Description

Technical Field

The present invention is concerned with an oral pharmaceutical preparation primarily but not solely for pediatric use, containing bacampicillin hydrochloride as the active substance with a bad taste, in which preparation the bad taste has been masked.

The object of the present invention is to provide a dry powder for use as a pharmaceutical mixture preparation, wherein the bad taste of the bacampicillin hydrochloride pharmacodynamic properties of the mixture.

Background Art

As tablets are inconvenient for pediatric use other types of formulation have to be chosen. An alternative form of administration for pediatric use is a solution or a suspension of the active principle in water — a mixture. The dry powder including the active principle and adjuvants which is to be dissolved or suspended is henceforward called dry powder for mixing.

The preparation is stored as a dry powder. Before administration the dry powder is dissolved or suspended in water giving rise to a liquid formulation for oral administration — a mixture.

Hitherto bitter medicines have been coated with ethyl cellulose alone or together with wax to mask their bad taste (microencapsulation). The polymer ethyl cellulose is not pH sensitive and is not soluble in water. Applied on granulates of a drug it retards the rate of dissolution.

The main way to control drug dissolution from this type of microcapsules is the amount of polymer applied. In order to mask taste, the rate of dissolution should be very slow, but from a bioavailability point of view it should be as fast as possible. However, when applying a coating thin enough to be acceptable from the bioavailability point of view it is unacceptable in view of its inability to mask the bad taste.

It has also been suggested (Japanese Kokai 80 129,224) to mask bitter taste by coating the granules with a coating agent containing ethyl cellulose and an antacid. This method has the drawback of causing difficulties when producing the preparation, particularly when producing larger quantities.

Disclosure of the Invention

The present invention makes it possible to overcome the difficulties attached to the methods of preparing formulations of microencapsulated bitter drugs previously used by adding a basic substance to the encapsulated drug powder.

The dry powder of the invention affords improved stability to the pharmaceutical mixture prepared therefrom.

The drug shall be in a form which is soluble or easily soluble at a low pH and unsoluble or difficult to dissolve at a high pH. For the drug which is used in accordance with this invention it means that it is soluble or easily soluble in salt form and insoluble or difficult to dissolve in base form.

The drug that is used in the invention is bacampicillin hydrochloride (11'-ethoxycarbonyloxyethyl 6-[D(-)-2-amino-2-phenylacetamido]-penicillanate hydrochloride), other epimeric forms and the racemic form of bacampicillin hydrochloride.

The encapsulation of the drug can be achieved in the form of microcapsules, but the encapsulation is not restricted to the micro size.

The drug is encapsulated in an insoluble material selected from ethylcellulose polyvinylacetate and polyvinylchloride or an acid soluble copolymer of dimethylaminoethyl methacrylate and methylmethacrylate, such as Eudragit^{R} E 100.

Basic substances according to the invention are carbonates, e.g. sodium bicarbonate; phosphates, e.g. disodium mono hydrogenphosphate; and citrates, e.g. trisodium citrate.

The preferred basic substance is sodium bicarbonate.

The amount of basic substance in the dry powder preparation is best represented as a molar ratio between basic substance and drug. This ratio is 0.2-10, preferably 0,5—2.

In one embodiment of the invention bacampicillin hydrochloride (BAPC) is encapsulated in an insoluble, microporous polymer, such as ethyl cellulose and sodium bicarbonate and customary adjuvants are added to make a dry powder for mixing.

In another embodiment of the invention BAPC is encapsulated in a polymer soluble in acid, such as Eudragit^{R} E 100 and sodium bicarbonate and customary adjuvants are added to make a dry powder for mixing.

Best mode of carrying out the invention

The preferred formulation is bacampicillin hydrochloride encapsulated in ethyl cellulose and with addition of sodium bicarbonate.

(9)

Working Examples

Example 1

Dry powder for mixing

100 g of the dry powder contains Bacampicillin hydrochloride microcapsules corresponding to bacampicillin hydrochloride 100%	5.00 g
Sodium bicarbonate	1.00 g
Sodium carboxymethyl cellulose	0.69 g
Flavouring agents	2.92 g
Sugars	to 100.00 g

The powders are mixed together giving a dry powder for mixing.

Example 2

Influence of microencapsulation and the addition of sodium bicarbonate upon the taste of bacampicillin hydrochloride

The taste of different products was evaluated by a taste panel consisting of 24 people. The tests were carried out in a randomized double-blind crossover fashion. The tests were of triangle and preference types. In the preference test the different products were compared to a standard product of a penicillin with acceptable taste.

The results from those tests can be summed up in the following way

Type of dry formulation	Taste
Plain bacampicillin HCl	Extremely bad
Bacampicillin HCl microcapsules	Not acceptable
Bacampicillin HCl microcapsules + sodium bicarbonate as buffer according to the invention	Acceptable

It is obvious that the taste is improved by using microcapsules of the bad tasting drug which are suspended in media which contain a buffering substance.

Leakage of bacampicillin hydrochloride from microcapsules in reconstituted suspension

In this study a composition according to Example 1 except flavouring agents were used. At low pH sodium bicarbonate was replaced by citrate buffer. 5 grams of the dry powder was suspended with 5 ml of water. After ten minutes the microcapsules were filtered off and the filtrate was analysed for drug content.

Results	% Leakage
Composition with sodium bicarbonate (pH = 7.5) according to the invention	0.6
Composition with citrage buffer (pH = 4.0)	1.8

This finding verifies that a low leakage results in a better taste than a product with more leadkage according to the taste tests which have been performed.

Dissolution of bacampicillin hydrochloride from microcapsules filtered off from a reconstituted suspension

An experiment was performed in order to simulate the behaviour of the composition according to the invention in gastric environment. Microcapsules containing bacampicillin hydrochloride in the composition in Example 1 were filtered off and washed with 0.1 M sodium bicarbonate solution. Dissolution of the microcapsules was performed in a flow-through apparatus. The dissolution medium was similated gastric fluid without enzymes (pH 1.2).

Result: There was no difference in dissolution rate between microcapcules which had been in contact with the suspension and with nontreated microcapsules.

This finding indicates that the constituents of the suspension will not affect the dissolution characteristics of the microcapcules.

Bioavailability of bacampicillin hydrochloride microcapsule suspension, according to the invention

Bioavailability of this suspension was studied on 12 adult volunteers. The does of the suspension was 400 mg of the drug. Blood samples were collected from each volunteer and analysed for ampicillin contents (Bacampicillin is a prodrug of ampicillin and is readily converted to ampicillin during the process of absorption).

Bioavailability studies of bacampicillin hydrochloride 400 mg tablets have been performed at several different occasions. A typical result is shown.

Results	AUC (ml/l·h)	T max (hrs)	Ind. C max (mg/l)
Tablets	12.2	0.88	9.0
Suspension	13.8	0.75	8.2

AUC = mean of area under the plasma concentration versus time curve

T max = median of the time required to reach plasma concentration maximum

Ind C max = the mean of individual plasma concentration maximum

According to the paramaters given there is no great difference between the two different formulations of bacampicillin hydrochloride. This means that the suspension has the same magnitude of bioavailability as the conventional dosage form, the tablet.

Conclusion

The experiments described in this example have shown that a mixture of bacampicillin hydrochloride based on ethyl cellulose microcapsules can be obtained. The suspension has a very low leakage of the penicillin from the formulation but upon dissolution of the microcapsules in vitro in an acidic environment the drug will dissolve rapidly.

It has been possible to obtain a formulation with above mentioned properties due to addition of a small amount of sodium bicarbonate which dramatically decreased the leakage of the penicillin from the formulation. The decreased leakage of the bitter substance means that the formulation will have no or a negligible bitter taste.

Example 3

Stability of bacampicillin hydrochloride microcapsule suspension

64 g of dry powder from Example 1 for mixing was reconstituted with 39 ml of water. The obtained suspensions were stored in a refrigerator (5°C) for 14 days and at room temperature (25°C) for 8 days. The content was analyzed and calculated in percent of the initial content. Five batches of dry mixture was tested.

Temperature °C	Time days	Content %
5	14	97.6
25	4	95.2
25	8	91.8

Claims for the Contracting States: BE DE FR GB IT SE

1. Dry powder for use as a pharmaceutical mixture preparation wherein the taste of a bad tasting drug is masked, comprising bacampicillin hydrochloride encapsulated in a material selected from ethyl cellulose, polyvinyl acetate, polyvinyl chloride and a copolymer of dimethylaminoethyl methacrylate and methyl methacrylate, and a basic substance selected from carbonates, phosphates and citrates.

2. Dry powder according to claim 1, characterized in that the basic substance is sodium bicarbonate.

Result: There was no difference in dissolution rate between microcapcules which had been in contact with the suspension and with nontreated microcapsules.

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2. Dry powder according to claim 1, characterized in that the basic substance is sodium bicarbonate.

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Claims for the Contracting State: AT

1. A method for preparing a dry powder for use as a pharmaceutical mixture preparation, wherein the taste of a bad tasting drug is masked, which comprises mixing bacampicillin hydrochloride, encapsulated in a material selected from ethyl cellulose, polyvinyl acetate, polyvinyl chloride and a copolymer of dimethylaminoethyl methacrylate and methyl methacrylate, and a basic substance selected from carbonates, phosphates and citrates.

2. A method according to claim 1, characterized in that the basic substance is sodium bicarbonate.

Patentansprüche für die Vertragsstaaten: BE DE FR GB IT SE

1. Trockenpulver zur Verwendung als pharmazeutische Mischpräparation, wobei der Geschmack eines übelschmeckenden Arzneimittels verdeckt ist, welches Bacampicillinhydrochlorid, verkapselt in einem Material ausgewählt aus Äthylcellulose, Polyvinylacetat, Polyvinylchlorid und einem Copolymerisat von Dimethylaminoäthylmethacrylat und Methylmethacrylat, und eine Basissubstanz ausgewählt aus Carbonaten, Phosphaten und Citraten, enthält.

2. Trockenpulver nach Anspruch 1, dadurch gekennzeichnet, daß die Basissubstanz Natriumbicarbonat ist.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines Trockenpulvers zur Verwendung als pharmazeutische Mischpräparation, wobei der Geschmack eines übelschmeckenden Arzneimittels verdeckt ist, welches Bacampicillinhydrochlorid, verkapselt in einem Material ausgewählt aus Äthylcellulose, Polyvinylacetat, Polyvinylchlorid und einem Copolymerisat von Dimethylaminoäthylmethacrylat und Methylmethacrylat, und eine Basissubstanz ausgewählt aus Carbonaten, Phosphaten und Citraten, enthält.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Basissubstanz Natriumbicarbonat ist.

Revendications pour les Etats contractants: BE DE FR GB IT SE

1. Poudre sèche destinée à l'emploi comme préparation en mélange pharmaceutique dans laquelle le mauvais goût d'un médicament est masqué, contenant du chlorhydrate de bacampicilline encapsulé dans une substance choisie parmi l'éthylcellulose, le poly(acétate de vinyle) et le poly(chlorure de vinyle) et un copolymère de méthylacrylate de diméthylaminoéthyle et de méthacrylate de méthyle, et une substance basique choisie parmi des carbonates, des phosphates et des citrates.

2. Poudre sèche selon la revendication 1, caractérisée en ce que la substance basique est le bicarbonate de sodium.

Revendications pour l'Etat contractant: AT

1. Un procédé pour la préparation d'une poudre sèche en vue de l'emploi comme préparation en mélange pharmaceutique dans laquelle le mauvais goût du médicament est masqué, qui comprend le mélange du chlorhydrate de bacampicilline encapsulé dans une substance choisie parmi l'éthylcellulose, le poly(acétate de vinyle), le poly(chlorure de vinyle) et un copolymère de méthacrylate de diméthylaminoéthyle et de méthacrylate de méthyle, et d'une substance basique choisie parmi des carbonates, des phosphates et des citrates.

2. Procédé selon la revendication 1, caractérisé en ce que la substance basique est le bicarbonate de sodium.

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