The invention relates to a process for preparation of a premixed form of piperacillin and tazobactam. The admixture is prepared by dissolving piperacillin acid and tazobactam acid in a definite ratio in the presence of sodium ethyl hexanoate which is then crystallised under specific conditions to obtain the homogeneous crystals of Piperacillin Sodium and Tazobactam Sodium.
CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of provisional specification no. 2101/DEL/201 e-filed on dated 25 July, 2011 filed by the applicant, which is incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates to pharmaceutical compositions, and more specifically it relates to a premix formulation of sodium salts of piperacillin and tazobactam.

BACKGROUND OF THE INVENTION

Polymicrobial infections are often caused by pathogens that produce beta-lactamase enzymes which causes resistance to penicillins and cephalosporins. A formulation of piperacillin sodium and tazobactam sodium is commonly used to treat such infections. Piperacillin is a broad-spectrum beta-lactam antibiotic while tazobactam assists in reducing piperacillin's vulnerability to the beta-lactamase producing bacteria.
The admixing of piperacillin and tazobactam is a skilled pharmaceutical procedure that is performed using aseptic techniques to ensure product quality. So far in the industry, the formulation is prepared by preparing both the drugs separately and then mixing them in a blender, which usually takes long batch process time and also entails cleaning of equipment after product changeover. The major concern of such methods is that of uniformity in particle size. The non-uniformity in the particle size of both drugs is a problem which results in a non-homogenous mixture thereby, making the formulation unacceptable for medical purposes.

An improved and a new process of forming a solid form of premixed piperacillin and tazobactum to fight polymicrobial infection is embodied herein in the present invention. In forming the present premix, many shortcomings of the prior arts such as contamination, dosage calculation errors and drug instability etc can be avoided.

The formulations as prepared by the method of the invention overcome the disadvantages of the reconstituted product as they are premixed and stable for longer durations at low temperature. Additionally, any potential causes for problems of contamination area voided, which makes the admixture convenient for use.

SUMMARY OF THE INVENTION
It is the object of the invention to provide a process for preparation of a pharmaceutical composition comprising piperacillin or a pharmaceutically acceptable salt thereof and tazobactam or a pharmaceutically acceptable salt thereof for treatment of bacterial infections.

It is another object of the invention to provide a process for preparing a pharmaceutical composition comprising piperacillin and tazobactam, wherein the process comprises dissolving acids of piperacillin and tazobactam in an organic solvent in a temperature regulated environment and adding a basic solvent to prepare a first solution. Preparing a second solution of sodium salt complex in a ketone and reacting this solution with the first solution. Finally, crystallization is done to obtain the pharmaceutical composition of the invention.

It is yet another object of the invention to provide a process for preparation of a premix stable and homogenous composition of piperacillin sodium and tazobactam sodium.

It is yet another object of the invention to provide a process for the preparation of an admixture of piperacillin sodium and tazobactam sodium in which both the drugs having similar particle size.

It is yet another object of the invention to provide a process for the preparation of piperacillin sodium.
It is yet another object of the invention to provide a cost effective and lesser contamination process for the preparation of a composition of piperacillin sodium and tazobactam sodium.

DETAILED DESCRIPTION OF THE INVENTION

In the detailed description of the invention, numerous specific details are described to provide a thorough understanding of the various embodiments of the invention. However, one skilled in the relevant art will recognize that an embodiment of the invention can be practiced without one or more of the specific details, or with other apparatus, systems, assemblies, methods, components, materials, parts, and/or the like. In other instances, well-known structures, materials, or operations are not specifically shown or described in detail to avoid obscuring aspects of embodiments of the invention.

The various aspects of the present invention leading to a process for the preparation of a pharmaceutical composition comprising piperacillin or a pharmaceutically acceptable salt thereof and tazobactam or a pharmaceutically acceptable salt thereof for treatment of bacterial infections is detailed below.

The invention provides to the art a pharmaceutical composition of premixed piperacillin-tazobactam which avoids the particulate formation of the prior art and is capable of being used for medical purposes without the need of
making the formulation of uniform particle size. The composition of the invention reduces the formation of particulates compared to the prior art.

Forming admixtures with homogenous particle size and characteristics is a technically challenging task. Instead of preparing both the drugs separately and then mixing them, the invention provides a new process where the drugs are dissolved in a suitable solvent and crystallised to produce a medically acceptable formulation.

In an embodiment of the invention, the acid forms of drugs, piperacillin and tazobactam are dissolved in an organic solvent and adding a basic solvent to prepare a solution. A separate solution of sodium salt complex in a ketone is prepared which is then slowly added to the piperacillin and tazobactam solution to convert them into their respective sodium salts. The resulting solution is then stirred for a predetermined time period and filtered, then crystallized to obtain the desired formulation which complies with the pharmacopeia requirement.

In a further embodiment of the invention, the organic solvent in which acids of piperacillin and tazobactam are dissolved is an aprotic solvent selected from the group consisting of acetone, ethyl methyl ketone or any other ketone or any other organic solvent.
In another embodiment of the invention, the basic solvent added to the solution of acid forms of drugs, piperacillin and tazobactam is a base or an amine preferably triethylamine.

In another embodiment of the invention, the acids of piperacillin and tazobactam are dissolved in the organic solvent in a definite ratio of 8:1. The acids are dissolved according to w/w ratio.

In another embodiment of the invention, the dissolving step of acids of piperacillin and tazobactam in the organic solvent with the addition of the basic solvent to the dissolved solution is temperature regulated process. The temperature required for this is 0-45°C. High temperature is required to make the dissolved solution of acids clearer and to increase the dissolution kinetics. The solution contents are then filtered.

In another embodiment of the invention, the sodium salt complex is 2-sodium ethyl hexanoate which is prepared in a ketone or aldehyde preferably acetone. This solution of sodium ethyl hexanoate in acetone is cooled to a temperature in the range of -10°C to 40°C.

In another embodiment of the invention, after the reaction of the sodium salt complex with the admixed solution of acid forms of piperacillin and tazobactam, the resulting solution is then stirred for predetermined time period, filtered and then, crystallised to obtain the desired formulation. Crystallization of
the pharmaceutical composition produced is done with the help of ketone preferably acetone as crystallization medium. The crystallization of the premixed solution of acids of piperacillin and tazobactam in a single medium helps in getting homogeneous mixture of crystals of piperacillin sodium and tazobactam sodium.

In another embodiment of the invention, the prepared premixed pharmaceutical composition comprises crystals of piperacillin sodium and tazobactam sodium of homogenous size and is stable in nature.

In another embodiment of the invention, Piperacillin Sodium can also be prepared individually using the process of the invention. The process for the preparation of Piperacillin Sodium comprises dissolving the acid form of piperacillin in an organic solvent. A separate solution of sodium salt complex in a ketone is prepared which is then slowly added to piperacillin solution to convert it into the respective sodium salt. The resulting solution is then stirred for predetermined time period and filtered, then crystallised to obtain the desired formulation.

As per prior art Tazobactum Sodium and Piperacillin Sodium can be prepared only by Lypholization but with the present invention we can use Crystallization process. Thus, we will be able to make product in facility where normally Pencillin Sterile products like Isoxazoles and Ampicillin Sodium and Amoxycillin Sodium is produced.
In the prior art, the premixing of piperacillin and tazobactam was not done due to which problem of homogenization of crystals of the product. But, the process of the invention involves the premixing of acids of piperacillin and tazobactam and thereafter crystallization due to which the problem of homogenization is rectified.

According to the invention, the problem of contamination and instability is also been rectified due to the maintenance of sterile environment, premixing of the acid forms of the drugs, usage of only one medium of solvent through the reaction i.e. acetone and no usage of water throughout the reaction which helps in lesser effluent.

This procedure of the invention is particularly advantageous as it substantially reduces time and cost of the preparation for the formulation. Traditionally, both the components, namely, piperacillin sodium and tazobactam sodium are prepared separately and blended together under sterile conditions to achieve at the desired formulation. In comparison to the process of the invention as embodied herein, the traditional process consumes more time, energy and consequently proves to be less productive at an industrial scale. Therefore the process as embodied herein is particularly efficacious and proves to generate significant feasibility for an industrial scale production of crystals of Piperacillin Sodium and Tazobactam Sodium of homogeneous size.
The process of the invention as embodied herein eliminates multiple steps by simultaneously dissolving acid forms of piperacillin and tazobactam in a suitable solvent. The acid forms are converted to their respective sodium salts in the solution by addition of sodium ethyl-2-hexanoate. Once the reaction is complete, the solution containing piperacillin sodium and tazobactam sodium is crystallised. This product is of a superior quality and doesn't require any subsequent reactions as opposed to the traditional process which requires an additional step to obtain a homogenous mixture.

Additionally, the process of the invention considerably reduces time required for analytical procedures such as sterility testing time which generally spans for minimum fourteen days, thereby escalating the infrastructure cost which reflects in the final cost of the finished formulation.

It is further mentioned that, if the processes vide the prior art were to be used, all or most of the above machinery/equipment will need to be used thereby increasing running expenditure on the bulk production of the named products. It is classified here, that the improvements are not limited to just the factors as mentioned herein.

Several variations in the processes and the methods herein disclosed will suggest themselves to those skilled in the art. However, it is to be understood that the present disclosure relates to the preferred embodiment of
the invention which is for purposes of illustration only and not to be construed as limiting the scope of the invention.

A pharmaceutical composition containing the product obtained according to the process of the invention has no need to be formulated with additional auxiliaries.

The present invention will now be illustrated in greater detail with reference to Examples, but the present invention should not be interpreted as being restricted thereto.
EXAMPLES

Example 1

In a flask about 140ml acetone is charged. Piperacillin Acid (8 gm) and Tazobactum acid (1 gm) are added to the flask. Triethylamine (about 1.2 gm) is added to the flask. In case clarity is not achieved, the reaction mixture may be heated to 40-45°C and stirred to complete dissolution. The solution contents are then filtered and labeled as Solution A.

In another flask, 3.3 gm of 2-Ethyl sodium hexanoate is dissolved in 33 ml acetone and stirred till clear solution. The contents of this flask are filtered and then added to Solution A in 30 minutes at room temperature. The contents are continuously stirred at 0-3°C for 5 hours and filtered and washed with cooled acetone to obtain the crystals of the product. The material is dried under vacuum to get a yield of not less than 9.0gm FG. The product obtained complies with the pharmacopeia requirement.

Example 2

Piperacillin Acid (48 gm) and Tazobactum acid (6gm) are dissolved in acetone (about 840 ml). Triethylamine (about 7.2 gm app.) is added to the flask. In case clarity is not achieved, the reaction mixture is heated to 30-40°C and stirred to complete dissolution. The solution contents are then filtered and labeled as Solution A.
In another flask, about 20 gm of 2-Ethyl sodium hexanoate is dissolved in 120 ml acetone and stirred till clear solution. The contents of this flask are filtered and then added to Solution A. The contents are continuously stirred at 0-3°C for at least 1 hour and filtered and washed with cooled acetone to obtain the crystals of the product. The material finally washed with isopropyl alcohol and dried under vacuum to get a yield of not less than 49 gm FG. The product obtained complies with the pharmacopeia requirement.
CLAIMS

What is claimed is:

1. A process for the preparation of a pharmaceutical composition comprising
   (a) piperacillin or a pharmaceutically acceptable salt thereof, and (b) tazobactam or a pharmaceutically acceptable salt thereof for treatment of
   bacterial infections,
   wherein the process is characterized by steps comprising:
   a. dissolving acids of piperacillin and tazobactam in an aprotic solvent
      in a temperature regulated environment;
   b. adding an alkylmine or any other base to the solution from step (a);
   c. dissolving a sodium salt complex in a ketone;
   d. reacting solution of step (c) with the solution of step (b);
   e. Crystallizing the solution of step (d) to obtain the pharmaceutical
      composition.

2. The process according to claim 1, wherein acids of piperacillin and
   tazobactam are dissolved in ratio of 8:1 (w/w) or any other required ratio.

3. The process of claim 1, wherein the aprotic solvent used for dissolution in
   step (a) is selected from the group consisting of any ketone or aldehyde or any other organic solvent.

4. The process according to claim 1, the ketone is selected from the group
   consisting of acetone or ethyl methyl ketone.
5. The process according to claim 1, wherein the alkylamine in step (b) is triethylamine.

6. The process according to claim 1, wherein the sodium salt complex in step (c) is 2-sodium ethyl hexanoate.

7. The process according to claim 1, wherein the temperature for dissolution in step (a) and step (b) is maintained in the range of 0°C to 45°C.

8. The process according to claim 1, wherein the solution in step (c) is cooled to a temperature in the range of -10°C to 40°C.

9. A process for preparation of a pharmaceutical composition comprising (a) piperacillin or a pharmaceutically acceptable salt thereof, and (b) tazobactam or a pharmaceutically acceptable salt thereof for treatment of bacterial infections,

   wherein the process is characterized by steps comprising:

   a. dissolving acids of piperacillin and tazobactam in acetone in a temperature regulated environment;

   b. adding a solution of triethylamine to the solution from step (a);

   c. dissolving sodium salt of ethyl hexanoic acid in acetone;

   d. reacting solution from step (c) with solution from step (b); and

   e. Crystallizing the solution of step (d) to obtain the pharmaceutical composition wherein the crystals formed are homogenous in size.

10. The process according to claim 9, wherein acids of piperacillin and tazobactam are dissolved in ratio 8:1 (w/w) or any other required ratio.
11. The process according to claim 9, wherein the temperature for dissolution in step (a) and step (b) is maintained in the range of 0°C to 45°C.

12. The process according to claim 9, wherein the solution in step (c) is cooled to a temperature in the range of -10°C to 40°C.
# INTERNATIONAL SEARCH REPORT

## A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K31/431; A61K31/43; A61K31/496; A61K31/429; A61K31/425; A61K31/41; A61K31/395; A61K31/33; A61P31/04

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DWPI, SIPOABS, CNKI, CPRSABS, GOOGLE; piperacillin, tazobactam, bacterial, ketone, aldehyde, acetone, triethylamine, hexanoate

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

** Document member of the same patent family

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### Date of the actual completion of the international search

04 Sep. 2012 (04.09.2012)

### Date of mailing of the international search report

**08 Nov. 2012 (08.11.2012)**

### Authorized officer

KANG, Xuliang

### Telephone No.

(86-10) 62414126
## INTERNATIONAL SEARCH REPORT

**Information on patent family members**

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INTERNATIONAL SEARCH REPORT

Continuation of: A. CLASSIFICATION OF SUBJECT MATTER

A61K31/431(2006.01)i
A61K31/43(2006.01)i
A61P31/04(2006.01)n

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