

Parenteral formulations

Injectable formulations of lipophilic water-insoluble drugs frequently consist of mixtures of water, organic cosolvents and surfactants. Limitations in using organic solvents in injectable formulations include possible drug precipitation, pain, inflammation and hemolysis upon injection. Sometimes it is possible to alleviate these side effects by designing a water-soluble prodrug of the lipophilic water-insoluble drug. However, a prodrug will change the pharmacokinetics of the parent drug. For example, due to the gradual metabolism of the prodrug to form the active drug the onset time of the drug (i.e. the time required for the drug to reach minimum effective plasma concentration) will be delayed. Organic solvents and surfactants can be replaced by isotonic aqueous cyclodextrin solutions (Table I). Numerous studies have shown that unlike prodrugs these aqueous cyclodextrin vehicles containing the active drug will in general not alter the intrinsic pharmacokinetics of a drug. Upon parenteral administration, especially after intravenous injection, the drug is both rapidly and quantitatively released from the cyclodextrin complex upon dilution, competitive replacement, and binding of drug molecules to plasma proteins and tissue. However, since cyclodextrins are rapidly eliminated in the urine cyclodextrins can increase renal clearance of lipophilic water-insoluble drugs. Finally, since the hydrophilic cyclodextrin derivatives, such as 2-hydroxypropyl- β -cyclodextrin and sulfobutylether β -cyclodextrin, are relatively non-toxic compared to organic solvents and surfactant formulations, and since they have minimal effect on the intrinsic pharmacokinetics of drugs, cyclodextrin containing formulations are increasingly being used during in vitro and in vivo screening of new pharmacologically active compounds.

Table I. Current marketed drug formulations (Handbook of Injectable Drugs) compared to cyclodextrin formulations.

	Commercial product	Cyclodextrin formulation
Diazepam iv solution (Roche)		
Diazepam	5 mg/ml	5 mg/ml
Propylene glycol	40%	
Ethyl alcohol	10%	
Sodium benzoate/benzoic acid	5%	
Benzyl alcohol	1.5%	
Water for injection	~43%	~93%
2-Hydroxypropyl- β -cyclodextrin		6%
Sodium chloride		0.6%
Phenytoin iv solution (Parke-Davis)		
Phenytoin sodium	50 mg/ml	50 mg/ml
Propylene glycol	40%	
Alcohol	10%	
Sodium hydroxide	adjust pH to 12	adjust pH to 11
Water for injection	~43%	~75%
2-Hydroxypropyl- β -cyclodextrin		20%