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(54) Title: CEFDITOREN PIVOXIL COMPOSITIONS WITH IMPROVED STABILITY AND PRODUCTION METHODS THEREOF

(57) Abstract: The present invention is a solid pharmaceutical formulation which comprises Cefditoren pivoxil and an antioxidant agent as stabilizer. It is found out that the impurity profiles of Cefditoren pivoxil film coated tablet and disintegrating tablet formulations which comprise Vitamin E as antioxidant were improved.

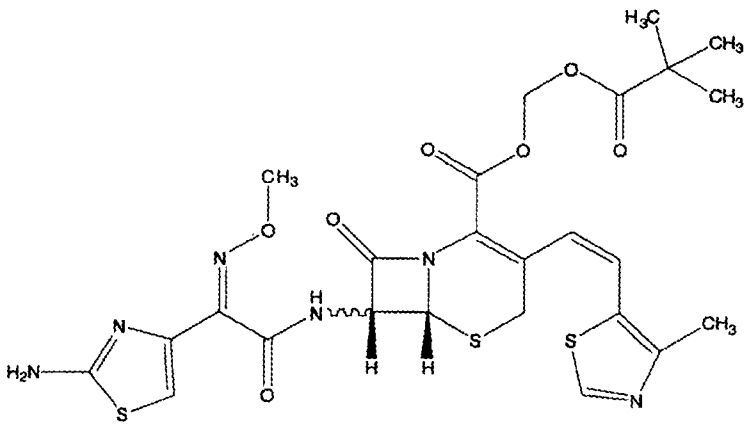
CEFDITOREN PIVOXIL COMPOSITIONS WITH IMPROVED STABILITY AND PRODUCTION METHODS THEREOF

Technical Field

This invention is related to film coated tablets and orally disintegrating formulations which are used in the treatment of respiratory tract infections and comprise cefditoren pivoxil with improved stability.

Prior Art

Cefditoren pivoxil is a third generation cephalosporin which is used in the treatment of respiratory tract infections (Formula I).



(I)

Cefditoren pivoxil film coated tablets are present in the market in the form of 200 mg and 400 mg oral dosage forms. Additionally, its 30 mg/0.3 g and 50 mg/0.5 g sachet forms are also available for pediatric usage.

Cefditoren pivoxil is first disclosed in patent application EP175610 A2 (US4839350). It has a wide antimicrobial spectrum and low toxicity when used orally. In related patents, the effectiveness of cefditoren pivoxil in the treatment infectious diseases caused by gram positive and negative bacteria is disclosed.

Cefditoren pivoxil freely dissolves in diluted hydrochloric acid. It is sparingly soluble in methanol, slightly soluble in acetonitrile and ethanol (95%), slightly soluble in diethylether and practically insoluble in water (less than O.lmg/ml).

In general, the dissolution rate of the medical products sparingly soluble in water largely affects the in vivo absorption.

Cefditoren pivoxil which does not practically dissolve in aqueous mediums usually shows a low dissolution profile. Therefore, compositions comprising cefditoren pivoxil which will show dissolution at an acceptable level are being searched.

EP0629404 A1 (Meiji Seika Pharma) is about a formulation using hydroxypropylcellulose to increase the wettability and solubility of Cefditoren pivoxil.

US5958915 (Meiji Seika Pharma) is related to Cefditoren pivoxil tablet formulation whose bitter taste is repressed and solubility in water and absorption is increased. The characteristic of the patent is that the formulation comprises water soluble casein salt (sodium and potassium caseinate).

EP1389462 (Meiji Seika Pharma) is related to obtaining amorphous cefditoren pivoxil by grinding the cefditoren pivoxil in crystal form with organic polymer.

EP1671635B1 and EP1555024B1 (Meiji Seika Pharma) are related to suspension formulations which contain sucrose fatty acid ester (DK Ester SS).

National patent application TR2011/12202 (Mahmut Bilgic) is related to pharmaceutical formulations comprising pharmaceutically acceptable excipients.

WO 99/34832 (Meiji Seika Pharma) is related to cephalosporin compositions with crystallographic stability and production methods thereof. It is related to formulations which provide the desired values in the dissolution of end product with the addition of water soluble and orally administrable polymer to the composition containing the amorphous form of cefditoren pivoxil.

WO 98/12200 (Meiji Seika Pharma) is related to formulations comprising cefditoren pivoxil in crystal form with high purity and thermal stability and also to the production processes with a first step of converting amorphous cefditoren pivoxil into crystal form.

Cefditoren pivoxil molecule decays under heat, light, basic, acidic and oxidative conditions. Additionally, its impurity profile contains many known impurities. Its vulnerability to environmental conditions adversely affects the stability of end products containing cefditoren pivoxil. Therefore, compositions comprising cefditoren pivoxil with impurity profiles at an acceptable level are still needed.

As a result of the studies carried out, the inventors have found out that it is possible to obtain a significant improvement both in the dissolution and stability of the products with the formulations developed for preparing dosage forms containing cefditoren pivoxil.

Description of the Invention

The present invention is related to the stable pharmaceutical formulations comprising orally administered cefditoren pivoxil and the preparation of said formulations.

Cefditoren pivoxil present in the pharmaceutical formulations according to present invention may be in the form of its pharmaceutically acceptable salts, hydrates, solvates, esters,

enantiomers, diastereomers or combinations thereof and may be in the form crystal, amorphous or combinations thereof in terms of polymorphic structure.

Pharmaceutical formulations may contain stabilizers in order to prevent the degradation of active substance and to provide a longer shelf life. As a stabilizer, excipients such as antioxidants, chelating compounds, photo-protective compounds, antimicrobial preservative agents may be used.

Usage of stabilizers to improve the stability of pharmaceutical formulations comprising cefditoren pivoxil was predicted. Antioxidant agent is preferred as stabilizer; the antioxidant agents used in pharmaceutical formulations are substances such as ascorbyl palmitate, ascorbic acid, butyl hydroxyanisol, butyl hydroxytoluen, potassium metabisulphite, sodium metabisulphite, propyl gallate and vitamin E. The inventors have found out that the impurity profiles of formulations comprising cefditoren pivoxil were improved when they contain Vitamin E as antioxidant.

From this point of view, the present invention is related to cefditoren pivoxil formulations comprising vitamin E alone as antioxidant or vitamin E in combination with another antioxidant.

Vitamin E is soluble in fat. The most effective tocopherol compound showing the effects of vitamin E is a-tocopherol.

The present invention is related to film coated tablets and orally disintegrating formulations which comprise vitamin E in an amount of 0.1-1.0%, preferably 0.1-0.5%, and more preferably 0.3% by the total weight of tablet.

Pharmaceutical formulations according to this invention are solid pharmaceutical formulations such as tablet, film coated tablet, dragee, orally disintegrating tablet, enteric tablet, modified release tablet. It is preferred that the solid pharmaceutical formulations are film coated tablet or orally disintegrating tablet.

In addition to active substance, the pharmaceutical formulations according to invention also comprise at least one pharmaceutically acceptable excipient selected from the group composed of filling agent, disintegrant, surfactant, stabilizer and lubricant.

The filling agent which may be used in the pharmaceutical forms according to the invention may be selected from the group comprising calcium carbonate, dibasic calcium phosphate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, maltose, mannitol, sorbitol, sodium caseinate, potassium caseinate, calcium caseinate.

The disintegrant which may be used in the pharmaceutical forms according to the invention may be selected from the group comprising carboxymethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, croscarmellose sodium, crospovidone, hydroxypropyl cellulose, microcrystalline cellulose, methyl cellulose, starch, sodium starch glycolate.

The surfactant which may be used in the pharmaceutical forms according to the invention may be selected among sodium lauryl sulphate, sodium tripolyphosphate, polysorbate, polyoxyethylene, polyoxypropylene glycol and similar agents.

The lubricant which may be used in the pharmaceutical forms according to the invention may be selected from the group comprising talc, magnesium stearate, PEG 6000, silicone dioxide, sodium benzoate, potassium benzoate, stearic acid, sodium stearyl fumarate and/or a combination thereof.

Aromatic agent according to the invention may be selected among peppermint, menthol, methyl salicylate, eucalyptol, cinnamon, 1-methyl acetate, sage, eugenol, oxanone, lemon, orange, strawberry, banana, blackberry, fruit mixture or mixture thereof.

Sweetener according to the invention may be selected from the group comprising acesulfame potassium, aspartame, fructose, maltitol, xylitol, saccharine, sodium cyclamate, sucraiose and sucrose.

Core tablets according to the invention may be coated with coating compositions comprising film coating agents, for example sugar based coating agents, water soluble film coating agents, enteric coating agents, coating agents prepared to provide various release features (fast release, slow release, controlled release etc.) or any combination thereof.

Water soluble film coating agents may be selected among cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methyl hydroxyl cellulose and sodium carboxymethyl cellulose, synthetic polymers such as polyvinyl acetal diethyl aminoacetate, aminoalkyl methacrylate copolymers and polyvinylpyrrolidone and polysaccharides such as pulluan or combinations thereof.

As a sugar coating agent saccharose may be used alone or optionally in combination with one of the agents such as talc, calcium carbonate, calcium phosphate, calcium sulphate, gelatin, gum Arabic, polyvinylpyrrolidone and pulluan or any combination thereof.

Film coated tablet formulations comprise 200 mg or 400 mg cefditoren pivoxil and excipients with the amounts (by total tablet weight) given below:

At least one filling agent 20% to 30% by weight,

At least one disintegrant 35% to 45% by weight,

At least one surfactant 5% to 10% by weight,

At least one stabilizer 0.1% to 1% by weight,

At least one lubricant 0.1% to 1% by weight.

At least one film coating agent 1% to 8% by weight,

Disintegrating tablet formulations comprise 30 mg or 50 mg cefditoren pivoxil and excipients with the amounts (by total tablet weight) given below:

At least one filling agent 30% to 40% by weight,

At least one disintegrant 20% to 30% by weight,

At least one surfactant 1% to 5% by weight,

At least one stabilizer 0.1% to 1% by weight,

At least one aromatic agent 1% to 10% by weight,

At least one sweetener 1% to 8% by weight,

At least one glidant 0.1% to 1% by weight,

At least one lubricant 0.1% to 1% by weight,

The pharmaceutical formulation according to the invention with appropriate stability and desired solubility values may be used in the treatment infectious diseases caused by gram positive and negative bacteria.

Examples

Film coated dosage forms are represented in Table 1. Core tablets contain about 43.8 % cefditoren pivoxil.

Table 1: Film coated dosage form formulations

	400 mg FCT	**200 mg FCT**
Inner Phase	**mg/tb**	**mg/tb**
Cefditoren pivoxil	490,4	245,2
Sodium caseinate	291,64	145,82
Croscarmellose sodium	284,6	142,3
Sodium tripolyphosphate	40,0	20,0
Vitamin E	3,36	1,68
Ethanol	k.m.	k.m.
Purified water	k.m.	k.m.
Outer Phase		
Magnesium Stearate	10,0	5,0
Tablet Weight	**1120,0**	**560,0**
Coating system*	**40,0**	**20,0**
Weight of film coated tablet	**1160,0**	**580,0**

Test formulations are manufactured by the process below.

1. Sodium tripolyphosphate is mixed in distilled water until it dissolves completely.

2. Vitamin E is dissolved in ethanol.

3. Cefditoren pivoxil, sodium caseinate and croscarmellose sodium are placed in HSM and mixed.

4. Sodium tripolyphosphate and vitamin E solutions are added onto the mixture in HSM successively and wet granulation is carried out.

5. The granules are dried at 50°C in oven, until the drying loss reaches 3 % (maximum).

6. Dried granules are sieved through 0.6 mm sieve, lubricated with magnesium stearate and compressed as tablets.

7. They are coated with film coating solution.

*HPMC or PVA based film coating system comprising at least one colorant, plasticizer, opacifier and glidant.

Table 2: Disintegrating tablet dosage form formulations

	50 mg DT	**30 mg DT**
Inner phase	**mg/tb**	**mg/tb**
Cefditoren pivoxil	61,300	36,78
Sodium caseinate	36,125	21,675
Croscarmellose sodium	35,575	21,345
Sodium tripolyphosphate	5,000	3,00
Vitamin E	0,750	0,45
Ethanol	k.m.	k.m.
Purified water	k.m.	k.m.
Outer Phase		
Mannitol SD 200	43,750	26,25
Crospovidone	25,000	15,00
Aspartam	10,000	6,00
Acesulfame K	10,000	6,00
Strawberry flavor	12,00	7,20
Banana aroma	8,00	4,8
Aerosil 200	1,25	0,75
Magnesium stearate	1,25	0,75
Table Weight	**250,00**	**150,00**

Test formulations are manufactured by the process below.

1. Sodium tripolyphosphate is mixed in distilled water until it dissolves completely.

2. Vitamin E is dissolved in ethanol.

3. Cefditoren pivoxil, sodium caseinate and croscarmellose sodium are placed in HSM and mixed.

4. Sodium tripolyphosphate and vitamin E solutions are added onto the mixture in HSM successively and wet granulation is carried out.

5. The granules are dried at 50°C in oven, until the drying loss reaches 3 % (maximum).

6. Dried granules are sieved through 0.6 mm sieve.

7. Crospovidone, aspartam, acesulfame K, aerosol 200, strawberry aroma banana aroma are added to the mannitol SD 200 present in the outer phase and mixed.

8. Magnesium stearate is added and mixed.

9. Tablets are compressed.

Dissolution

Reference products (film coated and sachet forms, Spectracef) and all formulations are tested under the dissolution conditions (stomach medium without enzyme, pallet method, 75 rpm, 900ml sample taken in 5th, 10th, 15th, 20th, 30th minutes) provided by FDA. The results of the tests are given in Table 3.

Table 3: Dissolution test results

Time (minute)	% Dissolution			
	Film coated tablet (FCT) formulation	Spectracef 400 mg FCT	Disintegrating tablet (DT) formulation	Spectracef 50 mg/0,5 g Sachet
0	0	0	0	0
5	45,8	32,4	93,6	97,6
10	80,8	67,0	94,9	95,7
15	91,5	87,8	94,0	97,3
20	94,0	95,4	93,2	96,8
30	95,5	94,8	91,7	96,4

As it can be seen in Table 3, test formulations and reference products have similar dissolution results and since their solubility in a dissolution medium having pH 1.2 is higher than 85% after 15 minutes, they are accepted as consistent according to CPMP/QWP/EWP/1401/98 without need for f_2 calculation.

In accordance with the results obtained above, also the 200 mg film coated tablet and 30 mg disintegrating tablet formulations are studied in direct proportion to the 400 mg film coated tablet and 50 mg disintegrating tablet and results similar to the results of high dosage products were obtained.

Stability

To carry out the impurity profile assay, stability tests were applied to the test formulations (400mg film coated tablet and 50mg orally disintegrating tablet), reference product (400mg tablet, Spectracef) and additionally one generic product (200mg tablet, Cefiten). The amounts of impurities were determined by HPLC method developed by the company. To examine the impurity profile in more detail, the samples were kept in high temperature and moisture (75% relative humidity at 50°C) for a month.

The results of respective impurity analyses are given in Table 4. In the test formulations comprising Vitamin E as stabilizer, a major decrease in the amount of unknown impurity and total impurity was observed.

Table 4 Impurity test results

		Initial period			
Specification		**Spectracef 400 mg FCT**	**Cefditoren 400 mg FCT**	**Cefiten 200 mg FCT**	**Cefditoren 50 mg DT**
Cefditoren	Max. 0.20%	0.144%	0.073%	0.11%	0.077%
Cefditoren Open Ring	Max. 1.0%	0.35%6	D.E.	0.310%	0.099%
Cefetamet Pivoksil	Max. 0.30%	0.007%	0.044%	0.022%	0.116%
Cefditoren Delta-3 Isomer	Max. 1.50%	1.171%	1.05%	1.160%	0.869%
Cefditoren Metoxy Methyl	Max. 0.20%	D.E.	0.116%	0.274%	0.07%
Cefditoren E-Isomer	Max. 1.0%	D.E.	0.004%	0.118%	0.130%
Cefditoren Dipivokxyl	Max. 0.30%	D.E.	D.E.	D.E.	DE
Cefditoren Pivaloyl	Max. 0.20%	0.146%	0.072%	0.156%	0.299%
Cefditoren Dimer	Max. 1.00%	0.633%	0.215%	D.E.	0.140%
Cefditoren Open Ring Dimer	Max. 1.0%0	D.E.	D.E.	D.E.	0.004%
Max. Unknown Impurity	Max. 0.10%	0.55%1	0.07%	0.539%	0.08%
Total Impurity	Max. 5.0%	3.440%	2.467%	3.340%	2.325%
		50°C 75% RH 1 month			
Cefditoren	Max. 0.20%	0.609%	0.109%	0.533%	0.182%
Cefditoren Open Ring	Max. 1.0%	2.779%	D.E.	1.977%	0.074%
Cefetamet Pivoksil	Max. 0.30%	D.E.	D.E.	0.080%	0.129%
Cefditoren Delta-3 Isomer	Max. 1.50%	5.123%	0.362%	3.524%	0.493%
Cefditoren Metoxy Methyl	Max. 0.20%	0.446%	0.048%	0.936%	0.110%
Cefditoren E-Isomer	Max. 1.0%	0.029%	D.E.	0.071%	0.080%
Cefditoren Dipivokxyl	Max. 0.30%	D.E.	D.E.	D.E.	DE
Cefditoren Pivaloyl	Max. 0.20%	0.286%	0.031%	0.302%	0.411%
Cefditoren Dimer	Max. 1.00%	1.933%	0.019%	0.014%	0.108%
Cefditoren Open Ring Dimer	Max. 1.00%	D.E.	D.E.	D.E.	DE
Max. Unknown Impurity	Max. 0.10%	9.123%	1.592%	3.896%	1.234%
Total Impurity	Max. 5.0%	35.226%	3.035%	20.328%	3.560%

Description of the Figures

Figure 1. The dissolution profiles of original product and 400 mg film coated tablet formulation in stomach medium without enzyme.

Figure 2. The dissolution profiles of original product and 50 mg disintegrating tablet formulation in stomach medium without enzyme.

CLAIMS

1. The solid pharmaceutical formulation comprising Cefditoren pivoxil, characterized in that it comprises at least one antioxidant agent as stabilizer.
2. Pharmaceutical formulation according to claim 1 wherein the antioxidant agent is vitamin E, ascorbyl palmitate, ascorbic acid, butyl hydroxyanisol, butyl hydroxytoluen, potassium metabisulphite, propyl gallate or mixtures thereof.
3. Pharmaceutical formulation according to claims 1-2, wherein the antioxidant agent is Vitamin E.
4. Pharmaceutical formulation according to claim 3, wherein the amount of Vitamin E is 0.1-1.0% and preferably 0.1-0.5% by the weight of tablet.
5. Pharmaceutical formulation according to Claim 1 wherein it is in the form of tablet, film coated tablet, dragee, orally disintegrating tablet, enteric tablet and modified release tablet.
6. Pharmaceutical formulation according to claim 5 wherein it is a film coated tablet.
7. Film coated tablet according to claim 6 wherein it comprises 200 mg or 400 mg cefditoren pivoxil.
8. Film coated tablet according to claim 7 wherein it comprises the excipients (by the weight of total tablet) below:

   At least one filling agent 20% to 30% by weight,
   At least one disintegrant 35% to 45% by weight,
   At least one surfactant 5% to 10% by weight,
   At least one stabilizer 0.1% to 1% by weight,
   At least one lubricant 0.1% to 1% by weight,
   At least one film coating agent 1% to 8% by weight.
9. Pharmaceutical formulation according to claim 5 wherein it is an orally disintegrating tablet.
10. Orally disintegrating tablet according to claim 9 wherein it comprises 30 mg or 50 mg cefditoren pivoxil.
11. Orally disintegrating tablet according to claim 10 wherein it comprises the excipients (by the weight of total tablet) below:

    At least one filling agent 30% to 40% by weight,
    At least one disintegrant 20% to 30% by weight,
    At least one surfactant 1% to 5% by weight,

At least one stabilizer 0.1% to 1% by weight,

At least one aromatic agent 1% to 10% by weight,

At least one sweetener 1% to 8% by weight,

At least one glidant 0.1% to 1% by weight,

At least one lubricant 0.1 % to 1% by weight.

AMENDED CLAIMS
received by the International Bureau on 03 May 2016, (03.05.2016)

1. The solid pharmaceutical formulation comprising Cefditoren pivoxil, characterized in that it comprises at least one antioxidant agent as stabilizer, wherein the antioxidant agent is Vitamin E.
2. Pharmaceutical formulation according to claim 1, wherein the amount of Vitamin E is 0.1-1.0% and preferably 0.1-0.5% by the weight of tablet.
3. Pharmaceutical formulation according to Claim 1 wherein it is in the form of tablet, film coated tablet, dragee, orally disintegrating tablet, enteric tablet and modified release tablet.
4. Pharmaceutical formulation according to claim 3 wherein it is a film coated tablet.
5. Film coated tablet according to claim 4 wherein it comprises 200 mg or 400 mg cefditoren pivoxil.
6. Film coated tablet according to claim 5 wherein *it* comprises the excipients (by the weight of total tablet) below:

   At least one filling agent 20% to 30% by weight,

   At least one disintegrant 35% to 45% by weight.

   At least one surfactant 5% to 10% by weight.

   At least one stabilizer 0.1% to 1% by weight, wherein the stabilizer is Vitamin E,

   At least one lubricant 0.1% to 1% by weight,

   At least one film coating agent 1% to 8% by weight.
7. Pharmaceutical formulation according to claim 3 wherein it is an orally disintegrating tablet.
8. Orally disintegrating tablet according to claim 7 wherein it comprises 30 mg or 50 mg cefditoren pivoxil
9. Orally disintegrating tablet according to claim 8 wherein it comprises the excipients (by the weight of total tablet) below:

   At least one filling agent 30% to 40% by weight.

   At least one disintegrant 20% to 30% by weight.

   At least one surfactant 1% to 5% by weight.

   At least one stabilizer 0.1% to 1% by weight, wherein the stabilizer is Vitamin E,

   At least one aromatic agent 1% to 10% by weight,

   At least one sweetener 1% to 8% by weight,

   At least one glidant 0.1% to 1% by weight.

   At least one lubricant 0.1% to 1% by weight.

Statement under Article 19(1)

Claim 1 and 3 are combined. Claim 2 is deleted. Vitamin E as stabilizer is added to novel claims 6 and 9 (previous claims 8 and 11). Other claims are unchanged.

In amended claims, stabilizer has been disclosed as Vitamin E. This amendment is supported by Page 3 Lines 11-21 of the original-filed application.

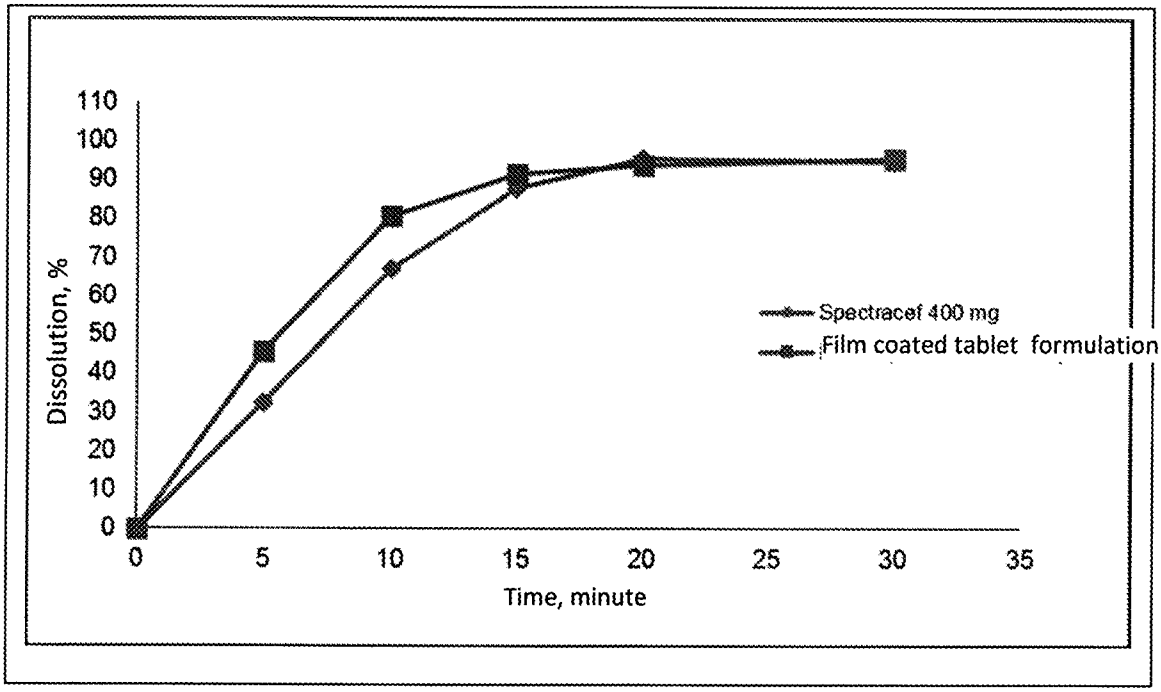


Figure 1

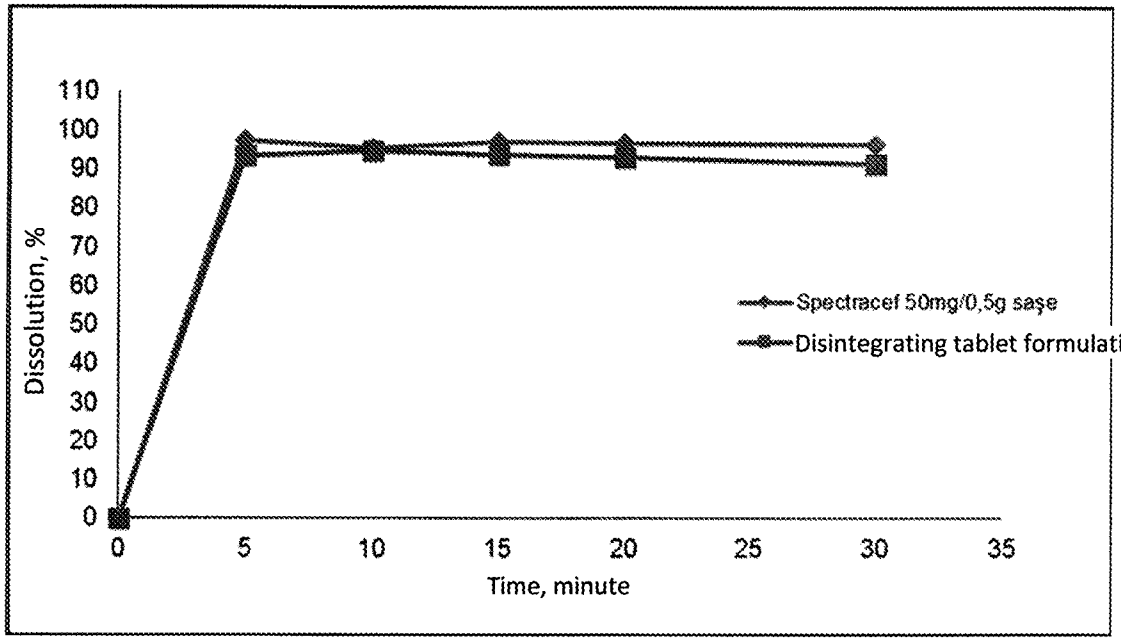


Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2015/0OQ016

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/546 A61K31/355
ADD.

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal , WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/010938 A2 (LUPIN LTD [IN] ; GUHA ASHISH [IN] ; METKAR BHARAT [IN] ; AVACHAT MAKRAND) 26 January 2012 (2012-01-26) page 4, lines 7-18 page 7, lines 8-18; claims 1-7; examples 1,2	1-11
X	WO 02/096354 A2 (TAP PHARMACEUTICAL PROD INC [US]) 5 December 2002 (2002-12-05) page 7, lines 5-15; examples 2,3; tables 1,2	1-11
A	EP 1 555 024 Al (MEIJI SEIKA KAISHA [JP]) 20 July 2005 (2005-07-20) the whole document	1-11

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

☒ See patent family annex.

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Information on patent family members

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