

Introduction to smart drug delivery system

Module objective

The module presents an introduction to the different types of smart stimuli responsive systems that are primarily developed for drug delivery applications. At the end of the module, the learner will be able to appreciate the importance of the selection of materials and suitable chemical modifications that impart stimuli responsiveness to the system.

Preface

“Being inexhaustible, life and nature are a constant stimulus for a creative mind”, said Hans Hofmann. The way Nature responds and adapts to different stimuli has been the source of inspiration for the development of a whole new class of smart systems that have been explored for intelligent drug delivery systems. This module gives an insight into the different types of environmental responsive drug delivery systems that have been developed in recent times. Future trends in the development of next generation of smart therapeutics have also been discussed in the final section of this module.

This lecture aims to introduce the concept of smartness in the context of drug delivery and discusses on the salient features of pH responsive nanogel systems.

1 What is a ‘smart’ system?

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.

Mimicking these concepts of smartness in the context of clinically relevant therapeutic and diagnostic systems can herald in a new era of ‘smart’ therapeutics that can improve the healthcare by leaps and bounds. Nano-dimensional systems already offer the basic level of smartness in that they can enter cells as well as cell organelles. Further modifications can enable them to overcome biological barriers and display environment-

driven response and functions. The response can be manifested in the form of change in shape, solubility, mobility, localization, swelling characteristics, interactions with molecules etc. Such responsiveness can be harnessed for therapeutic and diagnostic applications.

2 Need for a ‘smart’ drug delivery system

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*

The final aspect represents the most challenging quality for a drug delivery system that warrants highest level of smartness. While delivering the drug at the desired location requires surface modification with a suitable targeting moiety that will enable the carrier to bind to cells of interest, delivery of required amount of drug necessitates incorporation of a trigger that will control the amount of drug released at a given instant. The trigger could either be a stimulus provided externally (extrinsic triggers) or could be due to the internal environment of the system in which the drug delivery system is introduced (internal triggers). Examples of extrinsic triggers include electric field, magnetic field, ultrasound, electromagnetic radiation or temperature that could be used to turn on or off the drug release from the carrier while internal triggers include pH, temperature, ionic environment, proteins, carbohydrates etc.

How do these stimuli trigger release of the drug/payload from the delivery system? Obviously the stimulus should induce conformational changes or alter the packing characteristics or influence the associative forces between the carrier and drug molecule resulting in the release of the drug molecule from the carrier or contribute to its retention within the carrier matrix. How can we achieve this response to stimuli? Well, Mother Nature provides us with the inspiration! Consider the conduction of a nerve impulse in response to an external stimulus – say pressure due to touch. The stimulus causes release of chemical messengers called as neurotransmitters that bind to the nerve cell, which in turn causes a redistribution of ions on either side of the cell membrane. This changes the potential of the cell, which is now different from that of the neighbouring cell. This difference in potential, if above a certain threshold value known as action potential

induces the redistribution of ions in the neighbouring cell. This process now repeats between the neighbouring cell and its adjacent cell resulting in transmission of signal. In this case, we find that the mechanical stimulus (pressure due to touch) had altered the charge distribution in the cells and the transmission of the signal is driven by the potential gradient developed between the cells owing to this charge redistribution. The key factor here is the charge gradient or ionic gradient. Similarly, examples of concentration gradients and structural gradients resulting in a particular response are also available in the biological systems.

Thus, in order to develop a stimuli-responsive system, one needs to mimic the biological system by introducing various gradients, which then can be orchestrated to produce a desired change in the system in response to the stimulus. However, introducing such gradients or minute phase transformations in a material is a huge challenge and concerted efforts have been directed in developing such systems. Polymeric materials, especially hydrogels have been the most widely investigated systems for stimuli response and the following sections describe some of the classic examples of internal and extrinsic trigger stimulated systems. As most of the stimuli response occurs at the surface, nano-dimensional systems with a high surface area to volume ratio provide ample scope for rapid response to a stimulus. Figure 1 depicts a few types of stimuli-responsive systems that have been investigated for drug delivery applications.

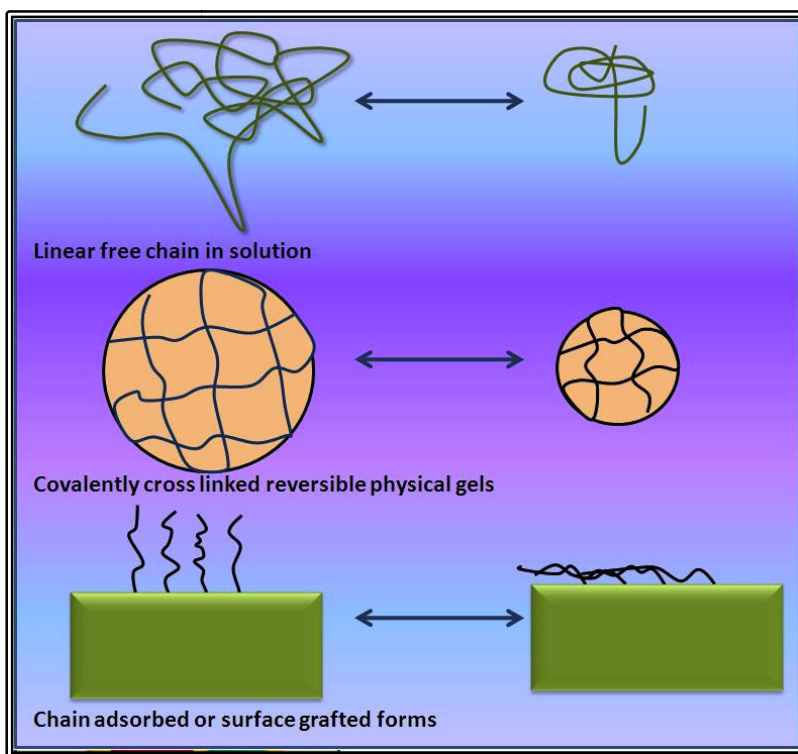


Fig. 1: Different categories of stimuli responsive polymer systems

Generally, three categories of polymeric systems can be employed for exhibiting stimuli-responsiveness. These are:

- a) Linear polymeric chains
- b) Cross-linked gels
- c) Surface grafted systems

The linear polymeric chains can undergo reversible solubility changes depending on the stimulus. These changes primarily arise due to alterations in their hydrophobicity and hydrophilicity. When such systems are introduced in an aqueous medium, if the stimulus induces an increase in the hydrophilic interactions, the polymer swells. On the contrary, if the stimulus promotes the shift to greater hydrophobicity, the polymer chains collapse and precipitate out of the solution.

The cross-linked gels (both covalently cross-linked or physically cross-linked) exhibit rapid response to even small changes in the stimulus. However, caution should be exercised in tightly regulating the extent of cross-linking as over-crosslinking will lead to loss in the swelling and deswelling property.

In the case of the grafted polymer chain systems, the swelling or deswelling can contribute to a change in the hydrophilicity or hydrophobicity of the substrate. Such phenomenon depends on the changes produced at the interface between the polymer chains and the environment and is now referred to as '*interfacial engineering*'.

3 pH-responsive systems

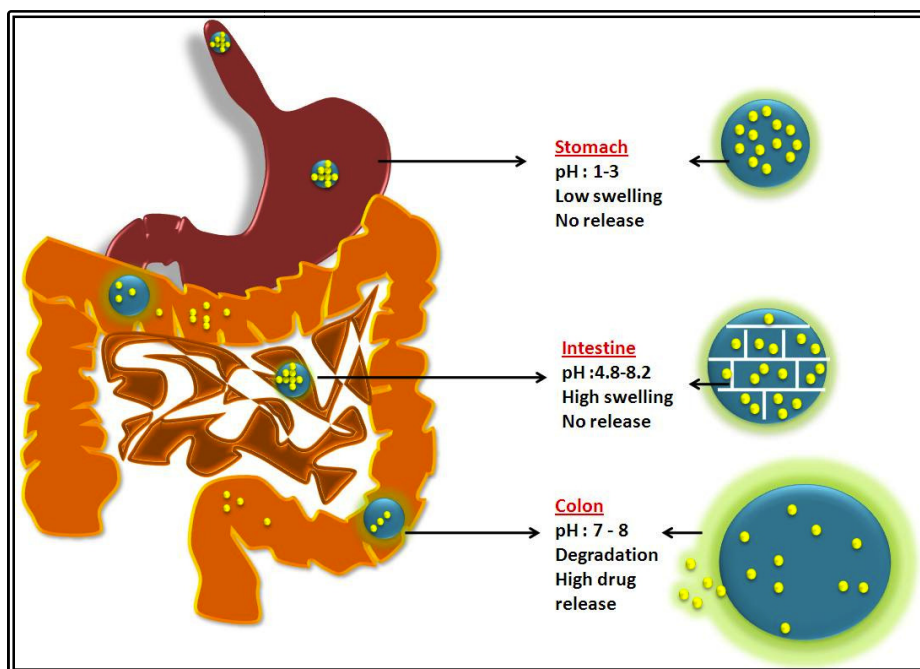
The pH responsive gels have the tendency to get protonated or deprotonated based on the pH. This alters the attractive forces between the individual polymer chains in the gel leading to modifications in the swelling behavior. Poly(acrylic acid), poly(methacrylic acid) and alginate gels exhibit maximum 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.

The biological system has many regions that have a distinct pH that can be used to design pH responsive systems for specific pH stimulated release in desired locations. Table 1 highlights the different pH found in the biological systems.

Table 1: pH of different biological tissues and cellular components

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

Let us consider an example of a pH responsive nanogel system that can release the drugs specifically in the colon. The polymer system consists of a copolymer of acrylic acid, N,N' dimethyl acrylamide, and t-butyl acrylamide. This polymer was cross-linked using N,N'-diaminocaprolydiaminoazobenzene. The polymer nanogels formed were loaded with the desired drug that has to be specifically delivered to the colon. As the nanoparticles are administered through the oral route, they encounter different pH zones. Figure 2 depicts a cartoon indicating the response of the hydrogel system as it passes through various pH in the gastrointestinal tract.

**Fig. 2: Response of the hydrogel carrier as it passes through zones of different pH in the gastrointestinal tract**

In the stomach, the nanogels exhibit minimal swelling as the acrylic acid moieties remain protonated and uncharged in the highly acidic pH. However, when they reach the small intestine, they encounter a higher pH(4.8-8.2) that causes deprotonation of the carboxylic groups. As a result, the negative carboxylate groups tend to attract an influx of water molecules as well as counter-ions from the surrounding medium resulting in swelling of the gel. However, as the azobenzene cross-links still exist, the quantity of drug released is still small. As the nanogel particles move into the colon, they remain swollen due to the mildly alkaline pH. This provides access to the azoreductase enzyme secreted by the intestinal bacteria that reside in the colon. This enzyme breaks the azoaromatic crosslinks in the gel causing the release of the drugs in the colon.

Now, let us consider yet another system whose pH responsiveness does not pertain to delivery of drugs. Another interesting demonstration of property changes in a substrate reversibly. Instead, its pH responsiveness can lead to changes in the hydrophilicity of a substrate reversibly. This property can have exciting applications in many biomedical applications. Figure 3 shows a schematic representation of such a system.

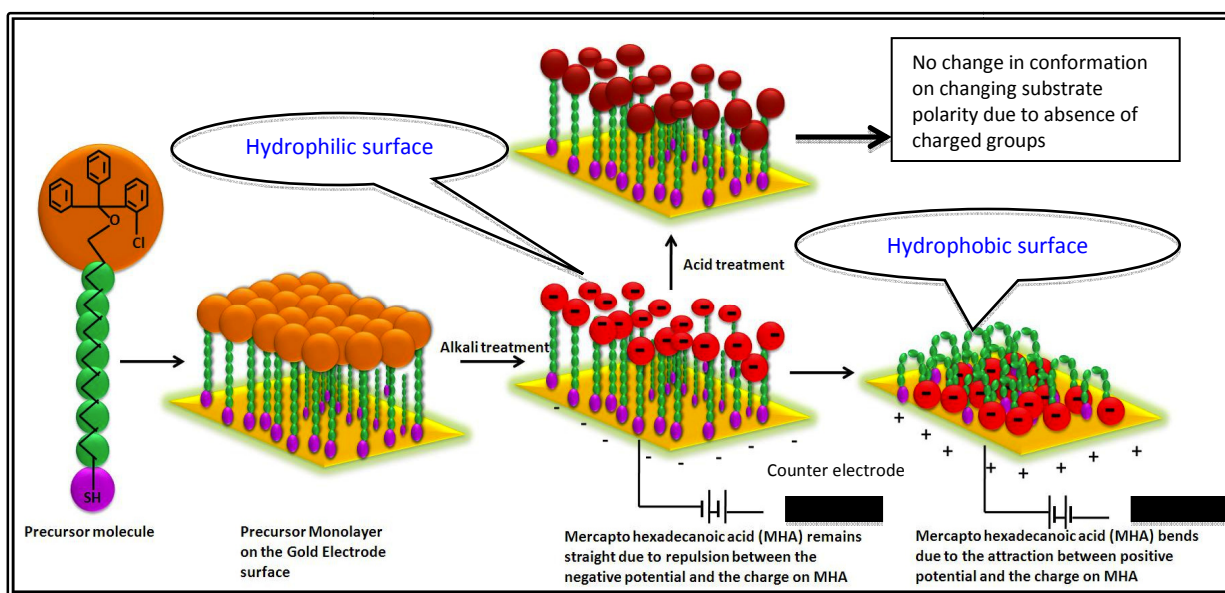


Fig. 3: Schematic representation of a pH responsive system that alters its hydrophilicity

A polymer with a long acyl chain containing a sulphhydryl group (-SH) at one terminus and a head group containing an ester bond is added to a gold substrate. Due to the affinity between gold and the sulphhydryl group, the polymer is covalently linked to the surface through Au-S bonds. Now on addition of a base, the ester groups at the surface of the polymers get hydrolysed followed by the deprotonation of the resulting carboxylic acid group. This confers a negative charge to the end of the polymer chains causing them to move apart from each other. If a negative potential is applied to the gold electrode, the negatively charged end groups remain facing away from the gold surface. On the other hand, if the gold electrode is given a positive potential, the chains bend towards the gold

surface due to electrostatic attraction. Such transitions can be exploited to alternate between a hydrophilic surface (when the polymer chains are facing away from the substrate with charged carboxylate groups) and a hydrophobic surface (when the chains are bend on the surface exposing the methylene backbone). Interestingly apart from the electric field applied, the pH of the environment will also play a role in determining the charges on the terminal groups. At acidic pH, such bending is not observed, as the carboxylate groups become protonated.

4 Reference

Smart Nanoparticles in Nanomedicine (The MML series, Vol. 8), Editors: Reza Arshady& Kenji Kono, Kentus Books, 2006

5 Additional reading

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2. Future perspectives and recent advances in stimuli-responsive materials, Debashish Roy, Jennifer N. Cambre, Brent S. Sumerlin, Progress in Polymer Science, 35 (2010), 278-301
3. Recent advances and challenges in designing stimuli-responsive polymers, Fang Liu, Marek W. Urban, Progress in Polymer Science, 35 (2010), 3-23

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