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(57) Abstract: The present invention relates to moxifloxacin composition with improved solubility and stability, preparation method of these compositions and medical use.



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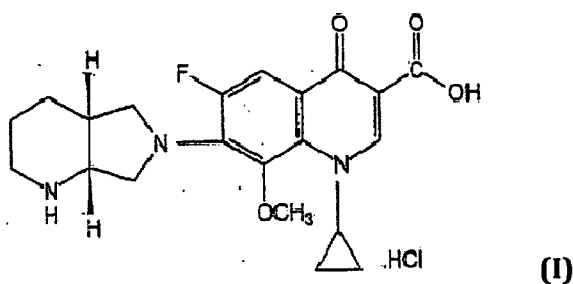
STABLE MICRONIZED GRANULES HAVING HIGH SOLUBILITY**Field of the Invention**

The present invention relates to moxifloxacin composition with improved solubility and stability, preparation method of these compositions and medical use.

Background of the Invention

The present invention relates to obtain effective moxifloxacin composition for the treatment of bacterial infection.

Moxifloxacin HCl is a fluoroquinolone which has a chemical name of 1- cyclopropyl -7-[(S,S)-2,8-diazabicyclo [4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid hydrochloride (Formula I).



Moxifloxacin is firstly described in the patent numbered US4990517 A. Processes for the preparation of moxifloxacin, pharmaceutical compositions comprising moxifloxacin and antibacterial activity of moxifloxacin are included in the application.

Moxifloxacin is a wide-spectrum and bacterially effective drug that is used by ophthalmic, oral and intravenous route. It's bactericid effect results from that it inhibits topoisomerase II ve topoisomerase IV which are needed for bacterial DNA replication, transcription, reparation and recombination. Moxifloxacin which presents in 8-methoxyfluoroquinolone group is effective against methoxyfloxacin gram-positive and gram-negative microorganism.

The present invention is aimed to produce a pharmaceutical formulation which comprises pharmaceutically acceptable, non-toxic and therapeutically effective amount of moxifloxacin and formulating of this agent in a pharmaceutical form such as tablet. However, several problems are faced during formulation process of moxifloxacin.

The first one of these problems is solubility. One of the usable techniques applied to adress the solubility problem of poorly soluble drugs such as moxifloxacin is particle size reduction . Because the dissolution rate of a particulate solid depends on the surface area and the surface area increases

as the particle size reduces, reducing particle size may increase dissolution rate. However, it is required that suitable particle size should be defined to develop solubility features.

Moreover, many hydrophobic drugs as moxifloxacin have a strong tendency to agglomerate while being transformed into larger particles during the dosage form manufacturing process depending on an overall decrease in effective surface area. Micronized drug particles stick together excessively and they are hardly wetted. This leads to decrease in dissolution rate.

Consequently a reproducible production method should be developed along the determination of suitable particle size to provide dissolution of drug particle effectively .

In the prior art, any study that is related to micronized moxifloxacin particles produced by a reproducible production method to solve solubility problem is not included.

In addition to the solubility problem of moxifloxacin, stability problem is also present. Moxifloxacin is a hygroscopic substance and it attracts water under unsuitable storage conditions or during production process of pharmaceutical dosage form. Therefore, the pharmaceutical compositions comprising moxifloxacin are the compounds that tend to be degrade depending on the production and storage conditions.

This situation bring along the necessity of the selection of suitable composition and manufacturing process so as to ensure stability of moxifloxacin in a pharmaceutical dosage form which is suitable for the invention.

The suggestions included in the prior art about developing solubility and stability features of moxifloxacin are generally aimed at production of different forms. For example patent applications numbered US5849752 A, WO2004091619 A1, WO2004039804 A1, WO2006134491 A1, WO2007010555 A2, WO2005054240 A1, WO2007148137 A1 and WO2008028959 A1 are related to monohydrate crystal form of moxifloxacin HCl, anhydrous form III crystal form, amorphous form, form A crystal form, anhydrous form X crystal form, form A and B crystal form, hydrate form and a new crystal form, respectively. However, a production process of each new form increases time and cost requirement.

Moreover it should be proved that said forms are therapeutically effective and safe. This situation brings about extra time and cost requirement.

The suggestions included in the prior art about the solubility problem of liquid fluoroquinolone formulation are generally aimed at forming high solubility complexes.

For example patent application numbered WO2007097889 A2 relates to liquid formulations including an organic solvent and a salt comprising a fluoroquinolone, carboxylate anion and a divalent metal cation.

The patent application numbered WO2007097888 A2 and WO2008094549 A1 relates to a liquid formulation including an organic solvent, a cyclodextrin and a salt comprising fluoroquinolone and carboxylic acid.

In the prior art, there are some suggestions related to the restriction of the concentrations of the components in an exact percentile range.

For example the patent numbered US6548079 B1 relates to aqueous formulations comprising moxifloxacin HCl in the range of 0.04 - 0.4 % and NaCl in the range of 0.4-0.9%.

However, mentioned suggestions are aimed for liquid dosage forms and they need unwieldy, restrictive and complicated production method for preparation of formulations whose solubility properties are claimed to be improved.

In the prior art, there are other methods tried to solve the solubility problem. One of them is nanoparticle technology that is applied for increasing surface area. However, it is faced with some technical and mechanic restrictions that does not allow drug particles to be broken into nanoparticles and some difficulties like stabilization of small drug particles in the process of producing nanoparticle.

Another method is to change the release properties for improving tableting properties. However, changing release properties for only this purpose is not a preferable method since it affects the drug effectiveness negatively. The another method applied for improving absorption of a poorly soluble and thus bioavailable drug is to use some additives like agent improving absorption and metabolism inhibitor. However, it should be proved that these substances provide not only desired effect and safety but also compatible with other compounds. This also brings about extra time and cost requirement.

In the prior art, there are also other methods that are tried to improve stability. The most preferable method is to add substances for retarding or decreasing decomposition. However, it should be proved that each added substance provides a stabilizing effect and safety but also it is compatible with other compounds. This also brings about extra time and cost requirement.

As a result, the solution suggestions included in the prior art fail to satisfy due to the reasons explained above. For this reason, new method searches which are acceptable for both application and cost are needed to get over solubility and stability problems of moxifloxacin.

The present invention provides a new production method and composition for formulating moxifloxacin without any solubility and stability problem.

Summary of the Invention

The present invention relates to a pharmaceutical composition comprising moxifloxacin HCl and at least one pharmaceutically acceptable excipient, characterized in that said composition comprises micronized moxifloxacin HCl anhydrate granules.

According to the invention, preparation method of pharmaceutical formulation comprising moxifloxacin HCl anhydrate in micronized form includes the following steps:

1. Blending moxifloxacin HCl anhydrate preferably with a disintegrant,
2. Obtaining the granulation solution by dissolving wet binding agent in deionized water,
3. Obtaining moxifloxacin HCl anhydrate granules by coating granulation solution on the blend obtained in step 1,
4. Drying the granules obtained in Step 3 wherein a maximum moisture ratio is 2.5%,
5. Sieving the dried granules in step 4 to maintain an average particle size distribution preferably $\leq 1200 \mu\text{m}$, more preferably $\leq 800 \mu\text{m}$, the most preferably $800 \mu\text{m}$,
6. Adding a lactose in anhydrate form, preferably β -lactose anhydrate to the granules obtained in step 5,
7. Obtaining the final mixture by adding at least one pharmaceutically acceptable excipient preferably at least one disintegrant and/or lubricant to the mixture obtained step 6,
8. Pressing the tablets in compliance with specifications by feeding the final mixture obtained to pressing machine in step 7,
9. Optionally coating the obtained tablets in step 8 with film coating.

Detailed Description of the Invention

The present invention is directed to obtain moxifloxacin compositions with improved solubility and stability that are effective for treatment of bacterial infection. A method, which is acceptable for both manufacturing and cost, is developed in order to obtain moxifloxacin composition with improved solubility and stability properties and the pharmaceutical acceptable, non-toxic and therapeutically effective amount of moxifloxacin and suitable amount of excipients are defined.

As a result of the studies, it is found that a pharmaceutical composition in accordance with the invention comprising micronized moxifloxacin HCl anhydrate granules both has improved stability and solubility properties and the composition is effective for the treatment of bacterial infections.

The present invention is characterized by obtaining micronized moxifloxacin HCl anhydrate granules. Moxifloxacin is an active agent that has both solubility problem and tendency to decomposition depending on production and storage conditions. Solubility and stability problems of moxifloxacin during the period of preparation of pharmaceutical formulation in accordance with invention. are incrementally examined.

At the first stage, it is determined that which form of moxifloxacin should be. Moxifloxacin can be present in its various salts (preferably HCl) and forms (amorph, crystal, anhydrate, hydrate, etc.). According to the results of the studies, it is observed that anhydrate form of moxifloxacin HCl is more effective on improving solubility properties. Therefore, the first aspect of the invention is that pharmaceutical compositions have preferably anhydrate form of moxifloxacin HCl.

At the second stage, obtaining stable moxifloxacin HCl anhydrate granules is tried as a first step of micronization period of moxifloxacin HCl anhydrate granules. However, before the granulation solution is coated on moxifloxacin HCl anhydrate, suitable wet binding agent in the solution should be determined.

As a result of the studies, it is observed that coating of moxifloxacin HCl anhydrate which is preferably mixed with a pharmaceutically acceptable disintegrant with a granulation solution comprising PVP as a wet binding agent is effective for improving stability properties by preventing moxifloxacin HCl anhydrate to dehumidify.

Moreover, it is determined that the coating comprising PVP has effect on improving solubility properties of moxifloxacin HCl anhydrate. Because of this reason, the second aspect of invention is to obtain granules with improved solubility and stability in which moxifloxacin HCl anhydrate preferably blended with dispersant is coated by granulation solution comprising PVP.

At the third stage, what should be the particle size range of micronized moxifloxacin HCl anhydrate granules is determined as a second step of micronized process of moxifloxacin HCl granules.

Reducing the particle size of moxifloxacin increases solubility via increasing surface area. However, this method applied for increasing solubility results in agglomeration of moxifloxacin while it is converted into larger particles during the production of pharmaceutical dosage form. Micronized drug particles stick together excessively and they are wetted hard. This situation leads to decrease in the dissolution rate.

Therefore, particle size should be reduced for improving solubility and a reproducible production method for better wetting drug particles prevent agglomeration should be improved.

As a result of studies, it is observed that the solubility of the granules wherein moxifloxacin HCl anhydrate blended preferably by a pharmaceutically acceptable disintegrant is coated by a granulation solution comprising PVP as wet binder and dried to have maximum 2.5% humidity and sieved to have preferably $\leq 1200 \mu\text{m}$, more preferably $\leq 800 \mu\text{m}$, the most preferably $800 \mu\text{m}$ average particle size distribution.

Moreover, micronized moxifloxacin HCl anhydrate granules obtained by said method do not faced with an agglomeration problem. Therefore, the third aspect of the invention is to obtain micronized granules developed without causing agglomeration depending on solubility in which the particle size distribution is present preferably $\leq 1200 \mu\text{m}$, more preferably $\leq 800 \mu\text{m}$, the most preferably $800 \mu\text{m}$.

At the fourth stage, a suitable diluent is chosen to provide that micronized moxifloxacin HCl anhydrate granules remain stable.

An excipient having low moisture content should be chosen to provide the stabilization of moxifloxacin which has tendency to disintegration because of being a hygroscopic substance.

Moreover, the said excipient should increase processability of micronized moxifloxacin HCl anhydrate granules and help them to provide reproducible tablet quality.

As a result of studies, it is observed that a β -lactose anhydrate form having low humidity content, preferably β -lactose anhydrate provides that moisture-sensitive micronized moxifloxacin HCl anhydrate granules remain stable.

The studies revealed that the humidity rate of lactose anhydrate having high β -content is negligible in comparison with the other lactose forms preferred in the prior art. Moreover, β -lactose anhydrate increases processability of the granules and provides to obtain reproducible tablet quality.

In addition to these, it is observed that the β -lactose anhydrate has much higher solubility than the other lactose anhydrate forms and thus it contributes to improve the solubility of micronized moxifloxacin HCl anhydrate granules. Studies have shown that β -lactose anhydrate has the best efficiency to improve solubility and stability preferably in the range of higher than 25% by weight, more preferably in the range of between 25 -40% by weight, the most preferably in the range of 30% by weight. Therefore, the fourth aspect of the invention is to obtain granules with improved solubility and stability as a result mixing micronized moxifloxacin HCl anhydrate granules with a lactose anhydrate, preferably β -lactose anhydrate form having low humidity content, in sufficient ratio.

At the final stage, the final mixture is obtained by adding at least one pharmaceutically acceptable excipient(s), preferably at least one disintegrant and/or lubricant onto micronized moxifloxacin hydrochloride anhydrous granules which was preferably blended with β -lactose anhydrate; the tablets are pressed in accordance with their specifications by feeding mixture to pressing machine and obtained tablets are optionally coated by film coating.

The pharmaceutical compositions in tablet form in accordance with the invention which is produced by mentioned manufacturing method has solubility $\geq 85\%$ in dissolution environment (USP II Apparatus, 900 ml 0.1 N HCl solution environment, 50 rpm rotation speed) in the first 15 minutes.

As explained previously, the pharmaceutical compositions in accordance with the invention are characterized by comprising moxifloxacin HCl anhydrate granules having preferably $\leq 1200 \mu\text{m}$, more preferably $\leq 800 \mu\text{m}$, the most preferably $800 \mu\text{m}$ average particle size distribution. Then, the solubility of pharmaceutical compositions which comprising granules having $> 1200 \mu\text{m}$ average particle size distribution is determined as maximum 40% in the first 15 minutes.

It is determined that the pharmaceutical compositions in accordance with the invention in tablet form obtained by applying the said production method remain stable during at least 6 months in accelerated stability studies ($40^\circ\text{C} \pm 2^\circ\text{C} / 75\% \pm 5\% \text{ RH}$) and during at least 12 months in long-term stability studies ($25^\circ\text{C} \pm 2^\circ\text{C} / 60\% \pm 5\% \text{ RH}$).

The pharmaceutical composition in accordance with the invention comprising moxifloxacin HCl anhydrate granules with improved solubility and stability properties comprises the steps shown below:

1. Blending moxifloxacin HCl anhydrate preferably with a disintegrant
2. Obtaining the granulation solution by dissolving wet binding agent in deionized water.
3. Obtaining moxifloxacin HCl anhydrate granules by coating granulation solution on blend obtained in step 1..
4. Drying the granules obtained in Step 3 wherein a maximum moisture ratio is 2.5%.
5. Sieving the dried granules in Step 4 to maintain an average particle size distribution preferably $\leq 1200 \mu\text{m}$, more preferably $\leq 800 \mu\text{m}$, the most preferably $800 \mu\text{m}$.
6. Adding lactose in anhydrate form, preferably β -lactose anhydrate to the granules obtained in Step 5,
7. Obtaining the final mixture by adding at least one pharmaceutically acceptable excipient preferably at least one disintegrant and/or lubricant to the mixture obtained Step 6,

8. Pressing the tablets in compliance with specifications by feeding final mixture obtained to pressing machine in Step 7,
9. Optionally Coating the obtained tablets in Step 8 by film coating.

The fifth aspect of invention is to determine a favorable solution of moxifloxacin HCl anhydrate and at least one pharmaceutical acceptable excipient which are selected from a group of diluent, binder, disintegrant, glidant and lubricant for used in the treatment of bacterial infections. The ratios are percentage by weight and calculated in terms of core tablet weight.

The expression of "a certain ratio" means moxifloxacin HCl anhydrate preferably in the ratio of at least 60% by weight. Moxifloxacin HCl anhydrate is present in an amount of 400 mg in pharmaceutical compositions in accordance with the invention.

The pharmaceutically acceptable diluents can be selected from lactose, microcrystalline cellulose, starch, pregelatinized starch, modified starch, calcium phosphate (dibasic or/and tribasic), calcium sulphate trihydrate, calcium sulphate dihydrate, calcium carbonate, kaolin, lactitol, powder cellulose, dextrose, dextrad, dextrin, sucrose, maltose, fructose, mannitol, sorbitol and xylitol. The pharmaceutical compositions according to the invention include preferably lactose, more preferably a lactose in anhydrate form, most preferably β -lactose anhydrate as a diluent. In the pharmaceutical compositions according to the invention, the diluent is present in the compositions preferably in the range of more than 25%, more preferably in the range of 25-40%, the most preferably in the range of 30% by weight.

The pharmaceutically acceptable binders can be selected from starch (such as potato starch, maize starch, wheat starch), sugar such as sucrose, glucose, dextrose, lactose, maltodextrin; natural and synthetic gum (such as accacia), gelatin, cellulose derivatives (such as microcrystalline cellulose, HPC, HEC, HPMC, carboxymethylcellulose, methylcellulose, ethylcellulose), PVP, polyethylene glycol, paraffin, calcium carbonate, calcium phosphate, alcohol (such as mannitol, sorbitol, xylitol) and water. In the pharmaceutical compositions according to the invention comprises preferably PVP as a binder. In the pharmaceutical compositions according to the invention, the binder is present in the compositions in the range of 0.1-5% by weight.

The pharmaceutically acceptable disintegrants can be selected from starch (maize starch, potato starch), sodium starch glycolate, pregelatinized starch, cellulose derivatives (such as croscarmellose sodium or microcrystalline cellulose), PVP, crospovidone, alginic acid, sodium alginate, clays (such as Xanthan gum or Veegum), ion exchange resins, food acid and the effervescent system based on alkaline carbonate compounds. In the compositions according to the invention, the disintegrant is present in the composition in the range of 0.1-5% by weight.

The pharmaceutically acceptable glidants can be selected from silicone dioxide, magnesium trisilicate, powder cellulose, starch, talc, tribasic calcium phosphate, metallic stearates, calcium silicate and metallic lauryl sulphate. The pharmaceutical compositions according to the invention comprises preferably silicone dioxide or talc as a glidant. In the composition according to the invention, the glidant is present in the compositions preferably in the range of lower than 1% by weight.

The pharmaceutically acceptable lubricants can be selected from metallic stearates (such as magnesium stearate, calcium stearate, aluminium stearate), fatty acid esters (such as sodium stearyl fumarate), fatty acids (such as stearic acid), fatty alcohol, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oil, leucine, polyethylene glycol, metallic lauryl sulphates (such as sodium lauryl sulphate, magnesium lauryl sulphate), sodium chloride, sodium benzoate, sodium acetate and talc. The pharmaceutical compositions in accordance with invention comprises magnesium stearate preferably as a lubricant. Lubricant is present preferably in the range of 0.1-5% by weight in the pharmaceutical composition in accordance with invention.

In addition to these, the other pharmaceutically acceptable excipients such as stabilized agents, surface active agents, solubility modulators, electrolytes, flavouring agents, coloring agents and coating agents can be used in formulation.

The examples of pharmaceutical formulation according to the invention is shown below. These examples are given only to explain invention but subject matter of the invention is not limited by them.

EXAMPLES

Example 1. The pharmaceutical formulation comprising 400 mg and its production method

Content	Amount (mg)
Moxifloxacin HCl anhydrate*	436.4
Lactose anhydrate	199.6
PVP	4.0
Croscarmellose sodium	15.0
Talc	4.0
Magnesium stearate	6.0
Core tablet weight	665
Coating material	15

* Equivalent to 400 mg moxifloxacin

The production method of the pharmaceutical formulation comprising 400 mg moxifloxacin comprises the followings;

- 436.4 mg moxifloxacin HCl anhydrate is blended with 7.5 mg croscarmellose sodium.
- Granulation solution is obtained by dissolving 4.0 mg PVP in 120 ml deionized water.
- The blend obtained in the first stage is fed to the fluidized bed granulating machine and then granulated by the granulation solution.
- The granules obtained wherein a maximum moisture ratio will be 2.5% is dried.
- The granules dried is sieved from a 800 μ m sieve.
- Adding firstly 199.6 mg β -lactose anhydrate form, then 7.5 mg croscarmellose sodium and 4.0 mg talc to the granules obtained.
- Finally, 6.0 mg magnesium stearate is added to the composition and then mixed.
- The final composition is fed into the tablet press machine and the tablets are obtained in compliance with their specifications.
- The obtained tablets are optionally coated by film coating.

Example 2. The pharmaceutical formulation comprising 200 mg moxifloxacin

Content	Amount (mg)
Moxifloxacin HCl anhydrate *	218.2
Lactose anhydrate	100.8
PVP	3.0
Croscarmellose sodium	8.0
Magnesium stearate	6.0
Seed tablet weight	336
Coating material	14

* equivalent to 200 mg moxifloxacin

Example 3. The pharmaceutical formulation comprising 100 mg moxifloxacin

İçerik	Miktar (mg)
Moxifloxacin HCl anhydrate *	109.1
Lactose anhydrate	50.3
PVP	1.6
Pregelatinized starch	4.0
Colloidal silicon dioxide	1.0
Magnesium stearate	2.0
Seed tablet weight	168
Coating material	12

* equivalent to 100 mg moxifloxacin

The production method described in Example 1 can be adjusted to other pharmaceutical formulations comprising moxifloxacin HCl anhydrate.

CLAIMS

1. The pharmaceutical composition comprising moxifloxacin HCl and at least one pharmaceutically acceptable excipient, characterized in that said composition comprises micronized moxifloxacin HCl anhydrate granules.
2. The pharmaceutical composition according to claim 1, characterized in that micronized moxifloxacin HCl anhydrate granules have an average particle size distribution of preferably $\leq 1200 \mu\text{m}$, more preferably $\leq 800 \mu\text{m}$, the most preferably $800 \mu\text{m}$.
3. The pharmaceutical composition according to claim 1, characterized in that moxifloxacin HCl anhydrate is present in the ratio of at least 60% by weight in the composition.
4. The pharmaceutical composition according to claim 1 characterized in that the pharmaceutically acceptable excipients are selected from preferably diluent, binder, dispersant, glidant and lubricant.
5. The pharmaceutical composition according to claim 4 characterized in that said composition comprises a pharmaceutically acceptable diluent having low moisture content.
6. The pharmaceutical composition according to claim 5 characterized in that said composition comprises preferably lactose, more preferably a lactose in anhydrate form, the most preferably β -lactose anhydrate as a diluent.
7. The pharmaceutical composition according to claim 6, characterized in that diluent is present preferably in an amount higher than 25%, more preferably in the range of 25-40%, the most preferably in an amount of 30% by weight.
8. The pharmaceutical composition according to claim 4, characterized in that the composition comprises a pharmaceutically acceptable wet binder.

9. The pharmaceutical composition according to claim 8, characterized in that the composition preferably comprises PVP as a wet binder.
10. The pharmaceutical composition according to claim 4, characterized in that the wet binder is present in the range of 0.1-5% by weight.
11. The pharmaceutical composition according to claim 4, characterized in that the composition comprises a pharmaceutically acceptable disintegrant.
12. The pharmaceutical composition according to claim 11, characterized in that the composition preferably comprises croscarmellose sodium or a starch derivative as a disintegrant.
13. The pharmaceutical composition according to claim 12, characterized in that the disintegrant is present preferably in the range of 0.1-5% by weight.
14. The pharmaceutical composition according to claim 4, characterized in that the composition comprises a pharmaceutically acceptable glidant.
15. The pharmaceutical composition according to claim 14, characterized in that the composition comprises preferably silicone dioxide or talc as a glidant.
16. The pharmaceutical composition according to claim 15, characterized in that in the glidant is present preferably in an amount lower than 1% by weight.
17. The pharmaceutical composition according to claim 4, characterized in that the composition comprises a pharmaceutically acceptable lubricant.
18. The pharmaceutical composition according to claim 17, characterized in that the composition preferably comprises silicone dioxide or talc as a as a lubricant.
19. The pharmaceutical composition according to claim 18, characterized in that in the lubricant is present preferably in the range of 0.1-5% by weight.

20. The pharmaceutical composition according to any of the previous claims, characterized in that the composition is in the solid dosage form for oral use.
21. The pharmaceutical composition according to claim 20, characterized in that in the solid dosage form is in tablet form, optionally in film tablet form.
22. The preparation of pharmaceutical composition according to any of the preceding claims characterized in that,
- Blending moxifloxacin HCl anhydrate preferably with a disintegrant.
 - Obtaining the granulation solution by dissolving wet binding agent in deionized water.
 - Obtaining moxifloxacin HCl anhydrate granules by coating granulation solution on blend obtained in the first step.
 - Drying the obtained granules wherein a maximum moisture ratio is 2.5%.
 - Sieving the dried granules to maintain an average particle size distribution preferably $\leq 1200\ \mu\text{m}$, more preferably $\leq 800\ \mu\text{m}$, the most preferably $800\ \mu\text{m}$.
 - Adding lactose in anhydrate form, preferably β -lactose anhydrate to the obtained granules,
 - Obtaining the final mixture by adding at least one pharmaceutically acceptable excipient preferably at least one disintegrant and/or lubricant to the obtained mixture.
 - Pressing the tablets in compliance with specifications by feeding final mixture to the tablet pressing machine.
 - Optionally, coating the obtained tablets by film coating.
23. The pharmaceutical composition according to any of the previous claims characterized in that the composition is used for the treatment of bacterial infection.