A REVIEW: ADVANCES IN DRUG DELIVERY

Roonal Pritam Kataria

Jai Hind Collge, Department Of Microbiology, A road, Churchgate, Mumbai 400 020

ABSTRACT

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. New drug delivery techniques aim to improve overall drug performance and efficacy, making patient’s lives easier. Drug delivery techniques are constantly evolving and improving to breach the biological barriers separating drugs from their target sites. Advances in drug delivery would not only improve the overall performance of the drug but are also expected to offer a host of additional advantages such as ease of administration, increased patient compliance, decreased side effects and cost reduction. While drug delivery plays an important role in enriching drug performance, researchers are concentrating on using drug delivery as a means to reduce drug dosage frequency, preferably through non-invasive methods. Multiple injections required per week or day could be replaced by once a month dosages or even longer intervals which would stabilise blood levels of the medications, thereby enhancing treatment outcomes and patient compliance. Over the past three decades, new approaches have been suggested for the development of novel carriers for drug delivery. This review describes general concepts and emerging research in this field of drug delivery.

KEY WORDS: Advanced drug delivery system, ease of administration, patient compliance, cost reduction.

INTRODUCTION

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. The introduction of drugs in human body may be accomplished by several anatomic routes. In order to achieve the therapeutic purpose, the choice of the most suitable administration route is of prime importance. Therefore, several factors must be taken into consideration when administering a drug, namely its own properties, the disease to be treated and the desired therapeutic time. The drugs can be administrated directly to the target tissue or organ or can be delivered by systemic routes. Pharmaceutical treatments started plenty of decades, or even centuries ago either with the oral administration of solid pills and liquids, or with injectable active chemical drugs. When either of these methods is applied, drug dose maintenance in the body is achieved by repeated administrations. Despite the effectiveness of these treatments, it is impossible to control the uniform drug level over a long period of time. During the past three decades, new approaches and strategies have been developed to control several parameters that are essential for enhancing the treatment performance such as the rate, period of time and targeting of delivery. This was the beginning of the so called drug delivery systems [15]

Drug Delivery Carriers

The main purpose of using a drug delivery system is not only to deliver a biologically active compound in a controlled manner but also to maintain drug level in the body within therapeutic window. Besides, one can direct the drug towards a specific organ or tissue (targeted drug delivery. [34] This can be done by using suitable drug carriers that could be manipulated in order to improve the efficiency of drug delivery system. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest).

Polymers: The earliest drug delivery systems, first introduced in the 1970s, were based on polymers formed from lactic acid. Today, polymeric materials still provide the most important avenues for research, primarily because of their ease of processing and the ability of researchers to readily control their chemical and physical properties via molecular synthesis. Polymers are formed by the linkage of a large number of smaller molecules called monomers. They are made in different shapes and sizes with drug either attached to it or inside the polymer construct. Biodegradable polymers are particularly attractive for application in DDS since, once introduced into the human body, they do not require removal or additional manipulation. Their degradation products are normal metabolites of the body or products that can be metabolized and easily
cleared from the body [1, 30]. Moreover, synthetic polymers offer a wide variety of compositions with adjustable properties which can be exploited for administration of drug (chemical, interfacial, mechanical and biological). Since their preparation is very reproducible, it is possible to prepare them with the same specifications quite easily. [33, 44]

Polymers can deliver drugs through dissolution, diffusion or osmosis. Polymers can be attached to antibodies to deliver drugs to a specific target. Basically, two broad categories of polymer systems have been studied: reservoir devices which involves the encapsulation of a pharmaceutical product within a polymer shell and matrix devices in which a drug is physically entrapped within a polymer network. Krishna et al [20] formulated a carboxymethylcellulose-sodium (CMC-Na) based transdermal system for propranolol, a beta-adrenoceptor blocker and reported its improved bioavailability in-vitro and in-vivo with CMC-Na as a carrier. Murthy et al [28] successfully formulated transdermal films of terbutaline sulphate using hydroxy propyl methylcellulose as a matrix for evaluation of pharmacokinetic and pharmacodynamic parameters in rabbits

**Liposomes:** Liposomes are fatty droplets made artificially in the laboratory by the addition of water solution to a phospholipid gel. Liposomes are long circulating macromolecular carriers that encapsulate active drugs to improve their delivery. The main mechanism of a liposome is simply fusing to the cell membrane or through endocytosis. [41] Currently approved liposomal drug delivery systems provide stable formulation, provide improved pharmacokinetics, and a degree of ‘passive’ or ‘physiological’ targeting to tumor tissue. Liposomal anthracyclines have achieved highly efficient drug encapsulation, resulting in significant anticancer activity with reduced cardiotoxicity. Mukhopadhyay et al [27] have developed conjugate of antineoplastic drug daunomycin with liposome as carrier. This study indicated that the drug was taken up with high efficiency by multi drug resistant murine macrophage tumor cell line. Pegylated liposomal doxorubicin has shown substantial efficacy in breast cancer treatment both as monotherapy and in combination with other chemotherapeutics. [35] These carriers do not directly target tumor cells. Additional liposome constructs are being developed for the delivery of other drugs. The next generation of delivery systems will 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 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). [31] Immunoliposomes also appear to be nonimmunogenic and capable of long circulation even with repeated administration. Anti-HER2 immunoliposomes are currently undergoing scale up for clinical studies. [27, 31]

**Nanodiamonds:** These are 2 nms in diameter in single particle form and can be manipulated to form clusters with diameters in the 50-100 nms range. This makes them ideal for drug delivery by shielding and slow releasing drugs trapped within the clusters. They provide large surface area and can trap nearly 5- times drug compared to conventional drug delivery method. Nanoparticles (including nanospheres and nanocapsules of size 10-200 nm) are in the solid state and are either amorphous or crystalline. They are able to adsorb and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation. Nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Nanoparticles as drug carriers can be formed from both biodegradable polymers [21] and non-biodegradable polymers. 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. [6, 39]

**Administration routes**
The choice of a delivery route is driven by patient acceptability, the properties of the drug (such as its solubility), access to a disease location, or effectiveness in dealing with the specific disease. The most important drug delivery route is the oral route. An increasing number of drugs are protein- and peptide-based. They offer the greatest potential for more effective therapeutics, but they do not easily cross mucosal surfaces and biological membranes; they are easily denatured or degraded, prone to rapid clearance in the liver and other body tissues and require precise dosing. At present, protein drugs are usually administered by injection, but this route is less pleasant and also poses problems of oscillating blood drug concentrations. Despite these barriers the oral route is still the most intensively investigated as it offers advantages of convenience and cheapness of administration, and potential manufacturing cost savings.
Inhalable Systems: Preservatives are commonly used in drug formulations and are well tolerated at low dosages. But for nasal spray delivery, they can be irritating to the patient mucosa causing itching and stops or slow down mucociliary clearance mechanism. Hence they are generally eliminated from nasal spray formulations. A specific multidose spraying device called preservative free systems (PFD) has been developed for intranasal delivery. Inhaled drug delivery is becoming quite popular as a drug delivery method today. In addition to treating simple ailments such as nasal congestion, the treatment and management of flu, pain, migraine, etc., is seeing increased acceptance with this delivery format. Also, the use of intranasal drug delivery for prophylactic vaccines is projected to grow significantly. New inhalers now have features such as dose counters and dosing feedback mechanisms that help assure the patient that they’ve received their medication. [7, 29]

Smoking therapeutic drugs: Therapeutic drugs can be smoked like cigarettes by staccato’s device such that the inhaled drugs in the form of aerosol hit the blood stream much quicker than with other techniques and effects thus seen within seconds. This device quickly vaporise a drug to form a small particle aerosol which can then be inhaled by the patient. The drug is then quickly absorbed through the lungs in the bloodstream. Aerosol drug delivery to the lungs has long been the route of choice for the treatment of respiratory diseases, including asthma and chronic obstructive airway disease. Metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers have been employed to successfully deliver a wide range of pharmaceuticals principally to the lungs for local action. [9, 26]

Microporation: With microporation, a small area of skin is covered by hundreds of needles that pierce only the stratum corneum. The microneedles are usually drug-coated projections of solid silicon or hollow drug-filled metal needles. Because the nerves located deeper in the skin are not stimulated, the patient does not experience pain or discomfort. Microneedles were first conceptualized for drug delivery many decades ago. They are manufactured in different forms based on their delivery mode. (i) solid microneedles for skin pre-treatment to increase skin permeability. They are delivered by poke with patch approach - Involves piercing the skin followed by application of the drug patch at the site of treatment. [2] (ii) microneedles coated with drug that dissolves off in the skin for which coat and poke approach- of delivery is used, [12] (iii) Biodegradable polymer microneedles that encapsulate drug and fully dissolve in the skin when inserted for delivery [18, 22] and (iv) hollow microneedles for drug infusion or injection into the skin. [25]

Microneedles have been used to deliver a broad range of different low molecular weight drugs, biotherapeutics and vaccines, including published human studies with a number of small-molecule and protein drugs and vaccines. Influenza vaccination using a hollow microneedle is in widespread clinical use and a number of solid microneedle products are sold for cosmetic purposes.[16, 46] Successful application of microneedles depends on device function that facilitates microneedle insertion and possible infusion into skin, skin recovery after microneedle removal, and drug stability during manufacturing, storage and delivery, and on patient outcomes, including lack of pain, skin irritation and skin infection, in addition to drug efficacy and safety. [3, 5, 19]

Iontophoresis: Iontophoresis involves transport of ionic (charged) molecule into a tissue by passage of a direct electric current through an electrolyte solution containing ionic molecule to be delivered using an appropriate electrode polarity. Typical currents range from 0.1–1.0 mA/cm². [10] It can be used for enhancement of transport of high molecular weight peptides and nonelectrolytes due to the indirect effect of electric current i.e. coupled flow of water (ion hydrokinesis). An electrode patch containing the drug is placed on the skin and acts as the working electrode, which can be either positive or negative depending upon the characteristics of the drug. Another electrode is placed elsewhere to complete the circuit. [13] While the electric field does provide a driving force, delivery is primarily by passive diffusion through the long-lived pores due to the short duration of the pulses (typically milliseconds). Iontophoresis enhances both the rate of release and the extent of penetration of the salt forms of the drugs across the skin. Iontophoresis, has a negligible effect on skin architecture at short treatment times. This is because of the low-voltage nature of the applied electric current. [47]

Nanda et al [31] showed that iontophoresis caused a significant increase in transdermal permeation of propranolol hydrochloride in vitro through skin. Bhat et al [4] prepared betamethasone dipropionate ointment and studied the effect of permeation enhancers such as surfactants, iontophoresis and sonophoresis using rat skin. It was seen that in vivo sonophoresis and iontophoresis enhanced permeation through rat skin. Kigasawa et al demonstrated that small interfering RNA (siRNA) was efficiently delivered into rat epidermis by iontophoresis. [17]

Electroporation: Electroporation uses electricity, to disrupt cellular membranes. Electric pulses of hundreds of volts, lasting for 10 μs-10 ms, are typical and result in the formation of aqueous pores in the lipid bilayers of the stratum corneum, as well as in the reversible disruption of cell membranes. [8]
The electronic patch injector system have been designed, which can deliver a large dose over an extended period of time, simplifies administration by automating processes and equipment, and can move drug infusion therapies from hospital-based to home-based settings. They offer significant benefits through the inclusion of electronic systems to control dose rate, volume and also provide feedback to help compliance. These injectable devices not only result in ease-of-use for the patient or administrator, but also potentially help manufacturers conserve costly drug product. [37] Eriksson et al [11] have tested safety, clinical efficacy and immunogenicity of a DNA vaccine coding for rhesus prostate specific antigen (PSA) delivered by intradermal injection and skin electroporation. No systemic toxicity was observed. This work showed that intradermal vaccination with skin electroporation can be easily performed with only minor discomfort for the patient.

Medicated tattoos: The temporary tattoos popular with children and young adults has been modified to contain active drug for transdermal delivery. A patch of tattoo is loaded with drug and usually applied on the skin to transport a specific dose of medication across the skin and into the blood circulation. [14] The adhesive serves two functions: It is glue in nature that keeps the patch adhered to the skin, and it acts as the suspension that holds the drug. The problems associated with this is the concentration of the drug within the adhesive directly affects the “stickiness” of the adhesive so if the large quantities of drug is to be administered, either the size of the patch have to be increased or the patch needs to be reapplied again and again. Several pharmaceuticals usually combined with substances, like alcohol, within the patch to improve its penetration via skin in order to improve absorption. They are also applied to clean dry skin in the same manner. [43]

Med-Tats is a modification of temporary tattoo which contains an active drug substance for transdermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms but provides no control of drug release rates. There is no predetermined duration of Med-tats. Instead the manufacturer provides a colour chart that can be compared to the colour of the patient’s tattoo to determine whether the tattoo should be removed. [43]

Sonophoresis: Ultrasound, especially in the frequencies between 20 to 100 KHz, [24] has shown to significantly increase the permeability of skin for facilitating transdermal drug delivery. Ultrasound induced cavitation leads to the formation of localized regions of high permeability. Skin could either be permeabilized with short application of ultrasound before the application of drug or drug and ultrasound could be applied simultaneously to the skin. Some parameters including frequency, intensity, function cycle and application time, can be adjusted to achieve a safe reversible breach in the skin. [4, 23]

The SonoPrep R device uses low frequency ultrasound (55 kHz) for an average duration of 15s to enhance skin permeability. This battery operated handheld device consists of a control unit, ultrasonic horn with control panel a disposable coupling medium cartridge, and a return electrode. The ability of the SonoPrep device to reduce the time of onset of action associated with the dermal delivery of local anaesthetic. The use of other small, lightweight novel ultrasound transducers to enhance the in vitro skin transport of insulin has also been reported by a range of workers. [24, 32]

Smart drugs: Also known as pro-drugs. These compounds works only when activated by certain components in the body. Eg: Specific enzyme and hence will be activated only in tissues that produces the specific enzymes. [45] Photolumination, a technique that uses light to turn a pro-drug into an active pharmaceutical drug via a photochemical reaction. It precisely controls the timing and the amount of drug formed as the process begins when light falls on the compounds and lasts only as long as the light continues to shine. Hence can be effectively used to target drug delivery thereby reducing side effects. A prodrug of paclitaxel which has a coumarin derivative conjugated to the amino acid moiety of isotaxel has been synthesized by Skwarczynski et al in 2006. [42] The prodrug was selectively converted to isotaxel by visible light irradiation (430 nm) with the cleavage of coumarin.

Dental implants: Dental delivery systems today are used in two ways: the main application is the local treatment of diseases affecting the oral cavity itself like periodontitis or fungal infections. The second is for systemic drug delivery. A dental prosthesis is introduced into two fake molars. Saliva enters the reservoir via a membrane, dissolves part of the solid drug and flows through a small duct into the mouth cavity, where it is absorbed by the mucous membrane in the patient’s cheek. Out of the two sensors, one measures the volume of liquid that enters the mouth while the other measures the concentration of medication in the liquid. This method is helpful for chronically ill patients suffering from dementia or drug addicts. [40]

CONCLUSION

The need for research into drug delivery systems extends beyond ways to administer new pharmaceutical therapies; the safety and efficacy of current treatments may be improved if their delivery rate, biodegradation, and site-specific targeting can be predicted, monitored, and controlled. From both a financial and a global health care perspective, finding ways to administer injectable-only medications in oral form and delivering costly, multiple-dose, long-term therapies in inexpensive,
potent, and time-releasing or self-triggering formulations are also needed. The promise of administration methods that allow patients to safely treat themselves is as significant as any other health care development, particularly in developing countries where doctors, clean syringes, sterile needles, and sophisticated treatments are few and far between.

With the recent advances, it has been found that oral types will remain the largest drug delivery category while parenteral, inhalation and implantable systems will grow the fastest. And eventually, parenteral formulations will surpass oral dosages due to changes in the market trends in the type of molecules that are being discovered and commercialized. Additionally, self-administered injectable devices are gaining in popularity especially for chronic diseases. Inhaled drug delivery systems are expanding to accommodate everything from pain medications to autoimmune disease targets and vaccines. Alternatively excipients, which can be used in conjunction with novel pharmaceutical combination devices or via different routes of administration, are being researched to avoid discarding promising compounds that can’t be delivered effectively.

In future, smarter and more novel delivery systems are being developed. For example, a controlled release microchip that houses, and delivers on demand, many different drugs (e.g., “pharmacy on a chip”) has recently been developed by Richards-Grayson et al. 2003 and Santini et al. 1999. [36, 38] These systems can potentially be preprogrammed or externally regulated to release drugs at any time, pattern, and rate. Such a system might one day enable novel combination therapies.

REFERENCES
22. Lee K, Lee CY, Jung H. Dissolving microneedles for transdermal drug administration prepared by


31. 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.


35. Reichert JM. Antibody-Based Therapeutics to Watch in 2011. MAbs. 2011; doi:10.4161/mabs.3.1.13895


