The TWAS–Lenovo Science Prize-winning work of R. A. Mashelkar

R. A. Mashelkar received the 2018 TWAS–Lenovo Science Prize in Trieste, Italy on 27 November 2018. The Prize consisting of a citation and a cash award of US$ 100,000 is given for contributions to basic research with the subject areas changing from year to year. For the 2018 Prize, TWAS had considered nominees with 'world-class achievement in engineering sciences'.

Mashelkar was awarded the Prize 'For his seminal contributions in mechanistic analysis, synthesis and application of novel stimuli responsive polymers'. Here we discuss some of the work that earned him this coveted recognition.

Mashelkar joined CSIR-National Chemical Laboratory (NCL), Pune in 1976, where he built a globally recognized research school in the area of polymer science and engineering. His entire research career was spent at NCL. His research has focused on transport phenomena in non-Newtonian fluids, polymer reaction engineering as well as dynamics and thermodynamics of swelling, super swelling and shrinking polymers, including smart hydrogels.

Smart hydrogels are water-swollen crosslinked networks of polymers which respond to external stimuli such as pH, temperature, electric field, etc. and undergo volume phase transition. They have potential applications as sensors, actuators, soft robots and controlled drug-delivery systems. Mashelkar's contributions to this area have provided new insights into the formation and behaviour of such materials, and have opened up several novel applications for them.

Biomimicking hydrogels

Mashelkar and co-workers demonstrated for the first time a new class of smart hydrogels that exhibit unique biomimicking functions: thermoresponsive volume phase transitions similar to sea cucumbers[1], self-organization into core–shell hollow structures similar to coconuts[2], shape memory as exhibited by living organisms[2], metal ion-mediated cementing similar to marine mussels[3], rapid self-healing in aqueous environment[4] and switchable biomimetic hydrogels showing enzyme-like activity (gelzymes)[5].

Self-organization

Self-organization at microscopic and macroscopic levels is commonly found in nature. However, examples of macroscopic self-organization in synthetic materials are somewhat rare.

Mashelkar and co-workers demonstrated a different type of self-organization in a hydrogel, wherein a cylindrical piece of gel transforms into a hollow spherical or ellipsoidal object in the presence of specific transition metal ions, and that too reversibly[2]. The unique hollow shape of this gel was similar to many hollow objects abundantly found in nature, such as coconut (at a macroscopic level), and amphiphilic siderophores produced by marine bacteria (at a microscopic level) which have been shown to self-assemble into a vesicle upon coordination with Fe(III). It was demonstrated that only certain gels which have a critical balance of hydrophilic and hydrophobic groups in their chemical structure exhibit such self-organization.

Self-healing hydrogels

Achieving self-healing in permanently crosslinked hydrogels had remained elusive because of the presence of water and irreversible crosslinks. Mashelkar and co-workers demonstrated for the first time that permanently crosslinked hydrogels can be engineered to exhibit self-healing behaviour in an aqueous environment[4]. This was achieved by providing the hydrogel network with flexible-pendant side chains having an optimal balance of hydrophilic and hydrophobic functionalities that allowed the side chains to mediate hydrogen bonds across the hydrogel interfaces with minimal steric hindrance and hydrophobic collapse. The self-healing reported was rapid, occurring within seconds of the insertion of a crack into the hydrogel or bringing together two separate hydrogel pieces. The healing was reversible and could be switched on and off via changes in pH, allowing external control over the healing process. The hydrogel sustained multiple cycles of healing and separation without compromising its mechanical properties and healing kinetics. This work provided a mechanistic insight into how weak secondary interactions could be harnessed to introduce new functions to chemically crosslinked polymeric systems.

Switching biomimetic hydrogels

Mashelkar and co-workers reported the first synthesis of novel enzyme mimicking hydrogel (gelzyme) in the form of a polymeric chymotrypsin mimic, whose hydrolytic activity could be rapidly, precisely and reversibly triggered on/off by UV light and pH[5]. Unlike the enzyme-based systems, gelzyme offered additional features, such as greater tailorability, complete reversibility and stability in aggressive environments. The photo switching was achieved by controlling the diffusion of the substrate into the polymer matrix, and pH switching by controlling the activity of the enzyme mimic. Both these were shown to be completely reversible.

Multi-stimuli responsive enzyme mimics could find applications in systems involving multiple enzymatic reactions in which selective switching could be used to alter reaction pathways, leading to selectivity control in enzyme-catalysed reactions.

Molecular tailoring of stimuli responsive gels

By judicious combination of theory and experiment, Mashelkar's group has explored thermoreversible swelling–collapse transition of gels which has opened the doors to the design of new materials with innovative applications. The molecular basis for the swelling–collapse transition in gels was unclear, which made the precise design by molecular tailoring difficult.

The LCST-type volume transitions of non-ionic gels such as poly (*N*-isopropyl acrylamide, PNIPA) were predicted by empirical modification of Flory's theory of polymeric networks. However, the theory did not take into account specific and weak interactions such as hydrogen bonding, which are intrinsic to hydrogels and play a critical role in determining its properties.

Mashelkar and co-workers developed a lattice fluid hydrogen bonding (LFHB)

model to show that the volume transition occurs as a result of the rearrangement of hydrogen bonds in the gel water system coupled with temperature-dependent hydrophobicity of the polymer[6]. The model predicted that a critical balance of hydrophilic and hydrophobic interactions is required for a gel to exhibit discontinuous volume transition.

The LFHB model opened the doors for molecular design of smart gels. The theory has stood the test of time. For example, it was shown that the theory could predict complex phenomena like the re-entrant volume transitions of poly(*n*-isopropyl acrylamide) gel in alcohol–water mixtures[7].

In the case of PNIPA gel, the monomer itself has a unique hydrophilic–hydrophobic balance, such that the gel can exhibit LCST behaviour. Mashelkar and co-workers reported that it is possible to develop a copolymer gel whose individual monomers do not show discontinuous transitions, but a clever balance of hydrophilic and hydrophobic interactions creates discontinuous transitions in the copolymers[8]. It was demonstrated that a subtle change either by changing the composition of the co-monomers by a small amount, or by slightly changing the hydrophobic group in the gel dramatically changes the swelling behaviour of the copolymer gel.

Further, Mashelkar and co-workers[9] showed experimentally and theoretically that a linear correlation exists between the transition temperature and length of the hydrophobic alkyl side group. By 'pin-point variation' of methyl to ethyl groups in L-alanine ester side chains in hydrogels containing methacrylol backbone, precise transition temperatures could be achieved.

Diffusion modulation through stimuli responsive gels

Mashelkar and his group have shown several interesting applications of volume transition in gels for diffusion control. For instance, they showed a novel approach to attain time-invariant diffusional flux through bilayered membranes with reversible barriers, which were formed by exploiting the phenomenon of volume transition in gels[10]. The novelty of the approach was that such bilayers could be formed *in situ*. The validity of the concept, as well as the quantitative predictability (with no curve-fit parameters) of the theoretical analysis was demonstrated by experimentation on model systems.

A6ACA: a unique trapeze artist

Mashelkar and co-workers have invoked the imagery of trapeze artistry for a diverse family of acryloyl amino acid monomers with balanced hydrophobicity and hydrophilicity. It was discovered that the gels made from acrylol-6-amino caproic acid (A6ACA) had the optimal balance of hydrophilic and hydrophobic interactions, endowing them with unique 'life-mimicking' functions. These gels showed reversible macroscopic self-organization leading to reversible shape transitions and remarkable rapid (few seconds) self-healing.

How do these A6ACA-based gels perform such delicate trapeze artistry? Using atomistic molecular simulations and spectroscopic measurements, it was shown that the healing was caused by hydrogen bonding between carboxyl end groups of A6ACA alkyl side chains across the interface of two pieces of gels, which required that the side chains stretch out across the interface and bond to each other[4]. Molecular simulations showed that shorter side chains could not reach each other for effective binding, whereas longer side chains collapsed onto themselves due to their higher hydrophobicity.

This seminal discovery of the ability of A6ACA gels to perform the aforementioned trapeze artistry has led to several breakthrough applications in amazingly diverse fields.

A6ACA functionalized biomedical implants have been shown to promote biomineralization with native bone tissue-like functions, leading to novel synthetic bone grafts and therapeutic interventions to assist bone regeneration and healing[11]. A6ACA has been shown to provide the best control of stem cell adhesion, migration and defection[12,13]. The pH-responsive self-healing property of A6ACA gels has been harnessed to develop devices that can be used to plug tissue damage in the gastrointestinal tract[4]. The amphiphilic nature of A6ACA polymers has been used to develop a novel, triggerable loss circulation material for plugging porosity of underwater geological strata to enable enhanced oil recovery[14]. Bob Langer's group at MIT, USA has developed A6ACA-based supramolecular gels that provide best-performing enteric implants thus far[15]. Extensive research on the use of A6ACA to develop self-healing materials with exceptional properties using graphene oxide[16] and carbon nanotubes[17] is in progress in laboratories around the world.

Finally, it is often said that Indian science must make a big difference to the scientific world. A6ACA, an amazing trapeze artist discovered in NCL, is an example of such a dream coming true.

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