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Nashik Maharashtra HDFC, Inventors/Applicants

Inventor(s):

Navi Plot MARK Applicant

Priority:

Shahu Khachane [IN/IN];

Applicant

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Abstract:

The present invention generally relates to a novel pharmaceutical composition containing Dextibuprofen and Paracetamol in the form of soft gelatin capsule dosage form and process for preparing the same.
"A NOVEL PHARMACEUTICAL SOFT GEL COMPOSITION CONTAINING
DEXIBuprofen AND PARACETAMOL"

BACKGROUND OF THE INVENTION

1. Technical Field

The present invention generally relates to a novel pharmaceutical composition containing Dexibuprofen and Paracetamol in the form of soft gelatin capsule dosage form and process for preparing the same.

2. Description of the Related Art

Pain has been defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. This definition is particularly relevant because it takes into account the emotional component of pain, which can modify the pain signal, and recognizes that tissue damage encompasses potential as well as actual damage.

Ibuprofen, an NSAID is marketed commercially and used clinically as a racemic mixture of S(+) and R(-)-enantiomers, which exist in equal amounts. Dexibuprofen is the S(+) (dextrorotatory)-enantiomer of ibuprofen and accounts for virtually all pharmacodynamic (analgesic, anti-inflammatory, antipyretic) activities of the racemic compound. In vitro, Dexibuprofen is over 100 times as potent as the R(-)-enantiomer as an inhibitor of prostaglandin biosynthesis. It has been suggested that any observable in vitro effect of R(-)-ibuprofen is secondary to small amounts of Dexibuprofen present as an impurity.
In vivo, the R(-)-enantiomer of racemic ibuprofen undergoes unidirectional enzy
chiral inversion to S(+)-enantiomer (Dexibuprofen). This occurs to the extent about 65%, whereas there is no bioinversion of S(+) to R(-)-ibuprofen. Although this would favor use of racemic ibuprofen, since most of its inactive enantiomer is converted to active form, proponents of Dexibuprofen suggest disadvantages of the racemic drug. It is argued that conversion of racemic ibuprofen to S(+)-ibuprofen results in variability of clinical response, including delayed onset of activity, and difficulty in achieving an optimal dose; it is also felt that the formation of coenzyme A (CoA) thioester during bioinversion of R(-) to S(+) ibuprofen may result in toxic effects (e.g., interference of lipid anabolism/catabolism), and that R(-)-ibuprofen bioactivation is susceptible to biological factors and certain drugs. There are some preclinical/clinical data to support these contentions.

Potential advantages of dexibuprofen over racemic ibuprofen include lesser toxicity, greater clinical efficacy and/or less variability in therapeutic effects achieved, and easier dose optimization, all at half the dose of ibuprofen. A more rapid onset is also claimed for dexibuprofen, and this was demonstrated in one well-conducted comparison of dexibuprofen and ibuprofen in dental surgery patients; greater peak analgesia was also seen with dexibuprofen.

Oral Dexibuprofen in usual daily doses of 900 to 1200 mg has shown efficacy in the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and other rheumatic diseases in uncontrolled studies and randomized comparisons with ibuprofen or diclofenac. The efficacy of Dexibuprofen and ibuprofen has been comparable with 50% lower doses of Dexibuprofen. Dexibuprofen has been shown to be as effective as Diclofenac and celecoxib in the treatment of osteoarthritis.

Chemically Paracetamol (also known as Acetaminophen) is known as para-acetyl-
aminophenol or 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occur as a white, odorless, crystalline powder, possessing a slightly bitter taste.
The analgesic efficacy of Paracetamol is essentially equivalent to that of NSAID. Paracetamol is not anti-inflammatory. The mechanism of action of Paracetamol is unknown, but prevailing evidence suggests that it involves a central component. Paracetamol inhibits COX-I, but in the brain rather than in the periphery.

Paracetamol is frequently used as a non-opioid analgesic in postoperative pain. Its mechanism of action is not fully understood, but it is generally accepted that Paracetamol is a centrally acting drug. The analgesic effect of Paracetamol is probably dependent on the rate and amount of active drug reaching the CNS, where its analgesic effect takes place. When pain relief is insufficient with Paracetamol alone, an NSAID may be added in combination.

NSAIDs inhibit prostaglandin synthesis in peripheral tissues. Some suggest a peripheral-central synergistic action of NSAIDs that varies depending on the particular NSAID and on the presence of an inflammatory process. Concomitant administration of two analgesics with presumably different mechanisms of action may be more effective than the use of either drug alone. The combination of Paracetamol and NSAIDs is widely used clinically.

U.S. Patent No 4,690,823 assigned to Dolorgeit describes an ibuprofen-containing soft gelatin capsule containing a solution of a polyoxyethylene-polyoxypropylene polymer.

U.S. Patent No 5,409,709 assigned to Lion Corporation describes antipyretic analgesic preparation comprising ibuprofen, magnesium-based antacids, and acetaminophen.

CA1336687 assigned to BMS claims the combination of ibuprofen, caffeine, and acetaminophen and process for the preparation.

WO2006004449 assigned to Aft Pharmaceuticals describes combination for the treatment of pain including about 125 mg to about 150 mg ibuprofen and about 475 mg to about 500 mg s Paracetamol.
Indian patent application 909/DELNP/2004 assigned to strides arcolab des< Dexibuprofen containing soft gelatin capsule and process for preparing the same. This patent does not disclose about the combination product, but claims use of sole ingredient Dexibuprofen in the form of soft gelatin capsule.

Indian patent application 204/MAS/2001 assigned to Dr. Reddys Laboratories discloses an invention for the soft gelatin capsule containing (s)(+)-ibuprofen. However, this application does not discuss about the combination of Paracetamol and (s)(+) ibuprofen combination in the form of soft gelatin capsule.

From the above prior art it has been understood that combination of Paracetamol with Dexibuprofen in soft gelatin capsule dosage form is not known. So, there remains the need for formulating a combination product that gives a synergistic effect, and manufactured specifically in soft gelatin capsule dosage form, to provide patient compliance. Due to the presence of drug in the soluble form, this soft gel dosage form will result into quick dissolution and satisfactory bioavailability of the composition.

SUMMARY OF THE INVENTION

The present invention generally relates to a novel pharmaceutical composition containing Dexibuprofen and Paracetamol in the form of soft gelatin capsule dosage form and process for preparing the same.

OBJECTIVES OF THE INVENTION

Accordingly, one embodiment of the present invention provides a novel pharmaceutical composition comprising combination product in the form of soft gel capsule containing therapeutically effective amount of Dexibuprofen and Paracetamol.

Another embodiment of the present invention is to provide a process for making the combination product of Dexibuprofen and Paracetamol in the form of soft gelatin capsule.
According to further embodiment of the present invention both the Dexibuprofen and Paracetamol are dissolved /dispersed in suitable solvent.

Another embodiment of the present invention provides a pharmaceutical composition comprising about 10Q-500mg of Dexibuprofen and 500-2000mg of Paracetamol.

Another embodiment of the present invention provides the use of Dexibuprofen and Paracetamol combination for the preparation of a pharmaceutical composition in the form of soft gelatin capsule as analgesic-antipyretic for the treatment of pain.

DETAILED DESCRIPTION OF THE INVENTION

Analgesic combinations offer a potential benefit over individual agents. Such benefits include increased compliance and reduced side effects if the same level of analgesia can be achieved with the lower doses of each component in the combination. Combining analgesics that have different mechanisms of action offers the additional potential advantage of being able to treat a broader spectrum of pain. Such an approach has been recommended by the World Health Organization and the American College of Rheumatology.

Dexibuprofen and Paracetamol produce analgesic effects by different mechanisms. NSAIDs like Dexibuprofen inhibit prostaglandin synthesis in peripheral tissues. Acetaminophen's mechanism of action appears to be due to inhibition of prostaglandin synthetase centrally. Specifically, it is a potent inhibitor of cyclo-oxygenase in the central nervous system. Hence, their actions can be complementary to each other. Since less dose of individual drugs is required, less chance of adverse effects of both the drugs.

Further, it is known that gastrointestinal (GI) tolerability of Dexibuprofen is better, and Paracetamol is also a well tolerated drug with good GI safety which improves compliance of the patient.

The present invention describes an oral pharmaceutical composition in the form of soft gelatin capsule having combination of one drug selected as Paracetamol and the other therapeutically effective component selected from the group of NSAID'S e.g. Dexibuprofen.
The term Surfactant used herein refer to the substances that helps in reduc
t surface tension between the two surfaces and helps in dissolving/dispersing the one phase into other. The compounds used as surfactants according to the present invention are selected from the group but are not limited to glycerol monostearate, polysorbates, sodium laurylsulfate and sucross esters of fatty acids, polyoxyl hydrogenated castor oil (of various grades) and combination thereof.

Solvent /vehicle used herein are the substances that help in dissolving or dispersing the active pharmaceutical compound or drug in the selected solvent. Solvents used according to the present invention are selected from the group but are not limited to benzyl alcohol, ethylene glycol phenyl ether, propylene glycol, propylene glycol phenyl ether, propylene carbonate, phenoxyethanol, dimethyl malonate, dimethyl succinate, diethyl succinate, dibutyl succinate, dimethyl glutarate, diethyl glutarate, dibutyl glutarate, dimethyl adipate, diethyl adipate, dibutyl adipate, various grades of polyethylene glycol or mixtures thereof.

This invention is not limited to the inactive excipients disclosed herein in this specification, but all those excipients that can be use to prepare soft gelatin capsule and is known to the person skilled in the art can be used to make the said Dexibuprofen and Paracetamol soft gelatin capsule.

The invention is further exemplified with following examples and is not intended to limit the scope of the inventions. It is obvious to those skilled in the art to find out the composition for other dosage forms and substitute the equivalent excipients as described in this specification or with the one known to the industry.

Example 1

**DEXIBuprofen AND PARACETAMol SOFT GELatin CAPSule**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Ingredients</th>
<th>Qty. Per capsule in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Polyethylene Glycol 400 (Macrogol 400)</td>
<td>400.00</td>
</tr>
<tr>
<td>2</td>
<td>Cremophor RH 40</td>
<td>50.00</td>
</tr>
</tbody>
</table>
Composition of Gelatin Mass

<table>
<thead>
<tr>
<th>S. No</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gelatin (Powder)</td>
</tr>
<tr>
<td>2</td>
<td>Glycerin</td>
</tr>
<tr>
<td>3</td>
<td>Sorbitol Solution 70 %</td>
</tr>
<tr>
<td>4</td>
<td>Sodium Methylparaben</td>
</tr>
<tr>
<td>5</td>
<td>Sodium Propylparaben</td>
</tr>
<tr>
<td>6</td>
<td>Purified Water</td>
</tr>
<tr>
<td>7</td>
<td>Sunset Yellow FCF</td>
</tr>
<tr>
<td>8</td>
<td>Ponceau 4R</td>
</tr>
<tr>
<td>9</td>
<td>Titanium Dioxide</td>
</tr>
</tbody>
</table>

Manufacturing process

In Stainless Steel bowl of mixer added Polyethylene Glycol 400 & Cremophor RH 40 (Polyoxyl 40 Hydrogenated Castor Oil). Heated the mixture to 50 to 55°C. Added & dissolved Dexibuprofen to the above material under mechnical stirring and continued stirring until a clear solution is obtained.

Added & dispersed Paracetamol to the above solution under mechnical stirring and stirred for 30 to 45 minutes until a homogeneous slurry is formed. Passed it through Tripple roller grinder milled with 80 # SS sieve & collected material in SS bowl. De-aerated by applying vacuum up to 25 Hg for 30 minutes.

Encapsulation

Encapsulate using Encapsulation machine having die roll size 23.20 minim with oblong shape using gelatin orange colored ribbon.

Polishing

The encapsulated capsules are polished with absorbent cloth through 3 semi dryers in series.
Drying
Dry the capsules using tray dryer maintaining the temperature Condition 25±5°C ,
Relative Humidity 25±5 %.
We claim:

1. A novel pharmaceutical composition comprising combination product in the form of soft gel capsule containing therapeutically effective amount of Dexibuprofen and Paracetamol.

2. Process for making the combination product of Dexibuprofen and Paracetamol in the form of soft gelatin capsules where in Polyethylene glycol and Polyoxyl 40 hydrogenated castor oil were heated to about 50 to 60°C, followed by addition of Dexibuprofen and Paracetamol under mechanical stirring and continued stirring until a clear solution is obtained.

3. A novel pharmaceutical combination product where in both the drugs Dexibuprofen and Paracetamol are dissolved /dispersed in suitable solvent.


6. Novel pharmaceutical composition of Dexibuprofen and Paracetamol comprising Polyethylene Glycol 400 (Macrogol 400) and Polyoxyl 40 Hydrogenated Castor Oil (Cremorphor RH 40).