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Stimuli-Responsive Drug Delivery System Based on SMP

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Abstract. In this paper, the research progress of stimulus-responsive application systems based on shape memory polymers (SMPs) is systematically reviewed. SMPs have shown great potential in the field of drug-controlled release due to their excellent biocompatibility, degradability and shape memory ability. With the continuous advancement of biomedical engineering and intelligent material science, SMP-based drug delivery systems have emerged as a promising strategy to achieve precise spatial and temporal control of drug release. These systems can respond to specific physiological or external stimuli, thereby improving therapeutic efficacy while minimizing side effects. This paper focuses on the design of SMP system under various stimuli-responsive mechanisms such as thermal response, enzyme response, magnetic response, light response and acoustic response, including multi-responsive fibers, electrospun membranes, balloons and other structural forms, and systematically evaluates its performance from the aspects of biocompatibility, drug release kinetics, on-demand release ability and physical properties. In addition, this paper also discusses the advantages and challenges of various response mechanisms, and puts forward prospects for the construction of multi-mode collaborative response systems, the promotion of animal and clinical experiments, and large-scale production in the future.

Keywords: Shape memory polymers, Enzyme-responsive materials, Stimuli-responsive materials

1. Introduction

The drug delivery system includes a combination of drug carriers, manufacturing techniques and pathways. Its role is to deliver therapeutic drugs to their target sites to achieve the desired therapeutic effect. An ideal drug delivery system ensures that the drug is effective within the required time, above the minimum effective concentration, below the maximum tolerable concentration, and does not have any adverse physiological effects on the surrounding tissue [1].

At present, more than 90 % of hospitalized patients are receiving some form of infusion therapy [2]. Although this method can recently transport drugs through the blood to the whole body, due to the limitations of this method, the uneven distribution of drugs and the lack of access to adequate drugs in the affected area are difficult to solve [3]. Furthermore, this method of administration may also lead to the delivery of drugs to healthy sites, leading to injury. At the same time, repeated infusion will also increase the risk of bacterial infection in patients, and better aseptic conditions are required all the time [4].

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Therefore, it is necessary to use a better and more intelligent drug-controlled release system. Among them, SMP stands out because of its good biocompatibility and biodegradability, and the ability to restore the original state under certain conditions.

At present, experts and scholars in various fields have proposed one novel and potential design scheme after another. This paper will focus on the introduction of various existing stimulus-responsive SMP application systems, compare their performance parameters, summarize their advantages, and analyze possible challenges and future.

2. Implementation strategy of programmability and controlled release ability

2.1. The theoretical basis of programmable controlled release

The SMP material itself has strong biocompatibility and shape memory ability, which gives the SMP material a certain degree of programmability. The design of the SMP material can make the resulting SMP drug-controlled release system have a certain degree of programmability. For example, Rokaya et al.studied a biodegradable amorphous polyester polyurethane SMP with a transition temperature of 54 °C in dry air and 36 °C in solvent. Therefore, when the implant is inserted into the body, it can open and release the drug without external stimulation [5].

On the other hand, the excellent physical properties of SMP also make it have good scalability. By carrying various response materials on the SMP substrate, the programmability and controlled release ability of the SMP drug-controlled release system can be enhanced. Whether it is to add a certain amount of thermogenic magnetic nanoparticles (mnps, γ-Fe_2O_3) to make a magnetic response system by using the magnetocaloric effect [6] [7], or to make a photoresponsive system by using the photothermal effect of polydopamine (PDA) [8], all reflect the scalability of SMP.

2.2. Design and introduction of five kinds of SMP materials

Multi-responsive SMP fiber is a shape memory polymer fiber material with poly (D, L-lactic acid) (PDLLA) as the substrate, poly (lactic-co-glycolic acid) (PLGA) as the membrane, and polydopamine (PDA) as the nano-coating. The interior of the fiber is designed with two channels for drug loading, and the surface is sealed by PLGA film. Its drug release behavior can be regulated by adjusting the composition ratio of PLGA and applying near-infrared light to the outside world, while causing fiber expansion and achieving shape fixation [8].

The electrospinning SMP fiber membrane application system was constructed by double electrospinning technology, which was based on polycaprolactone (PCL) and polyurethane elastomer (Pellethanol). PCL was used as the shape stationary phase and Pellethanol was used as the shape memory phase. The system can be degraded or structurally changed under the action of lipases (such as $HepG_2$), so as to achieve on-demand application and enzyme response [9, 10].

The SMP balloon system uses a biodegradable PCL cross-linked network as a shape memory matrix to load anticancer drug doxorubicin (DOX) and magnetic nanoparticles (MNPs). Under the action of an external magnetic field, a response occurs inside the system, causing the balloon to expand and release the drug [7].

The magnetically responsive SMP system uses three different types of SMP substrates and loads MNPs. An SMP material can be used as a substrate or a composite of two SMP materials with different response characteristics. The system can achieve diverse deformation and release behaviors through a single or differentiated material combination [6].

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The sonothermal SMP system is based on a thermally responsive shape memory polymer design. It can induce local thermal effects through directional ultrasound (FU), which in turn triggers material phase transition and drug release, with ultrasonic/thermal dual response capabilities [11].

2.3. Performance evaluation of materials fabricated by this type of strategy

2.3.1. Biocompatibility

As shown in Table 1, materials such as multi-responsive SMP fibers and electrospun SMP fibers showed high cell viability (usually > 75 %) when co-cultured with human dermal fibroblasts, NIH / 3T3 cells, etc. After some materials were treated with PDA coating or enzyme triggering, the cell activity could still be maintained at a high level. In addition, no obvious inflammatory response was observed in the simulated in vivo environment, which indicated that the SMP application system had good biocompatibility.

Table 1. Biocompatibility comparison [6-11]

Name	Testing methods	Cell type	Results
Multi-responsive SMP fiber	Calcein-AM / PI live / dead staining CCK-8Cell Proliferation	Human dermal fibroblasts (HDF)	>88% survival rate (5days)after PDA coating >90% (72h)
The electrospinning SMP fiber	Live / Dead coloring Indirect contact test	NIH/3T3 fibroblasts	>90% survival rate (7days)After the enzyme triggers >85%
The SMP balloon	Live/Deadcoloring	Human osteosarcoma cells (HOS)	>75% survival rate (7days)
The magnetically responsive SMP	Resazurin method	NIH/3T3 fibroblasts	> 75 % survival rate (72h)
The sonothermal SMP	In vitro simulation (pig femur model)	Vascular endothelial cells (indirect evidence)	No inflammatory reaction

2.3.2. Application kinetics

As shown in Table 2, this table compares the drug sustained and controlled release properties of various SMP drug-loaded systems. The results showed that different types of SMP systems could achieve effective loading and controlled release of DOX, curcumin and other model drugs. In particular, multi-responsive SMP fibers exhibit an ultra-long release period of up to 6 months and a very low cumulative release rate (< 20 %), while external stimulation regulation systems such as magnetic response, can achieve precise switching of drug release rate. These excellent sustained and controlled release properties indicate that SMP materials have broad application prospects in the field of advanced drug delivery to achieve long-term, on-demand administration.

Table 2. Pesticide kinetics comparison table [6-11]

Name	Testing drugs	Realizing	Releasing rate
Multi-responsive SMP fiber	DOX,curcumin(Cur)	6months	<20%
The electrospinning SMP fiber	DOX	7days	<5%
The SMP balloon	DOX	90days	Accumulation of 30 % in the first month

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Table 2. (continued)

The magnetically responsive SMP	DOX, 6-mercaptopurine (6-MP)	72h	Strain sample : very low Strainless sample : hydrophilic drug ~ 60 %
The sonothermal SMP	Stimulated drugs	6h	<5%

2.3.3. On-demand release capacity.

Table 3 compares the stimulus response performance of five different SMP application systems. The table shows that various systems can respond to various stimulation signals such as light, enzyme, magnetism, and sound, and exhibit different sensitivity and specificity. For example, multi-responsive SMP fibers have light / enzyme dual response characteristics, while SMP balloons and magnetic response systems mainly respond to magnetic fields. These diverse stimuli-responsive properties provide an important material basis for precise and controllable drug delivery in different physiological environments.

Table 3. Comparison of system on-demand release capacity [6-11]

Name	Stimulus response type	Sensitivity	Specificity	highlight
Multi-responsive SMP fiber	Light/ enzyme response	Power density : 1.5 W / cm 2 Response time : 17s	Sustained release in response to enzyme stimulation Responding to light stimulation for burst release	Different proportions of PLGA can be used to achieve programming purposes.
The electrospinning SMP fiber	lipase	Gradient response characteristics, the minimum concentration remained at 0.1 mg / ml. Response time : 7 days and below	Specific response to regions with high lipase concentration	Only response where the lipase is high enough
The SMP balloon	Magnetic / thermal response	ΔT≥10℃ trigger	Deformation in response to magnetic field	The expansion rate is up to 400 % and is almost thought to respond only to magnetic signals.
The magnetically responsive SMP	Magnetic / thermal response	ΔT: from 0 to 7℃ electric field intensity threshold: 0.5 mT	Deformation in response to magnetic field	Magnetic response, good specificity ; optional three SMP matrix, good programmability
The sonothermal SMP	Ultrasonic /thermal response	power threshold: 0.5 W/cm² response time:20s	Deformation in response to FU	FU signal has good directivity and strong controllability.

2.3.4. Physical property

Table 4 shows the physical properties of different systems, and most of the materials show excellent shape fixation rate and shape recovery rate. In addition, the degradation cycles of different devices are significantly different, ranging from 28 days to more than 6 months. Some systems (such as multi-responsive SMP fibers can change the degradation cycle by adjusting the ratio of PLGA; the

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electrospun SMP fiber can adjust the degradation cycle by adjusting the fiber orientation. The degradation cycle is also adjustable. These results show that the physical properties of SMP devices can be freely programmed through material and structural design to meet the needs of different medical application scenarios.

Table 4. Comparison of physical characteristics [6-11]

Name	Shape fixation rate (Rf)	Shape recovery rate (Rr)	degradable period
Multi-responsive SMP fiber	98.7%	99.9%	6months(adjustable)
The electrospinning SMP fiber	>93%	>85%	28days(adjustable)
The SMP balloon	99.9%	85.3%	>180days
The magnetically responsive SMP	>75%	>75%	>180days
The sonothermal SMP	none	90%	None

3. The mechanism of typical SMP materials with various response mechanisms

3.1. Response principle of materials

The on-demand drug release system achieves drug-controlled release through a variety of response mechanisms. Some materials have large Trans differences after water activation, so they can undergo sexual changes to release drugs after water activation in vivo. In addition, some materials can be specifically degraded by enzymes, or the part of the system responsible for controlled release can be degraded, thereby releasing the drug into the body fluid. At the same time, the magnetocaloric effect can also be used, such as mnps in the alternating magnetic field due to the magnetic moment in the direction of the magnetic moment constantly reverse heat generation, so that the system reaches Trans to release the drug.

The intelligent drug delivery system achieves precise controlled release through a variety of stimulus response mechanisms. Some materials have significant differences in Ttrans before and after water absorption, so they can deform after water activation in vivo to release drugs. In addition, some of the materials themselves can be specifically degraded by specific enzymes, or the part responsible for controlled release in the system can be degraded by enzymes, so that the drug-loaded site is exposed to the solvent, and the drug automatically diffuses into the body fluid. At the same time, the use of magnetocaloric effects, such as in an alternating magnetic field, the magnetic moment direction of the magnetic nanoparticles repeatedly flips with the magnetic field, overcoming the magnetocrystalline anisotropy to do work and generate heat, or friction in the fluid to generate heat, resulting in controlled-release partial degradation or deformation for application. In addition, with the help of photothermal effects such as PDA particles, the relevant structures can be partially degraded or deformed. Finally, some materials have the characteristics of absorbing acoustic energy. When focused ultrasound is used, the heat production of the material causes the local temperature to rise to Ttrans, thereby triggering deformation and releasing the drug. These mechanisms together provide an efficient and controllable drug delivery strategy for biomedical applications.

3.2. Advantages of stimulus-responsive SMP system

SMP stimuli-responsive drug delivery system has excellent biocompatibility, signal response ability and programmability, and has significant advantages in the field of drug delivery. First of all, the biocompatibility of the system is generally 75 %, and some systems can reach more than 90 %.

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Secondly, by selecting a reasonable load, the system can be given the ability to specifically respond to signals, so that the drug can be better released on demand. Finally, due to the programmability of the SMP material itself, the unified drug loading platform can load and regulate the release of 2 or more drugs, which has the ability of multi-drug synergistic treatment, can improve the efficiency of drug application and expand the potential of clinical application.

3.3. Possible challenges of the stimulus response mechanism

In the study of drug delivery systems for on-demand release, although systems based on various response mechanisms have shown good potential, there are still many problems to be solved. The transport effect of the enzyme response mechanism is extremely dependent on the local enzyme concentration of the individual, and the enzyme concentration in different individuals is significantly different, which may lead to slow or even completely insensitive drug release. In this response mechanism, the heat generated by the magnetocaloric effect lacks specificity and may affect surrounding healthy but cells and tissues. The light response mechanism has high requirements for equipment and individual conditions due to the insufficient penetration depth of light waves in biological tissues, and similar to magnetic response, the photothermal effect is not specific, which will cause damage to surrounding cells and tissues. The acoustic response mechanism relies on the targeted focusing of ultrasound, which puts forward the postgraduate entrance examination for the accuracy and power of the equipment, so it is difficult to apply in practice. The thermal response mechanism is difficult to ensure the specificity of drug release because its Trans needs to be designed close to body temperature, and its potential for on-demand application is lower than other mechanisms. These challenges indicate that there are still many areas for research improvement in the stimuli-responsive SMP application system.

In order to solve the above challenges, on the one hand, we can choose to build a multi-responsive intelligent application system and develop a multi-mode collaborative response system (such as light-magnetic, ultrasound-enzyme combination) to overcome their limitations. For example, magnetic field is used to solve the problem of insufficient light penetration depth, or ultrasonic local heating is used to accelerate the enzyme reaction rate. On the other hand, it can also solve the problems of individual differences and complex production through large-scale, standardized production and personalized production.

4. Conclusion

It is found that SMP materials bring new possibilities for drug controlled release : through molecular design and structural engineering, the designed SMP application system can accurately respond to external stimuli, and meet the requirements of on-demand release from three dimensions of time, space and drug type.

Specifically, first of all, the types of stimuli are diverse, including heat, enzymes, magnetism, light, and even ultrasound, which transcends the limitations of traditional drug carriers that rely on passive diffusion or can only respond to a single stimulus.

Secondly, the design of the material has a strong diversity and programmability, for example, by adjusting the crosslinking of the fiber membrane, the decomposition rate can be adjusted.

Finally, all studies showed good biocompatibility, which laid a solid foundation for subsequent clinical trials.

In a word, the stimulus-responsive SMP application system has a good prospect. Through the cooperation of experts in various fields, these application systems are expected to open a new

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chapter for the treatment of many diseases.

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