

United States Patent [19]
Thakkar

[11] 3,920,809
[45] Nov. 18, 1975



[54] DIBENZO[b,d]PYRANONE DISPERSIONS

3,636,058 1/1972 Fahrenholtz 260/345.3 X

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[22] Filed: Nov. 5, 1973

[21] Appl. No.: 413,012

[57] ABSTRACT

[52] U.S. Cl. 424/80; 424/283

[51] Int. Cl.² A61K 31/79

[58] Field of Search 260/345.3; 424/80

1-Hydroxy-3-alkyl-9-keto or 9-hydroxyhexahydro dibenzo[b,d]pyrans, useful as tranquilizers or hypotensive agents are dispersed with PVP or polyethylene glycol.

[56] References Cited

UNITED STATES PATENTS

4 Claims, No Drawings

3,507,885 4/1970 Fahrenholtz 260/345.3

FRANKIE H. GRAY, CLERK

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DIBENZO[b,d]PYRANONE DISPERSIONS

BACKGROUND OF THE INVENTION

1-Hydroxy-3-alkyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-ones, their ethers and esters are disclosed in U.S. Pat. 3,507,885 as intermediates for the preparation of Δ^8 or Δ^9 -tetrahydrocannabinols (Δ^8 or Δ^9 -THC). No other utility than as intermediates is disclosed for these compounds.

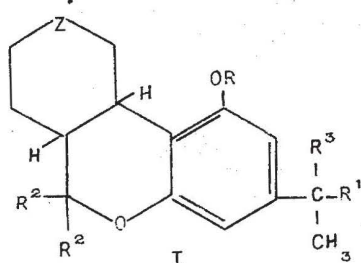
Polyvinylpyrrolidone (PVP) has been used to increase the solubility of aromatic compounds. Among these aromatic compounds have been several useful drugs. In particular, PVP complexing has been employed to increase the solubility of the drug for intravenous injection. The following papers deal with the use of PVP in injectable preparations containing Δ^9 -THC: D. C. Fennimore and P. R. Loy, *J. Pharm. Pharmac.* 23, 310 (1971) and H. Rosenkrantz et al., *J. Pharm. Sci.*, 61, 1106 (1972). Publication detailing the use of PVP complexes with other drugs include the following: E. I. Stupak and T. R. Bates, *J. Pharm. Sci.*, 61, 400 (1972) W. L. Chiou and S. Riegelman, *ibid.*, 60, 1281 (1971), 58, 1505 (1969), 59, 937 (1970), G. R. Svoboda, M. J. Sweeney and W. D. Walking, *ibid.*, 60, 33 (1971), P. Molyneux and H. Frank, *J. Am. Chem. Soc.*, 83, 3169 (1961), T. Higuchi et al., *J. Am. Pharm. Assoc., Sci. Ed.*, 43, 393 (1954), *ibid.*, 398 (1954). M. Mayersohn et al., *J. Pharm. Sci.*, 55, 1323 (1966), A. P. Simonelli et al., *J. Pharm. Sci.* 58, 538 (1969), and J. P. Davignon, *Bull. Parent Drug Assoc.*, 23, 83 (1969).

U.S. Pat. No. 3,673,163 discloses and claims a coprecipitate of the tricyclic compound, acronycine, with polyvinylpyrrolidone, said co-precipitate providing an acronycine dosage form of increased solubility.

Δ^9 -THC and other structurally related derivatives, either obtainable from natural sources or from various synthetic procedures, are known to be extremely insoluble in aqueous media. Consequently, there has been a continuing problem in determining the pharmacological activities of this group of compounds when administered by the oral route since there has been uncertainty as to the degree of absorption of these extremely insoluble substances after oral administration. Dispersions of dibenzo[b,d]pyran-9-ones with PVP or other similar materials for oral administration have not hitherto been described.

SUMMARY OF THE INVENTION

This invention provides dispersions of a compound represented by the formula



wherein Z is

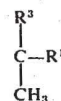


or



wherein each R is individually hydrogen or C₁-C₃ alkanoyl, wherein each R² is either hydrogen or methyl, and both R² groups are the same, wherein R³ is hydrogen or methyl, and wherein R¹ is C₁-C₆ alkyl or C₂-C₆ alkenyl with a polyvinylpyrrolidone (PVP) having a molecular weight in the range 10,000-360,000 or a polyethylene glycol having a molecular weight in the range 1000-6000.

In the above formula the term "C₁-C₃ alkanoyl" includes the groups: acetyl, propionyl, butyryl and isobutyryl. The scope of the grouping



is illustrated by the following radicals: 1,2-dimethylheptyl, 1,1-dimethylheptyl, 1,2-dimethylhexyl, 1,1-dimethylpentyl, 1,1-dimethylpropyl, 1-methylbutyl, 1-methyloctyl, 1-methylheptyl, 1-methylhexyl, 1,2-dimethyl-3-hexenyl, 1,1-dimethyl-2-heptenyl, 1-methyl-2-butenyl. The following tetrahydrodibenzopyrans are among compounds useful in the compositions of this invention:

1-hydroxy-3-n-heptyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one,

1-hydroxy-3-n-nonyl-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one

1-hydroxy-3-(1'-methyl-2'-butenyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one.

1-propionyloxy-3-(1'-methylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one,

1,9-dihydroxy-3-(1'-methylheptyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-dibenzo[b,d]pyran,

1,9-dihydroxy-3-(1',1'-dimethylheptyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-dibenzo[b,d]pyran,

1-butyroxy-3-(1',2'-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one

1,9-dihydroxy-3-(1',1'-dimethyl-2'-butenyl)-6a,7,8,9,10,10a-hexahydro-6H-dibenzo[b,d]pyran.

The dispersions of this invention contain from one part of a compound represented by the above formula to 2-20 parts of a PVP of molecular weight 10,000-360,000 or of a polyethylene glycol of molecular weight 1000-6000. The dispersions are prepared by dissolving the drug and the dispersing agent separately, preferably in a mutual solvent such as ethanol, mixing the two solutions and evaporating the solvent or solvents. Dispersions prepared in this fashion are useful in the preparation of pharmaceutical formulations of the above compounds for administration to mammals. For example, a complex containing one part of 1-hydroxy-3-(1',1'-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one and nine parts of PVP (molecular weight = 40,000) is mixed with an appropriate amount of a suitable excipient, for example, starch, and the mixture placed in telescoping gelatin capsules such that each capsule contains 10 mg. of drug. The capsules are then administered to mammals in need of treatment for anxiety and/or depression

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or who are in pain or require sedation. Similarly an aqueous suspension can be prepared from a complex containing 5 parts of drug to 45 parts of polyethylene glycol (molecular weight = 3000) to which one half-part by weight of a surfactant such as polyoxyethylene-sorbitan monooleate is added. Sufficient water is added to give a final concentration of 5 mg. of drug (as a polyoxyethylene complex) per ml. of suspension. The suspension is then administered by the oral route to a mammal requiring such medication.

The use of pharmaceutical formulations of drugs of formula I above as anti-anxiety and/or anti-depressant agents as analgesics, as sedatives or as hypotensive agents is more explicitly set forth in the copending applications of Robert A. Archer, Ser. Nos. 413,009 and 413,010, filed this even day herewith. According to those specifications, the dosage of drug represented by Formula I will vary from 0.001 to 100 mg. per day per patient or from 0.001 to 25 mg. per dose of a pharmaceutical formulation prepared as indicated above.

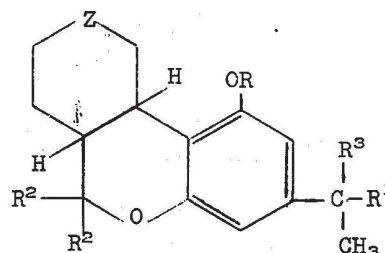
Prior art usages of PVP-drug combinations have without exception been directed toward providing materials of increased solubility for better oral absorption of the drug. Surprisingly, the PVP or polyethylene glycol dispersions of the dibenzo[b,d]pyrans of Formula I above are not necessarily more soluble, but are able to maintain their solubility for long periods of time such as 90 days or longer. Apparently, the PVP or polyethylene glycol is able to stabilize a particular polymorphic form of the drug in which, ordinarily, in the absence of the dispersing agent, the soluble polymorphic form changes to a less soluble polymorphic form. For example, an aqueous suspension similar to that illustrated above can be prepared by taking ten parts of a drug represented by formula I above, for example, 1-hydroxy-3-(1',1'-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo [b,d]pyran-9-one, in finally divided amorphous state as obtained after evaporation of an acetone solution of the drug and mixing the amorphous drug with one part by weight of polyoxyethylene-sorbitan monooleate or other suitable surfactant. Sufficient water is added to this mixture so as to provide a dose level of 5 mg. of drug per ml. If the suspension is allowed to stand for a period of four days, the drug apparently changes its crystalline form and begins to change in aqueous suspension to a polymorphic form of drug which is little, if at all, absorbed upon oral administration and gives negligible blood levels. I have found that a PVP-dibenzo[b,d]pyran-9-one dispersion prepared as indicated above and as furnished by this invention does not "recrystallize" when held in suspension for periods up to 4 days but instead is maintained in its readily absorbable form.

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Thus, there is no decrease in oral absorption and drug effectiveness when using pharmaceutical formulations for oral administration prepared in accordance with this invention as compared with those prepared by conventional means.

I claim:

1. A dispersion of 2-20 parts of polyvinylpyrrolidone having a molecular weight in the range 10,000-360,000 with one part of a compound of the formula



wherein Z is



or



wherein each R is individually hydrogen or C₁-C₃ alkanyl, wherein R³ is hydrogen or methyl, wherein each R² is either hydrogen or methyl, and both R² groups are the same, and wherein R¹ is C₁-C₆ alkyl.

2. A dispersion according to claim 1 containing 1 part of 1-hydroxy-3-(1',1'-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one and 9 part of a polyvinylpyrrolidone having a molecular weight in the range 10,000-360,000.

3. A dispersion according to claim 1 wherein the compound is 1-hydroxy-3-(1',1'-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one.

4. A dispersion according to claim 3 of polyvinylpyrrolidone of molecular weight 40,000 and 1-hydroxy-3-(1',1'-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one.

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LINK:**

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Dibenzo(b,d)pyranone dispersions

Abstract

1-Hydroxy-3-alkyl-9-keto or 9-hydroxyhexahydro dibenzo(b, d)pyrans, useful as tranquilizers or hypotensive agents are dispersed with PVP or polyethylene glycol.

Classifications

■ **A61K9/146** Intimate drug-carrier mixtures characterised by the carrier, e.g. ordered mixtures, adsorbates, solid solutions, eutectica, co-dried, co-solubilised, co-kneaded, co-milled, co-ground products, co-precipitates, co-evaporates, co-extrudates, co-melts; Drug nanoparticles with adsorbed surface modifiers with organic macromolecular compounds

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US3920809A

United States

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Inventor: [Arvind L Thakkar](#)

Current Assignee: [Eli Lilly and Co](#)

Worldwide applications

1973 • [US](#) 1974 • [IE](#) [ZA](#) [CA](#) [IL](#) [PH](#) [FR](#) [DE](#) [BE](#) [GB](#)

Application US413012A events ⓘ

1973-11-05 • Application filed by Eli Lilly and Co

1973-11-05 • Priority to US413012A