should be exercised to ensure that the (i) and (ii) variant is used and that the methods used to prepare such inocula do not prejudice the results by removing either the more or less sensitive fraction of the bacterial culture.

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Solid dispersion approach for overcoming bioavailability problems due to polymorphism of nabilone, a cannabinoid derivative

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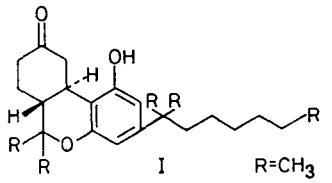
Nabilone, (±)-3-(1,1-dimethylheptyl)-6,6aβ,7,8,10aα-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]-pyran-9-one (I) is a potential anti-anxiety agent (Lemberger & Rowe, 1975a & b; Stark & Archer, 1975). This synthetic (Archer, Blanchard & others, 1977) cannabinoid is crystalline, unlike naturally occurring cannabinoids which tend to be resinous.



The aqueous solubility of nabilone is extremely low, less than 0·5 μg ml^{-1} at 25°.

Initial pharmacological testing of nabilone was done using an aqueous colloidal suspension prepared by mixing an acetone solution of the compound with 1% aqueous polysorbate 80 followed by removal of the acetone by evaporation. This preparation, given orally or parenterally, elicited pronounced cns activity in dogs at very low doses. A characteristically high-gaited ataxia was observed approximately 2·5 h after oral dosing. Other effects noted soon thereafter included body sway, head nod, hypothermia and sedation. The maximum intensity of these effects occurred within 4 h of dosing.

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Since a dry dosage form of nabilone was desired we prepared a formulation as follows: 1 g of nabilone was dissolved in ~50 ml of acetone, 9 g of starch U.S.P. was mixed in and the acetone removed by evaporation under vacuum. The residue was ground and filled into gelatin capsules. This dry formulation, when freshly prepared, elicited the same intensity of pharmacological response in dogs as did the aqueous colloidal preparation. The onset and duration of the cns effects were similar to those after an oral dose of the aqueous suspension.

After storage at room temperature (~25°) for 2 or 3 days, the dry formulation appeared much less active, and after 5 days became inactive. We extracted nabilone from the starch formulation and found, by t.l.c. and g.c., that no chemical degradation of nabilone had occurred. Evidently one bioavailable form of nabilone had converted to a non-bioavailable form. We, therefore, decided to investigate in detail the polymorphism of nabilone and to determine its impact on bioavailability.

Nabilone can occur in at least four distinct polymorphic forms depending upon the crystallization conditions and solvent. All the forms appeared to be equally hydrophobic and insoluble. Table 1 summarizes the bioavailability characteristics of the various forms. The polymorphs were characterized by DTA and X-ray diffraction powder patterns.

All the bioavailable forms tend to convert upon heating, grinding or prolonged storage to the non-bioavailable Form A, which is evidently the thermodynamically-stable form. An effective way to prevent this conversion is to keep nabilone dispersed in the water-soluble matrix of polyvinylpyrrolidone (PVP).

Table 1. *Nabilone: polymorphic forms and their bioavailability.*

Polymorph	Crystallization–solvent	Temp. (°C) of endothermic transitions in DTA[a]	Bioavailability in dogs[b]
A	Hexane	162	—
B	Ethanol–water[c]	155, 162	+
C	Ethanol–water[d]	132, 155, 162	+
D	Chloroform	120, 140, 162	—

[a] Differential thermal analysis.
[b] Cns activity noted in dogs after oral doses of nabilone included a characteristically high-gaited ataxia, head nod, body sway, hypothermia and sedation.
[c] Crystallization allowed to occur from warm ethanol–water solution.
[d] Crystallization forced by the addition of ethanol solution to water.

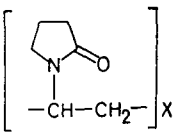
The solid dispersion technique to optimize the solubility and/or bioavailability of sparingly soluble, hydrophobic compounds has been extensively examined and reviewed (Chiou & Riegelman, 1971), but it appears not to have been used for preventing undesired crystalline transformations.

A 1:9 dispersion of nabilone in PVP was prepared by dissolving nabilone and PVP in 95% ethanol or chloroform and subsequent removal of the solvent by rotary-evaporation and vacuum drying. The dried preparation was ground and further dried to remove any residual solvent.

The PVP dispersion of nabilone appears to be noncrystalline, as seen from a diffuse X-ray diffraction pattern. Whereas nabilone itself is extremely hydrophobic, the PVP dispersion is hydrophilic. When the preparation is added to water, the PVP dissolves readily and nabilone is exposed in the form of a fine milky suspension. We attempted to determine the dissolution rate (in water) of nabilone from the PVP preparation and from the various polymorphs, but the low aqueous solubility (less than 0·5 $\mu g\ ml^{-1}$) prevented our obtaining any meaningful data.

When capsules containing nabilone dispersed in PVP were administered to dogs at 1 $mg\ kg^{-1}$, the onset of pharmacological response was within 1·5 h after dosing—with maximum intensity seen at 3–5 h. In normal volunteers, this preparation produces relaxant and sedative effects at a dose as low as 1 mg of nabilone (Lemberger & Rowe, 1975a). Effects were evident within 60–90 min and persisted 8–12 h. This PVP dispersion maintains nabilone in a bioavailable form for at least 2 years at room temperature.

It would seem that nabilone is molecularly dispersed in the PVP matrix, probably in a glass-like or amorphous state. Conversion to a crystalline state is effectively prevented. We have found evidence for a specific hydrogen bond interaction between nabilone and PVP in chloroform solution. The hydroxyl proton singlet in the nmr spectrum of nabilone shows progressive downfield shifts and signal broadening when increasing amounts of PVP are added to the $CDCl_3$ solution. The rest of the spectrum remains unaltered. The phenolic hydroxyl group of nabilone is probably hydrogen bonded to the amide carbonyl of PVP (II).



II

Such a bond might prevent nabilone from forming intermolecular hydrogen bonds as is presumably the case in the crystalline forms.

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