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Editorial

On-Demand (Smart) Drug Delivery Systems

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All the recent advances in the pharmaceutical and drug delivery science aim to deliver the right therapeutic dose to the right target with the right amount at the right time. This requires development of specifically designed drug delivery systems. One of the most recent drug delivery systems (DDS) is on-demand or smart systems which are systems directly controlled by an operator/practitioner, perhaps with a remote device triggering/affecting the implanted or injected drug carrier. Controlled drug release from these systems is achieved through accurate trigger control, either the trigger is external or internal. There are many different triggers or stimuli used, either alone or in combination, in smart drug-delivery systems including temperature, pH, light, electric field, magnetic field and ultrasound.

Temperature-triggered smart drug delivery systems

Temperature can be internal stimulus, such as temperature gradient between tumor and healthy surrounding tissue, or external stimulus by application of artificial heat on specific tissue for hyperthermia induction using infrared light, microwaves, hot water bath, ultrasound, or radiofrequency, depending on the location of the tissue. After its application, heat can be applied locally to stimulate drug release from the thermo-sensitive particles and also to increases the permeability of the heated tissue and cells, promoting intracellular uptake of drug or particle-drug conjugates. Thermo-responsive hydrogels are the most studied examples of these systems. Drug release profile from these hydrogels depends on the alteration in the polymer hydration states with change in temperature due to change in the hydrogen bonds strength between the water molecules and the functional groups attached to the polymer. The recent developments are interested in loading these hydrogels with biologically active solutes such as proteins, genes and heparin. Rysmon® TG is a temperature responsive eye drop for the treatment of glaucoma based on methylcellulose (MC) polymer. ThermoDox® is used for breast cancer and primary liver cancer using lysolipid thermally sensitive Liposome.

PH- triggered smart drug delivery systems

pH- responsive hydrogels are a cross-linked network of hydrophilic polymers with ionic pendant groups having the ability to absorb large amounts of water and swell, while maintaining their three-dimensional (3D) structure. They control the drug release through the ionizable groups which develop fixed charges on the polymer network, generating electrostatic repulsive forces responsible for pH-dependent swelling or de-swelling of the hydrogel thus any small change in the pH will result in corresponding change in the drug release due to change in the mesh size of the polymeric networks. Physiological pH change is known to occur in various sites of the body such as the gastrointestinal tract, rectum, vagina and blood vessels. Most commonly studied ionic polymers for pH-responsive behavior include poly(acrylamide) (PAAm), poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), etc. Moraxen™ which is Once-daily rectal slow release product of morphine sulfate used in end-stage cancer pain is a pH-sensitive formulated hydrogel. Another example is Cervidil® vaginal insert based on Poly(ethyleneoxide) and urethane containing 10 mg dinoprostone used for initiation and/or continuation of cervical ripening.

Light-triggered smart drug delivery systems

These systems depend on using biocompatible material attached to photosensitive functional groups such as derivatives of azobenzene and nitrobenzene which can absorb electromagnetic radiation especially in ultraviolet (UV), visible and near infrared (NIR) light causing structural damage and release of the loaded drug. They are designed either for single drug release due to irreversible structural damage or for pulsatile release by applying alternating light/dark cycles causing irreversible structural damage. Gold nanomaterials can absorb light of different wavelengths depending on their shape, so they are nowadays extensively studied by scientists. Visudyne® is a liposomal formulation containing verteporfin, a photosensitizer, for the treatment of choroidal neo-

vascularization, presumed ocular histoplasmosis and pathologic myopia. It is intravenously administrated and a cold laser is used to release the encapsulated verteporfin.

Magneto- triggered smart drug delivery systems

These systems are made by incorporating inorganic materials such as iron, cobalt and nickel which can cause local hyperthermia or create magnetic guidance after applying an extraneous magnet field on the DDS. This magnetic field causes the drug to be released and pulled to the target site. Practically, these systems haven't been yet widely applied as they require strong magnetic gradient as soon as the drug is released from the magnetic carrier with irregular pharmacokinetics and pharmacodynamics of the drug which hinders accurate distribution of the drug and may cause some systemic toxicity.

Electro-triggered drug delivery systems

They are designed by application and removal of an electrical field which controls the drug release through control of the magnitude of the electric current, the interval between pulses and direction of the current flow. Polyelectrolytes, polymers with ionizable functional groups attached to its backbone chain, are used to develop electro-responsive hydrogels. When these hydrogels are subjected to an electric field, they bend or de-swell releasing the drug. Driving the charged molecules across the cell membrane can be achieved by application of electrical potential gradient through non-invasive technique (Iontophoresis). EyeGate® II is an electro-responsive DDS used to deliver EGP - 437 for treatment of anterior uveitis, dry eye syndrome, macular edema and to control post- cataract surgery inflammation using iontophoresis technique.

Ultrasound-triggered smart delivery systems

Ultrasound can trigger and control the release of the encapsulated drug from the carrier by regulating its tissue penetration. This can be done through control of duty cycles, power density, frequency, and time of exposure of the applied ultrasound. Ultrasound is often used to enhance and facilitate drug permeation through biological barriers such as blood vessels and skin. SonoPrep® is a low frequency ultrasonic skin permeation device used to apply a low frequency ultrasound to the skin through the liquid coupling medium forming reversible micro-channels in the skin through which drugs, such as lidocaine, can be delivered or interstitial fluids can be extracted for diagnostic purposes such as glucose monitoring.

Although some of these techniques are well-established and utilized, extensive researches and efforts are required to enhance development of programmed delivery systems which may be the life- rescuer for chronic disease patients [1,2].

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