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Review of emerging drug delivery systems: Mechanisms, challenges and future prepectives

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Abstract
Drug delivery is the process of administering a pharmacological material to people or animals in order to achieve a therapeutic effect. When it comes to treating human diseases, the nasal and pulmonary routes of pharmaceutical administration are becoming increasingly important. Particularly for protein and peptide medicines, these mechanisms provide good alternatives to parenteral drug delivery. For this reason, a variety of drug delivery techniques have been created and are now being investigated for nasal and pulmonary delivery. Cyclodextrins, prodrugs, gels, microspheres, liposomes, and proliposomes are a few examples.
Nanoparticles made of biodegradable polymers show assurance in meeting a number of the stringent requirements placed on these delivery systems, including the ability to transfer 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 time frame.

Keywords: Liposomal, viral illnesses, brain targeting, lung ailments, micelles, and transdermal

Introduction
Developing a novel pharmaceutical molecule is an expensive and time-consuming process. Various strategies, including dose titration, therapeutic drug monitoring, and individualizing drug therapy, have been undertaken to increase the safety-effectiveness ratio of "old" drugs.
Targeted delivery, slow delivery, and controlled rate delivery are additional very attractive strategies that have been extensively investigated. It's noteworthy that Indian scholars have produced a substantial body of work and several publications from the United States and Europe [1, 3]. Numerous animal and human research have improved our understanding of the pharmacokinetic and pharmacodynamic principles guiding the action and disposition of powerful opioid analgesics, inhalation anesthetic agents, sedatives/hypnotics, and muscle relaxants. different routes for analgesia. and the use of anesthetic. Controlled-Release Technology (CRT) is the collective term for a number of innovative tools, concepts, and techniques that have been developed as a result of similar developments with other substances.

Beaded delivery methods
Although they are not used with oxybutylin, beaded delivery formulations represent an additional method for obtaining long-acting drug levels associated with the convenience of once-daily administration. Tolterodine tartrate has been successfully linked to this system, called Detrol LA (Pharmacia, Peapack, NJ). The beaded system is essentially composed of a number of tiny beads composed of inert materials (such as polystyrene). The beads are covered with a delivery capsule that holds the active drug.
Since the amount of medication released relies on the stomach's acidity, this system's drug delivery is acid sensitive. This method yields a pharmacokinetic pattern that is typically similar to a zero-order pattern; sustained values are recorded for 24 hours after the original dosage, and the C max is measured 4-6 hours after intake. When it comes to both efficacy (raising incontinence rates) and tolerability, Detrol LA outperforms immediate-release

tolterodine. While both formulations were statistically better than placebo in lowering frequency of urination and increasing volume of voiding, the LA formulation led to 18% fewer incontinence episodes than the immediate-release tolterodine in a double-blind, placebo-controlled, randomized study of 1529 patients.

The total dry mouth rate was 23% lower with tolterodine LA than with immediate-release tolterodine.

For every arm, withdrawal rates were similar. Van Kerrebroeck came to the conclusion that tolterodine's LA formulation was better than its immediate-release version [4, 5].

A liposomal and targeted drug delivery system

A molecularly targeted drug delivery technique called immunoliposomes involves coupling mAb fragments to liposomes [6]. Anti-HER2 immunoliposomes have been produced by attaching Fab' or scFv fragments to long-circulating liposomes. In preclinical studies, anti-HER2 immunoliposomes efficiently attach to and internalize in HER2-overexpressing cells, allowing for efficient intracellular administration of encapsulated medications. In comparison to all other tested treatments (free doxorubicin, liposomal doxorubicin, free mAb [trastuzumab], and combinations of liposomal doxorubicin or trotuzumab plus doxorubicin), doxorubicin-loaded anti-HER2 immunoliposomes showed strong and specific anticancer activity against HER2-overexpressing tumors [7].

Infectious ailments

Bacchawat and associates synthesized liposomal amphotericin and investigated it in animal models of fungal infection and leishmaniasis. Kshirsagar and associates modified the formulation to produce a "Patient Worthy" sterile pyrogen-free liposomal amphotericin preparation and examined its effects in patients with systemic fungal infections and leishmaniasis. Because it did not produce nephrotoxicity, patients with renal impairment could receive basic amphotericin in situations of systemic fungal infection, and it was found to be safe and to have far fewer side effects. It worked well for patients who were resistant to simple amphotericin and fluconazole. Unlike Ambisome (USA), which needs a dose of 3 mg/kg/day, this works well at 1 mg/kg/day. The same team examined several liposomal amphotericin dosage schedules using Aspergillus murine mode. After a fungal spore challenge, liposomal amphotericin was found to be more effective than an equivalent dose of free amphotericin B. A large single dose of liposomal amphotericin was more effective than two smaller doses, whether given before or after the spore challenge [8].

Drugs that fight cancer

Anticancer drugs provide current information on the clinical and experimental effects of both toxic and non-toxic cancer drugs, with the primary goal of enhancing cancer treatment. Mukhopadhya combined the anticancer drug Daunomycin (DNM) with maleylated bovine serum albumin. When the multidrug resistant variant JD100 of the murine macrophage tumor cell line J774A.1 effectively absorbed it via the scavenger receptors, DNA synthesis was halted. A different group of scientists developed and studied a thermosensitive liposomal taxol formulation (heat-mediated targeted drug delivery) in melanoma mice. The excipient cremophor causes negative side effects since taxol is poorly soluble in water. Temperature-sensitive liposomes containing taxol were made by combining egg phosphatidylcholine, cholesterol, and ethanol. The liposomes have a phase transition temperature of 43 °C [9].

Lung: Particular drug distribution

Pulmonary medication distribution offers several advantages over other modes of administration when treating respiratory disorders. Inhalation therapy allows for the direct administration of a medicine into the lungs. The local pulmonary deposition and dispersion of the provided medication allows for the targeted treatment of respiratory diseases, such as Pulmonary Arterial Hypertension (PAH), without necessitating high dose exposures through alternate delivery methods. Intravenous injection of short-acting vasodilators has been the recommended treatment for those with PAH for the past decade.

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The purpose of this study was to compare the pulmonary distribution and absorption characteristics of the hydrophilic model drug 5(6)-Carboxyfluorescein (CF) in an isolated rabbit lung model (IPL) after aerosolization as solution or encapsulated into nanoparticles. Using a modified solvent displacement approach, CF-nanoparticles were produced from a unique family of biocompatible, fast degrading, branched polyesters. Lung dye absorption and dispersion profiles after nebulization in an IPL were studied, along with physicochemical characteristics, morphology, encapsulation effectiveness, *in vitro* drug release, stability of nanoparticles to nebulization, and aerosol properties. Nanoparticles exhibit several advantages for the treatment of respiratory conditions among the various drug delivery techniques considered for pulmonary application, such as prolonged drug release, cell-specific targeted drug delivery, or modified biological distribution of drugs at the organ and cellular levels. First of all, it is important to recognize that producing chemicals and distributing them as aerosols are challenging processes. The resulting system has performance limitations in addition to the need to create a stable suspension or solution in a propellant, a medium that is less fully characterized than other systems. To successfully reach the lung, the formulation must be atomized into particles with aerodynamic sizes of around 1 to 5 µ. The selection of possible excipients during the formulation stage is severely constrained by these particle size limitations and concerns about inhalation toxicity. Maintaining adequate aerosol performance also requires limiting the concentration of excipients in a formulation. The intricacy of this interaction makes producing aerosols challenging. The effective pulmonary delivery drug formulation provides a helpful treatment approach despite its complexity. With the introduction of the Metered Dose Inhaler (MDI), medical treatment of lung diseases underwent a significant change. Since then, MDIs have been the most effective way to manage the symptoms of lung diseases such asthma and Chronic Obstructive Pulmonary Disease (COPD). Formulation modifications were later justified when the weakening of the ozone layer was linked to Chlorofluorocarbon (CFC) propellants (Molina and Rowland, 1974). MDIs are still widely used and well-liked by patients all throughout the world, even after the

successful transition to new propellant systems. Future advancements in delivery technology and formulation sciences, as well as the effectiveness, affordability, and ease of use of aerosol preparations, should result in an increase in the range of sickness treatments. Another medically undesirable feature of pulmonary drug administration is the rapid absorption of most drugs from the lung, including corticosteroids and bronchodilators, which requires frequent dose. Liposomes are believed to alleviate some of the problems related to traditional aerosol delivery because of their ability to: (i) serve as a solubilization matrix for poorly soluble agents; (ii) serve as a pulmonary sustained release reservoir; and (iii) facilitate intracellular delivery [10].

Brain targeting

There is a lot of interest in administering mucosal vaccinations since mucosal surfaces are the main point of entry for many illnesses. Among other mucosal locations, nasal administration is especially attractive for immunization because the nasal epithelium has a large number of immunocompetent cells, low enzymatic activity, and high permeability. In addition to these advantages, the nasal route may offer simpler, more affordable vaccination processes with greater patient compliance. Nanocarriers are a suitable means of delivering antigenic chemicals through the nose. In addition to improving protection and facilitating antigen transport, nanoparticulate delivery technologies may provide improved antigen detection by immune cells. These are essential to the optimal processing and presentation of the antigen and, as a result, to the subsequent elicitation of a suitable immune response.

In this sense, the creation of better vaccine nanocarriers offers a viable technique for nasal mucosal immunization. (11)

Intraventricular / Intrathecal delivery

In this case, an exit catheter was used to link the plastic reservoir to the brain's ventricles after it was implanted subcutaneously in the scalp. Only locations near the ventricles are appropriate for drug injection into the CSF [12].

Delivery of intranasal drugs

Medication first enters the respiratory epithelium after nasal administration. From there, it may reach the bloodstream through trancytosis, carrier-mediated transport, and passive absorption of cellular and paracellular components. When a nasal medication formulation penetrates sufficiently deep and high into the nasal cavity, the olfactory mucosa may be accessible and drug transport into the brain and/or CSF via the olfactory receptor neurons may occur [13].

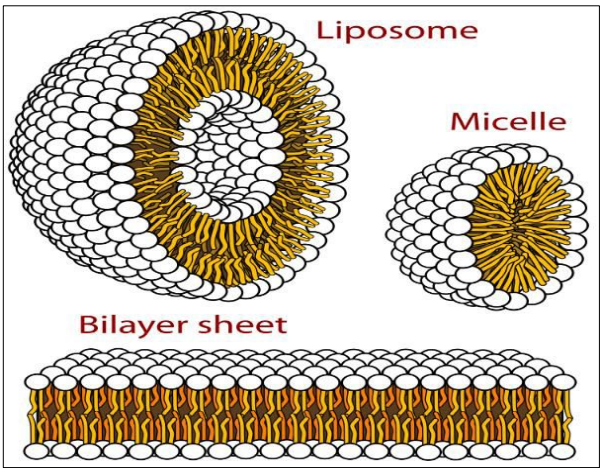
Potential Methods for Drug Delivery and Drug Colloidal Transportation Colloidal drug carrier systems, including micellar solutions, vesicle and liquid crystal dispersions, and nanoparticle dispersions composed of small particles, show great potential as drug delivery techniques. The objective is to produce systems with reduced toxicity, extended shelf life, and optimum drug loading and release characteristics. The integrated drug participates in the microstructure of the system and may potentially influence it due to molecular interactions, especially if the drug exhibits mesogenic or amphiphilic properties [14].

Micelles

Micelles that are formed when amphiphilic block copolymers (5-50 nm) self-assemble in aqueous solutions are extremely useful for drug delivery applications. Once the drugs are physically confined in the center of block copolymer micelles, they can be administered at quantities greater than their intrinsic water solubility. Furthermore, by establishing hydrogen bonds with the surrounding aqueous environment, the hydrophilic blocks can form a tight shell around the micellar core. As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzyme degradation. Additionally, because of the corona, the reticuloendothelial system could not be able to identify the micelles, which could lead to their initial removal from the bloodstream. Because of their easily modifiable chemical composition, total molecular weight, and block length ratios, the micelles' size and shape can be regulated. By adding cross-linkable groups to block copolymers, the related micelles' stability and temporal control can be increased [15].

A liposome

In 1961, Alec D. Bangham produced the first liposomes in England. One end of each molecule dissolves in water, but the other end does not. Fat-soluble drugs were integrated into the phospholipid layer, while water-soluble drugs introduced to the water were confined inside the hydrophobic end aggregation. Sometimes liposomes adhere to cell membranes and seem to fuse with them, facilitating the release of drugs into the cell. When phagocytic cells are engaged, the medication is released once the liposomes are absorbed and lysosomes work on the phospholipid walls. The precise mechanisms by which liposomal delivery systems function within the body, as well as methods of delivering them to specific diseased tissues, are still primarily in the experimental stage [16].



Nano technology Nanoparcticulate systems for brain delivery of drugs

One way to deliver drugs to the brain is by using nanoparticles. Nanoparticles are polymeric particles made of synthetic or natural polymers that range in size from 10 to 1000 nm (1 mm). Drugs can be bound in a solid solution or dispersion, adsorbed to the surface, or chemically bonded. So far, only poly (butylcyanoacrylate) nanoparticles have been successfully used to deliver drugs to the brain *in vivo*.

The first drug to be administered to the brain by nanoparticles was hexapeptidedalargin, a homologue of leu-enkephalin having opioid activity [17].

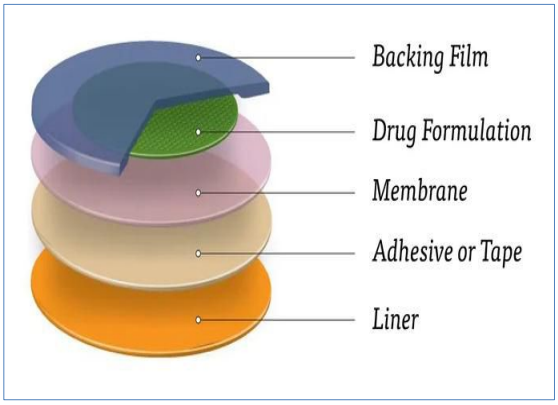
The elements of nanotechnology are as follows
1. Nanoparticles coated in
2. Pegylation of nanoparticles
3. Solid Lipids Nanoparticles (SLN)
4. Nanofibers

Transdermal delivery

A mesophasic proliposomal levonorgestral system was created. Most of the vesicles were unilamellar, however others were multilamellar. The release kinetics were zero order. Alcohol has a greater impact on transdermal flow than oils. *In vivo* studies indicated that a loading dosage was required since there was a discernible lag time before the therapeutic levels were reached. This liposome approach was found to perform better than the PEG-based ointment strategy. A liposomal reservoir system holding the local anesthetic benzocaine was developed for topical delivery that is controlled and localized [18].

Patches of transdermal

Transdermal patches offer a painless, patient-friendly interface to facilitate the delivery of systemic drugs. The essential elements of many approved transdermal patches are an adhesive layer that encourages skin contact, a reservoir that stores the medicine—ideally small and lipophilic—and a protective backing layer that prevents drug leakage [19]. To improve the regulated release of the medication, some techniques may include an extra layer. Many commercially available transdermal patches have been developed for a variety of purposes, such as birth control and quitting smoking. In 1979, the first FDA-approved patch was a 3-day patch that injected scopolamine to relieve motion sickness. As of right now, the FDA has authorized more than a dozen patches.



Delivery of drugs orally

The most extensively utilized technique of giving medications is oral administration. This is demonstrated by the number of oral formulations that broke into the top 100 selling drugs in 2013.

Systemic distribution, patient self-administration convenience, and fixed doses packaged into a single tablet or capsule are the main advantages of oral medication. There are numerous varieties of capsules on the market, and new capsule designs offer an opportunity to develop novel oral DDS. However, neither peptides nor proteins are currently taken orally due to their size-limited transit across the epithelium and rapid breakdown in the stomach. On the other hand, a lot of effort has gone into developing oral protein delivery systems, especially for insulin.

Replaceable systems

There are two types of implanted DDS release characteristics: passive delivery and active delivery. Passive DDS controls drug release by means of the properties of the materials that comprise the implant. Passive DDS can modify the quantity of drug released from the reservoir by controlling the rates of diffusion, osmosis, or concentration gradients. These passive release methods are influenced by drug choice, membrane composition, membrane pore size and tortuosity, and the combination of these design characteristics. On the other hand, active implant DDS controls drug release with a pump that can be activated through a number of methods, such as simple manual activation, physical pressure, and electrochemically driven devices that can alter the drug delivery rate. Since some implantable DDS involve micro and nanofabrication technologies, the FDA Office of Combination Product evaluation, which looks at medical therapies that include components from independently established domains, may result in longer approval delays [20]. Implantable DDS has substantially improved ocular medication delivery because traditional methods require numerous intravitreal injections, which can lead to a number of issues as are discussed below. The first of these intravitreal implants, Vitrasert®, will be the subject of this discussion.

Final report

Pharmaceutical research on medication delivery methods is being intensively undertaken in a number of Indian laboratories. These are being investigated *in vitro* for their release pattern and, less frequently, for their pharmacokinetic effectiveness in animals. There is a dearth of information about clinical trials and the DDS's efficacy in patients. Pharmacologists must participate in the investigation of the pharmacokinetics and pharmacodynamics of DDS whether the products have fulfilled their important objective of clinical use.

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