and instability of carrier composite may drastically affect over all disposition kinetics of drug in an unpredictable manner.

The parenteral drug delivery systems (PDDS) need to meet the basic requirements of parenteral products, i.e. sterility, apyrogenicity, reproducibility in performance, safety and efficacy. Methods of sterilization used are often the same, i.e. dry heat, moist heat, radiation and chemical means. However, every component of drug delivery device is ought to be sincerely scrutinized for effect of sterilization process on stability of the component and resultant effect on the formulation. It should also be considered, whether substitution of component would alleviate the problem or not. Similarly, a new possible option should be rigorously screened for its implications on the finished product. It appears that most of the colloidal dispersions are highly susceptible to heat and suffer peptization or aggregation. Therefore, ionization radiation in proper dose, which ensures absolute killing of microbial bioburden and also consoles and accounts for susceptibility of biotechnological drugs, should be used. The irradiation sterilization, however provides opportunity for graded approach, which could titre the precise dose of radiation optimum for complete killing of microorganisms. Furthermore, added to the existing problems, is the issue of bacterial 'death', which is defined as ceasing to exist. However, survival mechanisms devised by bacteria and viruses are now known, which raise an alarm in regard to their recovery of functionality. Nevertheless, complete removal of bioburden via aseptic filtration may offer working solution to the problem. Most of bacteria are of size larger than 1 μm but spherical forms are yet smaller in size. Therefore, the size range selected for removal should be at least three orders of magnitude, i.e. from 50 nm to 50 μm. Thus light sterilization or aseptic processing are seemingly suitable options. The products meant for parenteral administration should claim full sterility assurance level.

Different release mechanisms and biofate of parenterally administered systems are schematically shown in Figure 1-2. On intravenous administration the drug delivery systems traverse and span vascular compartment through pulmonary, systemic and tissue circulation. Oxygenated blood is pumped by left side of the heart through the aorta to body tissues. The deoxygenated blood from tissues is collected through veins and post vena cava in to the right part of the heart. It is then pumped through pulmonary vein to lungs for oxygenation. The circulation thus indicated the possible course of colloidal carrier(s) if they are not allowed to extravasate. The particles, which are sufficiently small to pass the pulmonary capillaries return to heart and circulated to tissues. Particles larger in size which escape pulmonary filter, are mechanically deposited in the capillaries or captured mainly by macrophages. The inflamed centres with excessive infiltrated macrophages thus become sites selectively traceable. Discontinuous basement membrane gives rise to small pores into endothelium. These are referred to as fenestrae with diameter from 30 nm to 100 nm. The particles smaller then 100 nm size escape circulation and taken up by hepatocytes. The capillaries of these organs are lined with active macrophages called Kupffer cells thus majority of particles escaping circulation for sequestration and retention by liver accumulate in Kupffer cells. The actively capturing system of liver is termed as reticuloendothelial system. Therefore, it is appreciated that to reach extravascular compartment the carrier must avoid opsonization and should be small enough in size. Furthermore, to be actively targetable it should be customized for site specificity using appropriate ligands. The release of drug may follow various patterns. The bystander explosive release is well exemplified by target sensitive immunoliposomes. The system typically based on conventional lipid with a derivatized lipid component; i.e. phosphatidylethylamine lined site specific immunoglobulin (PE-IgG). This conjugate participates in film structuring. On reaching the target under preferential affinity for target the PE-IgG mesogens laterally a partition leaving the vesicle leaky thus dumping the contents in the vicinity of target.

Cytosolic sustained drug release is based on strategy where a carrier construct enters a cellular target via receptor mediated endocytosis and categorically changes the pH of endosome. Due to change in pH the carrier loaded endosome does not fuse with lysosome thus remains as a cargo and

polymeric coat offers steric hindrance to opsonin or may promote adsorption of deopsonin to avoid macrophagic sequestration. Stealth nanoparticles may also be prepared by coating them with soluble polyoxyethylene (Leroux et al., 1996) or by using dialkyl polyoxyethylenes and phospholipids (Hodoshima et al., 1997). The hydrophobic portions of these amphiphilic molecules, in the latter case, comprise the core of matrix. Stealth nanoparticles increase the tumour accumulation and tumouricidal activity of anticancer drugs in mice. The accumulation of non-stealth doxorubicin nanoparticles within the Kupffer cells of the liver may be used to target hepatic neoplasm indirectly. The differential uptake of nanoparticles, i.e. by liver Kupffer cells but not by neoplasm cells could be exploited for bystander supplementation of drug(s) for the treatment of liver cancer.

In certain biomedical applications it is desirable and imperative that following i.v. administration, the colloidal particles should evade rapid recognition and uptake by the RES and subsequently achieve prolonged systemic circulation. These applications include a prolonged systemic drug delivery, use as an imaging agent or for site-specific localization of nanoparticles to organs other than the liver and spleen. This objective can be achieved by preparing nanoparticles from derivatized polymers or by surfacial modification of the preformed nanoparticles. Nanoparticles can be prepared with derivatized polymers, which orient their hydrophilic segment towards the aqueous bulk while hydrophobic segment(s) are shielded. Thus, the resultant surface has a hydrophilic characteristics and in effect evades recognition by RES (Gref et al., 1995). The alternative approach is surfacial modification of the preformed nanoparticles with different block co-polymers (Polaxamers™/ Pluronics™) or polyethylene glycols, which produce several fold higher systemic circulation time compared to unmodified nanoparticles (Torchilin and Trubetskoy, 1995).

Nanoparticles in Chemotherapy

The most promising application of nanoparticles is their use as carriers for antitumour agents (Couvreur et al., 1990; Kreuter, 1991). The tumours have enhanced endocytic activity and leaky vasculature, and this promotes accumulation of intravenously administered nanoparticles. The drug targeting to tumour tissues can be further facilitated and optimized by the "stealth" behaviour imparted by polyoxyethylene, which further effectively promotes extravasation. Stealth character can be imparted by coating plain nanoparticles with soluble polyoxyethylene, or by using dialykyl polyoxyethylene and phospholipids. PEGylated polystyrene nanoparticle and PEO grafted nanoparticle are shown in Figure 1-7 and 1-8, respectively.

Avoidance of Multidrug Resistance

The chemotherapeutic agents have limited success primarily due to the occurrence of multi-drug resistance (Endicott and Ling, 1989). It is often associated with the over-expression of a cell membrane glycoprotein of 170 kDa molecular weight (Kartner et al., 1985). The glycoprotein acts as an efflux pump and rejects positively charged amphipathic drugs from the cells as shown for bacterial transport proteins. Nanoparticles loaded drugs displayed better results in a number of chemotherapy refractory cancers both in animal and clinical models (Kubiak et al., 1989; Cuvier et al., 1992). As the particulate systems are localized in the lysosomes, it protects the loaded drug from the action of the P-glycoprotein, and also avoids immediate contact with P-glycoprotein transporter located at the plasma membrane.

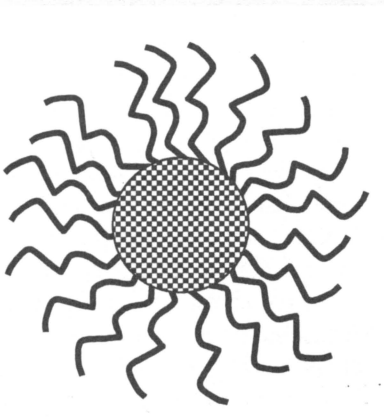
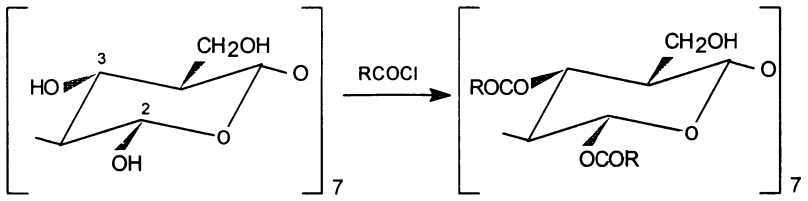


Fig. 1-7. PEGylated Polystyrene Nanoparticles



R	Compound
C_5H_{11}	β-CD-C_6
$C_{11}H_{23}$	β-CD-C_{12}
$C_{13}H_{27}$	β-CD-C_{14}

Fig. 1-15. Diacylation Reaction of β-cyclodextrin

of the drugs, which following parenteral administration undergo suitable changes (metabolize) yielding active principles at the site or body compartment exempting other body parts from unnecessary exposure to drugs. These systems could be designed specifically for body organs exploiting biochemistry and physiology of that organ. The organs, which could be targeted or delivered with active drugs, contain the enzyme responsible for metabolism of prodrug. The distribution of these enzymes is interestingly definite and specific. The various organs which have been delivered with the drug using this concept include, eye, kidney, liver, lungs, brain, lymphatics, etc. Further extensions of this technology include retrometabolic drug delivery or soft drugs. This is principally based on a lead compound which via inactive metabolite formation eventually generate an active drug thus it involves metabolism and activation processes. These systems are so designed that prodrug and generated metabolites both are soft to the biological system being isoelectronic or isosteric with drug metabolic analogues, they possess better pharmacodynamic activity and site specificity. Various systems based on this principle are discussed in chapter on chemical drug delivery.

Antibody Directed Enzyme Prodrug Therapy (ADEPT)

Several innovative strategies have been developed for the cell specific delivery of cytotoxic and antiviral agents and one such promising approach is the prodrug activation by antibody-enzyme conjugates. These antibody-coupled enzymes can be specifically targeted to the cells that express antigenic determinant (Senter et al. 1990). However, one of the major problems encountered with immuno-conjugates is the internalization of antibody. This problem can be duly addressed by ADEPT (antibody directed enzyme prodrug therapy). The generation of active derivatives in the proximity of the target cells leads to higher cellular and lower systemic concentration of the active drug. A Mab-β-glucuronidase conjugate as an activator of the prodrug epirubicin for the specific treatment of tumour has been reported (Hasima et al., 1992).

Another remarkable strategy for selective and specific chemotherapeutics is enzymosomes. Enzymosomes are basically liposomal constructs engineered to present a mini bioenvironment. In this strategy the enzymes are covalently immobilized or coupled to the surface of liposomes. Thus, following simultaneous administration of non-toxic prodrug and the immobilized enzyme, the former is transformed to a potent antitumour agent in the close proximity of tumour cell lines. The specificity of enzyme reaction limits the prodrug activation at the tumour site, through prior enzyme targeting by using liposomes, or via enzyme expressing gene delivery into the tumour cells (VDEPT). Figure 1-16 schematically presents the concept of targeted delivery of antitumour prodrug activating enzymes

(Chandrashekar and Udupa, 1996). Implants intended for parenteral administration are prepared from a variety of polymeric materials including polysaccharides (Chen et al., 1995), polylactic acid co-glycolic acid (Kunou et al., 1995), and the non-biodegradable methacrylates (Moo-Young et al., 1998). Various principles or mechanisms such as diffusion, dissolution, vapour pressure (Fig. 1-22), osmosis (Fig. 1-23), ion-exchange, etc. have been exploited for implantable systems. Biodegradable materials, such as polylactic acid co-glycolic acid, are preferred as this excludes the need for surgical removal of the implant after treatment ends. However, non-biodegradable materials do provide therapeutic levels of drug for up to one year *in vivo*. Solid implants typically exhibit biphasic release kinetics, with an initial burst of drug followed by a slower release. The initial burst is usually due to the release of drug deposited on the surface of the implant although zero order release kinetics may be achieved by, for example, coating the implant with a drug impermeable material. Overall drug release may be controlled by varying polymer composition. An increase in the level of lactic acid in a polylactic acid co-glycolic acid copolymer retards drug release and an increase in the polymer molecular weight also retards drug release and prolongs drug effects *in vivo* (Meyer et al., 1995).

Drug release could be biophysically modulated using stimuli, to which a system responds, such as electrical stimuli in polyelectrolyte systems. The conventional pulsatile delivery systems such as the electrically triggered release of insulin from polydimethylaminopropylacrylamide gels (Kagatani et al., 1997). Solid implants avoid the peak levels

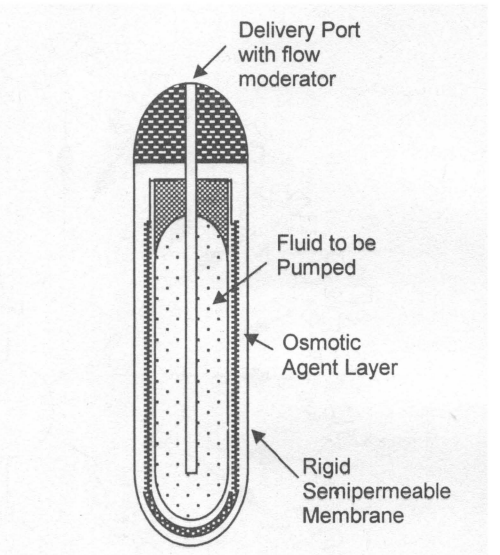


Fig. 1-23. Alzet® Implantable Osmotic Pump

associated with the administration of the drug in solution (Mestiri et al., 1995), thus limiting the toxic effects associated with the free drug. Implants are used for the delivery of anticancer agents as they are able to confine potentially toxic anticancer drugs to tumour sites and also allow sustained drug release. A viscous gelatin solution or galactoxyloglucan gel of mitomycin C administered intraperitoneally prolongs peritoneal and plasma clearance (Suisha et al., 1998). Tumoricidal activity of mitomycin C against a peritoneal ascites model was thus increased with use of the gelatin formulation in mice due to the presence of a depot of the gel in the peritoneum. Additionally, the intraperitoneal use of a 5-fluorouracil poly(ortho ester) implant improves the tumoricidal activity of

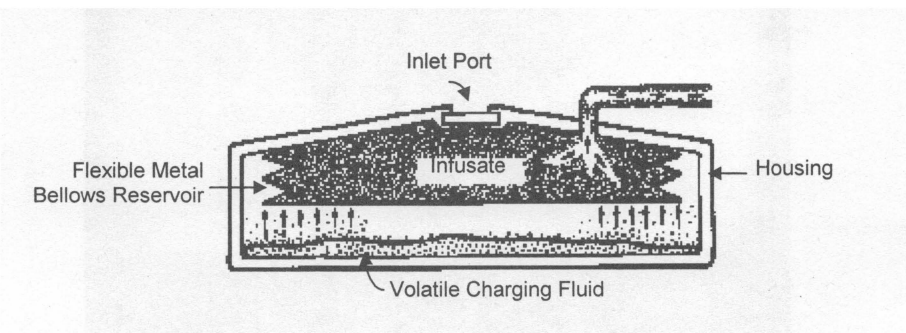


Fig. 1-22. Schematic Representation of a Vapour-Pressure Driven Pump (Rohde et al., 1988)