Review Article

Drug delivery systems: An updated review

Gaurav Tiwari, Ruchi Tiwari, Birendra Sriwastawa[1], L Bhati[2], S Pandey, P Pandey, Saurabh K Bannerjee[3]

Department of Pharmaceutics, Pranveer Singh Institute of Technology, Kanpur, Uttar Pradesh, [1]Jaipur National University, Jagatpura, Jaipur, Rajasthan, [2]Mankind Research Centre, Manesar, Gurgaon, [3]SVKM's Narsee Monjee Institute of Management Studies (NMIMS), School of Pharmacy and Technology Management, Dhule, Maharashtra, India

Abstract

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. For the treatment of human diseases, nasal and pulmonary routes of drug delivery are gaining increasing importance. These routes provide promising alternatives to parenteral drug delivery particularly for peptide and protein therapeutics. For this purpose, several drug delivery systems have been formulated and are being investigated for nasal and pulmonary delivery. These include liposomes, proliposomes, microspheres, gels, prodrugs, cyclodextrins, among others. Nanoparticles composed of biodegradable polymers show assurance in fulfilling the stringent requirements placed on these delivery systems, such as ability to be transferred into an aerosol, stability against forces generated during aerosolization, biocompatibility, targeting of specific sites or cell populations in the lung, release of the drug in a predetermined manner, and degradation within an acceptable period of time.

Key words: Brain targeting, infectious diseases, liposomal, lung diseases, micelles, transdermal

INTRODUCTION

Development of new drug molecule is expensive and time consuming. Improving safety efficacy ratio of "old" drugs has been attempted using different methods such as individualizing drug therapy, dose titration, and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery, targeted delivery are other very attractive methods and have been pursued vigorously. It is interesting to note that considerable work and many publications from USA, Europe are authored by Indian researchers.[1-3] Numerous animal and human investigations have provided an increased understanding of the pharmacokinetic and pharmacodynamic principles that govern the action and disposition of potent opioid analgesics, inhalation anesthetic agents, sedative/hypnotics, and muscle relaxants. These studies suggest that skin and buccal and nasal mucous membranes may have use as alternate routes of analgesic and anesthetic delivery. Similar developments with other compounds have produced a plethora of new devices, concepts, and techniques that have together been termed controlled-release technology (CRT). Some examples of CRTs are transdermal and transmucosal controlled-release delivery systems, ml6 nasal and buccal aerosol sprays, drug-impregnated lozenges, encapsulated cells, oral soft gels, iontophoretic devices to administer drugs through skin, and a variety of programmable, implanted drug-delivery devices. There are a number of factors stimulating interest in the development of these new devices, concepts, and techniques. Conventional drug administration methods, while widely utilized, have many problems that may be potentially overcome by these methods. Equally important, these advances may appear attractive relative to the costs of new drug development. Rising research and development costs, alternative investment opportunities for drug firms, fewer firms conducting pharmaceutical research, and erosion of effective patent life have resulted in a decline in the introduction of new chemical entities since the late 1950s. Bringing a new drug through discovery, clinical testing, development, and regulatory approval is currently estimated to take a decade and cost well over $ 120 million. Novel drug delivery systems may account for as much as 40% of US marketed drug products by 2000.[4-6]

Address for correspondence:
Dr. Gaurav Tiwari,
Department of Pharmaceutics, Jaipur National University,
Jagatpura, Jaipur, Rajasthan, India.
E-mail: tiwari_mpharm@rediffmail.com

Access this article online

Quick Response Code:

Website: www.jpionline.org

DOI: 10.4103/2230-973X.96920

BEADED DELIVERY SYSTEMS

Although not used with oxybutylin, beaded delivery formulations are another method used to achieve long-acting drug levels associated with the convenience of once-a-day dosing. This system has been successfully linked to tolterodine tartrate and is available as Detrol LA (Pharmacia, Peapack, NJ). Essentially, the beaded system consists of multiple, small beads that are

composed of inert substances (such as polystyrene). The active drug is overlaid on the beads and encased in a delivery capsule. The drug delivery from this system is acid sensitive, in that drug levels are dependent on gastric acidity for release. This process produces a pharmacokinetic pattern roughly similar to a zero-order pattern, with C max obtained approximately 4 to 6 hours after ingestion and sustained levels observed for 24 hours after initial dosing. Comparative advantages are seen for both efficacy (improved incontinence rates) and tolerability with Detrol LA over immediate-release tolterodine. In a double-blind, placebo-controlled, randomized study of 1529 patients the LA formulation resulted in 18% less incontinence episodes than the immediate-release tolterodine, whereas both formulations were statistically superior to placebo in reducing urinary frequency and increasing voided urinary volume. The overall dry mouth rate was 23% lower for tolterodine LA than immediate-release tolterodine. Rates of withdrawal were similar across all arms. Van Kerrebroeck concluded that the LA formulation of tolterodine was superior to the immediate-release formulation.[7-8]

LIPOSOMAL AND TARGETED DRUG DELIVERY SYSTEM

Drug delivery systems can in principle provide enhanced efficacy and/or reduced toxicity for anticancer agents. Long circulating macromolecular carriers such as liposomes can exploit the 'enhanced permeability and retention' effect for preferential extravasation from tumor vessels.[4] Liposomal anthracyclines have achieved highly efficient drug encapsulation, resulting in significant anticancer activity with reduced cardiotoxicity, and include versions with greatly prolonged circulation such as liposomal daunorubicin and pegylated liposomal doxorubicin. Pegylated liposomal doxorubucin has shown substantial efficacy in breast cancer treatment both as monotherapy and in combination with other chemotherapeutics. Additional liposome constructs are being developed for the delivery of other drugs. The next generation of delivery systems will include true molecular targeting; immunoliposomes and other ligand-directed constructs represent an integration of biological components capable of tumor recognition with delivery technologies.[5]

As discussed, currently approved liposomal drug delivery systems provide stable formulation, provide improved pharmacokinetics, and a degree of 'passive' or 'physiological' targeting to tumor tissue.[6] However, these carriers do not directly target tumor cells. The design modifications that protect liposomes from undesirable interactions with plasma proteins and cell membranes, and which contrast them with reactive carriers such as cationic liposomes, also prevent interactions with tumor cells. Instead, after extravasation into tumor tissue, liposomes remain within tumor stroma as a drug-loaded depot. Liposomes eventually become subject to enzymatic degradation and/or phagocytic attack, leading to release of drug for subsequent diffusion to tumor cells. The next generation of drug carriers under development features direct molecular targeting of cancer cells via antibody-mediated or other ligand-mediated interactions.

Immunoliposomes, in which mAb fragments are conjugated to liposomes, represent a strategy for molecularly targeted drug delivery.[9] Anti-HER2 immunoliposomes have been developed with either Fab' or scFv fragments linked to long-circulating liposomes. In preclinical studies, anti-HER2 immunoliposomes bound efficiently to and internalized in HER2-overexpressing cells, resulting in efficient intracellular delivery of encapsulated agents. Anti-HER2 immunoliposomes loaded with doxorubicin displayed potent and selective anticancer activity against HER2-overexpressing tumors, including significantly superior efficacy versus all other treatments tested (free doxorubicin, liposomal doxorubicin, free mAb [trastuzumab], and combinations of trastuzumab plus doxorubicin or liposomal doxorubicin).[10] Anti-HER2 immunoliposomes are currently undergoing scale up for clinical studies.[9,11]

The immunoliposome approach offers a number of theoretical advantages as compared with other antibody-based strategies. Anti-HER2 immunoliposome delivery of doxorubicin may circumvent the prohibitive cardiotoxicity associated with combined trastuzumab plus doxorubicin treatment. Anti-HER2 immunoliposomes can be constructed using scFv that, unlike trastuzumab, lack antiproliferative activity, are incapable of antibody-dependent cellular cytotoxicity, and require threshold levels of HER2 expression for delivery. In contrast to drug immunoconjugates, which consist of a small number of drugs (typically <10 drugs per mAb) directly coupled via linkers to selected residues on the mAb, immunoliposomes exploit the exponentially greater capacity of drug-loaded liposomes (up to 10^4 drugs per liposome). Immunoliposomes also appear to be nonimmunogenic and capable of long circulation even with repeated administration.[12] Antibody-based targeting is also being developed in conjunction with polymer systems. Similarly, ligand-based targeting using growth factors, hormones, vitamins (e.g., folate), peptides or other specific ligands is being pursued in conjunction with both liposomes and polymers. Liposomes are concentric bilayered structures made of amphipathic phospholipids and depending on the number of bilayer, liposomes are classified as multilamellar (MLV), small unilamellar (SUVs), or large unilamellar (LUVs). They range in size from 0.025-10 μ in diameter. The size and morphology of liposomes are regulated by the method of preparation and composition. Liposomes are used for delivery of drugs, vaccines, and genes for a variety of disorders.[13]

Infectious diseases

Bacchawat and co-workers developed liposomal amphotericin and investigated it in animal models of fungal infection and leishmaniasis. Kshirsagar and co-workers modified the formulation, developed a "Patient Worthy" sterile pyrogen free liposomal amphotericin preparation and investigated it in patients with systemic fungal infections and leishmaniasis. It was found to be safe producing significantly less adverse effects compared to

plain amphotericin in patients with systemic fungal infection, did not produce nephrotoxicity and could be given to patients with renal damage. It was effective in patients resistant to fluconazole and plain amphotericin. Unlike Ambisome (USA), which needs to be used in dose of 3 mg/kg/day this is effective at 1 mg/kg/day dose. The same group studied different dosage regimens of liposomal amphotericin using Aspergillus murine mode. It was found that liposomal amphotericin was more effective than equal dose of free amphotericin B given after fungal spore challenge. A large single dose of liposomal amphotericin was more effective, whether given before or after spore challenge, than given as two divided doses.[14] It was investigated in patients with visceral leishmaniasis and found to be effective in patients who had not responded to antimony, pentamidine, and amphotericin. Because of its safety, it can be given at 3 mg/kg/day dose thus reducing total duration of treatment. It was successfully used in a child suffering from visceral leishmaniasis. This is the first liposomal preparation developed outside of USA, which has been used in patients. In an attempt to improve efficacy and reduce toxicity further, liposomes with grafted ligand have been developed. Pentamidine isethionate and its methoxy derivative were encapsulated in sugar grafted liposomes and tested against experimental leishmaniasis *in vivo*. It was seen that sugar grafted liposomes specially the mannose grafted ones were potent in comparison to normal liposome encapsulated drug or free drug.[15]

Anticancer drugs

Anticancer drugs provide current information on the clinical and experimental effects of toxic and non-toxic cancer agents and is specifically directed towards breakthroughs in cancer treatment. Mukhopadhya developed conjugate of antineoplastic drug daunomycin (DNM) with maleylated bovine serum albumin. It was taken up with high efficiency by multi drug resistant variant JD100 of the murine-macrophage tumor cell line J774A.1 through the scavenger receptors resulting in cessation of DNA synthesis. A thermosensitive liposomal taxol formulation (heat mediated targeted drug delivery) in murine melanoma was developed and studied by another group of workers. Cremophor which is used as excipient due to the low aqueous solubility of taxol has toxic side effects. Temperature-sensitive liposomes encapsulating taxol were prepared using egg phosphatidylcholine and cholesterol in combination with ethanol. The liposomes have a phase transition temperature of 43°C.[16] A significant reduction in tumor volume was noted in tumor bearing mice treated with a combination of hyperthermia and theromosensitive liposome encapsulated taxol, compared to animals treated with free taxol with or without hyperthermia in B16F 10 murine melanoma transplanted into C57BI/6 mice. Sharma *et al.* also investigated the use of polyvinylpyrrolidone nanoparticles containing taxol prepared by reverse micro-emulsion method. The size of nanoparticle was found to be 50-60 nm. The antitumor effect of taxol was evaluated in B16F10 murine melanoma transplanted in C57 B 1/6 mice. *in vivo* efficacy of taxol containing nanoparticles as measured by reduction in tumor volume and increased survival time was significantly greater than that of an equivalent concentration of free taxol.[17]

Lung-specific drug delivery

Pulmonary drug delivery offers several advantages in the treatment of respiratory diseases over other routes of administration. Inhalation therapy enables the direct application of a drug within the lungs. The local pulmonary deposition and delivery of the administered drug facilitates a targeted treatment of respiratory diseases, such as pulmonary arterial hypertension (PAH), without the need for high dose exposures by other routes of administration. The intravenous application of short acting vasodilators has been the therapy of choice for patients with PAH over the past decade. The relative severity of side effects led to the development of newprostacyclin analogues and alternative routes of administration. One such analogue, iloprost (Ventavis®), is a worldwide approved therapeutic agent for treatment of PAH. Inhalation of this compound is an attractive concept minimizing the side effects by its pulmonary selectivity. Unfortunately, the short half-life of iloprost requires frequent inhalation manoeuvres, ranging up to 9 times a day. Therefore, an aerosolizable controlled release formulation would improve a patient's convenience and compliance. Controlled drug delivery systems have become increasingly attractive options for inhalation therapies. A large number of carrier systems have been developed and investigated as potential controlled drug delivery formulations to the lung, including drug loaded lipid and polymer based particles. The use of colloidal carrier systems for pulmonary drug delivery is an emerging field of interest in nanomedicine. The objective of this study was to compare the pulmonary absorption and distribution characteristics of the hydrophilic model drug 5(6)-carboxyfluorescein (CF) after aerosolization as solution or entrapped into nanoparticles in an isolated rabbit lung model (IPL). CF-nanoparticles were prepared from a new class of biocompatible, fast degrading, branched polyesters by a modified solvent displacement method. Physicochemical properties, morphology, encapsulation efficiency, *in vitro* drug release, stability of nanoparticles to nebulization, aerosol characteristics as well as pulmonary dye absorption and distribution profiles after nebulization in an IPL were investigated Among the various drug delivery systems considered for pulmonary application, nanoparticles demonstrate several advantages for the treatment of respiratory diseases, such as prolonged drug release, cell-specific targeted drug delivery or modified biological distribution of drugs, both at the cellular and organ level. It must first be recognized that formulating compounds and delivering them as aerosols is complex. Not only does it involve the formulation of a stable solution or suspension in a medium (propellant) that is not as well characterized as other systems, but the resultant system is also subject to performance limitations. In order to efficiently reach the lung, the formulation must be atomized into particles having aerodynamic sizes between approximately 1 and 5 μ. Due to these particle size constraints, as well as inhalation toxicology concerns, the range of possible excipients to choose from during the formulation phase is substantially reduced. Additionally, limiting the concentration of excipients in a formulation is crucial for maintaining adequate aerosol performance. Thus, given the complexity of this relationship, formulating aerosols is a challenging endeavor. Although

complex, the successful formulation of drugs for pulmonary delivery provides a valuable therapeutic route. Upon introduction of the metered dose inhaler (MDI), medical treatment of lung diseases changed significantly. Since that time, MDIs have become the most effective means of controlling symptoms of lung diseases such as asthma and chronic obstructive pulmonary disorder (COPD). More recently, formulation modifications were merited when chlorofluorocarbon (CFC) propellants were linked to the depletion of the ozone layer (Molina and Rowland, 1974). With the successful transition to new propellant systems, MDIs are still well accepted and highly utilized by patients across the globe today. Looking forward, the effectiveness, ease of use, and relatively low cost of aerosol preparations in combination with modifications in delivery technology and formulation sciences, will likely expand the treatment of diseases. Another, therapeutically undesirable aspect of pulmonary drug delivery is rapid absorption of most drugs from the lung, necessitating frequent dosing, e.g., of bronchodilators and corticosteroids. Liposomes are believed to alleviate some of the problems encountered with conventional aerosol delivery due to their ability to: (i) serve as a solubilization matrix for poorly soluble agents; (ii) act as a pulmonary sustained release reservoir; and (iii) facilitate intracellular delivery of [18]

Targeting to brain

The great interest in mucosal vaccine delivery arises from the fact that mucosal surfaces represent the major site of entry for many pathogens. Among other mucosal sites, nasal delivery is especially attractive for immunization, as the nasal epithelium is characterized by relatively high permeability, low enzymatic activity and by the presence of an important number of immunocompetent cells. In addition to these advantageous characteristics, the nasal route could offer simplified and more cost-effective protocols for vaccination with improved patient compliance. The use of nanocarriers provides a suitable way for the nasal delivery of antigenic molecules. Besides improved protection and facilitated transport of the antigen, nanoparticulate delivery systems could also provide more effective antigen recognition by immune cells. These represent key factors in the optimal processing and presentation of the antigen, and therefore in the subsequent development of a suitable immune response. In this sense, the design of optimized vaccine nanocarriers offers a promising way for nasal mucosal vaccination.[21]

The usual noninvasive approach to solving the brain drug delivery problem istolipidizethe drug, The water -soluble parts of the drugs restricts BBB transport conversion of water-soluble drug into lipid-soluble prodrug is the traditional chemistry driven solution to the BBB problem as in [Figure 1].

The treatment of CNS diseases is particularly challenging because the delivery of drug molecules to the brain is often precluded by a variety of physiological, metabolic and biochemical obstacles that collectively comprise the Blood Brain barrier, blood cerebrospinal fluid barrier, Blood tumor barrier. The present outlook for patients suffering from many types of brain diseases remains poor, but recent developments in drug delivery techniques provide reasonable hope that the formidable barriers shielding the brain may ultimately be overcome. Drug delivery directly to the brain interstitium has recently been markedly enhanced through the rational design of polymer-based drug delivery systems. Substantial progress will only come about, however, if continued vigorous research efforts to develop more therapeutic and less toxic drug molecules are paralleled by the aggressive pursuit of more effective mechanisms for delivering those drugs to brain targets.[19] Jain *et al.* developed dopamine hydrochloride bearing positively charged small liposomes by sonicating multilamellar vesicles and studied their physical attributes and drug leakage and release pattern. *In vivo* performance was assessed by periodic measurement of chlorpromazine induced catatonia in Sprague Dawley rats and was compared with plain dopamine hydrochloride, dopamine and levodopa carbidopa. The studies showed that dopamine can be effectively delivered into the brain and its degradation in circulation can be prevented by incorporating it into liposomes.[20]

Strategies for drug delivery to the brain

Several drugs do not have adequate physiochemical characteristics such as high lipid solubility, low molecular size and positive charge which are essential to succeed in traversing BBB.[21]

Disruption of the BBB

The thought behind this approach was to break down the barrier momentarily by injecting mannitol solution into arteries in the neck. The resulting high sugar concentration in brain capillaries takes up water out of the endothelial cells, shrinking them, thus opening tight junction. The effect lasts for 20-30 minute, during which time drugs diffuse freely, that would not normally cross the BBB. This method permitted the delivery of chemotherapeutic agents in patients with cerebral lymphoma, malignant glioma and disseminated CNS germ cell tumors. Physiological stress, transient increase in intracranial pressure, and unwanted delivery of anticancer agents to normal brain tissues are the undesired side-effects of this approach in humans.[10]

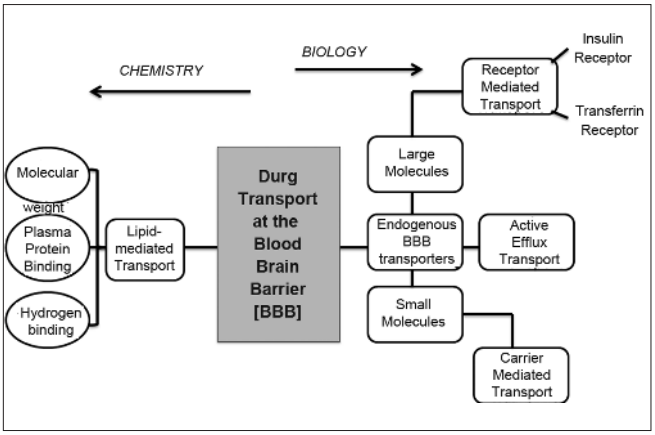

Figure 1: Outline of a program for developing blood-brain drug targeting strategies derived from either chemistry based or biology-based disciplines

Intraventricular/intrathecaldelivery

Here, using a plastic reservoir, which implanted subcutaneously in the scalp and connected to the ventricles within the brain by an outlet catheter. Drug injection into the CSF is a suitable strategy for sites close to the ventricles only.[22]

Intra nasal drug delivery

After nasal delivery drugs first reach the respiratory epithelium, where compounds can be absorbed into the systemic circulation by tran cellular and para cellular passive absorption, carrier-mediated transport, and absorption through trancytosis. When a nasal drug formulation is delivered deep and high enough into the nasal cavity, the olfactory mucosa may be reached and drug transport into the brain and/or CSF via the olfactory receptor neurons may occur.[23]

Possible systems for drug delivery-colloidal drug carriers

Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles show great promise as drug delivery systems. The goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties.[24]

Micelles

Micelles formed by self-assembly of amphiphilic block copolymers (5-50 nm) in aqueous solutions are of great interest for drug delivery applications. The drugs can be physically entrapped in the core of block copolymer micelles and transported at concentrations that can exceed their intrinsic water- solubility. Moreover, the hydrophilic blocks can form hydrogen bonds with the aqueous surroundings and form a tight shell around the micellar core. As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzymatic degradation. In addition, the corona may prevent recognition by the reticuloendothelial system and therefore preliminary elimination of the micelles from the bloodstream. The fact that their chemical composition, total molecular weight and block length ratios can be easily changed, which allows control of the size and morphology of the micelles. Functionalization of block copolymers with cross linkable groups can increase the stability of the corresponding micelles and improve their temporal control.[25]

Liposomes

Liposomes were first produced in England in 1961 by Alec D. Bangham. One end of each molecule is water soluble, while the opposite end is water insoluble. Water-soluble medications added to the water were trapped inside the aggregation of the hydrophobic ends; fat-soluble medications were incorporated into the phospholipid layer as in [Figure 2].

In some cases liposomes attach to cellular membranes and appear to fuse with them, releasing their or drugs into the cell.

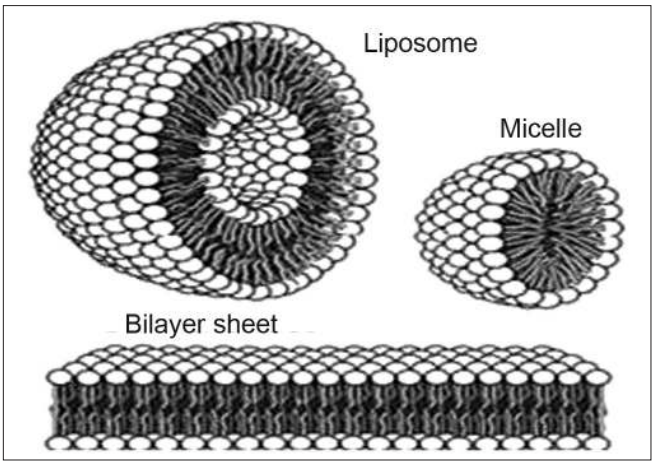

Figure 2: Liposomes, micelles, bilayer sheet

In the case of phagocytic cells, the liposomes are taken up, the phospholipid walls are acted upon by organelles called lysosomes, and the medication is released. Liposomal delivery systems are still largely experimental; the precise mechanisms of their action in the body are under study, as are ways in which to target them to specific diseased tissues.[26]

Nano technology

Nanoparticulate systems for brain delivery of drugs

One of the possibilities to deliver drugs to the brain is the employment of nanoparticles. Nanopartiacles are polymeric particles made of natural or artificial polymers ranging in size between about 10 and 1000 nm (1 mm). Drugs may be bound inform of a solid solution or dispersion or be adsorbed to the surface or chemically attached. Poly (butylcyanoacrylate) nanoparticles represent the onlynanoparticles that were so far successfully used for the *in vivo* delivery of drugs to the brain. The first drug that was de-livered to the brain using nanoparticles was the hexapeptidedalargin (Tyr-D-Ala- Gly- Phe-Leu-Arg), a Leu-enkephalin analogue with opioid activity.[27]

Nanoparticles and nanoformulations have already been applied as drug delivery systems with great success; and nanoparticulate drug delivery systems have still greater potential for many applications, including anti-tumors therapy, gene therapy, and AIDS therapy, radiotherapy, in the delivery of proteins, antibiotics, virostatics, and vaccines and as vesicles to pass the blood-brain barrier.[28]

Nanoparticles provide massive advantages regarding drug targeting, delivery and release, and with their additional potential to combine diagnosis and therapy, emerge as one of the major tools in nanomedicine. The main goals are to improve their stability in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers. The cytotoxicity of nanoparticles or their degradation products remains a major problem, and improvements in biocompatibility obviously are a main concern of future research.[29,30]

Nowadays nanotechnology is proved to be more efficient for enhancing drug delivery to brain. The nanoparticles are the drug carrier system which is made from a broad number of materials such as poly (alkylcyanoacrylates) (pacas),polyacetates, polysaccharides, and copolymers. The methods of preparation of nanoparticles, their characterization and medical application have been reviewed in detail.[31] The exact mechanism of nanoparticle transport into brain is not understood, but it is thought to depend on the particles size, material composition, and structure. In some cases it is reported to mimic molecules that would normally be transported to brain. For example, polysorbate-coated nanoparticles are thought to mimic low-density lipoprotein (LDL), allowing them to be transported across the capillary wall and into the brain by hitching a ride on the LDL receptor.[32]

The nanotechnology includes:

1. Coated nanoparticles
2. Pegylated nanoparticles
3. Solid Lipid nanoparticles (SLN)
4. Nanogels

Transdermal delivery

Bioadhesive liposomes bearing levonorgestrel as controlled drug delivery system has been studied.[26] Mesophasic proliposomal system for levonorgestral was prepared. The vesicles were mostly unilamellar and some were multilamellar. Release was of zero order kinetics. Alcohol as compared to oils had greater effect on transdermal flux. *In vivo* studies showed that a significant lag phase was observed before the therapeutic levels were reached indicating the requirement for a loading dose. This proliposomes system was found to be superior to PEG-based ointment system. Liposomal reservoir system bearing local anesthetic benzocaine was developed[33] for controlled and localized delivery via topical route. The liposomal suspension was incorporated into an ointment and gel base. The systems delivered the drug at a controlled rate ever 24 hr compared to plain ointment which had a rapidly decreased release rate. The drug delivery across human cadaver skin was very slow. *In vivo* studies showed a longer duration of action in the case of liposomal formulation.[34]

Miscellaneous

Nabar studied the effect of size and charge of liposome in the bio-distribution of 99m TC-DTPA encapsulated in liposome after intravenous injection in rats. They observed that multilamellar vesicles (MLV) were taken up to a greater extent as compared to SUVs in liver spleen and lungs. Positively charged MLVs than negative or neutral ones, were taken up more in liver, positively charged SUVs were taken up more in kidneys and neutral MLVs were taken up more in lungs than charged ones.[35] An attempt was made to improve stability of liposome by coupling the drug with the lipid bilayer using a cross linking agent.[36] Soya phosphatidylcholine (SPC) containing liposomes were prepared by calcium induced fusion method. Positively charged stearylamine was introduced in the bilayer. The liposomes were coupled to entrapped ibuprofen by EDAC (1-ethyl 3-(3-dimethyl aminopropyl) carbodiimide HCI) and the coupling was confirmed by UV spectrum. It was observed that EDAC in SPC containing stearylamine liposomes retarded the release of ibuprofen significantly. In albino rats, the various factors affecting systemic absorption of nasally applied gentamycin sulphate using *in situ* nasal perfusion technique was studied.[37] Tween 80 which is a surfactant increases permeation by altering membrane structure and permeability. In this study Tween 80 upto 1% w/v concentrations, increased permeability. Betacyclodextrin at 0.25% w/v concentration, another permeability enhancer was found to significantly increase permeability initially but was found to plateau off later on. However, both these permeability enhancer were found to decrease stability and potency of gentamycin.[38]

OTHER CONTROLLED DRUG DELIVERY SYSTEMS

Extended release, slow release and sustained release preparation have been developed by pharmaceutical industry and pharmacy departments and investigated *in vitro* for release pattern and *in vivo* for bio-equivalence.[39]

Oral

There is a great need in oral delivery of protein and peptide drugs, suitable devices for delivering the therapeutic agent incorporated microspheres selectively in the intestine. Gelatin capsules were coated with various concentrations of sodium alginate and cross-linked with appropriate concentrations of calcium chloride and tested *in vitro* for resistance to gastric and intestinal medium. Gelatin capsules coated with 20% w/v of the polymer, which gave the most promising result *in vitro,* were evaluated in human volunteers for their *in vivo* gastro intestinal tract behaviour. The radiographical studies show that while the un-coated gelatin capsules disintegrated in the stomach within 15 min of ingestion, the alginate-coated gelatin capsules remained intact as long as they were retained in the stomach (up to 3 h) and then migrated to the ileocecal region of the intestine and disintegrated.[40-43] Vanarase and Nagarsenkar prepared pellets of 1 mm and 1.65 mm size of prochlorperazine maleate using a modern pelletization technique. The pellets were coated with ethylcellulose and evaluated for *in vitro* release, using USP dissolution apparatus. They noted that release of PCPM can be reduced with increasing amount of ethylcellulose.[44-46] Rangaiah *et al.* prepared and studied the sustained release tablets of theophylline using Eudragit RL, RS, and Hydroxy propyl methyl cellulose. Bioavailability studies in volunteers showed that HPMC and Eudragit formulation produced sustained plasma concentration of the drug. Another group 35 formulated sustained release capsules of nifedipine containing an initial rapidly available loading dose in the form of solid dispersion and a sustained release part as micro particles coated with polyvinyl acetate (M.wt 45,000) film using a modified Wurster coating apparatus.[47] The products provided release of initial therapeutic dose of drug in less than 45 min and sustained release over 11-12 hours. The same group developed a diffusion

cell for the determination of drug release from a topical aerosol formulation.[48]

Parenteral

Kushwaha used a blend of synthetic polymer polyvinyl alcohol and natural macromolecule gum Arabica and found that duration and release of drug depends on the amount of drug loaded in the matrix and solubility of the drug in the matrix and the release medium. The advantage of this system is that the release kinetics of the drug from the system can be tailored by adjusting the plasticizer, homopolymer and cross linker composition. Chitosan microspheres of 45-300 μ were used for controlled delivery of progesterone.[49] *In vitro* and *in vivo* release was tested. It was seen that highly cross linked spheres released only 35% of incorporated steroids in 40 days compared to 70% from lightly cross linked spheres. Determination of *in vivo* bioavailability of the steroid from microsphere formulation by intramuscular injection in rabbits showed that a plasma concentration of 1-2 μg/ml was maintained upto 5 months without a high burst effect. The data suggests that cross linked chitosan microspheres would be an interesting system for long term delivery of steroids. Cross linked dextran beads were developed as a carrier for development of a single contact vaccine delivery system.[50-54] There has been extensive research on drug delivery by biodegradable polymeric devices since bioresorbable surgical sutures entered the market two decades ago. Among the different classes of biodegradable polymers, the thermoplastic aliphatic poly (esters) such as poly (lactide) (PLA), poly (glycolide) (PGA), and especially the copolymer of lactide and glycolide referred to as poly (lactide-co-glycolide) (PLGA) have generated tremendous interest because of their excellent bio-compatibility, biodegradability, and mechanical strength.[55] They are easy to formulate into various devices for carrying a variety of drug classes such as vaccines, peptides, proteins, and micromolecules. Most importantly, they have been approved by the United States Food and Drug.

Administration (FDA) for drug delivery. Dhiman and Khuller[56-59] found that mice immunized with microparticles of poly (DL-lactide-co-glycolide) (DLPLG) as delivery vehicles for 71-KDa cell wall associated protein of mycobacterium tuberculosis H37 Ra, exhibited significantly higher T cell stimulation and cytokine release in comparison to 71-KDa emulsified in Freund's incomplete adjuvant (FIA) as well as BCG vaccinated group. Further, the protective effect of 71KDa- PLG was compared with 71-KDa FIA on the basis of survival rates and viable bacilli load in different organs at 30 days post challenge and median lethal dose (LCD50) of *Mycobacterium tuberculosis* H37Rv. The 71-KDa PLG was more effective when challenge was given 16 week after immunization. Further, 71KaDa- PLG immunized group exhibited a significantly higher clearance of bacterial load from the lungs and livers in comparison to the 71KDa FIA immunized group. Poly (lactide-co-glycolide) (PLG) was used to deliver diclofenac in the form of microspheres and *in situ* gel-forming systems, subcutaneously. The pharmacokinetic and pharmacodynamics studies in the adjuvant - induced arthritic rats showed that microspheres produced steady therapeutic levels of the drug in the plasma for about 16 days following a single subcutaneous injection. The *in situ* gel-forming provided significantly higher maximum plasma concentration and inhibition of inflammation was maintained for about 10 days.[60-63]

Dental product

Somayaji *et al.* used an ethylcellulose strip as delivery medium for tetracycline and metronidazole to reduce sub-gingival microorganisms in periodontal pockets. Patients were given supragingival scaling and then divided into five groups, depending on the length of time the medication was in place. Sites were marked for tetracycline, metronidazole, and placebo. Sites were wiped and isolated, and baseline microbiology samples were taken for gram staining and culture methods.[64] After treatment, subgingival microbiological samples were taken again. The ethyl cellulose strips were removed and analyzed for any remaining drug. Results showed that tetracycline and metronidazole could both be applied locally to periodontal sites using ethyl cellulose strips and markedly supress the subgingival bacteria over a period of several days. The tetracycline showed a faster release; however, the metronidazole required a lesser concentration to achieve complete reduction of the subgingival flora. A saliva activated bio-adhesive drug delivery system was developed[65] for lidocaine hydrochloride and compared its effect with topical gel preparation in dentistry. It was found that DDS adhered to gingival within a minute and produced peak effect in 15 minutes and produced greater depth of anesthesia than the marketed topical gel.

Colon-specific drug delivery

The increasing number of peptide and protein drugs being investigated demands the development of dosage forms which exhibit site-specific release. Delivery of drugs into systemic circulation through colonic absorption represents a novel mode of introducing peptide and protein drug molecules and drugs that are poorly absorbed from the upper gastrointestinal (GI) tract.[66] Oral colon-specific drug delivery systems offer obvious advantages over parenteral administration. Colon targeting is naturally of value for the topical treatment of diseases of the colon such as Crohn's disease, ulcerative colitis and colorectal cancer. Sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina and arthritis. Peptides, proteins, oligonucleotides, and vaccines are the potential candidates of interest for colon-specific drug delivery. Sulfasalazine, ipsalazide, and olsalazine have been developed as colon-specific delivery systems for the treatment of inflammatory bowel disease (IBD).[65] The vast microflora and distinct enzymes present in the colon are being increasingly exploited to release drugs in the colon. Although the large intestine is a potential site for absorption of drugs, some difficulties are involved in the effective local delivery of drugs to the colon bypassing the stomach and small intestine.[67] Furthermore, differential pH conditions and long transit time during the passage of drug formulations from mouth to colon create numerous technical difficulties in the safe delivery of drugs to the colon. However, recent developments in pharmaceutical technology, including coating drugs with pH-sensitive and bacterial degradable polymers, embedding in bacterial degradable matrices and designing into prodrugs, have provided renewed

hope to effectively target drugs to the colon. The use of pH changes is analogous to the more common enteric coating and consists of employing a polymer with an appropriate pH solubility profile. The concept of using pH as a trigger to release a drug in the colon is based on the pH conditions that vary continuously down the GI tract.[68] Polysaccharide and azopolymer coating, which is refractory in the stomach and small intestine yet degraded by the colonic bacteria, have been used as carriers for colon-specific targeting. Finally, the availability of optimal preclinical models and clinical methods fueled the rapid development and evaluation of colon-specific drug delivery systems for clinical use. Future studies may hopefully lead to further refinements in the technology of colon-specific drug delivery systems and improve the pharmacotherapy of peptide drugs.[69]

The necessity and advantages of colon-specific drug delivery systems have been well recognized and documented.[70] In the past, the primary approaches to obtain colon-specific delivery achieved limited success and included prodrugs, pH- and time-dependent systems, and microflora-activated systems. Precise colon drug delivery requires that the triggering mechanism in the delivery system only respond to the physiological conditions particular to the colon. Hence, continuous efforts have been focused on designing colon-specific delivery systems with improved site specificity and versatile drug release kinetics to accommodate different therapeutic needs.[71]

Among the systems developed most recently for colon-specific delivery, four systems were unique in terms of achieving *in vivo* site specificity, design rationale, and feasibility of the manufacturing process (pressure-controlled colon delivery capsules (PCDCs), CODES, colonic drug delivery system based on pectin and galactomannan coating, and Azo hydrogels). The focus of this review is to provide detailed descriptions of the four systems, in particular, and *in vitro*/*in vivo* evaluation of colon-specific drug delivery systems, in general. Specific targeting of drugs to the colon is recognized to have several therapeutic advantages.[72] Drugs, which are destroyed by the stomach acid and/or metabolized by pancreatic enzymes, are slightly affected in the colon, and sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina and arthritis. Treatment of colonic diseases such as ulcerative colitis, colorectal cancer and Crohn's disease is more effective with direct delivery of drugs to the affected area. Likewise, colonic delivery of vermicides and colonic diagnostic agents require smaller doses. Prasad *et al.* developed a colon-specific oral tablet using guar gum as carrier.[73]

Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides.[74] To achieve successful colonic delivery, a drug needs to be protected from absorption and/or the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the proximal colon, which is considered the optimum site for colon-targeted delivery of drugs. Colon targeting is naturally of value for the topical treatment of diseases of colon such as Chron's diseases, ulcerative colitis, colorectal cancer and amebiasis. Peptides, proteins, oligonucleotides, and vaccines pose potential candidature for colon targeted drug delivery.[75]

Drug release studies under conditions mimicking mouth to colon transit have showed that guar gum protects the drug from being released completely in the physiological environment of stomach and small intestine. Guar gum at pH. 6.8 is susceptible to colonic bacterial enzyme action, with drug release. Pre-treatment of rats orally with aqueous dispersion of guar gum for 3 days, induced enzyme specifically acting on guar gum,[76] thereby increasing drug release. The result indicates usefulness of guar gum as a potential carrier for colon specific drug delivery. A novel colon-specific drug delivery system based on a polysaccharide, guar gum was evaluated in healthy human male volunteers, with gamma scintigraphic study using technetium 99m-DTPA as tracer. It was seen that some amount of tracer present on the surface of the tablets was released in stomach and small intestine and the bulk of the tracer present in the tablet mass was delivered to the colon. The colonic arrival time of the tablets was 2-4 hr. On entering the colon, the tablets were found to degrade. *In vitro* release studies of the incorporated 5-flurouracil was carried out in simulated gastric and intestinal fluids. *In vitro* release profile in presence of azoreductase in the culture of intestinal flora followed a zero order pattern.[77]

CONCLUSION

Pharmaceutical development of drug delivery system is being pursued enthusiastically in many laboratories in India. These are being investigated *in vitro* for release pattern and in some cases *in vivo* in animals for pharmacokinetics but less frequently for efficacy. There is a paucity of data on clinical studies and utility of the DDS in patients. It is necessary that pharmacologists should be involved in the investigation of pharmacokinetics and pharmacodynamics of DDS if the products have reached their meaningful outcome - the clinical use.

REFERENCES

1. Panchagnula R. Transdermal delivery of drugs. Indian J Pharmacol 1997;29:140-56.
2. Rao PR, Diwan PV. Formulation and *in vitro* evaluation of polymeric films of diltiazem hydrochloride and indomethacin for transdermal administration. Drug Dev Indian Pharm 1998;24:327-36.
3. Rao PR, Diwan PV. Permeability studies of cellulose acetate free films for transdermal use: Influence of plasticizers. Pharm Acta Helv 1997;72:47-51.
4. Thacharodi D, Rap KP. Development and *in vitro* evaluation of chitosan-based trandermal drug delivery system for the controlled delivery of propranolol hydrochloride. Biomaterials 1995;16:145-8.
5. Krishna R, Pandit JK. Carboxymethylcellulose-sodium based transdermal drug delivery system for propranolol. J Pharm Pharmacol 1996;48:367-70.

6. Bhat M, Shenoy DS, Udupa N, Srinivas CR. Optimization of delivery of betamethasone - dipropionate from skin preparation. Indian Drugs 1995;32:211-4.
7. Misra A, Pal R, Majumdar SS, Talwar GP, Singh O. Biphasic testosterone delivery profile observed with two different transdermal formulations. Pharm Res 1997;14:1264-8.
8. Thacharodi D, Rao KP. Rate-controlling biopolymer membranes as transdermal delivery systems for nifedipine: Development and *in vitro* evaluations. Biomaterials 1996;17:1307-11.
9. Nanda A, Khar RK. Permeability characteristics of free films were studied using the drugs such as diltiazem hydrochloride and indomethacin Drug Dev Indian Pharm 1994;20:3033-44.
10. Mukhopadhyay A, Mukhopadhyay B, Basu K. Circumvention of multidrug resistance in neoplastic cells through scavenger receptor mediated drug delivery. FEBS Lett 1995;276:95-8.
11. Nanda A, Khar RK. Pulsed mode constant current iontophonetic transdermal delivery of propranalol hydrochloride in acute hypertensive and normotensive rats. Indian Drugs 1998;35:274-80.
12. Murthy SN, Shobha Rani HS. Comparative pharmacokinetic and pharmacodynamic evaluation of oral vs transdermal delivery of terbutaline sulphate. Indian Drugs 1998;35:34-6.
13. Rao MY, Vani G, Chary BR. Design and evaluation of mucoadhesive drug delivery systems. Indian Drugs 1998;35:558-65.
14. Murthy NS, Satheesh M. Enhancer synergism of propylene glycol and PEG -400 in terbutaline sulphate transdermal drug delivery systems. Indian Drugs 1997;34:224-6.
15. Tatapudy H, Madan PL. Benzoyl peroxide microcapsules I. preparation of core material. Indian Drugs 1995;32:239-48.
16. Kshirsagar NA, Gokhale PC, Pandya SK. Liposomes as drug delivery system in leishmaniasis. J Assoc Physicians India 1995;43:46-8.
17. Kshirasagar NA, Bodhe PV, Kotwani RN. Targeted drug delivery in visceral leishmaniasis. J Par Dis 1997;21:21-4.
18. Kotwani RN, Gokhale PC, Kshirsagar NA, Pandya SK. Optimizing dosage regimens of liposomal amphotericin B using Aspergillus murine model. Indian J Pharmacol 1996;28:88-92.
19. Gokhale PC, Kshirsagar NA, Khan MU, Pandya SK, Meisheri YV, Thakur CP, *et al*. Successful treatment of resistant visceral leishmaniasis with liposomal amphotericin B. Trans Roy Soc Trop Med Hyg 1994;88:228.
20. Karande SC, John Boby KF, Lahiri KR, Jain MK, Kshirsagar NA, Gokhale PC, *et al*. Successful treatment of antimony - resistant visceral leishmaniasis with liposomal amphotericin B (L-amp-LRC) in child. Trop Doct 1995;25:80-1.
21. Banerjee G, Nandi G, Mahato SB, Pakrashi A, Basu MK. Drug delivery system: Targeting of pentamidines to specific sites using sugar grafted liposomes. J Antimicrob Chemother 1996;38:145-50.
22. Sharma D, Chelvi TP, Kaur J, Ralhan R. Thermosensitive liposomal taxol formulation: Heat-mediated targeted drug delivery in murine melanoma. Melanoma Res 1998;8:240-4.
23. Sharma D, Chelvi TP, Kaur J, Chakravorty K, De TK, Maitra A, *et al*. Novel taxol formulation: Polyvinylpyrrolidone nanoparticle-encapsulated taxol for drug delivery in cancer therapy. Oncol Res 1996;8:281-6.
24. Deol P, Khuller GK. Lung specific stealth liposomes: Stability, biodistribution and toxicity of liposomal antitubercular drugs in mice. Biochimica Biophysi Acta 1997;1334:161-72.
25. Jain NK, Rana AC, Jain SK. Brain drug delivery system bearing dopamine hydrochloride for effective management of parkinsonism. Drug Dev Ind Pharm 1998;24:671-5.
26. Uppadhyay AK, Dixit VK. Bioadhesive liposomes bearing levonorgestrel as controlled drug delivery system. Pharmazie 1998;53:421-2.
27. Deo Mr, Sant VP, Parekh SR, Khopade AJ, Banakar UV. Proliposome-based transdermal delivery of levonorgestrel. J Biomat App 1997;12:77-88.
28. Singh R, Vyas SP. Topical liposomal system for localized and controlled drug delivery. J Dermatol Sci 1996;13:107-11.
29. Nabar SJ, Nadkarni GD. Effect of size and charge of liposomes on biodistribution of encapsulated 99mTc – DTPA in rats. Indian J Pharmacol 1998;30:199-202.
30. Sivakumar PA, Mythily S, Alamelu S, Rao PK. Liposome - ibuprofen conjugate and the release characteristics of ibuprofen. Indian Drugs 1994;31:568-73.
31. Martin DB, Udupa N. Nasal drug delivery of gentamycin sulphate. Indian Drugs 1994;31:365-9.
32. Narayani R, Rao KP. Polymer-coated gelatin capsules as oral delivery devices and their gastrointestinal tract behavior in humans. J Biomater Sci Polym Ed 1995;7:39-48.
33. Vanarase SY, Nagarsenkar MS. *In-vitro* release studies of prochlorperazine pellets coated with ethylcellulose. Indian Drugs 1995;32:134-8.
34. Rangaiah KV, Madhusudhan S, Verma PR. Sustained release of theophylline from HPMC and Eudragit tablet. Indian Drugs 1995;32:543-7.
35. Asgar A, Sharma SN. Sustained release through coated microparticles of nifedipine. Indian Drugs 1996;33:30-5.
36. Asgar A, Radha S, Agarwal SP. Fabrication of a diffusion cell for the determination of drug release from topical aerosol formulations. Indian Drugs 1997;34:715-7.
37. Kushwaha V, Bhowmick A, Behera BK, Ray AR. Sustained release of antimicrobial drugs from polyvinylalcohol and gum arabica blend matrix. Art Cells Blood Subst Immobilization Biotechnol 1998;26:159-72.
38. Jameela SR, Kumary TV, Lal AV, Jayakrishnan A. Progressive loaded chitosan microspheres: A long acting biodegradable controlled delivery system. J Cont Rel 1998;52:17-24.
39. Diwan M, Misra A, Khar RK, Talwar GP. Long-term high immune response to diphtheria toxoid in rodents with diphtheria toxoid conjugated to dextran as a single contact point delivery system. Vaccine 1997;15:1867-71.
40. Jain R, Shah NH, Malick AW, Rhodes CT. Controlled drug delivery by biodegradable poly (ester) devices: Different preparative approaches. Drug Dev Indian Pharm 1998; 24:703-27.
41. Dhiman N, Khuller GK. Protective efficacy of mycobacterial 71-KDa cell wall associated protein using poly (DLlactide- co-glycolide) microparticles as carrier vehicles. FEMS Immunol Med Microbiol 1998;21:19-28.
42. Chandrashekar G, Udupa N. Biodegradable injectable implant systems for long term drug delivery using poly (lactic- co-glycolic) acid copolymers. J Pharm Pharmacol 1996;48:669-74.
43. Somayaji BV, Jariwala U, Jayachandran P, Vidyalakshmi K, Dudhani RV. Evaluation of antimicrobial efficacy and release pattern of tetracycline and metronidazole using a local delivery system. J Periodontol 1998;69:409-13.
44. Taware CP, Mazumdar S, Pendharkar M, Adani MH, Devarajan PV. A bioadhesive delivery system as an alternative to infiltration anesthesia. Oral Sur Oral Med Oral Pathol Oral Radiol Endodontics 1997;84:609-15.
45. Prasad YV, Krishnaiah YS, Satyanarayana S. *In vitro* evaluation of guar gum as a carrier for colon-specific drug delivery. J Control Relaese 1998;51:281-7.
46. Krishnaiah YS, Satyanarayana S, Rama Prasad YV, Narasimha Rao S. Gamma scintigraphic studies on guar gum matrix tablets for colonic drug delivery in healthy human volunteers. J Control Release 1998;55:245-52.
47. Shantha KL, Ravichandran P, Rao KP. Azo polymeric hydrogels

for colon targeted drug delivery. Biomaterials 1995;16:1313-8.

48. Khuller GK, Kapur M, Sharma S. Liposome technology for drug delivery against mycobacterial infections. Curr Pharm Des 2004;10:3263-74.
49. Bala I, Hariharan S, Kumar MN. PLGA nanoparticles in drug delivery: the state of the art. Crit Rev Ther Drug Carrier Syst 2004;21:387-422.
50. Vauthier C, Dubernet C, Fattal E, Pinto-Alphandary H, Couvreur P. Poly(alkylcyanoacrylates) as biodegradable materials for biomedical applications. Adv Drug Deliv Rev 2003;55:519-48.
51. Couvreur P, Barratt G, Fattal E, Legrand P, Vauthier C. Nanocapsule technology: A review. Crit Rev Ther Drug Carrier Syst 2002;19:99-134.
52. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release 2001;70:1-20.
53. Wissing SA, Kayser O, Muller RH. Solid lipid nanoparticles for parenteral drug delivery. Adv Drug Deliv Rev 2004;56: 1257-72.
54. Florence AT. Issues in oral nanoparticle drug carrier uptake and targeting. J Drug Target 2004;12:65-70.
55. Bummer PM. Physical chemical considerations of lipid-based oral drug delivery: Solid lipid nanoparticles. Crit Rev Ther Drug Carrier Syst 2004;21:1-20.
56. Florence AT, Hussain N. Transcytosis of nanoparticle and dendrimer delivery systems: Evolving vistas. Adv Drug Deliv Rev 2001;50: S69-89.
57. Pandey R, Zahoor A, Sharma S, Khuller GK. Nanoparticle encapsulated antitubercular drugs as a potential oral drug delivery system against murine tuberculosis. Tuberculosis 2003;83:373-8.
58. Sharma A, Pandey R, Sharma S, Khuller GK. Chemotherapeutic efficacy of poly (DL-lactide-co-glycolide) nanoparticle encapsulated antitubercular drugs at sub-therapeutic dose against experimental tuberculosis. Int J Antimicrob Agents 2004;24:599-604.
59. Ain Q, Sharma S, Garg SK, Khuller GK. Role of poly [DL-lactide-co-glycolide] in development of a sustained oral delivery system for antitubercular drug(s). Int J Pharm 2002;239:37-46.
60. Dutt M, Khuller GK. Chemotherapy of *Mycobacterium tuberculosis* infections in mice with a combination of isoniazid and rifampicin entrapped in poly (DL-lactide-co-glycolide) microparticles. J Antimicrob Chemother 2001;47:829-35.
61. Gabor F, Bogner E, Weissenboeck A, Wirth M. The lectin-cell interaction and its implications to intestinal lectin-mediated drug delivery. Adv Drug Deliv Rev 2004;56:459-80.
62. Sharma A, Sharma S, Khuller GK. Lectin-functionalized poly (lactide-co-glycolide) nanoparticles as oral/aerosolized antitubercular drug carriers for treatment of tuberculosis. J Antimicrob Chemother 2004;54:761-6.
63. Pandey R, Khuller GK. Antitubercular inhaled therapy: Opportunities, progress and challenges. J Antimicrob Chemother 2005;55:430-5.
64. Pandey R, Sharma A, Zahoor A, Sharma S, Khuller GK, Prasad B. Poly (DL-lactide-co-glycolide) nanoparticle-based inhalable sustained drug delivery system for experimental tuberculosis. J Antimicrob Chemother 2003;52:981-6.
65. Pandey R, Khuller GK. Solid lipid particle-based inhalable sustained drug delivery system against experimental tuberculosis. Tuberculosis (Edinb) 2005;85:227-34.
66. Pinto-Alphandary H, Andremont A, Couvreur P. Targeted delivery of antibiotics using liposomes and nanoparticles: Research and applications. Int J Antimicrob Agents 2000;13:155-68.
67. Kayser O, Olbrich C, Croft SL, Kiderlen AF. Formulation and biopharmaceutical issues in the development of drug delivery systems for antiparasitic drugs. Parasitol Res 2003;90: S63-70.
68. Anisimova YV, Gelperina SE, Peloquin CA, Heifets LB. Nanoparticles as antituberculosis drugs carriers: effect on activity against M. tuberculosis in human monocyte-derived macrophages. J Nanoparticle Res 2000;2:165-71.
69. Fawaz F, Bonini F, Maugein J, Lagueny AM. Ciprofloxacin-loaded polyisobutylcyanoacrylate nanoparticles: Pharmacokinetics and *in vitro* anti-microbial activity. Int J Pharm 1998;168:255-9.
70. Barrow EL, Winchester GA, Jay K, Staas JK, Quenelle DC, Barrow WW. Use of microsphere technology for targeted delivery of rifampin to Mycobacterium tuberculosis-infected macrophages. Antimicrob Agents Chemother 1998;42:2682-9.
71. Peters K, Leitzke S, Diederichs JE, Borner K, Hahn H, Muller RH, *et al*. Preparation of a clofazimine nanosuspension for intravenous use and evaluation of its therapeutic efficacy in murine Mycobacterium avium infection. J Antimicrob Chemother 2000;45:77-83.
72. Rabinow BE. Nanosuspensions in drug delivery. Nat Rev Drug Discov 2004;3:785-96.
73. Moghimi SM, Hunter AC, Murray JC. Long-circulating and target-specific nanoparticles: Theory to practice. Pharmacol Rev 2001;53:283-318.
74. Pandey R, Khuller GK. Subcutaneous nanoparticle-based antitubercular chemotherapy in an experimental model. J Antimicrob Chemother 2004;54:266-8.
75. Schmidt C, Bodmeier R. Incorporation of polymeric nanoparticles into solid dosage forms. J Control Release 1999;57:115-25.
76. Sham JO, Zhang Y, Finlay WH, Roa WH, Lobenberg R. Formulation and characterization of spray-dried powders containing nanoparticles for aerosol delivery to the lung. Int J Pharm 2004;269:457-67.
77. Tsapis N, Bennett D, Jackson B, Weitz DA, Edwards DA. Trojan particles: Large porous carriers of nanoparticles for drug delivery. Proc Natl Acad Sci 2002;99:12001-5.

How to cite this article: Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, Bannerjee SK. Drug delivery systems: An updated review. Int J Pharma Investig 2012;2:2-11.
Source of Support: Nil. Conflict of Interest: None declared.