**Title:** A PHARMACEUTICAL COMPOSITION CONTAINING CELECOXIB AND A PROCESS OF THE MANUFACTURE THEREOF

**Abstract:** The subject matter of the invention is a pharmaceutical composition containing celecoxib as the active substance and a pharmaceutically acceptable carrier. The pharmaceutical composition contains a cross-linked polymer. The subject matter of the invention also includes the process of manufacturing of the pharmaceutical composition.
A pharmaceutical composition containing celecoxib and a process of the manufacture thereof

The subject matter of the invention is a pharmaceutical composition containing celecoxib and a process of the manufacture thereof.

Celecoxib is a known compound with the following formula:

![Celecoxib structure](image)

Celecoxib selectively inhibits cyclooxygenase-2; therefore, it is used mainly in the treatment of inflammation and other inflammation-related disorders, such as treatment of rheumatoid arthritis.

Celecoxib belongs to Group II of medicines according to the Biopharmaceutical Classification System (BCS) which means that it is sparingly soluble in water, but it penetrates biological barriers easily. The bioavailability of medicines from this group is limited by their low solubility.

Active substances with low solubility used in pharmacy may contribute to difficulties during the formulation of pharmaceutical compositions. In the case of such substances, solubility-enhancing excipients are used for the formulation of pharmaceutical compositions, such as surfactants.
Pharmaceutical compositions which contain celecoxib as the active substance are described in a number of patent applications.

In the publication of international patent application WO 95/15316 (PL 180717 B) pharmaceutical compositions are disclosed which contain celecoxib as the active substance in a dose between 0.1 and 2000 mg, which, if present in the oral dosage form, can be admixed with pharmaceutically acceptable excipients, such as lactose, saccharose, starch powder and other typically used excipients.

In the publication of international patent application WO 02/15884 (PL 195955 B), in turn, several pharmaceutical compositions are disclosed which contain celecoxib intended for the administration via various routes (e.g. orally in the form of tablets, hard or soft gelatine capsules, etc.). Typical excipients employed in pharmacy can be used in the compositions in the form of tablets and capsules, such as lactose, saccharose, starch powder and other typically used excipients.

Based on patent specification EP 1049467 B (PL 200957 B), in which the composition of CELBREX ® is disclosed, it is known that a surfactant (sodium lauryl sulphate or polysorbate 80) is used in the formulation of the pharmaceutical composition. It is also disclosed that the preparation of the granulate for the formulation of the pharmaceutical composition is performed in two stages: At the first stage, crystalline celecoxib is milled until a mean particle size (D90) of below 25 µm is achieved; subsequently, the other ingredients of the composition are added and a wet granulation process is carried out. Such a process of preparing of the pharmaceutical composition is fairly time-consuming and not quite efficient. The wet granulation process is a complex and multi-stage one; therefore, it may affect the final quality of the finished product.

Furthermore, in order to ensure appropriate solubility and wettability of celecoxib, a surfactant in used in a range of 0.4% to even 10% by weight of the composition. The use of high concentration of the surfactant, such as sodium lauryl sulphate, which is irritating to mucous membranes of the gastro-intestinal tract, among other things, may lead to adverse effects experienced by patients.
It is known from literature that the use of the wet granulation process during granulate preparation for the formulation of pharmaceutical compositions containing celecoxib ensures that homogenous granulate with a very high compaction rate is obtained. However, it is necessary to use surfactants in order to achieve required wettability and solubility of celecoxib (based on X. Hea, M.R. Barone, PJ. Marsac, D.C. Sperry; Development of a rapidly dispersing tablet of a poorly wettable compound-formulation DOE and mechanistic study of effect of formulation excipients on wetting of celecoxib, Int. J. Pharm. 353 (2008) 176-186).

Furthermore, it is disclosed in the international publication of patent publication WO 02/15884 (EP 1309315 B) that due to the physicochemical properties of celecoxib, such as electrostatic properties, viscosity, low bulk volume as well as low compaction potential and weak flow properties, celecoxib crystals tend to separate from the other excipients during the mixing process and to form agglomerates.

Therefore, an oral composition for the formulation was suggested, with immediate release (so-called ODT, orodispersible tablet, which quickly disintegrates in the oral cavity) in which cellulose derivatives, starch and polyhydroxy alcohols, such as mannitol, sorbitol, etc., are used.

Furthermore, in the international publication of patent application WO 02/15884 (EP 1309315 B) it is also disclosed that the preparation of granulate for the formulation of the pharmaceutical composition does not require wet granulation; however, when the mixture of the active substance with excipients is in a liquid or semi-solid (paste) form, tablets form in the vacuum drying or freeze-drying process. The average concentration of celecoxib in the granulate manufactured using this process is approximately 20-50%.

Such a process of preparing of the oral pharmaceutical composition for the immediate release formulation containing celecoxib as the active substance is very difficult in terms of technology and expensive. Furthermore, the low concentration of celecoxib in the granulate prepared according to the process
disclosed in the publication in question prevents the granulate from being used for
the preparation of a composition in the form of capsules with a size acceptable by
patients.

It is known that celecoxib is a very adhesive substance, it forms agglomerates
easily and its crystals have a shape of needles; therefore, the use of typical
processes of granulate preparation for the formulation of a pharmaceutical
composition in the form of a capsule will not lead to the elimination of the
unfavourable physical parameters of celecoxib.

In addition, the active substance (celecoxib) contributes to the high percentage of
total capsule weight. This restricts the possibility of using large amounts of
excipients, because granulate volume is the parameter which determines capsule
size and, in consequence, the convenience of use by patients.

It turned out unexpectedly during the formulation of the pharmaceutical
composition containing celecoxib that the preparation of the granulate for the
formulation of a pharmaceutical composition in the dry granulation process and
use of a cross-linked polymer ensure the preparation of a pharmaceutical
composition with desired release profile parameters.

Furthermore, also unexpectedly, the use of the dry granulation process during
granulate preparation for the formulation of the pharmaceutical composition
proved to contribute to obtaining granulate with much reduced bulk volume;
therefore, smaller capsules can be used, which increases the convenience of its use
by patients.

The objective of the invention has been to develop a new pharmaceutical
composition containing celecoxib and to develop a new process of manufacturing
of a pharmaceutical composition containing celecoxib.
The pharmaceutical composition containing celecoxib as the active substance according to the invention is characterised in that it contains a cross-linked polymer as the pharmaceutically acceptable carrier. Crospovidone is preferably used as the pharmaceutically acceptable carrier in the pharmaceutical composition according to the invention.

Micronised crospovidone is preferably used as the pharmaceutically acceptable carrier in the pharmaceutical composition according to the invention. A mixture of crospovidone and polyethylene glycol (PEG) can be used as the pharmaceutically acceptable carrier in the pharmaceutical composition according to the invention.

The pharmaceutical composition according to the invention is characterised in that its quantitative composition is proportional. This means that respective doses of the formulation are prepared from the same granulate.

The process of manufacturing of the pharmaceutical composition containing celecoxib according to the invention is characterised in that it consists of the following stages:

a. the active substance (celecoxib) is subjected to granulation with at least one pharmaceutically acceptable carrier,
b. the resulting pellets are standardised,
c. the standardised granulate is mixed with the excipient,
d. capsules are manufactured from the granulate.

The granulation process is preferably carried out in dry conditions using the compaction process.

The compaction process consists in the compaction using high pressure forces of the active substance or a mixture thereof with an appropriate excipient.

The process of preparing of the pharmaceutical composition according to the invention preferably occurs during the celecoxib compaction process with one of the following carrier systems: crospovidone, crospovidone and PEG.
The excipient used as a glidant is preferably magnesium stearate.

Owing to the use of the compaction process of granulate preparation for the manufacture of the pharmaceutical composition containing celecoxib, the bulk volume of the granulate is largely reduced, its flow properties improve and the dusting effect and losses due to the adhesion of the active substance to manufacturing equipment are eliminated.

Furthermore, the dry granulation process involves three stages only, while wet granulation consists of at least six stages. Therefore, the use of the dry granulation process ensures better process control and, in consequence, higher quality of the finished product.

Owing to the use of compaction technology for celecoxib combined with at least one cross-linked polymer as the carrier, the size of celecoxib particles can be efficiently reduced and granulate with high integration of the active substance with the carrier can be obtained.

The resulting granulate is characterised by high celecoxib concentration. As a result, a smaller capsule size for large doses of the finished formulation can be used and, in consequence, the convenience of use of the medicine by patients is enhanced.

The embodiments of the subject matter of the invention are shown in the Figure and:

Fig. 1 shows the diagram of the manufacture of an exemplary composition containing celecoxib in the form of capsules whose quantitative and qualitative composition corresponds to that of Example 1.

Fig. 2 shows the diagram of the manufacture of an exemplary composition containing celecoxib in the form of capsules whose quantitative and qualitative composition corresponds to that of Example 2.

Fig. 3 shows the release profile of the celecoxib active substance for the composition of Example 1 and Example 2 in the form of hard gelatine capsules compared with the release profile for the reference medicine.
Fig. 4 shows the diagram of the manufacture of an exemplary composition containing celecoxib in the form of capsules whose quantitative and qualitative composition corresponds to that of Example 4.

Fig. 5 shows the release profile of the celecoxib active substance for the composition of Example 1 and Example 4 in the form of hard gelatine capsules compared with the release profile for the reference medicine.

The invention is illustrated by the following examples which in no way restrict its scope.

**Example 1.**

Powder for compaction in the amount of 3.0 kg, which contained in its composition substances specified in the table below, was prepared in a bin mixer with a bin volume of 20 l. by Zanchetta. The dry granulation process was carried out using an Alexanderwerk WP 150 Pharma compactor. A pressure force of 12 kN/cm² and a sieve with a mesh size of 0.8 mm were used to mill the resulting strips. A proportional composition of the granulate was used.

An example of the composition is shown in the table below.

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Mg / tabl.</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>200.0</td>
<td>66.7</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>98.5</td>
<td>32.8</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The flow chart of the manufacture of the composition is shown in Fig. 1.
Fig. 1. Diagram of the manufacture of an exemplary composition containing celecoxib in the form of capsules.

**Example 2.**

Powder for compaction in the amount of 3.0 kg, which contained in its composition substances specified in the table below, was prepared in a bin mixer with a bin volume of 20 l. by Zanchetta. The dry granulation process was carried out using an Alexanderwerk WP 150 Pharma compactor. A pressure force of 12 kN/cm² and a sieve with a mesh size of 0.8 mm were used to mill the resulting strips. A proportional composition of the granulate was used.

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Mg / tabl.</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>200.0</td>
<td>66.9</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>48.25</td>
<td>16.1</td>
</tr>
<tr>
<td>PEG 6000</td>
<td>49.25</td>
<td>16.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
The flow chart of the manufacture of the composition is shown in Fig. 2.

Fig. 2. Diagram of the manufacture of an exemplary composition containing celecoxib in the form of capsules.

Example 3.

This is a comparative example which illustrates the release profile for exemplary compositions according to the invention containing celecoxib in a 200 mg dose in the form of hard gelatine capsules and the brand-name product, Celebrex® 200 mg, Pfizer, commercially available in the form of hard gelatine capsules.

The same analytical procedure was used for all the products, selected based on the Food and Drug Administration (FDA) methodology.

It includes the evaluation of active substance release from the dosage form using an USP II paddle apparatus, that is, an apparatus equivalent to apparatus II
according to Ph. Eur., with a speed of 50 rpm in 0.1 M HCl solution with 2% sodium lauryl sulphate.

The results are presented below:

Fig. 3. The release profile of the celecoxib active substance from the composition of Example 1 and Example 2 in the form of hard gelatine capsules compared with the release profile for the reference medicine (0.1 M HCl with 2% sodium lauryl sulphate).

Example 4.

This is a comparative example which illustrates the release profile for exemplary compositions according to the invention containing celecoxib in a 200 mg dose in
the form of hard gelatine capsules whose quantitative and qualitative composition is shown in the table below, with two distinct granulation techniques used: dry granulation and wet granulation.

Dry granulation was carried out as described in Example 1; the flow chart of the preparation of the composition is shown in Fig. 1. Wet granulation, in turn, was carried out as described below.

Powder for granulation in the amount of 1.5 kg, which contained in its composition substances specified in the tables below, was prepared in a Zanchetta bin mixer. The wet granulation process was carried out using a Glatt VG5 WP 150 Pharma high-speed granulator. The granulate was wetted with water in the amount of 50% of powder weight during the process. The wet granulate was dried and homogenised using sieves with 0.8 mm mesh size.

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Mg / tabl.</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>200.0</td>
<td>66.0</td>
</tr>
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<td>Crospovidone</td>
<td>98.5</td>
<td>32.8</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The same analytical procedure was used for all the products, selected based on the FDA methodology.

It includes the evaluation of active substance release from the dosage form using an USP II paddle apparatus, that is, an apparatus equivalent to apparatus II according to Ph. Eur., with a speed of 50 rpm in 0.1 M HCl solution with 2% sodium lauryl sulphate.
The flow chart of the manufacture of the composition is shown in Fig. 5.
Fig. 5. Diagram of the manufacture of an exemplary composition containing celecoxib in the form of capsules (Example 4)

[legend:]

% release
time [min]

Celebrex® 200 mg, lot no. 610256534
Composition of Example 1
Composition of Example 4

Fig. 4. The release profile of the active substance from Celecoxib 200 mg hard gelatine capsules in which two distinct granulation processes were used (0.1 M HCl with 2% sodium lauryl sulphate).
Patent claims

1. A pharmaceutical composition containing celecoxib as the active substance and a pharmaceutically acceptable carrier, characterised in that it contains a cross-linked polymer as the pharmaceutically acceptable carrier.

2. A pharmaceutical composition according to Claim 1, characterised in that the pharmaceutically acceptable carrier contains crospovidone.

3. A pharmaceutical composition according to Claim 2, characterised in that the pharmaceutically acceptable carrier contains micronised crospovidone.

4. A pharmaceutical composition according to Claim 1, characterised in that the pharmaceutically acceptable carrier is crospovidone and PEG.

5. A pharmaceutical composition according to Claim 1, characterised in that its quantitative composition is proportional.

6. A process of manufacturing of the pharmaceutical composition containing celecoxib as the active substance, characterised in that it consists of the following stages:
   a. the active substance (celecoxib) is subjected to granulation with at least one pharmaceutically acceptable carrier,
   b. the resulting pellets are standardised,
   c. the standardised granulate is mixed with the excipient,
   d. capsules are manufactured from the granulate.

7. A process according to Claim 6, characterised in that the granulation process is carried out in dry conditions.

8. A process according to Claim 7, characterised in that dry granulation constitutes compaction.

9. A process according to Claim 6, characterised in that the resulting pellets are standardised by milling.

10. A process according to Claim 6, characterised in that a glidant, preferably magnesium stearate, is an excipient.