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Review Article

A Review on Stimuli Responsive Drug Delivery Systems

Marela Harisri*, Dr. M. Sunitha Reddy, Dr. K. Anie Vijetha

Department of pharmaceutics, JNTUH University College of Engineering, Science and Technology Hyderabad, Kukatpally, Telangana-500085.

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ABSTRACT

The drug delivery systems which respond to the stimuli are the most advanced systems, helps in diagnosing the diseases and treating them. Different types of stimuli have unique mechanism of drug release, which provides the targeted and controlled release of drug. Different stimuli such as temperature, pH, enzymatic, light, ultrasound, magnetic, mechanical, electrical and redox stimuli help in the drug delivery at the targeted regions in the body. Especially used for cancer chemotherapy. Based on the environment around the diseased state the drug will get release, high temperature around the cancer cell leads to the drug release when the drug is incorporated in the temperature sensitive polymer. In the same way different polymers respond in different ways based on the stimuli. There are many applications of stimuli responsive drug delivery systems such as cancer chemotherapy, in the treatment of inflammatory diseases, arthritis, Alzheimer's disease and cardiac diseases. Also had wide scope in tissue engineering.

INTRODUCTION

Microparticles, nanoparticles, liposomes, niosomes, transferosomes, ethosomes are the advanced systems, used as drug delivery and disease diagnosing purposes. Has the highest impact on targeted drug delivery in the controlled manner, which helps to reduce the side effects and increases the therapeutic activity. microparticles include different types such as microcapsules, micromatrices, microspheres... etc (Rohit Yadav, 6 June 2024). there are different preparation techniques such as polymerization method, double emulsion technique, single emulsion technique, solvent evaporation technique, spray drying and spray congealing method, phase separation coacervation technique and solvent extraction method (Sunita Thakur, 2022). Nano particles are the particles which are having the size range from 1 – 100nm. There are different preparation techniques for nano particles such as, Top-down methods which include, ball milling, laser

***Corresponding Author:** Marela Harisri
Address: *Department of pharmaceutics, JNTUH University College of Engineering, Science and Technology Hyderabad, Kukatpally, Telangana-500085.*
Email ✉: harisri.marella@gmail.com

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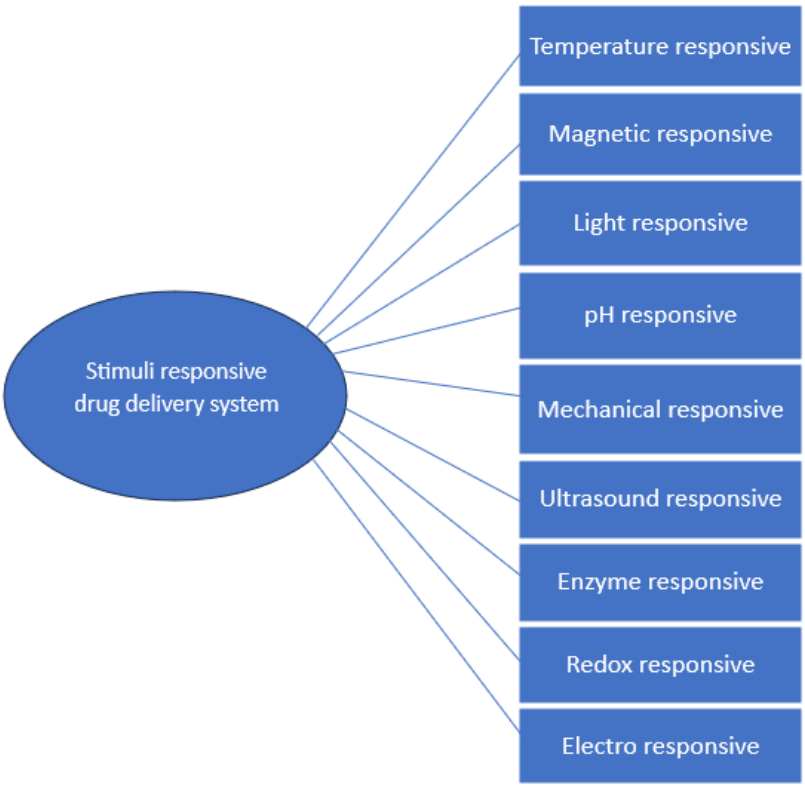
ablation, sputtering, electro explosion, etching, spark ablation. Bottom-up methods include chemical vapour deposition, molecular beam epitaxy, sol-gel processing atomic layer deposition, polymerization, precipitation, salting-out, electrodeposition and super critical fluid extraction (Bawoke Mekuye, 2023).Liposomes consist of phospholipid bilayers, there are different preparation methods of liposomes such as ethanol injection, reverse-phase evaporation, thin-film hydration, detergent removal method, microfluidization, sonication...etc. Niosomes are prepared through non-ionic surfactants and different preparation techniques are solvent evaporation, ether injection. Etc (Domenico Riccardi, 2024). Providing the stimuli either externally or internally leads the drug to reach the target. Various stimuli can be used for the drug delivery when the vehicle along with the drug shows the positive response in releasing the drug according to the stipulated conditions. Examples include, temperature, magnetic field, mechanical responsive, light, ultrasound, enzymes, pH, radiation, redox responsive…etc. Stimuli responsive mechanism is the advanced system which has the high utilization in chemotherapy, treatment and diagnosis of various diseases. The main objective of this article is to bring the various types of stimuli responsive drug delivery system under the same roof.



Temperature responsive drug delivery system:

The tumour cells have the different temperature when compared to the body temperature. Some tumours may have high temperature; some may have low and some others with both types. Some temperature sensitive polymers have the ability to deliver the drug at different temperatures. Low critical solution temperature (LCST) is the temperature below which there is high miscibility with in the compounds and above the LCST the compounds will lose the miscibility and starts to get separate. A temperature-sensitive polymer dissolves in water when the temperature is below its LCST (Lower critical solution temperature) due to the formation of hydrogen bonds between water molecules and the polymer's hydrophilic regions. Even the dosage form starts to swell with high miscibility at below LCST. When the polymer reaches the higher temperature around the tumour

or any other disease state i.e. above LCST the particle will lose the miscibility and get shrink to release/ expel the drug which is present in the particle. This happens as there is higher temperature which leads to the gradual diminution of hydrophilicity and the particle attains the hydrophobicity, phase transition takes place polymer changes its state from solution to gel like structure from where the drug releases in the controlled manner. (Muhammad Abdur Rahim, 2021). Upper critical solution temperature (UCST) is the temperature below which there will be low miscibility and the compounds will tend to separate and at above UCST miscibility increases. Mostly LCST Polymers plays a vital role in temperature sensitive drug delivery system.

Temperature sensitive polymers include: poly(N-isopropylacrylamide) (PNIPAM) (Mohammad javed ansari, 2022), Polyvinyl ethers, elastin-like polypeptides, polycaprolactone, cellulose, N-substituted acrylamide polymer, chitosan…etc. (Mohamadreza Amin, 2022) (Muhammad Abdur Rahim, 2021) (THAMARAI SELVAN DHANDAPANI, 26 Aug 2023)

Magnetic drug delivery system:

The particle size should be under nanometres, not exceed the limit because there is a chance of embolism of blood vessels. These particles preparation include magnetite, polymer, drug and other required solvents. Either in the form of suspension or solution these particles can be injectable through blood vessels, they travel from the blood vessels along with the blood and to reach the target tissue, external magnetic field is required. As the inner particle contains magnetite, when the externally magnetic field is provided at particular region then due to interactions the particle settle at the target region and the controlled drug release will occur. (Pranav sunil balgude, 2023), (Satinder Kakar, 2017)**.** For example, there is a co-precipitation technique to prepare the magnetite, in which iron salt solution is prepared first by dissolving Fecl3 and Fecl2 in deionized water in the presence of nitrogen gas to avoid oxidation of elements. Then the base should add drop wise with vigorous stirring, at around the pH 11 the magnetite will produce in the form of black coloured precipitated suspension (Hamidreza Mohammadi, 2021). There are various methods to prepare the magnetic Nanoparticles which include, chemical co-precipitation, thermal decomposition, microemulsion, hydrothermal, sonochemical and electrochemical methods. These magnetic microparticles have wide range use in the chemotherapy and diagnostic purposes such as Magnetic resonance image (MRI) scans (Kinga Mylkie, 2021).

Light sensitive drug delivery system:

There are some photo sensitive polymers when these polymers get expose to the light, they undergo some physical and chemical changes which eventually leads to the drug release. UV visible light has the low penetration capacity so this light can be use as stimuli for topical drug delivery system. For deep penetration in to the body near infrared light can be use as the stimuli. So that the particle along with the light sensitive polymer releases the drug based on the light exposure. (Valentina Marturano, 2016) There are some light absorbing particles, which absorbs the light and releases the encapsulated drug by the photocleavage activity, examples include titanium dioxide and silicone dioxide. (Chase S Linsley, 2017)

Mechanism of action includes photochemical reactions and photothermal mechanism.

Photochemical reactions include:

1. Photoisomerization: chemically the compounds change their isomerism, shape or configuration from one form to another form when it absorbs a photon of light, which leads to the drug release at desired condition and site. But without breaking any chemical bond.

Example: azobenzene changes its isomerism from trans to cis in the presence of UV light leads to the drug release (Shoko Kume, 2001).

2. Photocleavage: after the compound absorbs the light it will undergo through cleavage which is nothing but the breaking of chemical bonds which helps to release the drug. In some cases, the layer of the dosage form also may undergo degradation process.

3. Photo-induced cross linking: some polymers undergo crosslinking when exposed to the UV light due to the bond formation.

Example: when methacrylate and gelatine undergo through photo cross-linkage which is triggered by UV light and photo initiator leads to the formation of gelatine meth acryloyl. (Chase S Linsley, 2017), (Yanghui Xing, 16 December 2022)

Photothermal mechanism:

The near infrared light when it comes in contact with the light absorbers, absorption of light and conversion in to heat takes place, which leads to the degradation of polymer/shell and drug will get release. (Mi Zhang, 2022), (Chase S Linsley, 2017)

pH sensitive drug delivery system:

Different regions in the body have different pH environments like stomach is acidic, intestine has alkaline environment. There are different mechanisms of drug release from the pH sensitive dosage form such as due to change in the hydrophobicity, when it is exposed to the respective pH condition. Change in the charge of carrier molecules by deprotonation/protonation also leads to the drug release during the exposure. When the dosage form expose to the respective pH conditions the pH sensitive polymer may undergo cleavage of chemical bond to release the drug. The pH around the tumour cell will be different because there will be continuous growth of cells and even the availability of oxygen will be low. The polyacids will accept the protons. In basic conditions they undergo deprotonation and loses the proton to acquire the negative charge it leads to the repulsions which ultimately causes the swelling of the polymer to release the drug. Polybases will accept the protons at acidic conditions and acquire the positive charge which leads to the repulsions and swelling to release the drug. (Balamuralidhara Veeranna, 2011) (Shijie Zhuo, 2020)

Mechanical responsive drug delivery system:

There are different internal forces which helps in the drug release such as compression force, shear force and tension. The different tissues in the body will undergo through different forces like compression force by the bones and the stomach. Cardiovascular system consists of shear forces and muscle stretching include tension. When the dosage form with force responsive polymers, reach the condition containing the respective force, it will breakdown to release the drug.

Example: The microparticles with the PLGA polymer will release the drug when it reaches the high compression force. In tension responsive drug delivery systems, the pulling force plays a major role. Pulling force by the bones and muscles helps the polymer to produce the cracks to release the drug. Shear stress varies between healthy and pathological conditions. Shear stress is high in diseased blood vessels when it is compared with the healthy blood vessels. Based on the shear stress around the tissues drug will get release. (Panqin Ma, 2022)

Ultrasound responsive drug delivery system:

Internal electrical polarization will be produced by the piezoelectric materials such as quartz and ceramics, when the mechanical stress is applied. From the vibrations produced by the piezoelectric materials acoustic waves get generate ultrasound (above 20KHz). When a transducer converts the electrical signals in to vibrations through the medium two regions will produce low density (refraction) and high density (compression). At high density region pressure is more when compared to the lower density region. (Danqing Huang, 2023). Cavitation refers to the transformation of acoustic energy into other types of energy, like heat and mechanical force. There is a chance of generation of extreme temperature,

when it involves in formation and rapid collapse within a liquid. The ultrasound energy enters in to the bubble due to the high response and during the collapse, cavitation will provide the thermal and mechanical stimuli, through which the loaded drug will get release in to the system. (Muhammad Abdur Rahim, 2021) High intensity ultrasounds produce the undesirable side effects as well as it effects the biological system severely. So that using low intensity ultra sound is safer (Chase S Linsley, 2017). By incorporating the piezoelectric material in to the drug delivery systems such as microparticles, nanoparticles, liposomes….etc, with the drug and polymer leads to the production of ultrasound. (THAMARAI SELVAN DHANDAPANI, 26 Aug 2023) (Panqin Ma, 2022)

Enzyme responsive drug delivery system:

Based on the presence of particular enzymes around the diseased cells, enzyme responsive drug delivery system delivers the drug by responding to the stimuli(enzyme).

Example: This drug delivery system includes gold nanoparticles, quantum dots, polymer-based nanoparticles … etc. The drug reaches the target site when the enzyme triggers. There are various enzymes which trigger the dug releases such as oxidoreductases, proteases, phospholipases… etc. There are wide range of applications, such as in cancer chemotherapy, diagnostic purposes and anti-cancer treatment. (Quanyin Hu, 2014), (THAMARAI SELVAN DHANDAPANI, 26 Aug 2023)

Redox responsive drug delivery system:

The dosage forms which are made with redox responsive agents and loaded with the drug reaches the target site through the circulation of blood stream and the redox environment near the tumour/disease state will be different when compared around the normal healthy cells. The area containing the inflammation is rich in reactive oxygen species (ROS), so the dosage form will release the drug at that particular condition as ROS act as the stimuli. (Mi Zhang, 2022). The disulphide bonds, Di selenide bonds (Sonyabapu Yadav, 2023) and tetra sulphide bonds (Shiyi Zuo, 2024) will be intact during the Oxidizing environments but these bonds will cleave at high redox environments and due to the presence of reactive oxygen species such as hydrogen peroxides and super oxides and releases the drug. (Shiwei Fu, 2022).

Electro responsive drug delivery system:

Permeability of cell increases by electroshock therapy. This process depends on the electrical potential difference created by the applied field, which facilitates targeted drug release by creating a voltage gradient across the cell membrane. When an electric field is applied to the membrane, it affects properties such as polarity, ion concentration and pH, which in turn alters the osmotic pressure within polymers. These changes cause the polymer to swell, shrink, bend or break apart which leads to the release of the drug. This system is more advantageous because it is easy to apply, control, complex equipment is not required and can be easily integrated in to chip based devices. Example of electro-responsive material include carbon nanotubes. (THAMARAI SELVAN DHANDAPANI, 26 Aug 2023)

CONCLUSION:

The knowledge regarding various stimuli responsive drug delivery systems is briefly collected in this review article. These advanced stimuli drug delivery systems have wide scope in the future related to the treatment of various diseases. Each stimuli have unique mechanism to deliver the drug. These systems are also useful to deliver the drug in unconscious and bed ridden patients. Based on the different environmental conditions around the diseased area, the stimulation helps to release the drug. Most of the systems are under clinical trials to ensure the good therapeutic efficacy and safety, hope stimuli responsive drug delivery systems have versatile role to play in patient care.

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