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Novel Prospects of Non-aqueous Solvents for Designing Injectables Parenteral Formulation

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The most efficient method for delivering pharmaceutically active compounds with a limited therapeutic index and low bioavailability is via parenteral administration. Depending on the patient's location and the type of ailment being treated, injectable medication products are quite different and specialized. Water-insoluble medications have long been dissolved using non-aqueous solvents in subcutaneous or intramuscular pharmaceutical formulations. The necessity for these transporters has grown recently as a result of the drug discovery process' production of numerous medicines with poor water solubility. The formulator uses nonaqueous solvents to create stable, practical parenteral dosage forms. The drawbacks of suspensions, such as non-uniform dosing caking and the potential sluggish release of the medication when it is not wanted, are avoided by using a parenteral solution. These organic solvents, which are thought to be inert chemically and physiologically, could have toxicological and pharmacological consequences. Therefore, prior to

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their administration, especially when given undiluted, it is crucial to understand the tolerance and activity of nonaqueous solvents. Propylene glycol, polyethylene glycols, and ethanol are examples of well-researched organic solvents. Other solvents include those described for specific applications (dimethyl sulfoxide, N-methyl-2-pyrrolidone, glycofurol, Solketal, glycerol formal, acetone), those not reported for intravascular applications but potentially useful (tetrahydrofurfuryl alcohol, diglyme, dimethyl isosorbide, e In addition to some specialized and infrequently used nonaqueous solvents, this overview discusses their toxicity, chemical and physical characteristics, and applications in parenteral formulations.

Keywords: Parenteral route; non-aqueous solvents; organic solvents; natural nonaqueous solvents.

1. INTRODUCTION

The Greek para and enteron, which signify avoiding the intestine, are the roots of the phrase parenteral [1]. Parenteral articles are those preparations designed for injection via the skin or other exterior boundary tissue as opposed to the alimentary canal, allowing the active ingredients to be delivered directly into a blood vessel, organ, tissue, or lesion. Parenteral products are the mainstay of therapy for hospitalized patients in the modern healthcare environment [2]. Subcutaneous, intramuscular, intravenous, intradermal, and intraarterial parenteral routes of administration, among others, also have good qualities for drug absorption and bioavailability [3]. The approach provides many benefits for patients who cannot take the medication orally and need a quick commencement of the action, such as comatose patients [4]. Patients who are in hospitals or who are bedridden are entirely dependent on parenteral nutrition, such as fluids, electrolytes, or nutrients administered by the parenteral route [1]. Non-aqueous organic solvents can aid in the development of stable parenteral medicines when the drug's restricted solubility or chemical instability prevents the use of water to generate injectable solutions. In recent years, the medication development process has essentially produced compounds that aren't water-soluble, which has strengthened their requirement. New injectable nonaqueous solvents must be discovered for medication delivery [5].

2. WHAT ARE PARENTERAL (INJECTABLES) FORMULATIONS

Injectable medications are designed to be injected intravenously, intramuscularly, or subcutaneously into the human body. Fast onset, various parent routes of delivery, repeatable PK/efficacy profiles, excellent bioavailability due to avoiding the oral absorption barrier, and acceptability of administration in a hospital context are all benefits of injectables. Injectable solutions must be sterile, low pyrogen, and meet compendia specifications such as >90% label claim, related substance level below tox qualified level, content uniformity, pH, osmolality, particulate matter, essentially free of visual foreign matter, etc. in order to meet the safety, efficacy, and quality standards of parenteral dosage forms.

Many different types of medicinal substances are used in injections. More than 400 injection-related products are listed in USP. The medicine is delivered through an injection into the skin or mucous membranes in these dosage forms. Due to the chemical activity of enzymes, some medications cannot be taken orally. An isotonic aqueous solution, which has a pH near to that of blood and bodily tissues, is the most practical and basic form of an injectable substance (pH 7.4). These are meant to prevent microorganisms from growing that were unintentionally infused into the solution.

Parenteral refers to a method other than the oral route and is derived from the Greek terms para and enteron, which imply aside the gut. Drugs are supplied by injection through the parenteral route into bodily tissues, frequently directly into the blood, and sometimes under or through one or more layers of skin or mucous membrane. The therapeutic arsenal of today must include parenteral medicines. Compared to other dosage forms, they have a variety of benefits. The drug's effective administration and quick accessibility to the body. The principal defenses of the human body, the skin, and mucous membranes, are used to provide parenteral dosage forms, which set them apart from all other drug administration forms.

Because they are inactivated when taken orally in the gastrointestinal tract, some pharmacological drugs, most notably peptides, proteins, and many chemotherapeutic medicines, can only be administered parenterally. Parenterally given medications must be

administered to patients under rigorous control because they are typically highly potent and somewhat unstable.

The most notable improvements are in injectables, which are delicate to the digestive system. Additionally, it improves bioavailability. For a medication product to be administered in a straightforward and repeatable manner, parenteral delivery methods must be syringe- and injectable-compatible. The maintenance of stability is the following significant issue while preparing an injection.

Parenteral dosage forms face several challenges, including achieving formulation stability, drug substance compatibility with packaging components, and sufficient drug concentration within a reasonable pH range and without using excipient levels that could potentially cause blood incompatibility and tissue irritation problems. These requirements demand a thorough characterization of the medication.

Due to their quick onset, repeatable PK/efficacy profile, high bioavailability as a result of avoiding the oral absorption barrier, and suitability for administration in a hospital context, injectable solutions present an alluring option to oral dose forms. Parenteral dose forms have several obstacles, including achieving formulation stability, solubility, sterility, and a decrease in blood incompatibility and tissue irritation problems. Preformulation studies, prototype formulation development, accelerated stability studies, packaging choice, process development to evaluate key process parameters, scale-up, production of demonstration and GMP batches, and long-term stability studies can all be included in the development of injectable solution formulations.

3. EXCIPIENTS IN INJECTABLES

Substances, other than the active drug substance of finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture; protect; support; enhance stability; bioavailability; andor patient acceptability; assist in product identification.

The selection of vehicles should be:

- Non-irritating & Non-toxic
- Must not exert pharmacological activity/ must not affect the activity of medicinal agents.
- Physically and chemically stable at various pH levels
- Viscosity: must allow ease of injection
- Boiling point must be sufficient enough to permit heat sterilization

Pharmaceuticals have long included naturally occurring nonaqueous solvents like glycerin and fixed oils. This technique has been widespread for many years. The formulator uses nonaqueous solvents to create stable, practical parenteral dosage forms. Once a formulator decides that an aqueous system is not adequate, he or she runs into a number of issues. The chosen solvent must not be sensitizing, irritating, or poisonous. Additionally, it must not have any independent pharmacologic activity and must not impair the efficacy of the medication. There have been cases where a solvent potentiated the medication's activity, requiring a modification in dosage. The solvent's chemical and physical properties must be considered in addition to its pharmacological acceptability. Thus, the ideal solvent should be generally stable under typical pharmaceutical use circumstances and not be influenced by acids or alkalis. The solvent must maintain fluidity throughout a sizable temperature range and have a viscosity that makes injection simple. If the solvent has a high enough boiling point to enable heat sterilization, it is desirable. Miscibility with water and bodily fluids, degree of flammability, availability, source of supply, and consistent purity are further factors. There isn't yet a single solvent like that, of course. As a result, choosing a nonaqueous solvent for a parenteral vehicle requires striking a balance between the various determining parameters [6]. In addition to naturally occurring solvents, the development of modern chemical technology has resulted in the creation of numerous novel synthetic solvents. The toxicity, chemical and physical characteristics, and applications of a few of the more popular nonaqueous solvents, as well as a few specialized and infrequently used solvents, are discussed in this review.

4. PROPYLENE GLYCOL

Despite being commercially available, propylene glycol, which was first described in 1895, has garnered little to no interest in chemistry or medicine, according to Seidenfeld and Hanzlik [7] in 1932. It is one of the most used nonaqueous solvents in use today. With a specific gravity of 1.036, propylene glycol, also known as 1,2-propanediol, is a viscous hygroscopic liquid. It is miscible with water,

acetone, and chloroform but immiscible with fixed oils. It freezes at -59' and boils at 188'. While it is extremely stable under normal circumstances, high temperatures cause it to oxidize into propionaldehyde, lactic acid, pyruvic acid, and acetic acid [8,9]. The intravenous minimum lethal dose was 1.68 grams per kilogram for white rats and 5.25 grams per kilogram for rabbits, according to Seidenfeld and Hanzlik [7]. For rats and rabbits, the intramuscular minimum lethal dose was 14.7 grams per kilogram. Mice have a reduced tolerance for and are more sensitive to the solvent propylene glycol. The LDM for mice administered intraperitoneally was discovered to be 9.7 Gm/Rg [10]. According to reports, the subcutaneous and intravenous LDjo for mice were 18.5 Gm/Kg and 8.0 mg/Kg, respectively. Although propylene glycol's activity is only around one-third that of ethyl alcohol, it has a similar effect on dogs' central nervous systems [11]. According to Brittain and D'Arcy [12], administering propylene glycol in saline solution intravenously to rabbits for up to 50 years had no impact on their red blood cell, packed cell volume, hemoglobin, or total white blood cell counts. However, there was a decrease in lymphocytes and an increase in the number of circulating polymorphs.

Significantly less time was needed for blood to clot. Brass [13] created an intramuscular quinidine formulation of 75.0 ml of propylene glycol and 10.0 g of quinidine hydrochloride. Over the course of six months, this solution exhibited no symptoms of crystallization or discoloration. When quinidine is injected into a male, the effects are immediately noticeable and last for around two hours. A 20% solution of quinidine sulfate in propylene glycol was investigated by Gluck et al. [14] for its effects as a local irritant by intramuscular injection as well as for its action on the auricle in auricular fibrillation and flutter. The findings showed negligible local reactivity and a dosage response comparable to that observed with oral administration, with a peak effect being attained on average in about 3 hours, about half of the impact wearing off in about 8 hours, and the effect totally fading in less than 24 hours. McGavack and Vogel [15] have talked about using propylene glycol as a vehicle for the intravenous administration of desoxycorticosterone acetate at a concentration of 10 mg/ml. Since this substance crystallizes when diluted with water, a method that involves injecting the prepared slowly at a rate of no more than 2.5 ml per minute has been reported. This guarantees its quick dilution and stops any acicular precipitate from forming. In patients with auricular fibrillation, Ganz and colleagues [16] studied the intramuscular administration of digoxin in 40% propylene glycol and 10% ethanol and reported positive outcomes.

5. POLYETHYLENE GLYCOLS

The general formula for the polyethylene glycols (PEGs), as their name suggests, is HOCH2 (CH20CH2)n CH20H, where n denotes the typical number of ethylene oxide groups. The average molecular weight of these polymeric compounds is indicated by a number, which is used to identify them [17]. The liquid forms of polyethylene glycol 200, 300, 400, and 600 are colorless somewhat viscous, and mildly hygroscopic. They do not hydrolyze or degrade and are less volatile than glycerin [18]. They all dissolve in water to provide transparent solutions in all ratios [17]. White waxy solids are polyethylene glycol 1000, 1540, 4000, and 6000. We shall limit our views for the purposes of this discussion to liquid polyethylene glycols, which are more likely to be employed in parenteral formulations. There is, however, a dearth of information on parenteral delivery. In comparison to the other two liquid PEG series members, PEG 300 and 400 are better detailed. PEG 400 administered subcutaneously in doses up to 10 ml in rats—ten times the human dose—did not result in any long-term harm. "Blanching of the skin and scab formation in 48 hours" was the effects described. According to reports, the test results were identical to those for propylene glycol. Animals do not exhibit a foreign body reaction to PEG 300 or 400 [18]. Due to the material's unrestricted diffusion into the surrounding tissue, PEG is quickly removed from the injection site in dogs. 77% of the PEG 400 that was intravenously given into people recovered within the first 12 hours. When five to ten times the recommended human dosage levels of PEG 300 were injected intramuscularly into rats, the dose penetrated a muscle bundle and caused ischemia necrosis of the muscle fibers. A minor chemical irritation was the tissue reaction [19]. The toxicity of vancomycin in 50% PEG 200 and in PEG 200 alone was assessed by Lee and Anderson (G1). According to their findings, PEG 200 did not appear to have any harmful consequences when given to dogs in intramuscular doses of 1.0 ml/Kg every day for 80 days or of 0.5, 1.0, 2.5, and 5.0 ml/Kg as a single intravenous dose. Blood alkaline phosphatase, blood nonprotein nitrogen, and

venous carbon dioxide levels were all within normal ranges. Years ago, nitrofurantoin was sold in a dosage form for intravenous usage that also contained PEG 300. The daily treatment of 240 mg. of nitrofurantoin in PEG 300 to 30 patients resulted in severe metabolic acidosis and nephropathy in seven patients, leading to two fatalities, according to research by McCabe et al. [20,21]. Instead of nitrofurantoin, the PEG was blamed for these negative effects, and that dosage form was taken off the market. It should be noted that drug levels and toxicity reported for medications dissolved in PEGS may differ significantly from those reported for drugs reported in aqueous solutions or suspensions [19]. The stability of sodium pentobarbital in aqueous solutions containing 0 to 60% polyethylene glycol 400 was examined by Bodin and Taub [22]. Their findings suggested that the pH has an impact on the amount of polyethylene glycol 400 needed for ideal stability. Aseptic formulation of a stable product is feasible at a concentration of 30% and a pH of 10. 10% ethanol is added to allow for discoloration-free autoclaving sterilization It is also feasible to create formulations with a pH as low as 8, 60% glycol, and 10% ethanol. Additionally resistant to autoclaving are these solutions.

6. ETHANOL

The digitalis glycosides, in the example, occasionally use ethyl alcohol (ethanol) in parenteral preparations. Alcohol makes up 49% of a commercial digitoxin formulations for intramuscular or intravenous usage. When administered intramuscularly, this causes pain. According to the U.S.P. [22], such a product may contain 5 to 50% alcohol. Digoxin preparations that meet U.S.P. requirements and contain 10% alcohol may be administered intramuscularly or intravenously. There is also a deslanoside product with a 7.4% alcohol content. Subcutaneous injection of alcohol causes severe pain followed by anesthesia Neuritis and nerve deterioration may develop if an injection is administered close to a nerve. In order to alleviate severe pain, anesthesia is purposefully induced by injection into or close to nerves. The dosage of 95% alcohol used as an intravenous anesthetic is 2-4 ml/Kg. [23]. The LD50 in mice was reported to be 1973 mg/kg intravenously and 8285 mg/kg subcutaneously by Latven and Molitor [24]. 50% alcohol is present in a commercial intravenous hydrocortisone medication. Mephensin injection B.P. (1958) has a formula of 10 grams of mephenesin and 25 milliliters of alcohol (95% alcohol). pyrogen-free water and 15 ml of propylene glycol are combined to yield 100 ml.

7. ETHYL OLEATE

Ethyl oleate is accepted as an alternate vehicle in injections of deoxycortone acetate, estradiol monobenzoate, progesterone, and testosterone propionate by the British Pharmacopoeia [25]. It is a yellowish oily liquid that is miscible with alcohol, ether, and fixed oils but insoluble in water. Its characteristics are comparable to fixed oils', but it is less viscous, a better solvent, and is absorbed by tissues more quickly [26]. Ethyl oleate, unlike untreated sesame oil, stays clear at 5 OC, but it has the drawback of discoloring after standing. When ethyl oleate is utilized as a parenteral hormone vehicle in place of sesame oil, there are signs of increased hormone activity. Studies by Dekanski and Chapman [27] showed that testosterone phenylpropionate and testosterone propionate in ethyl oleate had better intensity and duration of action than the same androgens in sesame oil.

8. ISOPROPYL MYRISTATE

Platcow and Voss [28] reported using isopropyl myristate as a parenteral injectable vehicle. It has a specific gravity of 0.852 [29], is oil miscible, water-immiscible, chemically stable, and resistant to rancidity. Isopropyl myristate dominates, with only a trace amount of other saturated fatty acid isopropyl esters. Although studies on acute toxicity show a very low order of toxicity, attempts to establish an LDso in mice were unsuccessful because the test animals did not react to dosages of 100 ml/Kg. Following topical and parenteral injections, isopropyl myristate displays very little irritation and no sensitizing characteristics in rabbits and guinea pigs. It compared favorably with sesame oil as a repository vehicle for estrogens in studies on ovariectomized rats [28]. Donovan, et al. [30] examined the external pharmaceutical usage and found it to be an effective intermediate solvent for incorporating phenol, cocaine, resorcinol, and salicylic acid into liquid petrolatum.

9. BENZYL BENZOATE

A colorless, oily liquid with a nice aromatic smell is benzyl benzoate [31]. It has a specific gravity of 1.118, boils at 3230°C, and is not miscible with alcohol, chloroform, ether, or fixed oils. However, it is miscible with these substances. In

commercial preparations of hydroxyprogesterone benzoate, where it is present in concentrations of 30% for the 125mg product in sesame oil and 46% for the 250mg product in castor oil, benzyl benzoate has found some usage as a cosolvent in oleaginous injectables such as dimercaprol injection. It takes 5.0 grams of dimercaprol, 9.6 milliliters of benzyl benzoate, and 100 milliliters of peanut oil to make one milliliter of dimercaprol B.P. (1958).

10. DIOXOLANES

For pharmacists, dioxolanes represent a brand-new and intriguing class of synthetic solvents. These compounds are the byproducts of the reaction between glycerin and ketones when a dehydrating agent is present [32]. 2,2-dimethyl-1,3-dioxolane-4-methanol is the least hazardous substance in the group [33]. It has been claimed that this substance, also known as Solketal, isopropylidene glycerol, and glycerol dimethyl ketal [34], is a benign, nonirritating solvent that is miscible with water, alcohol, esters, aliphatic and aromatic hydrocarbons, as well as almost all other organic solvents. It is a water-white, odorless liquid with a medium viscosity that is unaffected by alkalies and stable during storage. Its specific gravity is 1.064 and its boiling point is 82 to 830C. However, it is hydrolyzed to acetone and glycerin by strong aqueous acid solutions [34]. According to Berger [33], dioxolanes (as a class) cause temporary paralysis and muscle relaxation. Instead of a peripheral, curare-like impact, these effects were brought on by a depressant's action on the central nervous system. After intraperitoneal administration to mice, the mean lethal dose (LD50) and the mean paralyzing dose (ED50) for 2,2-dimethyl-l,3-dioxolane-4-methanol was reported to be greater than 2.112 Gm/Kg (16.0 mM/Kg).

11. GLYCEROL FORMAL

A condensation product of glycerol and formaldehyde, glycerol formal is made up of 75% of 3-hydroxymethyl-l,3-dioxolane and 25% of 3-hydroxymethyl-l,3-dioxolane. It is a low viscous liquid that is chemically stable, colorless, odorless, and miscible with water in all ratios. The maximal symptomless dose was 1500 mg/Kg, according to Sanderson [35], and the LD100 for intraperitoneal injection in rats was 3000 mg/Kg. Glycerol formal has been proposed as a benign solvent for toxicity testing. The use of it as an industrial solvent has not been associated with any toxic effects.

12. GLYCOFUROL

A tetrahydro furfuryl alcohol polyethylene glycol ether with an average of two ethylene glycol units per molecule is known by the trade name "glycofurol" and is marketed by Hoffmann-LaRoche. It is a white liquid that is soluble in methanol, ethanol, n-propanol, and glycerin as well as miscible with water in all quantities. Its specific gravity is 1.078 and its boiling point ranges from 80 to 1550C. The pharmacology of this substance was thoroughly investigated by Spiegelberg and colleagues [36], who also reported on its use as a parented solvent. It is unpleasant when provided undiluted, but when diluted with water, it becomes harmless and unirritating. The mouse's intravenous LD50 is 3.38 grams (3.5 milliliters)/kg, and it is tolerated similarly to propylene glycol. Acetylcholine chloride is said to be unstable in propylene glycol solutions but stable in glycofurol solutions.

13. DIMETHYL ACETAMIDE

A fascinating solvent that merits some explanation is dimethylacetamide (DMA), also known as acetic acid diethylamide and acetyldimethylamine. It is a transparent, neutral liquid with a molecular weight of 87.12, a specific gravity of 0.943, and a boiling point of 165.50C. This solvent is miscible with water and alcohol in all quantities and is particularly soluble in mineral oil and organic solvents [37]. In order to study the long-term toxicity of DMA, Horn [38] exposed rats and dogs to an environment containing DMA at concentrations of 40.0, 64.4, 102, and 195 p.p.m. and applied DMA topically to dogs at dosage levels ranging from 0.1 to 4.0 mg/Kg. Unless there was clear harm, all experiments were conducted for 6 months. All concentrations more than 0.1 ml/kg dermally and 40 p.p.m. via inhalation resulted in liver damage. The use of a 50% DMA solution as a delivery system for a preconstituted oxytetracycline [39] solution and as a solvent in both soft and hard gelatin capsules [40] is mentioned in the patent literature. It has also been reported to be used as an anti-inflammatory in topical preparations [41]. When DMA was utilized as a medication solvent and supplied to 15 patients with advanced malignancies, doses exceeding 400 mg/Kg of body weight per day for 3 days or more created hallucinations [42]. The usual parenteral amount for DMA is 30 mg/Kg per day, nevertheless. Therefore, this hallucinogenic effect would not be anticipated in usual use.

14. ETHYL LACTATE

The chemical compound ethyl lactate, also known as ethyl a-hydroxypropionate, or CH3CH(OH) COOCH2CH3, is an odorless liquid with a specific gravity of 1.042 that is miscible with water. Some breakdown occurs in aqueous solutions [43]. The acute toxicity of ethyl lactate in mice was assessed by Latven and Molitor [44] using a subcutaneous and intravenous injection. When applied to rabbit eyes and administered intradermally to guinea pigs, ethanol proved irritant. An esterone injection in castor oil is solubilized to a concentration of 3.5 to 6.5 mg/ml by ethyl lactate (10–100%) [45]. At room temperature, this product is stable. There have been no harmful side effects associated with its use as an industrial solvent.

15. ETHYL CARBONATE

The solvents ethyl carbonate, diethyl carbonate, and CH3 CH2-OCOOCH2CH2 have also been employed to dissolve erythromycin, although little is known about their use or toxicity. It has a specific gravity of 0.975 and a boiling point of 1260C, and it is a liquid that is immiscible with water but miscible with alcohol and ether [46]. With no known toxic effects, this substance has also been applied as an industrial solvent [47].

16. 1, 3-BUTYLENE GLYCOL

A white, viscous liquid with a specific gravity of 1.005 and a boiling point of 2040C, 1,3-butylene glycol, also known as 1,3-butanediol, is soluble in both water and alcohol [48]. By selecting the right solubilizing agent, it is possible to change the way that medications work. We can alter a drug's effect in this way to make it stronger or weaker. Pentamethylenetetrazol's hazardous reactions can be stopped by 1,3-butylene glycol, according to Bornmann et al. [49] .'s research. Additionally, it was demonstrated that, as compared to aqueous solutions, the effects of morphine hydrochloride, meperidine hydrochloride, and methadone hydrochloride in 1,3-butylene glycol were stronger and lasted longer. As a result, by using this solvent, the dose may be reduced and unwanted side effects may be eliminated. Propylene and 1,3-butylene glycol were used as meprobamate solvents, according to Bornmann and Loeser [50]. Although both products were effective as drug solvents, it was discovered that the 1,3-butylene glycol preparation was slightly more toxic than the propylene glycol product.

17. N-(β-HYDROXYETHYL)-LACTAMIDE

Lactic acid carboxamide, also known as N-(hydroxyethyl)-lactamide, is a transparent, colorless, viscous liquid that is water miscible. The pure compound has a specific gravity of 1.192. The chemical that results from the reaction of methyl acetate and 2-aminoethanol is employed as a 50% solution. For a 50% w/v N-(hydroxyethy1)-lactamide solution, the acute subcutaneous, LDso, toxicity is 15.8 Gm lactamide/Kg in mice and 16.1 Gm lactamide/-Kg in rats. A preconstituted oxytetracycline solution has been dissolved in this substance and utilized in Europe as a solvent. This product, according to Neumann [51], was stable for several years and demonstrated improved tissue tolerability. The use of N-(hydroxyethy1)-lactamide as a solvent for oxytetracycline has also been reported by Dimmling [52]. After a single 250 mg dose, a measurable blood level was discovered after 24 hours in ten healthy individuals. The levels increased cumulatively following the second injection of 250 mg, given 24 hours later. Additional research on serum concentrations supports the earlier findings. The findings of Seeliger's [53] study using intramuscular oxytetracycline in N-(O-hydroxyethyl)-lactamide solution in patients have supported the earlier results obtained in healthy individuals. Over 24 hours' worth of effective serum concentration was provided by a single 250 mg injection. There were noticeable cumulative effects after multiple doses on consecutive days. Blood level findings and the clinical outcome agreed. 93.7% of the 380 injections that were performed showed virtually no pain in the survey of local tolerability; 6.3% of the injections showed mild and tolerable local reactions, which in no case persisted for longer than 2 or 3 hours. Hupe [54] reported that 250 mg of oxytetracycline intramuscular in this solvent, given once daily, was effective and well tolerated in 90 major surgical cases.

18. FIXED OILS

Drugs are manufactured in oily vehicles for a variety of reasons, including their insolubility in aqueous media, the irritancy of their aqueous formulations, their degradation and instability in aqueous media, or to provide sustained therapeutic effects after injection. The use of fixed oils as parenteral carriers is acknowledged by the USP [22]. Most fixed oils are combinations of unsaturated fatty acid esters that are liquid at 20°C. The oleic acid esters of glycerin are often what give the fluidity. Sesame oil, peanut oil,

cottonseed oil, and corn oil are the most widely used fixed oils [55]. Sometimes, castor oil and olive oil have been used. Vegetable oils are not very poisonous, although some people react allergically to certain vegetable oils. Therefore, the label must identify the exact oil present in the product when such oils are employed in vehicles. Fixed oils are known to occasionally result in nerve damage and other unfavorable local tissue reactions such as cysts and foreign-body granulomas. Due to the low solubility of the majority of medications in these solvents, the use of fixed oils is restricted. Drugs that have been dissolved may demonstrate a sustained-release action with a potential reduction in absorption since these oils are not miscible with water. Fixed oils cannot be used in unemulsified intravenous preparations due to aqueous insolubility. According to Lehr and coworkers [56], cottonseed oil has been utilized in intravenous fat emulsions given to surgical patients, and a commercial product is available. Dimercaprol, calciferol, and menadione, which are steroid hormones, are the principal medications found in oils. Fixed oils undergo oxidative alterations since they include unsaturated fatty acids, which may call for the usage of oil-soluble anti-oxidants such as propyl gallate, butylated hydroxyanisole, butylated hydroxytoluene, and tocopherols. Officially employing fixed oils as solvents in U.S.P. [22] and N.F. [57] parenteral solutions Desoxycorticosterone acetate, for example, U.S.P. Dimercaprol U.S.P. Benzoate of estradiol Estradiol cyclopentylpropionate U.S.P. N.F. Dipropionate of estradiol U.S.P. Estrone U.S.P. Progesterone U.S.P. Acetate of tcstosterone U.S.P. Dipropionate of diethylstilbestrol N.F. N.F. Menadione Winterized or treated oil should be used instead of regular sesame oil because regular sesame oil turns turbid when cooled to 50C.

19. DRUG ABSORPTION FROM OIL SOLUTIONS

Before a drug supplied in a non-aqueous formulation becomes accessible, it must be liberated from the formulation, absorbed into the bloodstream, and transported to the target site(s). Before diffusing into the nearby blood capillaries, a medication that has been dissolved in oil solutions divides from the oil medium into the aqueous interstitial fluid. The apparent partition coefficient, a defining equilibrium constant, can be thought of as the dynamic equilibrium between the drug in the oil phase and that in the aqueous phase during drug partitioning into the local interstitial fluid. The rate-limiting step regulating the drug release from oil solutions is thought to be the drug partitioning from the oil phase to the aqueous medium. It follows that by adjusting the elements affecting the partition coefficient, such as the type of oil or the lipophilicity of the active by the use of prodrugs, the absorption rate and, consequently, the depot properties can be altered. After IM and SC administration, Hirano et al. [58,59] reported that drug absorption from an oil solution follows first-order kinetics, such that

$$dC/dt = -kQC \quad (1)$$

Where C is the drug concentration in the oil and ka is the first-order absorption rate constant. The similar process applies to the absorption of medications that are poorly water-soluble from oil suspensions, with the exception that, in theory, the drug particles dissolve in the oil medium before the dissolved molecule partitions into the local interstitial fluid. As a medication reservoir, the suspended particles continuously dissolve to replace what is lost. The rate-limiting step in this instance is the dissolution of the drug particles in the oil phase, and the mean dissolution rate is determined by the Noyes-Whitney equation,

$$\text{Dissolution rate} = DA(Cs - C)/8 \quad (2)$$

Where Cs is the drug's saturation solubility in the medium, C is the concentration of dissolved drug in the medium, and 8 is the thickness of the hydrodynamic diffusion layer around the drug solids. D is the diffusion coefficient of the dissolved drug molecules in the medium. Thus, drug, particle, and oil medium parameters can be changed to affect the rate at which pharmaceuticals are absorbed from oil suspensions. In comparison to oily solutions, oily suspensions may offer a slower rate of drug absorption, and absorption is thought to have a zero-order profile [60]. However, when the drug particles suspended in the oil phase have a relatively high aqueous solubility, the drug can be released from the nonaqueous depot by directly attaching the drug crystals to the aqueous phase and allowing them to dissolve there without first dissolving in the oil phase [61–63]. A percolation effect will be noticeable at relatively high water-soluble medication concentrations. If surfactants are used to stabilise the suspension, this effect might be increased because the oil phase may form inverse micelles, which will facilitate the movement of water through the oil phase.

20. CONCLUSIONS

The pharmaceutical formulator currently has utilized a wide variety of organic solvents. The three most widely utilised nonaqueous solvents are polyethylene glycols, fixed oils, and propylene glycol. The remaining solvents are only occasionally used and are of modest significance. Parenteral products that use nonaqueous solvents have more freedom to create novel dose formulations. But only if a clear need is identified should such solvents be employed. Recognizing that any formulation employing a nonaqueous solvent may be a novel substance that requires adequate testing for pharmaceutical application, there is a need for novel, likely synthetic non-aqueous media, and particularly non-toxic solvents for medications that are easily formed as solutions.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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