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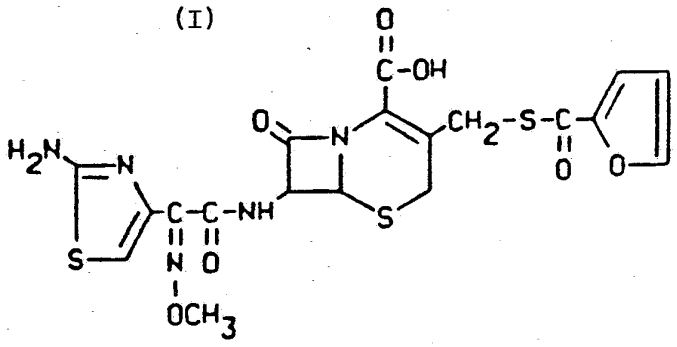
(54) Title: CONTROLLED RELEASE OF ANTIBIOTIC SALTS FROM AN IMPLANT

(I)



(57) Abstract

A controlled release implant antibiotic formulation comprising (a) a crystalline salt of the antibiotic; (b) an amorphous salt of the antibiotic; and (c) excipients; whereas the excipients comprise from 0% to 10% of the tablet by weight. A particularly effective formulation provided is made from the antibiotic ceftiofur which has formula (I).

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CONTROLLED RELEASE OF ANTIBIOTIC SALTS FROM AN IMPLANT

BACKGROUND OF THE INVENTION

The present invention provides for the controlled release of antibiotics. It is known in the pharmaceutical art to prepare compositions which provide for slow release of pharmacologically active substances contained in said compositions after oral administration to humans and animals. Such slow release compositions are used to delay absorption of a medicament until it has reached certain portions of the alimentary tract. Such controlled release of a medicament in the alimentary tract further maintains a desired concentration of said medicament in the blood stream for a longer duration than would occur if conventional rapid release dosage forms are administered.

INFORMATION DISCLOSURE

Ceftiofur, Formula I, is a known cephalosporin antibiotic, and is disclosed in U.S. patent 4,464,367.

A controlled release formulation comprising a matrix having dispersed therein both the pharmacologically active salt form of a medication and the free base form of the same medication is described in U.S. patent 4,443,428. In each of the formulations described therein, the amount of excipients were in excess 20% by weight. A similar formulation, but one that is based upon varying the water solubility of the active medicament, is described in Derwent 83519/-45.

Controlled release formulations containing mixed esters of a medicament are described in Derwent abstract 86-132837/21.

Derwent abstracts a European patent application where a mixture of crystalline diasteromeric salts of a medicament causing production of isomers to produce a sustained release effect.

SUMMARY OF THE INVENTION

The present invention particularly provides a formulation providing for the controlled release implant of an antibiotic comprising (a) a crystalline salt of the antibiotic; (b) an amorphous salt of the antibiotic; and (c) excipients; whereas the excipients comprise from 0% to 10% of the tablet by weight.

More particularly the invention provides a controlled release formulation for cephalosporins consisting of a crystalline salt of the cephalosporin and an amorphous salt of the cephalosporin.

In the present invention, intramuscular implantation is the preferred route of administration.

The amount of crystalline salt can vary from 20% to 90%, preferably 80% to 90%. Crystalline salts that can be used include the hydrohalide salts, i.e., ceftiofur hydrochloride, preferred ceftiofur hydrobromide and ceftiofur hydroiodide. In addition to the sodium salt other alkali metal salts that can be used are the potassium and lithium salts, i.e., ceftiofur sodium salt, ceftiofur potassium salt and ceftiofur lithium salt.

The crystalline and amorphous salts can be blended and compressed with or without additional excipients to yield an implant with controlled release characteristics.

A particularly effective formulation can be prepared utilizing 5-thia-1-azabicyclo[4.2.0]oct-2-ene-1-carboxylic acid, 7-[[2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetyl]amino]-3-[[(2-furanyl-carbonyl)thio]methyl]-8-oxo, monohydrochloride (ceftiofur monohydrochloride) as the crystalline salt and 5-thia-1-azabicyclo[4.2.0]oct-2-ene-1-carboxylic acid, 7-[[2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetyl]amino]3-3[[2-furanylcarbonyl)thio]methyl]-8-oxo,sodium salt, hydrate (ceftiofur sodium salt) as the amorphous salt.

Pellets of the formulations of this invention can be made by mixing the crystalline and amorphous salts and compressing them under standard press conditions. Particularly effective are formulations that contain no excipients.

Alternatively, excipients such as high molecular weight polyethylene glycols or polyvinyl pyrollidone up to 4% of total weight as excipients can be added to the formulation. Also, a lubricant and stabilizer such as stearic acid may be added. However, the weight of excipients should not exceed 10% and preferably 7% of the total tablet weight.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention is seen more fully by the example given below.

A powder mixture suitable for compression can readily be made by blending the proper weight to weight ratio (for example, 50/50) of the crystalline and amorphous salt forms in a glass mortar using appropriate mixing techniques. Portions of the mixture can be weighed and compressed using a standard laboratory Carver press and

tablet tooling capable of containing the entire sample (ex. 13/16 inch caplet tooling). Compression of up to 2000 pounds should be sufficient to generate an acceptable tablet. Painting the product contact surfaces of the tooling with a magnesium stearate/ethanol suspension will alleviate any problems with the compressed form sticking in the die.

The dissolution media should be made with normal care. While any buffered media should work, a pH 7.4, Sorenson's buffer was used in this case. The solution was filtered under vacuum through a 4.5 micron filter to remove particulates and deoxygenate the liquid. After filtration, the buffer should be used within eight hours to prevent effects from the reincorporation of oxygen.

A USP dissolution testing apparatus with paddles was used in this case. Paddle rotation was restricted to 50 rpm. The kettles were filled with 900 ml of the filtered buffer solution. Sampling was continuously performed by using a multi-channel, diastolic pump connected to a UV/VIS with six flow cells. The pump moved the liquid through the flow cells at 60 ml./minute. Each flow cell was monitored once every minute and the absorbance value at 332 nm was recorded.

The absorbance from freshly prepared standard solutions of both salt forms was recorded after each run. The concentrations selected exceeded the range anticipated from the complete dissolution of a given tablet in the 900 ml of buffer. Linear Least Squares fitting was performed on each standard curve set and used in extrapolating concentration values from the absorbance data.

Results for formulations containing different ratios of crystalline to amorphous charts are shown in Table 1.

TABLE 1

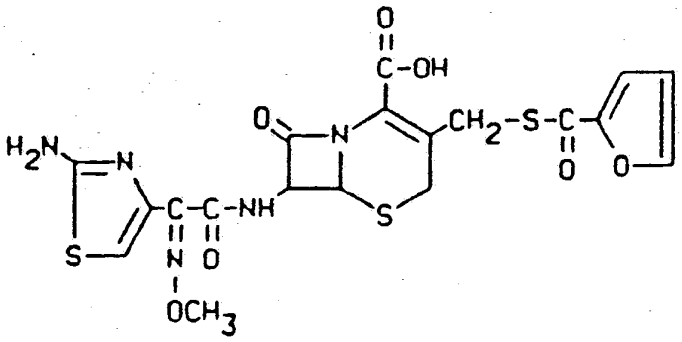
Results From Dissolution Data Using Procedure From Example 1. Time is in Minutes and Total Dissolution Time is an Approximation Based on Observation and Absorption Data. All Columns are the Average of Six, 600 mg. Tablets.

Percent HCl/Na	Average Time for 50% Dissolution	Average Time For Total Dissolution
0/100	6	20
20/80	10	45
40/60	23	90

60/40	34	140
80/20	53	175
100/0	66	400*

* = Estimated from partial data

FORMULA



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CLAIMS

1. A controlled release implant antibiotic formulation comprising (a) a crystalline salt of the antibiotic; (b) an amorphous salt of the antibiotic; and (c) excipients; whereas the excipients comprise from 0% to 10% of the formulation by weight.

2. A formulation of claim 1 providing for the controlled release of a cephalosporin consisting of an crystalline salt of the cephalosporin and a amorphous salt of the cephalosporin and wherein the excipients comprise from about 0% to about 7% of the tablet by weight.

3. An intramuscular implant formulation of claim 2 wherein the cephalosporin is ceftiofur.

4. A formulation according to claim 3 wherein the crystalline salt is ceftiofur hydrochloride and the amorphous salt is sodium ceftiofur.

5. A formulation according to claim 4 wherein the amount of ceftiofur hydrochloride present is about 20% to about 90% by weight.

6. A formulation according to claim 5 wherein the amount of ceftiofur hydrochloride salt is about 80% to about 90% by weight.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 88/02180

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/545; A 61 K 9/22

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	WO, A, 81/02975 (UNIVERSITY OF SOUTHERN CALIFORNIA) 29 October 1981, see claims 1-22 (cited in the application)	1-6
Y	US, A, 4443428 (B. OSHLACK et al.) 17 April 1984, see claims 1-9 (cited in the application)	1-6
A	US, A, 4464367 (LABEEUW et al.) 7 August 1984, see column 6, line 58 - column 7, line 14; claims 1-12 (cited in the application)	

* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20th September 1988	17 OCT 1988
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8802180 SA 23102

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 11/10/88
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