Various patterning techniques involved iin the fabrication of responsive system

This lecture discusses about photo-responsive systems, hybrid nanogel systems and molecular imprinting.

1 Photo-responsive system

Photo-responsive polymers exhibit responsive swelling when exposed to electromagnetic radiation. The duration of irradiation, the intensity and energy of the radiation determine the transformation. The photo-responsive groups are introduced as grafts or as part of the main chain of the polymer forming the nanogel. Exposure to a specific wavelength causes a transformation in the hydrophobicity or hydrophilicity of these domains containing the photo-responsive groups resulting in influx or efflux of water molecules. As the electromagnetic radiation is a non-invasive source, the photo-responsive polymers have been extensively investigated for various applications that include photo-stimulated release of drugs, photo-stimulated *in situ* gels for tissue engineering, photo-inducible switching of protein activity, photomechanical transducers and actuators etc. Let us explore a few examples of photo-responsive release strategies that have been developed.

A copolymer containing poly(ethylene oxide) blocks with poly(methacrylate) chains modified with pyrenylmethyl chromophoric moieties in the side chain was developed. The poly(ethylene oxide) block imparted hydrophilic nature while the pyrenylmethyl group modified poly(methacrylate) block was hydrophobic due to the chromophore in the side chain. This amphipathic copolymer when introduced into an aqueous medium self-assembled into micellar structures. On irradiation with ultraviolet light, the pyrenylmethyl side group was cleaved from the polymer by a reaction known as photosolvolysis. This causes the methacrylate domains to lose their hydrophobicity. As a result of this, the polymer loses its amphipathic nature causing the disruption of the micellar structure. Figure 1 shows the UV-induced change in the structure of pyrenylmethyl chromophoric system.

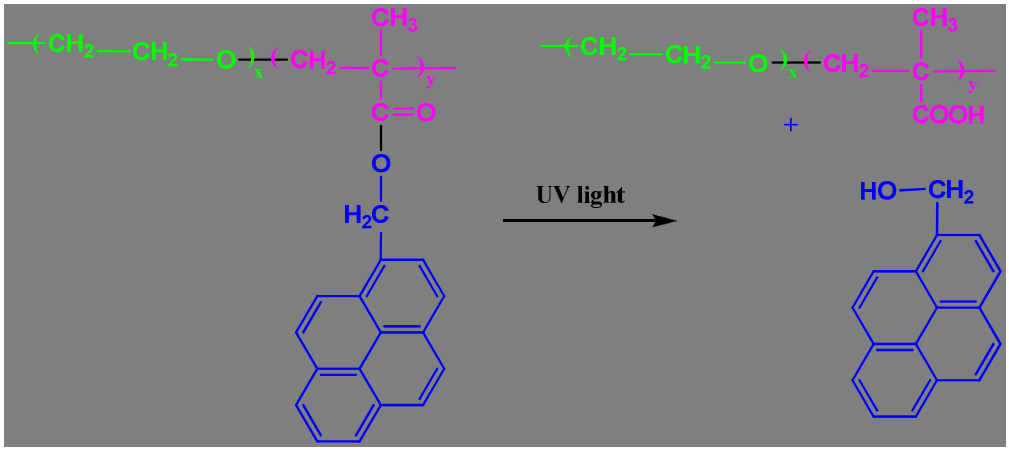

Fig. 1: Photosolvolysis of pyrenylmethyl chromophoric system

The above reaction occurs only in presence of nucleophilic solvents like water and alcohol. Substitution of the pyrenylmethyl group modified poly(methacrylate) with poly(2-nitrobenzyl methacrylate) facilitates the photochemical reaction to occur both in solution as well as in solid state. This strategy was successfully demonstrated for photo-mediated release of the magnetic contrast agent based on gadolinium. However, since ultraviolet radiation is a potential health hazard, use of lower energy radiation, especially in the infrared region will be preferable. Infrared responsiveness can be incorporated by introducing 2-diazo-1,2-naphthoquinone units, which on exposure to infrared radiation dissociate to form hydrophilic 3-indenecarboxylate moieties.

Another well-explored strategy is photo-induced *cis-trans* isomerization that can result in conformation changes or polarity changes. Azobenzene derivatives have been found to be extremely sensitive to radiation and undergo rapid isomerization resulting in changes in the polarity as well as geometry. Figure 2 shows the *cis-trans* isomerism in azobenzene.

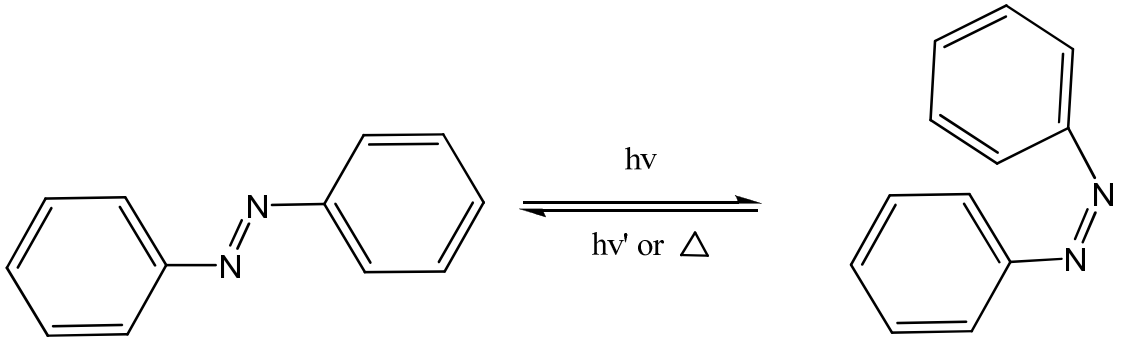

Fig. 2: Photo-induced cis-trans isomerism of azobenzene

The azobenzene moieties have been linked with different polymeric systems such as poly(acrylic acid), poly(N-isopropyl acrylamide) and poly(N-hydroxypropyl methacrylamide). An interesting system based on the azobenzene links consists of two cyclic peptides bridged by an azobenzene moiety. The structure of this cyclic peptide containing the azobenzene moiety is shown in Figure 3.

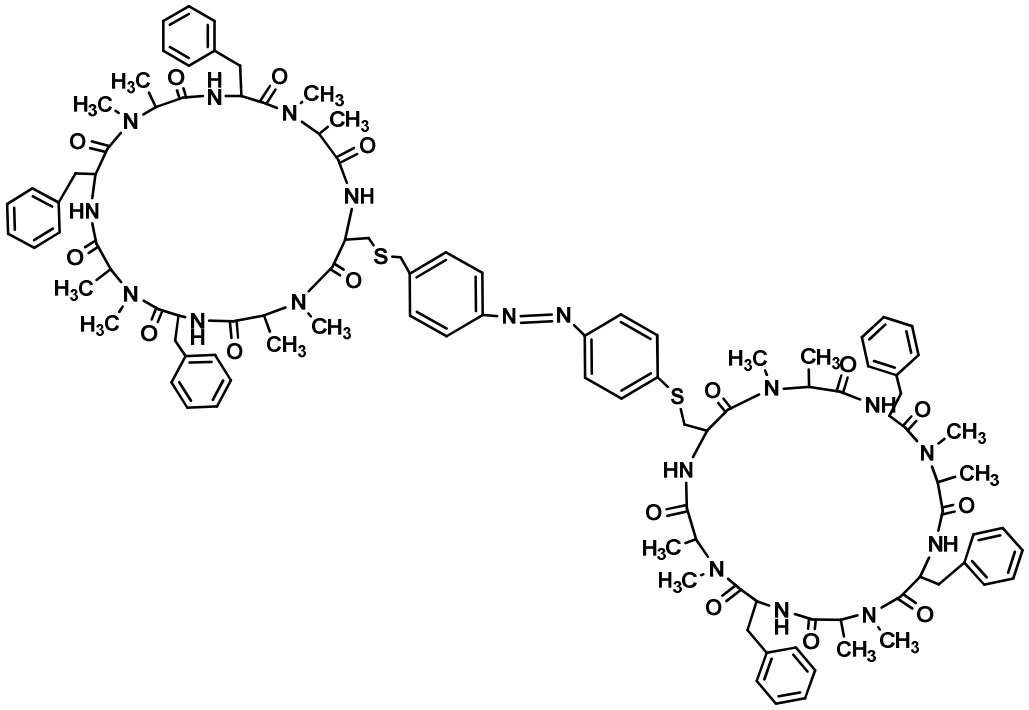

Fig. 3: Cyclic peptide system with photo-responsive azobenzene bridge

Initially, the azobenzene moiety is in the *trans* and extended conformation and as a result, the neighbouring cyclic peptide rings can associate through intermolecular hydrogen bonding. This causes extension of the structure to form a linear architecture. If the system is irradiated with ultraviolet radiation, the azobenzene units convert to their *cis* form. This results in the disruption of intermolecular hydrogen bonds and promotes formation of intramolecular hydrogen bonds. The linear structure is destroyed and instead only invidual monomers exist in the system. If the system is irradiated with visible radiation, the azobenzene moieties convert to the *trans* form. Thus formation of a supramolecular assembly can be controlled using electromagnetic radiation of a particular wavelength. Incorporation of these components into a flexible polymer film can bring about extension and bending of the film depending on the wavelength of irradiation. Figure 4 gives the pictorial depiction of this phenomenon.

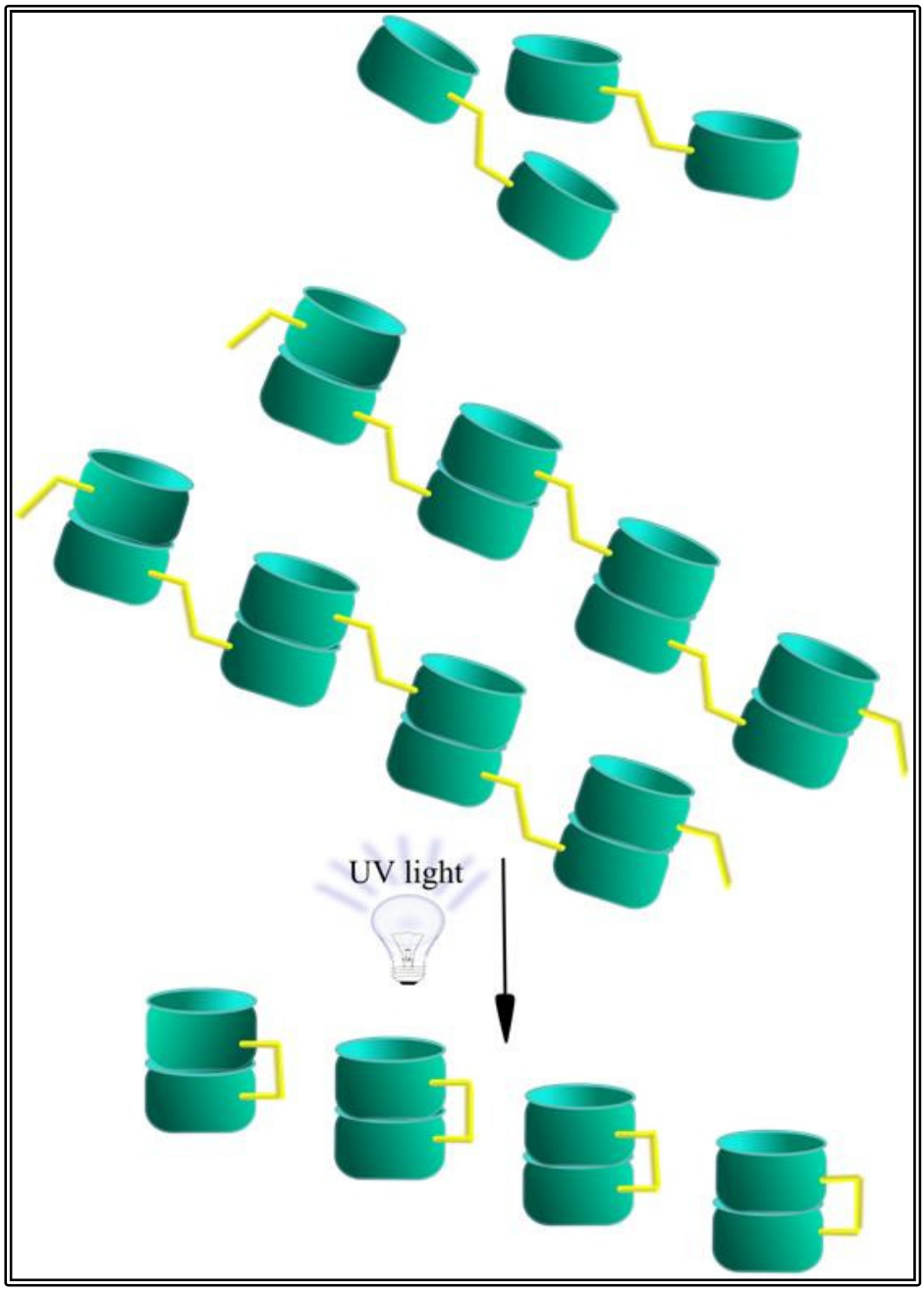

Fig.4: Photo-responsive system based on azobenzene crosslinks

Spiropyran is another photo-responsive component that has been extensively investigated for design of photo-responsive release systems. The spiropyran residues are covalently linked to the copolymer poly(N-isopropylacrylamide-*co*-acrylic acid) or to a pullulan chain. The spiropyran is hydrophobic in nature and hence when a pullulan-spiropyran system is introduced into an aqueous medium, it self-assembles to forma micelle structure. When irradiated with ultraviolet radiation, the spiropyran transforms to a more

hydrophilic merocyanine form that result in the disruption of the micelle structure. When exposed to visible radiation, the merocyanine converts to the hydrophobic spiropyran form resulting in the reassembly of the micelle structure. This reversible micelle formation can be exploited to develop photo-stimulated release systems. The same system can also serve as a molecular chaperone to aid renaturation of denatured proteins. Figure 5 gives the structural transformations that occur in spiropyran when exposed to electromagnetic radiation of appropriate wavelength.

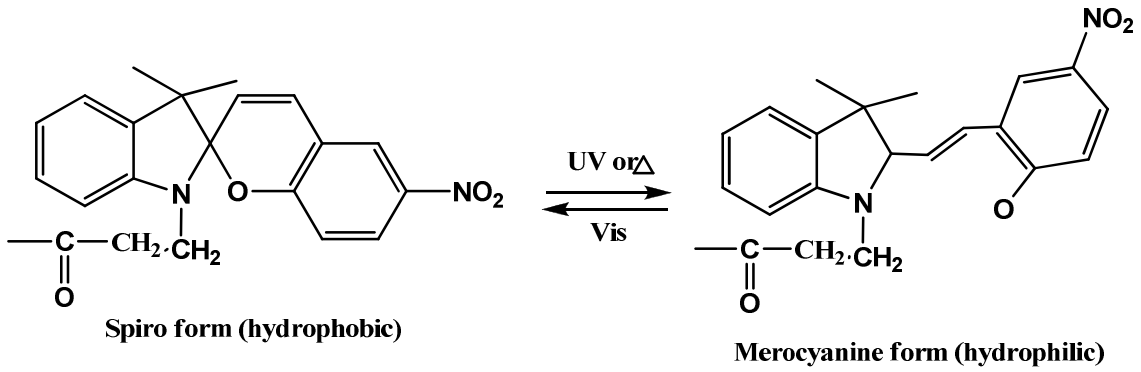

Fig.5: Photo-responsive transformation of spiropyran

2 Hybrid hydrogel

The hybrid hydrogel systems are actually multiple-stimuli responsive substances that can respond to more than one stimulus. For example, a copolymer of N-isopropyl acrylamide with acrylic acid can respond both to pH as well as temperature due to the presence of acrylic acid (pH sensitive) as well as N-isopropylacrylamide (thermo-sensitive) segments. Let us consider an example of poly(N-isopropyl acrylamide) (PNIPAM) main chain grafted with poly(2-vinyl pyridine) (PVPy) side chains. The PVPy is positively charged at acidic pH and hence exhibits maximum swelling at pH below 4.8. The PNIPAM is insensitive to pH changes but responds to temperature changes. Above its critical solution temperature of 32^{o}C, the polymer transforms from a swollen state to a deswollen gel state. When such a system is placed in a medium with pH < 4.8 and temperature < 32^{o}C, both the side chains as well as the main chain are in their swollen state resulting in maximum drug diffusion. When the temperature is increased above 32^{o}C at the same pH, the PNIPAM main chain collapses to form a gel while the PVPy side chains remain swollen. The amount of drug released at this pH will be low as only the drug molecules near the periphery can diffuse through the swollen PVPy chains. When the pH is increased to above 4.8 and the temperature is maintained above 32^{o}C, both main and side chains will collapse and hence hardly any drug will be released. If the pH is reduced to below 32^{o}C at the same pH, the PNIPAM chains alone will be swollen but the PVPy chains will be collapsed. As a result the diffusion of the drug will still remain poor.

Similarly, a copolymer of N-isopropyl acrylamide, acrylic acid and spiropyran-modified acrylamide will respond to pH changes (due to acrylic acid moiety), temperature changes (due to N-isopropyl acrylamide moiety) and electromagnetic radiation (due to spiropyran). A magnetic nanoparticle incorporated chitosan will respond both to pH changes as well as a magnetic field.

3 Molecular imprinting

Molecular imprinted gels are the next generation of smart materials that can revolutionalize sensing. What is molecular imprinting? It is the process of creating a template for a specific molecule in a polymer matrix. How is this going to be useful? If the polymer matrix is a hydrogel, then the specific binding of the molecule of interest to the template will cause a deswelling of the hydrogel matrix. This can be utilized for sensing the presence of the molecule of interest in the sample.

Let us consider an example. A poly(acrylamide) matrix was modified using lectins and vinyl monomers to create a template for α-fetoprotein, a tumour marker. When proteins containing α-fetoprotein were added, the binding of α-fetoprotein alone caused shrinking of the gel. All other proteins and biomolecules did not alter the swelling behaviour of the gel. The technique for molecular imprinting requires multiple carefully designed chemical steps. But it is possible to create a molecular memory for a specific molecule in the polymer matrix. This memory is not erased even after repeated swelling-deswelling cycles. Such systems are called 'Intelligent analyte sensitive hydrogels'. Similarly, molecular imprinted polymers (MIPs) can be used to trigger release of the drug based on the presence of a particular molecular species.

4 Reference

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

5 Additional reading

1. Stimuli-responsive polymers and their applications in drug delivery, Priya Bawa, Viness Pillay, Yahya E Choonara, Lisa C du Toit, Biomedical Materials, 4 (2009)
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

Source:
http://nptel.ac.in/courses/118106019/27