

PHARMACEUTICAL COMPOSITIONS FOR USE IN THE MANAGEMENT AND TREATMENT OF PAIN

FIELD OF INVENTION

[0001] The present invention discloses pharmaceutical compositions for treating pain in general. More particularly, this invention relates to pharmaceutical compositions for the treatment and management of pain broadly caused by tissue damage also called nociceptive pain and nerve damage also called neuropathic pain or central sensation or generalized pain or a mixed type of pain.

BACKGROUND OF THE INVENTION

[0002] Pain is a general term that describes uncomfortable sensations in the body. It results from activation of the nervous system. Pain may be sharp or dull or it may be intermittent, or it may be constant. Pain in general is classified into acute and chronic pain. Acute pain is intense and short-lived and can be of different types such as somatic pain, visceral pain and referred pain. While chronic pain is more severe than acute pain, often with no cure. It can also be either continuous, or intermittent.

[0003] Nociceptive pain is the most common type of pain. It can be either acute or chronic. It's caused by stimulation of nociceptors, which are pain receptors for tissue injury found throughout your body, especially in your skin and internal organs. When injured they send electrical signals to the brain, causing pain. The visceral pain results from injuries or damage to the internal organs. It's often not easy to pinpoint the exact location of pain. The somatic pain results from stimulation of the pain receptors in the tissues such as skin, muscles, joints, connective tissues, and bones.

[0004] The neuropathic pain results from damage to or dysfunction of the nervous system. Neuropathic pain can be due to diabetic conditions, infections, facial nerve problems, such as Bell's palsy, spinal nerve inflammation or compression, shingles, central nervous system disorders, such as multiple sclerosis or Parkinson's disease and accidents.

[0005] Pain can be treated using pain relief medication or by treating the underlying health issue. Different type of analgesics is used for pain management. Acetaminophen is commonly used analgesic as the over-the-counter and prescription drugs for treating moderate to severe pain. Other local anesthetics includes lidocaine, mepivacaine, ropivacaine and other which have local and systemic toxicity.

[0006] Nonsteroidal anti-inflammatory drugs (NSAIDs) are another type of analgesic commonly used in treating minor acute pains.

[0007] Opioids is a prescription drug for the most extreme acute pains, due to burns, cancer, surgery and bone fractures. Opioids are highly addictive and lose their effectiveness over time.

[0008] International Application No. PCT/IB2017/052247 discloses compositions and methods for the treatment of chronic pain. The content of which are incorporated in its entirety herein by reference. However, IA PCT/IB2017/052247 fails to disclose the pharmaceutical compositions, methods of preparation, various dosage forms, delivery methods, formulation and compositions for management of pain in various disease conditions.

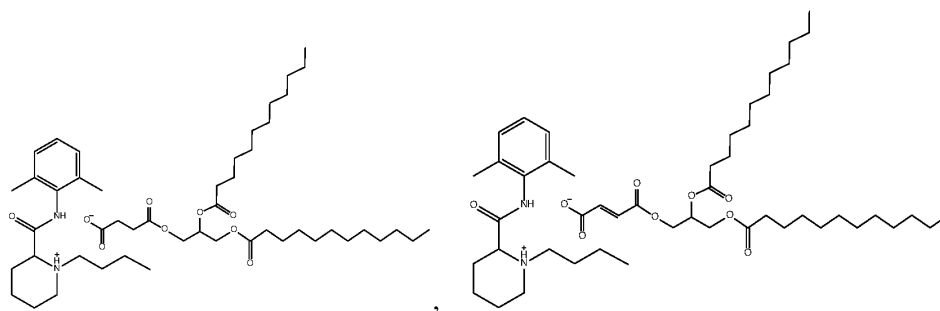
SUMMARY OF THE INVENTION

[0009] In an embodiment, the present invention provides pharmaceutical compositions or formulations and methods for improving pain relief by administering local anesthetic formulation to the site for the treatment of acute or chronic pain, neuropathic pain or nociceptive pain or central sensation or generalized pain or a mixed type of pain.

[0010] In an embodiment, the present invention provides pharmaceutical compositions comprising local anesthetic or a derivative or a pharmaceutically active salt thereof.

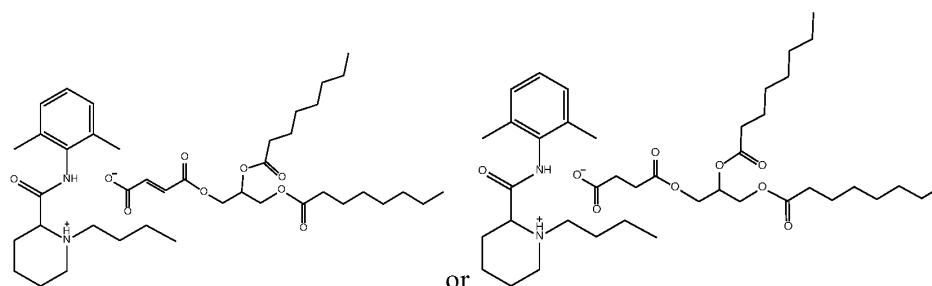
[0011] In another embodiment, the local anesthetic, pharmaceutically active salt, derivatives or a mixture thereof. Examples of local anesthetic include salts, derivatives or prodrugs of levo and dextro enantiomer of bupivacaine collectively called the compounds of bupivacaine of active ingredients. Levobupivacaine is the (S)-(-)-enantiomer of bupivacaine, with a longer duration of action and producing less vasodilation. Levobupivacaine or its derivative and any pharmaceutically active salts thereof, are included within the scope of the present invention.

In certain embodiments, the compounds of bupivacaine salt forms or a mixture of anion and cation forms containing bupivacaine (the active ingredient) and fatty acid derivative of glycerol fumarate or succinate as per the present invention is selected from the formulas I [bupivacaine glyceryl dilauryl succinate] or formula II [bupivacaine glyceryl dilauryl fumarate] or formula III [bupivacaine glyceryl dicapryl fumarate] or formula IV [bupivacaine glyceryl dicapryl succinate].



Formula I

Formula II



Formula III

Formula IV

[0012] In an embodiment, the present invention also provides pharmaceutical compositions comprising compounds of bupivacaine along with one or more pharmaceutically acceptable excipient, carriers, vehicles or diluents.

[0013] In an embodiment, the pharmaceutical composition may comprise of formula I or formula II or formula III or formula IV along with one or more pharmaceutically acceptable excipients. Further discloses the method of preparing such compositions and its use in the pain management and treatment.

[0014] In an embodiment, the present invention also discloses the suitable dosage forms comprising therapeutically effective amount of compound of Formula I or Formula II or Formula

III or Formula IV for treatment of pain which may be administered locally, topically, parenterally, or by infusion and/or orally.

[0015] In yet another embodiment, the present invention provides solid and liquid formulations of the pharmaceutical composition comprising compounds of Formula I or Formula II or Formula III or Formula IV for the treatment and management of pain.

[0016] In another embodiment, the present invention provides easy, convenient and patient friendly drug delivery system with better bioavailability and long-lasting effect for treatment of pain.

[0017] In an embodiment the compounds of Formula I or Formula II or Formula III or Formula IV are formulated for oral administration such as chewable tablets, buccal tablets, chewing gum, patches, tablets, cachets, lozenges, powder-based lozenges, syrup-based lozenges, granulated lozenges, pastilles and dispersible granules. Further, the oral formulation may be modified release formulation which includes a sustained or slow release formulation, extended release, or immediate release or fast release formulation, phased release formulation or any other modified release profile which are well known in the art of pharmaceutical formulation preparations.

[0018] In a specific embodiment, the pharmaceutical composition comprises compound of formula II formulated into a lozenge.

[0019] The composition containing compound of Formula I or Formula II or Formula III or Formula IV in an amount of 5 mg to 2 gm or 0.1 to 100 mg, preferably 0.1 to 75 mg, for example 5 mg, 10 mg, 25 mg or 50 mg, 60 mg, 65 mg, 70 mg, 71 mg, 72 mg, 73 mg or 75 mg equivalent to bupivacaine free base active form in an oral lozenge or oral chewable tablet or oral dispersible tablet or mucoadhesive tablet or buccal tablet or any oral local administration formulations thereof containing equivalent to bupivacaine active form.

[0020] The invention further relates to methods of manufacturing lozenges wherein, one step comprises a granulation step. The granulation step may be a wet granulation and/or dry granulation.

[0021] In another embodiment of the invention relates to a method for preparing the lozenge formulation. The method comprises:

- i. Step1: Dispensing all the required raw materials.

- ii. Step-2: Granulation fluid: the active ingredient is dissolved in suitable solvent and or cosolvent.
- iii. Step-3: Sifting the excipients: binder, disintegrants, sweetening agent, glidants, anticaking agent, taste masking agent, preservative, penetration enhancer, bioavailability enhancer, solubilizing agent, surfactant, co surfactant, flavoring agents through a sieve.
- iv. Step-4: Dry mixing: The sifted step 3 raw materials is mixed.
- v. Step-5: Granulation: Granulated step 4 blend with step 2 granulating fluid.
- vi. Step-6: Drying: The wet mass of step 5 is dried.
- vii. Step-7: Sizing: The dried material of step 6, is sifted using a sieve.
- viii. Step-8: Sifting: Extra-granular materials i.e. flavoring agents and lubricant is sieved.
- ix. Step-9: Lubrication: The sifted material of step 8 is added to step 7 and blended.
- x. Step-10: Compression: The lubricated blend of step 9 was compressed into lozenges with suitable punches on compression machine.

[0022] In an embodiment, the compounds of Formula I or Formula II or Formula III or Formula IV may be formulated for local administration. In certain embodiments, the formulation is a topical spray formulation. Furthermore, the spray formulation is a mucoadhesive and or bioadhesive formulation suitable for application to the skin or mucosal layer.

[0023] The present disclosure in certain aspects is directed to a method of treating pain comprising the administration of a polymeric film forming spray formulation which is applied locally via the utilization of a spray device. The spray formulation is formulated such that it increases the permeability of Formula I or Formula II or Formula III or Formula IV through the mucosal layer or the skin after spray administration by a pump.

[0024] The compound of Formula I or Formula II or Formula III or Formula IV thereof is preferably present in an amount of 5 mg to 2 gm or 0.1 to 100 mg, preferably 0.1 to 75 mg, for example 5 mg, 10 mg, 25 mg or 50 mg, 60 mg, 65 mg, 70 mg, 71 mg, 72 mg, 73 mg or 75 mg equivalent to bupivacaine in active form per pump of the spray. The compound of Formula I or Formula II or Formula III or Formula IV active form dose may be from about 0.1 to about 100 mg or 5 mg to 25 mg or is sprayed as a unit dose topical or local onto the skin or mucosal layer, to provide a film surface area from about 0.1 cm² to about 60 cm² per spray and may be dosed by

spraying from 1 to about 10 sprays per application of the unit dose local to the skin or mucosal layer. In certain embodiments, a further unit dose of the topical polymeric film forming composition may be sprayed topical to the site of action about 5 hours after application of a first unit dose. The unit dose may be sprayed using a metered pump delivering device.

[0025] In another embodiment of the invention relates to a method for preparing a spray formulation comprising:

- i. Step 1: A solution A is prepared by adding the purified water into a compounding vessel and dissolving disintegrants, binder, preservative, lubricant, sweetening agent, agents which enable penetration, bioavailability and retention time of the drug.
- ii. Step 2: Solution B is prepared by adding solubilizing agent, self-emulsifying agent in compounding vessel and dissolving active ingredient. The solution A is added to Solution B and stirring continuously until the drug is completely dissolved. Volume is made up to with the remaining quantity of purified water.
- iii. Step 3: The resultant solution is filtered under vacuum. This filtered solution is filled into glass vials and pump is crimped.

[0026] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention relates. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

[0027] As used herein, the following terms and phrases shall have the meanings set forth below. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art.

[0028] The phrase “pharmaceutically acceptable”, “pharmaceutically acceptable carriers”, “prodrug”, “prophylactic” or “therapeutic”, “treating”, “therapeutically effective amount”, “sustained release”, “systemic administration,” “administered systemically,” “peripheral administration” and “administered peripherally”, “substantially pure”, “metabolic condition”, “patient”, “subject”, “host”, “polymorph”, “enantiomers”, “racemic mixture” is art-recognized.

[0029] The phrase “pharmaceutical active ingredient”, means anesthetic analgesics refer to local anesthetics, include compounds of bupivacaine which include salts, derivatives, mixture, conjugates, or prodrugs of levo and dextro enantiomer forms of bupivacaine. The formula I, formula II, formula III or formula IV are examples of compounds of bupivacaine in ionic salt forms or a mixture of bupivacaine free base and glycerol fumarate fatty acid derivatives or mixture bupivacaine free base and glycerol succinate fatty acid derivatives.

[0030] As used herein the word “pain” means pain due to tissue damage also referred as nociceptive pain, nerve damage also referred as neuropathic pain, or central sensation or generalized pain or a mixed type of pain. The pain can be either acute pain or chronic pain. Further includes radicular pain, inflammatory pain, visceral pain, cancer pain, pain associated with stomatitis and mucositis, non-cancer pain, trauma pain, sport pain, surgical pain, wound pain, burn pain, musculoskeletal pain, postoperative pain, labor pains, pain associated with neurogenic bladder, ulcer, cankers and colitis, rest pain, surrounding mediated pain, main center mediated pain, chronic cephalalgia, migraine, sinus headache, tension headache, phantom limb pain, toothache, peripheral nerve injury and peripheral neuropathic pain such as post-herpetic neuralgia (PHN), pain due diabetic conditions such as painful peripheral diabetic neuropathy (pDPN), pain due to infections of open wounds, post-amputation pain, facial nerve problems such as Bell’s palsy, spinal nerve inflammation or compression, pain due to shingles, central nervous system disorders, such as multiple sclerosis or Parkinson’s disease, trigeminal neuralgia and accidents.

[0031] In the present invention the term “neuropathic pain” predominately includes peripheral neuropathy or central nervous injury such as PHP, DPN, lumbar or cervical radiculopathy, stenosis, tumor-related neuropathy, erythromelalgia, fibromyalgia, chemotherapy induced neuropathy, small fiber neuropathy, postoperative pain, phantom limb pain, chronic

radiculopathy, multiple sclerosis pain, trigeminal neuralgia, post stroke pain, pain from spinal cord injury, achondrogenesis, achondroplasia, achondroplastic dwarfism, acquired immunodeficiency syndrome (AIDS), HPV related rashes and pain, acute porphyrias, acute intermittent porphyria, acute shoulder neuritis, adrenomyeloneuropathy (AMN), adult dermatomyositis, amyotrophic lateral sclerosis, anal rectal malformations, arachnitis, arachnoiditis, arthritis, arthritis urethritica, astrocytoma, athetoid cerebral palsy, barrett esophagus, barrett ulcer, benign tumors of the central nervous system, bone tumor-epidermoid brachial neuritis, brachial plexus neuritis, brachial-plexus-neuropathy, brain tumors, bullosa hereditaria, bullous congenital ichthyosiform erythroderma, bullous ichthyosis, bullous pemphigoid, burkitt's lymphoma, calcaneal valgus, cavernous lymphangioma, central post-stroke pain, central form neurofibromatosis, cervical spinal stenosis, cervical vertebral fusion, charcot's disease, childhood dermatomyositis, chondrodystrophic myotonia, chondrodysplasia punctata, chondrodystrophia calcificans congenita, chondrodystrophia fetalis, chondrodystrophy, chondrodystrophy hyperplastic form, chondroectodermal dysplasias, chondrogenesis imperfecta, chondrohypostrophia, chondroosteodystrophy, chronic adhesive arachnoiditis, chronic idiopathic polyneuritis, chronic inflammatory demyelinating polyneuropathy, chronic inflammatory demyelinating polyradiculoneuropathy, cicatricial pemphigoid, complex regional pain syndrome, congenital dysmyelinating neuropathy, congenital cervical synostosis, congenital hypomyelination neuropathy, congenital ichthyosiform erythroderma, congenital tethered cervical spinal cord syndrome, cranial arteritis, crohn's disease, cutaneous porphyrias, degenerative lumbar spinal stenosis, diabetes mellitus, diabetes mellitus diabetes insulin dependent, diabetes mellitus addison's disease myxedema, demyelinating disease, discoid lupus, disseminated lupus erythematosus, disseminated neurodermatitis, disseminated sclerosis, EDS kyphoscoliotic, EDS mitis type, EDS ocular-scoliotic, elastosis dystrophica syndrome, encephalofacial angiomatosis, encephalotrigeminal angiomatosis, enchondromatosis with multiple cavernous hemangiomas, endemic polyneuritis, endometriosis, eosinophilic fasciitis, epidermolysis bullosa, epidermolysis bullosa acquisita, epidermolysis bullosa hereditaria, epidermolysis bullosa letalias, epidermolysis hereditaria tarda, epidermolytic hyperkeratosis, epidermolytic hyperkeratosis (bullous cie), facial nerve problems such as Bell's palsy, familial lumbar stenosis, familial lymphedema praecox,

fibromyalgia, fibromyalgia-fibromyositis, fibromyositis, fibrositis, fibrous ankylosis of multiple joints, fibrous dysplasia, fragile X syndrome, generalized fibromatosis, guillain-barre syndrome, hemangiomas chondrodystrophica, hereditary sensory and all autonomic neuropathy type pain, all type of hereditary sensory motor neuropathy, hereditary sensory radicular neuropathy, herpes zoster, hodgkin disease, hodgkin's lymphoma, hyperplastic epidermolysis bullosa, hypertrophic interstitial neuropathy, hypertrophic interstitial neuritis, hypertrophic interstitial radiculoneuropathy, hypertrophic neuropathy of refsum (ARD), idiopathic brachial plexus neuropathy, idiopathic cervical dystonia, juvenile (childhood) dermatomyositis, juvenile diabetes, juvenile rheumatoid arthritis, pes planus, leg ulcer, lumbar canal stenosis, lumbar spinal stenosis, lumbosacral spinal stenosis, lupus, lupus lymphangiomas, mononeuritis multiplex, mononeuritis peripheral, mononeuropathy peripheral, monostotic fibrous dysplasia, multiple cartilaginous enchondroses, multiple cartilaginous exostoses, multiple enchondromatosis, multiple myeloma, multiple neuritis of the shoulder girdle, multiple osteochondromatosis, multiple peripheral neuritis, neuropathic pain associated with spinal cord injury, multiple sclerosis, musculoskeletal pain syndrome, neuropathic amyloidosis, neuropathic beriberi, neuropathy of brachialpelxus syndrome, nieman pick disease (acute neuronopathic form), non-scarring epidermolysis bullosa, ochronotic arthritis, ocular herpes, onion-bulb neuropathy, osteogenesis imperfecta congenita, osteogenesis imperfecta tarda, peripheral neuritis, peripheral neuropathy, perthes disease, polyarteritis nodosa, polymyalgia rheumatica, polymyositis and dermatomyositis, polyneuritis peripheral, polyneuropathy peripheral, polyneuropathy and polyradiculoneuropathy, polyostotic fibrous dysplasia, polyostotic sclerosing histiocytosis, postmyelographic arachnoiditis, primary progressive multiple sclerosis, psoriasis, radial nerve palsy, radicular neuropathy sensory, radicular neuropathy sensory recessive, reflex sympathetic dystrophy syndrome, relapsing-remitting multiple sclerosis, sensory radicular neuropathy, sickle cell disease, spina bifida, spina bifida aperta, spinal arachnoiditis, spinal arteriovenous malformation, spinal ossifying arachnoiditis, spinal stenosis, stenosis of the lumbar vertebral canal, still's disease, syringomyelia, systemic sclerosis, talipes calcaneus, talipes equinovarus, talipes equinus, talipes varus, talipes valgus, tandem spinal stenosis, temporal arteritis/giant cell arteritis, temporal arteritis, tethered spinal cord syndrome, tethered cord malformation sequence, sciatica, tethered cord syndrome,

tethered cervical spinal cord syndrome, thalamic pain syndrome, thalamic hyperesthetic anesthesia, trigeminal neuralgia, vasculitis, variegate porphyria, vertebral ankylosing hyperostosis, immune pathologies induced by infectious agents, such as helminthic (e.g., leishmaniasis) and certain viral infections, bacterial infections, including tuberculosis and lepromatous leprosy, tissue transplant rejection, graft versus host disease and atopic conditions, such as asthma and allergy, gastrointestinal allergies, including food allergies, eosinophilia, conjunctivitis or glomerular nephritis amongst others.

[0032] In the present invention the term “nociceptive pain” are pain due to damage or injury to bone, joint, muscle, skin or connective tissue. It predominately includes osteoarthritis, rheumatoid arthritis, tendonitis bursitis, ankylosing spondylitis, gout, neck and back pain with pathology, tumor related nociceptive pain, inflammatory bowel disease amongst others.

[0033] In the present invention the term “central sensitization” predominately includes fibromyalgia, irritable bowel syndrome, tension-types headaches, intestinal cystitis, pelvic pain, restless leg syndrome.

[0034] In the present invention the term “generalized pain” means widespread pain throughout the body with diffuse tenderness to palpation throughout body with absence of significant trigger points may be associated with depression or poor sleep conditions or due to central sensitization.

[0035] The composition of the present invention is useful in treating radiation induced pain in mucositis and stomatitis patient. The irradiation-induced histological changes leading to oral mucositis, together with salivary quantitative and qualitative changes, have been reported to facilitate yeast growth. Inflammation of the mucosa is a common, dose limiting complication of high dose chemotherapy and radiotherapy in cancer patients. Server impairment of the patient's general condition is associated with subsequent bacterial superinfection. Long term hospitalization such cancer patients have substantial changes in oral microflora such microbial colonisation within the oral cavity aggravation of the mucositis leading to severe clinical symptoms. Ulceration of the oral mucosa interrupts the natural defense barrier or mucosal layer and provides oral microorganisms and inflammatory cytokines to entry into underlying tissues and the systemic blood supply. 93% oral colonization and infection are frequently noted in the patients. The prevalent bacterial pathogens species in mucositis is *Scardovia* spp.,

Lactobacillus spp., *Streptococcus* spp., *Actinomyces* spp., *Staphylococcus* spp., *Enterococcus* spp., *usobacterium* spp., *Prevotella* sp., *Actinobacillus* spp., and *Candida* spp. and others are observed in the oral cavity of radiotherapy, radio chemotherapy treated patients.

[0036] Microbial infections are also very common in open wounds, cuts, surgical wound, burns rashes commonly found pathogens include *Staphylococcus aureus*, *Escherichia coli*, *Staphylococcus epidermidis*, *S. aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Proteus mirabilis*, *Proteus vulgaris*, *S. mutans*, *A. actinomycetemcomitans*, *P. gingivalis*, *F. nucleatum*, and *S. gordonii* and the fungal pathogens are *Candida albicans*, *Aspergillus fumigatus* and others.

[0037] The antibacterial mode of action of Free Fatty Acids (FFA) is still poorly understood, the prime target of FFA action is the cell membrane, where FFAs disrupt the electron transport chain and oxidative phosphorylation; also, it can interfere with cellular energy production, generation of peroxidation and auto-oxidation degradation products or direct lysis of bacterial cells. Medium-chain saturated fatty acids that lack a kinked structure can be packed more tightly and can reduce membrane fluidity and disrupt electron transport perhaps by restricting the movement of carriers within the membrane. The antibacterial effect of long chain unsaturated fatty acids were due to their inhibition of fatty acid biosynthesis. One of the biological activities of the free fatty acids (FFAs) is their ability to kill or inhibit the growth of pathogenic bacteria.

[0038] The composition of the present invention comprises compound of formula I, formula II, formula III and formula IV are effective in not only reducing the pain but also inhibit the microbial growth.

[0039] In the present invention “compound of bupivacaine” means salts, mixtures, prodrugs and derivatives of bupivacaine. Further, includes the compounds disclosed in the International Application No. PCT/IB2017/052247, the contents of which are incorporated in its entirety herein by reference.

[0040] In order to understand the invention and to see how it may be carried out in practice, several specific embodiments will now be described.

[0041] In one embodiment, present invention envisages not only treating the pain but also anesthetizing the part of the body that feels pain.

[0042] In an embodiment, the present invention discloses compounds of bupivacaine as the anesthetic (numbing medicine) that blocks nerve impulses in the body.

[0043] In an embodiment, the present invention discloses how the salts, derivatives and prodrugs of bupivacaine is formulated for effectively reducing the pain by binding to the intracellular portion of voltage-gated sodium channels and blocks sodium influx into nerve cells, which prevents depolarization thus stopping initiation or conduction of a pain signal can occur. In one embodiment present invention provides a compound which is more lipid soluble local anesthetic with anti-microbial properties associated with the naturally occurring fatty acids to reduce pathogenic microbial flora as well as enable sustained release of the drug to reduce the pain.

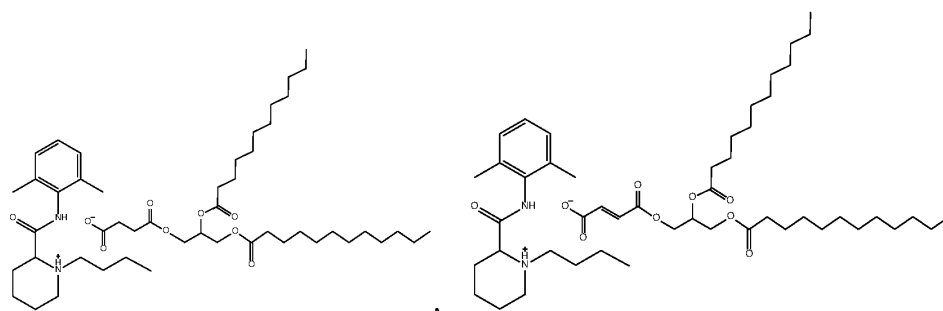
[0044] It an embodiment, the present invention provides pharmaceutical compositions or a formulations and methods thereof for providing pain relief by administering a dose of a local anesthetic formulation to the site for the treatment of acute or chronic pain, radiation induced pain, neuropathic pain or nociceptive pain or central sensation or generalized pain or a mixed type of pain as defined in the specification herein.

[0045] In an embodiment, the present invention provides pharmaceutical compositions for management/treatment of neuropathic pain or nociceptive pain or central sensation or generalized pain or a mixed type of pain.

[0046] In an embodiment, the present invention provides pharmaceutical compositions comprising local anesthetic or a pharmaceutically active salt, or a derivative or a mixture thereof.

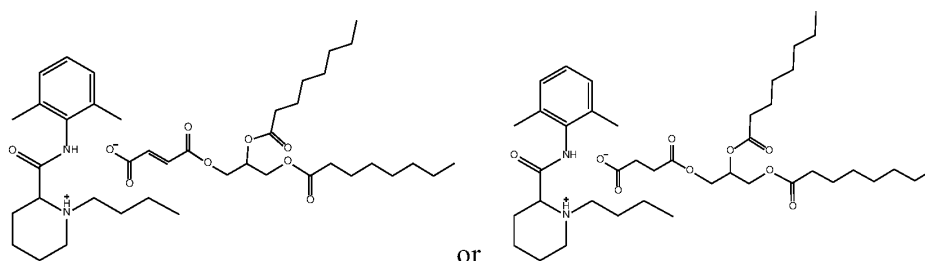
[0047] In another embodiment, the local anesthetic or a pharmaceutically active salt thereof includes salts, derivatives and prodrugs of levo and dextro enantiomer of bupivacaine collectively called the compounds of bupivacaine in a racemic form or levobupivacaine. Levobupivacaine is the (S)-(-)-enantiomer of bupivacaine, with a longer duration of action and producing less vasodilation. Levobupivacaine and any pharmaceutically active salts thereof, are included within the scope of the present invention.

[0048] In a certain embodiment, the instant invention provides pharmaceutical compositions comprising the compounds of bupivacaine (the active ingredient) selected from following chemical structures below. The composition is formulated based on the route of administration and is used in the pain management and treatment.



Formula I

Formula II



Formula III

Formula IV

[0049] The pharmaceutical compositions as disclosed comprises active ingredient selected from compounds of formula I [bupivacaine glyceryl dilauryl succinate] or formula II [bupivacaine glyceryl dilauryl fumarate/CLX-SYN-G161-C11] or formula III [bupivacaine glyceryl dicaprylyl fumarate] or formula IV [bupivacaine glyceryl dicaprylyl succinate/CLX-SYN-G161-C01] along with at least one pharmaceutically acceptable excipient or carrier or vehicles or diluents.

[0050] In an embodiment, the pharmaceutical composition may comprise of formula I or formula II or formula III or formula IV along with one or more pharmaceutically acceptable excipients. Such a formulation is used in the preparation of medicament that can be used in the pain treatment and pain management.

[0051] In an embodiment, the present invention also provides suitable dosage forms comprising therapeutically effective amount of compound of Formula I or Formula II or Formula III or

Formula IV for treatment of pain which can be administered locally, depot, infusion, spray, topical and/or orally.

[0052] In an embodiment the present invention also provides pharmaceutical composition comprising 0.1% to 70% w/w local anesthetic and rest 30-99.9% w/w pharmaceutically acceptable excipients.

[0053] In an embodiment the present invention provides easy, convenient, and patient friendly drug delivery system with better bioavailability and long-lasting effect for treatment of pain.

[0054] In an embodiment the compound of bupivacaine is formulated for oral administration such as chewable tablets, buccal tablets, chewing gum, oral dispersible tablet, mucoadhesive tablet, patches, tablets, cachets, lozenges, powder-based lozenges, syrup-based lozenges, granulated lozenges, pastilles and dispersible granules or any other oral administration formulation. Further, the oral formulation can be a sustained or slow-release formulation or immediate or fast release formulation, phased release formulation or any other modified release profile known in the art of pharmaceutical formulation.

[0055] The sustained-release composition is preferably formulated to provide sustained release of the compound of bupivacaine over time period of at least 1, 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80 minutes, 90 minutes or at least 100 minutes, for example up to about 2 hours, 3 hours, 4 hours, or 5 hours or hours or 10 hours. All of these values can be permuted to represent upper and lower limits of ranges of release time, for example the range can be 10 to 60 minutes.

[0056] In certain embodiment sustained-release composition is preferably formulated to provide sustained release of the compound of bupivacaine at least for 20 minutes, at least for 40 minutes, at least for 60 minutes, at least for 80 minutes, at least for 100 minutes or at least up to about 2 hours, at least up to 4 hours, at least up to 8 hours, or at least up to 10 hours.

[0057] A lozenge formulation contains 1 to 80 mg compound of Formula I or Formula II or Formula III or Formula IV equivalent to bupivacaine in an active form, in an embodiment of the invention and is suitable for use over extended periods.

[0058] In specific embodiment the pharmaceutical composition comprises compound of formula II [bupivacaine glyceryl dilauryl fumarate or CLX-SYN-G161-C11] is formulated into a lozenge.

[0059] In one embodiment, Formula I or Formula II or Formula III or Formula IV thereof is preferably present in an amount of 5 mg to 2 gm or 5 mg to 100mg, preferably 5 to 75 mg, for example 5 mg, 10 mg, 25 mg or 50 mg, 60mg, 65mg, 70mg, 71mg, 72mg, 73mg or 75mg per unit dosage form.

[0060] The invention further relates to methods of producing lozenges wherein one step comprises a granulation step. The granulation step may be a wet granulation and/or dry granulation.

[0061] In another embodiment of the invention relates to a method for preparing the lozenge formulation. The method comprises:

- xi. Step1: Dispensing all the required raw materials.
- xii. Step-2: Granulation fluid: the active ingredient is dissolved in suitable solvent and or co-solvent or any other vehicle.
- xiii. Step-3: Sifting any excipients: binder, disintegrants, sweetening agent, glidants, anticaking agent, taste masking agent, preservative, penetration enhancer, bioavailability enhancer, solubilizing agent, surfactant, co surfactant, flavoring agents or any other excipient through a sieve.
- xiv. Step-4: Dry mixing: The sifted step 3 raw materials is mixed.
- xv. Step-5: Granulation: Granulated step 4 blend with step 2 granulating fluid.
- xvi. Step-6: Drying: The wet mass of step 5 is dried.
- xvii. Step-7: Sizing: The dried material of step 6, is sifted using a sieve.
- xviii. Step-8: Sifting: Extra-granular materials i.e. flavoring agents and lubricant or any other excipient is sieved.
- xix. Step-9: Lubrication: The sifted material of step 8 is added to step 7 and blended.
- xx. Step-10: Compression: The lubricated blend of step 9 is compressed into lozenges with suitable punches on compression machine with each lozenge so prepared containing a therapeutically effective amount of the active agent/one of the compound of bupivacaine.

[0062] The lozenges prepared using the above method can last even longer in the mouth and seem not so dry for the patient when they suck them.

[0063] In an embodiment the compound of bupivacaine may be formulated for local and or topical administration. In certain embodiment the formulation may be a spray formulation.

[0064] The present disclosure in certain aspects is directed to a method of treating pain comprising the administration of a polymeric film forming spray formulation which is applied locally or topically to the target site via the utilization of a spray device.

[0065] The compound of bupivacaine thereof is preferably present in an amount of 5 mg to 2 gm or 5 mg to 100 mg, in a preferred embodiment 5 to 75 mg, or preferably 5 mg, 10 mg, 25 mg or 50 mg, 60 mg, 65 mg, 70 mg, 71 mg, 72 mg, 73 mg or 75 mg per ml of the spray.

[0066] In some embodiments, the composition is formulated as a liquid dosage form considering compounds of formula I, formula II, formula III or formula IV characteristics and route of administration. The excipients are selected based on dosage form, physicochemical characteristics of active ingredient, stability, and compatibility issues. To reduce dose heterogeneity and to improve ease of administration the formulation is packed in a sprayable device to deliver uniform dose from the bottle. The device comprises of an actuator with long cannula which enables to deliver the product to the affected area.

[0067] In one of the embodiments, the composition may have one or more polymer in the formulation to form a film upon administration and for sustained release of the active ingredient via compound of bupivacaine. Preservative and sweetening agents is included to increase microbiological stability and dose adherence by the patient.

[0068] In another embodiment the invention relates to a method for preparing a spray formulation comprising:

- iv.** Step 1: A solution A is prepared by adding the purified water into a compounding vessel and dissolving any excipient such as disintegrants, binder, preservative, lubricant, sweetening agent, agents which enable penetration, bioavailability, and retention time of the drug.
- v.** Step 2: Solution B is prepared by adding solubilizing agent, self-emulsifying agent or any other excipient in compounding vessel and dissolving active ingredient. The solution A is added to Solution B and stirring continuously until the drug is completely dissolved. Volume is made up to with the remaining quantity of purified water.

- vi. Step 3: The resultant solution is filtered under vacuum. This filtered solution is filled into glass vials and pump is crimped.

[0069] The pharmaceutical compositions as disclosed comprises compounds of formula I [bupivacaine glyceryl dilauryl succinate] or formula II [bupivacaine glyceryl dilauryl fumarate/CLX-SYN-G161-C11] or formula III [bupivacaine glyceryl dicaprylyl fumarate] or formula IV [bupivacaine glyceryl dicaprylyl succinate/CLX-SYN-G161-C01] along with at least with one or more pharmaceutical excipients which has high safety profile, slow release, better permeability, long lasting effect and low toxicity. Further, the pharmaceutical excipients examples include, anti-adherents, binders, coatings, penetration enhancers, solubilizer, surfactant, propellant agents, dispensing agents, colors, disintegrants, flavors, glidants, lubricants, preservatives, sorbents, sweeteners, vehicles.

[0070] In an embodiment, present invention discloses a pharmaceutical composition formulated into solid and liquid formulation for easy and convenient administration. In another embodiment provides a pharmaceutical composition for special patients' category such as geriatric and pediatric suffering from pain.

[0071] In yet another embodiment, the excipients used are suitable for spray formulation for pressurized packages, pressurized dosage forms such as NDDS for dispensing the compounds of the present invention to the systemic circulation as well as the local action is disclosed. The non-limiting examples of such excipients includes antioxidants, emollients, solvents and co-solvents, humectants, antifoaming agents, surfactants, film forming agents, preservatives and wetting agents.

[0072] In yet another embodiment, for sustained-release drug delivery system according to the present invention, the drug carrier may be a penicillin bottle, an ampule, a fillable injector, a spray bottle, or an aerosol bottle. Further, the system is plugged with a stopper and sealed with a cover to obtain the sustained-release of the active ingredient; wherein, in the case of the aerosol bottle, the stock solution is added first and the bottle is then charged with a propellant and sealed. Appropriate vessels and spray devices are available to one of skill in the art by referring to "Remington's Pharmaceutical Sciences."

[0073] In the present disclosure certain aspects is directed to a method of treating pain comprising the administration of a polymeric film forming spray formulation which is applied topical via the utilization of a spray device.

[0074] In certain embodiments present invention is directed to a topical polymeric film forming composition, comprising compounds of bupivacaine dispersed in a solvent together with a film forming polymer, which also acts as a permeation enhancer and improves or enhances the bioavailability of the drug and release the compound of bupivacaine in sustained manner. Addition the composition will have a lubricant, polymeric vehicle, preservative, sweetening agent and other excipient suitable for the spray formulation. This formulation being capable of being sprayed as a unit dose onto the site of pain via the use of a pump spray to provide droplets having a diameter from about 0.5 to about 1000 microns. In certain preferred embodiments, the topical polymeric film forming composition, when sprayed releases about 0.01% to about 50% of the active agent within the initial 1 to 5 hours of its application.

[0075] In an embodiment the permeation enhancers used for the spray formulation is selected from a group comprising isopropyl myristate, oleic acid, capric acid, lauric acid, Lauric acid, propylene glycol, diethylene glycol mono ethyl ether, methyloleate, lysophosphatidylcholine, phosphatidylcholine, cyclodextrin, dextran sulfate, polysorbate 80, ethanol, n - methyl - 2 - pyrrolidone, sodium lauryl sulfate, polyoxyl cetostearyl ether, polyoxyl oleyl ether, polyoxyl lauryl ether or a combination thereof and the like.

[0076] In certain embodiments, the formulation provides a compound of Formula I or Formula II or Formula III or Formula IV with dose ranging from about 5 mg to 2 gm or 5 mg to about 100 mg, or from about 1 mg to about 75 mg compound of bupivacaine, sprayed as a unit dose onto the skin, to provide a film surface area from about 1 cm² to about 40 cm² per spray. The unit dose may be from 1 to about 20 sprays per application of the unit dose onto the surface. In specific embodiments, the active agent comprises from 1 to 75 mg of formula II preferably 70mg or 71 mg or 72 mg or 73 mg or 74 mg or 75mg. The unit dose containing the bupivacaine may be, e.g., 73 mg, and the dose may be administered as 73 mg/ml per spray.

[0077] In certain embodiments, present invention provides a method of treating different types of pains, by spraying a unit dose of a topical polymeric film forming composition comprising a

therapeutically effective amount of a local anesthetic (one of the compound of bupivacaine active salt forms or mixtures, exemplified in formula II) dispersed in a suitable solvent together with a film forming polymer in an amount from about 2% to about 80%, by weight or 2% to 70% by weight (for examples 70% by weight) along with other excipient such as lubricant, polymeric vehicle, preservative and sweetening agent.

[0078] The formed film is sufficiently stable to provide a drug release to up to 24 hours. The polymeric solution is sprayed local to the site of action as a liquid and forms an almost invisible film in situ by volatile solvent evaporation. The film may be peelable and/or non-peelable in nature. The film is breathable, and microporous. It may be bioadhesive and mucoadhesive. The film may be non-greasy and non-sticky.

[0079] In an embodiment the pharmaceutical composition of present invention comprises local anesthetic along with pharmaceutically acceptable excipients selected from ethanol, Kolliphor RH40, PVP K30, sodium hyaluronate, sodium benzoate, povidone, mannitol, colloidal silicon dioxide, croscarmellose sodium, saccharin sodium dehydrate, citric acid monohydrate, xylitol, peppermint flavor, water and labrasol.

[0080] In an embodiment the lozenge composition of present invention comprises bupivacaine glyceryl dilauryl fumarate, povidone, mannitol, colloidal silicon dioxide, croscarmellose sodium, caprylocaproyl polyoxylglycerides 8, saccharin sodium dihydrate, citric acid monohydrate, peppermint flavor, magnesium stearate, sodium benzoate and dehydrated alcohol.

[0081] In certain embodiment the lozenge composition includes bupivacaine glyceryl dilauryl fumarate 9.70% (w/w), povidone 6.70%(w/w), mannitol 74.10% (w/w), colloidal silicon dioxide 6.70%(w/w), croscarmellose sodium 0.10%(w/w), saccharin sodium dihydrate 0.30 %(w/w), citric acid monohydrate 0.50%(w/w), peppermint flavor 0.70%(w/w), magnesium stearate 1.20%(w/w) and dehydrated alcohol.

[0082] In certain embodiment the lozenge composition includes bupivacaine glyceryl dilauryl succinate 9.70% (w/w), povidone 6.70%(w/w), mannitol 74.10% (w/w), colloidal silicon dioxide 6.70%(w/w), croscarmellose sodium 0.10%(w/w), saccharin sodium dihydrate 0.30 %(w/w), citric acid monohydrate 0.50%(w/w), peppermint flavor 0.70%(w/w), magnesium stearate 1.20%(w/w) and dehydrated alcohol.

[0083] In certain embodiment the lozenge composition includes bupivacaine glyceryl dicapryl fumarate 9.70% (w/w), povidone 6.70%(w/w), mannitol 74.10% (w/w), colloidal silicon dioxide 6.70%(w/w), croscarmellose sodium 0.10%(w/w), saccharin sodium dihydrate 0.30 %(w/w), citric acid monohydrate 0.50%(w/w), peppermint flavor 0.70%(w/w), magnesium stearate 1.20%(w/w) and dehydrated alcohol.

[0084] In certain embodiment the lozenge composition includes bupivacaine glyceryl dicapryl succinate 9.70% (w/w), povidone 6.70%(w/w), mannitol 74.10% (w/w), colloidal silicon dioxide 6.70%(w/w), croscarmellose sodium 0.10%(w/w), saccharin sodium dihydrate 0.30 %(w/w), citric acid monohydrate 0.50%(w/w), peppermint flavor 0.70%(w/w), magnesium stearate 1.20%(w/w) and dehydrated alcohol.

[0085] In an embodiment the spray formulation for topical or local application include bupivacaine glyceryl dilauryl fumarate, caprylocaproyl polyoxylglycerides 8, sodium hyaluronate, PVP K30, sodium benzoate, xylitol, and purified water.

[0086] In certain embodiment the spray formulation for topical or local application include bupivacaine glyceryl dilauryl fumarate 7.3% (w/w), caprylocaproyl polyoxylglycerides 8 70 % (w/w), sodium hyaluronate 0.1% (w/w), PVP K30 0.1% (w/w), sodium benzoate 0.1% (w/w), xylitol 0.1% (w/w) and purified water.

[0087] In certain embodiment the spray formulation for topical or local application include bupivacaine glyceryl dilauryl succinate 7.3% (w/w), caprylocaproyl polyoxylglycerides 8 70 % (w/w), sodium hyaluronate 0.1% (w/w), PVP K30 0.1% (w/w), sodium benzoate 0.1% (w/w), xylitol 0.1% (w/w) and purified water.

[0088] In certain embodiment the spray formulation for topical or local application include bupivacaine glyceryl dicapryl succinate 7.3% (w/w), caprylocaproyl polyoxylglycerides 8 70 % (w/w), sodium hyaluronate 0.1% (w/w), PVP K30 0.1% (w/w), sodium benzoate 0.1% (w/w), xylitol 0.1% (w/w) and purified water.

[0089] In certain embodiment the spray formulation for topical or local application include bupivacaine glyceryl dicapryl fumarate 7.3% (w/w), caprylocaproyl polyoxylglycerides 8 70 % (w/w), sodium hyaluronate 0.1% (w/w), PVP K30 0.1% (w/w), sodium benzoate 0.1% (w/w), xylitol 0.1% (w/w) and purified water.

[0090] In an embodiment present invention discloses one or more dosage form suitable for management and treatment of pain. In another embodiment pharmaceutical composition is formulated into dosage forms such as lozenge/troches, tablets, chewable tablets, buccal tablets/pastes and sublingual drops/sprays, capsule, mucoadhesive patches, suspension, dispersion, gels, cream, ointments, sprays, dermal patches, transcutaneous patches, implant and others. Other well-known pharmaceutical formulation known in the art can be suitable adopted for formulating the compounds of present invention.

[0091] In another embodiment present invention discloses a pharmaceutical composition with modified release criteria such as extended/prolonged release formulation, Immediate release, sustained release, delayed/lapsed release formulation and or multiphasic release formulation such as (biphasic or pulsatile), targeted release and immediate release. In another embodiment the formulation can be a combination of immediate and sustained release, or it can be immediate and lapsed release formulation. In another embodiment the pharmaceutical composition is formulated to releases sufficient therapeutic does of compound of the invention from the composition immediately within 1, 2, 5, 10, 15, 20, 30, 60 minutes of oral administration. In yet another aspect sustained formulations releases the compounds of the invention over a time period for example up to 5minutes, 25 minutes, 55 minutes, preferably up to 60 minutes, up to 90 minutes or up to 100 minutes, up to 5 hours or up to 10 hours or up to 24 hours or up to 48 hours.

[0092] In another embodiment present invention provides a topical formulation containing compound of the present invention, and a vehicle. The vehicle usually contains water, oil, alcohol or propylene glycol mixed with preservatives, emulsifiers, absorption promoters and fragrances.

[0093] In an embodiment present invention provides a film forming systems comprising the compound of the present invention for topical and transdermal drug delivery.

[0094] In an embodiment the present invention provides an targeted and extended duration pharmaceutical formulations such as liposomes, microspheres, micelles implantable drug depot , hydrophobic based polymer particles such as Poly(lactic-co-glycolic acid) microspheres, and solid polymers like Poly(sebacic-co-ricinoleic acid). In one embodiment the polymers are used for encapsulation of the compound of bupivacaine according to the present invention in a biodegradable carrier agent to provide a system for prolonged release, and hence extended

duration of action. As long as the active agent binds to the sodium channel protein, nerve transmission is stopped, and analgesia is effective. Without encapsulation, delivery of large doses of local anesthetic agents could be lethal. In yet another embodiment, the pharmaceutical composition along with biodegradable polymer (s), and the active ingredients may comprise surfactants, excipients, or other ingredients or combinations thereof. The non-limiting examples of biodegradable polymer includes poly (lactic acid coglycolide) (or poly (lactic acid coglycolic acid)) or poly (orthoester), D-lactide, D, L-lactide, L-lactide, D, L-lactide-caprolactone, and D, L-lactide coglycolide cocaprolactone or combinations thereof.

[0095] In other embodiments, the depot may comprise a biodegradable biopolymer that can provide immediate or sustained release of active ingredient. Non-limiting examples of biopolymers suitable for sustained release include, poly (α -hydroxy acid), poly (lactide coglycolide) (PLGA), polylactide (PLA), polyglycolide (PG), poly (α -hydroxy acid) Polyethylene glycol (PEG) conjugate, polyorthoester (POE), polyaspirin, polyphosphagen, collagen, starch, gelatinized starch, hyaluronic acid, chitosan, gelatin, alginate, albumin, fibrin, α -tocopheryl acetate, d -Vitamin E analogs such as alpha tocopheryl succinate, D, L-lactide, or L-lactide, -caprolactone, dextran, vinyl pyrrolidone, polyvinyl alcohol (PVA), PVA-g-PLGA, PEGT-PBT Polymer Polyactive), PEO-PPO-PAA copolymer, PLGA-PEO-PLGA, PEG-PLG, PLA-PLGA, poloxamer 407, PEG-PLGA-PEG triblock copolymer, SAIB (sucrose acetate isobutyrate), caprylocaproyl polyoxylglycerides (labrasol), lauroyl polyoxylglycerides (gelucire 44/14), linoleoyl polyoxylglycerides (labrafil M2125CS), oleoyl polyoxylglycerides (labrafil M1944CS) and stearyl polyoxylglycerides (gelucire 50/13). LD₅₀ values of gelucire 44/14, labrasol, and labrafil M1944CS, polyvinyl alcohol, polyvinyl acetate, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, dextrans, hyaluronic acid, cyclodextrins, polysaccharide polymers, polyvinyl caprolactam - polyvinyl acetate - polyethylene glycol graft copolymer or a combination of these is included.

[0096] In another embodiment, the surfactants useful for forming micelles include, but are not limited to, potassium laurate, sodium octane sulfonate, sodium decane sulfonate, sodium dodecane sulfonate, sodium lauryl sulfate, docusate sodium, decyltrimethylammonium bromide, dodecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide,

tetradecyltrimethyl-ammonium chloride, dodecylammonium chloride, polyoxyl 8 dodecyl ether, polyoxyl 12 dodecyl ether, nonoxynol 10 and nonoxynol 30. Micelle formulations can be used in the present invention either by incorporation into the reservoir of a topical or transdermal delivery system, or into a formulation to be applied to the body surface.

[0097] In an embodiment, present invention envisages a liposome drug delivery system. The liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. Examples of cationic liposomes are N-[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium liposomes are available under the tradename Lipofectin®. Examples of anionic and neutral liposomes are Avanti Polar Lipids or can be prepared using materials like phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline, dioleoylphosphatidyl glycerol, dioleoylphosphatidyl ethanolamine, among others. These materials can also be mixed with N-[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) in appropriate ratios. Methods for making liposomes are well known in the art.

[0098] In another embodiment, present invention envisages microspheres, as the drug delivery systems. Microspheres essentially encapsulate a drug or drug containing formulation. They are generally, although not necessarily, formed from lipids, preferably charged lipids such as phospholipids. Preparation of lipidic microspheres is well known in the art and described in the pertinent texts and literature.

[0099] As will be appreciated by those working in the field of pharmaceutical formulation, other suitable formulations such as ointments, creams, gels, lotions, solutions, pastes, and the like can also be formulated by selecting the known excipients.

[0100] In another embodiment, the composition is formulated into chewy or hard or caramel based lozenge, pastilles, troches, soft lozenge, center or liquid filled lozenge, power based lozenge, compressed lozenge, syrup based lozenge, granulated lozenge, buccal and sublingual tablets. The lozenges formulation of the invention will increase bioavailability, reducing gastric irritation and increase onset of action. Lozenges dosage forms are easy to administer for geriatric and pediatric patients who can't swallow tablets formulation. This formulation will help to keep the drug in contact to the oral cavity for longer time.

[00101] The oral administration formulation may be classified into rapidly disintegrating formulations for which the release of an active component from the formulations is not particularly controlled and release-controlled formulations for which the release is controlled according to the purposes by adjusting the dosage design and production method.

[00102] The composition can be a sustained release formulations wherein the release rate, release time and release site of an active component from the formulation is controlled with the purpose of reduction in the frequency of administration or reduction of side effects. The sustained release formulation may be generally produced by using an appropriate agent for sustained release.

[00103] Typically, the carrier material for lozenge preparation includes sugar such as sucrose, dextrose, etc. Recently consumers have become concerned about the excessive levels of sugar contained within their diets. This concern has caused a demand for sugar-free products, including sugar-free medications. Pharmaceutical manufacturers have attempted to find alternative carrier bases in order to provide sugar-free lozenges. One such alternative carrier is a polyhydric alcohol such as xylitol. Polyhydric alcohols are considered as a viable alternative because they provide a sweet taste will mask the bitter taste of many medicinal agents. Lozenges made from polyhydric alcohols do suffer from one serious disadvantage. They dissolve very rapidly when placed in the oral cavity. For example, a lozenge made from a xylitol-based carrier will dissolve completely within approximately 3 minutes of administration. Other polyhydric alcohols such as sorbitol or mannitol will also dissolve within 3 minutes of administration. Thus, the medicinal agents are released so rapidly that a large percentage of the dose is washed into the patients alimentary canal rather than having an opportunity to come in contact with the tissues of the oral cavity which are under treatment. Thus, it would be a valuable contribution to the art to produce polyhydric alcohol based lozenges having slower rates of dissolution within the oral cavity.

[00104] In an embodiment, non-limiting examples of excipients for preparing a compressed powder lozenge or compressed granulated lozenge, cast lozenge includes at least one diluents, at least one fillers, at least one glidants, at least one lubricants, at least one binders, at least one preservatives, at least one artificial or natural sweeteners or and at least one aroma/flavoring compounds

[00105] In an embodiment, Non-limiting examples of diluents, fillers or binder, disintegrants, sweetening agent, super disintegrants, anticaking agent absorbent, taste masking agent, antioxidant, solvent, co-solvent and other excipient are selected from the group consisting of mannitol, celluloses, lactose, starches, calcium salts, di calcium phosphate, calcium sulfate, polyvinylpyrrolidone, gelatine, sugars and sugar alcohols, microcrystalline cellulose, polyvinylpyrrolidone, polar solvent may be an alcoholic solvent such as industrial methylated spirit or isopropanol; example of glidants or lubricants includes talc, magnesium stearate, colloidal silicon dioxide, polyethyleneglycol (macrogol), and silicon dioxide. Examples of sugar-free vehicles includes mannitol, sorbitol, polyethylene glycol (PEG) 6000 and 8000 and sugar based vehicles include- sucrose, maltose, lactose, dextrose. Examples of aroma/flavoring agent compounds can be either natural or synthetic aromatic compounds including but not limited to fruit aromas, powders including but not limited to vanillin and menthol, peppermint or pharmaceutical acceptable essential oils. non-limiting examples of sweeteners includes, non-sugar sweetening agents such as aspartame, sorbitol, xylitol, isomalt, saccharin, sodium saccharin, calcium saccharin, sucralose, acesulfame-K, steviol, steviosin, mannitol, erythritol, lactitol, and sugar sweetening agents selected from the group consisting sucrose, fructose, or dextrose.

[00106] In an embodiments, the compositions are formulated as cast lozenges comprising of at least one base selected fructo-oligosaccharides, crystalline sugar, candy base, isomalt or stevia; at least one aromas selected natural aroma, essential oils such as citrus, mint oils, terpenes and sesquiterpenes, organic acids, alcohols, aldehydes, liquorice powder, menthol, peppermint oil or any fruit flavors. at least one taste enhancing ingredients such as saccharose, glutamic acid, E621 monosodium glutamate, MSG, E622 monopotassium glutamate, E623 calcium diglutamate, E625 Magnesium diglutamate); guanylic acid (a ribonucleotide) and its salts (E626 guanylic acid, E627 disodium guanylate, sodium guanylate, E628 dipotassium guanylate, E629 calcium guanylate); E630 inosinic acid, E631 disodium inosinate, E632 dipotassium inosinate, E633 calcium inosinate), E634 calcium 5'-ribonucleotides, E635 disodium 5'-ribonucleotides; E636 maltol, E637 ethyl maltol, E640 glycine and E641 L-leucine.

[00107] In an embodiment, the lozenge formulation contains compound bupivacaine in an amount of 5 mg to 2 gm per oral dosage form such as lozenge, tablet, capsule and others.

[00108] In another embodiment, the lozenge formulation contains compound of formula I or formula II or formula III or formula IV in an amount of 5 mg to 2 gms per oral dosage form.

[00109] The invention provides a pharmaceutical composition in the form of topical spray consisting essentially of: (a) pharmaceutical acceptable salts, derivatives or enantiomer of bupivacaine (b) additional excipients.

[00110] In one embodiment, active ingredients and excipients are mixed to form a sprayable topical formulation.

[00111] In another embodiment, the compounds of the invention can be generally formulated into sprays (oral, topical, thin-film, peel-forming, encapsulated, polymer based) by selecting one or more compounds of the invention with at least one pharmaceutically acceptable excipient. The non-limiting examples of excipients includes: a) solvents/ vehicles example includes organic solvents (acetone, acetic acid, acetonitrile, benzene, carbon tetrachloride, methylene chloride etc.) and inorganic solvents (liquid ammonia, liquid sulfur dioxide, sulfuric chloride and sulfuric chloride fluoride, phosphoryl chloride, dinitrogen tetroxide, antimony trichloride, bromine pentafluoride, hydrogen fluoride, pure sulfuric acid other well known in the art; b) Co-solvents example includes propylene glycol, glycerol, ethanol, low molecular weight PEGs; wetting agents/ surfactants polysorbates, sorbitan esters anionic (e.g., sodium dodecyl sulfate), cationic (e.g., trialkylammonium), zwitterionic (e.g., glycine and proteins) and nonionic (e.g., polyethylene glycol). Polyoxyethylene sorbitan monooleate (Tween 80), polyoxyethylene sorbitan monopalmitate (Tween 60), sodium oleate, polyoxyethylene stearate, potassium oleate; c) emollients: non-limiting example includes occlusive emollients such as lanolin, emulsifying ointment, and liquid paraffin; d) preservatives example includes acidic types are phenol, benzoic acid, boric acid, chloro-cresol, 9-phenyl phenol, alkyl esters of para-hydroxybenzoic acid, sorbic acid, and their respective salts, neutral preservatives include chlorobutanol, benzyl alcohol, beta-phenylethyl alcohol, methylparaben, ethylparaben, butylparaben, propylparaben, sodium benzoate, benzoic acid, or a mixture of these parabens with phenyl ethyl alcohol and other preservatives such as benzalkonium chloride, EDTA parabens, benzalkonium chloride; e) antioxidants example includes thiourea, butyl hydroxy toluene (BHT), tocopherols, ascorbic acid, sodium hyaluronate, sodium bisulphate, sodium metabisulfite; butylated hydroxytoluene; f)

antifoaming agents example includes simethicone (polymethylsiloxane), paraffin oils, organic phosphates, alcohols; g) film forming agents example includes polyvinylpyrrolidone (PVP), PVP 30, PVP 90, Kolliphor® RH 40 acrylates, acrylamides, and copolymers. carbomer or carbopol, Poloxamer (or pluronic), Polymethacrylates (Eudragits); h) humectants example includes propylene glycol, glycerol, polyethylene glycol, glycerin, mannitol. sorbitol; i) penetration enhancers examples includes terpenes, terpenoids or essential oils, pyrrolidones and azones, fatty acids and esters, fatty acids such as oleic acid (perturbation of intracellular lipids), a zone (1-dodecylazacycloheptan- 2-one) (increasing fluidity of intracellular lipids), and surfactants such as sodium lauryl sulfate (expansion of intracellular spaces) alcohols, glycols, glycerides, surfactants and phospholipids; j) solubilizers examples includes SLS (Sodium lauryl sulphate), polyhydric alcohols like propylene glycol or polyethylene glycols, Kolliphor® RH 40 vitamin E TGPS (tocopheryl polyethylene glycol 100 succinate), Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol (saturated polyglycolized C8- C10 glyceride); k) plasticizers examples includes triethyl citrate, dimethyl isosorbide, castor oil, polyhydric alcohols such as propylene glycol or polyethylene glycol; l) buffers examples includes sodium phosphate buffer, sodium citrate buffer, citric acid buffer; bioadhesive polymers examples includes CMC sodium, Carbopol, Polycarbophil, Tragacanth, Sodium alginate, HPMC, HPMC K 100M, HPMC E5, Gum karaya, gelatin, guar gum, pectin, acacia, chitosan, hydroxypropyl cellulose, polyacrylates and starch.

[00112] In some embodiment, the spray formulations as disclosed may deliver the compounds of bupivacaine in an amount (per spray) of about 0.05 mg to about 500 mg or 0.1 to about 100 mg.

[00113] In one embodiment, present invention discloses a transdermal patch wherein the drug reservoir comprises a polymeric matrix of a pharmaceutically acceptable adhesive material that serves to affix the system to the skin during drug delivery. Examples of suitable adhesive materials include, but are not limited to, the following: polyethylenes; polysiloxanes; polyisobutylenes; polyacrylates; polyacrylamides; polyurethanes; plasticized ethylene-vinyl acetate copolymers; and tacky rubbers such as polyisobutene, polybutadiene, polystyrene-

isoprene copolymers, polystyrene-butadiene copolymers, and neoprene (polychloroprene). Preferred adhesives are polyisobutylenes. Alternatively, the reservoir may be a hydrogel reservoir. Hydrogels are macromolecular networks that absorb water and thus swell but do not dissolve in water. Hydrogels comprise of crosslinked hydrophilic polymers such as a polyurethane, a polyvinyl alcohol, a polyacrylic acid, a polyoxyethylene, a polyvinylpyrrolidone, a poly(hydroxyethyl methacrylate) (poly(HEMA)), or a copolymer or mixture thereof. Particularly preferred hydrophilic polymers are copolymers of HEMA and polyvinylpyrrolidone.

[00114] In an embodiment the material used for the backing layer are generally derived from synthetic polymers (e.g., polyester, polyethylene, polypropylene, polyurethane, polyvinylidene chloride, and polyether amide), natural polymers (e.g., cellulosic materials), or macroporous woven and nonwoven materials.

[00115] Certain specific aspects and embodiments of the invention will be explained in more detail with reference to the following examples, which are provided for purposes of illustration only and should not be construed as limiting the scope of the invention in any manner.

[00116] **Non-limiting Examples:**

[00117] **Lozenge composition of compounds of Formula II:**

[00118] In a specific embodiment the active ingredient is the compound of bupivacaine, more specifically formula II (Bupivacaine glyceryl dilauryl fumarate), is formulated as lozenges to be dissolved slowly in the oral cavity. Each lozenge contains 73.08 mg of Bupivacaine glyceryl dilauryl fumarate. The pharmaceutically acceptable excipients or the inactive ingredients are Mannitol, Povidone, Croscarmellose sodium, Citric acid monohydrate, Saccharin sodium dihydrate, Silicon dioxide, Peppermint flavor 501500 TP0504, Magnesium stearate and dehydrated alcohol. The qualitative composition for product formulation was provided in Tables 1 and 2.

[00119] **Table 1: Composition of Bupivacaine dilauryl glyceryl fumarate Lozenges**

Ingredients	Quantities	
	mg/Unit	% w/w
Bupivacaine glyceryl dilauryl fumarate	73.08	9.70

Povidone	50.00	6.70
Mannitol	555.92	74.10
Colloidal silicon dioxide	50.00	6.70
Croscarmellose sodium	0.75	0.10
Saccharin sodium dihydrate	2.50	0.30
Citric acid monohydrate	3.75	0.50
Peppermint flavor 501500 TP0504	5.00	0.70
Magnesium stearate	9.00	1.20
Dehydrated alcohol	QS	-
Lozenge weight	750.00	100.00

[00120] Table 2: Batch Formula of Bupivacaine glyceryl dilauryl fumarate Lozenges

S. No.	Ingredients	mg/unit	Quantity per Lot (g)
1	Bupivacaine glyceryl dilauryl fumarate	73.08	14.616
2	Povidone	50.00	10.000
3	Mannitol	555.92	111.184
4	Colloidal silicon dioxide	50.00	10.000
5	Croscarmellose sodium	0.75	0.150
6	Saccharin sodium dihydrate	2.50	0.500
7	Citric acid monohydrate	3.75	0.750
8	Peppermint flavor 501500 TP0504	5.00	1.000
9	Magnesium stearate	9.00	1.800
10	Dehydrated Alcohol [#]	160.00	32.00
Total		750.00	150.000

[#] Dehydrated alcohol was removed during manufacturing process.

[00121] Formulation development was initiated with the inactive ingredients selected based on the literature and prior use in similar dosage form. Various polymers and disintegrant at different concentrations were evaluated for dissolution profile and impurity profile of drug product.

[00122] The physical and chemical parameters of lozenge composition manufactured with povidone (polymer) and croscarmellose sodium (disintegrants) were found satisfactory.

[00123] Wet granulation was selected as the manufacturing process considering the physical properties of drug substance to achieve desired flow properties of blend. Dehydrated alcohol was selected as a granulating solvent keeping in view of drug substance solubility.

[00124] The flow of blend and its compressibility into lozenges were found satisfactory using wet granulation method.

[00125] **Manufacturing Process and Process Controls**

Step-1: Dispensing: Dispensed all the required raw materials using a calibrated weighing balance.

Step-2: Granulation fluid: Bupivacaine glyceryl dilauryl fumarate was dissolved in 24 g (75% of total alcohol required for batch manufacturing) of dehydrated alcohol under stirring.

Step-3: Sifting: Sifted povidone, mannitol, colloidal silicon dioxide, saccharin sodium dihydrate, citric acid monohydrate, croscarmellose sodium through #30 ASTM sieve.

Step-4: Dry mixing: The sifted step 3 raw materials were mixed for 15 minutes.

Step-5: Granulation: Granulated step 4 blend with step 2 granulating fluid. Rinsed the container with remaining 6g of dehydrated alcohol and used as granulating solution.

Step-6: Drying: The wet mass of step 5 was dried at 45°C for 60 min.

Step-7: Sizing: The dried material of step 6, were sifted using #30 ASTM sieve.

Step-8: Sifting: Extra-granular materials i.e., peppermint flavor and magnesium stearate were passed through #60 ASTM sieve

Step-9: Lubrication: The sifted material of step 8 was added to step 7 and blended for 5 minutes.

Step-10: Compression: The lubricated blend of step 9 was compressed into lozenges with suitable punches on compression machine.

Step-11: Packaging: The compressed lozenges were packed along with silica gel bags, in 40 cc HDPE Bottle / 33 mm CRC at 15 lozenges per bottle.

Table 3: Chemical Parameters of Lozenges

Tests	Tentative Specification	Initial	40°C/75% RH				30°C/65% RH			25°C/60% RH		
			1M	1.5M	3M	6M	3M	6M	12M	1.5M	3M	6M
Description	Round, white to off white standard concave lozenge plain on both sides.	Complies	Complies	yellow, round shaped tablet	yellow, round shaped tablet	yellow, round shaped tablet	Complies	yellow, round shaped tablet	Light grey round shaped Tablets	Complies	Complies	Complies
Water content (%)	For information only	1.47	1.48	1.06	1.30	0.96	1.30	0.85	1.1	0.88	1.6	0.84
Assay (% w/w)												
Bupivacaine	90.0 – 110.0% w/w	99.9	100.3	97.3	97.7	98.7	98.6	100.1	98.4	98.7	100.2	100.2
Glyceryl dilauryl fumarate	90.0 – 110.0% w/w	100.1	98.2	90.6	82.2	63.5	93.8	93.0	83.1	97.1	97.5	95.4
Related Substances (%)												
Unspecified impurity at RRT 0.17	NMT 0.5%	BDL	0.37	0.64	BDL	7.24	BDL	1.28	2.12	0.12	BDL	0.65
Unspecified impurity at RRT 0.18	NMT 0.5%	BDL	3.38	5.74	15.70	26.73	3.97	8.27	13.31	1.57	2.31	4.03
Unspecified impurity at RRT 0.30	NMT 0.5%	BDL	BDL	BDL	BDL	0.13	BDL	BDL	0.09	BDL	BDL	BDL
Unspecified impurity at RRT 0.52	NMT 0.5%	BDL	BDL	BDL	BDL	0.06	BDL	BDL	0.06	BDL	BDL	BDL
Unspecified impurity at RRT 0.84	NMT 0.5%	BDL	0.10	0.03	BDL	0.04	BDL	0.04	0.36	0.03	BDL	BDL
Unspecified impurity at RRT 1.15	NMT 0.5%	0.11	0.10	0.10	0.10	0.10	0.12	0.10	0.1	0.12	0.12	0.10
Unspecified impurity at RRT 1.34	NMT 0.5%	0.37	0.35	0.34	0.34	0.34	0.40	0.31	0.33	0.38	0.41	0.35
Total Impurities	NMT 2.0 %	0.48	4.72	6.85	16.14	34.60	4.09	10.00	17.97	2.22	2.84	5.13

Table 2: Dissolution data of Lozenges

Time Hour s)	Dissolution Methodology: Medium: pH 6.8 Phosphate Buffer with 0.2% SLS, Speed: 50 RPM, Volume: 900 mL, Apparatus - Paddle																							
	Initial		40°C/75% RH								30°C/65% RH						25°C/60% RH							
			1M		1.5M		3M		6M		3M		6M		12M		1 Month		1.5M		3M		6M	
	Bupivacaine	Glyceryl dilauryl fumarate	Bupivacaine	Glyceryl dilauryl fumarate	Bupivacaine	Glyceryl dilauryl fumarate	Bupivacaine	Glyceryl dilauryl fumarate	Bupivacaine	Glyceryl dilauryl fumarate	Bupivacaine	Glyceryl dilauryl fumarate	Bupivacaine	Glyceryl dilauryl fumarate	Bupivacaine	Glyceryl dilauryl fumarate	Bupivacaine	Glyceryl dilauryl fumarate	Bupivacaine	Glyceryl dilauryl fumarate	Bupivacaine	Glyceryl dilauryl fumarate	Bupivacaine	Glyceryl dilauryl fumarate
	0.5	10	6	ND	ND	14	14	9	5	10	9	8	9	8	11	11	7	9	6	8	3	7	4	7
1.0	32	28	45	41	34	34	26	17	18	11	24	19	24	20	30	21	27	23	19	13	21	15	19	15

1.5	50	48	63	58	53	53	42	31	39	23	38	33	39	34	46	35	45	41	31	25	36	30	35	30
2.0	67	63	83	76	70	70	59	45	51	31	53	48	56	50	63	49	61	58	42	36	48	42	50	44
3.0	94	92	99	92	92	92	90	73	81	52	83	77	83	78	90	73	90	89	67	65	78	70	77	71
4.0	101	100	99	94	99	99	97	80	95	62	97	95	96	93	96	79	101	99	92	89	94	92	95	91

[00126] The composition is formulated as a liquid dosage form considering compound of bupivacaine characteristics and route of administration. The excipients are selected based on dosage form, physicochemical characteristics of active ingredient, stability and compatibility issues. To reduce dose heterogeneity and to improve ease of administration the formulation is packed in a sprayable device to deliver uniform dose from the bottle. The device comprises of an actuator with long cannula which enables to deliver the product to the affected area. In one of the embodiments, the composition may have one or more polymer in the formulation to form a film upon administration and for sustained release of the active ingredient via compound of bupivacaine. Preservative and sweetening agents are included to increase microbiological stability and dose adherence by the patient.

[00127] Table 8: Composition of Bupivacaine dilauryl glyceryl fumarate oral spray

Quantitative composition		
Ingredients	mg/ml	% w/w
CLX-SYN-G161-C11	73	7.3
Caprylocaproyl polyoxylglycerides 8	700	70
Sodium hyaluronate	1.0	0.1
PVP K30	1.0	0.1
Sodium Benzoate	1.0	0.1
Xylitol	1.0	0.1
Purified water	QS to 1 mL	QS to 100%

[00128] Table 9: Composition of Bupivacaine dilauryl glyceryl fumarate oral spray

Ingredient	mg/ ml	% w/w
CLX-SYN-G161-C11	73	7.3

Caprylocaproyl polyoxylglycerides 8	700	70
Sodium hyaluronate	10	0.1
PVP K30	10	0.1
Sodium Benzoate	10	0.1
Xylitol	10	0.1
Purified water	QS to 1 mL	QS to 100%

[00129] Manufacturing procedure of the spray formulation

Step 1: Solution A is prepared with the addition of 25% of batch quantity of purified water into a compounding vessel and dissolving PVP K-30, sodium benzoate sodium hyaluronate, and Xylitol.

Step 2: Solution B is prepared with the addition of batch quantity of Caprylocaproyl polyoxylglycerides 8 in compounding vessel and dissolving Bupivacaine dilauryl glyceryl fumarate (CLX-SYN-G161-C11) for 1 hour. The solution A is added to Solution B and stirring is continued until the drug is completely dissolved. Volume is made up to batch size with the remaining quantity of purified water

Step 3: The resultant solution is filtered using 0.45 μ PTFE filter under vacuum. This filtered solution is filled into 50 cc USP type-1 glass vials with fill volume of 50 ml and pump is crimped.

[00130] Container Closure Systems for Spray formulation:

[00131] It is necessary that the container/closure be integral to ensure that the product is within specifications throughout its shelf-life. In particular, the sterility of the product needs to be assured. The sterility assurance is maintained through the container closure integrity of the pump/vial configuration.

[00132] Table 10: Composition of bupivacaine dilauryl glyceryl fumarate

AC161C1141035E			
S. No.	Ingredients	Qty Per mL (w/v)	Qty Per 100 mL (w/v)
1	CLX-SYN-G161-C11	73 mg (74.55 mg)	7.3 g (7.455 g)
2	Labrasol	0.7 mL	70.0 mL
3	PVP K30	1.0 mg	100.0 mg

4	Sodium hyaluronate	1.0 mg	100.0 mg
5	Water	Q.s to 1 mL	Q.s to 100 mL

[00133] Table 11: Composition of bupivacaine dilauryl glyceryl fumarate

AC161C1141036D to AC161C1141040D					
Ingredients	036D	037D	038D	039D	040D
CLX-SYN-G161-C11	58.4 mg	58.4 mg	58.4 mg	58.4 mg	58.4 mg
Labrasol	0.7 mL	0.7 mL	0.7 mL	0.7 mL	0.7 mL
PVP K30	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg
Sodium hyaluronate	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg
Sodium Benzoate	1.0 mg			1.0 mg	1.0 mg
Xylitol		2.5 mg		2.5 mg	2.5 mg
Peppermint Flavor			1.0 mg		1.0 mg
Water	Q.s to 1 mL	Q.s to 1 mL	Q.s to 1 mL	Q.s to 1 mL	Q.s to 1 mL

[00134] Table 12: Composition of bupivacaine dilauryl glyceryl fumarate

AC161C1141041D			
S. No.	Ingredients	Qty Per mL (w/v)	Qty Per 100 mL (w/v)
1	CLX-SYN-G161-C11	58.4 mg (59.64 mg)	5.84 g (5.964 g)
2	Ethanol	58.4 mg	5.84 g
3	Kolliphor RH40	700 mg	70.0 g
4	PVP K30	1.0 mg	100.0 mg
5	Sodium hyaluronate	1.0 mg	100.0 mg
6	Sodium Benzoate	1.0 mg	100.0 mg
7	Xylitol	2.5 mg	250.0 mg
8	Peppermint Flavor	1.0 mg	100.0 mg
9	Water	Q.s to 1 mL	Q.s to 100 mL

Methods of Treatment

[00135] In an embodiment, the effective dosages and sites of administration of pharmaceutical composition of the present invention can be at the site or adjacent to the sites of pain to provide the much-needed relief. The composition can be administered once a day, for quick and temporary relief from pain, or more frequently, in a day, to maintain pain relief over a longer period.

[00136] In an embodiment the composition is applied once or more than once topically to a site of pain or adjacent that region. The dosing is applied to the region or area of pain in order to effect

pain relief while avoiding the side effects associated with systemic delivery. The compounds are applied such that the dosage is sufficient to provide an effective dose in the painful areas to eliminate pain and other unpleasant sensations associated with such pain.

[00137] In an embodiment the compositions according to the present disclosure when administered by spraying is done using commercially available spray devices and especially metered spray devices for treating pain.

[00138] In an embodiment the composition can be administered intradermally, using, for example, an insulin syringe. Care is taken to administer the smallest dose possible, and in all cases, topical or intradermal, care should be taken to avoid systemic levels or local toxicity.

[00139] In an embodiment the composition can be applied topically to a site of pain or adjacent to that region using transdermal patches to effect pain relief while avoiding the side effects associated with systemic delivery. The compounds are applied such that the dosage is sufficient to provide an effective dose in the painful areas to eliminate pain and other unpleasant sensations associated with such pain.

[00140] In an embodiment the formulations can be used to treat nociceptive pain, neuropathic pain, or central sensation or generalized pain or a mixed type of pain and others as disclosed in this specification.

INCORPORATION BY REFERENCE

[00141] All publications and patents mentioned herein, including those items listed above, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

CLAIMS:

1. A pharmaceutical composition comprising a local anesthetic or a salt or a derivative or a mixture thereof, formulated for local administration for use in the treatment of pain.
2. The pharmaceutical composition as claimed in claim 1 comprises
 - (a) 0.1% - 70% (w/w) local anesthetic.
 - (b) 30% - 99.9% (w/w) pharmaceutically acceptable excipients.
3. The pharmaceutical composition as claimed in claim 1 wherein, the local anesthetic is selected from bupivacaine glyceryl dilauryl fumarate, bupivacaine glyceryl dilauryl succinate, bupivacaine glyceryl dicapryl succinate or bupivacaine glyceryl dicapryl fumarate.
4. The pharmaceutical composition as claimed in claim 2 wherein, the composition is formulated into oral lozenge or oral chewable tablet or oral dispersible tablet or mucoadhesive tablet or buccal tablet for oral administration.
5. The pharmaceutical composition as claimed in claim 2 wherein, the composition is formulated into a topical spray, preferably into a polymeric film forming spray.
6. The pharmaceutical composition as claimed in claim 4 wherein, the composition is formulated into a sustained release formulation, extended release, modified release or an immediate release formulation.
7. The pharmaceutical composition as claimed in claim 2, wherein, the local anesthetic is present in an amount of 5 mg to 100 mg, or 5 mg to 75 mg, preferably 5 mg, 10 mg, 25 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg or 75 mg per unit dosage form.
8. The pharmaceutical composition as claimed in claim 6 is formulated to provide local anesthetic effect for at least 20 minutes, at least 40 minutes, at least 60 minutes, at least 80 minutes, at least 100 minutes or at least up to about 2 hours, at least up to 4 hours, at least up to 8 hours, or at least up to 10 hours.
9. The pharmaceutical composition as claimed in claim 2, wherein, the pharmaceutical acceptable excipient is selected from a binder, filler, lubricant, polymers, solubilizing

agent, surfactant, co-surfactant, solvent, co-solvent, preservatives, antioxidants, sweetening agent, flavoring agent, disintegrants, super disintegrants, taste masking agent, polymer which enhances permeation, bioavailability and retention time of the drug or a combination thereof.

10. The pharmaceutical composition as claimed in claim 4, wherein, the lozenge formulation comprises 5mg to 100 mg of local anesthetic and pharmaceutically acceptable excipient selected from mannitol, povidone, croscarmellose sodium, citric acid monohydrate, saccharin sodium dihydrate, colloidal silicon dioxide, peppermint flavor, magnesium stearate and dehydrated alcohol.
11. The pharmaceutical composition as claimed in claim 10, wherein, the lozenge formulation comprises 73.08 mg of bupivacaine glyceryl dilauryl fumarate and pharmaceutically acceptable excipient selected from mannitol, povidone, croscarmellose sodium, citric acid monohydrate, saccharin sodium dihydrate, colloidal silicon dioxide, peppermint flavor, magnesium stearate and dehydrated alcohol.
12. The pharmaceutical composition as claimed in claim 5, wherein, the spray formulation comprises 5-100 mg/ml of local anesthetic and pharmaceutically acceptable excipient selected from film forming polymer, preservative, sweetening agent, propelling agent and dispensing agent.
13. The pharmaceutical composition as claimed in claim 12, wherein, the spray formulation comprises 73 mg/ml of bupivacaine glyceryl dilauryl fumarate, caprylocaproyl polyoxylglycerides 8, sodium hyaluronate, PVP K30, sodium benzoate, xylitol, and purified water.
14. The pharmaceutical composition as claimed in claim 10, wherein, the bupivacaine glyceryl dilauryl fumarate is formulated as a sustained release formulation.
15. The pharmaceutical composition as claimed in claim 12, is formulated packed in a sprayable device to deliver uniform dose of bupivacaine glyceryl dilauryl fumarate.
16. The pharmaceutical composition as claimed in any of the preceding claims is used in the treatment of pain.

17. The pharmaceutical composition as claimed in claim 16, wherein, the pain is selected from the group consisting of chronic or acute pain, nociceptive pain, general pain, neuropathic pain, inflammation mediated pain, sports pain, dental pain, wound pain, burn pain, bone pain, cancer pain, chemotherapy induced neuropathy such as stomatitis and mucositis, musculoskeletal pain, ulcers, cankers surgical pain, viral rashes, HIV rashes, post-herpetic neuralgia, and sciatica pain.
18. A method of treating pain comprises administering the pharmaceutical composition as claimed in any one of the preceding claims by local administration of the composition.
19. The method as claimed in claim 18, wherein, the local administration is oral administration, spray, parenteral, depot or topical administration.