Overview of Drug Delivery Systems : a weapon against disease [Review]

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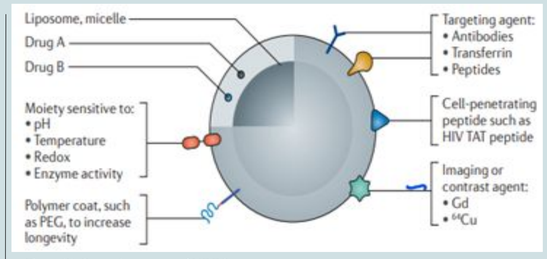
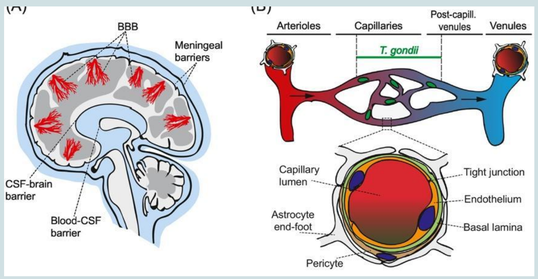
Nanoparticle

NDDSs (Nanoparticle drug delivery system) is common drug delivery system using in-vivo drug holding nanoparticles. General structure of NDDSs contains: nanocarriers, polymer coat to increase longevity, targeting agent, stimuli-responsive moiety, imaging or contrast agent, and cell penetrating peptides.(Figure(1)) NDDSs can overcome several problems that are associated with traditional drugs, such as poor aqueous solubility, low bioavailability, the extent a substance or drug becomes completely available to its intended biological destination(s), and nonspecific distribution in the body. The general process and main factors of NDDS is: (1)Drug storage (2)Longevity (3)Targeting (4)Drug releasing (5)Penetrating (6)Degradation. Especially first four are the most important factors.

Various nanoparticles, such as : liposomes; polymeric nanoparticles; polymeric micelles; silica, gold, silver and other metal nanoparticles are used as nanocarriers. Longevity is increased adsorption of plasma protein should be hindered. To do so, hydrophilic and flexible polymers are coated on the nanocarriers usually. There are 2 types of targeting: Passive targeting and active targeting. Passive targeting NDDSs tend to accumulate in tumours, probably through the EPR effect basis. In active targeting NDDSs, specific moieties attached to nanoparticulate pharmaceutical drug delivery systems force them to interact with a specific type of cell or tissue. The most important part of NDDS is how to release the drug. Drug releasing is executed in two ways: Exogenous, which drug is inside the NDDS and comes out due to the stimuli, and Endogenous, which drug is on outer layer of NDDS and activated by the stimuli.



Figure(1) General structure of NDDS



Figure(2) Schematic representation of blood-brain barrier

The blood-brain barrier (BBB) is the term that refers to the continuous nonfenestrated vessels of the central nervous system (CNS) that regulates the movement of molecules, ions, and cells between the blood and the CNS (Figure 2.). The tight capillary in the BBB is made from endothelial cells (ECs), pericytes, astrocytes, tight junctions (TJs), neurons, and basal membrane. The BBB can be disrupted due to various physiological conditions of diseases, including stroke, diabetes, seizures, hypertensive encephalopathy, acquired immunodeficiency syndrome, traumatic brain injuries, multiple sclerosis, Parkinson's disease (PD) and Alzheimer's disease (AD), and the disrupted BBB often becomes highly permeable. As a restricting barrier, it maintains the CNS homeostasis and prevents harmful substances such as pathogens and toxins from entering the CNS, as well as protects the CNS from diseases and inflammation. Thus, while it is an obstacle for the nanoparticles that aim to enter the CNS, a healthy brain's blood-brain barrier serves as a critical tool for proper neuronal function.

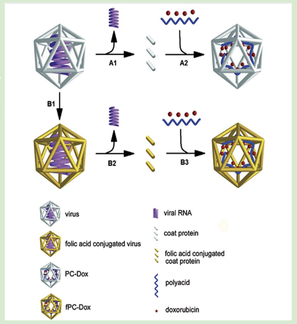
Green Nanoparticles refers to nanoparticles or nanomaterials obtained by combining biotechnology and nanotechnology using biological pathways or products such as proteins and lipids of living organisms (plants, microorganisms, viruses, etc.). They have the advantage of reducing the use of expensive chemicals, consuming less energy during production, and producing eco-friendly products than conventional physical and chemical technologies. The disadvantages of this technology include difficulty in obtaining raw materials, low yield, and long production time.

Natural Drug Delivery

NDD refers to transporting a therapeutic agent to a specific location and then releasing it at a specific speed using a delivery tool or carrier. It can be used to promote the transfer of small compounds as well as large molecules such as peptides, nucleic acids, polymers, and poorly soluble treatments. It can be obtained by extracting from various organisms such as plants, marine life, fungi, microorganisms, and invertebrates, and then concentrating, selecting, and refining them. NDD obtained in this way can be used to treat diabetes, cancer, neurodegenerative diseases, and infections.

Platelets, also known as thrombocytes, are cells that circulate within the blood that function in thrombosis and hemostasis in which they repair damaged blood vessels. They are known to play a major role in tumor cell proliferation by protecting the circulating tumor cells from physical obstacles including intravascular shear stress and helping them evade the host defense system. They also promote tumor extravasation and metastasis by allowing the tumor cells to migrate to secondary sites on the vascular wall, as well as facilitating tumor-related angiogenesis and growth by forming new blood vessels. Platelets can be used in the drug delivery system using their ability to secrete biologically active molecules in a soluble form or packaged into extracellular vesicles (EVs) upon activation, which can be delivered to different cells including cancer cells. Since the presence of the platelets in the microenvironment of different kinds of tumors has been confirmed, there has been considerable research done on the ability of the platelets loaded with anticancer drugs and their therapeutic effects.

Coating polyethylene glycol (PEG) to increase systematic circulation by stabilizing nanoparticles as well as protecting them from opsonization is the most well-understood method to create long-circulating nanoparticles. However, there have been several attempts to incorporate natural biomaterials into synthetic nanoparticles to make nature-inspired biomimetic delivery systems. This is the cell-membrane coating mechanism, also known as the "Trojan horse technology." The mechanism is about covering the nanoparticles that contain loaded drugs with the membranes of biological cells, including erythrocytes, mesenchymal stem cells, WBC, RBC, platelets, and cancer cells. The cell membrane-camouflaged nanoparticle achieves longer circulation, which allows sustained systemic delivery and improved targeting. To improve cell-specific targeting of the cell membrane-camouflaged nanoparticles, there have been studies on inserting lipids into the cell membranes, which is possible due to the fluid and dynamic nature of the membrane bilayers. In addition to this method, the cell membrane used to coat the nanoparticles can be utilized to have cell-specific binding.



Figure(3) Mechanism of loading doxorubicin chemotherapy into the protein cage alone (A1, A2) or simultaneously with the binding of the targeting agent (folic acid) to the protein cage (B1, B2, B3)

Robotics

Nowadays, not only images but also on-the-spot diagnosis and therapy is required, and various microrobots containing drugs and sometimes endoscopy are meeting such requirement. They have GI tract from the mouth to the anus by autonomic peristaltic movements (passive locomotion) as a pathway. Along with such pathway, microrobots should find the desired area and release the desired amount of drug accurately, and differently depending on the kind of therapy. Microrobots for drug delivery generally have two important factors: Releasing and Anchoring. Microrobot's releasing mechanism can be divided in two kinds: (1)Passive releasing, and (2)Active releasing. Their main difference is the availability of spontaneous monitoring through camera, can be related to diagnosis, and remote of activation based on it. In the passive releasing microrobots, the drug is exposed to the GI environment whenever an external trigger (e.g., pH or temperature). In the active releasing microrobots, the active expulsion of the drug is driven by the remote activation of the release mechanism. However, their trigger energy source and mechanism of drug release is almost same. To target an area of interest within the intestine, preventing rapid transit and allowing the capsule to be retrieved, and release drugs or implement the diagnosis, anchoring the microrobot to the area is necessary. String attachments or "leg"-based designs are the most used. They should be able to withstand the forces of peristalsis.

Respiratory drug delivery is a surprisingly complex process with a number of physical and biological challenges. Computational fluid dynamics (CFD) is a scientific simulation technique that is capable of providing spatially and temporally resolved predictions of many aspects related to respiratory drug delivery from initial aerosol formation through respiratory cellular drug absorption. The dynamic model and quantitative drug delivery model of the targeted drug delivery microrobot driven by the spiral jet structure are established, and the motion characteristics of the targeted drug delivery microrobot are simulated and analyzed by the method of Computational Fluid Dynamics (CFD)

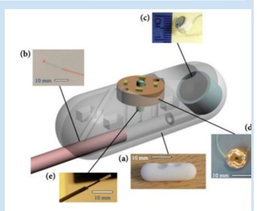
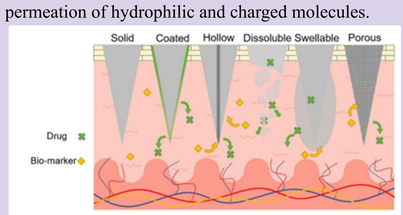


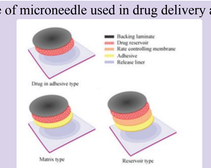
Figure (4) the form of typical active release microrobot platform.

In-vitro device

Iontophoresis is a method of administering drugs by applying a low voltage to non-invasive skin transmission technology. Macromolecular drugs have fewer side effects, high specificity, and high endogenous target binding affinity. However, these drugs do not pass through the epithelium well due to their large molecular size and high polarity and are very likely to be inactivated in the digestive tract by various digestive enzymes. Existing methods (such as parenteral administration/intra-vacuum or subcutaneous injection) had side effects, and non-invasive pathways are being studied to solve them. Iontophoresis relies on a low level of electrical action for transdermal drug delivery to promote skin permeation of hydrophilic and charged molecules.



Figure(5) 6 type of microneedle used in drug delivery and biosensing.



Figure(6) 4 types of transdermal patch

The most general methods of in-vitro drug delivery is done through the skin, whether it is invasive or non-invasive. In invasive way, there are hypodermic needle and microneedle(MN). In non-invasive way, there are topical cream and transdermal patch methods. These drug delivery systems through skin usually bypass the stratum corneum (SC) and immune cells of epidermis layer (especially the stratum spinosum, an epidermal layer), and be absorbed to dermis layer which many blood capillaries are located. The most important and potential drug delivery system among them is MN and transdermal patch.

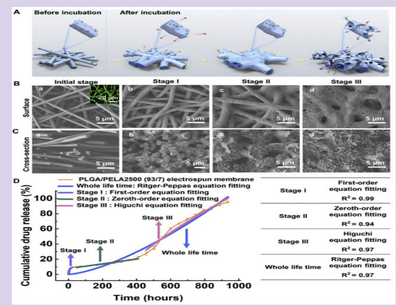
Microneedles (MNs) are micron-sized needles, on a solid support, with needle heights ranging between 25 and 2000 μm. These needles can pierce the SC and create microconduits, following insertion into the skin. MNs can be cylindrical, triangular, pointed, pentagonal, octagonal and are available in many more shape. MN can be sorted in 6 types: solid, coated, hollow, dissolving, hydrogel-forming(a.k.a swellable), and porous. (Figure(5))

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a time released dose of medication systemically for treating illnesses. Transdermal patch also utilize the fickian diffusion of drug as topical cream, which means it follows the Fick's law. Basic components of transdermal drug delivery systems are: Polymer matrix, the drug, permeation enhancers, adhesives, and backing membrane. There are 4 types of transdermal patch. Adhesive type has drug inside the adhesive layer. Matrix type has drug inside the polymer matrix. Reservoir type has the drug inside the rate controlling membrane. Lastly there is micro reservoir type which has both properties of reservoir and matrix type. (Figure(6))

The ultrasonic drug delivery is based on the enhancement of the therapeutic effect via the interaction between ultrasound and ultrasound-responsive materials, such as liposomes or microbubbles. As for designing the ultrasound-responsive materials, it is important to aim for a high therapeutic index (TI). TI is calculated as the drug dose that produces toxicity in 50% of the population divided by the minimum dose that is effective for 50% of the population. Thus, the drug's effectiveness in therapy increases proportionally with the dose required for toxicity and disproportionately with the dose required to take effect for half of the population.

The release of the drug cargo occurs with the ultrasound triggers, and the primary effect is pressure variation. The interaction of ultrasound with cells and tissues causes periodic pressure oscillations, and this simultaneous contracting and expanding from compression and refraction cycles from the ultrasound waves is the factor that facilitates drug release. The amplitude and frequency of the passing acoustic waves, as well as the size and material used to make the carrier determines the type of cavitation. The intensity of the ultrasound waves is understood via its mechanical index (MI), which is calculated by dividing the in situ peak negative pressure (PnP) by the center frequency (Fc). Additionally, there are four different types of mechanisms of cavitation-based ultrasound therapies: (a) acoustic streaming, (b) sonochemistry, (c) shock waves, and (d) liquid microjets.

Among all the alternatives, nanofibers produced with biodegradable and biocompatible polymers gained increasing interest due to their broad flexibility, effectiveness, and the unique physiochemical properties such as a large surface area, small diameter, and high aspect ratio. Also, targeted in situ application of nanofibrous scaffolds could minimize the disadvantages of systemic perfusion with the free drug or other drug delivery systems, and on the other hand maximize drug action pharmaceutical by a controlled and sustained release directly at the site of action. Another great advantage is given by the similarity of the fibers with the natural fibrillary extracellular matrix (ECM), which facilitates cell attachment and proliferation for biomedical applications. During the years, electrospinning proved to be one of the most cost-effective, simple and flexible fabrication techniques for the production of poly-mer nanofibers.



Figure(7) 3 stages of release kinetics