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Exploration of polymethacrylate structure-property correlations: Advances towards combinatorial and high-throughput methods for biomaterials discovery

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Abstract

In this review, we discuss the synthesis, characterization, physical properties, and applications of polymethacrylates and describe physical and biological structure-property correlations relevant to many high performance applications. We also track the advancement of material-property space from the ‘traditional’ mode of materials design to the emerging, state-of-the-art combinatorial and *in silico* methods. Particularly, this article places emphasis on recent advances in the automated combinatorial synthesis and development of high-throughput characterization methods. As a future perspective, we believe that the realization of combinatorial, high-throughput, and computational methods will allow for the rapid exploration of a vast polymethacrylate library property space.

Keywords

polymethacrylates; biomaterials application; combinatorial; high-throughput; polymer libraries

1. Introduction

Polymethacrylates are an important class of materials possessing a wide range of properties. Extensive studies by laboratories around the globe have lead to the discovery of many commercial applications for polymethacrylates spanning high-performance engineering plastics, energy storage materials, functional coatings, and biomaterials. More specifically, polymethacrylate derivatives have a long established role in biomedical devices and are utilized in restorative dental composites, contact lens materials, and bone cement [1–3]. Here we present a review of polymethacrylate literature that demonstrates the evolution of combined combinatorial synthetic and high-throughput screening methodologies in the correlation of structure-property relationships for the discovery and evaluation of new materials. We focus on the field of biomaterials and the development of computational modeling tools for the prediction of polymer properties and bio-response.

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2. Polymethacrylates as materials

In 1880, poly(methacrylic acid) became the first reported methacrylate polymer to be synthesized [4]. Forty-eight years later, poly(methyl methacrylate) (PMMA) was developed. PMMA was eventually marketed in 1933 and is now the world's most widely produced methacrylate polymer [5,6]. Today, worldwide annual production of methacrylate polymers exceeds 2 million metric tons.

2.1 Polymethacrylate adjustability

The extraordinarily diverse range of pendent functional ester groups that can be incorporated into the methacrylic repeat unit (Figure 1) is one feature that allows polymethacrylates to exhibit such varied properties. Literally, any pendent group chemical functionality can be considered: alkyl, aryl, acyl, charged, halogen, metal containing, or unsaturated groups. Some methacrylates are crystal clear with high mechanical strength and good outdoor weather resistance; this accounts for their many applications as protective coatings and glass substitutes. At the other end of the mechanical property spectrum, certain methacrylates, such as poly(2-hydroxyethyl methacrylate) (PHEMA) and its copolymers, are hydrophilic gels that are used in soft contact lenses.

Notwithstanding, it is also perhaps the ease at which homo-, co-, and terpolymers can be synthesized by free radical polymerization that allows for the 'tuning' of material properties by combining repeat units with varying functionalities. Although free radical polymerization is well established, recent renewed interest has generated technological advances that provide new synthetic techniques that yield homo-, co-, and terpolymers having architecturally complex structures with controlled molecular weight (MW) and polydispersity. As described in a later section, this is of particular importance in the fields of gene delivery and molecularly imprinted polymer development, where material performance is closely related to polymer MW and the degree of polymerization. By contrast, the versatile approach of photoinitiation polymerization of multifunctional methacrylate moieties yields crosslinked networks where such structures can exhibit, for example, hydrogel-like properties or unusually high strength. Material properties may also be governed by post polymerization processing. For instance, the blending of immiscible polymethacrylates results in multi-component phase separated systems and the annealing of semicrystalline materials alters the ratio of amorphous/crystalline regions.

2.2 Methacrylate libraries

Due to the large number of methacrylate ester monomers commercially available, the potential number of unique polymethacrylates is vast. For instance, considering only copolymers with composition steps of 5 mole %, the number of unique homopolymers and copolymers that can be synthesized from 50 different methacrylate monomers exceeds 20,000—the inclusion of terpolymers increases the potential library size to well over 300,000 members—and the addition of variations in polymer architecture (e.g., random vs. block or gradient structures) expands the potential library size to over a million members. Only a small subset of this large library of polymers has been studied and even less are commercially available. This vast, largely unexplored polymer library holds the potential for the identification of polymers with unique properties optimal for specific applications. Ideally, if one understood the relationship between molecular structure and polymer properties, polymer selection could be made without resorting to extensive lab work to synthesize and characterize many polymer candidates. While the widespread application of polymers as engineering plastics is supported by an extensive understanding of structure-performance correlations, *ab initio* calculations of structure-property relationships are not yet realized. For biomaterial applications, a comprehensive understanding of the interactions between the implanted polymers and the surrounding cells

and tissues has not yet been established; this makes it impossible to apply a rigorous, rational design process to the identification of new biomaterials [7,8].

3. Combinatorial and computational approaches in elucidating structure-property correlations

Traditionally, for the exploration of structure-property correlations or the tailoring of material properties for a specific application, a small series of 4–6 polymers with chemical variations are synthesized for investigation. The rationale behind functional monomer choice is usually based on the chemical intuition of a polymer chemist. While this approach may allow polymer chemists to identify materials with suitable properties, it is highly unlikely that this approach will identify the polymer with *the best possible properties* for the intended application. To address this, researchers have advanced the development of combinatorial methods that demonstrate that hundreds of individual samples can be prepared to allow for the investigation of systematic structural variations.

3.1 The combinatorial approach developed in the pharmaceutical industry

Combinatorial approaches developed by the pharmaceutical industry dramatically changed the way lead compounds for the development of new drugs are identified [9]. In the classical "CombiChem" approach, millions of moieties are combinatorially synthesized within a single reaction vessel before potentially active compounds are identified in a selective bioassay. This classical CombiChem approach for the discovery of materials cannot be used for the discovery of lead polymers, owing to several conceptual and experimental difficulties discussed in this review. Instead, material scientists have produced a number of advances in synthesis and characterization that are leading towards a truly combinatorial synthetic and rapid screening characterization approach for the identification of structure-property correlations in polymethacrylates.

3.2 The use of spatially resolved libraries

For material science and particularly polymer science, the approach of generating many different polymers within one single reaction vessel is limited by the difficulty of separating the mixture into individual polymers. The problems associated with separating mixtures of many different materials into discrete compositions were circumvented using spatially resolved libraries. This approach was applied for the first time in a combinatorial search for photoluminescent inorganic phosphor compositions by the creation of different material compositions within a two-dimensional XY grid. A simple optical reading of the photoluminescence provided the necessary high-throughput assay and enabled identification of lead compositions with potentially useful photoluminescence [10]. The concept of using spatially resolved libraries was later adapted at the National Institute for Standards and Technology (NIST) where researchers explored the properties of polymer blends within a two-dimensional grid in which all possible blend compositions were represented by a pair of XY coordinates [11–13].

The past decade has brought a considerable increase in the application of combinatorial, parallel synthesis, and high-throughput experimentation techniques in polymer science (see reviews [14–19]). Reports are now appearing where polymer libraries with hundreds of members and wide ranging properties or processing conditions are studied. Although this is a great improvement over traditional manual techniques, it still leaves the vast majority of possible polymers unexplored when the library size exceeds 10,000 members.

3.3 Utilizing computational modeling

Computational modeling offers a solution to the abovementioned dilemma. Computational models that relate polymer molecular structure to their properties and performance provide a means to create a virtual polymer library *in silico*. Virtual polymer libraries are large collections of polymer structures created using various molecular modeling tools. The model structures are then used to derive predictions of polymer properties, thereby providing a rational way to select a smaller subset of these virtual polymers for actual synthesis and exploration. This approach, commonly used in drug discovery, has only recently been explored as a tool in biomaterial design [20]. In this context, biomaterials scientists can learn much from the field of drug discovery where two powerful techniques, molecular similarity-diversity analysis and quantitative structure-property relationship models, enable prediction of target properties for a library of compounds. This can work to greatly accelerate and optimize the discovery process.

3.4 Combining combinatorial and computational modeling approaches

The very first example for of the simultaneous use of combinatorial synthesis and computational modeling approaches applied to polymeric materials was demonstrated by Kohn et al. with a library of 112 polyarylates [14,20]. Polycondensation polymerization of 14 different diphenols and 8 different diacids with systematic structural variations was conducted in a parallel fashion to obtain the library of (14×8) 112 polyarylates. A computer model was developed to determine the molecular-scale polymer properties that correlate to various biological responses. The model successfully predicted fibrinogen adsorption and rat lung fibroblast cell growth on polymer surfaces. Combinatorial and computational approaches for prediction of polymer performance have recently been reported for other applications, such as the prediction of pore size distribution in polymeric ultrafiltration membranes, the selection of functional monomers to synthesize effective molecularly imprinted polymers, and the optimization of polymer composition for photoembossing [21–23].

3.5 Use of a recursive neural network model

A recursive neural network (RecNN) modeling approach was developed to predict the T_g dependence from backbone stereoregularity by treating atactic methacrylic polymers together with polymer samples of different stereoregularity [24]. Based on structured molecular representations of the compounds, the RecNN model uses a direct and adaptive relationship between molecular structure and target properties. Here, the RecNN was trained to learn the T_g prediction using a library of 95 polymers (with glass transition temperatures between 197 and 501 K) that were divided into a disjointed training set of 80 and test set of 15 polymers. The experimental glass transition temperatures of the training set polymers were well reproduced by the RecNN and the model yielded good performance when applied to the test set of materials. The RecNN's ability to establish quantitative structure property relationship (QSRP) correlations using both molecular structure and average macromolecule characteristics is of paramount importance for prediction purposes. Quantitative structure property relationship approaches like the RecNN rely on molecular descriptors that cannot be calculated directly for high-MW molecules. QSPR models have been developed using approximate procedures or reduced representations (e.g., 20 repeat units at best), however, these do not consider average polymer properties that often govern material response. The challenge remains to extend the QSPR model representation to deal uniformly with both homopolymers and copolymers.

3.6 The potential of this approach

Future trends in this approach will lead to the exploration of the vast structure-property space of large polymer libraries. As an example, we discuss the potential benefit of applying these techniques to the discovery of new biomaterial applications for polymethacrylates. Given the

diverse set of methacrylate monomer building blocks, identifying optimum polymethacrylate polymers, in terms of composition and structure, for a given biomaterial application without having to synthesize and characterize a large quantity of polymer candidates is an attractive prospect for polymer chemists.

4. Polymethacrylate synthesis

For the discovery of lead polymers and structure-property correlations, it is only possible to screen useful material properties on test polymers with a state of high purity. While the chemical structure of a low-molecular weight drug candidate determines its biological activity, the chemical structure of a polymer's repeat unit is only one of the many parameters that affects its ultimate utility. Other equally important parameters are polymer molecular weight, molecular weight distribution, and fabrication method. However, an alternative to the simultaneous synthesis of many species within the same reaction vessel is the employment of a combinatorial search for optimized polymer structures through parallel synthesis (the simultaneous synthesis of a larger number of individual polymers within individual reaction vessels). With parallel synthesis, each individual material of the library is obtained in pure form.

4.1 Free Radical Polymerization

Polymethacrylates are produced using free radical addition polymerization, one of the most widely used methods for the commercial production of high molecular weight polymers [25]. In addition to being both cost effective and relatively simple to implement, free radical polymerization has the advantage of working with many monomer types and functional groups. Free radical polymerization of methacrylates is conducted by a variety of different methods, including bulk, solution, suspension, and emulsion [26]. In general, the mechanism of free radical addition polymerization involves formation of free radicals from an initiator species, reaction of the free radical with monomer to form a radical monomer species, and subsequent propagation to high polymer by repeated addition of monomer to the growing radical chain. Polymerization is terminated by radical-radical reaction through coupling or disproportionation.

4.2 Living Radical Polymerization

Within the past decade, a renewed interest in free radical addition polymerization has emerged with the development of new living radical polymerization (LRP) techniques. The three most commonly used LRPs are nitroxide-mediated polymerization (NMP), atom transfer radical polymerization (ATRP), and reversible addition-fragmentation chain transfer polymerization (RAFT) [27–30]. These techniques achieve near ideal living polymerization characteristics by suppressing irreversible chain termination steps through the addition of reagents that react with propagating radicals by reversible deactivation or reversible chain transfer. As a result, the majority of propagating chains are maintained in a dormant form, thereby minimizing radical-radical termination reactions. Rapid equilibration between active and dormant species relative to the propagation rate ensures that all chains will grow at an equal rate. Polymers synthesized by these LRPs exhibit living characteristics, such as a linear increase in molecular weight with conversion, narrow molecular weight distributions, and retention of active, functional chain ends. RAFT and ATRP are used with a wide range of monomer types including methacrylates, whereas NMP is much less versatile and not generally applicable to methacrylate monomers [31]. In depth reviews for NMP, ATRP, and RAFT have recently emerged [32–35].

LRP allows much greater control over the polymer composition, molecular weight, and architecture than standard free radical polymerization. The recent explosion in research activities on LRPs has resulted in the controlled synthesis of many polymer structures,

including block copolymers, gradient polymers, stars, brushes, and highly branched networks [31,34]. These developments are expected to lead to the commercial realization of many new polymeric materials that will significantly impact the materials industry.

5. Combinatorial studies of polymethacrylates in biological applications

There are relatively few combinatorial studies of polymethacrylates reported; those reported include studies of polymethacrylates for fluorescent sensor applications, studies of polymethacrylate terpolymers for x-ray nanolithography, studies aimed at optimizing polymer processing conditions for the synthesis of PMMA via ATRP, and studies of the RAFT polymerization of random and block copolymers [36–39].

A number of studies have focused on using polymethacrylates in biological applications. Two prime examples are the utilization of polymethacrylates in the development of gene delivery vehicles and molecularly imprinted polymers.

5.1 Gene delivery

Many genetic engineering methods are based on the delivery of foreign nucleic acids into intact cells. A leading class of nonviral gene delivery vector systems is the polyelectrolyte complex. These complexes are formed by the spontaneous self-assembly of cationic polymers with negatively charged plasmid DNA. This approach has led to an enhancement of DNA uptake into cells and an increase in transfection activity. However, the cationic nature of polymers such as poly(L-lysine), poly(ethylene imine), chitosan, and poly(2-(dimethylamino)ethyl methacrylate) can result in pronounced, acute cytotoxicity [40,41]. It is believed that while polymers with high cationic density condense DNA into structures amenable to cellular internalization via endocytosis, the high charge density also contributes to their cytotoxicity [42].

A number of reported studies have evaluated small libraries of various side group functionalized poly(amido-amine)s, poly(L-Lysine graft imidazoleacetic acid conjugates), and polymethacrylates on their ability to bind plasmid DNA, transfect cells, and assess cytotoxicity [41,43–46]. In the selection of polymers for gene delivery applications, a combinatorial approach for the systematic modification of the pendent functionality is helpful in elucidating the relation between structure and activity for the establishment of physicochemical trends. For instance, six synthetic cationic polymers closely related to poly(2-(dimethylamino)ethyl methacrylate) (p(DMAEMA)) were evaluated as transfectants *in vitro* [41]. Despite the fact that almost all of the cationic methacrylate/methacrylamide polymers were able to yield similar particulate sizes, ζ -potentials, and DNA polyplexes, the transfection efficiency and cytotoxicity of the polymers differed widely. All of the p(DMAEMA) polymer analogues were shown to exhibit lower cytotoxicity than p(DMAEMA). Although a reduction in toxicity was brought on by the incorporation of an amide instead of an ester group and a propyl instead of an ethyl side chain, no synergistic reduction in cytotoxicity was observed. Similarly, the permanently positively charged trimethyl amino group exhibited one fifth the toxicity of p(DMAEMA).

Polymer/plasmid polyplexes followed the same trend as the free polymer on cell viability. Transfection efficiency of the p(DMAEMA) analogues was 5 – 400 fold lower than that of p(DMAEMA). All polyplexes possessed the same physicochemical characteristics, yet their transfection efficiencies differed widely. It was found that while relatively small changes in the structure of p(DMAEMA) do not largely affect the condensing properties of the polymers, the effect on the cytotoxicity and transfection capability is substantial.

Since polyplexes have comparable physico-chemical characteristics, the reduced transfection efficiency cannot be ascribed to the formation of large complexes or differences in ζ -potential. However, the high cytotoxicity of p(DMAEMA) might be ascribed to its ability to destabilize endosomes. High cytotoxicity has been observed for other polycations as well [47].

Researchers studied a family of diblock methacrylamide and hydroxypropyl methacrylate (HPMA) copolymers of varying molecular weights and tested their ability to complex a single DNA molecule [44]. Complexes with a single DNA molecule were found to be best suited for uptake into cells; moreover, pendent quaternary ammonium groups with MWs lower than that of the PHPMA blocks and diblock copolymers with poly(hydroxypropyl methacrylate) were shown to be most amenable for uptake.

A similar copolymer system comprising N-(2-hydroxypropyl)-methacrylamide, developed as a precursor for drug conjugates and currently in Phase II trials in the UK for the treatment of cancer, has been further explored in order to exploit its biological advantages [48]. In an effort to examine how polymer properties correlate with biological profile, researchers prepared a library of copolymers with narrow MW distribution, same MW characteristics, and uniform pendent chain structure applying controlled ATRP. By adopting such a strategy, tedious fractionation procedures can be avoided for the preparation of narrow MW distribution specialty polymers for use in applications ranging from healthcare to consumer products.

5.2 Molecularly Imprinted Polymers

Combinatorial and high-throughput methods have been successfully applied in the search of polymeric materials with recognition properties for small molecules known as molecularly imprinted polymers (MIPs). MIPs are used as adsorbents for therapeutic use and are also used in areas such as solid-phase extraction as substrates for enantiomer separation. Given that it is difficult to predict the best recipe for imprinting a template, a common approach for acquiring high-performance molecularly imprinted receptors is to screen thousands of combinations and compositions of the agents under different polymerization conditions. Owing to their wide ranging properties, methacrylate based polymers have been largely explored in MIP applications.

The effective combination of a molecular imprinting concept and a combinatorial synthesis strategy was reported in the search for new MIP receptors [49]. An automated liquid handling system allowed for the synthesis of 49 poly(methacrylic acid-*co*-2-(fluoromethyl) acrylic acid)s crosslinked with ethylene glycol dimethacrylate. The screening of two artificial receptors for triazine herbicide, ametryn, and atrazine revealed that the imprinting efficiency differs depending on the functional monomer composition and the template molecule. The development of a combinatorial *in situ* molecular imprinting process provides a useful tool for evaluating large numbers of different MIPs in a short time. The chief advantage of the high-throughput screening method is that it can easily be extended to conduct saturation binding tests and probe matrix parameters such as the influence of additional functional monomers. In addition, the choice of solvent and cross-linker was shown to have a significant effect on the performance of the resultant polymers.

5.3 Mini-MIPs

Recognizing the aforementioned factors, researchers developed a rapid screening method approach coined “mini-MIPs” [50,51]. While similar to the abovementioned combinatorial approach, this protocol included screening steps that significantly accelerated the development of new molecular recognition elements [49]. Exploiting the low consumption of reagents, researchers further developed the advantages of a small-scale protocol by employing a 96-well plate for the preparation and screening of MIPs [52]. Using the workflow system illustrated in

Figure 2 incorporating an automated fluid handling and multifunctional plate reader, researchers were able to optimize a polymer successfully imprinted with the local anesthetic Bupivacaine in roughly one week. Automated fluid handling allowed for a library of 80 polymers to be prepared in 24 hours with the monomers methacrylic acid, 2-hydroxyethyl methacrylate, and ethylene glycol dimethacrylate (about 50 mg was obtained for each polymer). The quantification of Bupivacaine to a nonbound template in the supernatant fraction was reduced from 45 minutes using serial HPLC to ~1 minute using the multifunctional plate reader. High-throughput synthesis and evaluation of the polymer library successfully identified the MIP synthesis conditions for the selective extraction of Bupivacaine from blood plasma samples [52]. This approach holds promise for application in other diagnostic test systems.

Molecular modeling was used to gain insight into the interactions between plasmid DNA and polymers. Elongation of the side group was found to increase the number of interactions between the polymer cation and DNA. Molecular modeling suggests that, out of the polymers tested, p(DMAEMA) has the lowest number of interactions with DNA. Since easy dissociation of the vector-DNA complex within the endosome is a prerequisite for effective gene delivery, a combination of physico-chemical, biological, and modeling techniques are being developed to shed light onto the factors that determine the efficiency of polymeric transfectants.

In another study, chemists synthesized a combinatorial polycation library based on tertiary amine, quaternary ammonium, imidazole, and hydroxypropyl conjugated methacrylates block copolymerized with PEG [45]. The aim of this study was to use a minimal number of polymers to obtain relevant information about structure-property correlations. The selected pendant functional groups provide the cationic density required for DNA condensation and intracellular uptake that can permeabilize vesicular membranes at the acidic pH values found during endocytosis. The molecular weight characteristics, aqueous solubility, viscosity, and ability of the sixteen block copolymers to complex with plasmid DNA at pH 4.5 – 7.4 were determined in an effort to correlate the physicochemical and biological properties. The combinatorial library of cationic polymethacrylamides was synthesized to obtain the same degree of polymerization, however, the relative amount of PEG was found to subtly influence DNA association. For instance, only the histamine and dimethylamine copolymers that contained PEG blocks were able to complex DNA. Several 3-(dimethylamino)propyl amine containing polymers did not display evidence of DNA association. This study demonstrates how a combinatorial approach can be used to both identify lead polymers and exclude inactive materials from further study.

6. High-Throughput Screening Assays

High-throughput and combinatorial methods have become increasingly popular in material discovery, characterization, and optimization. Combinatorial methods have several advantages over traditional techniques, including fast data acquisition, more thorough examination of experimental variables, equal processing conditions for a given specimen, and low experimental error [53].

6.1 The 1728 polymer methacrylate array

Evaluating cell response, polymer chemists conducted a seminal proof of principle study employing high-throughput screening of the C2C12 embryonic muscle cell line (hES) on 1728 polymers using a single array format [54]. Exploiting the large commercial availability of monomers and their rapid polymerization by a light activated radical initiator, researchers developed a discrete nanoliter-scale microarray format that minimized reagent cost and provided an accurate high-throughput analysis platform for hES response on methacrylate polymers. Specifically, the array allowed for the investigation of varying levels of hES cell attachment and spreading, cell type specific growth, and growth factor-specific proliferation.

For the fabrication of this discrete array, pairwise combinations of 24 methacrylate monomers were printed as 576 spots in triplicate on a non-adhesive coated conventional glass slide (25 × 75 mm). Using a modified fluid handling system, researchers can fabricate up to 20 arrays comprising 1728 spots in one day. Each of the spots is 300 μm in diameter. The combination of poly(hydroxyethyl methacrylate), the non-adhesive coating, with the precise spot deposition control allowed materials to be spaced adequately to inhibit cell growth between polymers and ensured that material effects on cells were independent of neighboring materials. Importantly, the materials in this approach were compatible with and resistant to the aqueous conditions necessary for cell-based testing. This simple array format allows for the simultaneous screening of multiple cellular markers on a single glass slide. The hES response was analyzed by simultaneous staining using four-color fluorescence imaging of multiple slides. A variety of materials were identified that, in combination with proper solution conditions, allow for high levels of differentiation into cytokeratin-positive cells. While the mechanism underlying C2C12 embryonic muscle cell-specific differences is unclear, analysis of the cell-material interactions can identify the cell specific materials useful in the creation of complex tissue engineering constructs.

The above mentioned methacrylate array has been successfully extended to the field of mechanical property screening where the surveying of structure-processing-property relationships is crucial [54]. By providing systematic variations in materials that allow for correlations to be explored, combinatorial synthetic approaches spur development of materials for diverse applications: microelectronics, abrasion resistant palliative coatings, photonics compatible adhesives, and polymeric biomaterials. Researchers developed a precise high-throughput analysis of mechanical properties using the array of 1728 methacrylate polymers to facilitate subsequent correlation of these properties with material composition and functional performance metrics [55]. The mechanical properties of the 300 μm spots were assessed by nanoindentation using automated acquisition and analysis with a high degree of reproducibility. Interestingly, although the majority of comonomers did not strongly affect the modulus at low concentrations (30 vol.-%), certain monomers significantly and consistently lowered E-values. Similarly, the mechanical properties of some of the copolymers are not necessarily consistent with those of their bulk counterparts. This observation, not expected from structural or comonomer content, suggests that a microstructural and/or phase change may be correlated with a significant increase in mechanical stiffness. This study highlights the ability of combinatorial chemistry and high-throughput screening to enable material design through systematic variation in composition, processing, and/or microstructure.

6.2 The use of high-throughput screening for restorative dental material development

In the area of restorative dental materials, researchers are also using high-throughput screening. Here, the target is to explore the effects of monomer composition on reaction kinetics and monomer conversion. Nanoindentation was applied to characterize the mechanical properties of a model two-component dimethacrylate dental resin blend comprising triethylene glycol dimethacrylate and ethoxylated bisphenol-A dimethacrylate [1]. A high-throughput screening approach was adopted by using a 2D gradient array to explore the effects of comonomer composition and irradiation time on the modulus. While the application of nanodentation can be used to examine the mechanical properties of localized small material volumes, it is also ideal for measuring the mechanical properties across an interface. Methacrylate conversion was controlled using a programmable light source and characterized by near infrared spectroscopy. As a result, elastic modulus and hardness of the 2D gradient property space were found to display an excellent agreement with conversion (in the range from 40 to 85%). As expected, appreciable changes in modulus correlated with high conversions [1]. This trend is attributed to changes in network crosslink density at high conversion and illustrates the necessity of obtaining high reaction conversion in restorative dental composites. Relationships

between the chemical compositions were also evaluated, thus demonstrating that high-throughput analysis and combinatorial methods are effective for elucidating properties over a large parameter space in a single platform.

6.3 Gradient-responsive combinatorial tunable surfaces

Combinatorial tunable surfaces with gradient responsive properties were developed through surface initiated ATRP of n-butyl-*b*-2-(N,N'-dimethylamino)ethyl methacrylate. Chemists created a uniform poly(butyl methacrylate) bottom and a molecular mass gradient of poly(n-butyl-*b*-2-(N,N'-dimethylamino)ethyl methacrylate) for studying the influence of relative block length on the solvent responsive behavior of block copolymers [56]. The solvent response of the combinatorial polymer brush gradient libraries was evaluated by water contact angle measurement. The systematic variations in block copolymer length across the surface developed in this work let researchers observe phenomena that would otherwise be difficult to discern with uniform samples.

6.4 Addressing issues with polymer array fabrication

A recognized bottleneck in combinatorial materials research is sample preparation and characterization. A number of polymer array fabrication approaches can be discerned. For instance, in the simplest form, arrays of polymer dots obtained by dropcasting deposit virtually all the solute as a ring that marks the perimeter of the sessile droplet. This phenomenon, commonly referred to as the coffee-ring effect, yields nonhomogeneous films. Addressing this, researchers demonstrated the feasibility of combinatorial spin coated blend arrays with varying composition [57]. The parameter space of poly(methyl methacrylate) and polystyrene blends was probed using contact angle measurement and atomic force microscopy. Adapting a standard spin-coating method for producing polymer films, researchers coat several samples onto the same substrate and order them in a circular, rather than rectangular, fashion. This circular coating is achieved by "sector spin-coating" wherein a round glass substrate is divided into sectors using a template (Figure 3). This approach removes the need to change substrates between two samples, promotes the efficient use of expensive substrates, and allows for the identical post treatment of samples. Libraries of up to 16 samples onto one single substrate were characterized using automated atomic force microscopy and contact angle. The high-throughput analysis of combinatorial spin coated arrays allowed for the morphological measurement of 8 immiscible poly(methyl methacrylate) and polystyrene blends in 72 minutes, while the surface properties of 16 polyoxazolines could be characterized in 50 minutes.

An alternative strategy developed to study the location and nature of transitions in the surface-pattern morphology of symmetric methyl methacrylate and styrene block copolymers is the fabrication of "thickness gradient libraries". With the aim of characterizing physical properties, researchers fabricated thin films of varying thickness by using an automated solution flow coater and a computer controlled linear motion stage [11,12]. Film gradient libraries were validated by comparison to previous observations on surface-pattern formation in symmetric diblock copolymer films. A single thickness gradient library reproduced an entire range of surface pattern formation and allowed for the identification of new and important surface pattern phenomena. The vast property space probed may allow for enhanced development of modeling theories of pattern formation in block copolymer films.

7. Future Trends and Summary

As highlighted in this trends review, polymethacrylates are an extensively utilized and studied class of materials. We have shown that a shift from a 'traditional' mode of materials design is emerging through the realization of state-of-the-art combinatorial and *in silico* methods. This shift represents a significant advancement that permits the systematic investigation of a large,

mostly unexplored family of polymers. The advances in synthesis, both in automated combinatorial methods and methacrylate polymerization, are enabling the availability of material libraries with defined polymer properties. The increasing number of reports described in this article clearly demonstrates the utility of high-throughput screening methods in the elucidation of both physical and biological structure-property correlations extending to multiple applicable fields. However, to address the issue of exploring very large numbers of materials, we believe it is necessary to advance the development of computational modeling tools for the prediction of polymer properties and bio-response. Already, *in silico* methods are being realized in polymer libraries for the predication of materials properties. This approach ultimately holds the potential to remove the need to synthesize polymers for material property characterization.

Nomenclature

PMMA, poly(methyl methacrylate)
 PHEMA, poly(2-hydroxyethyl methacrylate)
 RecNN, recursive neural network
 QSPR, quantitative structure property relationship
 RAFT, reversible addition–fragmentation chain transfer polymerization
 LRP, living radical polymerization
 NMP, nitroxide-mediated polymerization
 ATRP, atom transfer radical polymerization
 MIP, molecularly imprinted polymer
 p(DMAEMA), poly(2-(dimethylamino)ethyl methacrylate)
 MALDI-TOF-MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
 MMD, molecular mass distribution
 PEG, poly(ethylene glycol)

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Figure 1.

The chemical structure of polymethacrylate repeat unit. Chemical diversity is created by using a wide range of different pendent "R" groups. Polymer properties can be further modified by using co- and terpolymers containing 2 or 3 different "R" groups simultaneously.

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Figure 2.

Semiautomated high-throughput procedure for the synthesis of mini-MIP libraries in microtiter plate format and evaluation of the library via serial (HPLC) or parallel (multifunctional plate reader) techniques from reference [52].

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Figure 3.

Principle of sector spin coating. (1) A star-shaped metal template is placed on top of a circular substrate that divides the substrate into 8 sectors. (2) The sectors are spin coated in series. (3) After the template is removed, one substrate with eight different polymer films is obtained [57].