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(54) **COMPOUNDED SOLUTIONS OF DICLOFENAC AND LIDOCAINE AND METHODS**

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(57) **ABSTRACT**

A compounded topical solution may include approximately 85% to approximately 95% (v/v) diclofenac sodium topical solution, 1.5% (w/w), and approximately 5% to approximately 15% (v/v) lidocaine hydrochloride topical solution, 4% USP.

7 Claims, 4 Drawing Sheets

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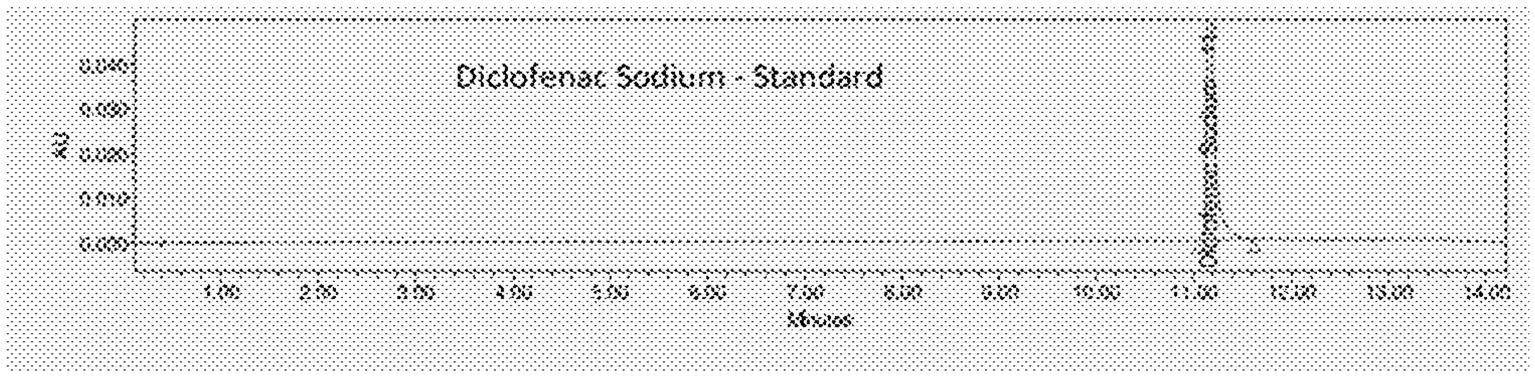
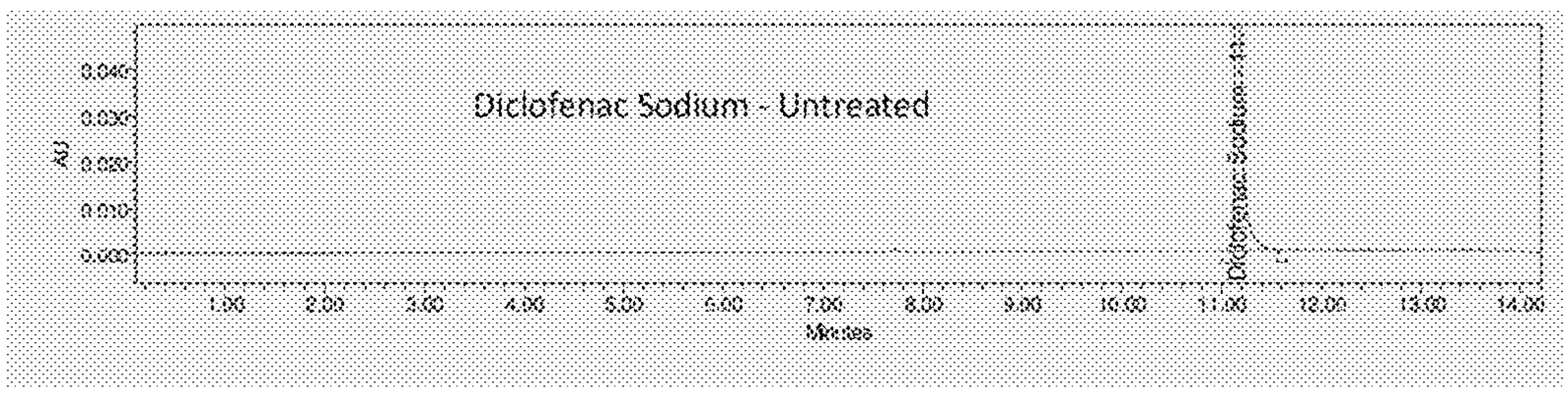


FIG. 1A



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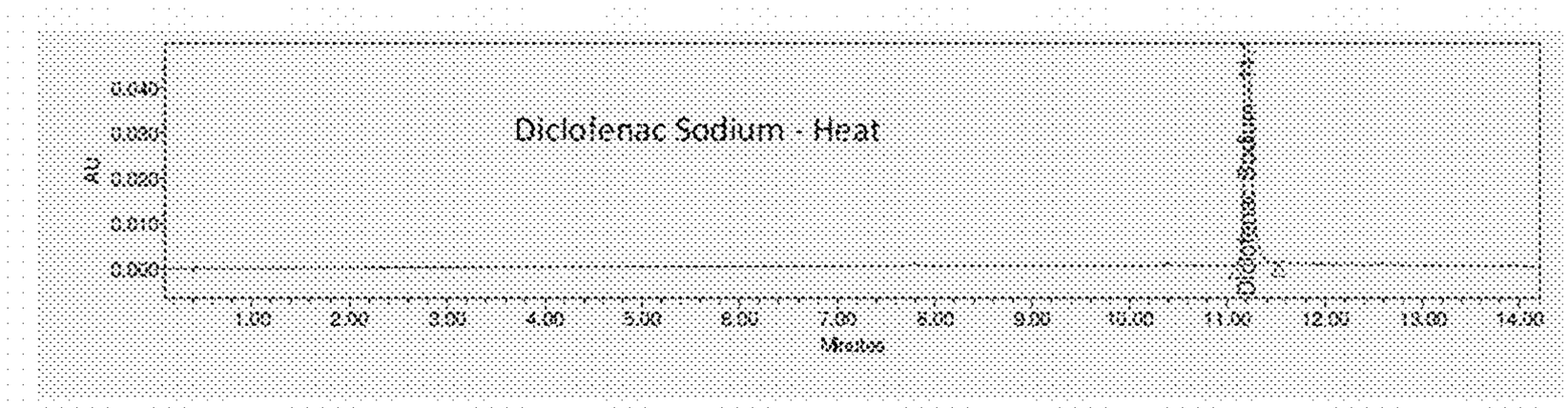
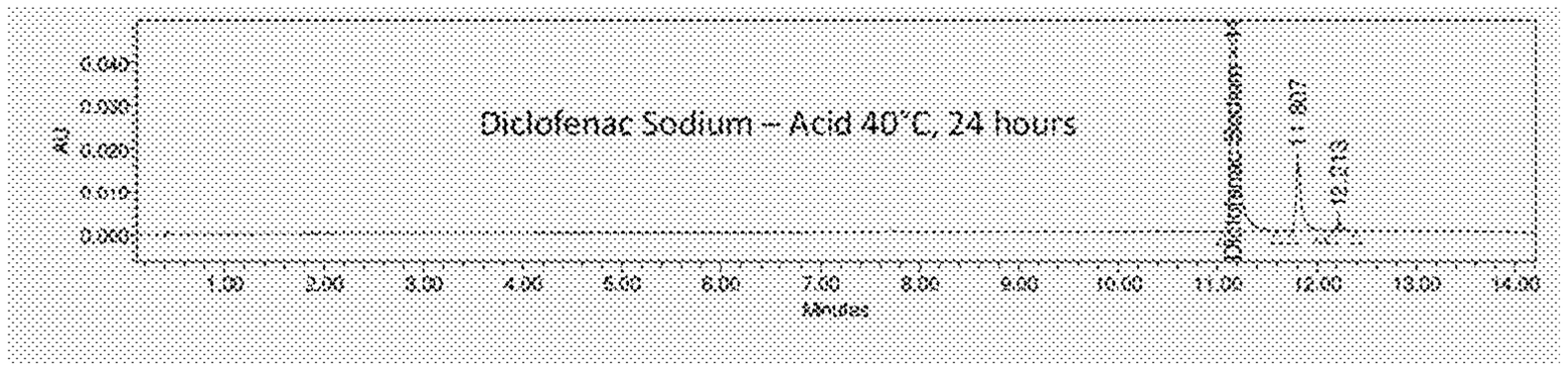


FIG. 1C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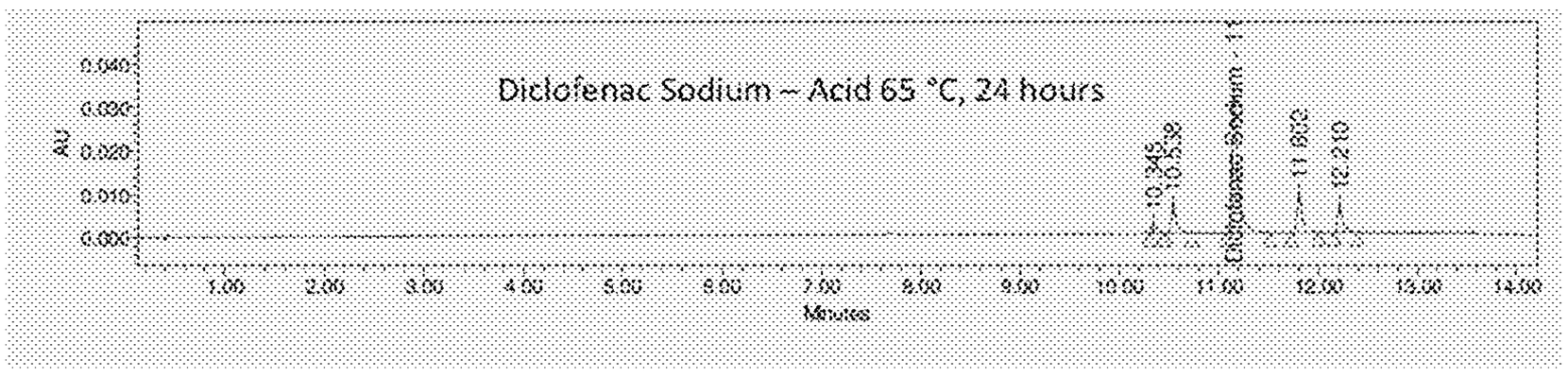
AU
Minutes
Diclofenac Sodium - Assay
11.807
12.213

FIG. 1D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Minutes
Diclofenac Sodium - Assay
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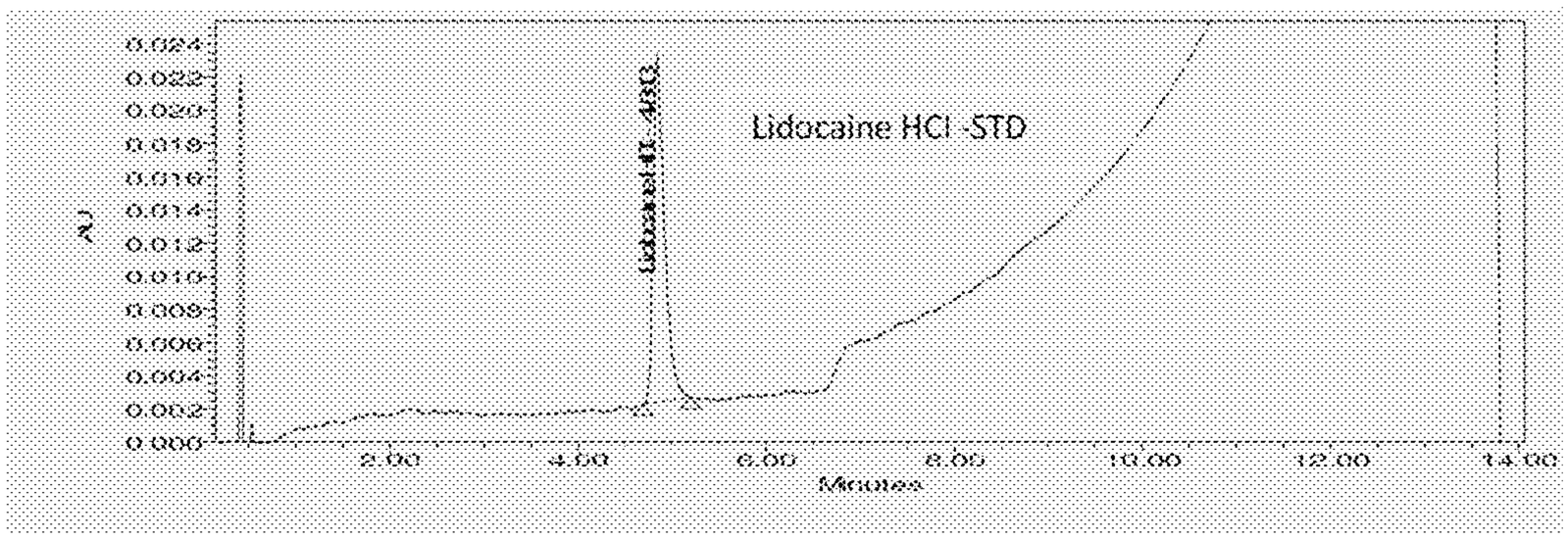
11.602
12.213

FIG. 1E


Lidocaine HCl -STD
AU
Minutes
0.024
0.022
0.020
0.018
0.016
0.014
0.012
0.010
0.008
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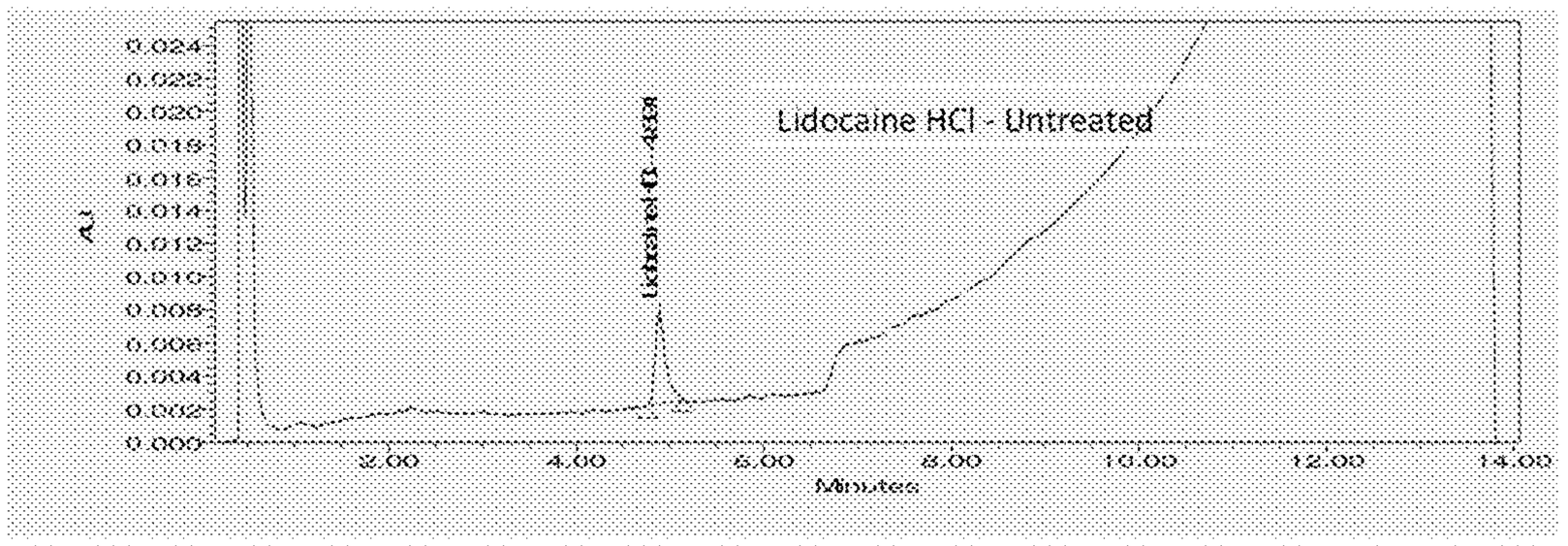
8.00
10.00
12.00
14.00

FIG. 2A


Lidocaine HCl - Untreated
AU
Minutes
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0.022
0.020
0.018
0.016
0.014
0.012
0.010
0.008
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4.00
6.00
8.00
10.00
12.00
14.00

FIG. 2B

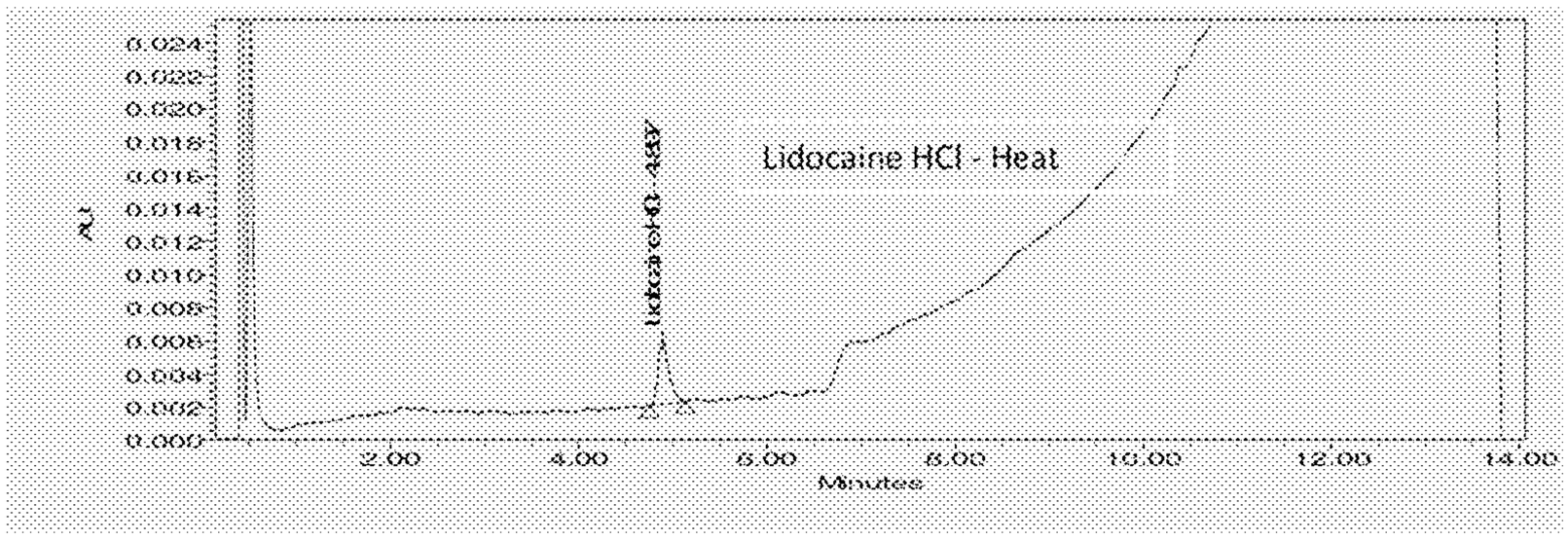
Lidocaine HCl - Heat
AU
0.024
0.022
0.020
0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes

FIG. 2C

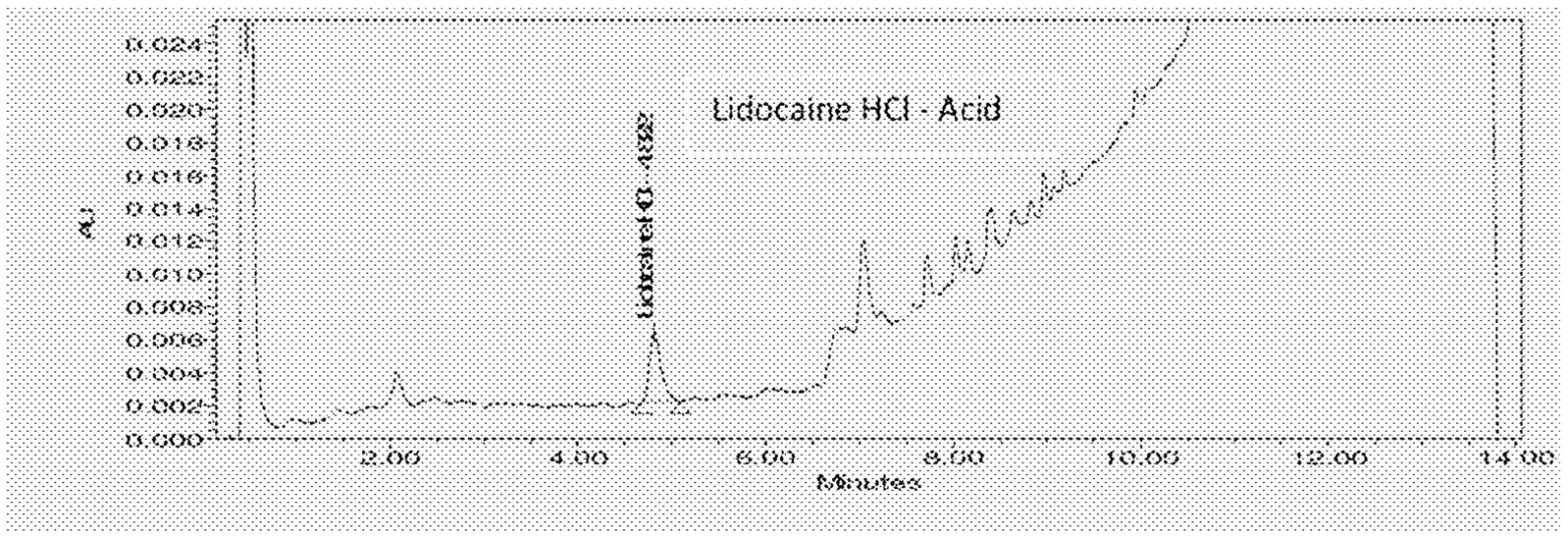
Lidocaine HCl - Acid
AU
0.024
0.022
0.020
0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes

FIG. 2D

COMPOUNDED SOLUTIONS OF DICLOFENAC AND LIDOCAINE AND METHODS

FIELD OF THE INVENTION

The present application relates to compounded medications. In particular, the present application relates to compounded topical solutions and methods of making and using such compounded topical solutions.

BACKGROUND

Diclofenac sodium topical solution is a non-steroidal anti-inflammatory drug (NSAID) indicated for the treatment of signs and symptoms of osteoarthritis of the knee. For the relief of such signs and symptoms, the recommended dose of diclofenac sodium topical solution, 1.5% (w/w), is 40 drops on each painful knee, 4 times a day.

Lidocaine hydrochloride topical solution is a local anesthetic agent indicated for the production of topical anesthesia of accessible mucous membranes of the oral and nasal cavities and proximal portions of the digestive tract. When used as a spray, or when applied by cotton applicators or packs, as when instilled into a cavity, the suggested dosage of Lidocaine Hydrochloride Topical Solution, 4%, is 1 to 5 mL (40 to 200 mg lidocaine HCl), i.e., 0.6 to 3 mg/kg or 0.3 to 1.5 mg/lb body weight. When spraying, the solution is to be transferred from its original container to an atomizer.

SUMMARY

In one aspect, a compounded topical solution may include approximately 85% to approximately 95% (v/v) diclofenac sodium topical solution, 1.5% (w/w). The compounded topical solution may further include approximately 5% to approximately 15% (v/v) lidocaine hydrochloride topical solution, 4% USP.

In one example, the diclofenac sodium topical solution, 1.5% (w/w), is present in an amount between approximately 90% and approximately 93% (v/v) of the compounded topical solution and the lidocaine hydrochloride topical solution, 4% USP, is present in an amount between approximately 7% and approximately 10% (v/v) of the compounded topical solution.

In another example, the diclofenac sodium topical solution, 1.5% (w/w), is present in an amount approximately 90% (v/v) or more of the compounded topical solution and the lidocaine hydrochloride topical solution, 4% USP, is present in an amount approximately 7% (v/v) or more of the compounded topical solution.

In yet another example, the diclofenac sodium topical solution, 1.5% (w/w), is present in an amount approximately 91.7% (v/v) of the compounded topical solution and the lidocaine hydrochloride topical solution, 4% USP, is present in an amount approximately 8.32% (v/v) of the compounded topical solution.

In still yet another example, the compounded topical solution includes approximately 1.47% (w/v) diclofenac sodium and approximately 0.333% (w/v) lidocaine hydrochloride.

In another aspect, a method of making a compounded topical solution includes combining diclofenac sodium topical solution, 1.5% (w/w), and lidocaine hydrochloride topical solution, 4% USP. The method may further include mixing the combined diclofenac sodium topical solution, 1.5% (w/w), and lidocaine hydrochloride topical solution, 4% USP. The diclofenac sodium topical solution, 1.5% (w/w), may be combined in an amount between approximately 85% and approximately 95% (v/v) of the compounded topical solution and the lidocaine hydrochloride topical solution, 4% USP, may be combined in an amount between approximately 5% and approximately 15% (v/v) of the compounded topical solution.

In one example, the diclofenac sodium topical solution, 1.5% (w/w), is combined in an amount between approximately 90% and approximately 93% (v/v) of compounded topical solution and the lidocaine hydrochloride topical solution, 4% USP, is combined in an amount between approximately 7% and approximately 10% (v/v) of the compounded topical solution.

In another example, the diclofenac sodium topical solution, 1.5% (w/w), is combined in an amount approximately 90% (v/v) or more of the compounded topical solution and the lidocaine hydrochloride topical solution, 4% USP, is combined in an amount approximately 7% (v/v) or more of the compounded topical solution.

In yet another example, the diclofenac sodium topical solution, 1.5% (w/w), is combined in an amount approximately 91.7% (v/v) of the compounded topical solution and the lidocaine hydrochloride topical solution, 4% USP, is combined in an amount approximately 8.32% (v/v) of the compounded topical solution.

In still yet another example, the compounded topical solution includes approximately 1.47% (w/v) diclofenac sodium and approximately 0.333% (w/v) lidocaine hydrochloride.

The above-described and other features and advantages of the present disclosure will be appreciated and understood by those skilled in the art from the following detailed description, drawings, and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1**A-**1**E are exemplary chromatograms of standard, untreated, heat treated, acid treated (45° C.), and acid treated (65° C.) Diclofenac Sodium samples, respectively, generated in a degradation study according to various embodiments described herein; and

FIGS. **2**A-**2**D are exemplary chromatograms of standard, untreated, heat treated, and acid treated Lidocaine HCl samples, respectively, generated in a degradation study according to various embodiments described herein.

DETAILED DESCRIPTION

The present embodiments may relate to topically delivered or deliverable solutions of compounded medications for treatment of various ailments, such as inflammation or pain.

The compounded medications may typically include topical solutions that may be topically administered at a body surface. In one embodiment, a compounded topical solution for the effective administration of multiple medications simultaneously for treatment of one or more ailments may be provided. The compounded topical solution may include at least two active agents including a local anesthetic and a Non-Steroidal Anti-Inflammatory Drug (NSAID). The compounded topical solution may include all or some of the active agents in aqueous solution. In some embodiments, the topical solution comprises a compounded topical solution comprising at least two commercially available topical solutions that are compounded together. For example, a compounded topical solution may include a commercially available NSAID topical solution and a commercially available

local anesthetic topical solution. In some embodiments, the compounded topical solution may further include multiple local anesthetics or NSAIDs obtained from commercially available solutions, commercially available creams, bulk powders, ground tablets, or combination thereof of such local anesthetics or NSAIDS.

In one embodiment, the compounded topical solution includes additional active agents selected from one or more anticonvulsants, nerve depressants, muscle relaxants, NMDA (N-Methyl-D-aspartate) receptor antagonists, opiate or opioid agonists, antidepressants, and/or other active agents.

The compounded topical solutions may be topically applied via any suitable mode of administration of the solution for the ailment treated, including, e.g., spray, drops, atomizer, wash, swab, sponge, absorbent dressing, instillation or irrigation. Ailments treated may include conditions such as inflammation, rheumatoid arthritis, osteoarthritis, lateral epicondylitis (tennis elbow), medial epicondylitis (golfer's elbow), chondromalacia patellae—CMP (runner's knee), tendonitis/carpel tunnel, soft tissue pain, fibromyalgia, diabetic neuropathy, peripheral neuropathy, neck pain, back pain, localized pain, plantar fasciitis, achilles tendonitis, tarsal tunnel—post-op massage, or heel pain. The compounded topical solution may exhibit excellent storage characteristics, and avoid separation and/or degradation of the active ingredients in the aqueous environment for substantial lengths of time.

As introduced above, the compounded topical solution may include a NSAID topical solution compounded with a local anesthetic topical solution. The NSAID component of the topical compounded solution may act to block the synthesis of prostaglandins by inhibiting cyclooxygenase-2 and cyclooxygenase-1, for example. In various embodiments, the NSAID may be selected from one or more salicylic acid derivatives (e.g., aspirin, diflunisal, salsalate, trilisate), one or more propionic acids (e.g., flurbiprofen, ibuprofen, ketoprofen, naproxen, oxaprozin), one or more acetic acids (e.g., diclofenac, etodolac, indomethacin, ketorolac, nabumetone, sulindac, tolmetin), one or more fenamates (e.g., meclofenamate), one or more oxicams (meloxicam, piroxicam), or one or more COX-2 inhibitors (e.g., celecoxib, rofecoxib, valdecoxib), or combinations thereof. For example, in one embodiment, the NSAID topical solution comprises a benzeneacetic acid derivative such as diclofenac or pharmaceutically acceptable salt thereof provided in an aqueous solution. In various embodiments, the local anesthetic may be selected from lidocaine, prilocaine, benzocaine, or combination thereof. The local anesthetic may be provided in an aqueous solution and compounded with the NSAID topical solution. One or both of the NSAID topical solution or the local anesthetic topical solution may be commercially available topical solutions. For example, the NSAID topical solution may include a commercially available diclofenac, or pharmaceutically acceptable salt thereof, topical solution and the local anesthetic topical solution may include a commercially available lidocaine, or pharmaceutically acceptable salt thereof, topical solution. In embodiments including one or more additional NSAIDs, local anesthetics, or both, the additional actives may be provided in commercially available solutions, creams, or pure powders or crushed commercial tablets and then combined with the compounded topical solution or a component thereof.

In various embodiments, the compounded topical solution may include a diclofenac topical solution comprising diclofenac in an aqueous solution. The diclofenac topical solution may be a commercially available diclofenac topical solution, such as diclofenac sodium solution for topical administration. The diclofenac sodium solution may contain, for example, 1.5% (w/w), diclofenac sodium wherein each 1 mL of solution contains approximately 16.05 mg of diclofenac sodium. In one embodiment, the diclofenac solution comprises a diclofenac sodium solution, 1.5% (w/w), such as that which is manufactured under the trade name PENNSAID® by Nuvo Manufacturing, Varennes, Quebec, Canada or Diclofenac Sodium Topical Solution, 1.5% (w/w), manufactured by Apotex Inc. Toronto, Ontario, Canada M9L 1T9 for Apotex Corp. Weston, Fla. 33326 for treating the pain of osteoarthritis of the knee. The diclofenac solution may also contain various inactive ingredients such as dimethyl sulfoxide USP (DMSO, 45.5% w/w), ethanol, glycerin, propylene glycol and purified water. In one embodiment, the diclofenac solution comprises a diclofenac sodium solution marketed under the trade name PENNSAID® and manufactured by Nuvo Manufacturing, Varennes, Quebec, Canada, in a 2% (w/w) diclofenac solution for treating the pain of osteoarthritis of the knee. Each gram of solution may contain approximately 20 mg of diclofenac sodium and various inactive ingredients such as dimethyl sulfoxide USP (DMSO, 45.5% w/w), ethanol, purified water, propylene glycol, and hydroxypropyl cellulose. In other embodiments, other concentrations of diclofenac solution, such as diclofenac sodium solutions, may be used.

In various embodiments, the compounded topical solution may include a lidocaine topical solution comprising lidocaine in an aqueous solution. The lidocaine topical solution may be a commercially available lidocaine topical solution, such as lidocaine hydrochloride solution for topical administration. The lidocaine hydrochloride solution may contain, for example, 4% lidocaine (w/v) wherein each mL includes 40 mg lidocaine HCl. For example, in one embodiment, the lidocaine topical solution may be Lidocaine Hydrochloride Topical Solution USP, 4% manufactured by IGI Labs, Inc., Buena, N.J., in 50 mL screw cap glass bottles. The lidocaine hydrochloride topical solution may contain various inactive ingredients such as methylparaben, purified water, and sodium hydroxide to adjust pH to 6.0-7.0.

The compounded topical solution formulated by combining a lidocaine hydrochloride topical solution and diclofenac sodium topical solution may include relatively low concentrations of the active ingredients compared to conventional topical formulations including one or more of the active ingredients. Due to the formulation and combination described herein, the present compounded topical solution may provide similar effectiveness while having an increased safety profile. The increased safety profile may be especially beneficial to patients with gastric bleeds, on blood thinners, etc. The compounded composition may also provide local anesthetics benefits while promoting deeper penetration into the skin and leveraging DMSO in the diclofenac sodium solution embedded into the compounded topical cream, e.g., 45.5% (w/w) of the diclofenac sodium solution compounded with the lidocaine hydrochloride solution.

In various embodiments, the compounded topical solution comprises diclofenac or diclofenac sodium at a concentration between 0.1% and 1.9% and lidocaine or lidocaine hydrochloride at a concentration of between 0.1% and 3.9%. In one example, the compounded topical solution includes approximately 0.5% or more, approximately 1.0% or more, or approximately 1.45% or more diclofenac or diclofenac sodium and approximately 0.2% or more, approximately 0.28% or more, or approximately 0.3% or more lidocaine or

lidocaine hydrochloride. As used herein, the term approximately means+/−10% of the stated value it modifies. In some embodiments, the compounded topical solution includes between approximately 1.0% and approximately 1.9%, approximately 1.1% and approximately 1.8%, approximately 1.2% and approximately 1.7%, approximately 1.2% and approximately 1.6%, approximately 1.2% and approximately 1.5%, approximately 1.2% and approximately 1.4%, approximately 1.2% and approximately 1.3%, approximately 1.3% and approximately 1.6%, approximately 1.3% and approximately 1.5%, approximately 1.3% and approximately 1.4%, approximately 1.4% and approximately 1.6%, approximately 1.4% and approximately 1.5% (w/v) diclofenac or diclofenac sodium and between approximately 1.0%, approximately 0.2% and approximately 0.8%, approximately 0.2% and approximately 0.7%, approximately 0.2% and approximately 0.6%, approximately 0.2% and approximately 0.5%, approximately 0.2% and approximately 0.4%, approximately 0.2% and approximately 0.3%, approximately 0.3% and approximately 0.7%, approximately 0.3% and approximately 0.6%, approximately 0.3% and approximately 0.5%, approximately 0.3% and approximately 0.4%, approximately 0.330% and approximately 0.340% (w/v) lidocaine or lidocaine hydrochloride. For example, in various embodiments, the compounded topical solution comprises between approximately 1.0% and approximately 2.0%, such as between approximately 1.3% and approximately 1.6%, (w/v) diclofenac sodium and between approximately 0.1% and approximately 0.5%, such as between approximately 0.3% and approximately 0.35%, (w/v) lidocaine hydrochloride. In one embodiment, the compounded topical solution includes approximately 1.47% (w/v) diclofenac sodium and approximately 0.333% (w/v) lidocaine hydrochloride. In another embodiment, the compounded topical solution includes approximately 1.35% (w/v) diclofenac and approximately 0.4% (w/v) lidocaine. In various embodiments, a method of formulating the compounded topical solution includes combining a commercially available diclofenac sodium solution, diclofenac sodium topical solution, 1.5% (w/w), or diclofenac sodium topical solution 2.0% (w/w) solution, with a commercially available lidocaine solution, such as lidocaine hydrochloride topical solution, 4% USP, to form a compounded topical solution having one of the above listed concentrations (w/v) of diclofenac sodium and lidocaine hydrochloride. Stronger or weaker concentrations of diclofenac or diclofenac sodium topical solutions and lidocaine or lidocaine hydrochloride topical solutions may be used wherein the amounts of such solutions added are modified to achieve the appropriate w/v concentrations.

In various embodiments, the compounded topical solution comprises a commercially available diclofenac sodium topical solution, 1.5% (w/w), compounded with a commercially available lidocaine hydrochloride topical solution, 4% USP, wherein the compounded topical solution includes diclofenac sodium topical solution, 1.5% (w/w), at a concentration between 0.1% and 99%, such as between 50% and 95%, (v/v) and lidocaine hydrochloride topical solution, 4% USP, at a concentration between 0.1% and 90%, such as 0.2% and 5%, (v/v). In one example, the compounded topical solution includes approximately 80% or more, approximately 90% or more, or approximately 91.7% (v/v) diclofenac sodium topical solution, 1.5% (w/w), and approximately 4% or more, approximately 7% or more, or approximately 8.32% (v/v) lidocaine hydrochloride topical solution, 4% USP. In one embodiment, the compounded topical solution includes approximately 90% (v/v) diclofenac sodium topical solution, 1.5% (w/w), and approximately 10% (v/v) lidocaine hydrochloride topical solution, 4% USP. In some embodiments, the compounded topical solution includes between approximately 50% and approximately 98%, approximately 55% and approximately 97%, approximately 60% and approximately 96%, approximately 70% and approximately 95%, approximately 80% and approximately 95%, approximately 85% and approximately 95%, approximately 90% and approximately 95%, approximately 90% and approximately 94%, approximately 90% and approximately 93%, approximately 90% and approximately 92%, approximately 91% and approximately 93%, approximately 91% and approximately 92% (v/v) diclofenac sodium topical solution, 1.5% (w/w), and between approximately 2% and approximately 20%, approximately 4% and approximately 18%, approximately 6% and approximately 16%, approximately 6% and approximately 16%, approximately 6% and approximately 12%, approximately 6% and approximately 10%, approximately 7% and approximately 14%, approximately 7% and approximately 12%, approximately 7% and approximately 10%, approximately 8% and approximately 14%, approximately 8% and approximately 12%, approximately 8% and approximately 10% (v/v) lidocaine hydrochloride topical solution, 4% USP. For example, in various embodiments, the compounded topical solution comprises between approximately 80% and approximately 95%, such as between approximately 90% and approximately 93% (v/v) diclofenac sodium topical solution, 1.5% (w/w), and between approximately 4% and approximately 14%, such as between approximately 7% and approximately 10% (v/v) lidocaine hydrochloride topical solution, 4% USP. In one embodiment, the compounded topical solution includes approximately 91.7% diclofenac sodium and approximately 8.32% lidocaine hydrochloride topical solution, 4% USP. In various embodiments, a method of formulating the compounded topical solution includes combining a commercially available diclofenac sodium solution, such as diclofenac sodium topical solution, 1.5% (w/w), with a commercially available lidocaine solution, such as lidocaine hydrochloride topical solution, 4% USP, to form a compounded topical solution having one of the above listed concentrations (v/v) of diclofenac sodium topical solution, 1.5% (w/w), and lidocaine hydrochloride topical solution, 4% USP. Stronger or weaker concentrations of diclofenac or diclofenac sodium topical solutions and lidocaine or lidocaine hydrochloride topical solutions may be used wherein the amounts of such solutions added are modified to achieve the appropriate v/v concentrations.

As introduced above, a method of making a compounded topical solution may include combining, e.g., adding to each other, two commercially available topical solutions. The method may further include mixing the two combined solutions to form a compounding topical solution for administration of multiple active agents. Example 1 presents a method of making a compounded topical solution that includes approximately 1.47% diclofenac sodium (w/v) and approximately 0.333% (w/v) lidocaine hydrochloride. However, the method may be applied to make compounded topical solutions having other active concentrations, such as those described herein.

Example 1—Diclofenac Sodium/Lidocaine HCl Compounded Topical Solution 1.47/0.333%

Diclofenac sodium topical solution, 1.5% (w/w), and lidocaine hydrochloride topical solution, 4% USP, were

compounded to make a compounded topical solution. Appropriate amounts of diclofenac sodium topical solution, 1.5% (w/w), and lidocaine hydrochloride topical solution, 4% USP, were measured. Diclofenac sodium topical solution, 1.5% (w/w), includes approximately 16.05 mg diclofenac sodium per mL. Accordingly, approximately 0.9167 mL of diclofenac sodium topical solution, 1.5% (w/w), was measured for every mL of compounded topical solution. Approximately 0.0832 mL of lidocaine hydrochloride topical solution, 4% USP, was measured for every mL of compounded topical solution. The measured ingredients where combined in a beaker. The beaker was placed on a magnetic stirring plate and a stir bar was placed in the beaker and rotated at a speed to create a small vortex for 5 minutes. The stirred solution was then placed in containers. Each mL of the compounded topical solution included approximately 91.7% (v/v) diclofenac sodium topical solution, 1.5% (w/w), and approximately 8.32% lidocaine hydrochloride topical solution, 4% USP.

Table I below depicts potency test results for the compounded topical solution of Example 1. Potency was determined via USP<621>HPLC, USP<851>Spectrophotometry, and specific monograph, using a High Performance Liquid Chromatography with an Ultraviolet/Photodiode Array Detector.

TABLE I

Potency Test

Analyte	Reported	Measured	Potency	Test Method
Lidocaine Hydrochloride	0.333%	0.336%	101%	HPLC with an Ultraviolet/ photodio de array
Diclofenac Sodium	1.47	1.51%	103%	HPLC

In further embodiments, the method may also include combining one or more additional active agents comprising one or more additional NSAIDs selected from salicylic acid derivatives (e.g., aspirin, diflunisal, salsalate, trilisate), one or more propionic acids (e.g., flurbiprofen, ibuprofen, ketoprofen, naproxen, oxaprozin), one or more acetic acids (e.g., etodolac, indomethacin, ketorolac, nabumetone, sulindac, tolmetin), one or more fenamates (e.g., meclofenamate), one or more oxicams (meloxicam, piroxicam), or one or more COX-2 inhibitors (e.g., celecoxib, rofecoxib, valdecoxib), or combinations thereof, one or more additional local anesthetics selected from prilocaine, benzocaine, or combination thereof, one or more muscle relaxants selected from baclofen, carisoprodol, orphenadrine, cyclobenzaprine, dantrolene, tizanidine, amitriptyline, or combinations thereof, one or more NMDA receptor antagonists such as ketamine, or one or more opioid or opiate agonists selected from oxycodone, morphine, fentanyl, hydrocodone, codeine, butalbital, tramadol, or combinations thereof, one or more nerve depressants selected from gabapentin, topiramate, lamotrigine, or combinations thereof, and/or other active agents. The additional active agents may be provided in powder form (e.g., pure powder or crushed tablets), suspension, gel, solution, or cream, e.g., emulsion. The additional active agents may comprise 0.1% to 5% (w/v) of the compounded topical solution.

In further embodiments, the compounded topical solution may be further compounded with a cream to form a compounded transdermal cream for topical/transdermal administration. As used herein, cream is intended to include a cream, ointment, lotion, gel, emulsion (oil in water or water in oil), etc. unless stated otherwise. In some embodiments, the compounded topical solution is compounded with a commercially available cream, which may or may not include additional active agents.

The compounded topical solution or derivative thereof may be topically applied to a body surface utilizing for example, spray, drops, atomizer, wash, swab, sponge, absorbent dressing, instillation or irrigation. Topical application may be with respect to body surfaces such as trunk, limbs, hands, feet, neck, head, cavities, etc. In various embodiments, the compounded topical solution may find orthopedic application, e.g., as part of a therapeutic treatment of rheumatoid arthritis/osteoarthritis, lateral epicondylitis (tennis elbow), medial epicondylitis (golfer's elbow), chondromalacia patellae—CMP (runner's knee), or tendonitis/carpel tunnel; rheumatologic application, e.g., as part of a therapeutic treatment of soft tissue pain, fibromyalgia, diabetic neuropathy, peripheral neuropathy, rheumatoid arthritis, or osteoarthritis; neurologic application, e.g., as part of a therapeutic treatment diabetic neuropathy, peripheral neuropathy, fibromyalgia, or localized pain; podiatric application, e.g., as part of a therapeutic treatment of diabetic neuropathy, peripheral neuropathy, plantar fasciitis, Achilles tendonitis, tarsal tunnel—post-op massage, or heel pain—which may include usage in conjunction with urea; pain management application, e.g., as part of a therapeutic treatment of soft tissue pain, fibromyalgia, diabetic/peripheral neuropathy, rheumatoid arthritis, osteoarthritis, or neck and back pain; or ear nose and throat or dental applications, e.g., as part of a therapeutic treatment of temporomandibular joint disorder (TMJD or TMJ), or trigeminal neuralgia.

The present disclosure also includes a stability-indicating method for the analysis of compounded solutions. As presented in the following example forced degradation study performed on a compounded solution preparation comprising Diclofenac Sodium/Lidocaine HCl Solution 1.47%/0.333%, the methods used are stability-indicating. The methods described below and similar may be used to establish stability-indicating methods for analysis of other compounded solutions using similarly designed forced degradation studies.

At least two degradation conditions may be used to determine specificity. In the exemplary protocol, two degradation conditions, heat and acid, were used. With respect to the heat degradation condition, 1 gram samplings of the preparation were heated at 40° C., 65° C., and 80° C. At day 2, day 6, and day 8 the treated samples were taken out and analyzed. With respect to the acid degradation condition, 120 uL of 0.1N HCl was added to 1 gram samplings of the preparation. The acid degradation treated samplings were then either kept at room temperature or heated at 40° C. and 65° C. At day 2, day 6, and day 8, the treated samplings were taken out and analyzed. Acid degradation condition also included 0.333 mL of sample incubated with 0.333 mL of concentrated sulfuric acid at 40° C. and 65° C. These treated samples where then analyzed after 14 hours and 18 hours of incubation. The 0.333 mL samples were prepared for analysis by dilution to 50 mL with methanol. Samplings of the heat and acid treated preparations were treated the same way. Lidocaine standard was prepared by accurately weighing and dissolving Lidocaine Hydrochloride USP Monohydrate (PCCA, C169931) in Methanol to a final concentration of 100 μg/mL. Diclofenac standard was prepared by accu-

rately weighing and dissolving Diclofenac Sodium USP (PCCA, C164795) in Methanol to a similar final concentration.

Standards and samples for were analyzed with a gradient method on a Waters Acquity UPLC equipped with a PDA detector. Eluent A was prepared by adding 1 mL of Trifluroacetic acid to 1 L of Dl Water. Eluent B was prepared by adding 1 mL of Trifluoroacetic acid to 1 L of Acetonitrile. The flow rate was 1 mL per minute. The column temperature was 50° C. The injection volume was 2 uL. The sample tray was kept at 22° C. The LC column was Acclaim RSLC PA2 Polar Advantage II, 2.2 um 120 A 2.1×150 mm from Thermo Scientific. The analysis time was 14 minutes with an additional 1 minute delay. The gradient was set as described in Table II. The processing wavelengths were 225 nm for Lidocaine and 276 nm for Diclofenac Sodium.

TABLE II

Gradient Used for Analysis of Standards and Samples

Minutes	Eluent A %	Fluent B %
0	98.0	2.0
6	88.0	12.0
13	20.0	80.0
13.2	98.0	2.0

Percent recoveries of Diclofenac Sodium for untreated and treated samples are shown in Table III. FIGS. **1**A-**1**E present exemplary chromatograms of standard, untreated, heat treated, acid treated at 45° C., and acid treated at 65° C. Diclofenac Sodium samples, respectively. Retention time for Diclofenac Sodium is at 11.5 minutes.

TABLE III

Recovery of Diclofenac Sodium (%)

	Day 0	Day 2	Day 6	Day 8
Untreated	103	104	104	104
40° C.		106	103	105
65° C.		106	101	103
80° C.		99.6	95.6	89.4
H+, RT		86.3	63.3	57.0
H+, 40° C.		70.8	44.5	28.0
H+, 65° C.		33.3	0.0	0.0

RT = 22-25° C.

Percent recoveries of Lidocaine HCl for untreated and treated samples are shown in Table IV. FIGS. **2**A-**2**D present exemplary chromatograms of standard, untreated, heat treated, and an acid treated Lidocaine HCl samples, respectively. Retention time for Lidocaine HCl is at 4.89 minutes.

TABLE IV

Recovery of Lidocaine HCl (%)

	Day 0	Day 2	Day 6	Day 8
Untreated	101	101	102	104
40° C.		100	99.4	104
65° C.		108	94.5	97.5
80° C.		96.0	99.9	75.6
H+, RT		98.5	96.5	101
H+, 40° C.		101	103	96.4
H+, 65° C.		97.0	102	101

RT = 22-25° C.

Percent recoveries of Lidocaine HCl for sulfuric acid treated samples are shown in Table V.

TABLE V

Recovery of Lidocaine HCl (%)

	14 Hours	18 Hours
Control	102	102
H2SO4, 40° C.	96.3	75.4
H2SO4, 65° C.	86.2	73.9

The above degradation study performed for Diclofenac Sodium and Lidocaine HCl Solution in Diclofenac Sodium/Lidocaine HCl Solution 1.47%/0.333% shows no co-elution or interference between degradants and API in all samples (stressed and untreated), thus, it demonstrates specificity. The methods used for this study are therefore stability-indicating methods.

The present disclosure may be embodied in other forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be had to the following claims rather than the foregoing specification as indicating the scope of the invention. Further, the illustrations of arrangements described herein are intended to provide a general understanding of the various embodiments, and they are not intended to serve as a complete description. Many other arrangements will be apparent to those of skill in the art upon reviewing the above description. Other arrangements may be utilized and derived therefrom, such that logical substitutions and changes may be made without departing from the scope of this disclosure.

This disclosure is intended to cover any and all adaptations or variations of various embodiments and arrangements of the invention. Combinations of the above arrangements, and other arrangements not specifically described herein, will be apparent to those of skill in the art upon reviewing the above description. Therefore, it is intended that the disclosure not be limited to the particular preferred arrangements disclosed for carrying out this invention, but that the invention will include all embodiments and arrangements falling within the scope of the appended claims.

What is claimed is:

1. A method of making a compounded topical solution, the method comprising:

combining a diclofenac sodium topical solution, 1.5% (w/w), and a lidocaine hydrochloride topical solution, 4% USP; and

mixing the combined diclofenac sodium topical solution, 1.5% (w/w), and lidocaine hydrochloride topical solution, 4% USP;

wherein the diclofenac sodium topical solution, 1.5% (w/w), comprises DMSO, 45.5% (w/w), and propylene glycol and is combined in an amount between approximately 85% and approximately 95% (v/v) of the compounded topical solution and the lidocaine hydrochloride topical solution, 4% USP, is combined in an amount between approximately 5% and approximately 15% (v/v) of the compounded topical solution.

2. The method of claim **1**, wherein the diclofenac sodium topical solution, 1.5% (w/w), is combined in an amount between approximately 90% and approximately 93% (v/v) of compounded topical solution and the lidocaine hydrochloride topical solution, 4% USP, is combined in an amount between approximately 7% and approximately 10% (v/v) of the compounded topical solution.

3. The method of claim **1**, wherein the diclofenac sodium topical solution, 1.5% (w/w), is combined in an amount approximately 90% (v/v) or more of the compounded topical solution and the lidocaine hydrochloride topical solution,

4% USP, is combined in an amount approximately 7% (v/v) or more of the compounded topical solution.

4. The method of claim **1**, wherein the diclofenac sodium topical solution, 1.5% (w/w), is combined in an amount approximately 91.7% (v/v) of the compounded topical solution and the lidocaine hydrochloride topical solution, 4% USP, is combined in an amount approximately 8.32% (v/v) of the compounded topical solution.

5. The method of claim **1**, wherein the compounded topical solution comprises approximately 1.47% (w/v) diclofenac sodium and approximately 0.333% (w/v) lidocaine hydrochloride.

6. The method of claim **1**, wherein the diclofenac sodium topical solution, 1.5% (w/w), is combined in an amount between approximately 90% and approximately 93% (v/v) of compounded topical solution and the lidocaine hydrochloride topical solution, 4% USP, is combined in an amount between approximately 7% and approximately 10% (v/v) of the compounded topical solution.

7. The method of claim **6**, wherein the compounded topical solution comprises approximately 1.47% (w/v) diclofenac sodium and approximately 0.333% (w/v) lidocaine hydrochloride.

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