Chapter 7

Novel pharmaceutical topical formulation containing major part of hydrophobic liquid:
7.0 Novel pharmaceutical topical formulation containing higher proportion of hydrophobic liquid

7.1 Field of the invention:

The present invention relates to a novel pharmaceutical topical formulation containing high proportion of hydrophobic liquid ranging from 60% by weight to 92% by weight based on the total weight of the formulation and solidifying agent such as glyceryl behenate along with other auxiliary solidifying excipients.

Additionally, the present invention also relates to a method of incorporating the higher proportion of hydrophobic liquid in pharmaceutical formulation to produce a highly stable formulation.

Furthermore, the present invention is also related to incorporating hydrophobic liquid containing drug in the pharmaceutical formulation to yield stable formulation with improved permeation.

7.2 Description of the related art:

Incorporation of large amount of hydrophobic liquid into a semisolid product is a challenging task because of the problem of phase separation. Hydrophobic liquid can be selected from the group or combination of groups of oils and eutectic mixtures. Preferably, the oils used are essential oils that show improved permeation of the active ingredients via skin.

Essential oils are widely used in semi solid dosage form as counter irritant, anti-inflammatory, analgesic and penetration enhancer. Essential
oil reduces inflammation by acting as antioxidants and interfering with leukocyte (white blood cell) activation.¹

A US Patent 6444238 describes the method for preparing a pain relief composition using mixture of aloe vera oil, eucalyptus oil, lemon oil, orange oil, peppermint oil and rosemary oil.⁵

Saify et al. reported that eucalyptus oil (1, 8-cineole) caused almost 83 fold increase in 5-fluorouracil permeability in excised rat skin.⁶ The mode of action of drug permeation acceleration was described by combined process of partition and diffusion.⁷ Cardamom essential oil (principally constituted of monocyclic terpenes) showed dramatic increase of the cutaneous permeation of the piroxicam via rat skin.⁷

A patent EP 0069385 describes eucalyptol or 1,8-cineole, as penetration enhancer for various drugs.⁸ A US patent 5079008 disclosed a monolithic system in which drug is dispersed within an adhesive matrix, together with essential oil as transdermal permeation enhancer.⁹

An International publication No. WO 91/05529 demonstrates the use of components of essential oils in pharmaceutical compositions to be administered by transdermal way.¹⁰ The transdermal system is suggested to be suitable for release of any drug, including steroids and nonsteroidal anti-inflammatory drugs.
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An International publication No. WO 98/37871 concerns the use of terpenes as permeation enhancer for transdermal systems containing testosterone. A patent No. RU2157697 describes compositions based on essential oils for prophylaxis and treatment of gastro enteric and dermatological disorders.

Essential oils can dissolve number of drugs including non-steroidal anti-inflammatory and antihypertensive drugs. The solubility of indomethacin, diclofenac, ketorolac, piroxicam, meloxicam, tenoxicam, ketoprofen, flurbiprofen, ibuprofen, nimesulide, naproxen, rofecoxib, celecoxib, salicylic acid, captopril, and other such substances increases between 2 and 25 fold. Essential oil used in the present investigation includes eucalyptus oil, clove oil, peppermint oil, methyl salicylate, ajwain oil, anise oil, black pepperrose oil, cardamom seed oil, carrot seed oil, chamomile oil, calamus root, cinnamon oil, citronella oil, coriander oil, cranberry seed oil, cumin oil/black seed oil, dill oil, fennel seed oil, frankincense oil, geranium oil, ginger oil, lemon oil, lemongrass mugwort oil, oregano oil, pennyroyal oil, pine oil, spearmint oil, thyme oil, borneol, cinnamyl alcohol, citronelloi, geraniol, linalool, benzyl alcohol and phenylethyl alcohol. Most preferably, the essential oil used is eucalyptus oil, clove oil or methyl salicylate. Methyl salicylate is used topically as a counter-irritant and chemical vasodilator. Oils or constituents thereof may be used alone or in combination with other oils or constituents.
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Eutectic mixture is a mixture of two or more components which has a lower melting temperature than any of its constituents. The proper ratio of solids is identified from phase diagram. Camphor, menthol, thymol resorcinol, phenol or substituted phenol derivatives and another such compounds are generally used to prepare eutectic mixture. The use of eutectic mixture is known in pharmaceutical industry for the preparation of the medicated and cosmetic compositions. The major problem with the use of eutectic mixture is phase separation and therefore the eutectic mixture is incorporated in limited amount in the topical formulation. Eutectic mixture is safe, non-toxic, exhibit synergistic behavior in anti-inflammatory action of NSAIDs due to anti-inflammatory properties of camphor, antifungal action of menthol and camphor and skin penetration enhancing properties of menthol.\(^ {14} \) Kaplun-Fischoff et al. observed that menthol forms a eutectic mixture with crystalline testosterone.\(^ {15} \) The composition demonstrated a significant improvement in transdermal penetration of testosterone. According to Kaplun-Frischoff et al., menthol affects skin permeation by a dual mechanism: by forming a eutectic with the penetrating compound, thereby increasing its solubility in skin ceramides and by altering the barrier properties of the stratum corneum.\(^ {15} \)

Menthol is chemically described as (1R, 2S, 5R)-5-methyl-2-(1-methylethyl)-cyclohexanol with a molecular weight of 156.27 and melting point of 42 °C. Menthol generally has a peppermint odor. It is well known as a skin irritant.\(^ {14} \) It is widely used in many topical formulations for relief of arthritic and rheumatic pain. Natural l-menthol exerts a cooling or refreshing
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sensation due to direct interaction with cold sensitive receptors in the skin.\textsuperscript{16}

Menthol has been used as mild local anesthetic and as essential aromatic component for breath relief in obstruction and cold treatment in Hughes et al.\textsuperscript{17}

Camphor is chemically known as 1,7,7 trimethylbicyclo[2,2,1] heptanone-2 having a molecular weight of 152.24. Camphor has a high melting point (180 °C) and is a very volatile substance with strong pine-like odor that sublimes even at room temperature and pressure. Camphor is mainly used as a component in topical preparations. It is often used in nasal decongestants and aromatic compositions.

A patent No. US20060211688 discloses the method of solubilizing the non steroidal anti inflammatory drugs using the eutectic mixture of at least two components selected from camphor, menthol and thymol.\textsuperscript{18} But in all the examples the incorporation of the eutectic mixture was limited from 5 to 15 % w/w only.

A patent No. US5013726 describes a lotion containing methyl salicylate, camphor and menthol.\textsuperscript{19} Menthol and camphor is widely used in topical formulations, mainly due to their irritant action, receptor interaction and specific traditional odor. Ben Gay.\textsuperscript{TM} ointment, Tiger.\textsuperscript{TM} balm, Menthol Chest Rub and similar compositions are well known and popular.

A patent No. US5124320 discloses a lotion containing menthol and camphor.\textsuperscript{20} A patent No. US5144081 is related to a pharmaceutical composition containing camphor.\textsuperscript{21} A patent No. US5175152 describes a composition with methyl salicylate, menthol and camphor.\textsuperscript{22}
An International publication No. WO 2005/117981 A1 describes formulations and methods for treatment of pain, and neuropathic pain using eutectic mixtures of a capsicainoid and a local anesthetic agent and/or antipuritic agent.23

In pharmaceutical formulations, glyceryl behenate is mainly used as a tablet and capsule lubricant and as a lipidic coating excipient.16 Glyceryl behenate has also been investigated for the encapsulation of various drugs such as retinoids in form of solid lipid nanoparticles.24 Glyceryl behenate is used in the preparation of sustained release tablets and as a matrix-forming agent for the controlled release of water soluble drugs.16 The inventors of the present invention have surprisingly found that the use of glyceryl behenate has not been explored in the preparation of topical semisolid products containing higher proportion of hydrophobic liquids/counter irritants/penetration enhancer materials with/without therapeutically active pharmaceutical ingredients.

RO121673 relates to an ointment having anti-inflammatory and analgesic effects, made by associating yellow beeswax with stearin, lanolin, methyl salicylate, eucalyptol, pine-tree essential oil, shark liver oil and calcium hydroxide solution.25

A patent No. US4731200 discloses a topical preparation for joint relief comprising an aqueous-alcohol composition containing benzylidene-camphor derivatives.26
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One can observe from the reported references that there is a need for a technique by which higher percentage (60-92% w/w) of the hydrophobic liquid can be incorporated in the pharmaceutical formulation without any manufacturing and stability related problems.

Inventors of the present invention have surprisingly explored a novel technique to incorporate the major part of the hydrophobic liquid in the pharmaceutical ointment formulation which also reduces the amount of other petrolatum base products which ultimately help in reduction of the cost.

7.3 Object of the invention:

The instant object of the present invention is to prepare a stable pharmaceutical formulation by incorporating major part of hydrophobic liquid containing active principle using atleast one of the ingredients as glyceryl behenate along with other auxiliary solidifying agents.

Another object of the invention is to prepare a pharmaceutical formulation having major part of the hydrophobic liquid which may or may not contain any therapeutically active ingredient.

7.4 Summary of the invention:

The present invention contemplates a stable pharmaceutical formulation in a semisolid form incorporating higher proportion of hydrophobic liquid. The formulation of the present invention utilizes compritol and other excipients. The invention also narrates the procedure for preparing highly stable pharmaceutical formulation.
7.5 Detailed description of the present invention:

The term "therapeutically active ingredient" as used herein means a therapeutically active compound, as well as any prodrugs thereof and pharmaceutically acceptable salts, hydrates, and solvates of the compound and the prodrugs.

The term "stable product" as used herein means a formulation without problem of phase separation when stored at 35±15°C, 75±20% RH, for a prolonged period of time like 3, 6, 12, 24 months in a suitable container.

Therapeutically active ingredient as used herein is selected from indomethacin, diclofenac, ketorolac, piroxicam, meloxicam, tenoxicam, ketoprofen, flurbiprofen, ibuprofen, nimesulide, naproxen, rofecoxib, celecoxib, salicylic acid, captopril and other such compounds.

Initial studies were carried out using auxiliary solidifying agents such as bees wax, carnauba wax, hard paraffin, white soft paraffin at a concentration greater than 35% w/w. The problem of phase separation of hydrophobic liquid was observed from the formulation when stored for 3 months at 35±15°C, 75±20% RH. Hence, in subsequent trials, combination of glyceryl behenate and auxiliary solidifying agent was tried.

Mono-, di- and triglycerides of behenic acid, are widely used as excipient in the field of cosmetics, foods and oral pharmaceutical formulations. It is an amphiphilic material with a high melting point (65-70°C) and, therefore, it can also be used to prepare aqueous colloidal dispersions. In cosmetics, it is mainly used as a viscosity increasing agent in emulsion. It is available under registered brand name Compritol® 888 ATO. Other
excipients having similar physico-chemical properties can be used in place of compritol® 888 ATO.

In the present invention, the amount of glyceryl behenate ranged from 2-30 % w/w of the total weight of the formulation.

Auxiliary solidifying agents includes bees wax, hard paraffin, carnauba waxes, cetyl alcohol, white soft paraffin, emulsifying waxes, stearic acid and substance like such. The preferred auxiliary solidifying excipients are bees wax, carnauba wax, hard paraffin and similar materials. The amount of auxiliary solidifying excipients ranged from 2-28% w/w.
The following examples demonstrate utility of invention.

**Example e.1**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac IP</td>
<td>1</td>
</tr>
<tr>
<td>Glyceryl behenate</td>
<td>4</td>
</tr>
<tr>
<td>White Bees Wax</td>
<td>7.5</td>
</tr>
<tr>
<td>(+) Camphor: l-Menthol (1:1)</td>
<td>q.s. to 100</td>
</tr>
</tbody>
</table>

**Preparation method:**

(+) Camphor and l-Menthol were mixed together until complete liquidification was achieved. Diclofenac was dissolved in eutectic mixture and heated gently at 65 to 70°C. Separately, required amount of glyceryl behenate and white bees wax were melted at 65 to 70°C. Diclofenac solution was then added to the melted mixture of glyceryl behenate and white bees wax and stirred for 1 min at 65 to 70°C. The molten mixture was then cooled to room temperature using cold water (10 to 15°C) jacket with continuous stirring to obtain a physically stable semisolid product. Diclofenac may be omitted to obtain physically stable blank semisolid product.
Example e.2

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac IP</td>
<td>1</td>
</tr>
<tr>
<td>Glyceryl behenate</td>
<td>4</td>
</tr>
<tr>
<td>Hard paraffin</td>
<td>12</td>
</tr>
<tr>
<td>(+) Camphor: l-Menthol (1:1)</td>
<td>q.s. to 100</td>
</tr>
</tbody>
</table>

Preparation method:

(+/-) Camphor and l-Menthol were mixed together until complete liquidification was achieved. Diclofenac was dissolved in eutectic mixture and heated gently at 65 to 70° C. Separately, required amount of glycercyl behenate and hard paraffin were melted at 65 to 70° C. Diclofenac solution was then added to the melted mixture of glycercyl behenate and hard paraffin and stirred for 1 min at 65 to 70° C. The molten mixture was then cooled to room temperature using cold water (10 and 15° C) jacket with continuous stirring to obtain a physically stable semisolid product. Diclofenac may be omitted to obtain physically stable blank semisolid product.
Example e.3

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac IP</td>
<td>1</td>
</tr>
<tr>
<td>Glyceryl behenate</td>
<td>4</td>
</tr>
<tr>
<td>Carnauba Wax</td>
<td>5</td>
</tr>
<tr>
<td>(+) Camphor: l-Menthol (1:1)</td>
<td>q.s. to 100</td>
</tr>
</tbody>
</table>

Preparation method:

(+) Camphor and l-Menthol were mixed together until complete liquidification was achieved. Diclofenac was dissolved in eutectic mixture and heated gently at 65 to 70°C. Separately, required amount of glyceryl behenate and carnauba wax were melted at 65 to 70°C. Diclofenac solution was then added to the melted mixture of glyceryl behenate and carnauba wax and stirred for 1 min at 65 to 70°C. The molten mixture was then cooled to room temperature using cold water (10 to 15°C) jacket with continuous stirring to obtain a physically stable semisolid product. Diclofenac may be omitted to obtain physically stable blank semisolid product.
Example e.4

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac IP</td>
<td>1</td>
</tr>
<tr>
<td>Glyceryl behenate</td>
<td>4</td>
</tr>
<tr>
<td>White Bees Wax</td>
<td>12</td>
</tr>
<tr>
<td>Methyl salicylate</td>
<td>q.s. to 100</td>
</tr>
</tbody>
</table>

Preparation method:

Diclofenac was dissolved in methyl salicylate and heated gently at 65 to 70° C. Separately, required amount of glycercyl behenate and white bees wax were melted at 65 to 70° C. Diclofenac solution was then added to the melted mixture of glycercyl behenate and white bees wax and stirred for 1 min at 65 to 70° C. The molten mixture was then cooled to room temperature using cold water (10 to 15° C) jacket with continuous stirring to obtain a physically stable semisolid product. Diclofenac may be omitted to obtain physically stable blank semisolid product.
Example e.5

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen IP</td>
<td>1</td>
</tr>
<tr>
<td>Glyceryl behenate</td>
<td>2</td>
</tr>
<tr>
<td>White bees wax</td>
<td>14</td>
</tr>
<tr>
<td>(+) Camphor: l-Menthol (1:1)</td>
<td>q.s. to 100</td>
</tr>
</tbody>
</table>

Preparation method:

(+ ) Camphor and l-Menthol were mixed together until complete liquidification was achieved. Ibuprofen was dissolved in eutectic mixture and heated gently at 65 to 70° C. Separately, required amount of glyceryl behenate and white bees wax were melted at 65 to 70° C. Ibuprofen solution was then added to the melted mixture of glyceryl behenate and white bees wax and stirred for 1 min at 65 to 70° C. The molten mixture was then cooled to room temperature using cold water (10 to 15° C) jacket with continuous stirring to obtain a physically stable semisolid product. Ibuprofen may be omitted to obtain physically stable blank semisolid product.
Example e.6

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen IP</td>
<td>1</td>
</tr>
<tr>
<td>Glyceryl behenate</td>
<td>6</td>
</tr>
<tr>
<td>White bees wax</td>
<td>4</td>
</tr>
<tr>
<td>(+) Camphor: l-Menthol (1:1)</td>
<td>q.s. to 100</td>
</tr>
</tbody>
</table>

**Preparation method:**

(+) Camphor and l-Menthol were mixed together until complete liquidification was achieved. Ibuprofen was dissolved in eutectic mixture and heated gently at 65 to 70° C. Separately, required amount of glyceryl behenate and white bees wax were melted at 65 to 70° C. Ibuprofen solution was then added to the melted mixture of glyceryl behenate and white bees wax and stirred for 1 min at 65 to 70° C. The molten mixture was then cooled to room temperature using cold water (10 to 15° C) jacket with continuous stirring to obtain a physically stable semisolid product. Ibuprofen may be omitted to obtain physically stable blank semisolid product.
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Example 7.7

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1</td>
</tr>
<tr>
<td>Glyceryl behenate</td>
<td>4</td>
</tr>
<tr>
<td>White bees wax</td>
<td>10</td>
</tr>
<tr>
<td>Eucalyptus oil</td>
<td>q.s. to 100</td>
</tr>
</tbody>
</table>

Preparation method:

Ibuprofen was dissolved in eucalyptus oil and heated gently at 65 to 70° C. Separately, required amount of glyceryl behenate and white bees wax were melted at 65 to 70° C. Ibuprofen solution was then added to the melted mixture of glyceryl behenate and white bees wax and stirred for 1 min at 65 to 70° C. The molten mixture was then cooled to room temperature using cold water (10 to 15° C) jacket with continuous stirring to obtain a physically stable semisolid product. Ibuprofen may be omitted to obtain physically stable blank semisolid product.
Example e.8

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1</td>
</tr>
<tr>
<td>Glyceryl behenate</td>
<td>4</td>
</tr>
<tr>
<td>Carnauba wax</td>
<td>2</td>
</tr>
<tr>
<td>Hard Paraffin</td>
<td>2</td>
</tr>
<tr>
<td>White bees wax</td>
<td>3</td>
</tr>
<tr>
<td>Blend of eucalyptus oil and eutectic mixture containing equal amount of (+) Camphor and l-Menthol</td>
<td>q.s. to 100</td>
</tr>
</tbody>
</table>

**Preparation method:**

(+) Camphor and l-Menthol were mixed together until complete liquidification was achieved. Ibuprofen was dissolved in eutectic mixture. Eucalyptus oil was added to the solution of ibuprofen and heated gently at 65 to 70° C. Separately, required amount of glyceryl behenate, carnauba wax, hard paraffin and white bees wax were melted at 65 to 70° C. Ibuprofen solution was then added to the melted mixture of glyceryl behenate, carnauba wax, hard paraffin and white bees wax and stirred for 1 min at 65 to 70° C. The molten mixture was then cooled to room temperature using cold water (10 to 15° C) jacket with continuous stirring to obtain a physically stable semisolid product. Ibuprofen may be omitted to obtain physically stable blank semisolid product.
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7.6 Claims:

We Claim,

1) A topical pharmaceutical formulation comprising hydrophobic liquid and glyceryl behenate along with auxiliary solidifying excipients/viscosity modifier.

2) A topical pharmaceutical formulation according to claim 1, wherein the hydrophobic liquid is present in the range of 60 to 92% w/w, glyceryl behenate is present in the range of 2 to 30% w/w.

3) A topical pharmaceutical formulation according to claim 1 wherein the auxiliary solidifying agents are selected from bees wax, hard paraffin, carnauba waxes, cetyl alcohol, white soft paraffin, emulsifying waxes and stearic acid and similar substances.

4) A topical pharmaceutical formulation according to claim 1 wherein the hydrophobic liquid is selected from oils, eutectic mixtures and mixtures thereof.

5) The eutectic mixture according to claim 4 comprises menthol, camphor, thymol or other such substances.

6) The eutectic mixture as described in claim 4 and 5 contains two components in a ratio from 2:1 to 1:2.

7) A topical pharmaceutical formulation according to claim 1, wherein the hydrophobic liquid may also contain therapeutically active ingredients in solution or dispersion form.

8) Process for preparing the pharmaceutical ointment formulation according to claim 1 comprising:

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a. Melting glyceryl behenate with one or more auxiliary solidifying agent

b. Dissolving/dispersing the therapeutically active ingredient in hydrophobic liquid. Warming the solution/dispersion.

c. Mixing the step a) & b) with stirring.

d. Solidify the content of step c) by cooling.
7.7 References:


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