Table 6-1 Most Commonly-Used Water-Miscible Co-Solvents in Injectable Products (Percent Range Approved by FDA[a])

Co-solvent	Per cent range	Product examples (all are trademarks or registered)
Ethanol (alcohol, dehydrated alcohol, ethyl alcohol)	0.6–80	Prograf, BiCNU, Nitro-Bid, Alkeran for Injection, Septra, Valium, VePesid, Triostat, Lanoxin, D.H.E 45, Nembutal Sodium, Dilantin, Toradol, Vumon, Taxol, Sandimmune
Propylene glycol	0.1–75	Terramycin, Loxitane, Septra, Lanoxin, Nembutal, Dalgan, Dilantin, Valium, Nitro-Bid, Alkeran,
Polyethylene glycol 300 or 400	0.15–100	VePesid, Robaxin, Bioclate, Ativan
Glycerin	0.04–70	Multitest CMI, D.H.E. 45, Sus-Phrine
Polyethylene glycol 3350	0.3–3.0	Depo-Medrol
Cremophor® EL	50–65	Taxol, Vumon, Sandimmune
Dimethylsulfoxide	<0.06	Eminase
Dimethylacetamide	2.0–6.0	Vumon
Sorbitol	0.2–50	Cardene, Aristospan, several vaccine products

[a]Must know the dose of injection to determine actual amount (mg/mL or %) of co-solvent injected per dose of active in product.

Water-Miscible Co-Solvents

A number of solvents that are miscible with water have been used as a portion of the vehicle in the formulation of parenterals. These solvents are used primarily to solubilize certain drugs in an aqueous vehicle and to reduce hydrolysis. The most important solvents in this group are ethyl alcohol, liquid polyethylene glycol, and propylene glycol. Ethyl alcohol is used particularly in the preparation of solutions of cardiac glycosides and the glycols in solutions of barbiturates, certain alkaloids, and certain antibiotics. Such preparations usually are given intramuscularly. There are limitations with the amount of these co-solvents that can be administered because of cellular toxicity concerns, greater potential for hemolysis, and potential for drug precipitation at the site of injection (9). Formulation scientists needing to use one or more of these solvents must consult the literature and toxicologists to ascertain the maximum amount of co-solvents allowed for their particular product (10). Several references provide information on concentrations of co-solvents used in approved commercial parenteral products. An alphabetical listing of acceptable co-solvents, based on their presence in one or more FDA-approved commercial products, is given in Table 6-1 along with some commercial examples.

Nonaqueous Vehicles

Oily vehicles cannot be administered by the intravenous route. The most important group of nonaqueous vehicles is the fixed oils. The USP provides specifications for such vehicles, indicating that the fixed oils must be of vegetable origin so that they will be metabolized, will be liquid at room temperature, and will not become rancid readily. The USP also specifies limits for the free fatty acid content, iodine value, and saponification value (oil heated with alkali to produce soap, i.e., alcohol plus acid salt). The oils most commonly used are corn oil, cottonseed oil, peanut oil, and sesame oil. Fixed oils are used particularly as vehicles for certain hormones (e.g., progesterone, testosterone, deoxycorticicosterone) and vitamin (e.g., Vitamin K, Vitamin E) preparations. The label must state the name of the vehicle so that the user may beware in case of known sensitivity or other reactions to it.

ADDED SUBSTANCES

The USP includes in this category all substances added to a preparation to improve or safeguard its quality. An added substance may

- Increase and maintain drug solubility. Examples include complexing agents and surface-active agents. The most commonly used complexing agents are the cyclodextrins, including Captisol®. The most commonly used surface-active agents are polyoxyethylene sorbitan monolaurate (Tween 20) and polyoxyethylene sorbitans monooleate (Tween 80).