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*Review Article*

**Use of Nonaqueous Solvents in Parenteral Products**

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**T**HE PRACTICE OF incorporating naturally occurring nonaqueous solvents such as fixed oils and glycerin in pharmaceuticals has been common for many years. Water is always the solvent of choice. However, when it is not possible for physical or chemical reasons (such as limited solubility and hydrolytic reactions) to use a wholly aqueous system, nonaqueous solvents aid the formulator in developing stable, convenient parenteral dosage forms. A parenteral solution avoids the disadvantages inherent in suspensions, such as nonuniform dosage, caking, and possible slow release of the medicament when it is not desired.

A formulator encounters many problems once he determines that an aqueous system is unsatisfactory. The chosen solvent must be nontoxic, nonirritating, and nonsensitizing. It also must exert no pharmacologic activity of its own, nor adversely affect the action of the medicament. There are reported instances in which a solvent potentiated the activity of the medicament necessitating a change of dosage level. This will be discussed in greater detail later in this review.

In addition to being pharmacologically acceptable, the chemical and physical properties of the solvent must be taken into account. Thus, the ideal solvent should not be affected by acids or alkalis and it should be generally stable under normal conditions of pharmaceutical use. The viscosity must be such as to allow for ease of in-

jection, and the solvent must remain fluid over a fairly wide temperature range. It is advantageous if the solvent has a sufficiently high boiling point to allow heat sterilization. Additional considerations are water and body fluid miscibility, the degree of flammability, availability, source of supply, and constant purity.

Obviously, no such individual solvent presently exists. Thus, the selection of a nonaqueous solvent for a parenteral vehicle is a compromise among the many influencing factors. The advent of modern chemical technology has produced many new synthetic solvents in addition to the naturally occurring ones.

This review presents the toxicity, chemical and physical properties, and applications of some of the more commonly used nonaqueous solvents, as well as some specialized and rarely used solvents in pharmaceutical formulations.

**FIXED OILS**

The U.S.P. (1) recognizes the use of fixed oils as parenteral vehicles. Fixed oils are mainly mixtures of esters of unsaturated fatty acids which are fluid at 20°. The fluidity is generally due to the presence of the oleic acid esters of glycerin. The most commonly used fixed oils are corn oil, cottonseed oil, peanut oil, and sesame oil (2). Castor oil and olive oil have been used occasionally. While the toxicities of vegetable oils are relatively low, some patients exhibit allergic reactions to specific vegetable oils. Therefore, when such oils are used as vehicles, the label must state the specific oil contained in the product. Fixed oils have been known to cause undesirable

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local tissue reactions, such as cysts, foreign-body granulomas and, occasionally, nerve injury.

The requirements for fixed oils to be used in parenteral products are specified in the U.S.P. (1). The use of fixed oils is limited because of the low solubility of most drugs in these solvents. Since these oils are not miscible with water, dissolved drugs may exhibit a sustained-release effect with a possible diminution of absorption. Aqueous insolubility also precludes the use of fixed oils in unemulsified intravenous products.

Cottonseed oil has been used in intravenous fat emulsions administered to surgical patients as reported by Lehr and co-workers (3) and a commercial product is available.

Drugs which are incorporated in oils are mainly the steroid hormones, dimercaprol, calciferol, and menadione. Since fixed oils contain unsaturated fatty acids, oxidative changes take place which may necessitate the use of oil soluble antioxidants such as propyl gallate, butylated hydroxyanisole, butylated hydroxytoluene, and tocopherols.

A list of the official U.S.P. (1) and N.F. (4) parenteral solutions using fixed oils as solvents is given in Table I.

TABLE I.—OFFICIAL INJECTIONS IN OIL

Desoxycorticosterone acetate U.S.P.
Dimercaprol U.S.P.
Estradiol benzoate U.S.P.
Estradiol cyclopentylpropionate N.F.
Estradiol dipropionate U.S.P.
Estrone U.S.P.
Progesterone U.S.P.
Testosterone propionate U.S.P.
Diethylstilbestrol dipropionate N.F.
Menadione N.F.

A typical intramuscular formula for a testosterone propionate oil solution, 50 mg./ml., is (5)

	Gm./1000 ml.
Testosterone propionate	50.0
Benzyl alcohol	21.0
Sesame oil	869.0

Since sesame oil becomes turbid on cooling, a "winterized" or treated oil should be used, so that the oil remains clear when cooled to 5°.

#### ETHYL OLEATE

The "British Pharmacopoeia" (6) recognizes ethyl oleate as an alternative vehicle in injections of deoxycortone acetate, estradiol monobenzoate, progesterone, and testosterone propionate.

It is a yellowish oily liquid which is insoluble in water and miscible with alcohol, ether, and fixed oils. It has properties similar to fixed oils, ex-

cept that it is less viscous, is a superior solvent, and is more rapidly absorbed by the tissues (7). Unlike untreated sesame oil, ethyl oleate remains clear at 5°, but it has the disadvantage of discoloring on standing.

There are indications of increased hormone activity when ethyl oleate is used in place of sesame oil as a parenteral hormone vehicle. Studies by Dekanski and Chapman (8) demonstrated improved intensity and duration of action of testosterone phenylpropionate and testosterone propionate in ethyl oleate over that of the same androgens in sesame oil.

#### ISOPROPYL MYRISTATE

The use of isopropyl myristate as a vehicle for parenteral injections has been reported by Platcow and Voss (9). It is an oil miscible, water immiscible, chemically stable substance, not susceptible to rancidity and having a specific gravity of 0.852 (10). It consists mainly of isopropyl myristate and a small amount of isopropyl esters of other saturated fatty acids. Acute toxicity studies indicate a very low order of toxicity, but attempts to establish an LD<sub>50</sub> in mice failed when dosages equivalent to 100 ml./Kg. did not affect the test animals. Isopropyl myristate shows a very low degree of irritability and exhibits no sensitizing properties in rabbits and guinea pigs following topical and parenteral administration. In experiments on ovariectomized rats it compared favorably with sesame oil as a repository vehicle for estrogens (9). The external pharmaceutical use has been evaluated by Donovan, *et al.* (11), who found it a useful intermediate solvent for the incorporation of phenol, cocaine, resorcinol, and salicylic acid into liquid petrolatum.

#### BENZYL BENZOATE

Benzyl benzoate (12) is a colorless, oily liquid with a pleasant aromatic odor. It has a specific gravity of 1.118, boils at 323°, and is insoluble in water or glycerin, but is miscible with alcohol, chloroform, ether, and fixed oils. Its structural formula is

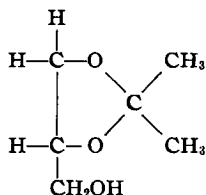


Benzyl benzoate has found some use as a co-solvent in oleaginous injectables such as dimercaprol injection, and in commercial preparations of hydroxyprogesterone benzoate where it is present in concentrations of 30% for the 125-mg. product in sesame oil and 46% for the 250 mg.

product in castor oil. The formula for the injection of dimercaprol B.P. (1958) is dimercaprol 5.0 Gm., benzyl benzoate 9.6 ml., and peanut oil, to make 100 ml.

### DIOXOLANES

The dioxolanes represent a new and interesting group of synthetic solvents for pharmacists. These substances are the reaction products of glycerin with ketones in the presence of a dehydrating agent (13). The least toxic member of the group is 2,2-dimethyl-1,3-dioxolane-4-methanol (14). This structural formula is



This compound [also known as Solketal, isopropylidene glycerol, and glycerol dimethylketal (15)] is reported to be a nontoxic, nonirritating solvent, miscible with water, alcohol, esters, aliphatic and aromatic hydrocarbons, and virtually all other organic solvents. It is a water-white, practically odorless liquid of medium viscosity, stable on storage, and unaffected by alkalis. Its boiling point is 82–83°, and has a specific gravity of 1.064. It is, however, hydrolyzed by strong aqueous acid solutions to acetone and glycerin (15–19).

Berger (14) reported the dioxolanes (as a class) produce transient muscular relaxation and paralysis. These effects were due to a depressant action on the central nervous system and not to a peripheral curare-like action. The mean paralyzing dose,  $ED_{50}$ , and the mean lethal dose,  $LD_{50}$ , for 2,2-dimethyl-1,3-dioxolane-4-methanol after intraperitoneal administration in mice was reported to be greater than 2.112 Gm./Kg. (16.0 mM/Kg.).

Teuber (20, 21) reported that the oral  $LD_{50}$  in mice is 4.0 to 7.2 Gm./Kg. (30–55 mM/Kg.). Dermatologic tests on rabbits produced no untoward reactions after 3 weeks of application.

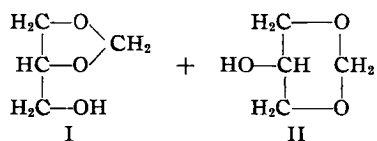
Guinea pigs exposed to aerosol sprays for 1 hour a day for 3 days exhibited no inflammation of mucous membranes. Huber (22) reported on the use of antibiotic aerosol sprays utilizing this solvent as a carrier for penicillin and oxytetracycline.

In this country, 2,2-dimethyl-1,3-dioxolane-4-methanol has been reported in the patent literature as a water-miscible solvent in gelatin

capsules (23) and as a parenteral vehicle for a tetracycline preparation (24).

### GLYCEROL FORMAL

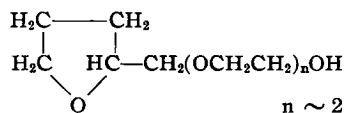
Glycerol formal is a condensation product of glycerol and formaldehyde consisting of 3-hydroxymethyl-1,3-dioxolane (I) (25%) and 5-hydroxy-dioxane (II) (75%). The structural formulas are



It is a chemically stable, colorless, odorless liquid of low viscosity and is miscible with water in all proportions. Sanderson (25) reported that the  $LD_{100}$  for rats by intraperitoneal administration was 3000 mg./Kg. and that the maximum symptomless dose was 1500 mg./Kg. The use of glycerol formal as a nontoxic solvent in toxicity testing has been suggested. It has been used as an industrial solvent and no toxic effects have been reported (25).

### GLYCOFUROL

Glycofurol is a Hoffmann-LaRoche trade name for a tetrahydrofurfuryl alcohol polyethylene glycol ether containing an average of two ethylene glycol units per molecule. It is a colorless liquid, miscible with water in all proportions and soluble in methanol, ethanol, *n*-propanol, and glycerin. It has a boiling point of 80–155° and a specific gravity of 1.078. The structure is (26)

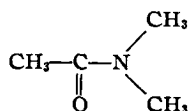


Spiegelberg and co-workers (26) extensively studied the pharmacology of this material and reported on its use as a parenteral solvent. Irritating when administered undiluted, it is nontoxic and nonirritating when diluted with water. The intravenous  $LD_{50}$  in the mouse is 3.78 Gm. (3.5 ml.)/Kg., and its tolerability equals that of propylene glycol. Acetylcholine chloride is reported to be stable in glycofurol solutions, while it is not stable in propylene glycol.

### DIMETHYLACETAMIDE

Dimethylacetamide (DMA), also known as acetic acid dimethylamide and acetyldimethylamine, is an interesting solvent which warrants some discussion. It is a clear, neutral liquid

having a boiling point of 165.5°, a specific gravity of 0.943, and a molecular weight of 87.12. The structural formula is



This solvent is miscible in all proportions with water and alcohol and very soluble in organic solvents and mineral oil (27).

Davis and Jenner (28) studied the acute toxicities of dimethylacetamide, dimethylformamide (DMF), and propylene glycol after single doses were administered intraperitoneally to mice. A 50% solution of DMA was used; however, the toxicity results are for the DMA content of the solution. The DMF and propylene glycol were administered undiluted. These results are as follows: the LD<sub>50</sub> for DMF was 1122 mg./Kg., for DMA 3236 mg./Kg., and for propylene glycol 11,400 mg./Kg. The LD<sub>100</sub> for DMA is 5012 mg./Kg.

Horn (29) investigated the chronic toxicity of DMA by dermal application in dogs at dosage levels of 0.1 to 4.0 mg./Kg. and by exposing both rats and dogs to an atmosphere containing DMA at concentrations of 40.0, 64.4, 102, and 195 p.p.m. All experiments were of 6-month duration unless obvious toxicity occurred. Liver damage occurred at all levels greater than 0.1 ml./Kg. dermally and 40 p.p.m. by inhalation.

The patent literature mentions the use of a 50% DMA solution as a vehicle for a preconstituted oxytetracycline (30) solution and as a solvent in soft and hard gelatin capsules (31). Its use as an anti-inflammatory agent in topical formulations is also reported (32).

Hammer, *et al.* (33), reported on a preconstituted intramuscular solution of oxytetracycline which consisted of a solution of an ethanolammonium magnesium salt of oxytetracycline in 50% N,N-dimethylacetamide. After testing in animals and humans, this formulation was found to be well tolerated and produced effective antibiotic serum levels. The stability was satisfactory for 2 years at room temperature.

A 50% solution of DMA is used as a solvent for a 250-mg./ml. chloramphenicol intravenous formulation, but it must be diluted with normal saline or 5% dextrose before administration.

A commercially available reserpine intramuscular product contains 10% DMA as a co-solvent (34).

DMA, when used as a drug solvent and administered to 15 patients with advanced malignancies produced hallucinations when given at

levels above 400 mg./Kg. of body weight per day for 3 days or more (35). However, the normal parenteral level for DMA is equivalent to 30 mg./Kg. per day. Thus, in normal use this hallucinogenic effect would not be expected.

An oxytetracycline 50-mg./ml. formula (30) was reported to have been composed of oxytetracycline, 50 mg.; magnesium chloride, hexahydrate 1.7%; ethanolamine, 20% aqueous 1.5%; sodium formaldehyde sulfoxylate 0.2%; lidocaine 2%; and N,N-dimethylacetamide 50%, to make 1.00 ml.

#### N-(β-HYDROXYETHYL)-LACTAMIDE

N-(β-Hydroxyethyl)-lactamide (36), also known as lactic acid carboxamide, is a clear, colorless, syrupy liquid which is water miscible. The specific gravity of the pure compound is 1.192. It is used as a 50% solution and has the following formula: CH<sub>3</sub>CHOHCONHCH<sub>2</sub>CH<sub>2</sub>OH. This compound is the reaction product of methyl acetate and 2-aminoethanol. The acute subcutaneous, LD<sub>50</sub>, toxicity (37) for a 50% w/v N-(β-hydroxyethyl)-lactamide solution is 15.8 Gm. lactamide/Kg. in mice and 16.1 Gm. lactamide/Kg. in rats. This compound has been used in Europe as a solvent for a preconstituted oxytetracycline solution. Neumann (37) reported that this product was stable for several years and showed improved tissue tolerability.

Dimmling (38) has also reported on the use of N-(β-hydroxyethyl)-lactamide as a solvent for oxytetracycline. After 24 hours, a detectable serum level was found after a single dose of 250 mg. in ten healthy persons. Following a second injection of 250 mg. after an interval of 24 hours, the levels showed a cumulative increase. Further studies (39) on the serum concentrations confirmed the previous findings.

The results of Seeliger's (40) investigation with oxytetracycline intramuscular in N-(β-hydroxyethyl)-lactamide solution in patients have confirmed the previous values obtained in healthy individuals. A single injection of 250 mg. gave an effective serum concentration for over 24 hours. Following repeated injections on consecutive days, marked cumulative effects were observed. The clinical effect was in accordance with blood level determinations. Survey of local tolerability showed practically no pain in 93.7% of the 380 injections performed; slight and tolerable local reactions, which in no case persisted for more than 2 or 3 hours, were found in 6.3%.

Hupe (41) reported that in 90 major surgical cases 250 mg. of oxytetracycline intramuscular in this solvent, once a day, was effective and well tolerated.

The patent literature also refers to the use of *N*-( $\beta$ -hydroxyethyl)-lactamide as a solvent for oxytetracycline injectables (30, 42). The use of other alkylol amides such as the amides of  $\beta$ -hydroxybutyric acid, succinic acid, adipic acid, tartaric acid, glycolic acid, and salicylic acid, was also mentioned (42). A typical formula for a 250 mg./3 ml. oxytetracycline product is

	Gm./100 ml.
Oxytetracycline hydrochloride	9.62
Magnesium chloride-hexahydrate	4.00
Sodium formaldehyde sulfoxylate	0.20
Water, pyrogen-free	44.20
<i>N</i> -( $\beta$ -hydroxyethyl)-lactamide	50.00
Monoethanolamine	2.30

### ETHYL LACTATE

Ethyl lactate, ethyl  $\alpha$ -hydroxypropionate,  $\text{CH}_3\text{CH}(\text{OH})\text{COOCH}_2\text{CH}_3$ , is a colorless liquid with a specific gravity of 1.042 which is miscible with water and has a characteristic odor. In aqueous solution some decomposition takes place (43).

Latven and Molitor (44) determined the acute toxicity of ethyl lactate in mice by subcutaneous and intravenous administration, and their results are shown in Table II.

TABLE II.—ACUTE TOXICITY OF ETHYL LACTATE

	LD <sub>0</sub>	LD <sub>50</sub>	LD <sub>100</sub>	Minimum Sympt. Dose	Maximum Nonsympt. Dose
Subcutaneous, ml./Kg.	2.0	2.5	3.0	1.0	0.8
Intravenous, ml./Kg.	0.2	0.6	1.0	0.3	0.2

Ethyl lactate was irritating on intradermal injection in guinea pigs and on application to the eyes of rabbits.

Ethyl lactate (10–100%) solubilizes an esterone injection in castor oil to a concentration of 3.5 to 6.5 mg./ml. (45). This product is stable at room temperature (46). It has been used as an industrial solvent and no toxic effects from its use have been recorded (47).

### ETHYL CARBONATE

Ethyl carbonate, diethyl carbonate,  $\text{CH}_3\text{CH}_2\text{-}$

$\text{OCOOCH}_2\text{CH}_3$ , has also been used as a solvent for erythromycin, but there is a paucity of literature on its use and toxicity. It is a liquid immiscible with water but miscible with alcohol and ether and has a specific gravity of 0.975 and a boiling point of 126° (48). This compound has also been used as an industrial solvent with no reported toxic effects (49).

### POLYETHYLENE GLYCOLS

The polyethylene glycols (PEGs), as the name implies, are polymers of ethylene oxide (50) with the general formula:  $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH}$ , where *n* represents the average number of ethylene oxide groups. These polymeric products are designated by a number which represents the average molecular weight (51). Polyethylene glycol 200, 300, 400, and 600 are moderately viscous, colorless, somewhat hygroscopic liquids. They are less volatile than glycerin and do not hydrolyze or deteriorate (52). They dissolve in water in all proportions to form clear solutions (51). Polyethylene glycol 1000, 1540, 4000, and 6000 are white waxy solids (Table III).

For the purpose of this discussion, we will confine our comments to the liquid polyethylene glycols which are more likely to be used in parenteral products. The literature abounds with papers discussing and describing measurements of the toxicity of the various PEGs by oral or topical routes (50–58). However, there is a scarcity of material on the parenteral administration. PEG 300 and 400 are better described than the other two members of the liquid PEG series. Only the parenteral LD<sub>50</sub>'s (as shown in Table IV) were found by the authors. Oral and dermal toxicity data are given in Tables V and VI.

Subcutaneous dosages of PEG 400 up to 10 ml. (ten times the human dose) in rats caused no permanent damage. The reactions were described as "blanching of the skin and scab formation in 48 hours." The test results were reported to be the same as with propylene glycol. PEG 300 and 400 do not elicit a foreign body reaction in animals (52). In dogs, the removal of PEG

TABLE III.—PHYSICAL PROPERTIES OF POLYETHYLENE GLYCOLS (51)

PEG	Av. Mol. Wt.	Sp. Gr., 20° C.	Freezing or Melting Range, ° C.	Viscosity, Cps. at 210° F.	Comparative Hygroscopicity Glycerol = 100
200	190–210	1.125	Super Cools	4.3	70
300	285–315	1.125	–15 to –8	5.8	60
400	380–420	1.125	4 to 8	7.3	55
600	570–630	...	20 to 25	10.5	40
1000	950–1050	1.151	37 to 40	17.4	35
1540	1300–1600	1.151	43 to 46	25–32	30
4000	3000–3700	1.204	53 to 56	75–85	...
6000	6000–7500	...	60 to 63	700–900	...

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