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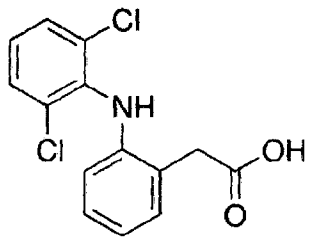
(54) Title: PRODUCTION METHOD FOR EFFERVESCENT FORMULATIONS COMPRISING DICLOFENAC

(57) Abstract: The present invention relates to a method used for production of effervescent formulations comprising diclofenac or a pharmaceutically acceptable salt thereof and effervescent formulations obtained by said method.

PRODUCTION METHOD FOR EFFERVESCENT FORMULATIONS COMPRISING DICLOFENAC

The present invention relates to a method used for production of effervescent formulations comprising diclofenac or a pharmaceutically acceptable salt thereof and to effervescent formulations obtained by said method.

2-[2-(2,6- dichlorophenyl) aminophenyl] ethanoic acid or diclofenac, which was first disclosed in the patent numbered US3558690, is shown with Formula I. Diclofenac and/or pharmaceutically acceptable salts thereof is an analgesic, anti-inflammatory and antirheumatismal drug belonging to the group of non-steroidal anti-inflammatory drugs (NSAID).



Formula I

Diclofenac has a white or almost-white colour and it is in form of crystalline powder. While it dissolves in methanol and ethanol, it sparingly dissolves in water.

In the prior art, the production method for non-effervescent but water-soluble tablets comprising diclofenac were disclosed in the patent application numbered EP0599767.

Diclofenac is a hygroscopic molecule. Furthermore, water solubility of this substance is fairly low. This situation causes problems such as late dissolution of water-soluble formulations comprising diclofenac in water and/or insufficient dissolution of the active substance they comprise. Therefore, an effective treatment cannot be carried out because a homogeneous solution cannot be obtained and not enough active substance can be absorbed during the administration of these formulations comprising diclofenac.

On the other hand, the active substance diclofenac has a bitter taste. Hence, it is inevitable that the formulation comprising diclofenac has a bad taste when dissolved in water or the residual active substance in the solution is taken by the patients without being dissolved. Therefore, this situation

results in negative outcomes like the patient being uncomfortable because of the bad taste of the medicine and therefore having difficulties of swallowing and use during the administration of the said medicines.

As is seen, there is need for formulations comprising diclofenac and/or a pharmaceutically acceptable salt thereof which are able to dissolve in water quickly and homogeneously, have high-absorption and pleasant taste; and methods used in the production of these formulations.

As a result of the studies they carried out in line with this need, the inventors has observed that effervescent formulations developed for preparation of medicine dosage forms comprising diclofenac and/or a pharmaceutically acceptable salt thereof solves problems such as late dissolution, low absorption and bad taste that are seen in the water soluble formulations in the prior art.

Surprisingly, the inventors have found out that effervescent formulations comprising diclofenac and prepared by a method comprising the steps of,

- Obtaining the first mixture by granulating diclofenac or a pharmaceutically acceptable salt thereof, effervescent base and some part of the effervescent acid,
- Obtaining a second mixture by granulating the rest of the effervescent acid and sweetener and/or taste regulating agent and,
- Mixing these two mixtures in the presence of at least one pharmaceutically acceptable excipient,

can dissolve quickly and homogeneously and have a pleasant taste.

According to this, the first aspect of the invention is a method for production of effervescent formulations comprising diclofenac or a pharmaceutically acceptable salt thereof characterized in that,

- The first mixture is obtained by granulating diclofenac or a pharmaceutically acceptable salt thereof with some part of the effervescent base and some part of the effervescent acid in step I,
- The second mixture is obtained by granulating the rest of the effervescent acid with sweetener and/or taste regulating agent and optionally adding at least one pharmaceutically acceptable excipient in step II,
- The final mixture is obtained by mixing the first and the second mixtures in the presence of at least one pharmaceutically acceptable excipient in step III.

Diclofenac which is used in the effervescent formulation prepared according to the production method of the invention can be in form of any salts thereof. Preferably, it is in form of diclofenac sodium or potassium, more preferably in form of diclofenac sodium.

The effervescent formulation prepared according to the production method of the invention comprises diclofenac or a pharmaceutically acceptable salt thereof in the range of 0,1-10%, preferably in the range of 0,2-8%, more preferably in the range of 0,5-5% by the total weight of the tablet.

The effervescent formulation prepared according to the production method of the invention comprises 5-250 mg, preferably 10-200 mg, more preferably 15-150 mg of diclofenac or a pharmaceutically acceptable salt thereof.

The effervescent formulation prepared according to the production method of the invention can be formulated in form of effervescent granule, effervescent powder or effervescent tablet. Preferably, it is in form of effervescent tablet.

The effervescent acid used in the effervescent formulations prepared according to the production method of the invention can be selected from a group comprising acids such as citric acid, tartaric acid, ascorbic acid, malic acid, fumaric acid, adipic and succinic acid, acetyl salicylic acid; acid salts such as sodium dihydrogen phosphate, sodium acid pyrophosphate, acid citrate salts, amino acid hydrochlorides, sodium acid sulphite; their hydrates and anhydrates. Preferably, citric acid is used.

The effervescent base used in the effervescent formulations prepared according to the production method of the invention can be selected from a group comprising potassium carbonate, potassium bicarbonate, potassium citrate, potassium hydroxide, sodium carbonate, sodium hydrogen carbonate, sodium hydrogen citrate or combinations thereof. Preferably, sodium hydrogen carbonate is used.

The effervescent formulations prepared according to the production method of the invention can further comprise other pharmaceutically acceptable excipients along with diclofenac or a pharmaceutically acceptable salt thereof, effervescent acid and effervescent base.

The effervescent formulation prepared according to the production method of the invention can comprise binder, lubricant, sweetener and/or taste regulating agent, filling agent, acidic agent, basic agent, wetting agent, dissolving agent, flavoring agent or combinations thereof.

The binder used in the effervescent formulations prepared according to the production method of the invention can be selected from, but not limited to, a group comprising starch, sucrose, glucose, dextrose, lactose, maltodextrin, gelatine; microcrystalline cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, polyvinylpyrrolidone (povidone), polyethylene glycol (PEG), calcium carbonate, calcium phosphate, sorbitol powder, xylitol, mannitol or a combination thereof.

The sweetener and/or taste regulating agent used in the effervescent formulations prepared according to the production method of the invention can be selected from, but not limited to, a group comprising sucralose, sucrose, fructose, glucose, galactose, xylose, dextrose, laevulose, lactose, maltose, maltodextrin, mannitol, maltitol, maltol, sorbitol, xylitol, erythritol, lactitol, isomalt, corn syrup, saccharine, saccharine salts, acesulfame potassium, aspartame, D-tryptophane, monoammonium glycyrrhizate, neohesperidin dihydrochalcone, thaumatine, neotame, alitame, stevioside and cyclamates or a combination thereof.

The flavouring agent used in the effervescent formulation prepared according to the production method of the invention can be selected from, but not limited to, a group comprising natural aroma oils, menthol, menthane, anethole, methyl salicylate, eucalyptol, cinnamon, lemon, orange, blackberry, cherry, vanillin or a combination thereof.

The lubricant used in the effervescent formulation prepared according to the production method of the invention can be selected from, but not limited to, a group comprising calcium stearate, magnesium stearate, polyethylene glycol, adipic acid, PEG 6000, polyvinyl alcohol, potassium benzoate, talc, sodium benzoate or a combination thereof.

The wetting agent used in the effervescent formulation prepared according to the production method of the invention can be selected from, but not limited to, a group comprising benzalkonium chloride, poloxamer, polyoxyethylene alkyl ester, docusate sodium and sodium lauryl sulphate.

The filling agent used in the effervescent formulation prepared according to the production method of the invention can be selected from, but not limited to, a group comprising ethyl cellulose, dicalcium phosphate, calcium phosphate, kaolin, lactose monohydrate, lactose anhydrous, mannitol, sodium chloride, starch, microcrystalline cellulose or a combination thereof.

The dissolving agent used in the effervescent formulation prepared according to the production method of the invention can be selected from, but not limited to, a group comprising ethanol,

glycerol, low molecular weight PEG, propylene glycol, dextrose and sorbitol or a combination thereof.

The acidic agent used in the effervescent formulations prepared according to the production method of the invention can be selected from, but not limited to, a group comprising acetic acid, citric acid, hydrochloric acid, lactic acid, malic acid, phosphoric acid, propionic acid, sulphuric acid, tartaric acid or a combination thereof.

The basic agent used in the effervescent formulation prepared according to the production method of the invention can be selected from, but not limited to, a group comprising calcium phosphate, monosodium glutamate, potassium citrate, sodium citrate dihydrate, sodium hydroxide, sodium phosphate, potassium bicarbonate, potassium hydroxide, sodium bicarbonate, sodium citrate dihydrate, triethanolamine or a combination thereof.

The method disclosed in the first step of the production method of the invention as granulating diclofenac or a pharmaceutically acceptable salt thereof with some part of the effervescent base and some part of the effervescent acid can comprise the steps of;

Ia. Mixing diclofenac or a pharmaceutically acceptable salt thereof with some part of the effervescent base and some part of the effervescent acid,

Ib. Preparing the first granulation solution comprising deionised water, binder, solvent, wetting agent and dissolving agent,

Granulating the mixture obtained in step Ia with the granulation solution obtained in step II, drying the granules and obtaining the first mixture. In step Ia, diclofenac or a pharmaceutically acceptable salt thereof; 25-75%, preferably 30-60% of the effervescent base by weight and 10-40%, preferably 15-35% of the effervescent acid by weight are mixed in a fluid bed dryer.

In step Ib, granulation solution is obtained by mixing wetting agent, disintegrant and dissolving agent along with deionised water and binder.

In step Ic, the mixture obtained in step Ia is granulated with the granulation solution obtained in step Ib and, the obtained granules are dried at a temperature in the range of 25-90°C, preferably in the range of 30-80°C, more preferably in the range of 40-75°C after the granulation process. The dried granules are sieved and the first mixture is obtained.

In the second step of the production method of the invention, the method which is disclosed as granulating the rest of the effervescent acid with sweetener and/or taste regulating agent and optionally adding at least one pharmaceutically acceptable excipient can comprise the steps of;

IIa. Mixing the rest of the effervescent acid with sweetener and/or taste regulating agent,

IIb. Preparing the second granulation solution comprising deionised water and acidic agent,

IIc. Granulating the mixture obtained in step IIa with the granulation solution obtained in step IIb,

IId. Obtaining the second mixture by adding the rest of the effervescent base, basic agent and at least one pharmaceutically acceptable excipient to the granules obtained in step IIc.

In step IIa; 60-90%, preferably 65-85% of the effervescent acid by weight, sweetener and/or taste regulating agent are mixed in fluid bed dryer.

In step IIb, the second granulation solution is obtained by dissolving acidic agent in deionised water.

In step IIc, the mixture obtained in step IIa is granulated with the granulation solution obtained in step IIb.

In step IId; 25-80%, preferably 40-70% of the effervescent base by weight, basic agent and lubricant are added to and mixed with the granules obtained in step IIc. After the second granulation process, this mixture is dried at a temperature in the range of 25-90°C, preferably in the range of 30-80°C, more preferably in the range of 40-75°C and the second mixture is obtained.

In the third step of the production method of the invention, the method which is disclosed as obtaining the final mixture by mixing the first and the second mixtures in the presence of at least one pharmaceutically acceptable excipient can comprise the steps of;

IIIa. Mixing the first and the second mixtures in the presence of at least one pharmaceutically acceptable excipient,

IIIb. Obtaining the final mixture in the step IIIa in a proper dosage form.

In the step IIIa, the final mixture is obtained by adding the second mixture obtained in step IId, filling agent and flavoring agent to the first mixture obtained in step Ic. The final mixture obtained is compressed in a proper dosage form, preferably in effervescent tablet form.

According to this, more specifically, a method for production of effervescent formulations comprising diclofenac or a pharmaceutically acceptable salt thereof characterized in that;

- In the first step, the first mixture is obtained by granulating diclofenac or a pharmaceutically acceptable salt thereof, 20-75% of the effervescent base by weight and 10-40% of the effervescent acid by weight;

- In the second step, the second mixture is obtained by granulating the rest of the effervescent acid with sweetener and/or taste regulating agent and adding lubricant to them;
- In the third step, the first and the second mixtures are mixed in the presence of at least one pharmaceutically acceptable excipient.

In more detail, a preferred embodiment of the production method of the invention comprises the following steps;

- In the first step, the first mixture is obtained by granulating diclofenac or a pharmaceutically acceptable salt thereof, 20-75% of the effervescent base by weight and 10-40% of the effervescent acid by weight, wherein said first mixture is obtained through the steps below:
  - Ia. Mixing diclofenac or a pharmaceutically acceptable thereof, 20-75% of the effervescent base by weight and 10-40% of the effervescent acid by weight,
  - Ib. Preparing the first granulation solution comprising deionised water, binder, solvent, wetting agent and dissolving agent,
  - Ic. Granulating the mixture obtained in step Ia with the granulation solution obtained in step II and obtaining the first mixture,
- In the second step, the second mixture is obtained by granulating the rest of the effervescent acid with sweetener and/or taste regulating agent and adding lubricant to it, wherein said second mixture is obtained through the steps below:
  - IIa. Mixing 60-90% of the effervescent acid by weight and sweetener and/or taste regulating agent,
  - IIb. Preparing the second granulation solution comprising deionised water and acidic agent,
  - IIc. Granulating the mixture obtained in the step IIa with the granulation solution obtained in step IIb,
  - IId. Obtaining the second mixture by adding 25-80% of the effervescent base by weight, basic agent and pharmaceutically acceptable lubricant to the granules obtained in step IIc.
- In the third step, the final mixture is obtained by mixing the first and the second mixtures in the presence of at least one pharmaceutically acceptable excipient, wherein said final composition is obtained through the steps below:
  - IIIa. Mixing the first and the second mixtures in the presence of a pharmaceutically acceptable filling agent and flavoring agent,
  - IIIb. Compressing the final mixture in form of tablet in step IIIa.

In the effervescent formulation prepared according to the production method of the invention comprises diclofenac or a pharmaceutically acceptable salt thereof in the range of 0,1-10%, effervescent acid in the range of 10-70%, effervescent base in the range of 5-50%, binder in the range of 0,01-3%, lubricant in the range of 1-10%, sweetener and/or taste regulating agent in the range of 0,2-5%, filling agent in the range of 2-15%, acidic agent in the range of 0,05-2%, basic agent in the range of 1-10%, wetting agent in the range of 0,01-2%, dissolving agent in the range of 0,05-4% and flavouring agent in the range of 0,2-3% in proportion to the total weight of the unit dose.

Effervescent formulations comprising diclofenac or a pharmaceutically acceptable salt thereof prepared according to the production method of the invention have analgesic, anti-inflammatory and antipyretic effect, and are used in the treatment of patients suffering from mild, moderate and severe pains, arthralgia, fever, toothache, dysmenorrhoea, toothache, myalgia, osteoarthritis, rheumatoid arthritis, backache.

The example below is given for the purpose of explaining the invention in more detail yet the invention is not limited to it:

EXAMPLE 1: Effervescent tablets comprising diclofenac

Component Name	% of amount in unit dose
Diclofenac Sodium	2,5%
Effervescent acid	45%
Effervescent base	28%
Binder	0,05%
Lubricant	4,25%
Sweetener and/or taste regulating agent	2,7%
Filling agent	6,68%
Acidic agent	0,5%
Basic agent	6,5%
Wetting agent	0,02%
Dissolving agent	1,7%
Flavoring agent	2,1%

In order to obtain the first mixture in the production method for preparation of the above mentioned effervescent tablets comprising diclofenac sodium;

Ia. Diclofenac sodium, 40% of the effervescent base by weight and 20% of the effervescent acid by weight are mixed.

Ib. The first granulation solution comprising deionised water, binder, solvent, wetting agent and dissolving agent is prepared.

Ic. The mixture obtained in step Ia is granulated with the granulation solution obtained in step Ib and dried.

In order to obtain the second mixture in the production method for the preparation of the above mentioned effervescent tablets comprising diclofenac sodium;

IIa. 80% of the effervescent acid by weight and sweetener and/or taste regulating agent are mixed.

IIb. The second granulation solution comprising deionised water and acidic agent is prepared.

IIc. The mixture obtained in step IIa is granulated with the granulation solution obtained in step IIb.

IIa. 60% of the effervescent base by weight, basic agent and lubricant are added to the granules obtained in step IIc.

Finally, the first and the second mixtures are mixed in the presence of filling agent and flavoring agent. The final mixture obtained is compressed in tablet form.

EXAMPLE 2: Effervescent granules comprising diclofenac

Component name	% of amount in unit dose
Diclofenac sodium	2,25%
Effervescent acid	48%
Effervescent base	26%
Binder	0,25%
Lubricant	4,5%
Sweetener and/or taste regulating agent	1,7%
Filling agent	7,2%
Acidic agent	0,1%
Basic agent	5%
Wetting agent	0,05%
Dissolving agent	1,95%
Flavoring agent	3%

In order to obtain the first mixture in the production method for the preparation of the above mentioned effervescent granules comprising diclofenac sodium;

Ia. Diclofenac sodium, 40% of the effervescent base by weight and 20% of the effervescent acid by weight are mixed.

Ib. The first granulation solution comprising deionised water, binder, solvent, wetting agent and dissolving agent is prepared.

Ic. The mixture obtained in step Ia is granulated with the granulation solution obtained in step Ib and dried.

In order to obtain the second mixture in the production method for the preparation of the above mentioned effervescent granules comprising diclofenac sodium;

IIa. 80% of the effervescent acid by weight and sweetener and/or taste regulating agent are mixed.

IIb. The second granulation solution comprising deionised water and acidic agent is prepared.

IIc. The mixture obtained in step IIa is granulated with the granulation solution obtained in step IIb.

IId. 60% of the effervescent base by weight, basic agent and lubricant are added to the granules obtained in step IIc.

Finally, the first and the second mixtures are mixed in the presence of filling agent and flavoring agent. The final mixture obtained in granule form is filled into sachets.

CLAIMS

1. A method for production of effervescent formulations comprising diclofenac or a pharmaceutically acceptable salt thereof characterized in that,
   - Diclofenac or a pharmaceutically acceptable salt thereof, some part of the effervescent base and some part of the effervescent acid are granulated and the first composition is obtained in the first step;
   - The rest of the effervescent acid is granulated with sweetener and/or taste regulating agent in the second step;
   - The first and the second mixtures are mixed in the presence of at least one pharmaceutically acceptable excipient in the third step.
2. The production method according to claim 1, wherein the second mixture is obtained by adding at least one pharmaceutically acceptable excipient to the granules obtained by granulating the rest of the effervescent acid with sweetener and/or taste regulating agent in the second step.
3. The production method according to claims 1 and 2, wherein the final mixture is obtained by mixing the mixtures obtained in the first and the second steps in the presence of at least one pharmaceutically acceptable excipient in the third step.
4. The production method according to any preceding claims characterized in that said method comprises the steps of,
   - Ia. Mixing diclofenac or a pharmaceutically acceptable salt thereof, some part of the effervescent base and some part of the effervescent acid,
   - Ib. Preparing the first granulation solution comprising deionised water, binder, solvent, wetting agent and dissolving agent,
   - Ic. Obtaining the first mixture by granulating the mixture obtained in step Ia with the granulation solution obtained in step Ib and drying them.
5. The production method according to any preceding claims characterized in that said method comprises the steps of,
   - IIa. Mixing the rest of the effervescent acid and sweetener and/or taste regulating agent,
   - IIb. Preparing the second granulation solution comprising deionised water and acidic agent,
   - IIc. Granulating the mixture obtained in step IIa with the granulation solution obtained in step IIb,

IId. Obtaining the second mixture by adding the rest of the effervescent base, basic agent and at least one pharmaceutically acceptable excipient to the granules obtained in step IIc.

6. The production method according to any preceding claims characterized in that said method comprises the steps of,

IIIa. Mixing the first and the second mixtures in the presence of at least one pharmaceutically acceptable excipient,

IIIb. Obtaining the final composition obtained in the step IIIa in a proper dosage form.

7. The production method according to claim 5, wherein the second mixture is obtained by adding 25-80% of the effervescent base by weight, basic agent and lubricant to the granules obtained in step IIc.

8. The production method according to claims 4-6, wherein the final mixture is obtained by adding the second mixture obtained in the IId, filling agent and flavoring agent to the first mixture obtained in step Ic.

9. The production method according to claims 4 and 5, wherein 20-75% of the effervescent base by weight is included in the first granulation process while 25-80% of it is included in the second mixture.

10. The production method according to claims 4 and 5, wherein 10-40% of the effervescent acid by weight is included in the first granulation process while 60-90% of it is included in the second granulation process.

11. The production method according to claims 4 and 5, wherein granules obtained after the first and second granulation processes are dried at a temperature between 25-90°C.

12. The production method according to claim 5, wherein the acidic agent is added to the second granulation solution while the basic agent is added to the second mixture.

13. An effervescent formulation prepared by a production method claimed in any preceding claims, wherein said formulation comprises diclofenac or a pharmaceutically acceptable salt thereof, effervescent acid, effervescent base, binder, lubricant, sweetener and/or taste regulating agent, filling agent, acidic agent, basic agent, wetting agent, dissolving agent, flavoring agent or a combination thereof.

14. The formulation according to claim 13, wherein diclofenac or a pharmaceutically acceptable salt thereof is diclofenac sodium and/or diclofenac potassium.

15. The formulation according to claims 13 and 14, wherein diclofenac or a pharmaceutically acceptable salt thereof is diclofenac sodium.

16. The formulation according to any claims between 13 and 15, wherein diclofenac or a pharmaceutically acceptable salt thereof comprises 0,1-10% of total tablet weight.

17. The formulation according to any claims between 13 and 16, wherein said formulation comprises 5-250 mg diclofenac or a pharmaceutically acceptable salt thereof.
18. The formulation according to any claims between 13 and 17 characterized in that said formulation is formulated in form of effervescent granule, effervescent powder or effervescent tablet.
19. The formulation according to any claims between 13 and 18, wherein said formulation is in effervescent tablet form.
20. The formulation according to any claims between 13 and 19, wherein the effervescent acid comprised in said formulation is selected from a group comprising acids like citric acid, tartaric acid, ascorbic acid, malic acid, fumaric acid, adipic and succinic acid, acetyl salicylic acid; acid salts like sodium dihydrogen phosphate, sodium acid pyrophosphate, acid citrate salts, amino acid hydrochlorides, sodium acid sulphite.
21. The formulation according to any claims between 13 and 20, wherein citric acid is used as the effervescent acid.
22. The formulation according to any claims between 13 and 21 wherein the effervescent base comprised in said formulation is selected from a group comprising potassium carbonate, potassium bicarbonate, potassium citrate, potassium hydroxide, sodium carbonate, sodium bicarbonate, sodium hydrogen citrate or combinations thereof.
23. The formulation according to any claims between 13 and 22, wherein sodium hydrogen carbonate is used as the effervescent base.
24. The formulation according to any claims between 13 and 23, wherein the binder comprised in said formulation is selected from a group comprising starch, sucrose, glucose, dextrose, lactose, maltodextrin, gelatine; microcrystalline cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose polyvinylpyrrolidone (povidone), polyethylene glycol (PEG), calcium carbonate, calcium phosphate, sorbitol powder, xylitol, mannitol or a combination thereof.
25. The formulation according to any claims between 13 and 24, wherein the sweetener and/or taste regulating agent comprised in said formulation is selected from a group comprising sucralose, sucrose, fructose, glucose, galactose, xylose, dextrose, laevulose, lactose, maltose, maltodextrin, mannitol, maltitol, maltol, sorbitol, xylitol, erythritol, lactitol, isomalt, corn syrup, saccharine, saccharine salts, acesulfame potassium, aspartame, D-tryptophan, monoammonium glycyrrhizinate, neohesperidin dihydrochalcone, thaumatine, neotame, alitame, stevioside and cyclamates or a combination thereof.
26. The formulation according to any claims between 13 and 25, wherein the flavouring agent comprised in said formulation is selected from a group comprising natural aroma oils,

menthol, menthane, anethole, methyl salicylate, eucalyptol, cinnamon, lemon, orange, blackberry, cherry, vanillin or a combination thereof.

27. The formulation according to any claims between 13 and 26, wherein the lubricant comprised in said formulation is selected from a group comprising calcium stearate, magnesium stearate, polyethylene glycol, adipic acid, PEG 6000, polyvinyl alcohol, potassium benzoate, talc, sodium benzoate or a combination thereof.
28. The formulation according to any claims between 13 and 27, wherein the wetting agent comprised in said formulation is selected from a group comprising benzalkonium chloride, poloxamer, polyethylene alkyl, ester, docusate sodium and sodium lauryl sulphate.
29. The formulation according to any claims between 13 and 28, wherein the filling agent comprised in said formulation is selected from a group comprising ethyl cellulose, dicalcium phosphate, calcium phosphate, kaolin, lactose monohydrate, lactose anhydrous, mannitol, sodium chloride, starch, microcrystalline cellulose or a combination thereof.
30. The formulation according to any claims between 13 and 29, wherein the dissolving agent comprised in said formulation is selected from a group comprising ethanol, glycerol, low molecular weight PEG, propylene glycol, dextrose and sorbitol or a combination thereof.
31. The formulation according to any claims between 13 and 30, wherein the acidic agent comprised in said formulation is selected from a group comprising acetic acid, citric acid, hydrochloric acid, lactic acid, malic acid, phosphoric acid, propionic acid, sulphuric acid, tartaric acid or a combination thereof.
32. The formulation according to any claims between 13 and 31, wherein the basic agent comprised in said formulation is selected from a group comprising calcium phosphate, monosodium glutamate, potassium citrate, sodium citrate dihydrate, sodium hydroxide, sodium phosphate, potassium bicarbonate, potassium hydroxide, sodium bicarbonate, sodium citrate dihydrate, triethanolamine or a combination thereof.
33. The formulation according to any claims between 13 and 32, wherein said formulation comprises diclofenac or a pharmaceutically acceptable salt thereof in the range of 0,1-10%; effervescent acid in the range of 10-70%; effervescent base in the range of 5-50%; binder in the range of 0,01-3%; lubricant in the range of 1-10%; sweetener and/or taste regulating agent in the range of 0,2-5%; filling agent in the range of 2-15%; acidic agent in the range of 0,05-2%; basic agent in the range of 1-10%; wetting agent in the range of 0,01-2%; dissolving agent in the range of 0,05-4% and flavouring agent in the range of 0,2-3% in proportion to total weight of the unit amount.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2012/000128

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20 A61K31/196 A61P29/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MC 200 018 A (SETEX SAM [MC]) 28 March 2001 (2001-03-28) page 3, line 16 - line 19 examples -----	1-33
A	EP 0 642 784 A1 (GERGELY GERHARD [AT]) 15 March 1995 (1995-03-15) column 1, line 38 - line 43 examples -----	1-33

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2013	14/02/2013

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2012/000128

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