REVIEW ARTICLE
Department of Pharmaceutics

Gourab et.al / UJPSR / 2 (2), 2016, 36-41
e ISSN: 2454-3764
Print ISSN: 2454-3756

DOI: 10.21276/UJPSR.2016.02.02.46

AN OVERVIEW ON SMART DRUG DELIVERY SYSTEM

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ARTICLE INFO:
Article history:
Received:
16 August 2016
Received in revised form:
25 September 2016
Accepted: 09 October 2016
Available online: 10 November 2016

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Abstract

In recent years, nanomaterials and nanotechnology have been applied in the medical field such as in disease diagnosis and therapy. Smart Drug Delivery Systems (SDDS) have emerged as panacea for many clinically useful drugs weighed down with toxicity. Integration of responsive materials into implantable depots, targetable nanocarriers and even insert able medical devices can endow them with activation-modulated and feedback-regulated control of drug release. This review offers a critical overview of therapeutically-interesting stimuli to trigger drug release and the evolution of responsive materials suitable as functional excipients, illustrated with recent examples of formulations in clinical trials or already commercially available, which can provide a perspective on the current state of the art on smart drug delivery systems.

Key words
Smart drug delivery system, pH responsive,
Smart polymeric material, Stimuli

INTRODUCTION

New material could automatically deliver medication inside your body. Smart drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. This means of delivery is largely founded on nanomedicine, which plans to employ nanoparticles-mediated drug delivery in order to combat the downfalls of conventional drug delivery. These nanoparticles would be loaded with drugs and targeted to specific parts of the body where there is solely diseased tissue, thereby avoiding interaction with healthy tissue. The goal of a targeted drug delivery system is to prolong, localize, target and have a protected drug interaction with the diseased tissue. The conventional drug delivery system is the absorption of the drug across a biological membrane, whereas the targeted release system releases the drug in a dosage form. The advantages to the targeted release system is the reduction in the frequency of the dosages taken by the patient, having a more uniform effect of the drug, reduction of drug side-effects, and reduced fluctuation in circulating drug levels. The disadvantage of the system is high cost, which makes productivity more difficult and the reduced ability to adjust the dosages **[1]**. A smart system is one that can alter its property in response to environmental changes. For example, a chameleon displays smartness in changing its skin colour to blend with the environment so as to escape from predators. In the case of water birds, the smartness to stay afloat in a water environment is provided by an oily coating on their feathers that confer them with buoyancy. In the biological system, each cell type is programmed to exhibit different levels of smartness. The cells of the immune system are programmed to migrate to specific locations depending on the concentration of specific chemical molecules known as cytokines. Likewise, the amount of glucose in the blood determines the amount of insulin produced by the beta cells in the islets of Langerhans. Thus, Nature offers a plethora of examples that display different levels of smartness both in the macroscopic level as well as in the microscopic level **[2]**.

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NEED FOR A 'SMART' DRUG DELIVERY SYSTEM [2]

An ideal drug delivery system needs to perform multiple functions, which requires the highest degree of smartness. Some of the major requisites of a drug delivery system are:

- Improve solubility and stability of the drug/payload.
- Reduce the dosage as well as the frequency of dosage.
- Reduce/eliminate adverse effects due to the drug.
- The carrier should be non-toxic to the biological system.
- Should not trigger adverse immune responses.
- Should be able to deliver the required amount of drug to the desired location over long period of time.

pH-responsive systems [2]

The pH responsive gels have the tendency to get protonated or deprotonated based on the pH. This alters the attractive forces between the individual polymer chains in the gel leading to modifications in the swelling behavior. Poly(acrylic acid), poly(methacrylic acid) and alginate gels exhibit maximum swelling in the alkaline pH while gels of chitosan, poly(L-lysine), poly(vinyl pyridine), poly(2-diisopropylaminoethyl methacrylate) etc. display acid dependent swelling. In their charged states, the neighbouring polymer chains experience repulsive forces. To offset this repulsion, counter-ions from the medium enter the gel matrix bringing along with them water molecules resulting in swelling of the gel. This phenomenon has been exploited well for bringing about controlled drug release in treatment of disorders especially of the gastrointestinal system.

Table 1: pH of different biological tissues and cellular components

Cellular compartment/ Tissue	pH range
Stomach	1.0-3.0
Early endosome	6.0
Late endosome	5.0
Lysosome	4.5
Golgi body	6.4
Extracellular medium of tumour	6.5-7.2
Duodenum	4.8-8.2
Colon	7.0-7.5
Blood	7.3-7.5

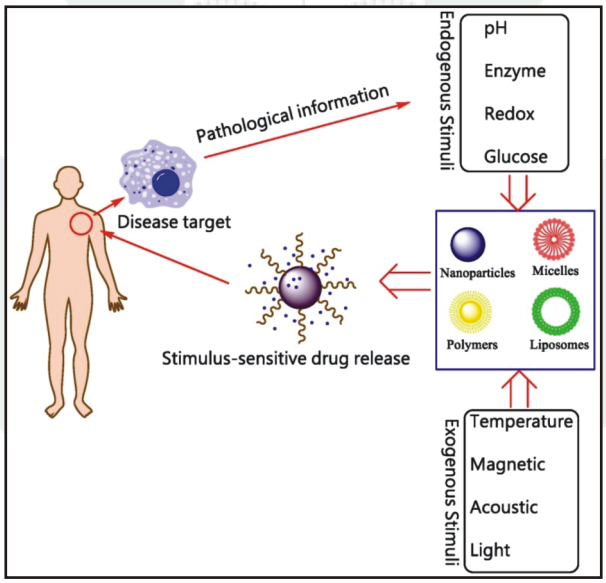

Fig.1: Schematic illustration for stimuli-responsive DDSs

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Redox-responsive [8]

Redox responsive stimuli have gained great attention for disease therapy and widely used in intracellular DDS. The redox potential in microenvironments is multivariate in different tissues, which can be exploited to design redox-sensitive delivery systems. The design and fabrication of nanoparticles responsive to Glutathione (GSH) can be a promising approach for targeting drug delivery. The GSH reduction is a well-known redox system within cancer cells. On one hand, concentrations of GSH in blood and normal extracellular matrices are reported to be 2-20 μM, at the same time GSH levels within cancer cell ranges from 2 to 10 mM, which is 100 to 500 fold higher than the normal ranges. Such significant difference in GSH level between cancer and normal cell has made redox responsive delivery systems to be an attractive strategy to design the DDSs for targeting specific tumor intracellular sites. On the other hand, by utilizing the high accumulation of reactive oxygen species (ROS) in some disease tissues, ROS-response DDS is also an effective mechanism to finely control the targeted drug release. It has been reported the mucosal ROS concentrations in inflammatory tissues and colon cancer were 10 to 100 fold higher than that of normal tissues. The exciting specificity and accuracy have been shown by the developed redox stimuli-responsive DDSs, however, it is difficult to achieve the specific redox molecular mechanism based controllability due to the complex biological environment and hetereogeniety of tumor cells.

Enzyme-responsive [8]

Enzymes used as triggers in the design of smart DDSs have been an emerging field in recent years owing to its unique superiorities, such as substrate specificity and high selectivity under mild conditions. Since enzymes (such as glycosidases, lipase, phospoholipases or proteases) are related to almost all the biological and metabolic process, they can be exploited to achieve enzyme-mediated drug release by the bio-catalytic action at the cancer or inflammation tissues. A major challenge in enzyme-responsive DDSs is to precisely control the initial response time of the systems.

Temperature-responsive [8]

Temperature is one of the most convenient and effective factors to control the drug release compared with other stimuli. Normally, pathophysiological conditions, such as inflammation and tumors, have higher temperatures than normal tissues. Considering the temperature difference between cancer tissues and normal tissues, functionalized nanoparticles can be triggered to enhance their drug release in tumors. Another temperature-responsive strategy is that the tumor site could be heated by external triggers (US, magnetic field, *etc.*) to improve the drug release within the tumor vasculature. In general, thermo-sensitive nanocarriers are designed to retain their payloads around the physiological temperature of 37°C, and release the payloads rapidly when temperature is increased higher than 40-45°C. Towards the thermo-responsive nanoplatforms, the current challenge is to maintain the safety of the platforms without sacrificing their sensitivity to slight temperature changes.

Light, magnetic, and US responsive [8]

Light-responsive systems represent a way to trigger drug release at the desired target by external light illumination. Photo sensitive carriers can achieve the on-off drug release event because the nanostructure may open or close when stimulated by either a one-time or repeatable light irradiation. However, considering the limitation of light wavelength for practical therapy, light penetration depth currently restrains the non-invasive applications for deep tissues. Magnetic stimuli may provide a non-invasive approach to temporally and spatially control of the carriers to the targets and release drugs under programmable exposure of external magnetic field. For example, the most commonly used core/shell magnetic nanoparticles (MNPs) exhibit a variety of unique magnetic properties. The large surface to volume ratio of MNPs provides abundant active sites for biomolecule conjugation, thus allowing precise design and engineering in order to gain their intended smart functions by applying a localized external magnetic field, such as long lasting circulation in the blood stream, target specificity to lesion tissues, and therapeutic delivery. Furthermore, when these nano-scaled MNPs were encapsulated in colloidal carriers, such as micelles, liposomes, or solid nanoparticles, the composite structures might become sensitive to an external magnetic field to realize multifunctional formulations for

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both diagnostic and therapeutic purposes. Recently, US has been extensively used in clinics for diagnosis and therapy due to its intrinsic tissue penetration and high safety. The development of ultrasonic sensitive nanocarriers for ultrasonography expands US techniques to be a unique and effective method to capture drug carriers and trigger drug release at the desired sites by tuning the US frequency, duty cycles and time of exposure.

Other responsive systems [8]

Apart from the above mentioned stimuli for smart DDSs, glucose and electro-responsive systems have also been employed to control the release of payloads within nanocarriers. Moreover, sensitivity to hybrid stimulus can further improve drug delivery accuracy. Dual stimuliresponsive DDSs are most common systems and have been investigated, such as thermo and pH responsive systems, thermo and light responsive systems, redox- and pH responsive systems, ultrasonic and magnetic responsive systems. In order to realize the smart characteristic of DDSs, a wide range of stimuli that are able to trigger the drug release at target place and expected time has been assembled in various nano-architectures. To ascertain the viability of these strategies, evidence for regulation of the response to each stimulus would be needed both *in vitro* and *in vivo*. In this review, we mainly discuss smart nanoplatforms with the most promising clinical potential in the application of stimuli-responsive DDSs. Smart DDSs for controlled drug release (*e.g.*, polymers, liposome, organic-inorganic hybrid biomaterials and exosomes) are discussed. Although smart nanoplatforms can be widely used in several diseased, such as neoplastic diseases, diabetes, infections, cardiovascular diseases and inflammatory diseases, this review is mainly focused on carcinoma diseases for the future clinical translation of smart DDSs.

ADVANCES IN SMART DRUG DELIVERY SYSTEM

SDDS refers to intelligent approaches in formulations technologies, focused on transporting an API from its dosage form to the target site as per the drug safety norms to achieve its intended therapeutic action in the body **[3]**. By taking into consideration both quantity and span of drug residency, it tries to provide logical site-targeting within the system along with facilitation of systemic pharmacokinetics. Conventional drug delivery, in contrast, is not only approached with API chemical modification, such as prodrug, but it also encompasses medical devices or drug-device combination products. These conventional drug delivery systems have been facing failures in precise and effective therapeutic delivery of dosage form with suitable route of administration **[4]**. The modification of the drug release profile, absorption, distribution, and elimination by the drug delivery technologies helps in facilitating not only the product safety and effectiveness but in turn also leads to patient suitability and compliance. The drug release from these systems mainly takes place by diffusion, degradation, swelling, and affinity based mechanisms **[5]**. The noninvasive per oral, topical, transmucosal (nasal, buccal/sublingual, vaginal, ocular, and rectal) and inhalation routes are the most preferred routes of administration utilized by SDDS **[6]**. There are in general, many medications such as peptide and protein, antibody, vaccine, and gene based drugs that cannot be delivered using these routes because of the drug's vulnerability to enzymatic degradation and low bioavailability problems due to molecular size and charge disputes. Therefore many protein and peptide drugs have to be administered by injection or a nano needle array. For example, many immunizations are based on the delivery of protein drugs and are often done by injection. Current efforts in the spectrum of drug delivery involve the upgradation of targeted delivery, which delivers the drug only to the target area of the body (e.g., in cancerous tissues) and to provide sustained or controlled release of drug from the formulations over a period of time to provide effective therapy in patients. In order to achieve proficient targeted delivery, the designed system mustbe capable of escaping the host's defense mechanisms and reach its anticipated site of action **[7]**.

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Table 2: Application of smart polymeric materials in drug delivery systems

Smart polymeric material	Stimuli	Induced transitions	Applications in drug delivery systems
Poly (N-isopropyl acrylamide)	Temperature	Water soluble coils to water insoluble globules followed by subsequent collapse of polymer or precipitation from solution or adsorption/desorption	Intelligent carriers in a diverse range of applications including thermo sensitive doxorubicin magnetic nanoparticles and in separations.
Hydroxy propyl cellulose		Hydrated swollen state to dehydrated shrunken state	Size-exclusion chromatography
Poly (acrylic acid) Poly (N,N'-dimethyl amino ethyl methacrylate)	pH	Compact unionized state to swollen ionized state	Colon specific drug delivery. Specifically for delivery of anticancer drugs for treating colon cancer.Drug delivery in the stomach for treatment of peptic ulcers, stomach cancer, etc.
Poly (N-isopropyl acrylamide) hydrogels containing ferromagnetic material, Ethylene-co-vinyl acetate (EVAc)	Magnetic field	Reversible collapsing of the hydrogel under the influence of magnetic field	Polymer used in the treatment of intercellular hyperthermia. For insulin delivery
Polythiophene gel, Poly (2-hydroxyethyl methacrylate) (PHEMA)	Electric field	Swelling and de- swelling induced by electric field	Potential use as small-scale actuators and valves in micro-systems application. Administration of propranolol hydrochloride
Dodecyl isocyanate Poly (ethylene glycol) grafted poly (2-Hydroxy ethyl methacrylate)	Ultrasound	Disrupt the orderly chains on the surface of the drug-containing polymer	Controlled drug delivery in various chronic diseases
Poly (N-isopropyl acrylamide) with tri sodium salt of copper	Light	Reversible collapse of gel	Potential use as a photo-responsive artificial muscle or switch
Poly (acrylic acid) and poly (oxy propylene - co-oxy ethylene) glycol	Inflammation	Mucoadhesive liquid composition that undergoes sol –gel transformation at body temperature can be tailored for stimuli-responsive drug delivery.	Used for development of ophthalmic, buccal, nasal, vaginal, transdermal, injectable, implantable, and nonaerosol pulmonary drug delivery systems.
Ethylene-co-vinyl acetate (EVAc), Polypyrrole	Glucose	Detection of high glucose levels in the body by amperometric or potentiometric technique using glucose oxidase enzyme for substrate polymer crosslinking.	Insulin release due to high glucose concentration, i.e., in hyperglycemia as glucose biosensors.
Methyl vinyl ether-co-maleic anhydride	Morphine	Reversible collapsing of the hydrogel	Naltrexone
Poly (ethylene-co-vinyl acetate)	Antibody	Reversible collapsing of the hydrogel	Naltrexone, ethinyl estradiol drug delivery

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Polypyrrole	Urea	Amperometry, Potentiometry, Conductometry, Capacitance Measurement are the detection techniques in high urea levels using urease enzyme for substrate polymer crosslinking.	In treatment of Hyperuremia as urea biosensors
Polyaniline, Polypyrrole, Polyacetylene	Metal	Conducting polymers	Biosensors

CONCLUSION

This article represents introduction to the different types of smart stimuli responsive systems that are primarily developed for drug delivery applications. The reduction in costs can also be achieved due to minimization of doses in SDDS, hence rendering the medicines universally affordable. With the development of material science, pharmaceutical science and biomedical science, various controlled releasing nanomaterials will be used for smart DDSs in the future. Although smart nano-DDSs have shown to be much more efficient in both diagnosis and therapy, potential drug ability still needs to be evaluated before the smart DDSs reach to clinics.

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