PARENTERAL DEZOCINE COMPOSITIONS

This invention relates to parenteral compositions containing dezocine. Dezocine[(-)-13β-amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol] is an orally and parenterally active analgesic agent possessing a narcotic antagonist activity. As the hydrobromide salt, dezocine is a pale, cream-coloured odourless crystalline powder which is soluble in water at a concentration greater than 20 mg/ml. Initial clinical studies employing this drug at concentrations of 1, 2, 3, 4 and 5 mg/ml in saline were conducted with lyophilized product reconstituted at the time of administration.

It has now been discovered that ready-made injectable solutions of dezocine hydrobromide discolour and/or form insoluble material in less than one year when stored at room temperature and at 35°C. In addition, many of the solutions prepared using the base form of dezocine also form insoluble material. The insoluble material formed is generally a fine, light-coloured and amorphous solid. However, in one instance (Formulation A, infra) insoluble crystals were produced in sufficient quantity to permit identification as dezocine sulphate, a product of oxidation of the metabisulphite to sulphate. The other insoluble materials are of unknown constitution. In the presence of monothioglycerol employed as an antioxidant, up to about a 10 percent potency loss in six months at room temperature storage has been observed.

Because it is most desirable to provide ready-made injectables with a room temperature shelf life of approximately two years, an improved injectable formulation for parenteral administration is needed.

Thus, in accordance with this invention there is provided a parenterally acceptable aqueous composition consisting essentially of from 0.2 to 2 percent weight/volume of (-)-13β-amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol; from 30

to 45 percent weight/volume of propylene glycol; from 0.5 to 2 percent weight/volume of lactic acid; buffered with a pharmaceutically acceptable base to afford a pH of from 3.5 to 5; and from 0 to 0.02 percent weight/volume of sodium or potassium metabisulphite, in water for injection. By "water for injection" is meant water suitable for use in a parenteral composition.

Prefered formulations for parenteral administration contain, in water for injection;

from 0.5 to 1.5 percent weight per volume dezocine;

0.0075 to 0.015 percent weight per volume sodium metabisulphite;

0.6 to 1.0 percent weight per volume lactic acid;

30 to 42.5 percent weight per volume propylene glycol;

enough base such as sodium hydroxide to produce a pH of 3.5 to 5.0.

Because the formation of dezocine sulphate can occur, as noted supra, the amount of metabisulphite present may be decreased with increased quantities of drug to insure the theoretical maximum dezocine sulphate formation is solubilized. Thus, it is preferred to limit the metabisulphite to a maximum of 0.02 percent for 0.5 percent dezocine; 0.015 percent for 1.0 percent dezocine; and 0.005 percent for 2.0 percent dezocine.

The formulations of this invention are self-preserving [as established by the technique published in U.S. Pharmacopoeia XX, pp. 873-874 (1980)] and need no additive preservative ingredient. The formulations of the invention demonstrate acceptable storage stability throughout the drug concentration for at least twenty-four months at room temperature when made-up in ampoules, Tubex cartridge-needle units, and vials, employing several different elastomers in the vial and Tubex closures. ("Tubex" is

the trademark for an injection syringe system comprising a re-usable metal holder adapted to receive a disposable, prefilled unit dose cartridge-needle assembly). At elevated temperatures under accelerated storage test conditions (6 months at 45°C or 18 months at 35°C), some insoluble formation occurred in a few cases in the absence of an antioxidant. Therefore, the formulations containing an antioxidant are preferred. The main difference between the formulations containing an antioxidant and those with no antioxidant is that the latter darken more, although they remain acceptable for at least 24 months stored at room temperature.

Thus, the formulations of this invention provide solutions of dezocine suitable for parenteral injection. These new formulations are stable in storage for at least two years and provide a dosage form which may be maintained in ready-to-use form thereby avoiding separate packaging of diluent and drug and the necessity for reconstitution at the time of administration.

Although propylene glycol has been used heretofore as a non-aqueous solvent for the purpose of improving aqueous solubility of active drug substances and is classified as a non-aqueous solvent, it is not employed for that purpose in the formulation of this invention. Dezocine, in the form of its acid addition salts, is very soluble in water (greater than 100 mg/ml H_2O in lactic acid buffer at pH 4 to 5) and needs no additional solvent. For purposes of this invention, propylene glycol has been found to prevent the formation of unknown trace insolubles which develop in completely aqueous formulations containing dezocine.

Specifically preferred formulations of this invention contain 0.5, 1.0, 1.5 and 2.0 percent weight per volume of dezocine and are constituted as follows:

	Percent (wt/vol)			
Dezocine	0.5	1.0	1.5	2.0
Sodium Metabisulphite (NF)	0.015	0.015	0.0075	0.005
Propylene Glycol (USP)	31	31	31	31
Lactic Acid (USP)	0.6	0.8	1.0	1.3
NaOH (NF)	qs pH 4.0	qs pH 4.0	qs pH 4.0	qs pH 4.0
H_2O	qs 1 mL	qs 1 mL	qs 1 mL	qs 1 mL

The compositions of the invention may be prepared by bringing the ingredients of the composition into association with sufficient water for injection to afford a composition containing the desired ingredient composition.

Although other orders of mixing are possible, the formulations of this invention are most readily prepared by dissolving the lactic acid and sodium metabisulphite in a portion of the water for injection, dissolving the dezocine in this solution, adjusting the pH, adding the propylene glycol and mixing thoroughly before making the final volume adjustment.

The following formulations for parenteral administration of dezocine illustrate additional unsuccessful attempts to prevent the formulation of insoluble material in ready-made unit dosage forms, as well as stable formulations of this invention. Table I presents formulations in addition to the simple saline solutions and aqueous solutions referred to supra, which do not avoid the problem of insolubles formation and Table II presents formulations which do avoid the problem. The acceptability or unacceptability of a given formulation was determined by filling the experimental formulations into packages (ampoules, vials, Tubex cartridge-needle units, etc.) of the type and sizes conventionally used with parenteral drugs. These packages were stored at temperatures from 5°C to 60°C. At various times, samples were examined for colour change and development of insoluble material. The pH was measured and chemical assays performed to ascertain whether significant chemical loss had occurred and to assure maintenance of

potency. If a sample developed insolubles at any time during its projected shelf-life (two years at room temperature) it was considered unsuitable. Although formulations N and O did not produce insolubles in stability studies in ampoules, vials, or Tubex cartridge-needle units, they are considered unacceptable because from calculations based upon equilibrium solubility measurements there is sufficient sodium metabisulphite present that were it to all be oxidized to sulphate, the dezocine sulphate could exceed saturation and precipitate at room temperature. Otherwise, all of the formulations in Table I developed insoluble material at one or more time-temperature points. In addition, many of them discoloured markedly. These problems did not occur with samples stored at room temperature with formulations taken from Table II.

TABLE I Unacceptable Formulations - % (wt/vol)

Active Ingredient	A	B	C	D	E	F	G
Dezocine	1.5	10.3	10.3	2.0	2.0	2.0	1.5
Antioxidants							
Sodium Metabisulfite	0.025	-	-	-	-	-	-
Ascorbic Acid	-	-	-	-	-	0.50	-
Monothioglycerol	-	-	-	-	-	-	-
Cysteine·HCl	-	-	-	0.20	-	-	-
Propyl Gallate	-	-	-	-	-	-	0.02 or 0.10
Solubilizing Agents							
Benzethonium chloride	-	-	-	-	-	-	-
Propylene Glycol	-	-	-	-	21	21	31
Buffer							
Lactic Acid	1.3	8.4	8.4	1.7	1.7	1.7	1.0
Sodium Hydroxide	q.s. pH 4.5	q.s. pH 4.5	q.s. pH 4.5	q.s. pH 4.0 or pH 4.5	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0
Preservative							
Methyl Paraben	0.10	0.10	-	-	-	-	-
Diluent							
H_2O	qs	qs	qs	qs	qs	qs	qs

TABLE I Unacceptable Formulations - % (wt/vol) (Continued)

Active Ingredient	H	I	J	K	L	M	N
Dezocine	2.0	2.0	2.0	2.0	2.0	2.0	1.5
Antioxidants							
Sodium Metabisulfite	-	-	-	-	-	-	0.025
Ascorbic Acid	-	-	-	-	-	-	-
Monothioglycerol	0.5	0.5	-	0.5	0.5	0.5	-
Cysteine·HCl	0.2	-	0.2	0.2	-	-	-
Propyl Gallate	-	-	-	-	-	-	-
Solubilizing Agents							
Benzethonium chloride	-	-	-	-	-	0.01	-
Propylene Glycol	42	42	21	21	21	21	31
Buffer							
Lactic Acid	1.7	1.7	1.7	1.7	1.7	1.7	1.0
Sodium Hydroxide	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0
Preservative							
Methyl Paraben	-	-	-	-	-	-	-
Diluent							
H_2O	qs	qs	qs	qs	qs	qs	qs

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TABLE I Unacceptable Formulations - % (wt/vol) (Continued)

Active Ingredient	**O**
Dezocine	1.0
Antioxidants	
Sodium Metabisulfite	0.025
Ascorbic Acid	-
Monothioglycerol	-
Cysteine-HCl	-
Propyl Gallate	-
Solubilizing Agents	
Benzethonium chloride	-
Propylene Glycol	31
Buffer	
Lactic Acid	0.8
Sodium Hydroxide	q.s. pH 4.0
Preservative	
Methyl Paraben	-
Diluent	
H_2O	qs

TABLE II Acceptable Dezocine Formulations - % (wt/vol)

Ingredient						
Dezocine	0.5	1.0	1.5	0.5	1.0	1.0
Antioxidant						
Sodium Metabisulfite	0.015	0.015	0.0075	-	-	-
Solubilizing Agents						
Propylene Glycol	31	31	31	31	31	31
Buffer						
Lactic Acid	0.6	0.8	1.0	0.6	0.8	1.0
Sodium Hydroxide	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0
Diluent						
H_2O	qs	qs	qs	qs	qs	qs

* C L M S *

CLAIMS

1. A parenterally acceptable aqueous composition consisting essentially of from 0.2 to 2 percent weight/volume of (-)-13β-amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol; from 30 to 45 percent weight/volume of propylene glycol; from 0.5 to 2 percent weight/volume of lactic acid; sufficient pharmaceutically acceptable base to afford a pH of from 3.5 to 5; and from 0 to 0.02 percent weight/volume of sodium or potassium metabisulphite, in water for injection.

2. A composition according to Claim 1 which contains 0.0075 to 0.015 weight/volume sodium metabisulphite.

3. A composition according to Claim 1 or 2 in which the pharmaceutically acceptable base is sodium hydroxide.

4. A composition according to any one of Claims 1 to 3 which contains 0.5 to 1.5 percent weight/volume (-)-13β-amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5-11-methanobenzocyclodecen-3-ol.

5. A composition according to any one of Claims 1 to 4 which contains 30 to 42.5 percent weight/volume of propylene glycol.

6. A composition according to any one of Claims 1 to 5 which contains 0.6 to 1.0 weight/volume of lactic acid.

7. A parenterally acceptable aqueous composition which comprises about 0.5 percent weight/volume (-)-13β-amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol; about 0.015 percent weight/volume sodium metabisulphite; about 31 percent weight/volume propylene glycol; about 0.6 percent weight/volume lactic acid; sufficient sodium hydroxide to afford a pH of about 4.0 and sufficient water for injection to afford an aqueous solution containing the recited ingredient concentration.

8. A parenterally acceptable aqueous composition which comprises about 1.0 percent weight/volume (-)-13β-amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol; about 0.015 percent weight/volume sodium metabisulphite; about 31 percent weight/volume propylene glycol; about 0.8 percent weight/volume lactic acid; sufficient sodium hydroxide to afford a pH of about 4.0 and sufficient water for injection to afford an aqueous solution containing the recited ingredient concentration.

9. A parenterally acceptable aqueous composition which comprises about 1.5 percent weight/volume (-)-13β-amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol; about 0.0075 percent weight/volume sodium metabisulphite; about 31 percent weight/volume propylene glycol; about 1.0 percent weight/volume lactic acid; sufficient sodium hydroxide to afford a pH of about 4.0 and sufficient water for injection to afford an aqueous solution containing the recited ingredient concentration.

10. A process for preparing a parenterally acceptable aqueous formulation which comprises bringing into association a composition consisting essentially of from 0.2 to 2 percent weight/volume of (-)-13β-amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol; from 30 to 45 percent weight/volume of propylene glycol; from 0.5 to 2 percent weight/volume of lactic acid; sufficient pharmaceutically acceptable base to afford a pH of from 3.5 to 5; from 0 to 0.02 percent weight/volume of sodium or potassium metabisulphite and sufficient water for injection to afford a composition containing the recited ingredient concentration.

11. A process according to Claim 10 in which the lactic acid and the sodium or potassium metabisulphite, if present, is added to a portion of the water for injection, the (-)-13β-amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol is dissolved in the resulting solution, the pH is adjusted to 3.5 to 5 with the pharmaceutically acceptable base, the propylene glycol is added and the resulting composition is made up to volume with water for injection.

12. A formulation whenever prepared by the process claimed in Claim 10 or 11.

13. A parenterally acceptable aqueous composition substantially as hereinbefore described with reference to any one of the formulations given in Table II.