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*Review Article*

# Recent advancement in drug delivery system

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**Abstract**

Ease of drug administration, safety, affordability and efficacy are the major concerns in pharmacotherapy leading to exploration of better drug delivery systems. Liposomes are lyotropic liquid crystals composed mainly of ampiphilic bilayers and these are more frequently used as drug carriers. Liposomes help reduce the toxicity and deliver the drug to the target tissue. So far, liposomes have been the most intensively studied lipid-based delivery system. In liposomes, a hydrophilic drug can be trapped in aqueous interior or channels between successive phospholipids bilayers whereas a hydrophobic drug can reside with the bilayer itself. The non-toxic and nonimmunogenic bilayers dissipate allowing the diffusion of the drug into the tissues. Attachment of polyethyl glycol to the surface of liposome (known as stealth liposome) aids in the better targeting of the drug to the tissues. Pegylated proteins and polymers of lactic and glycolic acids have been well studied as drug carriers and found to be resistant to phagocytosis and complement activation. Newer DNA based strategies including DNA vaccination and antisense oligonucleotides and immunomodulation show good results for new therapeutic systems. Though the DNA based therapeutic systems have high selectivity and specificity with few adverse effects, these systems are so far restricted to animal models and clinical trials.

**Key words:** stealth liposome, microspheres, pegylated protein, polymers, antibody, DNA

Medicine is ever-changing science. Pharmacology is one of the most rapidly expanding and transforming medical disciplines. Prescribing drugs has not only to be rational but also evidence based, safe, easy and economical. Ease of drug administration and affordability are the two most important factors for the better patient compliance with the drug treatment. To achieve this goal new technologies and recent advances are on the way. New drug delivery system has been developed and is being modified to achieve the therapeutic goal in the effective way. Different carriers used in new drug delivery systems are liposomes, microspheres (intramuscular) and nanoparticles (intravenous), pegylated proteins, polymeric gels, implants and anti-IgE monoclonal antibody.

Basically, these are carrier systems in the colloidal range (1 nm - 0.5 mm), which allow improved targeting to tissues and decreased immune detection. Drugs are either loaded into or attached to the carrier system. Colloidal size still attracts macrophages of the reticuloendothelial system as they are passed through liver and spleen. This defeats the purpose of selective targeting as drug builds up at these sites. New polymer coatings have increased ability to avoid detection.

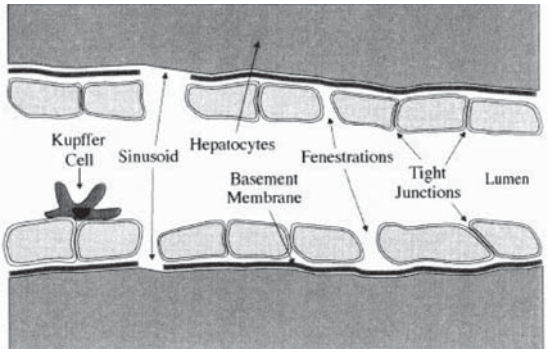


**Fig 1:** Kupffer cell in the capillary lining which attacks drug preparation and release the contents in the liver.

## 1. Liposomes

These are phospholipid bilayers with an aqueous interior that can carry drug in the bilayer or aqueous interior. They might be either anionic or cationic depending upon the surface charge and they might be unilamellar or multilamellar depending upon the number of layers present[1]. Attachment of polyethyl glycol (PEG) polymers

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to the surface of the liposome aids in avoiding detection by Kupffer cells. A PEGylated liposome is termed a stealth liposome[2]. A method for preparing protein-liposome conjugates based on micelles as intermediates was developed. These protein-micelle conjugates into liposome solutions resulted in reproducible batches of protein-liposome conjugates. The method represents a general approach to the preparation of well defined and reproducible protein-liposome-based drug formulations[3].

The anti-tumor efficacy of liposomal formulations of cell cycle dependent anticancer drugs is critically dependent on the rates at which the drugs are released from the liposomes. Liposomal formulations with higher drug-to-lipid ratios exhibit reduced release rates[4].

***Mechanism of targeting***

Stealth liposomes are relatively impermeable to drug. Conventional carrier strategies permit the mononuclear phagocyte system to be targeted by the drugs. Stealthy strategies avoid major uptake by these cells and extend the systemic presence of these carriers. It seems clear that such drug carriers allow increased drug concentration at infected sites but reduce drug toxicity[5]. While mechanistic details are not known, release of drug probably involves:

i) Diffusing out of (the highly leaky) tumor capillary bed
ii) Fusion with cellular membranes with the drug contents endocytosed into the cell.

Liposomal amphoterisin B is more advantageous than the conventional preparation[6] because of better efficacy and other desirable properties of liposomal preparations which have been reported both in *vitro* and *vivo*[7,8].

The $t_{1/2}$ for stealth liposomal doxorubicin was 55 hours, whereas the $t_{1/2}$ for the HCl salt alone is 26 hours. This preparation has got improved targeting for solid tumors and decreased cardiac toxicity (cardiac toxicity is the dose limiting organ toxicity).

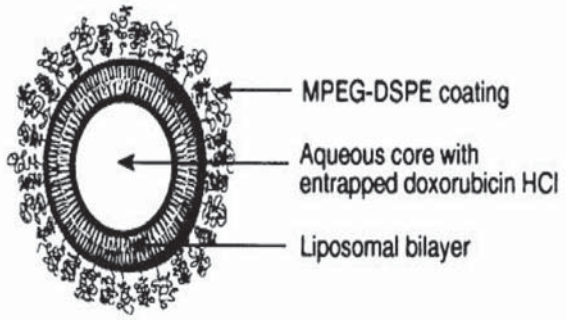


**Fig 2:** Structure of stealth liposome, *MPEG-DSPE – Methoxypolyethylene glycol–diacylphosphotidyl etholamine*

Studies are going on for production of wrapped liposomal drug formulations. Novel wrapped liposomes comprising of polyanion drug and cationic lipid complexes wrapped with neutral lipids were prepared using an efficient, innovative procedure. During the process, neutral lipids accumulated around the complexes and eventually covered the complexes. The resulting liposomes were 120-140 nm in diameter and the encapsulation efficiency was up to 90%. Formulations based on this technology could offer important advantages for the administration of many types of drug including antisense oligonucleotides, plasmids and RNAs which may therefore lead to improved therapeutic effectiveness of this range of drugs[9]. Another new approach in the liposomal formulation is passive targeting of the drug by sterically stabilized liposomes combined with efficient intracellular delivery which may be a very useful strategy to improve the antitumor efficacy for the anticancer agents. Studies suggested that this technique may be a feasible intracellular targeting carrier for efficient delivery of chemotherapeutic agents into tumor cells[10].

**2. Microspheres and Nanoparticles**

Microspheres are polyester polymers typically consisting of lactic and glycolic acids that form a cage around the drug (PLGA). Particle size is 100 nm to 1 μm (those at the small end of the scale are referred to as nanoparticles). This polymer is susceptible to biodegradation by esterases, so the method is similar to enteric coatings (in that the coating first dissolves. Of course for enterics, the dissolution is by ionization of carboxyl groups at higher pH and not by esterases). The fact that the drug is not accessible for degradation lends this formulation to depoting of protein drugs. Studies have shown that these nanoparticles have better physical stability and storage capability[11].

***Mechanism of targeting***

As with liposomes when targeting solid tumors, the micropheres and nanoparticles rely on the leaky vasculature to differentially move drug to the tumor cells. Microspheres can be formulated to be injected on the arterial side so that the microsphere embeds in the capillary network. The result is direct delivery to the afflicted organ. The only difficulty is that the arterial side is relatively buried and under higher pressure. It is also a sound method of depot protein injection intramuscularly.

Based on different studies, it is clear that the microsperes and nanoparticles will become an important component of targeted clinical pharmacotherapeutics in patients with different diseases in the future[12].

**3. Pegylated proteins**

In this carrier system polyethylene glycol (PEG) in the 40 kDa range (which is approximately the size of a protein) attached directly to the therapeutic protein. PEG molecules were resistant to phagocytosis and activated the human complement system poorly. So, these molecules might be the important aspects of drug depots and implantable devices[13]. Enhanced solubility, decreased proteolysis, decreased immunogenicity, and increased half life are the important properties of pegylated potiens. Polylactic acid and polyethylene glycol nanoparticles have been studied as new carriers for the delivery of plasmid DNA and have produced satisfactory results[14].

***Mechanism of targeting***

This is largely due to sustained plasma concentration. Hormone proteins do not require very high plasma concentration. These are essentially PEGylated prodrugs, since the ester or amide linkage must be removed to obtain the active protein drug. These micellar systems can be used for the safe and effective delivery of insoluble bioactive[15].

**4. Polymeric gels**

They are essentially PLGA polyesters (as above for microencapsulation; also used for biodegradable sutures) which are injected in liquid form and become semisolids later on. Drug is slowly released as the polymer is hydrolyzed.

**5. Implants**

Many pellet type of preparation of steroids using cholesterol as matrix material were tried for subdermal implants to simulate the production of hormones, e.g. Orentron pellet which contains 75 mg of testosterone having cylindrical shape having diameter 3.2 mm, length 8-9 mm for treating testosterone deficiency which maintains testosterone activity for 4 months. Semisolid phospholipid dispersions of vesicular morphology, so-called vesicular phospholipid gels (VPGs), were prepared by high-pressure homogenisation and tested in vitro for their suitability as implantable sustained release system for the decapeptide cetrorelix, a potent LH-RH antagonist. The VPGs contained 300-500 mg/g egg phosphatidylcholine (E80) and 0.5-10 mg/g cetrorelix acetate (CXA). Erosion of the phospholipid matrix, i.e. release of phospholipid vesicles was found to be the main release mechanism, following zero order or first order kinetics depending on the composition of the VPG, CXA-concentration[16]. Surface modification of biodegradable polyesters with fatty acid conjugates improves drug targeting and facilitates prolonged release for several weeks[17]. A biodegradable delivery system (copolymer of poly-D,L-lactic acid segments with randomly inserted p-dioxanone and polyethylene glycol (PLA-DX-PEG)) as implants for antibiotics and recombinant human bone morphogenetic protein has been studied and has produced significant results[18].

**6. Anti- IgE monoclonal antibody**

Understanding of the cellular and molecular mechanisms in asthma has lead to the recognition of a number of potential therapeutic targets, a few of which have been evaluated in clinical studies. Omalizumab is the first anti-IgE monoclonal antibody developed for the treatment of moderate to severe asthmatics to receive FDA approval. Newer DNA based therapeutic strategies including DNA vaccination and the antisense oligonucleotides show promise but thus far have only been tested in animal models[19].

**7. DNA delivery system**

Several years have been spent in the evolution of gene medicine from an experimental technology into a viable strategy for developing therapeutics for a wide range of human disorders. Numerous prototype DNA-based biopharmaceuticals can now control disease progression by induction and/or inhibition of genes. Selection of drugs on the basis of DNA sequence and structure has a reduced potential for toxicity, should result in fewer side effects, and therefore should eventually yield safer drugs than those currently available. These predictions are based on the high selectivity and specificity of such molecules for recognition of their molecular targets. However, poor cellular uptake and rapid in vivo degradation of DNA-based therapeutics necessitate the use of delivery systems to facilitate cellular internalization and preserve their activity[20].

***New drug delivery systems[21]***

Drug delivery systems are essential components of controlled drug release system. In the last decade, several drug delivery technologies have emerged including capsules, liposomes, microparticles, nanoparticles, and polymers. These components must be biocompatible, biodegradable, and display a desired biodistribution providing a long-term availability of the therapy at specific target over time[22].

The modes of drug delivery at the moment are:

**1. Transdermal drug delivery system**

The skin acts as a major target as well as a principle barrier for topical/transdermal (TT) drug delivery. The stratum corneum plays a crucial role in barrier function for TT drug delivery. Recently developed are devices in the form of adhesive patches of various shapes and sizes (5-20cm$^2$) which deliver the contained drug at a constant rate into systemic circulation via stratum cornium. A study has been done for evaluating the transdermal route as an alternative to the oral route for improving the systemic bioavailability and sustaining

the constant therapeutic plasma level of Zidovudine (AZT). The study demonstrated that elastic liposomes increased the transdermal flux, prolonged the release, improved the site specificity of AZT and represented an attractive strategy for sustained and targeted delivery of AZT[23]. Preparation available for use are Nitroglycerine, Nicotine, Estradiol, Hyoscine, Isosorbide dinitrate and Scopolamine. For example, Scopolamine is used for treating motion sickness. The vision is not affected and occurrence of dry mouth is also less frequent. It releases the drug at the rate of 10 mcg / hr for about 72 hrs[24].

Various liposoamal formulations with phospholipids of different origins have been used for cosmetic preparartions. Liposomes composed of different phospholipids showed differing effects on skin humidity. The maximal effect was achieved within 30 min and constant values were reached after 1.5 h for all formulations. Within the liposome formulations, egg phospholipids showed the highest transepidermal water loss values during the first 30 min, representing the strongest interactions with the skin barrier function, whereas for the other liposome formulations lower transepidermal water loss values were measured[25]. Encapsulation of lipophilic compounds in polymeric nanoparticles is able to improve topical delivery to the skin and such formulation has increased the concentration of the drug within stratum corneum[26].

***Iontophoresis:*** it is a process causing increased penetration of solutes into tissues using applied current. It is safe, economical and convenient to administer charged or uncharged drugs transdermally. When a potential difference is applied across the skin, an external force directs electrostatic repulsion. For transporting a positively charged drug across the skin, we can place anode in electric contact with a solution containing the drug. When a voltage is applied, the positively charged drug will be repelled from anode through the skin and into systemic circulation[21].

***Sonophoresis:*** it is the process by which permeation is enhanced with ultrasound[21].

**2. Ocular drug delivery**

Approximately 90% of all ophthalmic drug formulations are now applied as eye drops. Although eye drops are convenient and well accepted by patients, about 95% of the drug contained in the drops is lost due to absorption through the conjunctiva or through the tear drainage. A major fraction of the drug eventually enters the bloodstream and may cause side effects. To reduce drug loss and side effects, it is proposed to encapsulate the ophthalmic drug formulations in liposomes and to disperse the drug-laden liposomes in the lens material. Contact lenses made of particle-laden gels are expected to deliver drugs at therapeutic levels for a few days. The delivery rates can be tailored by controlling the particle and the drug loading[27], e.g. ocusert containing pilocarpine useful for treatment of glaucoma; pilocarpine medicated core is sandwiched between two transparent rate controlling ethylene vinyl acetate copolymer membranes. When it is placed under the upper or lower eyelid, pilocarpine dissolves into lacrimal fluid, penetrates through rate controlling membrane at a predetermined rate.

**3. Nasal drug delivery system**

Nasal drug administration has been used as an alternative route for the systemic availability of drugs restricted to intravenous administration. This is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism, and ready accessibility. The nasal administration of drugs, including numerous compound, peptide and protein drugs, for systemic medication has been widely investigated in recent years. These drug delivery systems have the ability to control the rate of drug clearance from the nasal cavity as well as protect the drug from enzymatic degradation in nasal secretions. The mechanisms and effectiveness of these drug delivery systems are described in order to guide the development of specific and effective therapies for the future development of peptide preparations and other drugs that otherwise should be administered parenterally. As a consequence, bioavailability and residence time of the drugs that are administered via the nasal route can be increased by bioadhesive[28] drug delivery systems. Although the majority of this work involving the use of microspheres, liposomes and gels is limited to the delivery of macromolecules (e.g., insulin and growth hormone), the general principles involved could be applied to other drug candidates. It must be emphasized that many drugs can be absorbed well if the contact time between formulation and the nasal mucosa is optimized[29].

**4. Dental drug delivery system**

*Controlled release preparation*- polycarboxylate cement and glass ionomer cement contain stannous fluoride ($SnF_2$) and release fluoride for prolonged period. This action helps prevent the dental caries (recurrent dental caries at the margins of restorations) as the fluoride has the anticariogenic activity. Fiber device made up of copolymer of hydroxyethyl methacrylate (HEMA) and methyl methcrylate (MMA) impregnated with the drug chlorhexidine has been used in the treatment of periodontal pockets. This device is placed into the periodontal pocket which can produce local drug concentration 100 times higher than the systemically administered preparation by reducing the total dose by over 400 times[21].

**5. Targeted drug delivery system**

*Liposomal and stealth liposomal preparation* (described above), and *Niosomal preparation*

Niosomes are alternative to liposomes. Niosomes or non-ionic surfactant vesicles prepared from synthetic non-ionic surfactant can be considered to be synthetic analogue of liposome. These niosomes can entrap solutes and are osmotically active, stable and behave in vivo like liposomes. Moreover, storage and handling characteristics of these non-ionic surfactants need no special care. Studies have shown that niosomes and liposomal drug formulations of sodium stibogluconate were equally active[21].

**6. Parenteral controlled release preparation**

***Dissolution type***- By preparing salt or complexes solubility can be decreased and rate of release can be controlled if they are administerd in gel type of oily vehicles containing aluminium monosterate. Drugs like penicillin G, Depot –Provera (Sangini sui), testosterone isobutyrate I.M./S.C. implants, etc may be used.

***Adsorption type***-Vaccines in which antigen can be bound to aluminium hydroxide gel by adsorption process can sustain the release of antigen for the stimulation of antibody formation.

***Encapsulated type***- Biodegradable or bioabsorbable macromolecules like gelatin, dextran, phospholipids, long chain fatty acids, liposomes, etc can be used to encapsulate drug like naltrexone palmoate, norethindrine for prolonged administration of drugs.

***Esterification type of depot preparation***- Biodegradable esters of drugs like testosterone cypionate in oily vehicles will be useful for prolonged action of parenteral preparation. For example testosterone.

**7. Buccal drug delivery**

Buccal preparations have been developed to allow prolonged localized therapy and enhanced systemic delivery. The bioadhesive polymers used in buccal drug delivery to retain a formulation are typically hydrophilic macro-molecules containing numerous hydrogen bonding groups. Newer generation bioadhesives have been developed and these include modified or new polymers that allow enhanced adhesion and/or drug delivery. Currently, this route is restricted to the delivery of a limited number of small lipophilic molecules that readily cross the buccal mucosa. However, this route could become a significant means for the delivery of a range of active agents in coming years, if the barriers to buccal drug delivery are overcome[30]. Chitosan (CS) has been widely used as an adhesive coating polymer for oral liposomal drug delivery systems because of its adhesive properties on mucous layers. The coating mechanism or interaction of chitosan and liposomes or mucin mainly depends on electrostatic forces. Thus, to enhance the adhesive properties of chitosan, a hydrophobically modified chitosan, i.e., dodecylated chitosan (DC) was synthesized and it has been shown to be a more suitable polymer for coating neutral-charge liposomes than CS because the hydrophobic side chain of DC inserts itself into the lipid bilayer of liposomes[31].

**Conclusion**

Newer drug delivery systems are more advantageous than the conventional therapy. These systems have better patient compliance, smooth plasma concentrations, ease of application, good delivery to the target tissues and less side effects. Liposomes, microspheres, pegylated proteins, polymeric gels and implants are the carrier systems and are part and parcel of newer drug delivery systems. Immunomodulation based therapies are proved to be effective in some conditions where as gene therapy is still in laboratory and clinical trial phase.

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