Description

This invention relates to a pharmaceutical composition, in particular to a pharmaceutical composition for the relief of mild to severe pain and for the treatment of inflammation in musculo- skeletal disorders.

Narcotic analgesics, such as codeine and dihydrocodeine, have been used in the relief of pain, especially mild to severe pain. Severe pain, in particular, requires the use of large and increasing doses of a narcotic analgesic.

A major disadvantage of narcotic analgesics is that patients may develop a dependence and tolerance to their action. Further adverse reactions, such as respiratory and circulatory depression, are observed when large doses of narcotic analgesics are used.

Non-steroidal anti-inflammatory drugs, such as ibuprofen, have been used in rheumatic and degenerative diseases of the joints, for reducing platelet adhesiveness and for dental pain.

European Patent Application No. 68838A (Upjohn) describes the synergistic effect obtained for the management of moderate to severe pain when a combination of narcotic analgesic and ibuprofen is administered.

In the Examples of EP 68838A, tablets containing morphine, ibuprofen and magnesium stearate as lubricant, are disclosed. The applicant also states, at page 9, lines 22 to 26, that tablets containing ibuprofen and codeine may be prepared simply by replacing the morphine in the exemplified tablets with codeine.

The present inventors have found that tablets containing a narcotic analgesic, such as codeine, a non-steroidal anti-inflammatory carboxylic acid, such as ibuprofen, and magnesium stearate, as described in EP 68838A, exhibit serious incompatability, poor crushing strength and long disintegration times.

It is therefore a primary object of the present invention to provide a tablet containing both a narcotic analgesic and a non-steroidal anti-inflammatory carboxylic acid which overcomes, to a substantial degree, the above problems.

Other objects and advantages of the present invention will become apparent from the following detailed description thereof.

According to the present invention there is provided a pharmaceutical composition in the form of a multiphase tablet comprising at least one narcotic analgesic phase containing a therapeutically effective quantity of a narcotic analgesic or an analgesically effective salt thereof and at least one non-steroidal anti-inflammatory phase containing a therapeutically effective quantity of a non-steroidal anti-inflammatory carboxylic acid or an anti-inflammatory salt or ester thereof wherein the at least one narcotic analgesic phase is free from a non-steroidal anti-inflammatory carboxylic acid or salt or ester thereof, stearic acid and a stearate salt, and the at least one non-steroidal anti-inflammatory phase is free from a narcotic analgesic or salt thereof, stearic acid and a stearate salt, and further wherein, both the at least one narcotic analgesic phase and the at least one non-steroidal anti-inflammatory phase contain at least one self-lubricating, compression aid.

Preferably the self-lubricating compression aid is a self-lubricating, direct compression aid.

Preferably the composition is in the form of a layered tablet, especially a bilayer tablet. Optionally the layered tablet may be film coated.

The narcotic analgesic may be naturally occurring, semi-synthetic or synthetic. Examples include pentazocine (HCl salt), pethidine (HCl salt) and phenazocine (HBr salt). Preferably, however, the narcotic analgesic is a morphinan-6-ol or a morphinan-6-one derivative, especially morphine (sulphate), ethylmorphine (HCl salt), hydromorphone (HCl salt), hydrocodone (tartrate), dihydrocodeine (tartrate) and, which is particularly preferred, codeine (phosphate).

Analgesically effective salts of the narcotic analgesics of the present invention must be pharmaceutically acceptable.

The non-steroidal anti-inflammatory carboxylic acid will generally be an aromatic or heterocyclic carboxylic acid. Examples include aspirin, fenbufen, flufenamic acid, indomethacin, meclofenamic acid (sodium salt), sulindac and tolmetin (sodium salt). Preferably, however, the non-steroidal anti-inflammatory carboxylic acid is a benzeneacetic acid, such as alclofenac, diclofenac (sodium salt) and fenclofenac, a 2-naphthylpropionic acid, such as naproxen (sodium salt), or, which is particularly preferred, a 2-phenylpropionic acid, such as fenoprofen (sodium or calcium salt), flurbiprofen, indoprofen, ketoprofen and, especially, ibuprofen.

Anti-inflammatory effective salts or esters of the non-steroidal anti-inflammatory carboxylic acids of the present invention must be pharmaceutically acceptable, e.g. alkali metal salt and C_1-C_6 alkyl esters.

Therapeutically effective quantities of the present narcotic analgesics or salts thereof and non-steroidal anti- inflammatory carboxylic acids or salts or esters thereof will be sufficient, in combination, either to relieve mild to severe pain or to treat inflammatory conditions.

Preferred therapeutically effective quantities of the preferred narcotic analgesics and the preferred non-steroidal anti-inflammatory carboxylic acids of this invention are listed in the Table.

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Table

Narcotic Analgesic	Therapeutically effective quantity	
	Preferred Single Dose	Particularly Preferred Single Dose
Codeine	5–60 mg	7.5–30 mg
Dihydrocodeine	10–60 mg	20–40 mg
Ethylmorphine	5–60 mg	
Hydrocodone	5–20 mg	
Hydromorphone	1–5 mg	
Morphine	2–120 mg	5–100 mg
Pentazocine	10–100 mg	
Pethidine	20–150 mg	
Phenazocine	2.5–20 mg	
Non Steroidal Anti-inflammatory Carboxylic Acid		
Aspirin	200–1000 mg	300–900 mg
Alclofenac	400–1000 mg	
Diclofenac	25–75 mg	25–50 mg
Fenbufen	200–900 mg	300–600 mg
Fenclofenac	200–600 mg	
Fenoprofen	200–800 mg	300–600 mg
Flufenamic acid	50–250 mg	
Flurbiprofen	25–100 mg	
Ibuprofen	50–800 mg	200–600 mg
Indomethacin	20–100 mg	25–75 mg
Indoprofen	50–200 mg	100–200 mg
Ketoprofen	50–200 mg	
Meclofenamic acid	50–200 mg	
Naproxen	250–1000 mg	500–750 mg
Sulindac	100–200 mg	
Tolmetin	200–600 mg	200–600 mg

In a particularly preferred embodiment of the present composition the narcotic analgesic phase contains codeine (as its phosphate salt) and the non-steroidal anti-inflammatory phase contains ibuprofen (as the free acid).

As mentioned above, when the present inventors attempted to prepare narcotic analgesic/non-steroidal anti-inflammatory carboxylic acid (especially codeine/ibuprofen) tablets as in EP 66838A they found that the tablets exhibited poor pharmaceutical qualities. This was surprisingly found to be caused primarily by incompatability between the narcotic analgesic (codeine), the non-steroidal anti-inflammatory carboxylic acid (ibuprofen) and the lubricant employed, magnesium stearate.

Having made this observation, the present inventors then overcame these problems by an inventive combination of devices. These were

(i) Separating the narcotic analgesic or salt thereof and the non-steroidal anti-inflammatory carboxylic acid or salt or ester thereof in a multi-phase, preferably layered, tablet,

(ii) Removing stearic acid and/or stearate salts (especially magnesium stearate) from the composition, and

(iii) Adding at least one self lubricating, direct compression aid, preferably a self lubricating, direct compression aid, to the mixtures used to form both the at least one narcotic analgesic and the at least one non-steroidal anti-inflammatory phases of the tablet in order to provide the lubrication necessary in tablet formation.

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The self lubricating compression aids, preferably self lubricating, direct compression aids, employed in the present pharmaceutical composition combine at least two properties required of tablet vehicles. First they produce hard, stable tablets via compression, preferably via direct compression, and second they act as a lubricant to facilitate tablet ejection after compression. Examples of such compression aids will be well known to those skilled in the tablet formulation art. Amongst the aids that are preferred in the present composition are Elcema G-250 (Trade Mark, Degussa, cellulose granules derived from powdered cellulose N.F.), Starch 1500 (Trade Mark, Colorcon, a free flowing, directly compressible starch), and, which is particularly preferred, microcrystalline cellulose, especially Avicel (Trade Mark, FMC).

In addition to self lubricating, compression aids, the present composition may also contain, in one or more of its phases, other additives and components, provided they are compatible with the narcotic analgesic or salt thereof and the non-steroidal anti-inflammatory carboxylic acid or salt or ester thereof. Suitable materials include

(a) Binders, such as cellulose and its derivatives, e.g. ethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, starches, polyvinyl pyrrolidone, natural gums and gelatin,
(b) Glidants, such as talc and fumed silica,
(c) Anti-Adherents, such as talc, fumed silica and corn starch,
(d) Disintegrants, such as starch and its derivatives, (e.g. sodium starch glycollate), microcrystalline cellulose, croscarmellose sodium (Ac-Di-Sol, Trade Mark), low substituted hydroxypropyl cellulose and cross-linked polyvinylpyrrolidone,
(e) Colorants, Flavorants and Sweeteners.

In addition to the above materials, in á further aspect of the present composition, the at least one non-steroidal anti-inflammatory and/or narcotic analgesic phases may also contain substances suitable for the formation of a controlled release formulation. In particular the phase or phases may contain a hydrated water soluble hydroxy alkyl cellulose, especially hydroxyethyl cellulose, and a higher aliphatic alcohol, especially cetostearyl alcohol, as described in British Patent No. 1405088 (equivalent to US 3965256 and US 4235870), the contents of which documents are herein incorporated by way of reference.

Advantageously, the present multi-phase tablet may have, as one of its phases, a protective coating which may, for example, serve to mask the taste of both the non-steroidal anti-inflammatory carboxylic acid or salt or ester thereof and the narcotic analgesic or salt thereof. Suitable coating materials, which must be compatible with both the anti-inflammatory carboxylic acid or salt or ester thereof and the narcotic analgesic or salt thereof will be known to those skilled in this art. An example favoured by the present inventors uses hydroxypropyl methyl cellulose as the film former and propylene glycol as the plasticiser.

The precise amount of non-steroidal anti-inflammatory carboxylic acid or salt or ester thereof and narcotic analgesic or salt thereof present in the present pharmaceutical composition will be determined by, amongst other factors,

(a) the number of times per day the composition is to be administered,
(b) whether the at least one non-steroidal anti-inflammatory and/or narcotic analgesic phases are a normal or controlled release formulation, and
(c) the type of treatment required and stage of treatment reached by the patient.

For most of the therapeutic applications (e.g. treatment of pain and inflammation) envisaged by the present inventors, tablets of the present type will contain an amount of narcotic analgesic and non-steroidal anti-inflammatory carboxylic acid as set out in the Table above. If a salt or ester is employed the dose will be adjusted accordingly to give the required amount of base or acid. Thus, tablets containing ibuprofen and codeine will preferably contain between 50 and 800 mg, especially between 200 and 600 mg, of ibuprofen and between 5 and 60 mg, especially between 7.5 and 30 mg, of codeine.

The amount and/or ratio of self lubricating, compression aids, together with, as required, binders, glidants, anti-adherents, disintegrants, colorants, flavorants, sweeteners, etc. contained in the present pharmaceutical composition is determined by, amongst other factors,

(a) the amount of non-steroidal anti-inflammatory carboxylic acid or salt or ester thereof and narcotic analgesic or salt thereof present in the tablet's phases,
(b) the requirement of tablet integrity,
(c) the time for tablet disintegration required,
(d) the rate of tablet dissolution required,
(e) the requirement of tablet content uniformity, and
(f) the weight, thickness and size of the tablet.

Given the number of variables involved in the formulation of a pharmaceutical composition according to the present invention, it is difficult to give specific ranges for the concentrations of the above materials. In a preferred embodiment of the present pharmaceutical composition, however, especially wherein the at least one self lubricating compression aid comprises microcrystalline cellulose, the concentration

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of the compression aid in the at least one non-steroidal anti-inflammatory phase is between 10% and 90%, especially between 15% and 40%, by wt. (of the phase), whilst the concentration of the compression aid in the at least one narcotic analgesic phase is between 50% and 99%, especially between [illegible] and 95%, by wt. of the phase.

The present pharmaceutical composition may be prepared by direct compression, but is preferably prepared by wet granulation techniques. Thus, in a further aspect of the present invention, there is provided a wet granulation process for the preparation of a pharmaceutical composition according to this invention comprising

(a) granulating a narcotic analgesic or an analgesically effective salt thereof with at least one self lubricating, compression aid to form narcotic analgesic granules,

(b) granulating a non-steroidal anti-inflammatory carboxylic acid or an anti-inflammatory salt or ester thereof with at least one self lubricating, compression aid to form non-steroidal anti-inflammatory granules, and

(c) compressing the narcotic analgesic granules and the non-steroidal anti-inflammatory granules to form a multi-phase tablet.

In both steps (a) and (b) of the above process two methods of granulation may be used. In the first method, the drug, the compression aid and a binder are dry mixed. The mixed powders are then granulated by wetting with a solvent. In the second method, the drug and the compression aid are dry mixed and then granulated by wetting with a solution of a binder.

Suitable binders for these methods are hydroxypropylmethyl cellulose or polyvinylpyrrolidone.

The present pharmaceutical composition, together with processes for its preparation, will now be described by way of example only.

Comparative Examples

A. Combination of Ibuprofen and Codeine within a Single Layer Tablet with Magnesium Stearate as Lubricant

Single layer tablets were prepared from the following ingredients using a wet granulation process.

	mg/tablet
Ibuprofen	200.00
Codeine Phosphate	12.50
Microcrystalline Cellulose (Avicel PH 102)	23.75
Croscarmellose Sodium (Ac-Di-Sol)	5.00
Hydroxypropylmethyl cellulose (6 cps)	3.75
Magnesium Stearate	2.45

These tablets had poor disintegration times, poor crushing strengths and exhibited sticking problems on compression.

B. Combination of Ibuprofen and Codeine within a Single Layer Tablet

Single layer tablets were prepared from the following ingredients using a wet granulation process.

	mg/tablet
Ibuprofen	200.0
Codeine Phosphate	12.5
Microcrystalline cellulose (Avicel PH 102. Trade Mark)	95.4
Sodium Starch Glycollate (Explotab, Trade Mark)	45.0
Hydroxypropyl methyl cellulose (viscosity, 3 cps)	7.1

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When tablets prepared in this manner were compressed to crushing strengths of 2.0–3.8 kN (9–17 kp), they exhibited sticking and ejection problems. The tablets, when prepared, had unacceptably long disintegration times.

C. Bi-Layer Formulation with Magnesium Stearate Present as a Lubricant

An ibuprofen layer having the following ingredients (in mg) was prepared by a wet granulation process.

Ibuprofen	200.00
Microcrystalline cellulose (Avicel PH 102)	70.84
Sodium Starch Glycollate (Explotab)	45.00
Hydroxypropylmethyl cellulose (3 cps)	8.16
Sodium Lauryl Sulphate	1.00
Erythrosine Aluminium Lake	3.28

A codeine layer having the following ingredients (in mg) was prepared by a wet granulation process,

Codeine Phosphate	12.5
Dicalcium Phosphate	259.5
Hydroxypropylmethyl cellulose (3 cps)	8.7
Sodium Starch Glycollate	12.6
Magnesium Stearate	1.7

When the two layers were compressed together the codeine content decreased markedly after short term stability at room and elevated temperatures. Also a brown colour formed, especially at the interface between the two layers.

D. Bi-Layer Formulation with Magnesium Stearate as Lubricant

The ibuprofen layer was prepared as described in Example C. The codeine layer was prepared from the following ingredients (in mg) by a wet granulation process,

Codeine Phosphate	12.5
Microcrystalline cellulose (Avicel PH 102)	267.0
Hydroxypropyl methyl cellulose (3 cps)	7.0
Sodium Starch Glycollate (intragranular)	3.0
Sodium Starch Glycollate (extragranular)	9.0
Magnesium Stearate	1.5

When the codeine layer was compressed it was found that crushing strengths above 1.3 kN (6 kp) were difficult to achieve even with increasing compression forces.

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Examples According to the Invention

Example 1

Ibuprofen layer

An ibuprofen layer having the following ingredients (in mg) was prepared by a wet granulation process.

Ibuprofen	200.0
Microcrystalline cellulose (Avicel PH 102)	65.0
Sodium Starch Glycollate	20.0
Hydroxypropylmethyl cellulose (3 cps)	15.0

The ibuprofen, microcrystalline cellulose, sodium starch glycollate and hydroxypropyl methyl cellulose were dry mixed. Water was then added to the dry powder and the mixture was granulated to give pharmaceutical ibuprofen containing granules.

Codeine layer

A codeine layer containing the following ingredients (in mg) was prepared by a wet granulation process.

Codeine Phosphate	12.50
Microcrystalline cellulose (Avicel PH 102)	227.47
Starch 1500 (Trade Mark), Ingragranular	20.00
Starch 1500, Extragranular	40.00

Codeine Phosphate, microcrystalline cellulose and intragranular Starch 1500 were dry mixed. Water was then added and the mixture was granulated to form pharmaceutical, codeine containing granules. Starch 1500 was then mixed with the granules. Finally the codeine and ibuprofen granules were compressed to give an ibuprofen-codeine bilayer tablet with a crushing strength of 2.5–2.7 kN (11–12 kp).

Example 2

The procedure of Example 1 was followed except that the ibuprofen layer had the following composition (in mg),

Ibuprofen	200.00
Microcrystalline cellulose (Avicel PH 102)	50.00
Sodium Starch Glycollate	12.50
Hydroxypropylmethyl cellulose (3 cps)	12.50

Example 3

The procedure of Example 1 was followed except that the ibuprofen layer had the following composition (in mg),

Ibuprofen	200.0
Microcrystalline cellulose (Avicel PH 102)	70.84
Sodium Starch Glycollate	45.00
Hydroxypropylmethyl cellulose (3 cps)	8.16
Sodium Lauryl Sulphate	1.00
Erythrosine Aluminium Lake	3.28

The sodium lauryl sulphate and the erythrosine aluminium lake were mixed in the dry powder prior to the addition of water. In this case the resulting tablet was coated using hydroxypropylmethyl cellulose as film former, and PEG400 as plasticiser.

Example 4

Ibuprofen layer

This was prepared as described in Example 3.

Codeine layer

A codeine layer containing the following ingredients (in mg) was prepared by a wet granulation process.

Codeine Phosphate	12.50
Microcrystalline cellulose (Avicel PH 102)	227.50
Starch 1500	40.00
Polyvinylpyrrolidone (Kollidon K30, Trade Mark)	10.00
Microcrystalline cellulose (Avicel PH 101)	40.00

Codeine Phosphate, microcrystalline cellulose (Avicel PH102) and Starch 1500 were dry mixed. An aqueous solution of polyvinylpyrrolidone was then added to the dry powder and the mixture was granulated to give codeine granules. Microcrystalline cellulose (Avicel PH101) was then mixed with the granules. Finally the codeine and ibuprofen granules were compressed to give an ibuprofen-codeine bilayer tablet with a crushing strength of 2.5–2.7 kN (11–12 kp).

Example 5

The procedure of Example 4 was followed except that the ibuprofen layer had the following composition (in mg).

Ibuprofen	200.00
Microcrystalline cellulose (Avicel PH 102)	68.59
Sodium Starch Glycollate	45.00
Hydroxypropylmethyl cellulose (3 cps)	8.16
Erythrosine Aluminium Lake	3.25

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Example 6

The procedure of Example 5 was followed except that the amount of Starch 1500 in the codeine layer was reduced to 25.0 mg. In this case the resulting bilayer tablet was coated with hydroxypropylmethylcellulose as film former, and propylene glycol as plasticiser.

Tablets prepared in accordance with Examples 1 to 6 above exhibited pharmaceutically acceptable properties with regard to stability, disintegration times and dissolution rates.

Example 7

Ibuprofen Layer

Ibuprofen (30g), microcrystalline cellulose (Avicel pH 102, 5.01g), lactose anhydrous (5.01g), hydroxyethyl cellulose (0.5g), hydroxypropylmethyl cellulose (5cps, 0.95g) and trisodium 7-hydroxy-8-(4-sulphonato-1-naphthylazo) naphthalene-1,3-di sulphonate (onceau 4R, Trade Mark, 0.43g) were dry blended. To the mixture was added sufficient water to produce a granulated mass.

The wet granules were then partially dried in a Fluid Bed dryer at 50°C. The partially dried mass was granulated through a 12 mesh screen and then further dried. The dried granules were passed through a 16 mesh screen.

Molten cetostearyl alcohol (1.0g) was then added, with mixing, to the granules. Finally, talc (0.4g) was blended with the granules.

Codeine Layer

Codeine granules were prepared as described in Example 4 above.

Finally the codeine and the ibuprofen granules were compressed to give an ibuprofen-codeine bilayer tablet containing 300mg ibuprofen/12.5mg codeine phosphate and having a controlled release ibuprofen layer and a normal release codeine layer.

Tablets prepared in accordance with Example 7 exhibited pharmaceutically acceptable properties with regard to stability, disintegration times and dissolution rates.

Example 8

The procedure of Example 7 was followed except that the codeine layer had the following composition (in mg),

Codeine Phosphate	20.0
Microcrystalline cellulose (Avicel PH 102)	364.0
Starch 1500	40.0
Polyvinylpyrrolidone	16.0
Microcrystalline cellulose	64.0

Again, tablets prepared in accordance with Example 8 exhibited pharmaceutically acceptable properties with regard to stability, disintegration times and dissolution rates.

Example 9

The procedure of Example 8 was followed. The tablets were then film coated with hydroxypropylmethyl cellulose as film former and propylene glycol as plasticiser.

Example 10

The procedure of Example 4 was followed except that the codeine layer had the following composition (in mg),

Codeine Phosphate	12.5
Microcrystalline cellulose (Avicel PH 102)	227.5
Starch 1500	60.0

The tablets were film coated with hydroxypropylmethyl cellulose as film former and polyethylene glycol as plasticiser.

Example 11

The procedure of Example 4 was followed except that dihydrocodeine tartrate replaced codeine phosphate and the dihydrocodeine layer had the following composition (in mg),

Dihydrocodeine tartrate	30.0
Microcrystalline cellulose (Avicel PH 102)	200.0
Starch 1500	40.0
Polyvinylpyrrolidone (PVP–K30)	10.0
Microcrystalline cellulose (Avicel PH 101)	30.0

Example 12

The procedure of Example 4 was followed except that naproxen replaced ibuprofen and the naproxen layer had the following composition (in mg),

Naproxen	500.0
Microcrystalline cellulose (Avicel PH 102)	150.0
Starch 1500	45.0
Sodium Starch Glycollate (Explotab)	100.0
Hydroxypropylmethyl cellulose	20.0

Example 13

The procedure of Example 4 was followed except that flurbiprofen replaced ibuprofen and the flurbiprofen layer had the following composition (in mg),

Flurbiprofen	100.0
Microcrystalline cellulose (Avicel PH 102)	36.0
Sodium Starch Glycollate	20.0
Hydroxypropylmethyl cellulose	5.0
Erythrosine Aluminium Lake	1.5

Claims for the Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A pharmaceutical composition in the form of a multiphase tablet comprising at least one narcotic analgesic phase containing a therapeutically effective quantity of a narcotic analgesic or an analgesically effective salt thereof and at least one non-steroidal anti-inflammatory phase containing a therapeutically effective quantity of a non-steroidal anti-inflammatory carboxylic acid or an anti-inflammatory salt or ester thereof wherein the at least one narcotic analgesic phase is free from a non-steroidal anti-inflammatory carboxylic acid or salt or ester thereof, stearic acid and a stearate salt, and the at least one non-steroidal anti-inflammatory phase is free from a narcotic analgesic or salt thereof, stearic acid and a stearate salt, and further wherein both the at least one narcotic analgesic phase and the at least one non-steroidal anti-inflammatory phase contain at least one self-lubricating, compression aid, preferably at least one self lubricating, direct compression aid.

2. A composition according to claim 1 characterised in that the narcotic analgesic comprises a morphinan-6-ol or a morphinan-6-one derivative, preferably morphine, ethylmorphine, hydromorphone, hydrocodone, dihydrocodeine or codeine.

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3. A composition according to claim 1 characterised in that the analgesically effective salt of the narcotic analgesic comprises codeine phosphate.

4. A composition according to any one of claims 1 to 3 characterised in that the non-steroidal anti-inflammatory carboxylic acid comprises a benzeneacetic acid, preferably alclofenac, diclofenac, fenclofenac, a 2-naphthylpropionic acid, preferably naproxen, or a 2-phenylpropionic acid, preferably fenoprofen, flurbiprofen, indoprofen, ketoprofen or ibuprofen.

5. A composition according to claim 4 characterised in that the non-steroidal anti-inflammatory carboxylic acid comprises ibuprofen.

6. A composition according to any one of claims 1 to 5 characterised in that the at least one self lubricating, compression aid is selected from microcrystalline cellulose and a free flowing, directly compressible starch.

7. A composition according to any one of claims 1 to 6 characterised in that the concentration of the compression aid in the at least one non-steroidal anti-inflammatory phase is between 10% and 90%, preferably between 15% and 40%, by wt.

8. A composition according to any one of claims 1 to 7 characterised in that the concentration of the compression aid in the at least one narcotic analgesic phase is between 50% and 99%, preferably between 70% and 95%, by wt.

9. A composition according to any one of claims 1 to 8 in the form of a layered, preferably bilayered, tablet.

10. A wet granulation process for the preparation of a pharmaceutical composition according to claim 1 comprising

(a) granulating a narcotic analgesic or an analgesically effective salt thereof with at least one self lubricating, compression aid to form narcotic analgesic granules,

(b) granulating a non-steroidal anti-inflammatory carboxylic acid or an anti-inflammatory salt or ester thereof with at least one self lubricating, compression aid to form non-steroidal anti-inflammatory granules, and

(c) compressing the narcotic analgesic granules and the non-steroidal anti-inflammatory granules to form a multiphase tablet.

Claims for the Contracting State: AT

1. A process for the preparation of a pharmaceutical composition comprising forming a multiphase tablet in which at least one narcotic analgesic phase contains a therapeutically effective quantity of a narcotic analgesic or an analgesically effective salt thereof and at least one non-steroidal anti-inflammatory phase contains a therapeutically effective quantity of a non-steroidal anti-inflammatory carboxylic acid or an anti-inflammatory salt or ester thereof wherein the at least one narcotic analgesic phase is free from a non-steroidal anti-inflammatory carboxylic acid, or salt or ester thereof, stearic acid and a stearate salt, and the at least one non-steroidal anti-inflammatory phase is free from a narcotic analgesic, or salt thereof, stearic acid and a stearate salt, and further wherein both the at least one narcotic analgesic phase and the at least one non-steroidal anti-inflammatory phase contain at least one self-lubricating, compression aid, preferably at least one self-lubricating, direct compression aid.

2. A process according to claim 1 characterised in that the narcotic analgesic comprises a morphinan-6-ol or a morphinan-6-one derivative, preferably morphine, ethylmorphine, hydromorphone, hydrocodone, dihydrocodeine or codeine.

3. A process according to claim 1 characterised in that the analgesically effective salt of the narcotic analgesic comprises codeine phosphate.

4. A process according to any one of claims 1 to 3 characterised in that the non-steroidal anti-inflammatory carboxylic acid comprises a benzeneacetic acid, preferably alclofenac, diclofenac or fenclofenac, a 2-naphthylpropionic acid, preferably naproxen, or a 2-phenylpropionic acid, preferably fenoprofen, flurbiprofen, indoprofen, ketoprofen or ibuprofen.

5. A process according to claim 4 characterised in that the non-steroidal anti-inflammatory carboxylic acid comprises ibuprofen.

6. A process according to any one of claims 1 to 5 characterised in that the at least one self lubricating, compression aid is selected from microcrystalline cellulose and a free flowing, directly compressible starch.

7. A process according to any one of claims 1 to 6 characterised in that the concentration of the compression aid in the at least one non-steroidal anti-inflammatory phase is between 10% and 90%, preferably between 15% and 40%, by wt.

8. A process according to any one of claims 1 to 7 characterised in that the concentration of the compression aid in the at least one narcotic analgesic phase is between 50% and 99%, preferably between 70% and 95%, by wt.

9. A process according to any one of claims 1 to 8 in the form of a layered, preferably bilayered, tablet.

10. A wet granulation process for the preparation of a pharmaceutical composition according to claim 1 comprising

3. A composition according to claim 1 characterised in that the analgesically effective salt of the narcotic analgesic comprises codeine phosphate.

4. A composition according to any one of claims 1 to 3 characterised in that the non-steroidal anti-inflammatory carboxylic acid comprises a benzeneacetic acid, preferably alclofenac, diclofenac or fenclofenac, a 2-naphthylpropionic acid, preferably naproxen, or a 2-phenylpropionic acid, preferably fenoprofen, flurbiprofen, indoprofen, ketoprofen or ibuprofen.

5. A composition according to claim 4 characterised in that the non-steroidal anti-inflammatory carboxylic acid comprises ibuprofen.

6. A composition according to any one of claims 1 to 5 characterised in that the at least one self lubricating, compression aid is selected from microcrystalline cellulose and a free flowing, directly compressible starch.

7. A composition according to any one of claims 1 to 6 characterised in that the concentration of the compression aid in the at least one non-steroidal anti-inflammatory phase is between 10% and 90%, preferably between 15% and 40%, by wt.

8. A composition according to any one of claims 1 to 7 characterised in that the concentration of the compression aid in the at least one narcotic analgesic phase is between 50% and 99%, preferably between 70% and 95%, by wt.

9. A composition according to any one of claims 1 to 8 in the form of a layered, preferably bilayered, tablet.

10. A wet granulation process for the preparation of a pharmaceutical composition according to claim 1 comprising

(a) granulating a narcotic analgesic or an analgesically effective salt thereof with at least one self lubricating, compression aid to form narcotic analgesic granules,

(b) granulating a non-steroidal anti-inflammatory carboxylic acid or an anti-inflammatory salt or ester thereof with at least one self lubricating, compression aid to form non-steroidal anti-inflammatory granules, and

(c) compressing the narcotic analgesic granules and the non-steroidal anti-inflammatory granules to form a multiphase tablet.

Claims for the Contracting State: AT

1. A process for the preparation of a pharmaceutical composition comprising forming a multiphase tablet in which at least one narcotic analgesic phase contains a therapeutically effective quantity of a narcotic analgesic or an analgesically effective salt thereof and at least one non-steroidal anti-inflammatory phase contains a therapeutically effective quantity of a non-steroidal anti-inflammatory carboxylic acid or an anti-inflammatory salt or ester thereof wherein the at least one narcotic analgesic phase is free from a non-steroidal anti-inflammatory carboxylic acid, or salt or ester thereof, stearic acid and a stearate salt, and the at least one non-steroidal anti-inflammatory phase is free from a narcotic analgesic, or salt thereof, stearic acid and a stearate salt, and further wherein both the at least one narcotic analgesic phase and the at least one non-steroidal anti-inflammatory phase contain at least one self-lubricating, compression aid, preferably at least one self-lubricating, direct compression aid.

2. A process according to claim 1 characterised in that the narcotic analgesic comprises a morphinan-6-ol or a morphinan-6-one derivative, preferably morphine, ethylmorphine, hydromorphone, hydrocodone, dihydrocodeine or codeine.

3. A process according to claim 1 characterised in that the analgesically effective salt of the narcotic analgesic comprises codeine phosphate.

4. A process according to any one of claims 1 to 3 characterised in that the non-steroidal anti-inflammatory carboxylic acid comprises a benzeneacetic acid, preferably alclofenac, diclofenac or fenclofenac, a 2-naphthylpropionic acid, preferably naproxen, or a 2-phenylpropionic acid, preferably fenoprofen, flurbiprofen, indoprofen, ketoprofen or ibuprofen.

5. A process according to claim 4 characterised in that the non-steroidal anti-inflammatory carboxylic acid comprises ibuprofen.

6. A process according to any one of claims 1 to 5 characterised in that the at least one self lubricating, compression aid is selected from microcrystalline cellulose and a free flowing, directly compressible starch.

7. A process according to any one of claims 1 to 6 characterised in that the concentration of the compression aid in the at least one non-steroidal anti-inflammatory phase is between 10% and 90%, preferably between 15% and 40%, by wt.

8. A process according to any one of claims 1 to 7 characterised in that the concentration of the compression aid in the at least one narcotic analgesic phase is between 50% and 99%, preferably between 70% and 95%, by wt.

9. A process according to any one of claims 1 to 8 in the form of a layered, preferably bilayered, tablet.

10. A wet granulation process for the preparation of a pharmaceutical composition according to claim 1 comprising

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(a) granulating a narcotic analgesic or an analgesically effective salt thereof with at least one self lubricating, compression aid to form narcotic analgesic granules.
(b) granulating a non-steroidal anti-inflammatory carboxylic acid or an anti-inflammatory salt or ester thereof with at least one self lubricating, compression aid to form non-steroidal anti-inflammatory granules, and
(c) compressing the narcotic analgesic granules and the non-steroidal anti-inflammatory granules to form a multiphase tablet.

Patentansprüche für die Vertragsstaaten: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Pharmazeutische Zusammensetzung in Form einer mehrphasigen Tablette, die aus mindestens einer narkotisch-analgetischen Phase mit einer therapeutisch wirksamen Menge eines narkotischen Analgetikums oder eines analgetisch wirksamen Salzes davon und mindestens einer steroidfreien entzündungshemmenden Phase mit einer therapeutisch wirksamen Menge einer steroidfreien entzündungshemmenden Carbonsäure oder eines entzündungshemmenden Salzes oder Esters davon besteht, worin die mindestens eine narkotisch-analgetische Phase keine steroidfreie entzündungshemmende Carbonsäure oder deren Salz oder Ester, Stearinsäure und Stearatsalz sowie die mindestens eine steroidfreie entzündungshemmende Phase kein narkotisches Analgetikum oder dessen Salz, Stearinsäure und Stearatsalz enthält, und worin ferner sowohl die mindestens eine narkotisch-analgetische Phase als auch die mindestens eine steroidfreie entzündungshemmende Phase mindestens ein selbstschmierendes Tablettierhilfsmittel, vorzugsweise mindestens ein selbstschmierendes Direkttablettierhilfsmittel enthalten.

2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß das narkotische Analgetikum aus einem 6-Morphinanol- oder einem 6-Morphinanonderivat, vorzugsweise Morphin, Ethylmorphin, Hydromorphon, Hydrocodon, Dihydrokodein oder Kodein, besteht.

3. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß das analgetisch wirksame Salz des narkotischen Analgetikums aus Kodeinphosphat besteht.

4. Zusammensetzung nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß die steroidfreie entzündungshemmende Carbonsäure aus einer Benzolessigsäure, vorzugsweise Alclofenac, Diclofenac oder Fenclofenac, einer 2-Naphthylpropionsäure, vorzugsweise Naproxen, oder einer 2-Phenylpropionsäure, vorzugsweise Fenoprofen, Flurbiprofen, Indoprofen, Ketoprofen oder Ibuprofen, besteht.

5. Zusammensetzung nach Anspruch 4, dadurch gekennzeichnet, daß die steroidfreie entzündungshemmende Carbonsäure aus Ibuprofen besteht.

6. Zusammensetzung nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß das mindestens eine selbstschmierende Tablettierhilfsmittel unter mikrokristalliner Cellulose und einer fließfähigen, direkt tablettierbaren Stärke ausgewählt ist.

7. Zusammensetzung nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die Konzentration an Tablettierhilfsmittel in der mindestens einen steroidfreien entzündungshemmenden Phase zwischen 10% und 90%, vorzugsweise zwischen 15% und 40 Gewichtsprozent, liegt.

8. Zusammensetzung nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß die Konzentration an Tablettierhilfsmittel in der mindestens einen narkotisch-analgetischen Phase zwischen 50% und 99%, vorzugsweise zwischen 70% und 95 Gewichtsprozent, liegt.

9. Zusammensetzung nach einem der Ansprüche 1 bis 8 in Form einer geschichteten, vorzugsweise zweischichtigen Tablette.

10. Naßgranulierungsverfahren zur Herstellung einer pharmazeutischen Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß man
(a) ein narkotisches Analgetikum oder ein analgetisch wirksames Salz davon mit mindestens einem selbstschmierenden Tablettierhilfsmittel zur Bildung narkotisch-analgetischen Granulats granuliert,
(b) eine steroidfreie entzündungshemmende Carbonsäure oder ein entzündungshemmendes Salz bzw. Ester davon mit mindestens einem selbstschmierenden Tablettierhilfsmittel zur Bildung steroidfreien entzündungshemmenden Granulats granuliert und
(c) das narkotisch-analgetische Granulat und das steroidfreie entzündungshemmende Granulat zur Bildung einer mehrphasigen Tablette verpreßt.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, bei dem man eine mehrphasige Tablette bildet, in welcher mindestens eine narkotisch-analgetische Phase eine therapeutisch wirksame Menge eines narkotischen Analgetikums oder eines analgetisch wirksamen Salzes davon und mindestens eine steroidfreie entzündungshemmende Phase eine therapeutisch wirksame Menge einer steroidfreien entzündungshemmenden Carbonsäure oder eines entzündungshemmenden Salzes oder Esters davon enthält, worin die mindestens eine narkotisch-analgetische Phase keine steroidfreie entzündungshemmende Carbonsäure oder deren Salz oder Ester, Stearinsäure und Stearatsalz sowie die mindestens eine steroidfreie entzündungshemmende Phase kein narkotisches Analgetikum oder dessen

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Salz, Stearinsäure und Stearatsalz enthält, und worin ferner sowohl die mindestens eine narkotisch-analgetische Phase als auch die mindestens eine steroidfreie entzündungshemmende Phase mindestens ein selbstschmierendes Tablettierhilfsmittel, vorzugsweise mindestens ein selbstschmierendes Direkttablettierhilfsmittel enthalten.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das narkotische Analgetikum aus einem 6-Morphinanol- oder einem 6-Morphinanonderivat, vorzugsweise Morphin, Ethylmorphin, Hydromorphon, Hydrocodon, Dihydrokodein oder Kodein, besteht.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das analgetisch wirksame Salz des narkotischen Analgetikums aus Kodeinphosphat besteht.

4. Verfahren nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß die steroidfreie entzündungshemmende Carbonsäure aus einer Benzolessigsäure, vorzugsweise Alclofenac, Diclofenac oder Fenclofenac, einer 2-Naphthylpropionsäure, vorzugsweise Naproxen, oder einer 2-Phenylpropionsäure, vorzugsweise Fenoprofen, Flurbiprofen, Indoprofen, Ketoprofen oder Ibuprofen, besteht.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß die steroidfreie entzündungshemmende Carbonsäure aus Ibuprofen besteht.

6. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß das mindestens ein selbstschmierendes Tablettierhilfsmittel unter mikrokristalliner Cellulose und einer fließfähigen, direkt tablettierbaren Stärke ausgewählt ist.

7. Verfahren nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die Konzentration an Tablettierhilfsmittel in der mindestens einen steroidfreien entzündungshemmenden Phase zwischen 10% und 90%, vorzugsweise zwischen 15% und 40 Gewichtsprozent, liegt.

8. Verfahren nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß die Konzentration an Tablettierhilfsmittel in der mindestens einen narkotisch-analgetischen Phase zwischen 50% und 99%, vorzugsweise zwischen 70% und 95 Gewichtsprozent, liegt.

9. Verfahren nach einem der Ansprüche 1 bis 8 zur Herstellung einer Tablette in geschichteter, vorzugsweise zweischichtiger, Form.

10. Naßgranulierungsverfahren zur Herstellung einer pharmazeutischen Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß man

(a) ein narkotisches Analgetikum oder ein analgetisch wirksames Salz davon mit mindestens einem selbstschmierenden Tablettierhilfsmittel zur Bildung narkotisch-analgetischen Granulats granuliert,

(b) eine steroidfreie entzündungshemmende Carbonsäure oder ein entzündungshemmendes Salz bzw. Ester davon mit mindestens einem selbstschmierenden Tablettierhilfsmittel zur Bildung steroidfreien entzündungshemmenden Granulats granuliert und

c) das narkotisch-analgetische Granulat und das steroidfreie entzündungshemmende Granulat zur Bildung einer mehrphasigen Tablette verpreßt.

Revendications pour les Etats contractants: BE, CH, DE, FR, GB, IT, LU, NL, SE

1. Composition pharmaceutique sous forme d'un comprimé multiphase comprenant au moins une phase d'analgésique narcotique contenant une quantité thérapeutiquement efficace d'un analgésique narcotique ou d'un sel à efficacité analgésique de celui-ci et au moins une phase d'anti-inflammatoire non stéroïdien contenant une quantité thérapeutiquement efficace d'un acide carboxylique anti-inflammatoire non stéroïdien ou d'un sel ou d'un ester anti-inflammatoire de celui-ci, dans laquelle la ou les phases d'analgésique narcotique sont exemptes d'acide carboxylique anti-inflammatoire non stéroïdien ou d'un sel ou d'un ester de celui-ci, d'acide stéarique et d'un sel stéarate, et la ou les phases d'anti-inflammatoire non stéroïdien sont exemptes d'analgésique narcotique ou d'un sel de celui-ci, d'acide stéarique et d'un sel stéarate, et dans laquelle, en outre, à la fois la ou les phases d'analgésique narcotique et la ou les phases d'anti-inflammatoire non stéroïdien contiennent au moins un auxiliaire de compression autolubrifiant, de préférence un auxiliaire de compression directe autolubrifiant.

2. Composition selon la revendication 1, caractérisée en ce que l'analgésique narcotique comprend un morphinanol-6 ou un dérivé de morphinanone-6, de préférence la morphine, l'éthylmorphine, l'hydromorphone, l'hydrocodone, l'hydrocodéine ou la codéine.

3. Compositions selon la revendication 1, caractérisée en ce que le sel à efficacité analgésique de l'analgésique narcotique comprend du phosphate de codéine.

4. Composition selon l'une quelconque des revendications 1 à 3, caractérisée en ce que l'acide carboxylique anti-inflammatoire non stéroïdien comprend un acide benzène-acétique, de préférence l'alclofénac, le diclofénac ou le fenclofénac, un acide 2-naphtylpropionique, de préférence le naproxen, ou un acide 2-phénylpropionique, de préférence le fénoprofen, le flurbiprofen, l'indoprofen, le kétoprofen ou l'ibuprofen.

5. Composition selon la revendication 4, caractérisée en ce que l'acide carboxylique anti-inflammatoire non stéroïdien comprend l'ibuprofen.

6. Composition selon l'une quelconque des revendications 1 à 5, caractérisée en ce que le ou les auxiliaires de compression autolubrifiants sont choisis parmi la cellulose microcristalline et un amidon directement compressible, fluide.

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7. Composition selon l'une quelconque des revendications 1 à 6, caractérisée en ce que la concentration de l'auxiliaire de compression dans la ou les phases d'anti-inflammatoire non stéroïdien est comprise entre 10% et 90%, de préférence entre 15% et 40%, en poids.

8. Composition selon l'une quelconque des revendications 1 à 7, caractérisée en ce que la concentration de l'auxiliaire de compression dans la ou les phases d'analgésique narcotique est comprise entre 50% et 99%, de préférence entre 70% et 95%, en poids.

9. Composition selon l'une quelconque des revendications 1 à 8, sous forme d'un comprimé à couches, de préférence à deux couches.

10. Procédé de granulation par voie humide pour la préparation d'une composition pharmaceutique selon la revendication 1, comprenant

(a) la granulation d'un analgésique narcotique ou d'un sel à efficacité analgésique de celui-ci avec au moins un auxiliaire de compression autolubrifiant, pour former des granules d'analgésique narcotique,

(b) la granulation d'un acide carboxylique anti-inflammatoire non stéroïdien ou d'un sel ou ester anti-inflammatoire de celui-ci avec au moins un auxiliaire de compression autolubrifiant, pour former des granules d'anti-inflammatoire non stéroïdien, et

(c) la compression des granules d'analgésique narcotique et des granules d'anti-inflammatoire non stéroïdien pour former un comprimé multiphase.

Revendications pour l'Etat contractant: AT

1. **Procédé de préparation d'une composition pharmaceutique, comprenant la formation d'un comprimé multiphase dans lequel au moins une phase d'analgésique narcotique contient une quantité thérapeutiquement efficace d'un analgésique narcotique ou d'un sel à efficacité analgésique de celui-ci et au moins une phase d'anti-inflammatoire non stéroïdien contient une quantité thérapeutiquement efficace d'un acide carboxylique anti-inflammatoire non stéroïdien ou d'un sel ou d'un ester anti-inflammatoire de celui-ci, dans lequel la ou les phases d'analgésique narcotique sont exemptes d'acide carboxylique anti-inflammatoire non stéroïdien ou d'un sel ou d'un ester de celui-ci, d'acide stéarique et d'un sel stéarate, et la ou les phases d'anti-inflammatoire non stéroïdien sont exemptes d'analgésique narcotique ou d'un sel de celui-ci, d'acide stéarique et d'un sel stéarate, et dans lequel, en outre, à la fois la ou les phases d'analgésique narcotique et la ou les phases d'anti-inflammatoire non stéroïdien contiennent au moins un auxiliaire de compression autolubrifiant, de préférence au moins un auxiliaire de compression directe autolubrifiant.**

2. Procédé selon la revendication 1, caractérisé en ce que l'analgésique narcotique comprend un morphinanol-6 ou un dérivé de morphinanone-6, de préférence la morphine, l'éthylmorphine, l'hydromorphone, l'hydrocodone, l'hydrocodéine ou la codéine.

3. Procédé selon la revendication 1, caractérisé en ce que le sel à efficacité analgésique de l'analgésique narcotique comprend du phosphate de codéine.

4. Procédé selon l'une quelconque des revendications 1 à 3, caractérisé en ce que l'acide carboxylique anti-inflammatoire non stéroïdien comprend un acide benzène-acétique, de préférence l'alcloténac, le diclofénac ou le fenclofénac, un acide 2-naphtylpropionique, de préférence le naproxen, ou un acide 2-phénylpropionique, de préférence le fénoprofen, le flurbiprofen, l'indoprofen, le kétoprofen ou l'ibuprofen.

5. Procédé selon la revendication 4, caractérisé en ce que l'acide carboxylique anti-inflammatoire non stéroïdien comprend l'ibuprofen.

6. Procédé selon l'une quelconque des revendications 1 à 5, caractérisé en ce que l'auxiliaire de compression autolubrifiant est choisi parmi la cellulose microcristalline et un amidon directement compressible, fluide.

7. Procédé selon l'une quelconque des revendications 1 à 6, caractérisé en ce que la concentration de l'auxiliaire de compression dans la ou les phases d'anti-inflammatoire non stéroïdien est comprise entre 10% et 90%, de préférence entre 15% et 40%, en poids.

8. Procédé selon l'une quelconque des revendications 1 à 7, caractérisé en ce que la concentration de l'auxiliaire de compression dans la ou les phases d'analgésique narcotique est comprise entre 50% et 99%, de préférence entre 70% et 95%, en poids.

9. Procédé selon l'une quelconque des revendications 1 à 8, sous forme d'un comprimé à couches, de préférence à deux couches.

10. Procédé de granulation par voie humide pour la préparation d'une composition pharmaceutique selon la revendication 1, comprenant

(a) la granulation d'un analgésique narcotique ou d'un sel à efficacité analgésique de celui-ci avec au moins un auxiliaire de compression autolubrifiant, pour former des granules d'analgésique narcotique,

(b) la granulation d'un acide carboxylique anti-inflammatoire non stéroïdien ou d'un sel ou ester anti-inflammatoire de celui-ci avec au moins un auxiliaire de compression autolubrifiant, pour former des granules d'anti-inflammatoire non stéroïdien, et

(c) la compression des granules d'analgésique narcotique et des granules d'anti-inflammatoire non stéroïdien pour former un comprimé multiphase.

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