 mg; about 360-400 mg; about 400-450 mg; about 450-500 mg; about 500-600 mg; about 250-350 mg; about 100-600 mg; about 40-2000 mg; about 40-800 mg; about 100-900 mg; about 100-800 mg; about 40-1000 mg; about 50-1000 mg; about 100-1000 mg; about 10-80 mg; about 10-40 mg; about 20-30 mg; or any monthly dose in a range bounded by, or between, any of these values. A monthly dose may be given as a single dose, or as two or more individual doses administered during the month. In some embodiments, the monthly dose is administered bi-weekly in 2 or 3 divided doses. In some embodiments, the monthly dose is administered weekly in 4 or 5 divided doses. In some embodiments, the monthly dose is administered daily in 28 to 31 divided doses, or in 56 to 62 divided doses or more. In some embodiments, the monthly dose is administered in 5 to 15 individual doses during the month. The monthly dose may be administered for only 1 month, or may be repeatedly administered for 2, 3, 4, 5, 6, or more months.

In some embodiments, the monthly dose of rizatriptan, or a total dose administered within a period of a month, is about 5000 mg or less; about 4000 mg or less; about 3000 mg or less; about 2000 mg or less; about 1000 mg or less; about 700 mg or less; about 600 mg or less; about 1-4000 mg; about 1-1000 mg; about 10-1000 mg; about 50-1000 mg; about 10-600 mg; about 40-600 mg; about 50-600 mg; about 150-2400 mg, about 150-200 mg; about 160-210 mg; about 170-220 mg; about 180-230 mg; about 190-240 mg; about 200-250 mg; about 210-260 mg; about 220-270 mg; about 230-280 mg; about 240-290 mg; about 250-300 mg; about 260-310 mg; about 270-320 mg; about 280-330 mg; about 290-340 mg; about 300-350 mg; about 310-360 mg; about 320-370 mg; about 330-380 mg; about 340-390 mg; about 350-400 mg; about 360-410 mg; about 370-420 mg; about 380-430 mg; about 390-440 mg; about 400-450 mg; about 410-460 mg; about 420-470 mg; about 430-480 mg; about 440-490 mg;

about 450-500 mg; about 460-510 mg; about 470-520 mg; about 480–530 mg; about 490–540 mg; about 500–550 mg; about 510–560 mg; about 520–570 mg; about 530-580 mg; about 540-590 mg; about 550-600 mg; about 560-610 mg; about 570-620 mg; about 580-630 mg; about 590-640 mg; about 600-650 mg; about 610-660 mg; about 620-670 mg; about 630-680 mg; about 640-690 mg; about 650-700 mg; about 660-710 mg; about 670-720 mg; about 680-730 mg; about 690-740 mg; about 700-750 mg; about 710-760 mg; about 720-770 mg; about 730-780 mg; about 740-790 mg; about 750-800 mg; about 760-810 mg; about 770-820 mg; about 780-830 mg; about 790-840 mg; about 800-850 mg; about 810-860 mg; about 820-870 mg; about 830-880 mg; about 840-890 mg; about 850-900 mg; about 860-910 mg; about 870-920 mg; about 880-930 mg; about 890-940 mg; about 900-950 mg; about 910-960 mg; about 920-970 mg; about 930-980 mg; about 940-990 mg; about 950-1000 mg; about 960-1010 mg; about 970-1020 mg; about 980-1030 mg; about 990-1040 mg; about 1000-1050 mg; about 1010-1060 mg; about 1020-1070 mg; about 1030-1080 mg; about 1040-1090 mg; about 1050-1100 mg; about 1060-1110 mg; about 1070-1120 mg; about 1080-1130 mg; about 1090-1140 mg; about 1100-1150 mg; about 1110-1160 mg; about 1120-1170 mg; about 1130-1180 mg; about 1140-1190 mg; about 1150-1200 mg; about 1160-1210 mg; about 1170-1220 mg; about 1180-1230 mg; about 1190-1240 mg; about 1200-1250 mg; about 1210-1260 mg; about 1220-1270 mg; about 1230-1280 mg; about 1240-1290 mg; about 1250-1300 mg; about 1260-1310 mg; about 1270-1320 mg; about 1280-1330 mg; about 1290-1340 mg; about 1300-1350 mg; about 1310-1360 mg; about 1320-1370 mg; about 1330-1380 mg; about 1340-1390 mg; about 1350-1400 mg; about 1360-1410 mg; about 1370-1420 mg; about 1380-1430 mg; about 1390-1440 mg; about 1400-1450 mg; about 1410-1460 mg; about 1420-1470 mg; about 1430-1480 mg; about 1440-1490 mg; about 1450-1500 mg; about 1460-1510 mg; about 1470-1520 mg; about 1480-1530 mg; about 1490-1540 mg; about 1500-1550 mg; about 1510-1560 mg; about 1520-1570 mg; about 1530-1580 mg; about 1540-1590 mg; about 1550-1600 mg; about 1560-1610 mg; about 1570-1620 mg; about 1580-1630 mg; about 1590-1640 mg; about 1600-1650 mg; about 1610-1660 mg; about 1620-1670 mg; about 1630-1680 mg; about 1640-1690 mg; about 1650-1700 mg; about 1660-1710 mg; about 1670-1720 mg; about 1680-1730 mg; about 1690-1740 mg; about 1700-1750 mg; about 1710-1760 mg; about 1720-1770 mg; about 1730-1780 mg; about 1740-1790 mg; about 1750-1800 mg; about 1760-1810 mg; about 1770-1820 mg; about 1780-1830 mg; about 1790-1840 mg; about 1800-1850 mg; about 1810-1860 mg;

about 1820-1870 mg; about 1830-1880 mg; about 1840-1890 mg; about 1850-1900 mg; about 1860-1910 mg; about 1870-1920 mg; about 1880-1930 mg; about 1890-1940 mg; about 1900-1950 mg; about 1910-1960 mg; about 1920-1970 mg; about 1930-1980 mg; about 1940-1990 mg; about 1950-2000 mg; about 1960-2010 mg; about 1970-2020 mg; about 1980-2030 mg; about 1990-2040 mg; about 2000-2050 mg; about 2010-2060 mg; about 2020-2070 mg; about 2030-2080 mg; about 2040-2090 mg; about 2050-2100 mg; about 2060-2110 mg; about 2070-2120 mg; about 2080-2130 mg; about 2090-2140 mg; about 2100-2150 mg; about 2110-2160 mg; about 2120-2170 mg; about 2130-2180 mg; about 2140-2190 mg; about 2150-2200 mg; about 2160-2210 mg; about 2170-2220 mg; about 2180-2230 mg; about 2190-2240 mg; about 2200-2250 mg; about 2210-2260 mg; about 2220-2270 mg; about 2230-2280 mg; about 2240-2290 mg; about 2250-2300 mg; about 2260-2310 mg; about 2270-2320 mg; about 2280-2330 mg; about 2290-2340 mg; about 2300-2350 mg; about 2310-2360 mg; about 2320-2370 mg; about 2330-2380 mg; about 2340-2390 mg; about 2350-2400 mg; about 40-400 mg; about 50-200 mg; about 200-240 mg; about 240-280 mg; about 280-320 mg; about 320-360 mg; about 360-400 mg; about 400-450 mg; about 450-500 mg; about 500-600 mg; about 250-350 mg; about 100-600 mg; about 40-2000 mg; about 40-800 mg; about 100-900 mg; about 100-800 mg; about 40-1000 mg; about 50-1000 mg; about 100-1000 mg; about 10-80 mg; about 10-40 mg; about 20-30 mg; or any monthly dose in a range bounded by, or between, any of these values. A monthly dose may be given as a single dose, or as two or more individual doses administered during the month. In some embodiments, the monthly dose is administered bi-weekly in 2 or 3 divided doses. In some embodiments, the monthly dose is administered weekly in 4 or 5 divided doses. In some embodiments, the monthly dose is administered daily in 28 to 31 divided doses, or in 56 to 62 divided doses or more. In some embodiments, the monthly dose is administered in 5 to 15 individual doses during the month. The monthly dose may be administered for only 1 month, or may be repeatedly administered for 2, 3, 4, 5, 6, or more months.

In other embodiments, the dosage form or the subject combination may be administered weekly for about one, two, three, four, or more consecutive weeks, every other week or bi-weekly, or once every three weeks. This regimen may be repeated once weekly, twice in a month, three times in a month, once monthly, once every two months, once every three months, or as directed by a medical professional.

In certain embodiments, administering the pharmaceutical composition results in improvement of pharmacokinetics, for example in fasted human subjects, such as increased bioavailability (e.g., reduced T_{max}, increased C_{max}, increased AUC, etc.) of a drug, such as meloxicam or another NSAID, rizatriptan, frovatriptan, or another triptan, in the dosage form as compared to a dosage form containing the drug but not containing a cyclodextrin, an acid inhibitor, or a buffering agent (such as a bicarbonate). In some embodiments, the bioavailability of the drug will increase with repeated dosing. For example, the bioavailability of the drug (such as meloxicam or another NSAID, rizatriptan, frovatriptan, or another triptan) in the dosage form, for example in fasted human subjects, may increase after about 1-10 days of repeated dosing; about 2-6 days of repeated dosing; about 3-5 days of repeated dosing; about 4-6 days of repeated dosing; about 5-8 days of repeated dosing; about 5 days of repeated dosing; about 6 days of repeated dosing; about 7 days of repeated dosing; about 8 days of repeated dosing; about 10 days of repeated dosing; about 15 days of repeated dosing; or time period in any range bounded by, or between, any of these values; as compared to the bioavailability of the drug in a dosage form not containing a cyclodextrin, an acid inhibitor, or a buffering agent (such as a bicarbonate). Administering a drug in any dosage forms described herein to a human subject or patient may improve or achieve the desired oral pharmacokinetic properties of the drug.

Any reference to T_{max}, C_{max}, AUC, or any other pharmacokinetic parameter should be understood to include an average, mean, or median value in human beings, such as human patients or human subjects.

Administering some of the dosage forms or the subject combination to a human being may result in a desired range for an area under the plasma concentration curve (AUC) of meloxicam. The subject combination may be administered in an amount and manner intended to target therapeutically effective plasma concentrations. For example, an area under the plasma concentration curve (AUC) of meloxicam, such as a median, mean, or average AUC of meloxicam in human beings, of about 1-150 µg·hr/mL; may be targeted, such as about 10-30 µg·hr/mL; about 20-40 µg·hr/mL; about 30-50 µg·hr/mL; about 40-60 µg·hr/mL; about 50-70 µg·hr/mL; about 60-80 µg·hr/mL; about 70-90 µg·hr/mL; about 80-100 µg·hr/mL; about 10-100 µg·hr/mL; about 50-150 µg·hr/mL; about 25-125 µg·hr/mL; about 75-150 µg·hr/mL; about 20-50 µg·hr/mL; about 40-70 µg·hr/mL; about 60-90 µg·hr/mL; about 80-

110 μg·hr/mL; about 100-130 μg·hr/mL; about 120-150 μg·hr/mL; about 100-150 μg·hr/mL; about 20-30 μg·hr/mL; about 30-40 μg·hr/mL; about 40-50 μg·hr/mL; about 50-60 μg·hr/mL; about 20-25 μg·hr/mL, about 25-30 μg·hr/mL, about 30-35 μg·hr/mL, about 35-40 μg·hr/mL, about 40-45 μg·hr/mL, about 45-50 μg·hr/mL, or any AUC in a range bounded by, or between, any of these values.

Administering some of the dosage forms to a human being may result in a desired range for an area under the plasma concentration curve (AUC) of frovatriptan. For example the dosage forms with frovatriptan or another triptan may result in an AUC of frovatriptan, such as a median, mean, or average AUC of frovatriptan in human beings, or another triptan of about 1-150 μg·hr/mL; about 10-30 μg·hr/mL; about 20-40 μg·hr/mL; about 30-50 μg·hr/mL; about 40-60 μg·hr/mL; about 50-70 μg·hr/mL; about 60-80 μg·hr/mL; about 70-90 μg·hr/mL; about 80-100 μg·hr/mL; about 10-100 μg·hr/mL; about 50-150 μg·hr/mL; about 25-125 μg·hr/mL; about 75-150 μg·hr/mL; about 20-50 μg·hr/mL; about 40-70 μg·hr/mL; about 60-90 μg·hr/mL; about 80-110 μg·hr/mL; about 100-130 μg·hr/mL; about 120-150 μg·hr/mL; or any AUC in a range bounded by, or between, any of these values.

Unless otherwise indicated, the AUC refers to the AUC calculated to the last measured concentration (AUC_{0-t}), such as, over a period of 6 hours (AUC_{0-6}), over a period of 12 hours (AUC_{0-12}), over a period of 24 hours (AUC_{0-24}), or extrapolated to infinity (AUC_{0-inf}).

In Example 3 below, the AUC_{0-24} of meloxicam in human beings for an oral dosage form containing sodium bicarbonate and sulfobutylether β-cyclodextrin (SBEβCD) was about 27 μg·hr/mL. This dosage form contained 15 mg of meloxicam.

The 15 mg IV and intramuscular doses also provide an AUC_{0-24} of meloxicam in human beings that is about 27 μg·hr/mL. The AUC of meloxicam is believed to be approximately dose proportional. So for this oral dosage form, or for an IV or intramuscular dosage form, a meloxicam dose of, for example, approximately 17 mg to about 30 mg would be expected to result in an AUC_{0-24} of meloxicam of about 30-50 μg·hr/mL.

For some acute pain conditions, such as migraine and other types of headache, the AUC for a short period after oral administration, such as an AUC measured over 6 hours (or AUC_{0-6}), may be of particular interest, e.g. for quick pain relief. For example, some dosage forms may result in an AUC_{0-6} of meloxicam, such as a median, mean, or average AUC_{0-6} of meloxicam in human beings, that is at least about 5 μg·hr/mL (or 5,000 ng·hr/mL); at least

about 6 μg·hr/mL (or 6,000 ng·hr/mL); at least about 7 μg·hr/mL (or 7,000 ng·hr/mL); at least about 8 μg·hr/mL (or 8,000 ng·hr/mL); at least about 9 μg·hr/mL (or 9,000 ng·hr/mL); about 6-10 μg·hr/mL; about 7-11 μg·hr/mL; about 8-12 μg·hr/mL; about 9-13 μg·hr/mL; about 10-14 μg·hr/mL; or any AUC_{0-6} in a range bounded by, or between, any of these values.

In some embodiments, the dosage form or subject combination is administered in a manner that result in a C_{max} of meloxicam, such as a median, mean, or average C_{max} of meloxicam in human beings, of about 10-2500 ng/mL; about 100-2250 ng/mL; about 500-2000 ng/mL; about 1000-2500 ng/mL; about 1000-2000 ng/mL; about 100-900 ng/mL; about 750-1500 ng/mL; about 1250-2000 ng/mL; about 1500-2300 ng/mL; about 800-1200 ng/mL; about 1900-2400 ng/mL; about 50-500 ng/mL; about 400-950 ng/mL; about 900-1500 ng/mL; about 1100-2200 ng/mL; about 1300-1600 ng/mL; about 1200-1500 ng/mL; about 1400-2100 ng/mL; about 1500-1900 ng/mL; about 1600-2100 ng/mL; about 1700-2000 ng/mL; about 1900-2500 ng/mL; about 1500-1700 ng/mL; about 1600-1800 ng/mL; about 1700-1900 ng/mL; about 1800-2000 ng/mL; about 1900-2100 ng/mL; about 2000-2200 ng/mL; about 2100-2300 ng/mL; about 2200-2400 ng/mL; about 2300-2500 ng/mL; about 2500-3000 ng/mL; at least about 1400 ng/mL; at least about 1500 ng/mL; at least about 1600 ng/mL; at least about 1700 ng/mL; at least about 1800 ng/mL; at least about 1900 ng/mL; at least about 2000 ng/mL; at least about 2100 ng/mL; at least about 2200 ng/mL; at least about 2300 ng/mL; at least about 2400 ng/mL; at least about 2500 ng/mL; or any C_{max} in a range bounded by, or between, any of these values.

In some embodiments, the dosage form may result in a C_{max} of frovatriptan, such as a median, mean, or average C_{max} of frovatriptan in human beings, of about 10-2500 ng/mL; about 100-2250 ng/mL; about 500-2000 ng/mL; about 1000-2500 ng/mL; about 1000-2000 ng/mL; about 100-900 ng/mL; about 750-1500 ng/mL; about 1250-2000 ng/mL; about 1500-2300 ng/mL; about 800-1200 ng/mL; about 1900-2400 ng/mL; about 50-500 ng/mL; about 400-950 ng/mL; about 900-1500 ng/mL; about 1100-2200 ng/mL; about 1300-1600 ng/mL; about 1200-1500 ng/mL; about 1400-2100 ng/mL; about 1500-1900 ng/mL; about 1600-2100 ng/mL; about 1700-2000 ng/mL; about 1900-2500 ng/mL; about 150-1700 ng/mL; about 1600-1800 ng/mL; about 1700-1900 ng/mL; about 1800-2000 ng/mL; about 1900-2100 ng/mL; about 2000-2200 ng/mL; about 2100-2300 ng/mL; about 2200-2400 ng/mL; about

2300-2500 ng/mL; about 2500-3000 ng/mL; or any C_{max} in a range bounded by, or between, any of these values.

For example, a method described herein may reduce the T_{max} of meloxicam, such as a median, mean, or average T_{max} of meloxicam in human beings. In some embodiments, the method may include treating a patient to achieve the T_{max} of meloxicam in the patient within about 10 minutes; within about 20 minutes; within about 30 minutes; within about 40 minutes; within about 50 minutes; within about 60 minutes; within about 70 minutes; within about 80 minutes; within about 90 minutes; within about 100 minutes; within about 110 minutes; within about 120 minutes; within about 180 minutes; about 10-30 minutes; about 20-40 minutes, about 30-50 minutes, about 40-60 minutes; about 50-70 minutes; about 60-90 minutes; about 70-100 minutes; about 80-110 minutes; about 90-120 minutes; about 1-10 hr; about 2-9 hr; about 3-7 hr; about 4-6 hr; about 1-5 hr; about 2-7 hr; about 3-8 hr; about 4-9 hr; about 1-4 hr; about 2-5 hr; about 3-6 hr; about 4-7 hr; about 5-8 hr; about 6-9 hr; about 7-10 hr; or any T_{max} in a range bounded by, or between, any of these values; after administration of the dosage forms described above.

In some embodiments, the methods described herein relate to administration of the subject combination in a human being in a manner that results in a relatively short T_{max} of meloxicam, such as a T_{max} within about 10 minutes; within about 20 minutes; within about 30 minutes; within about 40 minutes; within about 50 minutes; within about 60 minutes; within about 70 minutes; within about 80 minutes; within about 90 minutes; within about 100 minutes; within about 110 minutes; within about 120 minutes; within about 180 minutes; about 10-30 minutes; about 20-40 minutes, about 30-50 minutes, about 40-60 minutes; about 50-70 minutes; about 60-90 minutes; about 70-100 minutes; about 80-110 minutes; about 90-120 minutes; or any T_{max} in a range bounded by, or between, any of these values after administration of the subject combination.

In some embodiments, an oral dosage form may have a T_{max} of meloxicam, such as a median, mean, or average T_{max} of meloxicam in human being, that is shorter than would be achieved by administering meloxicam by intramuscular injection. In some embodiments, an oral dosage form may have a T_{max} of meloxicam that is shorter, or may increase meloxicam plasma levels at a faster rate, by a factor of at least about 1.5, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 12, about 15, about 20, or by a factor

of about 1.1-2, about 1.5-3, about 2-4, about 3-5, about 4-6, about 1.5-1000, about 2-100, about 3-100, about 4-100, about 5-100, about 6-100, about 7-100, about 8-100, about 9-100, about 10-100, about 12-100, about 15-100, about 20-100, or by a factor in a range bounded by any of these values, as compared to that observed by intramuscular injection.

In some embodiments, an oral dosage form or a subject combination is administered in a manner such that a time to half-maximal plasma concentration of meloxicam, such as a median, mean, or average time to half-maximal plasma concentration in human beings, that is less than about 5 minutes; less than about 10 minutes; less than about 15 minutes; less than about 20 minutes; less than about 25 minutes; less than about 30 minutes; less than about 35 minutes; less than about 40 minutes; less than about 45 minutes; less than about 50 minutes; less than about 55 minutes; less than about 60 minutes; less than about 90 minutes; about 5-15 minutes; about 10-20 minutes, about 15-25 minutes, about 20-30 minutes; about 25-35 minutes; about 30-45 minutes; about 35-50 minutes; about 40-55 minutes; about 45-60 minutes; about 0.5-5 hours; or any time in a range bounded by any of these values.

For example, a method described herein may reduce the T_{max} of frovatriptan, such as a median, mean, or average T_{max} of frovatriptan in human beings. In some embodiments, the method may include treating a patient to achieve the T_{max} of frovatriptan in the patient within about 10 minutes; about 20 minutes; about 30 minutes; about 40 minutes; about 50 minutes; about 60 minutes; about 70 minutes; about 80 minutes; about 90 minutes; about 100 minutes; about 110 minutes; about 120 minutes; about 180 minutes; about 10-30 minutes; about 20-40 minutes; about 30-50 minutes; about 40-60 minutes; about 50-70 minutes; about 60-80 minutes; about 70-90 minutes; about 0.1-1 hour; about 0.1-0.5 hour; about 0.5-1 hour; about 1-10 hr; about 2-9 hr; about 3-7 hr; about 4-6 hr; about 1-5 hr; about 2-7 hr; about 3-8 hr; about 4-9 hr; about 1-4 hr; about 2-5 hr; about 3-6 hr; about 4-7 hr; about 5-8 hr; about 6-9 hr; about 7-10 hr; after administration or any T_{max} in a range bounded by, or between, any of these values.

For example, a method described herein may reduce the T_{max} of rizatriptan, such as a median, mean, or average T_{max} of rizatriptan in human beings. In some embodiments, the method may include treating a patient to achieve the T_{max} of rizatriptan in the patient within about 60 minutes; within about 70 minutes; within about 80 minutes; within about 90 minutes; within about 100 minutes; within about 110 minutes; within about 2 hours; within

about 3 hours; within about 4 hours; about 10-30 minutes; about 20-40 minutes; about 30-50 minutes; about 40-60 minutes; about 50-70 minutes; about 60-80 minutes; about 70-90 minutes; about 0.1-1 hour; about 0.1-0.5 hours; about 0.5-1 hour; about 1-10 h; about 2-9 h; about 3-7 h; about 4-6 h; about 1-5 h; about 2-7 h; about 3-8 h; about 4-9 h; about 1-4 h; about 2-5 h; about 3-6 h; about 4-7 h; about 5-8 h; about 6-9 h; about 7-10 h; or any T_{max} in a range bounded by, or between, any of these values after administration of the dosage forms or the subject combination described herein.

The oral dosage form of Example 3 below gave a T_{max} of meloxicam of approximately 30 minutes. The T_{max} of intravenous meloxicam is approximately 30 minutes for an infusion or 3 minutes for a bolus. The T_{max} of intramuscular meloxicam is approximately 60-84 minutes.

In some embodiments, a dosage form comprising meloxicam, such as a dosage form comprising the subject combination, may be administered in a manner that result in a plasma concentration of meloxicam, such as a median, mean, or average plasma concentration of meloxicam in human beings, at 12 hours that is about 0.01-0.5 µg/mL; about 0.5-0.7 µg/mL; about 0.6-0.8 µg/mL; about 0.7-0.9 µg/mL; about 0.8-1 µg/mL; about 0.01-1 µg/mL; about 0.9-1.1 µg/mL; about 1-1.2 µg/mL; about 1.1-1.3 µg/mL; about 1.2-1.4 µg/mL; about 1.3-1.5 µg/mL; about 1-1.5 µg/mL; about 1.4-1.6 µg/mL; about 1.5-1.7 µg/mL; about 1.6-1.8 µg/mL; about 1.7-1.9 µg/mL; about 1.8-2 µg/mL; about 1.5-2 µg/mL; about 1.9-2.1 µg/mL; about 2-2.2 µg/mL; about 2.1-2.3 µg/mL; about 2.2-2.4 µg/mL; about 2.3-2.5 µg/mL; about 2-2.5 µg/mL; about 2.4-2.6 µg/mL; about 2.5-2.7 µg/mL; about 2.6-2.8 µg/mL; about 2.7-2.9 µg/mL; about 2.8-3 µg/mL; about 2.5-3 µg/mL; about 2.9-3.1 µg/mL; about 3-3.2 µg/mL; about 3.1-3.3 µg/mL; about 3.2-3.4 µg/mL; about 3.3-3.5 µg/mL; about 3-3.5 µg/mL; about 3.4-3.6 µg/mL; about 3.5-3.7 µg/mL; about 3.6-3.8 µg/mL; about 3.7-3.9 µg/mL; about 3.8-4 µg/mL; about 3.5-4 µg/mL; or any plasma concentration of meloxicam at 12 hours in a range bounded by, or between, any of these values.

In some embodiments, meloxicam is administered at a dose that results in a meloxicam average plasma level (such as a C_{ave}, or average plasma level) of about 0.01-0.5 µg/mL; about 0.5-0.7 µg/mL; about 0.6-0.8 µg/mL; about 0.7-0.9 µg/mL; about 0.8-1 µg/mL; about 0.01-1 µg/mL; about 0.9-1.1 µg/mL; about 1-1.2 µg/mL; about 1.1-1.3 µg/mL; about 1.2-1.4 µg/mL; about 1.3-1.5 µg/mL; about 1.4-1.6 µg/mL; about 1.5-1.7 µg/mL; about 1.6-1.8 µg/mL; about 1.7-1.9 µg/mL; about 1.8-2 µg/mL; about 1-2 µg/mL; about 0.01-3 µg/mL; about

1.9-2.1 μg/mL; about 2-2.2 μg/mL; about 2.1-2.3 μg/mL; about 2.2-2.4 μg/mL; about 2.3-2.5 μg/mL; about 2.4-2.6 μg/mL; about 2.5-2.7 μg/mL; about 2.6-2.8 μg/mL; about 2.7-2.9 μg/mL; about 2.8-3 μg/mL; about 2-3 μg/mL; about 2.9-3.1 μg/mL; about 3-3.2 μg/mL; about 3.1-3.3 μg/mL; about 3.2-3.4 μg/mL; about 3.3-3.5 μg/mL; about 3.4-3.6 μg/mL; about 3.5-3.7 μg/mL; about 3.6-3.8 μg/mL; about 3.7-3.9 μg/mL; about 3.8-4 μg/mL; about 3-4 μg/mL; about 2-4 μg/mL; about 0.01-4 μg/mL; about 0.1-20 μg/mL; about 0.5-15 μg/mL; about 0.5-10 μg/mL; about 5-15 μg/mL; about 10-20 μg/mL; about 7.5-15 μg/mL; about 2-10 μg/mL; about 1-8 μg/mL; about 1-6 μg/mL; about 1-2 μg/mL; about 0.5-3.5 μg/mL; about 0.5-7 μg/mL; about 12-20 μg/mL; about 8-12 μg/mL; about 1-4 μg/mL; about 4-7 μg/mL; about 7-11 μg/mL; about 11-15 μg/mL; about 15-19 μg/mL; about 16-20 μg/mL; or any meloxicam average plasma level in a range bounded by, or between, any of these values.

In some embodiments, a dosage form comprising frovatriptan may result in a plasma concentration of frovatriptan at 12 hours that is about 0.01-0.5 μg/mL; about 0.5-0.7 μg/mL; about 0.6-0.8 μg/mL; about 0.7-0.9 μg/mL; about 0.8-1 μg/mL; about 0.9-1.1 μg/mL; about 1-1.2 μg/mL; about 1.1-1.3 μg/mL; about 1.2-1.4 μg/mL; about 1.3-1.5 μg/mL; about 1.4-1.6 μg/mL; about 1.5-1.7 μg/mL; about 1.6-1.8 μg/mL; about 1.7-1.9 μg/mL; about 1.8-2 μg/mL; about 1.9-2.1 μg/mL; about 2-2.2 μg/mL; about 2.1-2.3 μg/mL; about 2.2-2.4 μg/mL; about 2.3-2.5 μg/mL; about 2.4-2.6 μg/mL; about 2.5-2.7 μg/mL; about 2.6-2.8 μg/mL; about 2.7-2.9 μg/mL; about 2.8-3 μg/mL; about 2.9-3.1 μg/mL; about 3-3.2 μg/mL; about 3.1-3.3 μg/mL; about 3.2-3.4 μg/mL; about 3.3-3.5 μg/mL; about 3.4-3.6 μg/mL; about 3.5-3.7 μg/mL; about 3.6-3.8 μg/mL; about 3.7-3.9 μg/mL; about 3.8-4 μg/mL; or any plasma concentration of frovatriptan at 12 hours in a range bounded by, or between, any of these values.

In some embodiments, frovatriptan is administered at a dose that results in an average frovatriptan plasma level (such as a C_{ave}, or average plasma level) of about 0.01-0.5 μg/mL; about 0.5-0.7 μg/mL; about 0.6-0.8 μg/mL; about 0.7-0.9 μg/mL; about 0.8-1 μg/mL; about 0.9-1.1 μg/mL; about 1-1.2 μg/mL; about 1.1-1.3 μg/mL; about 1.2-1.4 μg/mL; about 1.3-1.5 μg/mL; about 1.4-1.6 μg/mL; about 1.5-1.7 μg/mL; about 1.6-1.8 μg/mL; about 1.7-1.9 μg/mL; about 1.8-2 μg/mL; about 1.9-2.1 μg/mL; about 2-2.2 μg/mL; about 2.1-2.3 μg/mL; about 2.2-2.4 μg/mL; about 2.3-2.5 μg/mL; about 2.4-2.6 μg/mL; about 2.5-2.7 μg/mL; about 2.6-2.8 μg/mL; about 2.7-2.9 μg/mL; about 2.8-3 μg/mL; about 2.9-3.1 μg/mL; about 3-3.2 μg/mL; about 3.1-3.3 μg/mL; about 3.2-3.4 μg/mL; about 3.3-3.5 μg/mL; about 3.4-3.6 μg/mL; about

3.5-3.7 μg/mL; about 3.6-3.8 μg/mL; about 3.7-3.9 μg/mL; about 3.8-4 μg/mL; about 0.1-20 μg/mL; about 0.5-15 μg/mL; about 0.5-10 μg/mL; about 5-15 μg/mL; about 10-20 μg/mL; about 7.5-15 μg/mL; about 2-10 μg/mL; about 1-8 μg/mL; about 1-6 μg/mL; about 1-2 μg/mL; about 0.5-3.5 μg/mL; about 0.5-7 μg/mL; about 12-20 μg/mL; about 8-12 μg/mL; about 1-4 μg/mL; about 4-7 μg/mL; about 7-11 μg/mL; about 11-15 μg/mL; about 15-19 μg/mL; about 16-20 μg/mL; or any amount of frovatriptan average plasma level in a range bounded by, or between, any of these values.

Use of a bicarbonate may help to increase the solubility of an NSAID, such as meloxicam, and/or the solubility of a triptan, such as rizatriptan, in a human stomach.

In some embodiments, after the dosage form is orally administered, the amount of the NSAID, such as meloxicam, dissolved in the stomach fluid of the human being is greater than the amount of the NSAID, such as meloxicam, that would be dissolved in the stomach fluid of the human being as a result of orally administering a reference dosage form containing: 1) the same amount of meloxicam, and 2) no bicarbonate,

In some embodiments, 30 minutes after the dosage form is orally administered, the amount of the NSAID, such as meloxicam, dissolved in the stomach fluid of the human being is greater than the amount of the NSAID, such as meloxicam, that would be dissolved in the stomach fluid of the human being as a result of orally administering a reference dosage form containing: 1) the same amount of meloxicam, and 2) no bicarbonate

In some embodiments, 60 minutes after the dosage form is orally administered, the amount of NSAID, such as meloxicam, dissolved in the stomach fluid of the human being is greater than the amount of the NSAID, such as meloxicam, that would be dissolved in the stomach fluid of the human being as a result of orally administering a reference dosage form containing: 1) the same amount of meloxicam, and 2) no bicarbonate

In some embodiments, about 15 minutes after the dosage form is orally administered, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% of the NSAID, such as meloxicam, in the dosage form is dissolved in the stomach fluid of the human being

In some embodiments, about 30 minutes after the dosage form is orally administered, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about

70%, at least about 80%, or at least about 90% of the NSAID, such as meloxicam, in the dosage form is dissolved the stomach fluid of the human being.

In some embodiments, about 60 minutes after the dosage form is orally administered, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% of the NSAID, such as meloxicam, in the dosage form is dissolved in the stomach fluid of the human being.

In some embodiments, 15 minutes after the dosage form is orally administered, the amount of the triptan, such as rizatriptan, dissolved in the stomach fluid of the human being is greater than the amount of the triptan, such as rizatriptan that would be dissolved in the stomach fluid of the human being as a result of orally administering a reference dosage form containing: 1) the same amount of triptan, such as rizatriptan, and 2) no bicarbonate.

In some embodiments, 30 minutes after the dosage form is orally administered, the amount of the triptan, such as rizatriptan, dissolved in the stomach fluid of the human being is greater than the amount of the triptan, such as rizatriptan that would be dissolved in the stomach fluid of the human being as a result of orally administering a reference dosage form containing: 1) the same amount of triptan, such as rizatriptan, and 2) no bicarbonate.

In some embodiments, 60 minutes after the dosage form is orally administered, the amount of the triptan, such as rizatriptan, dissolved in the stomach fluid of the human being is greater than the amount of the triptan, such as rizatriptan that would be dissolved in the stomach fluid of the human being as a result of orally administering a reference dosage form containing: 1) the same amount of triptan, such as rizatriptan, and 2) no bicarbonate.

In some embodiments, about 15 minutes after the dosage form is orally administered, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% of the triptan, such as rizatriptan, in the dosage form is dissolved in the stomach fluid of the human being.

In some embodiments, about 30 minutes after the dosage form is orally administered, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% of the triptan, such as rizatriptan, in the dosage form is dissolved in the stomach fluid of the human being.

In some embodiments, about 60 minutes after the dosage form is orally administered, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about

70%, at least about 80%, or at least about 90% of the triptan, such as rizatriptan, in the dosage form is dissolved in the stomach fluid of the human being.

Some dosage forms may have improved dissolution of the NSAID, such as meloxicam, as compared to a reference dosage form containing: 1) the same amount of NSAID, such as meloxicam, and 2) no bicarbonate.

In some embodiments, improved dissolution of the NSAID, such as meloxicam, or the triptan, such as rizatriptan, may be determined by a dissolution test. For these embodiments, the dissolution test is: adding the dosage form or the reference dosage form to 500 mL of a 0.01 N HCl aqueous solution, stirring at 75 revolutions per minute (RPM) with a USP paddle apparatus II at 37 °C, and determining the amount of the NSAID, such as meloxicam, or the triptan, such as rizatriptan dissolved in the 0.01 N HCl aqueous solution after a designated time.

With respect to the dissolution test, the term of "designated time" herein represents a period of time selected to do the dissolution test. For example, for an NSAID such as meloxicam or a triptan such as rizatriptan, the designated time can be about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 40 minutes, about 45 minutes, about 50 minutes, about 55 minutes, about 60 minutes, about 65 minutes, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, and etc.

In some embodiments, improved dissolution of the NSAID, such as meloxicam, may be observed at a designated time such as 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, or 120 minutes.

In some embodiments, at a designated time of about 15 minutes, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% of the NSAID, such as meloxicam, is dissolved in the 0.01 N HCl aqueous solution according to the dissolution test identified above.

In some embodiments, at a designated time of about 30 minutes, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% of the NSAID, such as meloxicam, is dissolved in the 0.01 N HCl aqueous solution according to the dissolution test identified above.

In some embodiments, at a designated time of about 60 minutes, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% of the NSAID, such as meloxicam, is dissolved in the 0.01 N HCl aqueous solution according to the dissolution test identified above.

In some embodiments, at a designated time of about 120 minutes, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% of the NSAID, such as meloxicam, is dissolved in the 0.01 N HCl aqueous solution according to the dissolution test identified above.

Some dosage forms may have improved dissolution of the triptan, such as rizatriptan, as compared to a reference dosage form containing: 1) the same amount of triptan, such as rizatriptan, and 2) no bicarbonate.

In some embodiments, 30 minutes after the dosage form is orally administered, the amount of the triptan, such as rizatriptan, dissolved in the stomach fluid of the human being is greater than the amount of the triptan, such as rizatriptan that would be dissolved in the stomach fluid of the human being as a result of orally administering a reference dosage form containing: 1) the same amount of triptan, such as rizatriptan, and 2) no bicarbonate.

In some embodiments, improved dissolution of the triptan, such as rizatriptan, may be observed at a designated time such as 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, or 120 minutes.

In some embodiments, at a designated time of about 15 minutes, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% of the triptan, such as rizatriptan, is dissolved in the 0.01 N HCl aqueous solution according to the dissolution test identified above.

In some embodiments, at a designated time of about 30 minutes, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% of the triptan, such as rizatriptan, is dissolved in the 0.01 N HCl aqueous solution according to the dissolution test identified above.

In some embodiments, at a designated time of about 60 minutes, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% of the triptan, such as rizatriptan, is dissolved in the 0.01 N HCl aqueous solution according to the dissolution test identified above.

In some embodiments, at a designated time of about 120 minutes, at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% of the triptan, such as rizatriptan, is dissolved in the 0.01 N HCl aqueous solution according to the dissolution test identified above.

In some embodiments, a dosage form containing meloxicam, rizatriptan, or both, may be formulated for oral administration, for example, with an inert diluent or with an edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, compressed into tablets, or incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, coated tablets, troches, capsules, elixirs, dispersions, suspensions, solutions, syrups, wafers, patches, and the like.

Tablets, troches, pills, capsules and the like may also contain one or more of the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient, such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coating, for instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. It may be desirable for material in a dosage form or pharmaceutical composition to be pharmaceutically pure and substantially non-toxic in the amounts employed.

In addition to meloxicam, a cyclodextrin, a triptan, and a bicarbonate, some dosage forms may contain excipients such as microcrystalline cellulose (e.g. about 1-20%), starch (e.g. about 1-10%), fumed silica (e.g. 0.1-10%), polyvinylpyrrolidone (e.g. about 1-10%), and/or magnesium stearate (e.g. about 0.1-10%).

Some single dosage forms contain both meloxicam and rizatriptan may further contain, a cyclodextrin which may be complexed with meloxicam, and a bicarbonate. In addition, some dosage forms may contain excipients such as microcrystalline cellulose (e.g.

about 1-20%), starch (e.g. about 1-10%), fumed silica (e.g. 0.1-10%), polyvinylpyrrolidone (e.g. about 1-10%), and/or magnesium stearate (e.g. about 0.1-10%).

Some compositions or dosage forms may be a liquid, or may comprise a solid phase dispersed in a liquid.

The dosage form may further comprise an additional therapeutically active agents, such as an acid inhibitor or an analgesic.

In some embodiments, the dosage form may further comprise an acid inhibitor present in an amount effective to raise the gastric pH of a patient to at least 2, to at least 2.5, to at least 3, to at least 3.5, to at least 4, and more to at least 5, when one or more unit dosage forms are administered. The term "acid inhibitor" refers to agents that inhibit gastric acid secretion and increase gastric pH. Specific H_2 blockers, also referred to as H_2 antagonists or histamine H_2 blockers or antagonists, which may be used include but are not limited to cimetidine, ranitidine, ebrotidine, pabutidine, lafutidine, loxtidine, famotidine, or combinations thereof.

Other agents that may be effectively used as acid inhibitors are the proton pump inhibitors such as omeprazole, esomeprazole, pantoprazole, lansoprazole, dexlansoprazole, rabeprazole, pariprazole, leminoprazole and tenatoprazole. In some embodiments the daily dose of the acid inhibitor, such as esomeprazole, is about 1-200 mg, about 1-100 mg, about 50-100 mg, about 1-50 mg, about 40-80 mg, about 5-50 mg, about 20-40 mg, about 10-50 mg, about 10-20 mg, about 20-40 mg, about 15-50 mg, about 30-60 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg or any other amount in a range bounded by, or between, any of these values.

Examples of particular proton pump inhibitors include esomeprazole, present in unit dosage forms in an amount of between 5 mg and 50 mg; omeprazole, present in unit dosage forms in an amount of between 5 mg and 50 mg; lansoprazole, present in unit dosage forms in an amount of between 5 mg and 150 mg (and preferably at between 5 mg and 30 mg); and pantoprazole, present in unit dosage forms in an amount of between 10 mg and 200 mg. In some embodiments, the proton pump inhibitor (such as esomeprazole) is present in the dosage form in an amount of about 10-30 mg, about 20-40 mg, about 30-50 mg, about 40-60 mg, about 50-70 mg, about 60-80 mg, about 70-90 mg, or about 80-100 mg. Recently, a newer class of acid inhibitor has been developed which competes with potassium at the acid pump.

The compounds in this class have been referred to as “reversible proton pump inhibitors” or “acid pump antagonists” and may also be used. Examples include AZD-0865, AR-H047108, CS-526, pumaprazole, revaprazan and soraprazan (see WO9605177 and WO9605199). Other compounds in this group are H-335/25 (AstraZeneca, Dialog file 128, accession number 020806); Sch-28080 (Schering Plough, Dialog file 128, accession number 009663); Sch-32651 (Schering Plough, Dialog file 128, accession number 006883) and SK&F-96067 (CAS Registry no. 115607-61-9).

Additional therapeutically active agents may include an analgesic such as a second non-steroidal anti-inflammatory drug, an opioid, a steroid, a triptan, etc. In some embodiments, the dosage form or treatment also further comprises administering a second non-steroidal anti-inflammatory drug in an amount effective to reduce or eliminate pain or inflammation. It will be understood that, for the purposes of the present disclosure, reference to an acid inhibitor, NSAID, or analgesic agent will include all of the common forms of these compounds and, in particular, their pharmaceutically acceptable salts. The amounts of NSAIDs which are therapeutically effective may be lower in the current embodiments than otherwise found in practice due to potential positive kinetic interaction and NSAID absorption in the presence of an acid inhibitor, and or in the presence of a buffering agent.

In other embodiments, the dosage form or treatment may further comprise administering an opioid in an amount effective to reduce or eliminate pain or inflammation. The opioid may include, but is not limited to, (dextro)propoxyphene, A-methylfentanyl, alfentanil, allylprodine, bezitramide, buprenorphine, butorphanol, carfentanyl, desmethylprodine, dextromoramide, dezocine, diacetylmorphine, dihydrocodeinone, dihydroetorphine, dimorphone, diphenoxylate, dipipanone, etorphine, fentanyl, ketobemidone, lefetamine, levacetylmethadol, levomethorphan, levorphanol, loperamide, meperidine, meptazinol, methadone, methylmorphine, morphine, nalbuphine, nalmefene, naloxone, naltrexone, nicomorphine, ohmefentanyl, oripavine, oxycodone, oxymorphone, PEPAP, paramorphine, pentazocine, phenazocine, piritramide, prodine, remifentanil, sufentanil, tapentadol, tilidine, tramadol, or combinations thereof.

The term “unit dosage form” as used herein refers to a single entity for drug administration. For example, a single tablet or capsule combining both a triptan and an NSAID would be a unit dosage form. A “unit dosage form” (or “unit dose form”) may also be referred

to as a “fixed dosage form” (or “fixed dose form”) or “fixed dosage combination” (or “fixed dose combination”) and are otherwise interchangeable. In one embodiment, the unit dosage form is a multilayer tablet.

In another embodiment, the unit dosage form is suitable for oral administration to a patient. In yet another embodiment, the unit dosage form is a tablet. In still another embodiment, the unit dosage form is a multilayer tablet comprising a single core and one or more layers outside of the core. In some embodiments, the pharmaceutical composition may have an effective amount of a triptan (such as rizatriptan or frovatriptan), a cyclodextrin, and a bicarbonate to increase bioavailability of rizatriptan or frovatriptan. In other embodiments, the pharmaceutical composition may have an effective amount of the triptan, sulfobutylether-β-cyclodextrin (SBEβCD), and sodium bicarbonate to increase bioavailability of the triptan or reduce the T_{max} of the triptan.

Some dosage forms may comprise a first layer comprising meloxicam, an SBEβCD, and a bicarbonate; and a second layer comprising a triptan and a bicarbonate.

The first layer may contain, for example, any amount of meloxicam in one of the ranges recited above. For example, all of the meloxicam in the dosage form may be present in the first layer. The second layer may contain all of triptan, such that any amount in the ranges recited above with respect to the triptan may apply to the second layer.

In some embodiments, the first layer contains about 10-200 mg, about 50-150 mg, about 50-100 mg, about 70-120 mg, about 90-140 mg, or about 100 mg of the bicarbonate, such as sodium bicarbonate, or any amount of the bicarbonate in a range bounded by any of these values.

In some embodiments, the second layer contains about 100-500 mg, about 200-500 mg, about 300-500 mg, about 350-450 mg, about 380-420 mg, or about 400 mg of the bicarbonate, such as sodium bicarbonate, or any amount of the bicarbonate in a range bounded by any of these values.

Some oral dosage forms may have enteric coatings or film coatings. In some embodiments, a dosage form may comprise a tablet or a capsule having an enteric coating. In some embodiments, a dosage form may comprise a tablet or a capsule having a film coating.

An embodiment of the present disclosure is directed to a pharmaceutical composition in unit dosage form suitable for administration to a patient, comprising:

(a) dexketoprofen, which may or may not be surrounded by an enteric coating;

(b) sodium or potassium bicarbonate and/or sodium or potassium carbonate; and

(c) frovatriptan, which may or may not be formulated with a cyclodextrin, and which may or may not be surrounded by an enteric coating

In certain embodiments, the pharmaceutical composition results in faster release or dissolution of a drug (e.g. meloxicam or another NSAID, rizatriptan, frovatriptan, or another triptan) from the dosage form as compared to a dosage form containing the same drug but not containing the acid inhibitor, or not containing the buffering agent.

The following embodiments are contemplated:

Embodiment 1. An inclusion complex of meloxicam in a cyclodextrin.

Embodiment 2. A dosage form comprising: 1) the inclusion complex of embodiment 1, or 2) meloxicam and a carbonate or a bicarbonate.

Embodiment 3. The dosage form of embodiment 2 comprising the inclusion complex, wherein the cyclodextrin comprises substituted β-cyclodextrin.

Embodiment 4. The dosage form of embodiment 3, wherein the substituted β-cyclodextrin is a sulfobutyl ether β-cyclodextrin (SBEβCD) or hydroxypropyl β-cyclodextrin (HPBCD).

Embodiment 5. The dosage form of embodiment 4, wherein the cyclodextrin is the SBEβCD.

Embodiment 6. The dosage form of embodiment 5, wherein the SBEβCD has about 6 to about 7 sulfobutyl ether groups for each molecule of β-cyclodextrin.

Embodiment 7. The dosage form of embodiment 6, wherein the meloxicam and the SBEβCD have a molar ratio of about 0.8 to about 1.2.

Embodiment 8. The dosage form of embodiment 6, wherein the meloxicam and the SBEβCD have a molar ratio of about 1.

Embodiment 9. The dosage form of embodiment 2, 3, 4, 5, 6, 7, or 8, comprising a bicarbonate.

Embodiment 10. The dosage form of embodiment 9, wherein the bicarbonate comprises sodium bicarbonate.

Embodiment 11. The dosage form of embodiment 2, 3, 4, 5, 6, 7, 8, 9, or 10, which is an oral dosage form.

Embodiment 12. The dosage form of embodiment 2, 3, 4, 5, 6, 9, 10, or 11, wherein about 50 mg to about 200 mg of SBEβCD is present in the dosage form.

Embodiment 13. The dosage form of embodiment 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, wherein the carbonate or bicarbonate is present in an amount in a range of about 400 mg to about 600 mg.

Embodiment 14. The dosage form of embodiment 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, wherein the T_{max} of meloxicam is decreased as compared to a dosage form not having a carbonate, a bicarbonate, or a cyclodextrin.

Embodiment 15. The method of embodiment 14, wherein the T_{max} of meloxicam is achieved in the patient at a time in a range of about 10 minutes to about 180 minutes after administration.

Embodiment 16. The dosage form of embodiment 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15, having an oral bioavailability of meloxicam that is higher than a dosage form not having a carbonate, a bicarbonate, or a cyclodextrin.

Embodiment 17. The dosage form of embodiment 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16, further comprising an acid inhibitor.

Embodiment 18. The dosage form of embodiment 17, wherein the acid inhibitor is a proton pump inhibitor.

Embodiment 19. The dosage form of embodiment 18, wherein the proton pump inhibitor is esomeprazole.

Embodiment 20. The dosage form of embodiment 19, wherein about 30 mg to about 50 mg of esomeprazole is present in the dosage form.

Embodiment 21. A method of administering meloxicam orally, comprising orally administering a dosage form of embodiment 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 to a patient in need of treatment.

Embodiment 22. The method of embodiment 21, wherein the dosage form is administered to treat pain.

Embodiment 23. The method of embodiment 21, wherein the dosage form is administered to treat inflammatory pain.

Embodiment 24. The method of embodiment 21, wherein the dosage form is administered to treat osteoarthritis, rheumatoid arthritis, or juvenile rheumatoid arthritis.

Embodiment 25. A method of administering meloxicam intravenously, comprising intravenously administering a dosage form of embodiment 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, or 15, to a patient in need of treatment.

Embodiment 26. An inclusion complex of frovatriptan in a cyclodextrin.

Embodiment 2-1. A dosage form comprising: 1) the inclusion complex of frovatriptan in a cyclodextrin, or 2) frovatriptan and a carbonate or a bicarbonate.

Embodiment 2-2. The dosage form of Emodiment 2-1, comprising the inclusion complex, wherein the cyclodextrin comprises a sulfobutyl ether β-cyclodextrin (SBEβCD) or a hydroxypropyl β-cyclodextrin (HPβCD).

Embodiment 2-3. The dosage form of Embodiment 2-2, wherein the cyclodextrin is the SBEβCD and has about 6 to about 7 sulfobutyl ether groups for each molecule of β-cyclodextrin.

Embodiment 2-4. The dosage form of Embodiment 2-3, further comprising a bicarbonate.

Embodiment 2-5. The dosage form of Embodiment 2-4, wherein the bicarbonate comprises sodium bicarbonate.

Embodiment 2-6. The dosage form of Embodiment 2-3, wherein the frovatriptan and the SBEβCD have a molar ratio of about 0.8 to about 1.2.

Embodiment 2-7. The dosage form of Embodiment 2-6, further comprising a bicarbonate.

Embodiment 2-8. The dosage form of Embodiment 2-7, wherein the bicarbonate comprises sodium bicarbonate.

Embodiment 2-9. The dosage form of Embodiment 2-1, which is an oral dosage form.

Embodiment 2-10. The dosage form of Embodiment 2-2, comprising the inclusion complex, wherein about 50 mg to about 200 mg of the SBEβCD is present in a unit dosage form.

Embodiment 2-11. The dosage form of Embodiment 2-1, comprising frovatriptan and the carbonate or the bicarbonate.

Embodiment 2-12. The dosage form of Embodiment 2-1, wherein the T_{max} of frovatriptan is decreased as compared to a dosage form without a carbonate, a bicarbonate, or a cyclodextrin.

Embodiment 2-13. The method of Embodiment 2-1, wherein the T_{max} of frovatriptan is achieved in the patient at a time in a range of about 10 minutes to about 180 minutes after administration.

Embodiment 2-14. The dosage form of Embodiment 2-1, having an oral bioavailability of frovatriptan that is higher than a dosage form without a carbonate, a bicarbonate, or a cyclodextrin.

Embodiment 2-15. The dosage form of Embodiment 2-11, wherein the carbonate or the bicarbonate is present in a unit dosage form at an amount in a range of about 400 mg to about 600 mg.

Embodiment 2-16. The dosage form of Embodiment 2-15, wherein the carbonate or the bicarbonate is sodium bicarbonate.

Embodiment 2-17. The dosage form of Embodiment 2-11, further comprising an NSAID.

Embodiment 2-18. The dosage form of Embodiment 2-17, wherein the NSAID is a dexketoprofen or meloxicam.

Embodiment 2-19. The dosage form of Embodiment 2-18, wherein the NSAID is dexketoprofen.

Embodiment 2-20. The dosage form of Embodiment 2-19, wherein about 10 mg to about 50 mg of dexketoprofen is present in a unit dosage form.

Embodiment 2-21. A method of administering frovatriptan orally, comprising orally administering the dosage form of Embodiment 2-1 to a patient in need of treatment.

Embodiment 2-22. The method of Embodiment 2-21, wherein the dosage form comprises the inclusion complex, wherein the cyclodextrin is SBEβCD, and further comprises a bicarbonate.

Embodiment 2-23. The method of Embodiment 2-22, wherein the bicarbonate is sodium bicarbonate.

Embodiment 2-24. The method of Embodiment 2-23, wherein a unit dosage form contains about 300 mg to about 600 mg of sodium bicarbonate.

Embodiment 2-25. The method of Embodiment 2-22, wherein the dosage form further comprises a NSAID.

Embodiment 2-26. The method of Embodiment 2-25, wherein the NSAID is dexketoprofen, meloxicam, naproxen, ibuprofen, or celecoxib.

Embodiment 2-27. The method of Embodiment 2-21, wherein the dosage form is administered to treat pain.

Embodiment 2-28. The method of Embodiment 2-21, wherein the dosage form is administered to treat inflammatory pain.

Embodiment 2-29. The method of Embodiment 2-21, wherein the dosage form is administered to treat osteoarthritis, rheumatoid arthritis, or juvenile rheumatoid arthritis.

Embodiment P-1. A dosage form comprising:

meloxicam;

a sulfobutyl ether β-cyclodextrin (SBEβCD);

a bicarbonate; and

a triptan

wherein the dosage form is an oral dosage form having a shorter T_{max} of meloxicam than a reference dosage form that: 1) contains the same amount of meloxicam, 2) does not contain an SBEβCD, and 3) does not contain a bicarbonate.

Embodiment P-2. The dosage form of Embodiment P-1, comprising an inclusion complex of 1) the meloxicam or the triptan and 2) the SBEβCD.

Embodiment P-3. The dosage form of Embodiment P-1 or P-2, containing about 10 mg to about 20 mg of meloxicam.

Embodiment P-4. The dosage form of Embodiment P-3, containing about 15 mg of meloxicam.

Embodiment P-5. The dosage form of Embodiment P-1, P-2, P-3, or P-4, wherein the SBEβCD has about 6 to about 7 sulfobutyl ether groups for each molecule of β-cyclodextrin.

Embodiment P-6. The dosage form of Embodiment P-1, P-2, P-3, P-4, or P-5, containing about 50 mg to about 200 mg of the SBEβCD.

Embodiment P-7. The dosage form of Embodiment P-1, P-2, P-3, P-4, P-5, or P-6, wherein the triptan is rizatriptan.

Embodiment P-8. The dosage form of Embodiment P-7, containing about 5 mg to about 20 mg of rizatriptan.

Embodiment P-9. The dosage form of Embodiment P-8, containing about 10 mg of rizatriptan.

Embodiment P-10. The dosage form of Embodiment P-6, containing about 100 mg of SBEβCD.

Embodiment P-11. The dosage form of Embodiment P-1, P-2, P-3, P-4, P-5, P-6, P-7, P-8, P-9, or P-10, wherein the bicarbonate comprises sodium bicarbonate.

Embodiment P-12. The dosage form of Embodiment P-10, containing about 400 mg to about 600 mg of the bicarbonate.

Embodiment P-13. The dosage form of Embodiment P-12, containing about 500 mg of sodium bicarbonate.

Embodiment P-14. The dosage form of Embodiment P-1, P-2, P-3, P-4, P-5, P-6, P-7, P-8, P-9, P-10, P-11, or P-12, wherein the oral dosage form has been shown to have a mean T_{max} of meloxicam that is less than about 3 hours.

Embodiment P-15. The dosage form of Embodiment P-14, wherein the oral dosage form has been shown to have a mean T_{max} of meloxicam that is less than about 2 hours.

Embodiment P-16. The dosage form of Embodiment P-14, wherein the oral dosage form has been shown to have a mean T_{max} of meloxicam that is less than about 1 hour.

Embodiment P-17. The dosage form of Embodiment P-1, P-2, P-3, P-4, P-5, P-6, P-7, P-8, P-9, P-10, P-11, P-12, P-13, P-14, P-15, or P-16, wherein the oral dosage form has increased bioavailability of meloxicam as compared to the reference dosage form when administered to a mammal.

Embodiment P-18. The dosage form of Embodiment P-1, P-2, P-3, P-4, P-5, P-6, P-7, P-8, P-9, P-10, P-11, P-12, P-13, P-14, P-15, P-16, or P-17, wherein the oral dosage form has improved pharmacokinetics of meloxicam as compared to the reference dosage form when administered to a mammal.

Embodiment P-19. The dosage form of Embodiment P-1, P-2, P-3, P-4, P-5, P-6, P-7, P-8, P-9, P-10, P-11, P-12, P-13, P-14, P-15, P-16, P-17, or P-18, wherein the oral dosage form has increased bioavailability of the triptan as compared to the reference dosage form when administered to a mammal.

Embodiment P-20. The dosage form of Embodiment P-1, P-2, P-3, P-4, P-5, P-6, P-7, P-8, P-9, P-10, P-11, P-12, P-13, P-14, P-15, P-16, P-17, P-18, or P-19, wherein the oral dosage form has improved pharmacokinetics of the triptan as compared to the reference dosage form when administered to a mammal.

Embodiment P-21. A method of improving the pharmacokinetics of a triptan or an NSAID, comprising orally administering a dosage form of Embodiment P-1, P-2, P-3, P-4, P-5, P-6, P-7, P-8, P-9, P-10, P-11, P-12, P-13, P-14, P-15, P-16, P-17, P-18, P-19, or P-20 to a mammal or human being in need of treatment with the triptan or the NSAID.

Embodiment P-22. The method of treating pain, comprising orally administering a dosage form of Embodiment P-1, P-2, P-3, P-4, P-5, P-6, P-7, P-8, P-9, P-10, P-11, P-12, P-13, P-14, P-15, P-16, P-17, P-18, P-19, or P-20 to a mammal or human being in need thereof.

Embodiment P-23. The method of Embodiment P-22, wherein the pain is migraine.

Embodiment P-24. The method of Embodiment P-22, wherein the pain is inflammatory pain.

Example 1

The effect of varying amounts of potassium carbonate (K_2CO_3) and sodium bicarbonate ($NaHCO_3$) on the pH of acidic media was tested. The acidic media was chosen to simulate gastric conditions. K_2CO_3 or $NaHCO_3$ was added to 50 mL of a 0.01 N HCl solution (pH 2). The pH of the solution was measured after addition of the K_2CO_3 or NaHCO3. Deionized water (240 mL) was then added to the mixture and pH was measured again. The results are shown in Tables 1-4.

Table 1. Results with K_2CO_3 (0.01 N HCl)

K_2CO_3 (mg)	pH
25	2.84
35	6.29
45	8.05
50	8.29
100	9.43
200	10.14
300	10.39
400	10.55
450	10.58

Table 2. Results with K_2CO_3 (0.01 N HCl + Water)

K_2CO_3 (mg)	pH
200	10.27
300	10.46
400	10.57
450	10.63

Table 3. Results with $NaHCO_3$ (0.01 N HCl)

$NaHCO_3$ (mg)	pH
200	5.28
300	5.90
400	6.44
450	6.86
500	8.23
750	8.30
1000	8.36

Table 4. Results with $NaHCO_3$ (0.01 N HCl + Water)

$NaHCO_3$ (mg)	pH
200	5.41
300	5.89
400	6.11
450	6.46
500	8.33
750	8.54
1000	8.60

Example 2

Tablets containing meloxicam and combinations of cyclodextrin, K_2CO3, or $NaHCO_3$ were manufactured and tested for dissolution. Tablets containing meloxicam alone (MOBIC®) were purchased and also tested for dissolution. The tested tablets are listed in Table 5. Meloxicam in the form of meloxicam/cyclodextrin inclusion complexes was used in the tablets containing meloxicam and cyclodextrin. The inclusion complexes were formed by mixing meloxicam and cyclodextrin in an aqueous pH-adjusted solution. The pH of the solution was adjusted using buffering agents. The resulting soluble meloxicam/cyclodextrin inclusion

complexes were then spray dried. This spray-dried dispersion was used in the manufacture of the tablets containing cyclodextrin.

Table 5. Tablets

Tablet A	15 mg meloxicam + 25 mg K_2CO3
Tablet B	15 mg meloxicam + 50 mg K_2CO3
Tablet C	15 mg meloxicam + 100 mg K_2CO3
Tablet D	15 mg meloxicam + 150 mg K_2CO3
Tablet E	15 mg meloxicam + 500 mg NaHCO3
Tablet F	15 mg meloxicam + 100 mg SBEβCD
Tablet G	15 mg meloxicam + 100 mg SBEβCD + 25 mg K_2CO3
Tablet H	15 mg meloxicam + 100 mg SBEβCD + 50 mg K_2CO3
Tablet I	15 mg meloxicam + 100 mg SBEβCD + 100 mg K_2CO3
Tablet J	15 mg meloxicam + 100 mg SBEβCD + 150 mg K_2CO3
Tablet K	15 mg meloxicam + 100 mg SBEβCD + 500 mg NaHCO3
Tablet L	15 mg meloxicam (MOBIC®)

Dissolution testing in acidic medium (chosen to simulate gastric conditions) was performed by placing the tablets in a 0.01 N HCl solution, at an agitation rate of 75 RPM, and vessel temperature of approximately 37 °C. The results are presented in Tables 6 and in Figures 1-10. Results at various time points (0, 15, 30, 45, 60, 90, and 120 minutes) are presented as percent (%) of meloxicam dissolved.

Table 6. Dissolution Results

	0 mins	15 mins	30 mins	45 mins	60 mins	90 mins	120 mins
Tablet A	0%	23%	17%	15%	13%	12%	11%
Tablet B	0%	27%	20%	17%	16%	17%	15%
Tablet C	0%	31%	26%	25%	24%	23%	21%
Tablet D	0%	30%	26%	25%	24%	23%	22%
Tablet E	0%	50%	66%	77%	84%	92%	95%
Tablet F	0%	26%	17%	14%	12%	11%	10%
Tablet G	0%	48%	39%	26%	20%	16%	14%
Tablet H	0%	44%	30%	22%	17%	16%	13%
Tablet I	0%	32%	33%	27%	21%	16%	15%
Tablet J	0%	26%	27%	19%	15%	12%	11%
Tablet K	0%	85%	86%	86%	86%	86%	86%
Tablet L	0%	2%	2%	2%	2%	2%	2%

Dissolution of meloxicam was greater with the tablets containing various combinations of meloxicam and cyclodextrin, K_2CO_3, or $NaHCO_3$, as compared to tablets containing meloxicam alone. For example, after 120 minutes, dissolution of meloxicam tablets containing $NaHCO_3$ was 95% as compared to 2% for tablets containing meloxicam alone.

Dissolution of meloxicam increases with increasing amounts of K_2CO_3 in the absence of cyclodextrin. However, in the presence of cyclodextrin, increasing amounts of K_2CO_3 did not appear to increase meloxicam dissolution. At the highest dose of potassium carbonate tested, meloxicam dissolution in the presence of cyclodextrin was reduced by approximately 50% as compared to meloxicam dissolution in the absence of cyclodextrin at 120 minutes.

Dissolution of meloxicam with $NaHCO_3$ was significantly greater than that observed with the highest dose of K_2CO_3 at 15 minutes (50% versus 30%), and at 120 minutes (92% versus 23%). Meloxicam dissolution in the presence of cyclodextrin was also significantly greater with $NaHCO_3$ as compared to the highest dose of K_2CO_3 at 15 minutes (85% versus 26%), and at 120 minutes (86% versus 12%). $NaHCO_3$ in the presence of cyclodextrin increased meloxicam dissolution at 15 minutes as compared to potassium bicarbonate which resulted in a reduction in dissolution.

Example 3

A bilayer tablet containing 1) an inclusion complex of SBEβCD with meloxicam prepared as described in Example 2 below, and 2) sodium bicarbonate was prepared (SBEβCD-Meloxicam/Bicarbonate). The first layer contained an inclusion complex of 15 mg meloxicam and 100 mg SBEβCD, and 100 mg of sodium bicarbonate. The second layer contained 40 mg of esomeprazole and 400 mg of sodium bicarbonate.

A total of 20 human subjects were randomly assigned in a 1:1 ratio to treatment with the SBEβCD-Meloxicam/Bicarbonate tablets described above or Mobic® tablets (15 mg meloxicam), once daily for 6 days under fasting conditions.

On the first day of dosing, plasma samples were collected for concentration analysis of meloxicam at several time points. Concentrations of meloxicam were determined using LC-MS/MS. Pharmacokinetic parameters were calculated. The results are depicted in FIG. 11.

The median T_{max} for meloxicam, the trial's primary endpoint, was 9 times faster for the SBEβCD-Meloxicam/Bicarbonate tablets as compared to Mobic® (0.5 hour versus 4.5 hours respectively, $p<0.0001$).

The SBEβCD-Meloxicam/Bicarbonate tablets also demonstrated higher mean maximum plasma concentration (C_{max}) (p=0.0018), faster time to therapeutic plasma concentration (p<0.0001), and faster time to half-maximal plasma concentration (p<0.0001) as compared to Mobic®.

Meloxicam in the form of meloxicam/cyclodextrin inclusion complexes was used in the tablets containing meloxicam and cyclodextrin. The inclusion complexes were formed by mixing meloxicam and cyclodextrin in an aqueous pH-adjusted solution. The pH of the solution was adjusted using buffering agents. The resulting soluble meloxicam/cyclodextrin inclusion complexes were then spray dried. This spray-dried dispersion was used in the manufacture of the tablets containing cyclodextrin.

Example 4

A monolayer tablet containing 1) the inclusion complex of SBEβCD with meloxicam; 2) rizatriptan; and 3) sodium bicarbonate was prepared (SBEβCD-Meloxicam/rizatriptan/Bicarbonate). The monolayer tablet contained 20 mg of meloxicam, 10 mg of rizatriptan, and 500 mg of sodium bicarbonate. The inclusion complex was the same as the inclusion complex of Example 3.

Dissolution testing of the tablets in acidic medium (chosen to simulate gastric conditions) was performed by placing the tablets in a 0.01 N HCl solution, at an agitation rate of 75 RPM, and vessel temperature of approximately 37 °C. The results are presented in Tables 7. Results at various time points (0, 15, 30, 45, 60, 90, and 120 minutes) are presented as percent (%) of meloxicam, and percent (%) of rizatriptan dissolved.

Table 7. Dissolution Results

Time-point (minutes	0 min	15 min	30 min	45 min	60 min	90 min	120 min
Rizatriptan	0%	89%	102%	103%	103%	103%	103%
Meloxicam	0%	79%	92%	93%	93%	93%	94%

As shown in Table 7, the dissolution results of the tablets in Example 4 are very similar to the dissolution result of Example 2. Therefore, we expect the pharmacokinetic properties,

including bioavailability, T_{max}, etc., of the tablets in Example 4 to be similar to those described in Example 3 and FIG. 11.

Example 5

The monolayer tablet of Example 4 was administered to six human subjects. On the first day of dosing, plasma samples were collected for concentration analysis of rizatriptan at several time points. Concentrations of rizatriptan and meloxicam were determined using LC-MS/MS. Pharmacokinetic parameters were calculated. The results for meloxicam were comparable to those reported for the bilayer dosage form of Example 3. The median T_{max} of rizatriptan was 0.75 hours and the mean C_{max} of rizatriptan was 20.710 ng/mL. By comparison, the reported T_{max} of the commercial rizatriptan dosage form, Maxalt®, is 1.0-1.5 hours.

Various embodiments may be defined in the following Statements:

Statement 1: a method of treating migraine, comprising administering a dosage form comprising meloxicam, at least 400 mg of a bicarbonate, and a rizatriptan to a human being suffering from migraine; wherein the T_{max} of rizatriptan in the dosage form is shorter than that in a reference dosage form comprising a) same amount of rizatriptan; 2) no meloxicam; and c) no bicarbonate.

Statement 2: The method of Statement 1, wherein about 8 mg to about 13 mg of the rizatriptan is present in the dosage form based upon the weight of the rizatriptan in the free base form.

Statement 3: The method of Statement 2, wherein the rizatriptan is present in a salt form in an amount that is a molar equivalent of about 10 mg of the rizatriptan in the free base form.

Statement 4: The method of Statement 3, wherein the rizatriptan is present as rizatriptan benzoate.

Statement 5: The method of Statement 1, wherein the dosage form contains about 15 mg to about 25 mg of meloxicam.

Statement 6: The method of Statement 5, wherein the dosage form contains about 20 mg of meloxicam.

Statement 7: The method of Statement 1, wherein the dosage form further comprises a cyclodextrin.

Statement 8: The method of Statement 7, wherein the dosage form contains about 100 mg to about 175 mg of the cyclodextrin.

Statement 9: The method of Statement 7, wherein the dosage form contains about 100 mg to about 140 mg of the cyclodextrin.

Statement 10: The method of Statement 1, wherein the bicarbonate comprises sodium bicarbonate.

Statement 11: The method of Statement 1, wherein the dosage form contains about 400 mg to about 600 mg of the bicarbonate.

Statement 12: The method of Statement 1, wherein the dosage form contains about 500 mg of sodium bicarbonate.

Statement 13: The method of Statement 1, wherein the dosage form contains about 50% to about 90% of the bicarbonate by weight.

Statement 14: The method of Statement 1, wherein the dosage form has the property that 15 minutes after the dosage form is added to a simulated gastric fluid, the amount of the meloxicam dissolved in the simulated gastric fluid of the human being is greater than the amount of the meloxicam that is dissolved in the simulated gastric fluid of the human being as a result of adding a reference dosage form to the simulated gastric fluid, wherein the reference dosage form contains: 1) the same amount of meloxicam, and 2) no bicarbonate.

Statement 15: The method of Statement 1, wherein the dosage form has the property that 15 minutes after the dosage form is added to a simulated gastric fluid, the amount of the rizatriptan dissolved in the simulated gastric fluid is greater than the amount of the meloxicam.

Statement 16: The method of Statement 1, wherein the human being experiences pain relief sooner than would be experienced as a result of orally administering a reference dosage form containing: 1) the same amount of meloxicam, and 2) no bicarbonate.

Statement 17: The method of Statement 1, wherein the dosage form has the property that 30 minutes after the dosage form is added to a simulated gastric fluid, at least about 50% of the rizatriptan in the dosage form is dissolved in the simulated gastric fluid.

Statement 18: The method of Statement 1, wherein the dosage form has the property that 30 minutes after the dosage form is added to a simulated gastric fluid, at least about 50% of the meloxicam in the dosage form is dissolved in the simulated gastric fluid.

Statement 19: The method of Statement 1, wherein the T_{max} of meloxicam in the dosage form is less than about 1 hours.

Statement 20: The method of Statement 1, wherein the T_{max} of rizatriptan in the dosage form is less than about 2 hours.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood in all instances as indicating both the exact values as shown and as being modified by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

The terms "a," "an," "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of any claim. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

Certain embodiments are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, the claims include all modifications and equivalents of the subject matter recited in the claims as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is contemplated unless otherwise indicated herein or otherwise clearly contradicted by context.

In closing, it is to be understood that the embodiments disclosed herein are illustrative of the principles of the claims. Other modifications that may be employed are within the scope of the claims. Thus, by way of example, but not of limitation, alternative embodiments may be utilized in accordance with the teachings herein. Accordingly, the claims are not limited to embodiments precisely as shown and described.

CLAIMS

Claim 1:

Use of a composition comprising a meloxicam, or a pharmaceutically acceptable salt thereof, at least 400 mg of a bicarbonate, a, a cyclodextrin derivative, or a pharmaceutically acceptable salt thereof, and a rizatriptan, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating migraine in a human being suffering from migraine, wherein the composition is in an oral dosage form; wherein the human being has a history of inadequate response to prior migraine treatments; and wherein the T_{max} of rizatriptan in the human being after administering the oral dosage form is shorter than that would result from administering an oral reference dosage form comprising a) the same amount of rizatriptan; b) no meloxicam; and c) no bicarbonate.

Claim 2:

The use according to claim 1, wherein about 8 mg to about 13 mg of the rizatriptan, or a molar equivalent amount of the pharmaceutically acceptable salt of rizatriptan, is present in the oral dosage form.

Claim 3:

The use according to claim 2, wherein the pharmaceutically acceptable salt of rizatriptan is present in the dosage form in an amount that is a molar equivalent of about 10 mg of rizatriptan.

Claim 4:

The use according to claim 3, wherein the pharmaceutically acceptable salt of rizatriptan is rizatriptan benzoate.

Claim 5:

The use according to claim 1, wherein the oral dosage form contains about 15 mg to about 25 mg of the meloxicam.

Claim 6:

The use according to claim 1, wherein the oral dosage form contains about 20 mg of the meloxicam.

Claim 7:

The use according to claim 1, wherein the oral dosage form contains about 100 mg to about 175 mg of a sulfobutyl ether β-cyclodextrin (SBEβCD).

Claim 8:

The use according to claim 1, wherein the oral dosage form contains about 100 mg to about 140 mg of a SBEβCD.

Claim 9:

The use according to claim 1, wherein the bicarbonate comprises sodium bicarbonate.

Claim 10:

The use according to claim 9, wherein the oral dosage form contains about 400 mg to about 600 mg of sodium bicarbonate.

Claim 11:

The use according to claim 9, wherein the oral dosage form contains about 500 mg of sodium bicarbonate.

Claim 12:

The use according to claim 1, wherein the oral dosage form contains about 50% to about 90% of the bicarbonate by weight.

Claim 13:

The use according to claim 1, wherein the oral dosage form has the property that 15 minutes after the dosage form is added to a simulated gastric fluid, the amount of the meloxicam dissolved in the simulated gastric fluid of the human being is greater than the

amount of the meloxicam that is dissolved in the simulated gastric fluid of the human being as a result of adding an oral reference dosage form to the simulated gastric fluid, wherein the oral reference dosage form contains: 1) the same amount of meloxicam, 2) no rizatriptan, and 3) no bicarbonate.

Claim 14:

The use according to claim 1, wherein the oral dosage form has the property that 15 minutes after the oral dosage form is added to a simulated gastric fluid, the percentage of the rizatriptan dissolved in the simulated gastric fluid is greater than the percentage of the meloxicam dissolved in the simulated gastric fluid.

Claim 15:

The use according to claim 1, wherein after administering the oral dosage form, the human being experiences pain relief sooner than would be experienced as a result of orally administering an oral reference dosage form containing: 1) the same amount of meloxicam, 2) no rizatriptan, and 3) no bicarbonate.

Claim 16:

The use according to claim 1, wherein the oral dosage form has the property that 30 minutes after the oral dosage form is added to a simulated gastric fluid, at least 50% of the rizatriptan in the oral dosage form is dissolved in the simulated gastric fluid.

Claim 17:

The use according to claim 1, wherein the oral dosage form has the property that 30 minutes after the oral dosage form is added to a simulated gastric fluid, at least 50% of the meloxicam in the oral dosage form is dissolved in the simulated gastric fluid.

Claim 18:

The use according to claim 1, wherein the T_{max} of meloxicam in the human being after administering the oral dosage form is less than 1 hour.

Claim 19:

The use according to claim 1, wherein the T_{max} of rizatriptan in the human being after administering the oral dosage form is less than 2 hours.