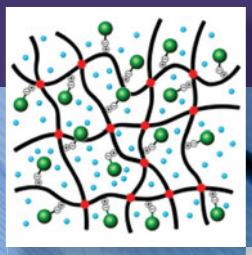


Biodegradable thermogelling polymers for biomedical applications

Sing Shy Liow, Anis Abdul Karim, and Xian Jun Loh

Thermogelling polymers belong to a class of stimuli-responsive hydrogels that undergo a macroscopic sol-to-gel transition in response to temperature. Much of the ongoing research in this field is focused on hydrogels for biomedical applications as an injectable sustained drug-release matrix or scaffolds for tissue regeneration. Despite robust developments in biodegradable thermogelling polymers in recent decades, the field still faces challenges in the optimization of materials properties. Thorough investigation must be performed to understand the effectiveness of drug delivery using hydrogel-forming polymer carriers. A highlighted case study on OncoGel, an experimental drug delivery depot formulation, sheds some light on the shortcomings of biodegradable thermogelling polymers as drug delivery systems. In this article, we highlight developments in biodegradable thermoresponsive polymers for biomedical applications over the past three years, with a focus on materials/technical challenges and the approaches used to resolve these problems.

Introduction

The past decade has seen substantial developments in research, especially on biomaterials. A biomaterials class of great interest is stimuli-responsive biodegradable hydrogels, since they exhibit satisfactory performance *in vivo* in both tissue and blood-contacting environments. These hydrogels can be easily fabricated into different morphologies by altering the physical properties, for example, by changing the polymer concentration in an aqueous solution to obtain a soft or hard gel, for given applications.

Thermogelling hydrogels, also known as thermogels, are a class of stimuli-responsive hydrogels that have gained much interest because they undergo macroscopic sol-to-gel transitions in response to temperature.[1–5] They liquefy when cooled below room temperature and form a gel when heated to room or body temperature. This thermogelation feature runs contrary to typical natural phenomena, where water freezes or jelly solutions solidify at low temperatures. The process is reversible when the themogelling polymers are composed of physically cross-linked polymeric networks. This unique property of thermogels finds use in a wide range of biomedical applications, including injectable hydrogels to deliver drugs,[6–8] tissue engineering scaffolds[9–15] for cardiac, nerve, and cartilage tissues for regenerative medicine, and anti-adhesion fillers.[16]

The mechanism behind the property of thermogelation lies in the aggregation of a micellar network structure, which is an interconnected lattice formed by the aggregation of self-assembled micelles (spherically shaped lipid molecules) in an aqueous solution.[17] Thermogelling copolymers consist of hydrophilic and hydrophobic segments that can self-assemble into micelles in an aqueous solution. As the temperature increases, hydrophobic association of the core drives the individual micelles to aggregate into close-packed structures, leading to macroscopic gelation. The low critical solution temperature (LCST), below which the compounds in the mixture are miscible at all compositions, is also a factor in the micelle-forming thermogelation mechanism. For example, poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG) have LCST ranges of 100–150°C and 10–30°C in water, respectively. Above the LCST, the polymer segments become hydrophobic and immiscible. When a PEG-PPG amphiphilic copolymer forms with a balanced hydrophilic–hydrophobic segment ratio, thermogelling behavior can be observed at or above the LCST of PPG (i.e., at room temperature or body temperature); the PPG segments become hydrophobic, which induces the formation of micelles.

Scarpa et al. conducted the first study on thermoresponsive polymers in 1967 and described the reversible phase-change behavior of poly(*N*-isopropylacrylamide) (PNIPAAm).[18]

Sing Shy Liow, Institute of Materials Research and Engineering, A*STAR, Singapore; liowss@imre.a-star.edu.sg
Anis Abdul Karim, Institute of Materials Research and Engineering, A*STAR, Singapore; anisak@imre.a-star.edu.sg
Xian Jun Loh, A*STAR Personal Care Program; and National University of Singapore, Singapore; lohxj@imre.a-star.edu.sg
doi:10.1557/mrs.2016.139

However, PNIPAAm-based thermogels are not biodegradable. When they are used as implants for drug release, surgery was needed to remove the implanted gel after it had served its purpose, resulting in more complications. As a result, there was a push toward the development of biodegradable thermogelling polymers. These polymers could biodegrade into smaller fragments that are excreted from the body via metabolism or renal excretion. To impart biodegradability, hydrolytic degradable polyesters, such as poly(ε-caprolactone) (PCL)[19] and poly(D,L-lactide-*co*-glycolide) (PLGA),[20,21] were employed as degradable blocks. This work has since been expanded to developing polypeptide-based thermogelling polymers consisting of enzymatically degradable peptides, such as poly(L-alanine) (PA)[11] and chitosan.[10,22] These thermogels show good stability in aqueous solution during storage and for withstanding degrades in the presence of proteolytic enzymes in the body.

Despite robust development of biodegradable thermogelling polymers over the past few decades, the field still faces challenges related to the material properties under certain conditions: (1) long and unfavorable dissolution times to prepare thermogels; (2) inability of chitosan-based thermogels to dissolve under physiological conditions; and (3) collapse of polymeric networks and the expulsion of water when the thermogelling solution solidifies into a gel. These issues have motivated further research into understanding the material properties that affect thermogelation. These include adding another component to the copolymers (either by physical mixing or chemical interaction), substituting with another component, or altering the groups slightly to modify the structure. By overcoming these challenges, biodegradable thermogelling polymers with improved physical properties can be developed for a range of applications.

This review summarizes recent developments in biodegradable, thermogelling polymers for biomedical applications, such as drug delivery, tissue engineering scaffolding, and anti-adhesion fillers. In particular, recent advancements in PEG-based thermogels—Pluronics, PEO/PPG-based triblock copolymers (A and B blocks that are linked in an ordered manner: ABA and BAB types), PEG-based diblock copolymers, and PEG/PPG-based polyurethanes are described. Under materials challenges, we consider gel collapse, insoluble chitosan-based systems, and long dissolution times. Biomedical applications considered include drug delivery systems, where we focus on the technical challenge of burst release (initial rapid release of the surface drug that may lead to overdosing), and incomplete release (slow to no release of the drug at the ending stage that may lead to underdosing). A case study of OncoGel is then highlighted, followed by consideration of ongoing opportunities and challenges.

Recent advances in thermogels

PEG/PPG-based systems

PEG-PPG-PEG (or Pluronics, commercially available in different molecular weights and PEG/PPG ratios) is the most commonly studied thermogelling polymer. For example, Pluronic F127 (PF127) consists of 30% PPG hydrophobic segments and 70% PEG hydrophilic segments. However, these thermogels are limited by their nondegradability due to the presence of the carbon–carbon polyether backbone. In addition, these thermogels are limited by fast gel-erosion characteristics—they exhibit short retention times in the body of a few days, with detrimental consequences for long-term drug delivery applications. Studies have reported modifications to this system to impart enhanced mechanical properties and longer term drug release. These include cross-linking by glutaraldehyde to generate cross-linked networks with carboxymethyl chitosan interpenetrated in Pluronics gels,[23] copolymerization of random poly(methyl vinyl ether-*co*-maleic anhydride) and PF127 copolymers (GZ–PF127),[24] or substituting other polyesters, such as PCL, with PPG.[19]

PEG/PPG-based triblock copolymers

Classic thermogelling polymers have triblock (ABA type) structures similar to PEG-PPG-PEG. These ABA type triblock copolymers are synthesized in a two-step reaction—ring-opening polymerization (ROP) of B-block using methoxy-PEG as the initiator, followed by a condensation reaction to couple the two B-blocks using diisocyanate. Numerous studies have been carried out on these thermogelling polymers over the past 20 years. Recently, this method has been further refined to synthesize hybrid metal-containing thermogelling copolymers for triggered drug release. Using modified selenium[7] or platinum[8] with terminal-acid groups as the coupling agent, hybrid PEG-PLGA-PEG[7] and PEG-PLA-PEG[8] thermogelling copolymers were prepared, where PLA is poly(D,L-lactide). PLGA and PLA segments impart biodegradability and hydrophobicity to the thermogels, while the metallic segments serve as drug-coordination moieties (**Figure 1**).

BAB type triblock thermogelling copolymers are easier to prepare than ABA types. PLGA-PEG-PLGA can be synthesized in a one-step ROP reaction using PEG as the telechelic initiator (a polymer or oligomer that is used to initiate a ring opening or other forms of further polymerization through its reactive end groups). One recent study reported the use of PLGA-PEG-PLGA thermogels as an effective barrier to the reduction of epidural scarring, which can result in chronic back pain and nerve disorder, in a postlaminectomy (post spinal surgery) rat model.[25] This is applicable to postoperative intestinal surgery as a promising anti-adhesion material, where the thermogel acts as a mechanical barrier between the surgically exposed spinal cord outer membrane and the surrounding muscles, and prevents the formation of scar tissue. A major concern in drug delivery is that the efficacy of drug release could be affected by specific interactions between the drugs and thermogels. A study showed that the delivery of the moderately soluble antitumor drug irinotecan (IRN) is enhanced by mixing the drug with the thermogelling triblock copolymer PLGA-PEG-PLGA.[6] IRN, from the camptothecin (antitumor) family of drugs, is easily susceptible to hydrolysis, which

https://doi.org/10.1557/mrs.2016.139 Published online by Cambridge University Press

alters its structure from an effective antitumor (lactone form) to an ineffective carboxylate form. This decreases its therapeutic efficiency and leads to severe side effects (**Figure 2**). By mixing IRN with the copolymer, the drug is sustainably released for approximately two weeks. It does not exhibit a significant initial burst followed by almost complete release of the drug.

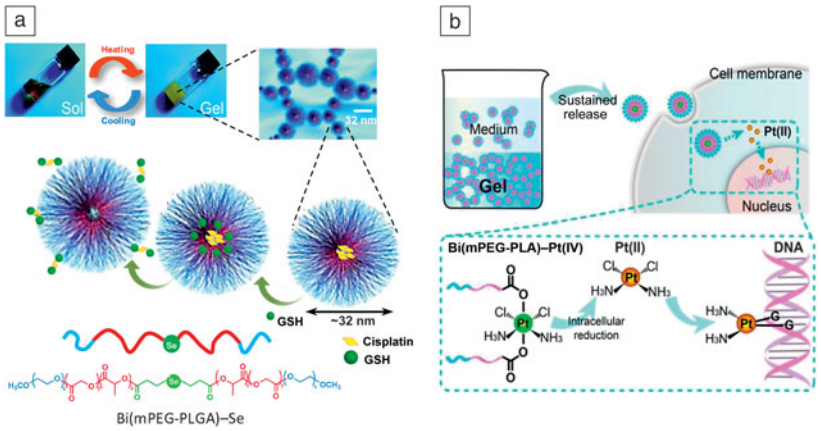


Figure 1. (a) Amphiphilic selenium-containing Bi(mPEG-PLGA)–Se conjugate thermogel could self-assemble into micelles in an aqueous medium. The concentrated aqueous solution exhibited a reversible sol-gel transition with increasing temperature. Selenium-containing diblock copolymer Bi(mPEG-PLGA)–Se coordinates with the antitumor drug cisplatin and then is released by the addition of its coordination competitor glutathione (GSH). Adapted with permission from Reference 7. © 2015 Royal Society of Chemistry. (b) Amphiphilic Bi(mPEG-PLA)–Pt(IV) conjugate thermogel consisting of micelles that readily enter cancerous cells via endocytosis (cell ingestion); then, the micelles were broken into carrier polymers, and the Pt(IV) is reduced by intracellular reducing agents to the active Pt(II) species of the antitumor drug cisplatin; finally, cisplatin is bound to DNA through the guanine (G) base pair and becomes efficacious. Adapted with permission from Reference 8. © 2015 American Chemical Society. Note: mPEG, methoxyl poly(ethylene glycol); PLGA, poly(lactic-*co*-glycolic acid); PLA, poly(D,L-lactide).

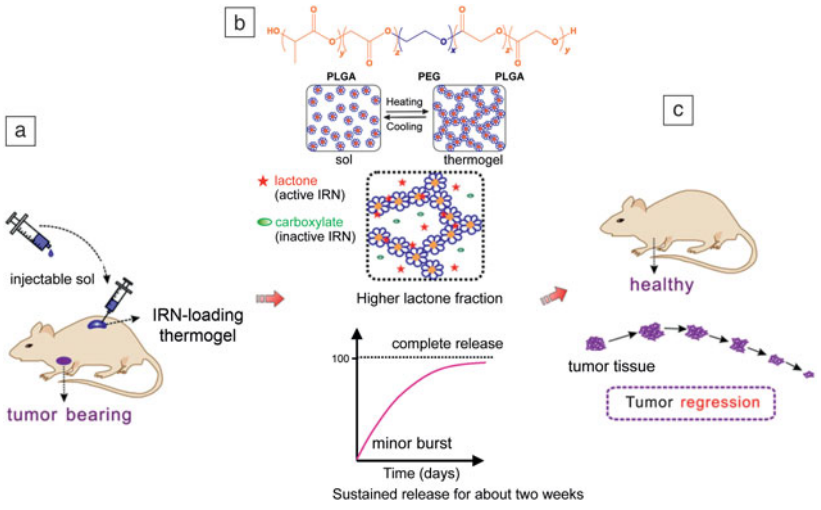


Figure 2. Main procedures of the irinotecan (IRN)/thermogel system and its functions in tumor treatment. (a) The IRN-loaded polymer solution is injectable; the injected mixture is gelled *in vivo* at body temperature. (b) IRN can be sustainably released for approximately two weeks without a significant initial burst and with almost complete release. Its active lactone fraction (glycolic acid to lactic acid mole ratio) in the thermogel is enhanced significantly, much higher than that in phosphate buffer saline solution. (c) The tumor volume eventually decreases compared with the initial size. Adapted with permission from Reference 6. © 2014 Nature. Note: PLGA, poly(lactic-*co*-glycolic acid); PEG, poly(ethylene glycol).

PEG-based diblock copolymers

ROP is also employed to prepare PEG-oligopeptides thermogelling diblock copolymers using methoxy-PEG as an initiator. Unlike the previously described triblock copolymers based on PLGA, PLA, and PCL, these peptide-based themogelling diblock copolymers can be degraded by enzymes. A study demonstrated the synthesis of PEG-poly(L-alanine) (PEG-L-PA) with L-PA of varying molecular weights with PEG fixed at 5000 Dalton.[11] The sol-gel transition temperature decreased inversely with the molecular weight of PA. With increasing temperature, the α-helical structure of PA with higher molecular weights undergoes a transition to a random-coil structure. This induces interaction with the PEG segment, which strengthens micelle formation. Another study reported the synthesis of PEG-poly(L-alanine-*co*-L-phenyl alanine) (PEG-PAF) with different PEG molecular weights (hydrophilic-hydrophobic ratio is fixed).[26] It was reported that samples with higher PEG and PAF molecular weights tend to form superior micelle aggregates and gels with higher moduli at lower polymer concentrations.

PEG/PPG-based polyurethane

Polycondensation is used to prepare biodegradable multiblock thermogelling polyurethanes.[2] These copolymers are prepared by reacting low-molecular-weight polymer diols—PEG and PPG—with diisocyanate as the coupling agent. Hydrolytically degradable, low-molecular-weight polyester segments such as poly(1,4-butylene adipate) diol, poly(tetrahydrofuran carbonate) (PTHF) diol, PCL diol, or poly([*R*]-3-hydroxybutyrate) diol are added in small amounts (1–5 wt%) to impart biodegradability. A study showed that Pluronics F127 or $(PEG)_{99}$-$(PPG)_{69}$-$(PEG)_{99}$ can be chemically modified by reacting with PTHF diol using a polyurethane reaction.[27] The poly(F127/PTHF urethane)s showed lower critical gelation concentrations (CGC) than Pluronics F127, with micelles forming at lower concentrations. Sustained release of natamycin, an antibiotic, was demonstrated with this system. It was shown that the material is not cytotoxic when tested against L929 cells (mouse fibroblast cells), and it could be used for the future treatment of eye infections.

https://doi.org/10.1557/mrs.2016.139 Published online by Cambridge University Press

Materials challenges

Gel collapse

PNIPAAm thermoresponsive polymers are known to be nonbiodegradable. To impart biodegradability, hydrolytic or enzymatic degradable segments have to be incorporated in the system. Another limitation is that thermogel collapses at physiological temperatures (above the LCST of PNIPAAm at 32°C).[28] This phenomenon results in significant discharge of water, which is also known as the syneresis effect. This renders PNIPAAm-based thermogels unsuitable as drug delivery depots and tissue engineering scaffolds. A recent study, however, showed that PNIPAAm-based macromer with chemically cross-linkable methacrylate groups can mitigate hydrogel syneresis.[29] This dual-gelling system is soluble at room temperature. At 37°C, a cross-linked hydrogel forms from the thermogelation of PNIPAAm segments with chemically cross-linked methacrylate double bonds at the pendant groups (dangling branches from the main backbone). The thermoresponsive copolymer is susceptible to hydrolytic degradation at the phosphate ester bond, which imparts biodegradability to the thermogel. Another study incorporated enzymatically degradable moieties. A dextrin/PNIPAAm covalently cross-linked thermoresponsive hydrogel was prepared via a Michael-type addition reaction, which involves the addition of a stable carbon nucleophile to an unsaturated carbonyl compound.[30] The enzymatically degradable dextrin yields a biodegradable hydrogel.

In a recent study, a poly(PEG-citric-NIPAAm) (PPCN) copolymer was developed via polycondensation and radical polymerization to obtain a biodegradable system suitable for protein and cell delivery.[31] Citric acid, PEG, and glycerol 1,3-diglycerolate diacrylate were heated to 140°C to prepare prepolymer (poly(polyethylene glycol citrate) acrylate prepolymer, PPCac) via polycondensation. Subsequently, radical polymerization of NIPAAm occurred in the presence of the initiator azobis-(isobutyronitrile) (AIBN) (**Figure 3**). The PEG-citric segments not only provide biodegradability, but also impart antioxidant properties to enhance wound healing by reducing oxidative stress in the tissue. In addition, PEG citric segments in PPCN reduced the syneresis effect above the LCST of PNIPAAm by decreasing water expulsion from the PNIPAAm segments. As compared to the previously described covalently cross-linked thermogels, synthesis of the PPCN copolymer is relatively simple and can be readily scaled up. Furthermore, the sol-gel transition is reversible, as the material does not contain covalent cross-links.

Insoluble chitosan-based systems

The limited solubility range of chitosan, a biocompatible and abundant polysaccharide derived from the outer shell of crabs, lobsters, and shrimp in acidic conditions (pH < 6.2) has been a major hurdle for the development of chitosan-based biomaterials for drug-/protein-delivery systems.[32] At the same time, acidic environments are harsh on cells and often cause protein denaturation. The combination of chitosan with polyol phosphate[22] and control over the degree of acetylation of glycol chitosan[33] could produce thermoresponsive systems that are soluble under physiological conditions. Recent advances in chitosan-based systems have been achieved by integrating other functional moieties to introduce additional useful properties. The combination of chitosan with glutathione can suppress oxidative stress in cardiomyocytes (heart muscle).[10] Incorporation of ferulic acid in chitosan-based thermogel was effective in reducing the oxidative stress in nucleus pulposus cells, which are found in the core of the spinal disc.[14] One particular rheological study revealed that the incorporation of polyol phosphate as a gelling agent induced the thermogelation of chitosan derivatives.[22] Incorporation of polyol phosphate formed a weak hydration layer around the chitosan chains. An increase in the temperature induces gel formation by hydrophobic association of chitosan due to dehydration of the layer (**Figure 4**).

Long dissolution times

The long preparation times required to form thermogels offer a significant barrier to the clinical use of injectable polymers (IPs). It is necessary for medical personnel to be able to easily prepare an IP formulation in a typical clinical setting. Dissolution of thermogelling copolymers typically occurs overnight in a refrigerator at 4°C. The preparation time of PCL-PEG thermogelling solutions can be reduced by heating above the melting point of the copolymer. However, heating

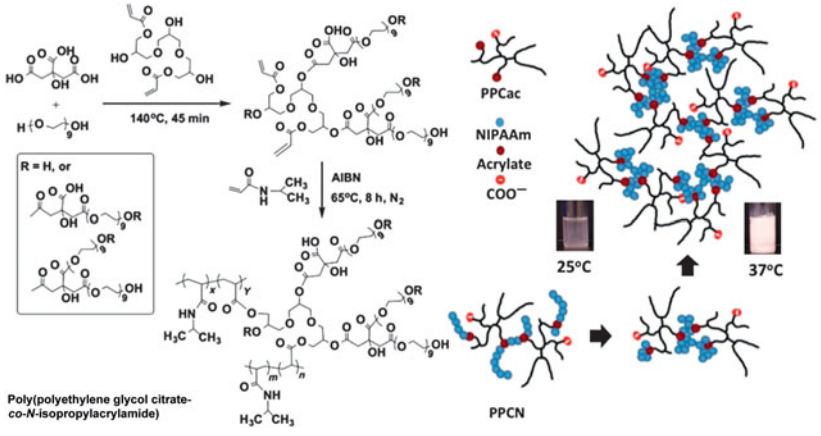


Figure 3. Synthesis route of poly(polyethylene glycol citrate-*co*-*N*-isopropylacrylamide) (PPCN) copolymer using a low-molecular-weight poly(polyethylene glycol citrate) acrylate (PPCac) prepolymer that is partially functionalized with acrylate chemical groups for subsequent polymerization with *N*-isopropylacrylamide (NIPAAm). The R-group can be simple hydrogen or a more complex polymeric group. PPCN exhibits thermoresponsive behavior to produce a highly branched gel with intrinsic antioxidant properties. Reproduced with permission from Reference 31. © 2014 American Chemical Society. Note: AIBN, azobis-(isobutyronitrile); PEG, poly(ethylene glycol); *x*, *y*, *m*, and *n*, number of repeating units for each polymer segment.

https://doi.org/10.1557/mrs.2016.139 Published online by Cambridge University Press

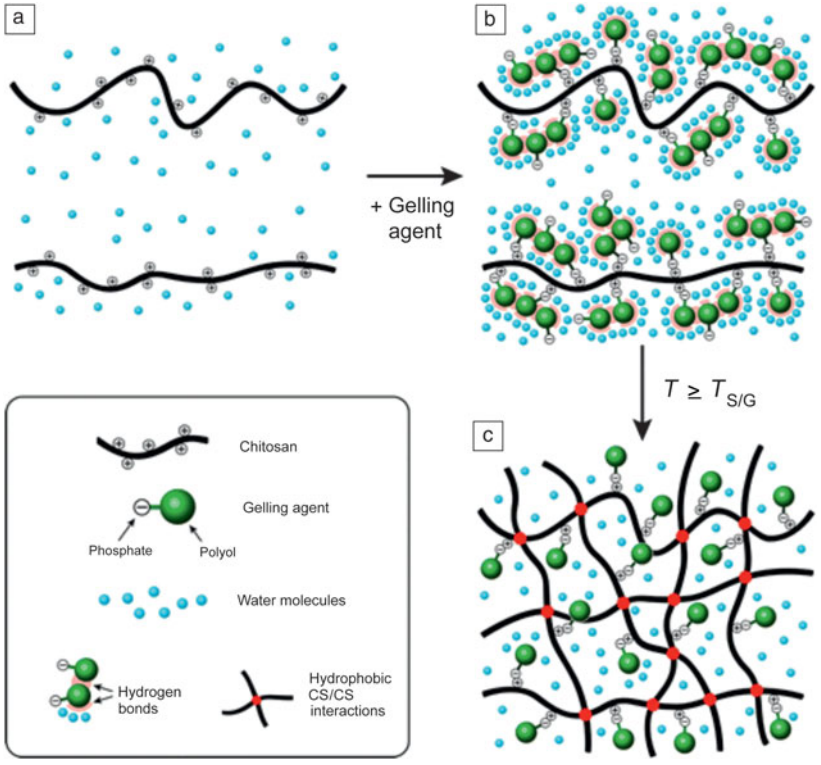


Figure 4. Representation of the thermogelation mechanism of chitosan/polyol-phosphate solutions. (a) Chitosan (CS) macromolecules are soluble in acidic conditions due to the charge repulsion of the amino groups. (b) Addition of gelling agents containing negatively charged phosphate parts neutralize the majority of the positive charges on CS. At low temperature ($T \leq T_{S/G}$), however, the polyol structure of the gelling agent contributes to the formation of a hydrated shell, protecting the polymer molecules from gelation. Therefore, CS remains soluble even at physiological pH values. (c) At $T \geq T_{S/G}$, hydration of the CS chains is not strong enough to maintain solubilization in the aqueous phase. In addition, the attractive interactions between the polymer chains can be achieved via hydrogen bonding and hydrophobic interactions, leading to gelation. Reproduced with permission from Reference 22. © 2013 American Chemical Society. Note: T, temperature; $T_{S/G}$, sol-gel transition temperature.

is not desirable for applications involving the delivery of temperature-sensitive actives. Yoshida et al. prepared poly(ε-caprolactone-*co*-glycolide)-*b*-PEG-poly(ε-caprolactone-*co*-glycolide) (PCGA-*b*-PEG-*b*-PCGA) triblock copolymers, where the addition of 10 wt% of PEG 2000 (PEG with molecular weight of 2000 g·mol^{-1}) was used as an additive before the freeze-drying process shortened its dissolution time to <1 min.[34]

Biomedical application: Drug delivery

The biodegradability of thermogels is important and useful in drug delivery applications. The rate of drug release is closely related to drug–gel interactions, gel erosion, degradation, and diffusion mechanisms. A number of recent reviews have summarized the use of biodegradable thermogels for drug-release applications, the pathway of fragment formation, and their subsequent elimination from the body.[35,36] After incubation *in vitro* and *in vivo,* typical characterization techniques, including gel permeation chromatography, scanning electron microscopy, nuclear magnetic resonance, thermogravimetric analysis, and matrix-assisted laser desorption/ionization (time of flight), were used to understand the biodegradation of thermogels through molecular-weight measurement, mass loss, visual analysis, and structural integrity examination. The degradation mechanisms of thermogels differ from their parent copolymers. Typical biodegradable polymers are susceptible to either surface or bulk degradation. Owing to the high water content in the thermogels, additional factors, such as diffusion and erosion, must be considered in drug-release studies.[36]

Technical challenge: Burst release and incomplete release

Thermogels incorporating hydrophilic drugs typically suffer from significant initial burst release due to fast diffusion of the water-soluble drugs contained in the thermogel. Hydrophilic drugs encapsulated in the aqueous phase of the gel typically instantly diffuse into the body fluids. This initial burst release of drugs may result in localized and systemic toxicity due to high-dosage exposure. Recent studies have proposed a number of ways to mitigate this issue.

Ding et al. explored the use of PEG, sucrose, and zinc acetate as an excipient (inert compound) to reduce the initial burst release of a hydrophilic peptide drug exenatide (EXT).[37] The initial burst release was reduced significantly when zinc acetate was added into the formulation. Incomplete drug release was observed, however, as the concentration of zinc acetate was increased. To compensate for this drawback, the formulation was refined by adding the three excipients simultaneously. It was suggested that the initial burst release was reduced due to the formation of an insoluble Zn-EXT complex, while the PEG/sucrose addition induced a porogen effect (i.e., draining out residual drugs at later stages of incubation) (**Figure 5**). Another *in vivo* study showed that PEG-PAF thermogels exhibited a lower initial burst release of the protein drug (rhGH) with higher molecular weights of PEG.[26] The study established that the thermogel not only served as a release depot, but also reduced the degradation of rhGH.

Highlight—Case study: OncoGel

OncoGel is an experimental drug delivery system that enables the controlled release of paclitaxel (a chemotherapy drug used to block the growth of cancer cells) from the thermogel directly into the target site. OncoGel consists of a paclitaxel-loaded ReGel (a triblock copolymer with the basic structure PLGA-PEG-PLGA) thermogelling system that is applied to

https://doi.org/10.1557/mrs.2016.139 Published online by Cambridge University Press

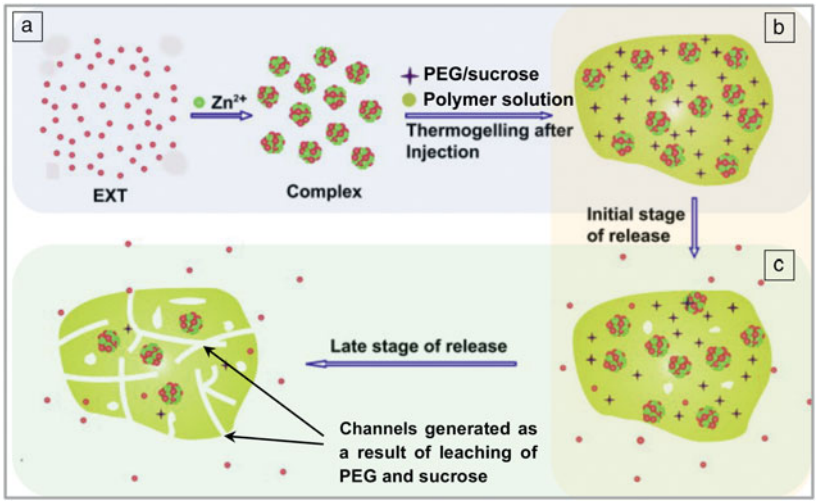


Figure 5. Schematic drawing of the roles of poly(ethlene glycol) (PEG), sucrose, and Zn acetate excipients during a drug-release process. (a) Formation of Zn–EXT (exenatide) nanoparticles embedded in the thermogel. (b) Synergistic effect of sucrose, PEG, and zinc acetate as additives decrease the initial burst release rate, (c) followed by the gradual leaching of PEG and sucrose to generate channels in the hydrogel interior, which promotes the late-stage release of EXT and ensures almost complete release at this late stage. Reproduced with permission from Reference 37. © 2013 Elsevier.

inoperable solid tumors.[38,39] The significance of this localized system is that it has similar therapeutic effects as conventional drug delivery systems, even for reduced doses of paclitaxel, from 17 mg m^{-2} (conventional therapy under constant intravenous infusion via the bloodstream) to 0.48 mg m^{-2} (OncoGel under single dose).[40,41] Upon intratumoral injection, paclitaxel undergoes slow, continuous release due to gel degradation over four to six weeks.[40,42–44] The sustained release of the therapeutic drug results in minimal toxicity.

Preclinical trials revealed that OncoGel could be used as an adjuvant treatment prior to or after surgery to minimize or prevent tumor growth.[40,42,43,45,46] Adjuvant treatment is an additional treatment designed to reduce the risk against recurring growth of cancer cells. Experimental efficacy studies on rodents revealed that combined treatment with Oncogel and temozolomide (an oral chemotherapy drug) + radiotherapy resulted in 100% long-term survival, indicating a strong therapeutic effect (**Figure 6**).[47] This motivated the evaluation of OncoGel in clinical trials.[41,48,49]

The preference of most patients diagnosed with a tumor for surgery rather than a slower treatment using a thermogel narrowed down the application of OncoGel to inoperable local tumors, such as esophageal cancer. Clinical studies on esophageal carcinoma patients with a noticeable tumor mass protruding from under the skin surface confirmed that OncoGel can offer a standalone treatment or be used as a component in combination therapies.[41,48,49]

Despite multiple promising preclinical/clinical results, cancer patients were not convinced of the reliability of the OncoGel system. These clinical studies failed to demonstrate an enhanced efficacy of OncoGel chemoradiotherapy as compared to systemic administration. OncoGel was then terminated as a potential therapy for esophageal cancer in 2010.[50]

This case study illustrates the potential and pitfalls of OncoGel as a drug delivery system. The inherent complexity of biological systems results in limitations and uncertainties in delivery systems for biomedical research. A combination of safety and efficacy studies, computational mass-transport simulations,[51] advanced-imaging techniques,[52,53] and hydrogel properties modification (i.e., degradation rate, pore size, hydrophobicity)[54,55] should be carried out to understand the discrepancy between preclinical and clinical trials and to investigate the effectiveness of drug delivery using hydrogel-forming polymer carriers.

Opportunities and challenges

The development of thermogels for biomedical applications continues to evolve to deliver innovative approaches to the encapsulation and delivery of active ingredients. Even so, these innovations are not without challenges. In the delivery of bioactive ingredients (drugs, genetic material, cells, and proteins), complications could arise owing to the multiple interactions present in the delivery systems. The challenge is to translate materials research to real-life applications after consideration of external factors, such as the incorporation of drugs and the interactions present in complex biological environments.

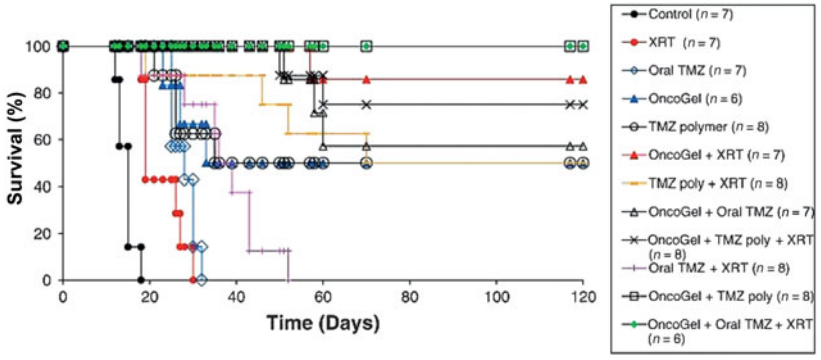


Figure 6. This study shows various treatment combinations of rats with intracranially implanted tumors. Animals that received either OncoGel and temozolomide (TMZ) poly (local TMZ; open squares) or the triple combination of OncoGel, oral TMZ, and radiotherapy (XRT; filled green circles) survived up to 120 days, with both groups having 100% survival. The combination of OncoGel (paclitaxel) with oral or local TMZ is safe, effective, and synergistic in the treatment. Adjuvant radiation therapy such as XRT further increases the efficacy of this combination therapy. Reproduced with permission from Reference 47. © 2013 SpringerLink. Note: *n*, number of animals.

https://doi.org/10.1557/mrs.2016.139 Published online by Cambridge University Press

These elements could affect the overall material structure and properties, which will in turn affect the efficacy and efficiency of drug delivery. Thermogelling polymers based on PLA, PGA, and their copolymers PLGA and PCL could be used as hydrogels and porous sponges for cell delivery in cartilage regeneration. The FDA-approved PCL could endow a gel with good mechanical properties, and this material can maintain phenotype and promote chondrocyte (cartilage cell) proliferation. This research, however, is in its infancy. Although the porous polymer scaffold can provide superior mechanical support as well as biocompatibility, early reports have shown that most cells tended to attach and proliferate only on pore surfaces. More work needs to be done to encapsulate the gel in 3D to create an injectable cell suspension.

A lesson can also be drawn from the development of OncoGel. The key limitation of the OncoGel system lies in the failure to demonstrate enhanced efficacy of OncoGel chemoradiotherapy as compared to systemic administration. A solution to this problem is to modify a ReGel polymer with optimized release characteristics to achieve the desired properties. In one study, ReGel was incorporated into PLGA microspheres as a sustained-release system for the perivascular delivery of dipyridamole—a medication that inhibits blood clot formation to keep heart blood vessels open after heart valve replacement.[54] The PLGA microspheres decreased the initial burst release, and the dipyridamole release was extended from 23 to 35 days by increasing the molecular weight of PLGA. Another ReGel study for Type 2 diabetes mellitus incorporated zinc-complexed GLP-1 (ZnGLP-1), where GLP-1 is an incretin hormone glucagon-like peptide-1.[55] The study reported *in vitro* and *in vivo* studies of zinc complexation stabilizing the GLP-1 against aggregation, preventing initial burst release, and slowing down its release such that it exhibited sustained release for two weeks. Animal studies demonstrated increases in plasma insulin levels, and the blood glucose level was controlled for two weeks following a single injection of the ReGel/ZnGLP-1 formulation.

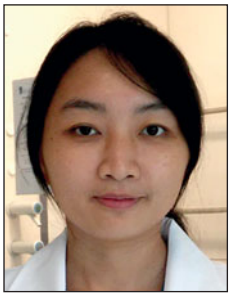
Understanding the material properties of biodegradable thermogels provides only one step toward their development for biomedical applications. Going forward, modifications in the material properties, coupled with advanced computational and imaging techniques, will give a more accurate understanding of drug delivery mechanisms and their importance in clinical studies. More research needs to be done for real clinical applications of thermogels for drug delivery applications.

References

1. D. Roy, W.L. Brooks, B.S. Sumerlin, *Chem. Soc. Rev.* **42**, 7214 (2013).
2. Q.Q. Dou, S.S. Liow, E. Ye, R. Lakshminarayanan, X.J. Loh, *Adv. Healthc. Mater.* **3**, 977 (2014).
3. Z. Li, X.J. Loh, *Chem. Soc. Rev.* **44**, 2865 (2015).
4. E. Ye, P.L. Chee, A. Prasad, X. Fang, C. Owh, V.J.J. Yeo, X.J. Loh, *Mater. Today* **17**, 194 (2014).
5. X.J. Loh, *Mater. Horiz.* **1**, 185 (2014).
6. T. Ci, L. Chen, L. Yu, J. Ding, *Sci. Rep.* **4**, 5473 (2014).
7. J. Luan, W. Shen, C. Chen, K. Lei, L. Yu, J. Ding, *RSC Adv.* **5**, 97975 (2015).
8. W. Shen, J. Luan, L. Cao, J. Sun, L. Yu, J. Ding, *Biomacromolecules* **16**, 105 (2015).
9. Y. Xia, K. Zhu, H. Lai, M. Lang, Y. Xiao, S. Lian, C. Guo, C. Wang, *Exp. Biol. Med. (Maywood)* **240**, 593 (2015).
10. J. Li, Y. Shu, T. Hao, Y. Wang, Y. Qian, C. Duan, H. Sun, Q. Lin, C. Wang, *Biomaterials* **34**, 9071 (2013).
11. B. Yeon, M.H. Park, H.J. Moon, S.J. Kim, Y.W. Cheon, B. Jeong, *Biomacromolecules* **14**, 3256 (2013).
12. M. Patel, H.J. Moon, B.K. Jung, B. Jeong, *Adv. Healthc. Mater.* **4**, 1565 (2015).
13. T.C. Tseng, L. Tao, F.Y. Hsieh, Y. Wei, I.M. Chiu, S.H. Hsu, *Adv. Mater.* **27**, 3518 (2015).
14. Y.H. Cheng, S.H. Yang, C.C. Liu, A. Gefen, F.H. Lin, *Carbohydr. Polym.* **92**, 1512 (2013).
15. L. Huang, R. Li, W. Liu, J. Dai, Z. Du, X. Wang, J. Ma, J. Zhao, *Neural Regen. Res.* **9**, 1371 (2014).
16. L. Yu, H. Hu, L. Chen, X. Bao, Y. Li, L. Chen, G. Xu, X. Ye, J. Ding, *Biomater. Sci.* **2**, 1100 (2014).
17. H.J. Moon, Y.K. Du, M.H. Park, M.K. Joo, B. Jeong, *Chem. Soc. Rev.* **41**, 4860 (2012).
18. J.S. Scarpa, D.D. Mueller, I.M. Klotz, *J. Am. Chem. Soc.* **89**, 6024 (1967).
19. M. Boffito, P. Sirianni, A.M. Di Rienzo, V. Chiono, *J. Biomed. Mater. Res. A* **103**, 1276 (2015).
20. L. Chen, T. Ci, T. Li, L. Yu, J. Ding, *Macromolecules* **47**, 5895 (2014).
21. L. Chen, T. Ci, L. Yu, J. Ding, *Macromolecules* **48**, 3662 (2015).
22. S. Supper, N. Anton, N. Seidel, M. Riemenschnitter, C. Schoch, T. Vandamme, *Langmuir* **29**, 10229 (2013).
23. C. Ju, J. Sun, P. Zi, X. Jin, C. Zhang, *J. Pharm. Sci.* **102**, 2707 (2013).
24. E. Moreno, J. Schwartz, E. Larrañeta, P.A. Nguewa, C. Sanmartín, M. Agüeros, J.M. Irache, S. Espuelas, *Int. J. Pharm.* **459**, 1 (2014).
25. X. Li, L. Chen, H. Lin, L. Cao, J. Cheng, J. Dong, L. Yu, J. Ding, *J. Spinal Disord. Tech.*, published online November 12, 2014, http://dx.doi.org/10.1097/BSD.0000000000000221.
26. U.P. Shinde, H.J. Moon, Y.K. Du, B.K. Jung, B. Jeong, *Biomacromolecules* **16**, 1461 (2015).
27. X.J. Loh, H.X. Gan, H. Wang, S.J.E. Tan, K.Y. Neoh, S.S.J. Tan, H.F. Diong, J.J. Kim, W.L.S. Lee, X. Fang, O. Cally, S.S. Yap, K.P. Liong, K.H. Chan, *J. Appl. Polym. Sci.* **131**, 39924 (2014).
28. Rice University, "A Hydrogel That Knows When to Go (w/Video)," (May 7, 2014) available at http://phys.org/news/2014-05-hydrogel-video.html.
29. B.M. Watson, F.K. Kasper, P.S. Engel, A.G. Mikos, *Biomacromolecules* **15**, 1788 (2014).
30. D. Das, P. Ghosh, A. Ghosh, C. Haldar, S. Dhara, A.B. Panda, S. Pal, *ACS Appl. Mater. Interfaces* **7**, 14338 (2015).
31. J. Yang, R. van Lith, K. Baler, R.A. Hoshi, G.A. Ameer, *Biomacromolecules* **15**, 3942 (2014).
32. BioSyntech Inc., "Thermogelling Polymer Solution for Tissue Regeneration and Delivery of Therapeutics," available at http://www.growthconsulting.frost.com/web/images.nsf/0/55AF07A21D798D1565256F9A001F8E95/$File/Pharma%20TI%20Alert%20NA.htm. News release, undated.
33. Z. Li, S. Cho, I.C. Kwon, M.M. Janat-Amsbury, K.M. Huh, *Carbohydr. Polym.* **92**, 2267 (2013).
34. Y. Yoshida, A. Takahashi, A. Kuzuya, Y. Ohya, *Polym. J.* **46**, 632 (2014).
35. M.H. Park, M.K. Joo, B.G. Choi, B. Jeong, *Acc. Chem. Res.* **45**, 424 (2012).
36. S.S. Liow, Q. Dou, D. Kai, A.A. Karim, K. Zhang, F. Xu, X.J. Loh, *ACS Biomater. Sci. Eng.* **2**, 295 (2016).
37. K. Li, L. Yu, X. Liu, C. Chen, Q. Chen, J. Ding, *Biomaterials* **34**, 2834 (2013).
38. N.L. Elstad, K.D. Fowers, *Adv. Drug Deliv. Rev.* **61**, 785 (2009).
39. E.K. Rowinsky, E.A. Eisenhauer, V. Chaudhry, S.G. Arbuck, R.C. Donehower, *Semin. Oncol.* **20**, 1 (1993).
40. G.M. Zentner, R. Rathi, C. Shih, J.C. McRea, M.H. Seo, H. Oh, B.G. Rhee, J. Mestecky, Z. Moldoveanu, M. Morgan, S. Weitman, *J. Control. Release* **72**, 203 (2001).
41. S.J. Vukelja, S.P. Anthony, J.C. Arseneau, B.S. Berman, C.C. Cunningham, J.J. Nemunaitis, W.E. Samlowski, K.D. Fowers, *Anticancer Drugs* **18**, 283 (2007).
42. C.A. Bagley, M.J. Bookland, J.A. Pindrik, T. Ozmen, Z.L. Gokaslan, T.F. Witham, *J. Neurosurg. Spine* **7**, 194 (2007).
43. B. Gok, M.J. McGirt, D.M. Sciubba, G. Garces-Ambrossi, C. Nelson, J. Noggle, A. Bydon, T.F. Witham, J.P. Wolinsky, Z.L. Gokaslan, *Neurosurgery* **65**, 193 (2009).
44. B. Tyler, K.D. Fowers, K.W. Li, V.R. Recinos, J.M. Caplan, A. Hdeib, R. Grossman, L. Basaldella, K. Bekelis, G. Pradilla, F. Legnani, H. Brem, *J. Neurosurg.* **113**, 210 (2010).
45. K. Matthes, M. Mino-Kenudson, D.V. Sahani, N. Holalkere, K.D. Fowers, R. Rathi, W.R. Brugge, *Gastrointest. Endosc.* **65**, 448 (2007).
46. E. Linghu, K. Matthes, M. Mino-Kenudson, W.R. Brugge, *Endoscopy* **37**, 1140 (2005).
47. A.K. Vellimana, V.R. Recinos, L. Hwang, K.D. Fowers, K.W. Li, Y. Zhang, S. Okonma, C.G. Eberhart, H. Brem, B.M. Tyler, *J. Neurooncol.* **111**, 229 (2013).
48. G.A. DuVall, D. Tarabar, R.H. Seidel, N.L. Elstad, K.D. Fowers, *Anticancer Drugs* **20**, 89 (2009).

https://doi.org/10.1557/mrs.2016.139 Published online by Cambridge University Press

49. J.M. DeWitt, S. Krishnamurthy, R. Ardhanari, C. Neoral, V. Nosek, G.A. Duvall, M. Kaminski, G. Wallner, P. Litka, C. Daugherty, K. Fowers, *Gastrointest. Endosc.* **73** (Suppl.), AB136 (2011).
50. R. Williams, *Expert Opin. Invest. Drugs* **22**, 9 (2013).
51. A.J. Torres, C. Zhu, M.L. Shuler, S. Pannullo, *Biotechnol. Prog.* **27**, 1478 (2011).
52. K. Lei, W. Shen, L. Cao, L. Yu, J. Ding, *Chem. Commun.* **51**, 6080 (2015).
53. B.M. Tyler, A. Hdeib, J. Caplan, F.G. Legnani, K.D. Fowers, H. Brem, G. Jallo, G. Pradilla, *J. Neurosurg. Spine* **16**, 93 (2012).
54. W. Zhu, T. Masaki, Y.H. Bae, R. Rathi, A.K. Cheung, S.E. Kern, *J. Biomed. Mater. Res. B* **77**, 135 (2006).
55. S. Choi, M. Baudys, S.W. Kim, *Pharm. Res.* **21**, 827 (2004). □



Sing Shy Liow is a scientist at the Institute of Materials Research and Engineering, A*STAR. She obtained her PhD degree in polymer science from Nanyang Technological University, Singapore, in 2013. Her research interests include the synthesis of antimicrobial polymers, stimuli-responsive polymers, and hydrogels. Liow can be reached by email at liowss@imre.a-star.edu.sg.

Anis Abdul Karim is a research specialist at the Institute of Materials Research and Engineering, A*STAR, in the Consumer Care Technology Program. She obtained her BSc degree in chemistry and biological chemistry from the School of Physical and Chemical Sciences, Nanyang Technological University, Singapore, in 2012. Her research interests include the development of supramolecular hydrogels and polymer antimicrobials for applications, ranging from drug delivery to cosmetics. Karim can be reached by email at anisak@imre.a-star.edu.sg.

Xian Jun Loh is a polymer chemist working in the interdisciplinary field of biomaterials. He is the program manager of the A*STAR Personal Care Program and an assistant professor at the National University of Singapore. His research interests include designing supramolecular and stimuli-responsive polymers and hydrogels for biomedical and personal care applications. He is the author or co-author of 110 journal papers, 14 patents, 20 book chapters, and four books. Loh can be reached by email at lohxj@imre.a-star.edu.sg.

https://doi.org/10.1557/mrs.2016.139 Published online by Cambridge University Press

MRS Communications

2016
Volume 6, Issue 2

RESEARCH LETTERS

Thermal conductivity of synthetic boron-doped single-crystal HPHT diamond from 20 to 400 K

D. Prikhodko, Technological Institute for Superhard and Novel Carbon Materials and Moscow Institute of Physics and Technology, Russia; **S. Tarelkin**, Technological Institute for Superhard and Novel Carbon Materials, Moscow Institute of Physics and Technology, and National University of Science and Technology MISiS, Russia; **V. Bormashov** and **A. Golovanov**, Technological Institute for Superhard and Novel Carbon Materials and Moscow Institute of Physics and Technology, Russia; **M. Kuznetsov** and **D. Teteruk**, Technological Institute for Superhard and Novel Carbon Materials, Russia; and **A. Volkov** and **S. Buga**, Technological Institute for Superhard and Novel Carbon Materials and Moscow Institute of Physics and Technology, Russia

Thermal conductivity of single-crystal boron-doped diamond (BDD) was studied in comparison with high-quality pure IIa-type diamond in the temperature range from 20 to 400 K. Boron content in BDD was about 10^{19} cm^{-3} that is a typical value of p+ substrates used for power device applications. The thermal conductivity of BDD is about 10 times less than that of IIa diamond near 100 K, but above room temperature the difference is <30%. The observed deviation mostly takes place due to acoustic phonon scattering on extended structural defects occurring in synthetic diamond at high boron content.
DOI:10.1557/mrc.2016.12

Fabricating high refractive index titanium dioxide film using electron beam evaporation for all-dielectric metasurfaces

Ning An, **Kaiyang Wang**, **Haohan Wei**, **Qinghai Song**, and **Shumin Xiao**, Harbin Institute of Technology, China

Transparent high refractive index materials are of the central importance for the development of metasurface in visible range. Titanium dioxide (TiO_2) has been considered as a perfect candidate due to its wide band gap and high refractive index. However, till now, it is still quite challenging to fabricate high-quality TiO_2 films with high refractive indices and low losses. Here we demonstrate the fabrication of high-quality TiO_2 film using an electron-beam evaporation method. We show that the post-annealing conditions play key roles in the microstructure crystallographic and the optical refractive index of the TiO_2 films. A predominately oriented TiO_2 film has been achieved by annealing at 700 °C in oxygen ambient. The refractive index is as high as 2.4, and the corresponding loss is negligible at 632 nm. Further studies on dielectric antennas show that our TiO_2 film can be an ideal platform to fabricate metasurface in visible frequency range. We believe that our research will be important for the advances of all-dielectric metasurfaces. DOI:10.1557/mrc.2016.13

Effect of the ligand in the crystal structure of zinc oxide: an x-ray powder diffraction, x-ray absorption near-edge structure, and an extended x-ray absorption fine structure study

María de los A. Cepeda-Pérez, **Cristina M. Reyes-Marte**, **Valerie Ann Carrasquillo**, **William A. Muñiz**, and **Edgar J. Trujillo**, Universidad Metropolitana, Puerto Rico; **Rahul Singhal**, Central Connecticut State University, USA; **Harry Rivera**, Inter American University of Puerto Rico; and **Mitk'El B. Santiago-Berríos**, Universidad Metropolitana, Puerto Rico

We analyze the effect of functionalization in the surface of zinc oxide crystal structure by 3-mercaptopropionic acid. X-ray powder diffraction data and extended x-ray absorption fine structure studies confirms a wurtzite structure. However, the morphology of the surface seems to be reduced and shows a film-like surface as demonstrated by x-ray absorption near edge structure and scanning electron microscopy. As a result of surface functionalization, the energy levels of the semiconductor were shifted toward reductive potentials (by 50 mV) as determined by diffuse reflectance and cyclic voltammetry. DOI:10.1557/mrc.2016.14

https://doi.org/10.1557/mrs.2016.139 Published online by Cambridge University Press

Empirical relation between Pauling electronegativity and self-energy cutoffs in local-density approximation-1/2 quasi-particle approach applied to the calculation of band gaps of binary compound semiconductors

Mauro Ribeiro, Jr., Office of Operational Research for Business Intelligence & Technology, USA

The local-density approximation (LDA)-1/2 technique has been successfully applied to surmount current limitations in density-functional theory to determine excited-states properties of solids via LDAs to the exchange-correlation functional. The main task to properly apply this technique is to choose the "cut-off" radius to truncate the long-ranged self-energy function, originated by the procedure of removing the spurious self-energy of electrons (and/or holes). The usual procedure is by choosing an extreme of the variation of the band gap as a function of this cutoff. This work examines the relationship between that cut-off parameter and the electronegativity difference between cation and anion in binary compounds calculated self-consistently with LDA-1/2. DOI:10.1557/mrc.2016.16

Local-structure-affected behavior during self-driven grain boundary migration

X.M. Luo, Chinese Academy of Sciences, China; **B. Zhang**, Northeastern University, China; **X.F. Zhu** and **Y.T. Zhou**, Chinese Academy of Sciences, China; **T.Y. Xiao**, Northeastern University, China; and **G.P. Zhang**, Chinese Academy of Sciences, China

In nanocrystalline (nc) metals, it is still not clear how local grain boundary (GB) structures accommodate GB migration at atomic scales and what dominates the motion of atoms at the inherently unstable GB front. Here, we report the adjustment of the local GB structures at atomic scales during self-driven GB migration, simultaneously involving GB dissociation, partial dislocation emission from GB, and faceting/defaceting in the nc Cu. Furthermore, we reveal that the fundamental of GB migration ability is closely related to the local structure, i.e. the GB segment consisting of "hybrid" structural units and delocalized GB dislocations is relatively unstable. DOI:10.1557/mrc.2016.10

SPECIAL ISSUE PROSPECTIVE ARTICLE: PLASMONICS, PHOTONICS, AND METAMATERIALS

An integral equation based domain decomposition method for solving large-size substrate-supported aperiodic plasmonic array platforms

Shifei Tao, **Jierong Cheng**, and **Hossein Mosallaei**, Northeastern University, USA

We propose a surface integral equation simulation scheme which incorporates the integral equation fast Fourier transform accelerative algorithm and domain decomposition method. Such scheme provides efficient and accurate solutions for substrate-supported non-periodic plasmonic array platforms with large number of building blocks and complex element geometry. The effect of array defects can be systematically and successfully studied taking advantage of the considerable flexibility of the domain decomposition approach. The proposed model will be of great advantage for fast and accurate characterization of graded-pattern plasmonic materials and metasurfaces. DOI:10.1557/mrc.2016.11

SPECIAL ISSUE RESEARCH LETTER: PLASMONICS, PHOTONICS, AND METAMATERIALS

Efficiency enhancement via metal-coated porous amorphous silicon back reflectors incorporated in amorphous silicon solar cells

Shweta Bhandaru, Vanderbilt University, USA; **Angelo Bozzola** and **Marco Liscidini**, University of Pavia, Italy; and **Sharon M. Weiss**, Vanderbilt University, USA

We present two straightforward and cost-effective methods, based on metal-assisted chemical etching and a direct imprinting technique, to fabricate metal-covered porous amorphous silicon back reflectors for amorphous silicon solar cells. We demonstrate an increase of approximately 30% in both short-circuit current and overall efficiency with respect to a cell with a flat metal back reflector. This is achieved by implementing light trapping via either a roughened porous amorphous silicon layer or an imprinted periodic grating. This work provides a pathway to increase amorphous silicon solar cell efficiency via increased absorption without significantly impacting processing costs. DOI:10.1557/mrc.2016.15

https://doi.org/10.1557/mrs.2016.139 Published online by Cambridge University Press