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Drug delivery systems: A modified review

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Abstract
A large number of potential drug target have been identified from biochemical studies of different enzyme/receptor/ channel-inhibitor systems. These data provide the basis for homology search in biological databases. Identification of homologous sequence is the primary step of drug target development. Successful utilization of such target in designing effective drug molecules will largely depend on the prediction of three dimensional structures. Experimental techniques like x-ray crystallography or NMR spectroscopy provide 3-D structural information.

The proprietory name or Brand name or trade name for particular drug is the name given to a particular composition by their respective pharmaceutical company. Each drug is also given a generic name that any pharmaceuticals company can use to identify their product.

The goal of the medical chemist to find compounds that have potent effects on given diseases with minimum side effects. Various herbs have been used which has been providing the starting point for the development of the current arsenal of drugs. Once the naturally occurring drug is isloted then it is treated as a prototype. This prototype is the LEAD compound. Analogs of the lead compound are synthesized in order to find one that might have been lesser side effect and improved therapeutics. Changing the structure of the lead compound is known as Molecular Modification.

It is changing the structure of the lead compound in order to get a new drug that offers better therapeutic results and lesser side effect. Example is development of synthetical local anesthetic from cocaine.

Drug candidates that are natural products are usually discovered by fractionation of organism in which they occur. Thus *in vitro* screen are used such as the degree of binding the drug candidate to the enzyme that is implicated in the disease of interest.

In the search for a grug target for osteoporosis, a cDNA library was prepared from an osteoclastoma. Around 4% of the cDNAs encodes unknown protease which was named catepsim K which gets increased at high level in osteosclasts.

Keywords: 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. 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.

Beaded Delivery System

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.

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. 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.

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. 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. 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). Anti-HER2 immunoliposomes are currently undergoing scale up for clinical studies

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. 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.

Anti-cancer drugs

Anticancer, or antineoplastic, drugs are used to treat malignancies, or cancerous growths. Drug therapy may be usedalone, or in combination with other treatments such as surgery or radiationtherapy. Several classes of drugs may be used in cancer treatment, depending on the nature of the organ involved. For example, breast cancers are commonly stimulated by estrogens, and may be treated with drugs that inactivate the sex hormones. Similarly, prostatecancer may be treated with drugs that inactivate androgens, the male sex hormone. However, themajority of antineoplastic drugs act by interfering with cell growth. Since cancerous cells grow more rapidly than othercells, the drugs target those cells that are in the process of reproducing themselves. As a result, antineoplastic drugs willcommonly affect not only the cancerous cells, but others cells that commonly reproduce quickly, including hair follicles,ovaries and testes, and the blood-forming organs.

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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