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A REVIEW: DRUG DELIVERY SYSTEMS

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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 controlledrelease 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]

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 zeroorder 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, placebocontrolled, randomized study of 1529 patients the LA formulation resulted in 18% less incontinence episodes than the immediaterelease 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,nleading 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]

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.

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 43oC.[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, cellspecific 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.

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]

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]

OTHER CONTROLLED DRUG DELIVERY SYSTEMS

Extended release, slow release and sustained release preparation have been developed by pharmaceutical industry and pharmacy ndepartments 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 crosslinked 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.

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 (lactideco-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.

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 colonspecific 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]

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.

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