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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE TOPICAL ADMINISTRATION IN THE ORAL CAVITY OF NON-STEROID ANTI-INFLAMMATORY DRUGS USEFUL FOR THE STOMATOLOGIC, MOUTH AND ORAL CAVITY ANTI-INFLAMMATORY AND ANALGESIC THERAPIES

(57) Abstract: Pharmaceutical composition containing non-steroid anti-inflammatory drugs useful for the administration of said drugs in the analgesic therapy and in the prevention and treatment of stomatological and buccal inflammatory diseases, are capable of adhering to the mucosae of the absorption site, thereby promoting high absorption of the active ingredient in districts which are difficult to reach by the systemic administration, if not through very large dosages.

PHARMACEUTICAL COMPOSITIONS FOR THE TOPICAL ADMINISTRATION IN THE ORAL CAVITY OF NON-STEROID ANTI-INFLAMMATORY DRUGS USEFUL FOR THE STOMATOLOGIC, MOUTH AND ORAL CAVITY ANTI-INFLAMMATORY AND ANALGESIC THERAPIES

Disclosure of the invention.

The present invention relates to pharmaceutical compositions for the topical administration in the oral cavity of non-steroid anti-inflammatory drugs useful for the stomatologic, mouth and oral cavity anti-inflammatory and analgesic therapies.

The use of non-steroid anti-inflammatory drugs is the first therapeutical intervention in case of inflammatory diseases of the mouth and dental system. This class of medicaments is, in fact, known to have some analgesic activity which is only exerted when blood drug levels reach a comparatively higher concentration than that necessary to exert the real anti-inflammatory activity. To obtain a high drug concentration in blood, the so-called "fast release" formulations are made use of, wherein the dissolution of the active ingredient is promoted by suitably formulating it, for example through salification with high solubility counterions or amorphous dispersion of the drug on high solubility carriers: the acceleration of the drug dissolution rate immediately gives rise to a concentration peak at the absorption site, which corresponds to a higher concentration peak in the circulation thus exceeding the analgesic activity concentration threshold.

Therefore, in the case of systemic administration, a drug high concentration in blood is mandatory to obtain a suitable concentration reaching the analgesic threshold also at the oral district. As a consequence, high amounts of active ingredient are administered which thus exerts its action not only at the desired peripheral district, but at the whole body, even if it is not necessary.

Such drawback could be overcome by topically administering the active

ingredient formulated in pharmaceutical compositions providing sufficient absorption to reach effective concentration levels. At present, the commercially available formulations useful for the topical administration of anti-inflammatory drugs do not meet such requirement: they usually are, in fact, solutions or collutories in which the drug is dissolved in a mainly aqueous carrier, which remains in contact with the absorption site for a short time due to the immediate dilution with saliva and is quickly removed from the administration site, thus not reaching effective absorption levels.

It has now surprisingly been found that the administration of a non-steroid anti-inflammatory drug in a carrier with suitable anhydricity and amphiphilia characteristics promotes the absorption of the drug at the administration topical site until attaining an analgesically effective concentration, without making use of the higher dosages which would be necessary to obtain a comparable activity through systemic administration.

The invention therefore relates to compositions for the topical administration in the oral cavity of non-steroid anti-inflammatory drugs in the form of anhydrous semisolid gelled formulations.

Poorly hydrophilc active ingredients, which are difficult to formulate in the conventional aqueous carriers, are most suitable for this formulation in that they are hardly washed and diluted in biological fluids; examples of said drugs include Nimesulide, which is sparingly soluble in aqueous medium, Diclofenac acid and the arylpropionic anti-inflammatory derivatives, in a carrier with acidity characteristics which limit ionic dissociation.

The compositions of the invention preferably contain an anhydrous solvent optionally combined with viscosity-increasing/bioadhesive agents.

Examples of suitable solvents for use in the invention comprise polyglycols, glycerol and the short-chain ethers or esters thereof, optionally polyethoxylated semi-synthetic glycerides, sorbitan or sorbitol esters or ethers. Glycerol, polyethylene glycol 200 or 400 and diethylene glycol monoethyl ether (Transcutol®) are particularly

preferred.

The viscosity-increasing/bioadhesive agents are selected from acrylic or methacrylic acid polymers or copolymers, polyvinyl polymers, cellulose or carboxyalkylcellulose derivatives having high viscosity upon hydration. Particularly preferred is the use of a carboxyvinyl polymer. The compositions of the invention can further contain compounds providing the carrier with specific organoleptic characteristics, such as flavours, flavour and pH adjusters, dyes, sweetening agents, surfactants.

The compositions of the invention in the form of anhydrous gel will contain the active ingredient in a range from 0.5 to 10%, preferably from 1 to 5%.

The compositions of the invention will typically have viscosity ranging from 1,000 to 200,000 cps, preferably 5,000-100,000 cps.

The percentages of anhydrous solvent in the compositions can range from 5 to 50% by weight in the case of polyethylene glycol 200 or 400, from 5 to 30% in the case of glycerol and from 10 to 80% in the case of Transcutol®).

On the other hand, the bioadhesive agents will usually be present in 0.1 to 5% weight percentages.

The invention further relates to the process for the preparation of the formulations, which comprises the dissolution of the active ingredient in the anhydrous solvent and the successive addition of the viscosity-increasing/bioadhesive agents and optionally other excipients.

The formulations of the invention will usually be presented in the form of a anhydrous gel, clear, easy to spread by means of a spatula or more simply with a finger on the mucosae under treatment. The anhydricity of the preparation allows for the active ingredient to remain for a long time at the administration site, which is also favored by the hydration-induced bioadhesion which secures grafting through the polymer hydrophilic chains of the viscosity-increasing bioadhesive, thus ensuring a long-lasting, effective absorption of the active ingredient.

The following examples further illustrate the characteristics of the invention.

Example 1

30 g of Nimesulide are dissolved in a mixture prepared with 400 g Polyethylene glycol 200, 350 g of Polyethylene glycol 400, 100 g of propylene glycol and 100 g of diethylene glycol monoethyl ether. After dissolution of the active ingredient, 20 g of carboxyvinyl polymer known as Carbomer 934 ® are added: the final product is an anhydrous gel, smooth and easy to spread, which is distributed in aluminium tubes internally coated with polyethene.

Example 2

300 g of Nimesulide are dissolved in a mixture of anhydrous solvents consisting of 4 kg of diethylene glycol monoethyl ether, 3400 g of Polyethylene glycol 400, 1 kg of propylene glycol. The resulting mixture is added with 1 kg of glycerol and 300 g of Carbomer ® viscosity agent. The formulation is flavored with small amounts of flavor before being distributed in aluminium tubes internally coated with polyethene.

This formulation was clinically tested to reveal an absorption profile of 500 to 200,000 cPs.

Example 3

20 g of Ketoprofen are dissolved in a mixture consisting of 300 g of polyethylene glycol 400, 360 g of diethylene glycol monoethyl ether, 150 g of glycerol, 150 g of propylene glycol. The resulting solution is thickened by addition of 20 g of carboxyvinyl polymer and partitioned in aluminium tubes internally coated with polyethene. The final formulation is a clear anhydrous gel which is easy to spread and shows no tolerability problems.

CLAIMS

1. Compositions for the topical administration in the oral cavity of non-steroid anti-inflammatory drugs in the form of anhydrous gelled semisolid formulations.

2. Compositions as claimed in claim 1 wherein the non-steroid anti-inflammatory drugs cted from Nimesulide, Ketoprofen, Diclofenac and/or arylpropionic compounds.

3. Compositions as claimed in the above claims containing Nimesulide.

4. Compositions as claimed in claim 3, wherein Nimesulide or Ketoprofen are present in concentrations ranging from 0.5 to 10% w/w.

5. Compositions as claimed in claim 4, wherein Nimesulide or Ketoprofen are present in concentrations ranging from 1 to 5% w/w.

6. Compositions as claimed in any one of the above claims wherein the active ingredient is dissolved in an anhydrous solvent selected from polyglycols, glycerol and the short chain ethers or esters thereof, optionally polyethoxylated semi-synthetic glycerides, sorbitan or sorbitol ethers or esters.

7. Compositions as claimed in claim 6, wherein the solvent is selected from glycerol, polyethylene glycol 200 or 400, diethylene glycol monoethyl ether.

8. Compositions as claimed in any one of the above claims containing viscosity-increasing/bioadhesive agents.

9. Compositions as claimed in claim 8, wherein the viscosity-increasing/bioadhesive agents are selected from acrylic or methacrylic acid polymers or copolymers, polyvinyl polymers, cellulose derivatives or carboxyalkylcellulose with high viscosity after hydration.

10. Compositions as claimed in claim 9, wherein the viscosity-increasing/bioadhesive agents is a carboxyvinyl polymer.

11. Compositions as claimed in any one of the above claims further containing one or more excipients selected from surfactants, flavours, flavour or pH adjusters, sweetening agents, dyes.

12. Compositions as claimed in any one of the above claims with viscosities ranging from 1,000 to 200,000 cPs.

13. A process for the preparation of the formulations of claims 1-12 which comprises the dissolution of the active ingredient in the anhydrous solvent and the successive addition of the viscosity-increasing/bioadhesive agent and optionally other excipients.