We claim:

1. A stable semisolid topically administrable pharmaceutical composition comprising a non steroidal anti-inflammatory analgesic, aceclofenac as the active ingredient in combination with a penetration enhancing adjuvant, a counter irritant and other pharmaceutically acceptable excipients.

2. The stable pharmaceutical composition as claimed in claim 1, wherein said semi-solid topically administrable pharmaceutical composition is in the form of clear translucent gel.

3. The stable pharmaceutical composition as claimed in claim 1, wherein said semi-solid topically administrable pharmaceutical composition is in the form emulsified cream.

4. The stable pharmaceutical composition as claimed in claim 1, wherein said active ingredient, aceclofenac is present in an amount from 0.5% to 5% by weight of the composition.

5. The stable pharmaceutical composition as claimed in claim 1, wherein said penetration enhancing adjuvant is menthol.

6. The stable pharmaceutical composition as claimed in claim 1, wherein said counter-irritant agent is methyl salicylate.

7. The stable pharmaceutical composition as claimed in claim 1, wherein said excipients comprise butylhydroxy anisole and butylhydroxy toluene as anti-oxidants.

8. The stable pharmaceutical composition as claimed in claim 1, wherein said excipients comprise benzyl alcohol as non-aqueous solvent.

9. The stable pharmaceutical composition as claimed in claims 1 to 3, wherein the pH of said composition is a physiologically compatible acidic pH.

10. The stable pharmaceutical composition as claimed in claims 1,2,3 and 9 wherein the pH of said composition ranges from 3 to 5.

11. The stable pharmaceutical composition as claimed in claims 1 and 2, wherein said translucent gel comprises a non-aqueous acrylic polymer, carbopol 974P.

12. The stable pharmaceutical composition as claimed in claims 1,2 and 11, wherein said carbopol 974P functions as viscosity increasing agent, suspending agent and pH adjusting agent.

13. The translucent gel composition as claimed in claim 2, wherein said gel comprises, based on the total weight of the composition,

(i) aceclofenac from 0.5 to 5.0%,

(ii) 5 to 15% of methyl salicylate,

(iii) 2 to 10% of menthol,

(iv) 1 to 6% of linseed oil,

(v) 65-80% of propylene glycol,

(vi) 1 to 5% of Carbopol 974P,

(vii) 0.005 to 0.05% Butylhydroxy anisole and Butylhydroxy toluene and

(viii) 1% Benzyl alcohol.

14. The translucent gel composition as claimed in claim 2, wherein said composition has a viscosity of from 6,00,000 to about 9,00,000 cps at 25 DEG C.

15. The stable pharmaceutical composition as claimed in claims 1 and 3, wherein said emulsified cream comprises a poloxamer, Lutrol F127.

16. The emulsified cream composition as claimed in claim 3, wherein said cream comprises, based on the total weight of the composition,

(i) aceclofenac, from 0.5 to 5.0%,

(ii) 5 to 15% of methyl salicylate,

(iii) 2 to 10% of menthol,

(iv) 2 to 10% of polyethylene glycol 400,

(v) 5 to 15% of migloyl 812,

(vi) 1 to 6% of linseed oil,

(vii) 5 to 12% of Lutrol F127,

(viii) 0.005 to 0.05% Butylhydroxy anisole and Butylhydroxy toluene,

(ix) 1% Benzyl alcohol and

(x) 1% of Isopropyl alcohol.

17. The emulsified cream composition as claimed in claim 3, wherein said cream has a viscosity of from 9,00,000 to about 12,00,000 cps at 25 DEG C.

18. The translucent gel composition as claimed in claim 2, wherein said gel is prepared by a process comprising:

a) Heating propylene glycol to 60°C and dissolving butylhydroxy anisole and butylhydroxy toluene into it;

b) Cooling mixture of step (a) to 40°C and dissolving aceclofenac in it;

c) Introducing methyl salicylate and menthol into the mixture of step (b) in a weight ratio range of 2:1;

d) Adding linseed oil and benzyl alcohol to © and mixing uniformly;

e) Adding carbomer slowly to (d) to form a clear translucent gel;

f) Finally adding propylene glycol to (e) to make up the weight and

g) Stirring at low rpm at room temperature to form a uniform eutectic mixture of a clear translucent gel.

19. The emulsified cream composition as claimed in claim 3, wherein said cream is prepared by a *comprising:*

a) Dispersing aceclofenac in polyethylene glycol and migloyl;

b) Dissolving methyl salicylate and menthol under stirring and adding linseed oil;

c) Mixing components of (a) and (b) under stirring;

d) Adding benzyl alcohol to © and mixing uniformly;

e) Dissolving butylhydroxy anisole and butylhydroxy toluene in isopropyl alcohol and adding to (d) and

f) Finally adding lutrol under stirring to form the emulsified cream.

20. A stable semisolid topically administrable pharmaceutical composition comprising a non steroidal anti-inflammatory analgesic, aceclofenac as the active ingredient in combination with a penetration enhancing adjuvant, a counter irritant and pharmaceutically acceptable excipients and process for its preparation as substantially described herein with reference to foregoing examples 1 to 3.

Dated this 8th day of November 2005

DR. GOPAKUMAR G. NAIR
Agent for the Applicant

FORM 2

THE PATENT ACT 1970

(39 of 1970)

&

The Patents Rules, 2003

COMPLETE SPECIFICATION

(See section 10 and rule13)

1. TITLE OF THE INVENTION:

"An improved process for the preparation of Valsartan and its intermediates"

2. APPLICANT

(a) NAME : IPCA LABORATORIES LIMITED

(b)NATIONALITY : Indian Company incorporated under the Indian Companies ACT, 1956

(c) ADDRESS : 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India

3.PREAMBLE TO THE DESCRIPTION

The following specification particularly describes the invention and the manner in which it is to be performed

Technical Field of the Invention

The present invention is directed to novel combinations and methods of preparation thereof, suitable for formulating a semi-solid transdermal gel and emulsified cream containing a poorly water soluble pharmaceutical agent in the form of non-steroidal anti-inflammatory drug. More particularly, the invention is directed to stable and efficacious pharmaceutical formulations comprising a non-steroidal anti-inflammatory drug, aceclofenac, in combination with a counter-irritant agent, methyl-salicylate and skin-penetrator, menthol in the form of translucent gel or white emulsified cream.

Background and Prior Art

Aceclofenac (2- [(2, 6 dichlorophenyl) amino] phenylacetoxyacetic acid), first disclosed in Spanish patent 8404783, is a non-steroidal anti-inflammatory drug (NSAID), and has characteristics in that, it is readily soluble in organic solvent and relatively poorly soluble in water. Its method of preparation and efficacy are disclosed in detail in publications including Pat. No. WO 99/62865 and WO 99/55660, and the journal "Drugs" (Vol. 52 (1), 113-124 (1996))

United States Patent No. 6,929,805 discloses tablet preparations of combinations of a rapid action analgesic with a systemically acting analgesic having sustained action that is selected from the group consisting of aceclofenac, among many others.

United States Patent No. 6,818,224 describes a method for preparing a fluid pharmaceutical composition as well as their use for treating periodontitis, gingivitis, dental abscesses, mouth ulcers and mycoses. This preparation has the property for gelling in aqueous phase and allows the controlled release of at least one active substance (mostly antiseptic agents, antibiotic or anti-infective agents, steroidal or other anti-inflammatory agents or peptide active substances) prepared in the presence of phospholipid, fatty acid and solvent.

The present invention addresses the need for a novel combination in the form of anti-inflammatory gel and emulsified cream for treating pain, inflammation and other

pathological conditions affecting musculo-skeletal tissues. Further the process for preparation of this novel stabilized combination in both the dosage forms is disclosed.

The formulations of the present invention specifically relate to the novel combination of an anti-inflammatory compound, aceclofenac. Aceclofenac has poor skin penetration properties, resulting in poor transdermal absorption of the drug. Due to this property, it is combined with a suitable skin penetrating agent in the instant invention. Aceclofenac is further combined with a counter-irritant. These agents cause the blood vessels of the skin to dilate, resulting in a warm soothing feeling. Counter-irritant refers to the idea that irritation of the sensory nerve endings alters or offsets pain in the underlying muscle or joints that are served by the same nerves. Both the skin penetrating agent and the counter-irritant are present in amounts sufficient to enable the anti-inflammatory compound aceclofenac to penetrate into both epidermis and dermis. The main aim of such a combination in the present invention is that it can be formulated into semisolid preparations, creams and gels, which have the advantage of high in vivo drug absorption rate and thus a more rapid therapeutic effect. The present invention also discloses the processes to manufacture the gel and emulsified cream formulations by simple methods which substantially reduce the manufacturing cost, thus deriving economic benefits from the invention.

Objectives of the invention:

Therefore the objective of the invention is to formulate the NSAID drug, aceclofenac in a stable topical dosage form, such that the drug has a very high degree of in-vivo absorption.

A further objective of the invention is to combine aceclofenac with a penetration enhancing adjuvant and a counter-irritant to ensure a high degree and rate of in-vivo absorption.

Another objective is to formulate aceclofenac in combination with a penetration enhancing adjuvant and a counter-irritant as topical dosage forms in the form of a gel and an emulsified cream and to provide the manufacturing processes for the same.

Yet another objective of the invention is to formulate and process the gel and emulsified cream of aceclofenac such that economic benefits can be derived from the invention, making the cost of therapy in chronic pain conditions less.

Summary of the invention:

The present invention discloses a novel combination of a NSAID, aceclofenac with a skin penetration enhancer such as menthol and a counter-irritant such as methyl salicylate in the form of a gel or a emulsified cream. This unique combination results in enhanced in-vivo bioavailability of the drug in chronic musculo-skeletal conditions. The invention also discloses the process of preparation of the gel and cream formulations. These processes are simple and substantially reduce the manufacturing cost, thus deriving economic benefits from the invention.

Detailed description of the invention:

In the following disclosure, novel combination of aceclofenac, menthol and methyl salicylate and compositions of these ingredients as stable semi-solid formulations in the form of an emulsified cream and hydroalcoholic gel have been exemplified.

One embodiment, for example, includes a topical system that can administer a therapeutically effective amount of a non-steroidal anti-inflammatory drug, aceclofenac in combination with menthol and methyl salicylate in the form of emulsified cream.

Another embodiment includes the topical system to administer effective amounts of aceclofenac, menthol and methyl salicylate in the form of clear translucent gel. The stable formulations of the combination are for topical application in the form of an emulsified cream and hydroalcoholic gel suitable for the treatment of inflammatory diseases. The preferred range of aceclofenac to elicit its therapeutic effect in the compositions is 0.5-5.0 % by weight of the compositions.

Topical preparations include skin penetration enhancing adjuvants selected from fatty acids, glycerol derivatives, menthol derivatives, certain herbal ingredients and such like. In the present invention, menthol is selected for its superior penetration enhancing ability and also because it causes low skin irritation. It is used in the range of 2-10% by weight of the composition.

Counter irritants included in topical preparations are usually selected from capsicum oleoresin, choline salicylate, ethyl salicylate, glycol salicylate, methyl salicylate,

menthol, salicylic acid, turpentine oil and such like. In this invention, methyl salicylate in the range of 5-15% by weight of the composition plays the role of counter irritant.

The process for preparing the semi-solid cream compositions of the present invention comprises adding solvents, bases, vehicles, viscosity-increasing agents, emulsifiers, preservatives, anti-oxidants and so on.

The gel and cream vehicles, solvents and bases which are essential components of the present compositions, are polymers polyethylene glycol and propylene glycol. More useful herein are those which are liquids at room temperature or have a melting point slightly thereabove. Preferred are the polyethylene glycols having a molecular weight range from about 400 to about 1000. Moreover, mixtures of two or more polyethylene glycols of different molecular weight range can also be employed in the present invention. Propylene glycol in the range of 65-80% by weight of the composition of the gel and polyethylene glycol 400 in the range of 2-10% by weight of the composition of the cream are examples of incorporation of these agents in the compositions of the present invention. Benzyl alcohol is the most preferred preservative, mild local anesthetic and solvent for use in the processes of the instant invention, usually employed at 1% by weight of the composition. Medium chain triglycerides like migloyl was used as base for preparation of emulsified cream. Migloyl 812 was the most preferred grade and was most useful in the range of 5-15% by weight of the composition. Butylhydroxy anisole (BHA) and Butylhydroxy toluene (BHT) were incorporated for their anti-oxidant properties in the range of 0.005 to 0.05% by weight of the composition. Lutrol and its various grades which are essentially poloxamers, are included in cream formulation as thickening agent and gel former and as a co-emulsifier and viscosity enhancer, thus stabilizing the formulation. In the present invention, the grade used is Lutrol F 127, in the range of 5-12% by weight of the cream composition. Further linseed oil was incorporated in the compositions in the range of 1-6% by weight of the composition.

An improved or enhanced pearlescent appearance is attained in the gel by the incorporation of non-acqueous, crosslinked acrylate polymers such as carbomers. Furthermore, the polymer prevented the sedimentation or precipitation of the other

ingredients in the formulation. Though the primary role of carbomer in the composition was that of a suspending or viscosity-increasing agent, its bio-adhesive nature helped in skin adherence and made the formulation water-washable. Additionally, it is believed that the polymeric rheology modifier serves to hold all the ingredients in place in the final formulation. Various grades of carbomers are available for such application such as Carbopol, Carbopol 974, Carbopol 974P and such like. In the instant invention the preferred grade is Carbopol 974P. The amount of the carbomer generally used is from about 0.05% to about 10% and desirably from about 0.5% to about 5% by weight based upon the total weight of the stabilized composition.

It is the general practice to adjust pH of gel formulations in the desirable range, which is dependent on the drug being formulated, with suitable acid or alkali. This aids in maintaining the drug in the body of the gel, thus enhancing the stability of the formulation. It has been additionally found in the present invention that the addition of carbopol 974P results in the attainment of the desired pH of the gel preparation. Thus, carbopol functions as the gelling agent and pH adjusting agent, not only stabilizing the formulation but also eliminating the need to add any further ingredient for the important step of pH adjustment. This results in greater economic benefits since not only is an ingredient reduced from the formulation, also one step in manufacturing is eliminated.

Preferably, the pH of the composition is in the acidic pH range, desirably within the range of from about 2 to about 6, more preferably, about 2 to about 5, even more preferably about 3 to about 5, and optimally about 3.5 to 4.5.

In addition to the above mentioned ingredients, other components which can be incorporated into the compositions of the invention include colorings, flavorings, humectants, preservatives, lubricants, flow-enhancers, pH buffers, filling aids, antioxidants, essences. Various other ingredients can optionally be utilized in the stable composition of the present invention such as fragrances, perfumes, preservatives, disinfectants, antioxidants, and other aesthetically pleasing components.

The resultant mixture was a smooth feeling delivery vehicle, which delivered aceclofenac and methyl salicylate to the skin in an effective and stable manner.

The following non-limiting examples set forth herein below illustrate certain aspects of the invention. All parts and percentages are by weight unless otherwise noted and all temperatures are in degrees Celsius.

Example 1

A clear translucent gel formulation containing aceclofenac is prepared by blending the following ingredients.

Ingredients	Weight percent
Aceclofenac	1.5%
Methyl salicylate	10%
Menthol	5%
Linseed oil	3%
Propylene glycol	q.s. (about 72%)
Carbomer	3.2%
Butylhydroxy anisole (BHA)	0.02%
Butylhydroxy toluene (BHT)	0.01%
Benzyl alcohol	1%

Properties at 25°C	Observation
Appearance	Firm translucent gel
Viscosity* (cps)	6,00,000 to 9,00,000 cps
pH	3.96
Stability 40°±2°C/ 75%±5% RH, 30°±2°C/ 65%±5% RH & 25°±2°C/ 60%±5% RH	Passes 3 months
Freeze/thaw studies	Passes 5 cycles freeze/thaw

Brookfield Helipath @ 0.3 rpm, 25°C, # S96 spindle

Formulating Techniques : The present invention can be made in a number of ways. Method of manufacture of a composition of matter for use as a topical gel comprises of warming propylene glycol to 60°C, dissolving Butylhydroxy anisole and Butylhydroxy toluene into warm propylene glycol and then cooling the mixture to 40°C and dissolving Aceclofenac into it. This was followed by adding methyl salicylate and menthol into the mixer, then linseed oil and benzyl alcohol were added and mixed uniformly. Finally the carbomer was added slowly to form a clear translucent gel and propylene glycol was added to make up the weight and stirred at low rpm at room temperature to form a uniform eutectic mixture of aceclofenac gel.

Example 2

Alternatively aceclofenac cream formulation is made up by blending the following ingredients.

Ingredients	Weight percent
Aceclofenac	1.5%
Polyethylene glycol 400	4.9%
Migloyl 812	9.9%
Linseed oil	3.0%
Menthol	5.0%
Methyl salicylate	10.0%
Butylhydroxy anisole (BHA)	0.02%
Butylhydroxy toluene (BHT)	0.01%
Isopropyl alcohol	1%
Lutrol F127	9.0%
Benzyl alcohol	1.0%
D.M.Water	q.s.

Properties at 25°C	Observation
Appearance	Emulsified cream
Viscosity* (cps)	9,00,000 to 12,00,000 cps
pH	4.0
Stability	Passes 3 months

40°±2°C/ 75%±5% RH, 30°±2°C/ 65%±5% RH & 25°±2°C/ 60%±5% RH	
Freeze/thaw studies	Passes 5 cycles freeze/thaw

Brookfield Helipath @ 0.3 rpm, 25°C, # S96 spindle

Formulating Techniques : Aceclofenac was dispersed in polyethylene glycol and migloyl under stirring. Menthol was dissolved in methyl salicylate under stirring and after linseed oil was added, the mixture was mixed uniformly. Butylhydroxy anisole and Butylhydroxy toluene was dissolved into isopropyl alcohol and added to the cream under stirring. Finally Lutrol was added to the bulk to form the cream.

Example 3

Storage Stability Study

Products or compositions made in accordance to the present invention were considered stable as they meet one or more of the following criteria:

- There was no phase separation, settling, or creaming of any material in the composition. The composition should remain completely homogenous throughout its bulk. Separation is herein defined as the visible existence of 2 or more distinct layers or phases of any component in the formulation, including but not limited to insoluble matter, soluble matter, oily substances and the like.
- The viscosity of the composition did not significantly increase or decrease over time, generally less than 50%, preferably less than 35%, and most preferably less than 20%.
- The pH of the composition did not increase or decrease more than two pH units, preferably not more than one unit, and most preferably not more than one-half unit.
- The rheology and texture of the composition did not significantly change over time to that which was unacceptable.

Products or compositions made according to the present invention would have been considered unstable if they had not met one or more of the above listed criteria.

Stability studies were conducted for conditions of 40°±2°C/ 75%±5% RH, 30°±2°C/ 65%±5% RH and room temperature (25°±2°C/ 60%±5% RH) in order to predict the shelf life of the compositions. Samples of aceclofenac gel and cream (30 gm) were packed individually in aluminium tubes. The aluminium tubes were then sealed and placed in storage. All compositions were found to be relatively stable for the studied period. Additionally, freeze-thaw cycling was employed wherein the composition is cycled between a freezing temperature, usually 0° C., and an ambient temperature, usually 20-25° C. All compositions passed a minimum of 1 freeze-thaw cycle, many passed 3 cycles, and most passed 5 cycles.

Physical/Chemical Properties of the Preparations

	Formulation A (gel)	Formulation B (cream)
pH:	3.5-4.5	3.5-4.5
Density:	not done	0.8 to 0.9 g/ml (25.degree. C.)
Viscosity:	9,00,000 cps	9,50,000 cps

We claim:

1. A stable semisolid topically administrable pharmaceutical composition comprising a non steroidal anti-inflammatory analgesic, aceclofenac as the active ingredient in combination with a penetration enhancing adjuvant, a counter irritant and other pharmaceutically acceptable excipients.

2. The stable pharmaceutical composition as claimed in claim 1, wherein said semi-solid topically administrable pharmaceutical composition is in the form of clear translucent gel.

3. The stable pharmaceutical composition as claimed in claim 1, wherein said semi-solid topically administrable pharmaceutical composition is in the form emulsified cream.

4. The stable pharmaceutical composition as claimed in claim 1, wherein said active ingredient, aceclofenac is present in an amount from 0.5% to 5% by weight of the composition.

5. The stable pharmaceutical composition as claimed in claim 1, wherein said penetration enhancing adjuvant is menthol.

6. The stable pharmaceutical composition as claimed in claim 1, wherein said counter-irritant agent is methyl salicylate.

7. The stable pharmaceutical composition as claimed in claim 1, wherein said excipients comprise butylhydroxy anisole and butylhydroxy toluene as anti-oxidants.

8. The stable pharmaceutical composition as claimed in claim 1, wherein said excipients comprise benzyl alcohol as non-aqueous solvent.

9. The stable pharmaceutical composition as claimed in claims 1 to 3, wherein the pH of said composition is a physiologically compatible acidic pH.

10. The stable pharmaceutical composition as claimed in claims 1,2,3 and 9 wherein the pH of said composition ranges from 3 to 5.

11. The stable pharmaceutical composition as claimed in claims 1 and 2, wherein said translucent gel comprises a non-aqueous acrylic polymer, carbopol 974P.

12. The stable pharmaceutical composition as claimed in claims 1,2 and 11, wherein said carbopol 974P functions as viscosity increasing agent, suspending agent and pH adjusting agent.

13. The translucent gel composition as claimed in claim 2, wherein said gel comprises, based on the total weight of the composition,

(i) aceclofenac from 0.5 to 5.0%,

(ii) 5 to 15% of methyl salicylate,

(iii) 2 to 10% of menthol,

(iv) 1 to 6% of linseed oil,

(v) 65-80% of propylene glycol,

(vi) 1 to 5% of Carbopol 974P,

(vii) 0.005 to 0.05% Butylhydroxy anisole and Butylhydroxy toluene and

(viii) 1% Benzyl alcohol.

14. The translucent gel composition as claimed in claim 2, wherein said composition has a viscosity of from 6,00,000 to about 9,00,000 cps at 25 DEG C.

15. The stable pharmaceutical composition as claimed in claims 1 and 3, wherein said emulsified cream comprises a poloxamer, Lutrol F127.

16. The emulsified cream composition as claimed in claim 3, wherein said cream comprises, based on the total weight of the composition,

(i) aceclofenac, from 0.5 to 5.0%,

(ii) 5 to 15% of methyl salicylate,

(iii) 2 to 10% of menthol,

(iv) 2 to 10% of polyethylene glycol 400,

(v) 5 to 15% of migloyl 812,

(vi) 1 to 6% of linseed oil,

(vii) 5 to 12% of Lutrol F127,

(viii) 0.005 to 0.05% Butylhydroxy anisole and Butylhydroxy toluene,

(ix) 1% Benzyl alcohol and

(x) 1% of Isopropyl alcohol.

17. The emulsified cream composition as claimed in claim 3, wherein said cream has a viscosity of from 9,00,000 to about 12,00,000 cps at 25 DEG C.

18. The translucent gel composition as claimed in claim 2, wherein said gel is prepared by a process comprising:

a) Heating propylene glycol to 60°C and dissolving butylhydroxy anisole and butylhydroxy toluene into it;

b) Cooling mixture of step (a) to 40°C and dissolving aceclofenac in it;

c) Introducing methyl salicylate and menthol into the mixture of step (b) in a weight ratio range of 2:1;

d) Adding linseed oil and benzyl alcohol to © and mixing uniformly;

e) Adding carbomer slowly to (d) to form a clear translucent gel;

f) Finally adding propylene glycol to (e) to make up the weight and

g) Stirring at low rpm at room temperature to form a uniform eutectic mixture of a clear translucent gel.

19. The emulsified cream composition as claimed in claim 3, wherein said cream is prepared by a *comprising:*

a) Dispersing aceclofenac in polyethylene glycol and migloyl;

b) Dissolving methyl salicylate and menthol under stirring and adding linseed oil;

c) Mixing components of (a) and (b) under stirring;

d) Adding benzyl alcohol to © and mixing uniformly;

e) Dissolving butylhydroxy anisole and butylhydroxy toluene in isopropyl alcohol and adding to (d) and

f) Finally adding lutrol under stirring to form the emulsified cream.

20. A stable semisolid topically administrable pharmaceutical composition comprising a non steroidal anti-inflammatory analgesic, aceclofenac as the active ingredient in combination with a penetration enhancing adjuvant, a counter irritant and pharmaceutically acceptable excipients and process for its preparation as substantially described herein with reference to foregoing examples 1 to 3.

Dated this 8th day of November 2005

DR. GOPAKUMAR G. NAIR
Agent for the Applicant