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Review

Biocompatible Anisotropic Polymeric Particles: Synthesis, Characterization, and Biomedical Applications

Ifra Mirza and Sampa Saha*

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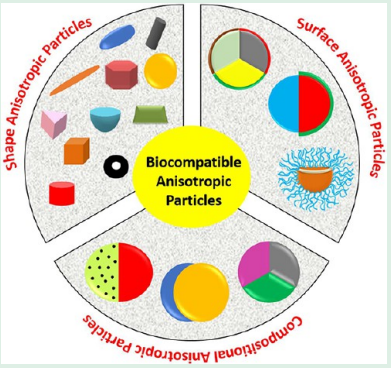
ABSTRACT: Recently, biocompatible anisotropic particles have emerged as a powerful platform in the biomedical field, especially in the areas such as therapeutics, theranostics, biosensor, targeted drug delivery, triggered drug delivery, cellular uptake, targeted cellular internalization, etc., because of their unique characteristics and superior performances over their isotropic analogues. Macromolecular anisotropic particles can primarily be classified into three different categories, such as shape anisotropy, compositional anisotropy, and surface anisotropy, i.e., heterogeneous surface chemistry leading to anisotropic surface patches. In this review, we have attempted to give an overview on the biocompatible anisotropic polymeric particles related to their synthesis and applications in biomedical arena with emphasis on their fascinating properties over spherical particles. A brief summary of their future developments is also highlighted.



KEYWORDS: *Anisotropic polymeric particles, Shape anisotropy, Compositional anisotropy, Janus particles, Patchy surface, Drug delivery*

1. INTRODUCTION

Multifunctional polymeric colloids/particles have shown extraordinary revolution because of their promising properties and applications in various areas such as electronics, nanotechnology, biotechnology, reusable energy, etc.[1−5] Because of the biocompatibility and targeting ability, biocompatible polymeric particles are particularly attractive as drug-delivery carriers.[6] Among precisely engineered colloidal particles, anisotropy is increasingly gaining attention as one of the design parameters while fabricating colloidal particles of micrometer and nanosize for various applications such as drug delivery, biosensors, contrast agent and imaging, etc.[7−12] In past decades, biomaterials research was traditionally focused on isotropic/spherical particles, but recently, the focus has been turned toward nonspherical or anisotropic particles because of their superior biological performance.[10,11,13−16]

In a particle system, anisotropy can be generated in various domains such as shape, composition, and surface or a combination of them. Particles with shape anisotropy have homogeneous composition throughout the particle with anisotropy in shape, whereas compositional anisotropy arises from heterogeneous composition in a single particle, e.g., multicompartmental or Janus particles. In past few years, a wide variety of anisotropically shaped biocompatible polymeric particles have been introduced such as ellipsoid,[17] needle shaped,[18] disks,[19] cubic shape,[20] rod shape,[21] cylinders,[22] cups,[23] trojan,[24] toroidal spiral,[25] etc., where particle shape has been shown to have profound influence on cellular uptake,[26] targeted drug delivery,[27] targeted gene delivery,[28] optical properties,[29] enhanced binding,[30] targeted cellular internalization etc.,[31] thus inspiring the researchers to further develop novel strategies to synthesize anisotropic particles. On the other side, Janus or multicompartmental particles are a kind of particle system that exhibits a good control over multifunctional properties (chemical or physical or both) spaced in different compartments, e.g., it provides a facile route to directly incorporate two or more drugs/therapeutic agents in a single particle with independent release rates depending on the matrix of individual compartments, opening a new paradigm for drug-delivery applications.[32] Another interesting class of anisotropic particles is patchy particles, i.e., particles with heterogeneous surface patch.[33] Spatioselective surface modification of a portion of a particle may lead to surface patches selectively only on that part of a particle. These types of patchy particles may find their application as targeted drug-delivery carrier by suitably modifying the surface with a targeting moiety, which may work as ligand to bind to the receptor from a targeted site, thus facilitating the transport of drug to the appropriate location.[34]

Anisotropic particles have drawn significant attention of researchers because of their enhanced physical, chemical, and

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biological properties compared to their isotropic analogues.[10] One of the most sought after properties of the shape anisotropic particles/nonspherical particles is the inhibition of nonspecific cellular uptake leading to enhanced *in vivo* biodistribution and increased targeting capabilities due to the high radius of curvature for bent particles.[10] Various researchers have investigated their properties in detail specifically for biomedical applications. For example, Sharma et al. demonstrated the interaction of anisotropic shaped particles with macrophages where prolate shaped particles were found to attach with cells more efficiently as compared to oblate-shaped or spherical particles. However, cell uptake by prolate-shaped particles was inhibited by 50%, whereas for oblate-shaped particles, it was observed to be enhanced by 300% when compared with spheres.[35] Furthermore, drug-delivery vehicles composed of shape anisotropic particles provide long circulation times and higher specific targeting as compared to spheres.[10] Apart from these, compositionally anisotropic particles allowed the incorporation of two or more drugs/functional agents/imaging agents in a single particle that can be released or modified independently, which is difficult to achieve through their isotropic analogues. Synthesis of uniform anisotropic particles is tough and challenging, because thermodynamics generally favor the formation of spherical particles owing to the minimal surface tension effect, however several efforts have been attempted by various research groups toward the creation of novel nanostructured anisotropic materials. In this review, we have discussed about the various types of biocompatible anisotropic polymeric particles based on their shape, composition, and surface modifications (patchy particle), emphasizing on their synthetic strategies and applications in biomedical field. Still, a great deal of collaborative effort is required from researchers including material scientists, biologists, chemists, and physicists to develop innovative strategies for fabricating anisotropic biocompatible polymeric particles and to address several biological problems that may not be solved by their spherical analogues.

2. SHAPE ANISOTROPY

This class includes the particles having a homogeneous surface that is made of one type of material but linear physical dimensions are different. A number of excellent reviews have been reported that demonstrated the shape of particles as an essential property influencing their performance and thus encourage researchers to focus on the investigations of nonspherical particles.[8,12,36] The anisotropic particles have been utilized for the delivery of therapeutics including RNA, DNA, and gene delivery and have been shown to outperform to their spherical analogues.[37] For examples, rod shaped particles delivered therapeutic agent with enhanced biodistribution, micellar rods having a high aspect ratio exhibited increased capability to deliver antitumor drug to the cancer cells, cylindrical-shaped PLGA particles delivered chemotherapeutic in environmentally triggered fashion, whereas ellipsoidal particles showed better antigen specific activation of T-cells in comparison to spheres, etc.[38−41]

Over the past few years, a large number of fabrication methods have been introduced to prepare biocompatible anisotropic shaped particles. Fabrication methods are classified in two categories: (a) synthesis of new nonspherical particles and (b) post modification of previously fabricated particles. Examples of synthetic techniques from category a include microfluidics,[42] lithography,[43] seed polymerization[44] and electrospraying[45] whereas film stretching[46] is the example of manipulation methods (category b). Utilizing these methods, a large variety of anisotropic shapes have been developed; a detailed discussion of a few important ones has been given below:

2.1. Droplet Microfluidics. The droplet microfluidic technique enables the fabrication of various type of particles such as spherical, anisotropic, and Janus particles (particles having two chemically distinguished compartments that are placed in side-by-side fashion) with controlled and tunable structures as well as compositions. It allows direct encapsulation of actives or drugs into polymeric particles and have a great potential in wide variety of biomedical applications such as drug delivery and other biomedical applications.[47,48] Particles synthesized by emulsion technique generally suffer from high polydispersity because of the formation of polydispersed emulsion droplets owing to the nonuniform shear stressed applied during emulsion formation. However, in microfluidic technique, an alternative and versatile route is offered by microfluidic devices to produce almost monodispersed emulsion by precisely making one drop at a time leading to the fabrication of monodispersed particles. Basically, synthesis of microparticles by droplet microfluidics technique involves three steps: (1) formation of droplet by microfluidic generator, (2) shaping of droplets in microchannel, and (3) solidification of microdroplets to convert them into particles.[48]

First, monodispersed droplets are produced by using microfluidic devices that provide a well-controlled balance between the various forces (such as viscous force, inertial force, interfacial tension, etc.) acting on the fluid. The phenomenon of droplet breakup in microfluidic devices can be determined by two dimensionless numbers, i.e., Capillary number (Ca) and Weber number (We), that are directly related to the channel geometries, fluid properties, and flow conditions and decide the flow behavior in the channel. The Capillary number represents the balance between surface tension and viscous force whereas Weber number represents balance between surface tension and inertial force. For a single emulsion, droplets are produced by means of dripping mode when Ca of the continuous phase and We of the dispersed phase are typically low.[48] Various types of microfluidic devices have been utilized for the fabrication of particles but the most popular devices to generate emulsion droplets are glass capillary devices and PDMS (poly(dimethylsiloxane) devices. A detailed description of microfluidic devices, emulsion droplet generation, and droplet formation mechanism can be found in some other excellent reviews.[48,49] In the next step, the droplets produced by microfluidic devices can be further dispersed in a third continuous phase to produce double emulsion to tune their size, architecture, and morphology, thus broadening the scope of the process. In the last step, the microfluidically produced emulsions work as templates and droplets are converted into solid particles by using various methods such as polymerization, solvent evaporation, ionic cross-linking, etc. Schematic diagram of the complete particle fabrication process through microfluidic technique including droplets generation and solidification (e.g., UV-induced polymerization) is shown in Figure 1.

In this process, shape anisotropy in the particles can be simply introduced by tuning the channel geometry or by using patterned templates (these are called photomasks). When the droplet produced by microfluidic generators enters the channels, the volume of the droplet decides the shape of the droplet and hence the shape of final particle. When the volume of the actual droplet is larger than ideal droplet volume, which can be easily

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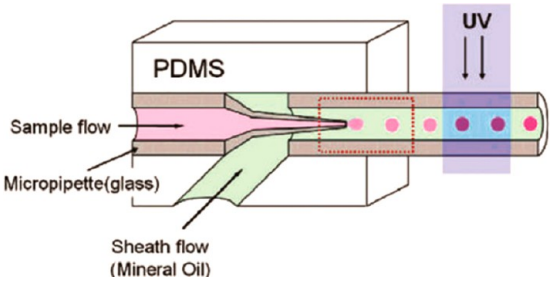

Figure 1. Schematic diagram indicating the emulsion formation by PDMS microfluidic device and its solidification via UV induced polymerization. Reproduced with permission from ref 50. Copyright 2005 American Chemical Society.

accommodated by the channel, so that the spherical droplet can deform its shape into ellipsoid, rod, disk, or in any other anisotropic shape.[51] These deformed droplets are solidified to produce shape anisotropic particles. Another method to prepare shape anisotropic particle is a combination of photomasking and photochemistry. In this method, a droplet is passed through a photomask (template) that contains a pattern of desired shape. When the droplet flows through the template, photoinitiated polymerization occurs to solidify the particles.[51] Xu et. al[52] produced nonspherical microparticles of various shape by using photoinitiated polymerization of monomers such as tripropylene glycol diacrylate (TPGDA), divinylbenzene (DVB), dimethacrylate oxypropyldimethylsiloxane (DMOS), pentaerythritol triacrylate, ethylene glycol diacrylate, etc. through droplet microfluidics technique. In a typical procedure, monomer liquid droplets were prepared by passing them through microfluidic devices made from either poly(dimethylsiloxane) or poly(urethane), using sodium dodecyl sulfate as surfactant. Subsequently, monomers containing photoinitiator (1-hydroxycyclohexylphenyl ketone) were polymerized in microfluidic channel under UV radiation to solidify the droplets (Figure 2d–f). Shape of the microparticles was tuned by controlling the volume of the droplet and by changing the cross-sectional area of the microchannels, as shown in Figure 2a–c.

Baah[53] and co-workers demonstrated the fabrication of anisotropic particles made from poly(ethylene glycol) diacrylate (PEG-DA) of various shapes such as square, hexagonal, triangular, circular, pentagonal, etc., by microfluidic technique. The aspect ratio of the particles was varied by using microfluidic devices of different channels depths, typically in the range of 60–80, 100–150, and 220–250 μm, whereas shapes were controlled by using photomask corresponding to the desired shape. The produced droplets of PEG-DA were photopolymerized in the presence of 2-hydroxy-2-methyl propiophenon as photoinitiator

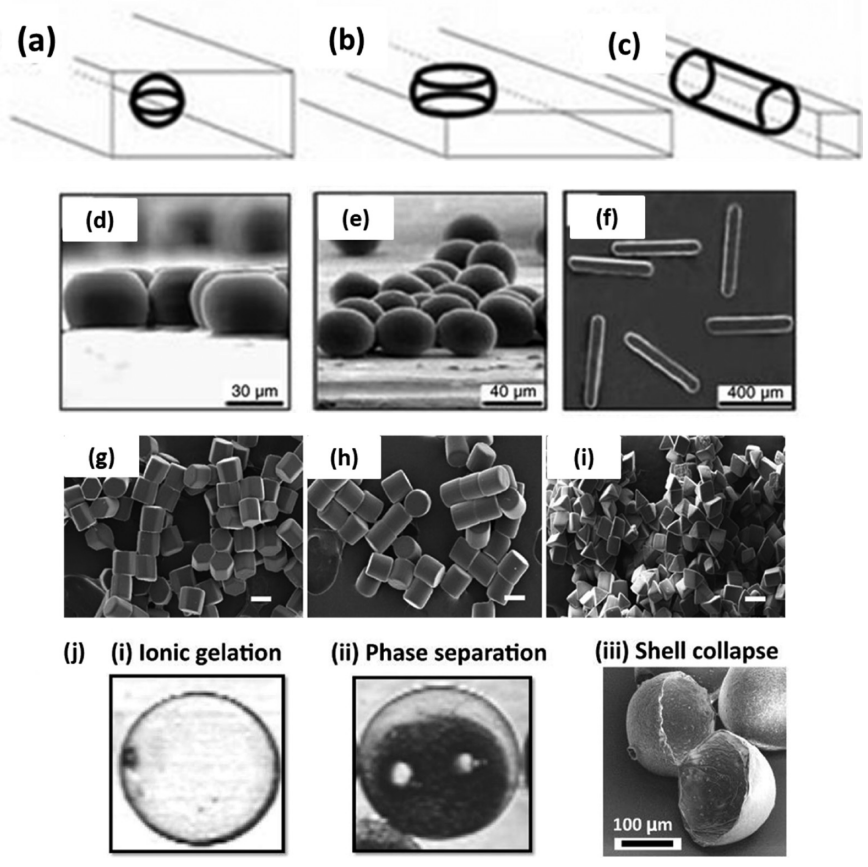

Figure 2. (a–c) Schematic representation of deformed droplets (disk, ellipsoid, rod). Reproduced with permission from ref 52. Copyright 2005 Wiley–VCH. (d) polyTPGDA disk-shaped particles. Reproduced with permission from ref 52. Copyright 2005 Wiley–VCH. (e) polyTPGDA elliptical-shaped particles. Reproduced with permission from ref 52. Copyright 2005 Wiley–VCH. (f) polyTPGDA rod-shaped particles. Reproduced with permission from ref 52. Copyright 2005 Wiley–VCH. (g) PEG-DA hexagonal-shaped particles. Reproduced with permission from ref 53. Copyright 2012 Springer. (h) PEG-DA circular-shaped particles. Reproduced with permission from ref 53. Copyright 2012 Springer. (i) PEG-DA triangular-shaped particles. Reproduced with permission from ref 53. Copyright 2012 Springer. (j) PLA-based crescent-shaped particles. Reproduced with permission from ref 54. Copyright 2017 Elsevier. Scale bar is 100 μm for g–i.

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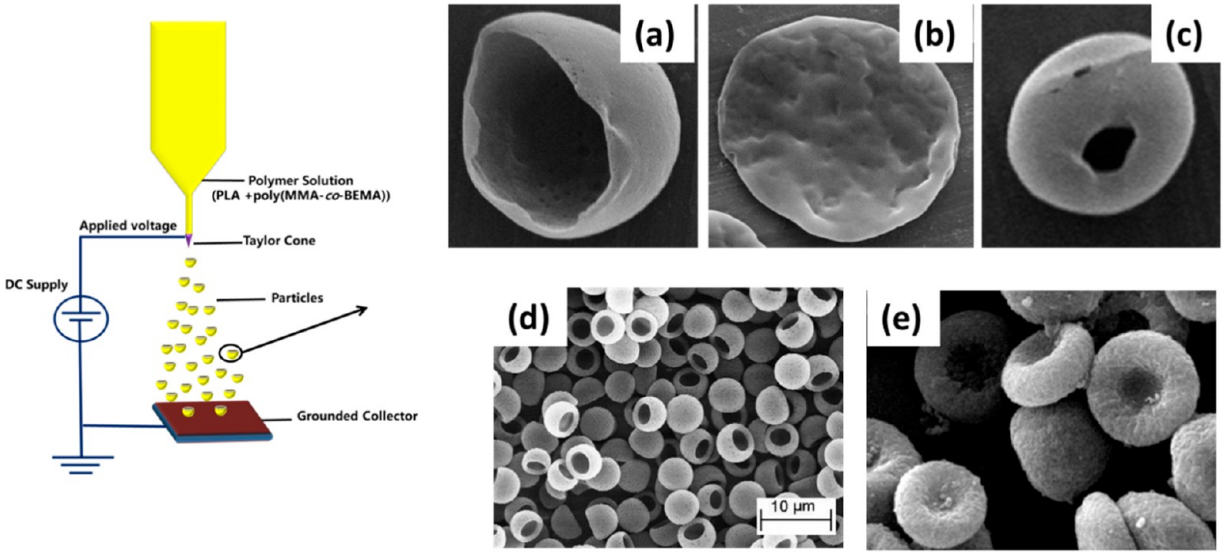

Figure 3. Scanning electron microscopy (SEM) images of (a) PLA/poly(MMA-*co*-BEMA) cup-shaped particles. Reproduced with permission from ref 23. Copyright 2019 Elsevier. (b) PLA/poly(MMA-*co*-BEMA) disc-shaped particles. Reproduced with permission from ref 23. Copyright 2019 Elsevier. (c) PLA/poly(MMA-*co*-BEMA) spherical particles with one hole. Reproduced with permission from ref 23. Copyright 2019 Elsevier. (d) PMMA cups. Reproduced with permission from ref 62. Copyright 2008 Wiley−VCH. (e) chitosan-based, red-blood-shaped particles. Reproduced with permission from ref 63. Copyright 2017 Elsevier.

(Figure 2g−i). Recently, Ekanem and co-workers[54] have developed PLA-based core−shell microparticles by producing W/O/W emulsion droplets by microfluidics with 96% water entrapment efficiency. The fabricated particles that contained 5 wt % aqueous Eudragit (methacrylic acid-methyl methacrylate copolymer (1:2)) in the core and PLA as shell, were incubated with HCl solution. Consequently, H^+ ions diffused through PLA shell resulting in ionic gelation of the core by neutralizing the charge of Eudragit chains originated from the carboxyl functional groups of methacrylic acid part. As a result, Eudragit turned from hydrophilic to hydrophobic state at pH <7. This led to the phase separation between polymer region (in crescent shape) and water region and, subsequent drying of these phase separated particles produced crescent shaped particles of 200 μm (Figure 2j). Mao and co-workers have filed a patent on their invention of synthesis of nonspherical polymeric particles made from polypropylene glycol diacrylate. The synthetic method includes disposing of one fluid phase containing polymer and photoinitiator (hydroxycyclohexyl phenyl ketone) into second fluid phase, a water-based magnetite ferrofluid, through a microfluidic device. The nonspherical droplets are actually produced in the microfluidic device by means of applying external magnetic field. The shape of the particles could be controlled by flow rate and external magnetic field. Later, the nonspherical polymer droplets containing photoinitiator were polymerized in the presence of light to yield anisotropic particles.[55]

Weitz and co-workers have reported a microfluidic device to generate double emulsions in a single step to produce polymersomes. The device consists of a cylindrical glass tube nested with an inner square glass tube where the outer diameter of the round tube was kept same as inner dimension. They achieved a high control over shell diameter as well as inner core diameter by varying the diameter of the outer and inner drops.[56]

2.2. Electrospraying. Electrospraying or electrohydrodynamic jetting is another facile technique to fabricate anisotropic polymeric micro/nanoparticles with specific shapes or morphologies in a single step for biomedical application, specifically for drug encapsulation.[45,57−61]

The basic setup of electrospraying consists of a syringe system to hold polymer solutions with an attached needle, a syringe pump which can control flow rate of the polymeric solution, a high voltage supplier and a grounded collector (Figure 3). When high voltage is applied on the droplet of polymeric solution at the tip of the needle, electrostatic repulsive forces generated between the surface charges and Coulombic forces exerted from the external field, overcome the surface tension of the ejected droplet which results in distortion of the droplet into Taylor cone. This Taylor cone sprays an electrified jet in a form of secondary droplets (in case of low viscous solutions), and hence formation of the polymeric particles takes place onto the grounded electrode. The size and shape of the polymeric particles can be controlled by varying solution parameters (such as polymer concentration, viscosity, molecular weight of polymer, electrical conductivity, etc.), processing parameters (e.g., applied voltage, flow rate, etc.), and equipment parameters (e.g., needle to collector distance, needle diameter, etc.). In general, morphology or shape change occurs by variation in charge density, viscosity, and surface tension of polymeric solution.[23] Electrospraying technique has several advantages such as flexibility to work with many solvents, drugs, polymer, monomers, etc. It allows a good control over particle's shape and size, also a narrow size distribution having small standard deviation can be obtained (Figure 3).

Recently, Ifra et. al[23] have studied the effect of various solution and processing parameters on the shape of electrojetted polymeric particles. They have demonstrated the fabrication of biodegradable/biocompatible polymeric particles composed of a blend of poly(lactide)(PLA) and poly[methyl methacrylate-*co*-2-(2-bromopropionyloxy) ethyl methacrylate] (poly(MMA-*co*-BEMA)) of various shapes such as cups, discs, spherical particles with one hole etc.[23] (Figures 3a−c). They have also attempted to establish the mechanism for cup shape formation by electrojetting of polymeric solutions. The study revealed that the high electrical conductivity along with low viscosity of

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polymeric solution favors the formation of cup. They have directly jetted a blend of PLA and a polyacrylate-based functional polymer to generate cup shaped particles. Therefore, in addition to PLA, the jetted particles were partly composed of a polyacrylate containing ATRP (atom transfer radical polymerization) initiating bromo functional groups which were further utilized to grow pH responsive PDMAEMA (poly(2-dimethylamino ethyl methacrylate)) brushes by "grafting from" approach via surface initiated atom transfer radical polymerization (SIATRP)[23] (detailed discussion is given under section 5). Similarly, Liu[62] and co-workers have demonstrated the fabrication of poly(methyl methacrylate) (PMMA) cups and studied the effect of different solvent systems on the morphology of PMMA-based polymeric particles during electrospraying process. They have also established a quantitative relation between solvent properties and particle morphology (Figure 3d). They have tabulated R^2_{ij} values for different solvents to classify them as good or poor solvent. R^2_{ij} can be defined as $R^2_{ij} = 4[(\delta_{d1} - \delta_{d2})^2 + (\delta_{p1} - \delta_{p2})^2 + (\delta_{h1} - \delta_{h2})^2]$ where δ_{d1}, δ_{p1}, and δ_{h1} are the three-dimensional solubility parameters (dispersive, polar, and H-bonding) for solvent, whereas δ_{d2}, δ_{p2}, and δ_{h2} are the three-dimensional solubility parameters for polymer. Several observations based on the quality of the solvent and their evaporation ability have been made, such as a good solvent having fast evaporation tendency results in polygonal porous particles, whereas medium evaporative solvent produces solid polygonal particles. Porosity was linked with the rate of solvent evaporation; viz. porous particles were formed because of rapid evaporation of solvent. PMMA cups were obtained by tailoring the concentration of the solution (varying from 6 to 12 wt %) in various solvents of high dielectric constant such as acetonitrile and nitromethane. By choosing a proper solvent and by tailoring the electrospinning conditions, a wide variety of particle shape can be achieved.

Another interesting geometry such as red blood cell type can also be generated by electrojetting. Ju and co-workers[63] reported the fabrication of red-blood-cell-shaped microparticles composed of chitosan via a simple combination of electrospraying and solvent diffusion process controlled by solvent evaporation (Figure 3e). In their process, an evaporative solvent and diffusible solvent were added to the aqueous solution of chitosan, which was jetted and collected directly in a collection solvent (a mixture of n-hexanol, *n*-octane, and toluene which contained N,N,N_,N_-tetramethylethylenediamine (TMEDA), terephthalaldehyde, and polyglycerol polyricinoleate). During the electrospraying process, evaporating solvent was able to evaporate rapidly (due to high temperature inside the chamber), leading to a decrease in droplet temperature, which resulted in phase separation between diffusible solvent and chitosan polymer. As a droplet reaches the surface of collection solution, diffusible solvent on the lower side of the droplet was diffused to the collection solution rapidly because of the miscibility between the two leading to the formation of dent inward. However, cross-linker (terephthalaldehyde) reacts with chitosan polymer on the edge of droplet, leading to the formation of concave morphology. Consequently, RBC-shaped chitosan microparticles were generated, which were then used as drug-delivery vehicles.

2.3. Self-Assembly of Block Copolymers. Self-assembly of block copolymers is another elegant approach to design anisotropic particles. It is well-known that block copolymers get self-assembled when immersed in a suitable solvent.[64] The morphology of the resulting particles based on self-assembled block copolymers can be dictated by relative volume fractions of individual blocks. The most common methods for the self-assembly of block copolymers are self-organization rapid precipitation (SORP) and flash nanoprecipitation. In the SORP method, a poor solvent is added to the block copolymer already dissolved in a good solvent, and the good solvent is then allowed to evaporate, leaving the block copolymer in poor solvent where polymer chains get collapsed and arranged in a particular fashion to form particles of various shapes. A wide variety of morphologies is obtained as a result of inherent molecular curvature, which directly influences the packing of copolymer chains.[65] The morphology will depend on the dimensionless packing parameter *p*, which is defined as

$$P = v/a_0 l_c$$

where v is the volume of hydrophobic chain, a_0 is the optimal area of headgroup, and l_c is the length of the hydrophobic chain. The packing parameter p decides the morphology of the resultant self-assembled chains and can be correlated with the obtained shape as follows:

$$\text{spherical morphology, } p \leq 1/3$$

$$\text{cylindrical morphology, } 1/3 \leq p \leq 1/2$$

$$\text{vesicles, } 1/2 \leq p \leq 1$$

During the self-assembly of block copolymers, aggregation of the hydrophobic part occurs when progressive addition of the precipitant takes place. However, aggregated hydrophobic parts then get stabilized by hydrophilic part. When the process is under thermodynamic control, the shape of the micelle formed depends on the composition and/or temperature of the system. On the other hand, under the kinetically controlled process, the shape can be the result of adhesive collisions between primary aggregates (spheres, rods, or vesicles) or collision between polymer chains and aggregates, including the structural rearrangement of one morphology to the other resulting in the formation of various anisotropic particles. Conclusively, when the self-assembly is under kinetic control, the shape of the micelle/particle is governed by hydrodynamic interaction between the aggregates and/or polymer chains.[66]

For instance, Schmidt and co-workers[67] have prepared shape anisotropic nanoparticles via self-assembly of poly(ferrocenylsilane)-*b*-poly(2-vinylpyridine) (PFS-*b*-P2VP) block copolymers. They could produce elliptical particles having axially stacked lamellar structure and nanosheets with a hexagonal structure of PFS cylinders. The shapes were achieved by changing the volume fraction of PFS and P2VP block and by wetting of the blocks by functional surfactants (a combination of cetyltrimethylammonium bromide (CTAB) and 16-hydroxycetyl triethylammonium bromide (CTAB−OH)). Furthermore, these shapes can be achieved by tuning the crystallization of PFS domains via blending with homopolymers of PFS (Figure 4a).

Self-assembly of block copolymers can occur in solid as well as in solution. In solution, shape anisotropic micelles such as worms, rods, vesicles, ellipsoids, etc., have been prepared via post polymerization processing conducted in dilute solution, which limits its application for commercial usage as the industrial scale may not be cost-effective. Polymerization-induced self-assembly (PISA) is an interesting technique where a soluble block is used as a precursor and a monomer is chosen whose homopolymer is insoluble in that particular solvent. When polymerization is carried out, the second block

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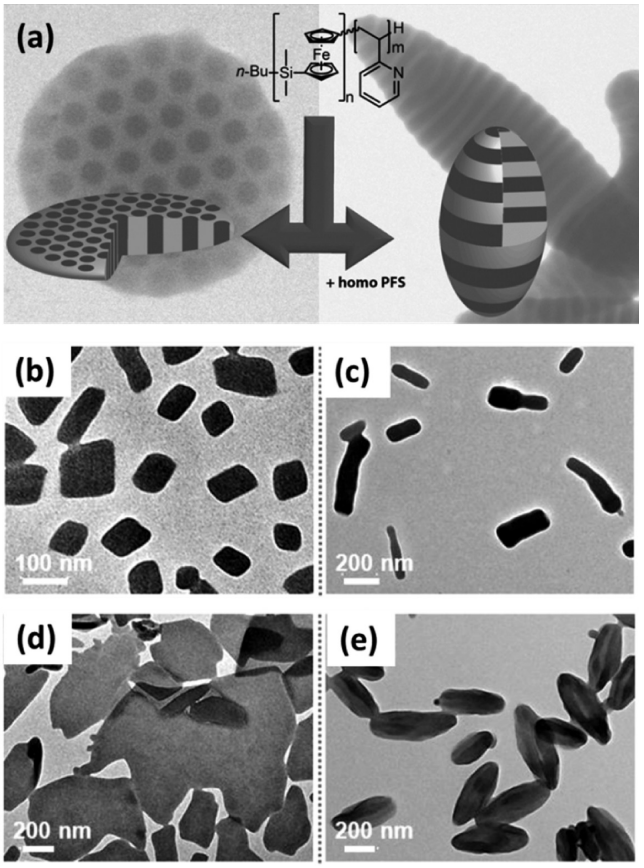

Figure 4. (a) Ellipsoidal particles having an axially stacked lamellar structure and nanosheets having hexagonal structure of PFS cylinders composed of PFS-*b*-P2VP). Reproduced with permission from ref 67. Copyright 2015 American Chemical Society. (b–e) Cuboids made from $PMAA_{112}$-*b*-$PMAAz_{66}$ (subscript indicates DP (degree of polymerization) of particular block), short belts made from $PMAA_{112}$-*b*-$PMAAz_{89}$, lamellae made from $PMAA_{112}$-*b*-$PMAAz_{115}$, and ellipsoidal vesicles made from $PMAA_{112}$-*b*-$PMAAz_{142}$, respectively. Reproduced with permission from ref 70. Copyright 2018 American Chemical Society.

grows and becomes insoluble in the reaction medium. At a particular degree of polymerization, self-assembly of the block copolymer occurs, leading to the formation of shape anisotropic particles/micelles.[68,69] Recently, Guan[70] has demonstrated the preparation of anisotropic particles of various shapes such as lamellae, cuboids, short belts, ellipsoidal vesicles, etc., via polymerization-induced hierarchical self-assembly of azobenzene containing block copolymers. At first, they synthesized a block copolymer of PMAAz (azobenzene containing poly(methacrylate)) and PMAA (poly(methacrylic acid), as the stabilizer block) of varying chain lengths and form self-assembled particles via PISA (polymerization induced self-assembly) in ethanol. During PISA, the LC (liquid crystal) ordering of the core forming block segments (PMAAz) occurs. This results in a hierarchical self-assembled structure where internal LC ordering as well as self-assembly takes place simultaneously. The various shapes were produced by changing the volume fractions of the individual block segments (Figure 4b–e). Later, LC ordering was removed under UV illumination as azobenzene moieties were changed from the trans to cis form upon illumination due to the loss of LC packing. Consequently, anisotropic particles changed their shapes to a spherical one. These kinds of particles may find applications as actuators and photocontrolled drug-delivery vehicles.

2.4. Film Stretching Method. In this method, previously fabricated particles are immobilized in a thin film that is heated above the T_g (glass transition temperature) of the polymeric particles and the film is allowed to stretch, resulting in deformation of the particles.[71] The film stretching method exhibits the advantage of manipulating a wide variety of shapes from the same stock of polymeric particles, but the polydispersity of the fabricated particles depends on the polydispersity of the spherical stock particles which can only be controlled by the selection of right kind of source spherical particles. Stretching or compressing ratio, thickness of the film, and method of liquefaction (a procedure in which particles are liquefied by means of solvent or heating the particles above T_g) have been found to control the shape and size of the particles.[72]

A prominent example demonstrated by Fan and co-workers deserves a mention. They have developed biocompatible and

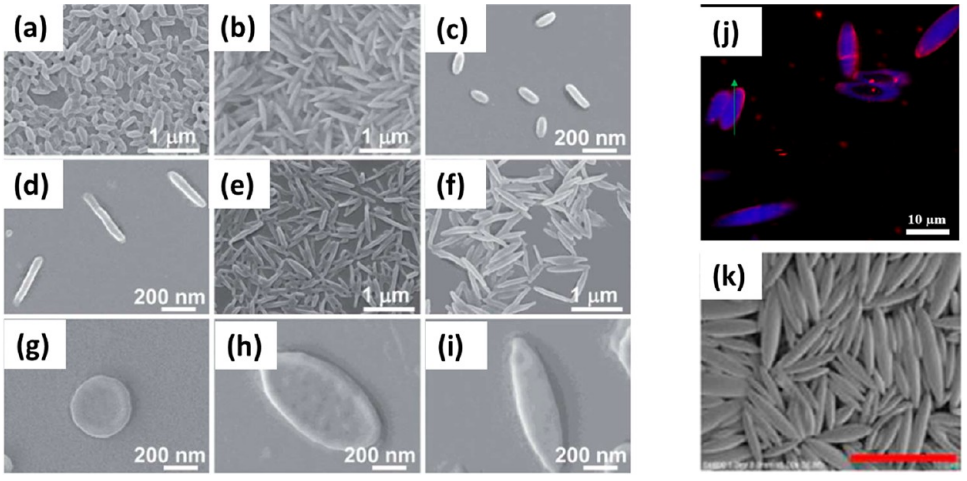

Figure 5. Scanning electron microscopy (SEM) of (a, b) PLGE nanoellipsoids fabricated by cold stretching (100 and 200%, respectively), (c–f) PLGE nanorods fabricated by hot stretching (60, 120, 120, and 150%, respectively) (g–i) PLGE nanodisks fabricated by hot compressing (200, 200, and 100%, respectively). Reproduced with permission from ref 72. Copyright 2014 Royal Society of Chemistry. (j) PLGA lipid-coated particles. Reproduced with permission from ref 74. Copyright 2018 Elsevier. (k) PLGA microrods fabricated from different ratios of PEMA (poly(ethylene-*alt*-maleic acid))/PVA. Reproduced with permission from ref 71. Copyright 2019 Elsevier. Scale bar is 10 μm for k.

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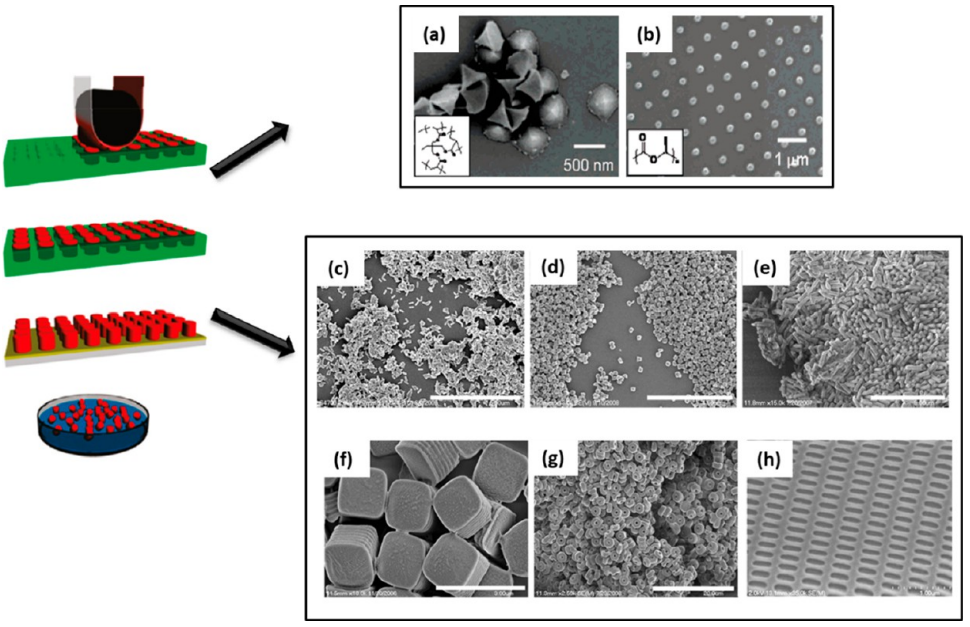

Figure 6. Schematic diagram for PRINT Technique. Reproduced with permission from ref 76. Copyright 2009 American Chemical Society. Scanning electron microscopy (SEM) images of (a) conical triacrylate particles and (b) PLA trapezoidal particles. Panels a and b reproduced with permission from ref 80. Copyright 2005 American Chemical Society. (c–g) PLGA particles (80 nm × 320 nm cylinders, 200 nm × 200 nm cylinders, 200 nm × 600 nm cylinders, 2 μm cubes with ridges, and 3 μm particles with center fenestrations, respectively). Reproduced with permission from ref 81. Copyright 2011 American Chemical Society. (h) Acid labile drug containing PLGA particles. Reproduced with permission from ref 82. Copyright 2014 American Chemical Society. Scale bars: (c) 5, (d) 4, (e) 3, (f) 3, (g) 20, and (h) 1 μm.

biodegradable PLGE (poly(lactide-*co*-glycolide-*b*-ethylene glycol-*b*-lactide-*co*-glycolide)) spherical nanoparticles of different sizes, which were changed to nanorods, nanoellipsoids, circular disks, and elliptical nanodisks via a stretching/compressing method[72] (Figure 5a–i). The stretching of spherical particles led to the formation of nanorods or nanoellipsoids, where the compression method resulted in nanodisks. These particles were loaded with Nile Red (NR), the release of which was found to be a sustained one when it was eluting from particles of anisotropic shapes (nanorods, nanoellipsoids, circular disks, and elliptical nanodisks). However, burst release of dye was observed from their spherical mother particles, thus opening a new avenue for designing drug-delivery carriers to achieve desired release profiles.

Mitragotri and co-workers invented and patented their innovative film stretching technique by which micro- and nano- polymeric particles of various shapes such as rectangular disks, prolate ellipses, oblate ellipses, worms, circular disks, pulleys, pills, ravioli, bicones, diamond disks, tacos, etc., can be produced. In this method, spherical particle embedded film must be stretched either in one dimension or in two dimension. The resulting nonspherical particles can be used to alter uptake by phagocytic cells and clearance by reticuloendothelial system. A wide variety of polymers such as copolymers of lactic acid and glycolic acid, polyanhydrides, poly(urethanes), poly(ortho)-esters, poly(lactide-*co*-caprolactone), etc., can be used by this technique to produce particles having anisotropic shape.[73]

An interesting work was published by Randall and co-workers, where they have reported the synthesis of elliptical PLGA (poly(lactic-*co*-glycolic acid) particles coated with lipid (a mixture of 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) and cholesterol) using emulsion technique followed by film stretching (Figure 5j). The spherical (PLGA) particles prepared by emulsion solvent evaporation technique were dispersed in PVA and glycerol. The dispersed particles were casted into a rectangular Petri dish to form a film that was then allowed to dry. The dried film was mounted onto an automated thin film stretcher; the apparatus was heated up to 90 °C and then the film was stretched into one direction (2-fold). After cooling, the film was dissolved into water and particles were collected after repeated washing.[74]

More recently, Cao and co-workers[71] have produced rod shaped PLGA micro and nanoparticles having a sufficient number of − COOH groups on the surface by dispersing spherical PLGA particle into a mixture of PVA and poly-(ethylene-*alt*-maleic acid) (PEMA) solution bearing − COOH groups (Figure 5k). Then, a film was casted, dried and finally stretched to achieve anisotropy. The PEMA/PVA blend film was used instead of PVA film to incorporate the carboxylic groups on the surface of anisotropic rod shaped particles. The fabricated micro and nanorods were then conjugated with transferrin (Tf). Tf-conjugated nanorods manipulated with PEMA were found to exhibit high cellular uptake by KB human carcinoma cells in comparison to those fabricated by PVA film, thus citing the advantage of introducing carboxylic groups on the surface of anisotropic particles.[71]

2.5. Particle Replication in Nonwetting Templates (PRINT). Particle replication in nonwetting templates (PRINT) is a modern soft lithography technique enabling particle fabrication with various shapes and sizes down to below 100 nm. It represents a simple and straightforward way to tune size, shape, and surface functionalities of particles and to encapsulate a wide variety of bioactive agents such as proteins, DNA, etc.[75−78] PRINT technique utilizes PFPE (perfluoropolyether) elastomers as molds, templated on patterned silicon masters (various shapes can be produced by using different kind of patterned surfaces). In a typical procedure, liquid PFPE precursor is poured onto silicon master, spread evenly, and

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photocured to prepare an elastomeric mold. Then, liquid monomer or polymer solution (preparticle liquid) is added to the mold by the roll-to-roll technique and particle liquid is trapped inside the cavities through capillary force. After that, particles are solidified by different methods such as UV irradiation, lyophilization, solvent evaporation, thermal effect, etc. The soft lithography technique is also utilized to cross-link PDMS (poly(dimethylsiloxane)), which is used as mold to fabricate polymeric particles. Recently, nonspherical poly(ε-caprolactone) (PCL) particles were fabricated using PVP (poly(vinylpyrrolidone)) layer which was imprinted on a PDMS mold to obtain nonspherical particles such as disks and hemispheres.[79] To show the wide applicability of these particles, researchers simultaneously loaded doxorubicin (a chemotherapeutic agent) and Fe_3O_4 nanoparticles (imaging agent) and used them as theranostics. Similarly, hemispherical hollow PCL particles were also prepared by using a PCL (poly(ε-caprolactone))/PEO (poly(ethylene oxide)) immiscible polymer blend because of the dissolution of PEO phase in aqueous medium during the mold release of the particles.[79] The particles fabricated by the soft lithography technique are connected by a flash layer or "scum layer", resulting in embossed film rather than separated particles and results in chemical permeation of PDMS, which leads to swelling and loss of geometrical fidelity. This disadvantage has been overcome in the PRINT technique, as the PFPE mold has been proven to be more effective than PDMS templates, with the additional advantages of compatibility of PFPE mold with a number of organic solvents and easy removal of particles from the template because of the highly fluorinated nature of the mold.[76] Various types of unique shapes composed of biocompatible polymers have been prepared through the PRINT technique.

Using PRINT technique, Rolland and co-workers[80] have demonstrated the fabrication of monodisperse conical/trapezoidal-shaped particles (200 nm size) composed of PEG (poly(ethylene glycol), PLA, and other polymers. In their study, they used PEG particles to encapsulate fluorescently labeled 24 bp (base pair) oligonucleotide, fluorescently labeled avidin, and doxorubicin (a chemotherapy agent) (Figure 6a). First, dimethaacrylate-functionalized PFPE oligomer was photocured on patterned silicon master templates (conical or trapezoidal) to generate PFPE replica molds. Conical-shaped PEG particles were produced by introducing PEG-diacrylate liquid monomer into conical-shape-patterned PFPE molds and then photopolymerization proceeded at room temperature. The biomolecules were added before photopolymerization process of PEG-acrylate (directly with the monomer) for encapsulation without the addition of surfactant or condensation agent. Trapezoidal PLA particles were fabricated by introducing a small amount of (3*S*)-*cis*-3,6-dimethyl-1,4-dioxane-2,5-dione (lactide monomer) and stannous octoate (a catalyst) in trapezoidal shape patterned PFPE mold and the mixture was heated at 110 °C for polymerization (Figure 6b).Several other groups have also reported the synthesis of PLGA nanoparticles via PRINT technique. Various anisotropic shapes of PLGA particles such as 80 nm × 320 nm cylinders, 200 nm × 200 nm cylinders, 200 nm × 600 nm cylinders, 2 μm cubes with ridges, and 3 μm particles with center fenestrations were prepared with efficient loadings of docetaxel (encapsulation efficiencies >90%)[81] (Figure 6c−g). Chu and co-workers also demonstrated the fabrication of cylindrical PLGA particles encapsulated with acid labile drug via the PRINT technique. They used the particles for targeted delivery to a solid tumor in an A549 subcutaneous xenograft model[82] (Figure 6h) and demonstrated the advantage of using cylindrical-shaped particles.

3. COMPOSITIONAL ANISOTROPY

This class includes the anisotropic particles in which anisotropy arises because of their heterogeneous chemical composition. A control over internal architecture provides compositional anisotropic particles. Multicompartmental particles having ordered polymer domain or composition such as dumbbell shape particles, acorn like particles, bicompartmental particles, and snowmenlike particles are the examples of this class (Figure 7).

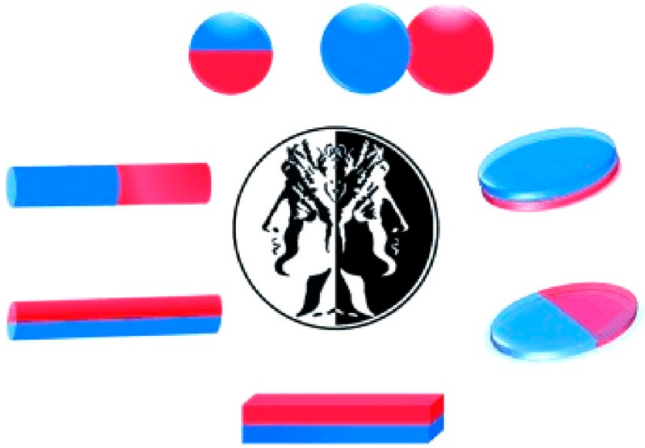

Figure 7. Common forms of compositionally anisotropic particles or Janus particles. Reproduced with permission from ref 83. Copyright 2014 Wiley−VCH.

Prominent methods for the fabrication of compositional anisotropic particles include the electrohydrodynamic cojetting technique,[84] seeded polymerization,[85] droplet microfluidics,[51] self-assembly,[86] etc. A detailed description of selective synthetic methodologies along with examples is given below:

3.1. Electrohydrodynamic Cojetting Technique. The electrohydrodynamic cojetting (EHDC) technique is a one-step method for the fabrication of multicompartmental polymeric particles.[87] When particles with multifunctional properties in terms of both chemical and physical properties are needed, precise particle compartmentalization comes into the picture. Its working principle is similar to the electrospraying technique but it has a different needle system. In EHDC technique, two or more needles are arranged in a side by side manner so that it allows independent designing or modification of each compartment (Figure 8a). Side-by-side configuration facilitates the direct incorporation of two or more drugs/functional molecules with 100% encapsulation efficiency into the each side of the particles along with an independent choice of polymers, though polymers forming different compartments must be compatible with each other to induce enough adhesion force between the compartments, necessary to maintain the structure of the compartments. Like the electrospraying technique, EHDC setup consists of a high-voltage supplier to apply voltage, a syringe pump to control flow rate of polymeric solutions and a grounded collector to collect the particles. Shapes and sizes of the polymeric particles can be easily controlled by varying various parameters such as concentration, flow rate, molecular weight of polymer, applied voltage etc.[84,88−90] Recently, Parthipan and co-workers[91] demonstrated the fabrication of bicompartmental

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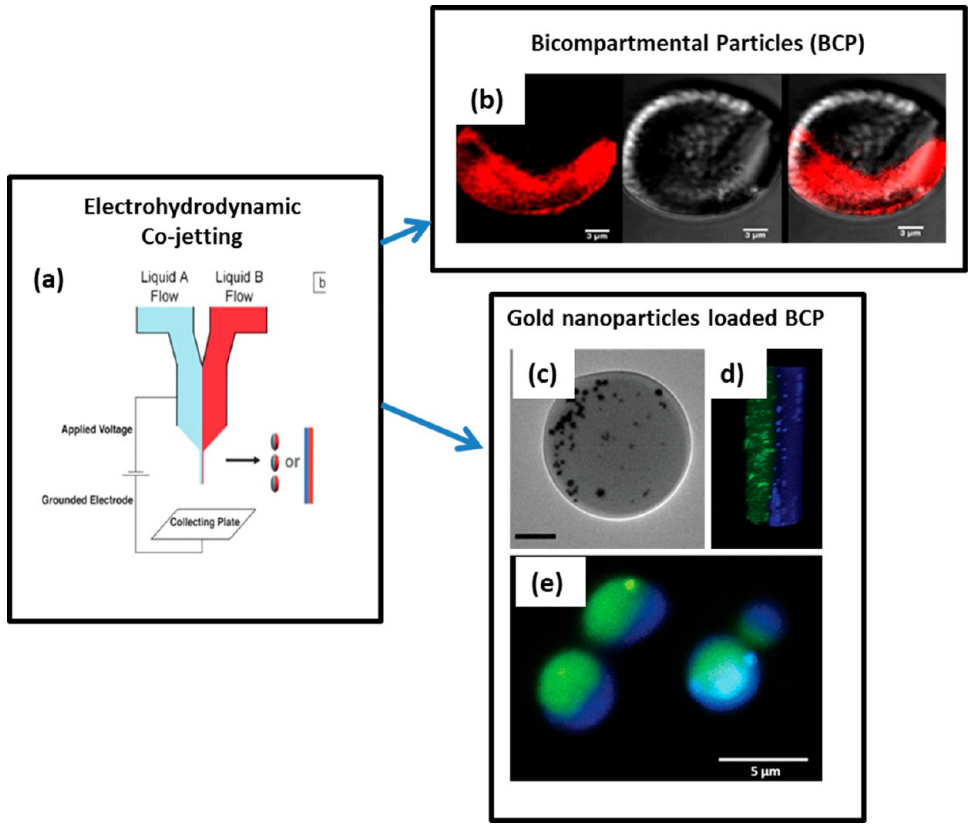

Figure 8. (a) General setup for electrohydrodynamic cojetting technique. Reproduced with permission from ref 84. Copyright 2011 Wiley–VCH. (b, c) DIC image of PLA/PLGA biphasic particles encapsulated with levodopa and carbidopa. Reproduced with permission from ref 91. Copyright 2018 Springer. (c–e) SER-tagged gold-nanoparticle-encapsulated biphasic particles composed of PLGA. Reproduced with permission from ref 95. Copyright 2017 Wiley–VCH. Scale bars: (b) 3 μm, (c) 4 μm, and (e) 500 nm.

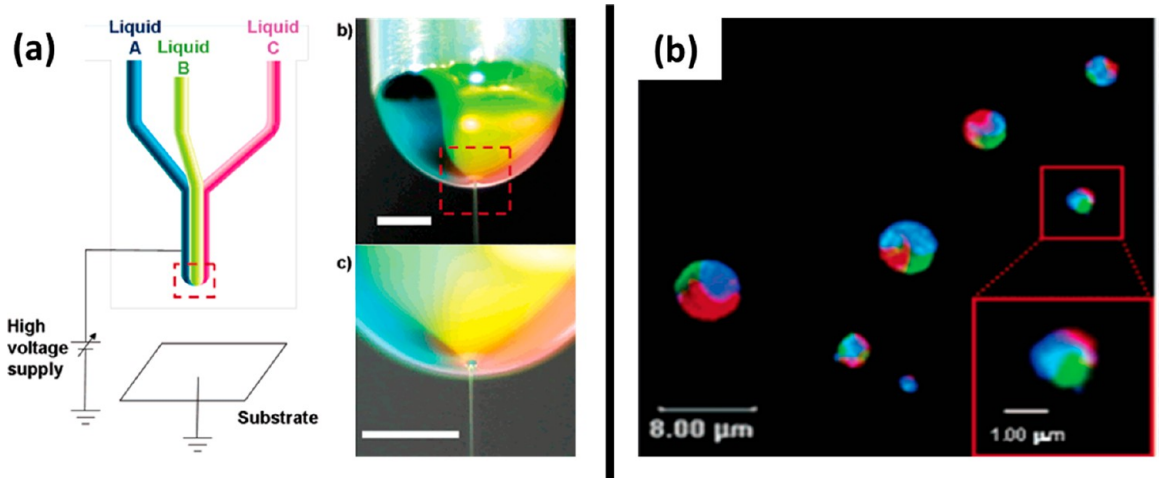

Figure 9. (a) Basic setup to fabricate triphasic particles. (b) Scanning electron microscopy (SEM) image of PEO-based triphasic particles. Reproduced with permission from ref 93. Copyright 2006 American Chemical Society.

anisotropic disk-shaped particles composed from poly(lactic acid)(PLA) and poly(lactide-*co*-glycolic acid)(PLGA) to encapsulate two different Parkinson's disease (PD) drugs, levodopa (LD), and carbidopa (CD) in two separate compartments via electrohydrodynamic cojetting technique (Figure 8b). The anisotropy in the particle arises from the difference in crystallinity between the compartments, viz. being crystalline, PLA compartment produces rough surface whereas amorphous PLGA phase appears to be smooth. Drug-release studies from bicompartmental particles showed independent and sustained release of both drugs in comparison to Syndopa, a commercial tablet consisting of both LD and CD. Moreover, the release rate of both drugs can be desirably matched with each other by placing them in suitable polymeric compartments. Under a similar environment, the Syndopa tablet showed a burst release of both drugs within 30 min, leading to the requirement of consuming multiple doses that may cause side effects in patients suffering from Parkinson's. However, jetted bicompartmental particles can potentially be an efficient PD drug carrier causing minimal or no side effects. The same group of researchers

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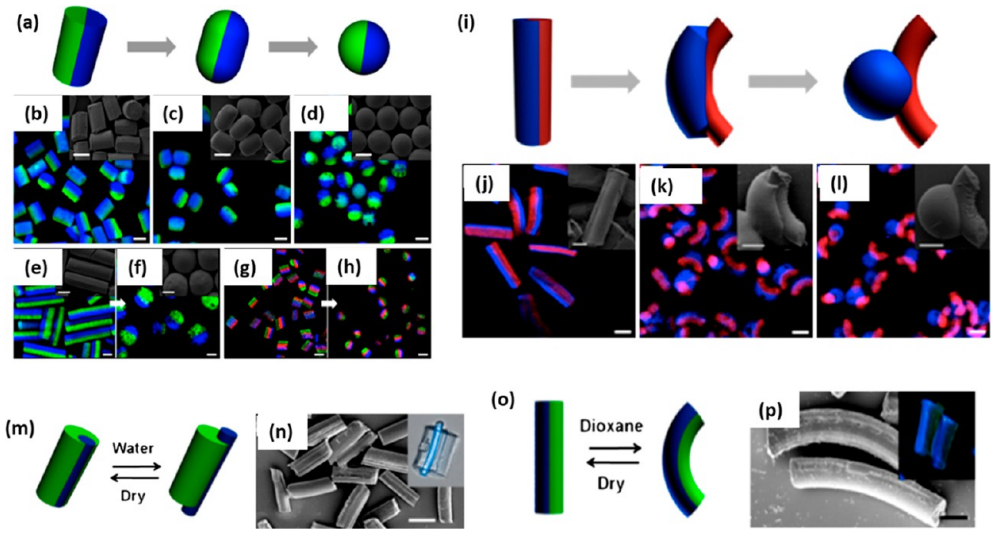

Figure 10. (a–d) Shape shifting of bicompartmental PLGA/PLGA cylindrical microparticles (30 μm in length) (panel c is the intermediate stage) by ultrasound heat treatment. (e, f) Shape shifting of bicompartmental PLGA/PLGA cylindrical microparticles (70 μm in length) by ultrasound heat treatment. (g, h) Shape shifting of tricompartmental cylindrical particles by ultrasound heat treatment. (i–l) Shape shifting of bicompartmental PLGA/PMMA cylindrical microparticles by heat treatment: only PLGA part gets reconfigure. (m, n) Reversible shifting of hydrogel/PLGA (core/shell) microcylinders by swelling/deswelling mechanisms. (o, p) Reversible shape bending of PEO/PVCi microcylinders in the presence/absence of dioxane. Reproduced with permission from ref 96. Copyright 2018 PNAS. Scale bars: (b–h) 20, (j–l) 10, (n) 50, and (p) 50 μm.

expanded the research by encapsulating benzoic acid (antibacterial agent) into the similar bicompartmental particles composed of PLA/PLGA phases and observed the antibacterial activity of released benzoic acid against Gram-negative and Gram-positive bacteria for 30 days. And the study revealed that 100% bacterial growth reduction can be achieved from these bicompartmental particles over a period of 30 days.[92] The versatility of electrohydrodynamic cojetting was further explored by fabricating triphasic or tricompartmental PEO-based particles consisted of three distinct compartments (made from PEG) mixed with different dyes such as fluorescein-conjugated dextran (green), Alexa Fluor 647-conjugated bovine serum albumin (blue), and Rhodamine B-conjugated dextran (red)[93] A schematic diagram to fabricate tricompartmental particle is shown in Figure 9. The CLSM (confocal laser scanning microscope) images shown in Figure 9b confirm that almost every particle has three distinct phases, as three dyes can be visualized as separate compartments. These particles may find their potential applications in theranostics as they are capable of encapsulating two/three different drugs and imaging agent in a single particle.

The drug-release profiles of a bicompartmental system can be selectively modified by incorporation of stimuli responsive polymers in a particular compartment by directly using them as polymer matrix while jetting. In an interesting example shown by Lahann et al., biphasic particles consisting of PLGA on one side and PLGA+PEI(poly(ethylenimine)) on another side were fabricated by EHDC, where PEI works as a pH-responsive compartment as it gets swollen at acidic pH due to electrostatic repulsion of protonated amine groups. Further, these biphasic nanoparticles conjugated with Si-RNA through PEI compartment were also used as SiRNA delivery vehicle.[94]

For a specific application, performance of the bicompartmental particles can be augmented by incorporating additional materials such as nanoparticle/functional materials, etc.; for example, gold nanostars containing multicompartmental PLGA-based microparticles or microcylinders were made by electrohydrodynamic jetting technique where dispersed gold nanoparticles in organic solvent were added into one of the jetting solutions made of PLGA to capture gold nanoparticles selectively in one of the compartments[95] (Figure 8c–e). Gold nanoparticles were further tagged with several surface-enhanced Raman scattering (SERS) active molecules and the fabricated multicompartmental particles were imaged by 3D-SERS, thus opening a new way of imaging the particle, useful to tracking down the fate of drug carriers inside the body.

These type of responsive multicompartmental particles are strongly capable of reconfiguring their shapes under the exposure of various stimulus such as temperature, pH, solvent, ultrasound variation etc. Lee and co-workers[96] have reported the shape reconfigurable microcylinders that could shift their shape depending on the composition of individual compartments. For example, bicompartmental PLGA-based microcylinders (both side made of PLGA), obtained via microsectioning of jetted microfibers (bicompartment), were treated with ultrasound in water. As a result of ultrasound treatment, the temperature of the medium raised above the T_g of PLGA (47–48 °C) that led to shape shifting of microcylinders to spherical particles due to minimization of surface to volume ratio, with the retention of bicompartmental character (Figure 10a–h). Bicompartmental microcylinders consisting of PLGA and PMMA were also fabricated and heated at a temperature between T_g of PMMA (115–116 °C) and PLGA (47–48 °C). Consequently, only PLGA (above T_g) underwent selective shape shifting leaving the PMMA compartment unaltered (Figure 10i–l).[96] Another swelling–deswelling-based shape reconfigurable system was achieved by jetting PLGA solution as shell stream and a hydrogel (a mixture of branched polyethylenimine and polyethylene glycol diglycidyl ether) as core. On treatment with acidic water, the hydrogel compartment was swollen (280%); however, the PLGA compartment retained its original shape as shown in Figure 10m–n. The bicompartmental microcylinders comprising poly(vinyl cinnamate) (PVCi, capable of undergoing photo-cross-linking) and poly(ethylene oxide) (PEO) (fabricated by a side by side arrangement) showed a reversible bending upon immersion into dioxane as PVCi got swollen in dioxane after

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cross-linking and PEO retained its shape, the a result of which is that reversible shape bending occurred (Figure 10o, p.

In another study, Gil and co-workers fabricated helical PLGA microfibers that were twisted in situ by using an additional motor during EHDC. Cryosectioning of these helical microfibers revealed helically decorated microcylinders, which could shift their shape to helically patterned compartmental spheres under various stimuli such as ultrasonication or temperature.[97] The helical microcylinders shift their shape to spheres when heated above the T_g of PLGA (47−48 °C). A wide variety of spheres with different pattern can be produced using these helical microcylinders, shape of which can be directly controlled by varying the helicity degree in synthesized microfibers during electrojetting (Figure 11). In simple words, the inner

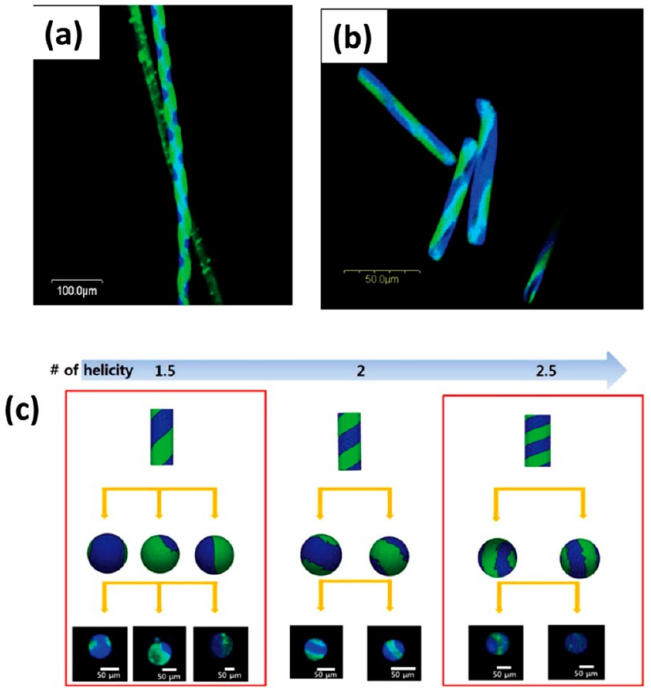

Figure 11. (a) Helically compartmentalized microfibers having diameter around 30 μm. (b) Helically compartmentalized microcylinders after cryosectioning of microfibers. (c) Shape reconfiguration of microcylinders (with different degree of helicity) to spheres. Reproduced with permission from ref 97. Copyright 2018 Wiley−VCH. Scale bars: (a) 100, (b) 50, and (c) 50 μm.

architecture of microspheres is highly dependent on the helicity of initial microcylinders, which further depends on the pitch size and handedness of the helix.

It is worth mentioning here that the technology of a multicompartmental particle system has been already commercialized by Seventh Sense Biosystems, Inc. They have signed a license with University of Michigan, where the company was initially formed, to commercialize multiphasic particle technology and desired to use technology to produce a wide range of anisotropic particles such as biphasic nanoparticles, multiphasic capsules, and multiphasic colorants as functional elements in various applications, e.g., paints, coatings, plastics, displays, etc.[98]

3.2. Emulsion Technique. One of the most sought after techniques to prepare compositionally anisotropic particles is the emulsion solvent evaporation method because of its simplicity, cost-effectiveness, and scalability.[99−102] Various drug-loaded compositionally anisotropic/Janus particles have been prepared using this technique and the mechanism of the control over particle morphology has also been established. Bicompartmental/Janus particles were only produced if they fulfill the requirements of classic spreading coefficient theory, which can be defined on the basis of Harkin's equation (eq 1).[103] According to this theory, spreading coefficients (S) can be determined by the interfacial tensions between the different phases and different combinations of these spreading coefficients directly affect the degree of polymer engulfment during phase separation. According to Harkin's definition, positive spreading coefficient indicates the spreading, whereas negative spreading coefficient implies the contraction of material. While making the Janus (biphasic) particles by emulsion techniques, usually three phases coexist in the emulsion droplet, first oil phase containing polymer 1 (phase 1), water phase (phase 2), and second oil phase containing polymer 2 (phase 3). The combinations of different spreading coefficient corresponding to these different phases, given in eqs 2 and 3 will give an idea whether core−shell or Janus particles will be formed.[103]

$$\text{Harkin's equation: } S_i = \gamma_{jk} - (\gamma_{ij} + \gamma_{ik}) \quad (1)$$

$$\text{Core−shell: } S_1 < 0,\ S_2 < 0,\ S_3 > 0 \text{ or } S_1 > 0,\ S_2 < 0,\ S_3 < 0 \quad (2)$$

$$\text{Janus: } S_1 < 0,\ S_2 < 0,\ S_3 < 0 \quad (3)$$

Where γ_{jk}, γ_{ij}, and γ_{ik} are interfacial tensions between different phases (i,j and k) and Si is the spreading coefficient of a particular phase.

Romanski and co-workers have demonstrated the formation of self-assembled biphasic polymer/polymer (PLGA/PCL) and polymer/lipid (PLGA/precirol) particles using a modified solvent evaporation technique[104] (Figure 12a, b). Lipids were chosen because lipids and polymers have different wetting properties that were supposed to increase the anisotropic character during particle formation and an interesting geometry (cone-shaped tail bound to a spherical head) could be generated. Similarly, PLGA/PCL-based drug-loaded (i.e., glibenclamide, tolbutamine, rapamycin, and lidocaine) Janus particles were synthesized. The formation of Janus morphology was found to be thermodynamically driven in accordance to the classical spreading coefficient theory, controlled by interfacial tensions. They proved that interfacial tension between the two interacting polymers with the water phase is a key factor to control the Janus structure. These interfacial tensions are highly dependent on the net charge of drug molecules (because addition of charged drug molecules may change the interfacial tension between different phases) as well as polymer weight ratio, hence by tuning these two factors, formation of Janus morphology can be easily achieved (Figure 12c, d).[103]

More recently, Biswal et. al have reported the synthesis of biphasic Janus particles consisting of poly(L-lactic acid) (PLLA) and poly(lactic-*co*-glycolic acid)(PLGA) via oil-in-water emulsion technique.[105] A nonvolatile poor solvent (mustard oil) was added which resulted in controlled phase separation of miscible polymers (PLLA and PLGA) with hierarchical porous structure. A transition between multilayer (trilayer/bilayer in core−shell fashion) and biphasic (Janus) morphology could be controlled by varying the amount of mustard oil, viscosity or crystallinity of polymers incorporated. Dual actives such as benzoic acid

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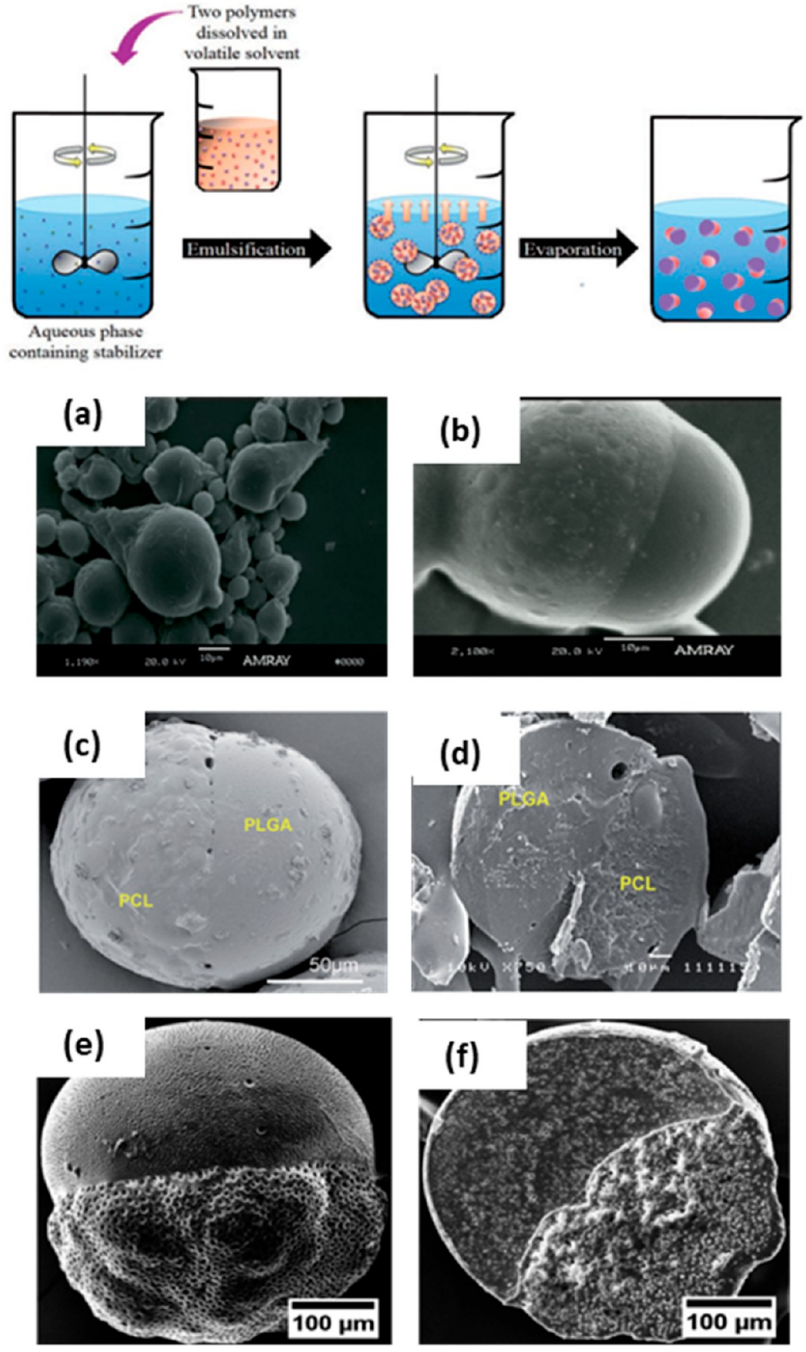

Figure 12. Scanning electron microscopy Images of (a) polymer/precirol particles. Reproduced with permission from ref 104. Copyright 2012 American Chemical Society. (b) PLGA/PCL particle. Reproduced with permission from ref 104. Copyright 2012 American Chemical Society. (c) Glibenclamide-loaded microparticles composed of PLGA/PCL. Reproduced with permission from ref 103. Copyright 2018 Royal Society of Chemistry. (d) Cross-sectional view of bicompartmental with a PLGA/PCL ratio (20/10). Reproduced with permission from ref 103. Copyright 2018 Royal Society of Chemistry. (e) PLGA/PLLA biphasic particles. Reproduced with permission from ref 105. Copyright 2020 Elsevier. (f) Cross-sectional view of bicompartmental PLGA/PLLA biphasic particles. Reproduced with permission from ref 105. Copyright 2020 Elsevier.

(antibacterial) and tocopherol (antioxidant) were incorporated in different compartments of biphasic particles that were released in controlled fashion over a long period of time (60 days). The active release was profoundly influenced by the hierarchical porosity of the system, thought to be originated from the addition of mustard oil (Figure 12e, f).[105] The Janus particles were found to provide better antibacterial as well as antioxidant activity for prolonged period of time as compared to their isotropic analogues.

Winkler and co-workers[106] extended the application of similarly prepared PLGA/PCL based biphasic particles (composed of polymer and lipid) as dual-drug-loaded system. They have utilized the fabricated particles to coencapsulate either two hydrophobic compounds (curcumin and quercetin) by O/W emulsion technique or a combination of hydrophobic and hydrophilic (naproxen/acetaminophen) compounds by a double emulsion technique in which phase separation of associated polymers can be primarily controlled by manipulating the interfacial tension between them.

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3.3. Droplet Microfluidics. Janus or bicompartmental particles can also be synthesized using microfluidics by producing Janus droplets or phase-separated homogeneous droplets. Shah and co-workers[107] demonstrated the fabrication of Janus particles, which were composed of a hydrogel, poly(acrylamide) (PAAm), and aggregated PNIPAM (poly(*N*-isopropylacrylamide) nanoparticles by using a glass capillary microfluidic device. Initially, they have prepared cross-linked PNIPAM nanoparticles of 500 nm size by precipitation polymerization using N,N′-methylene bis(acrylamide) as cross-linker. Allylamine (5 mol %) was also copolymerized along with PNIPAM to introduce amine groups into the nanoparticles to make them cationic in nature. To this microgel suspension a water-soluble polymer was added, i.e., poly(acrylic acid), to induce clustering by electrostatic interactions between ammonium ions of nanoparticles and carboxyl groups of polyacrylic acids. Later, 10 wt % acrylamide was added to microgel suspension along with a cross-linker (methylene-bis-acrylamide) and a photoinitiator (2-hydroxy-2-methylpropiophenone) and the complete mixture was emulsified in an oil (poly(dimethylsiloxane) fluid), and heated in an oven at 65 °C. Above the phase transition temperature of PNIPAM, aggregated PNIPAM particles shrunk and compacted to the one side of the droplet and pushed the acrylamide containing water phase on the another side of the droplet. The acrylamide monomer was then polymerized and cross-linked under UV radiation resulting in the formation of phase-separated particles as shown in Figure 13a.

To show the wide diversity of the microfluidic process, Marquis and co-workers[108] have demonstrated the fabrication of homo Janus (made from the same polymer, e.g., pectin−pectin) and hetero Janus (made from different polymers, e.g., pectin-alginate) microparticles from biopolymeric hydrogel by using a flow focusing device. The Janus droplets were produced by emulsifying the coflow of two aqueous solutions of biopolymers into an organic phase, inside a microfluidic device. The Janus droplets (hetero or homo) contained pectin and/or alginate and $CaCO_3$ (as cross-linking agent), whereas the continuous phase consisted of acetic acid. The acetic acid diffused into the droplets and triggered the release of calcium ions, which resulted in the cross-linking of the polysaccharides chains and led to the formation of a biopolymer network (Figure 13b, c), creating cross-linked Janus particles, which is useful for the controlled release of active substances in various applications such as food, medicine, etc. In another interesting example, biodegradable polymers such as PLGA/PCL biphasic particles were synthesized by microfluidics without inducing any covalent bond formation in any phase.[109] The Janus as well as microcapsules based on PLGA and PCL were achieved simply by changing the organic solvent between dichloromethane and dimethyl carbonate, which mainly manipulated the interfacial tension between the water and oil phases. The differentially degradable Janus particles made of easily degradable PLGA and slowly degrading PCL were demonstrated to be useful as controlled and programmable drug-release vehicles, which may carry and release multiple drugs at desired fashions (Figure 13d).

A summary table (Table 1) regarding the composition, technique, and applications of shape anisotropic and compositional anisotropic particles along with references is been provided here.

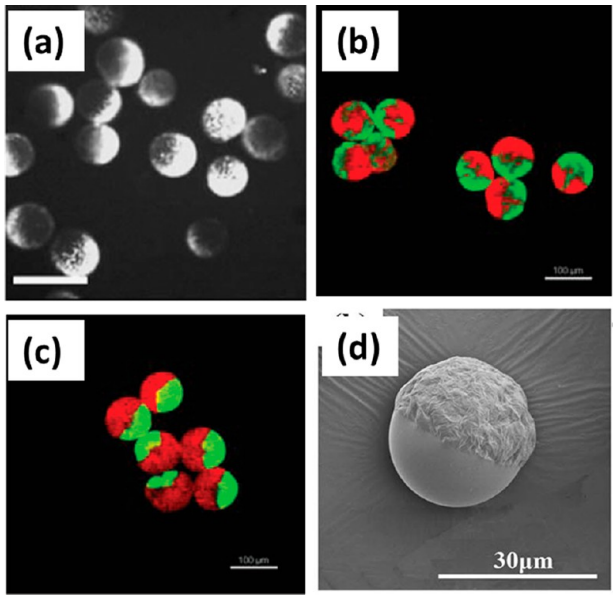

Figure 13. (a) Fluorescent microscopic image of polyacrylamide particles containing PNIPAM nanoparticles on one side. Reproduced with permission from ref 107. Copyright 2009 Wiley−VCH. (b, c) Scanning electron microscopic images of pectin/pectin homo Janus and alginate/pectin hetero Janus particles. Reproduced with permission from ref 108. Copyright 2012 American Chemical Society. (d) PLGA/PCL bicompartmental particles. Reproduced with permission from ref 109. Copyright 2015 Royal Society of Chemistry. Scale bars: (a) 200 μm.

4. SURFACE ANISOTROPY

4.1. Anisotropic Patchy Particles. In this class, we discuss the anisotropic patchy particles that are a sort of patterned particle having at least one well-defined patch on the surface through which the particles experience anisotropy. In general, anisotropic patchy particles can be produced by spatioselective surface modification or functionalization of isotropic/anisotropic particles possessing potential applications mainly in targeted drug delivery.[34] Many methods exist for the fabrication of patchy particles exhibiting multiple functionalities. Among them, post modification techniques mainly predominate, e.g., colloidal assembly, lithography, emulsion polymerization, and electrohydrodynamic cojetting technique.[110−112] Out of all these fabrication methods, the electrohydrodynamic cojetting technique is the most convenient and easy way to produce biocompatible patchy particles where bicompartmental/tricompartmental/multicompartment particles can be fabricated in a single step with orthogonal functionalities. Various compartments with orthogonal functionalities in a single particle provide a suitable platform for spatioselective surface modifications/patch formation onto the surface of individual compartment.

Bhaskar and co-workers[33] fabricated PLGA-based bicompartmental particles containing alkyne-functionalized PLGA as one of the compartments. This particular example demonstrates an excellent combination of electrohydrodynamic cojetting technique and spatioselective surface modification via Huisgen 1,3-dipolar cycloaddition (click chemistry) for the preparation of selectively modified compartmentalized particles. First, micrometer-sized bicompartmental particles loaded with fluorescent macromolecule (for imaging purposes) were prepared by taking only PLGA and a blend of PLGA and alkyne-functionalized PLGA in two different needles framed in a side-by-side fashion and electrojetted. The jetted particles were then allowed to react with O-(2-aminoethyl)-O′-(2-azidoethyl) heptaethylene glycol,

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Table 1. Fabrication Methods, Compositions, Shapes, and Applications of Shape Anisotropic and Compositional Anisotropic Particles

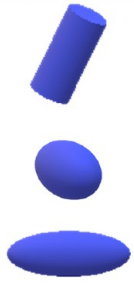
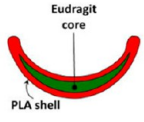
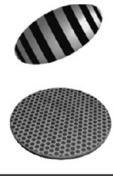
Anisotropy category	Polymer	Method of Fabrication	Shape	Schematic	Application	Reference
Anisotopic shape	TPGDA	Droplet Microfluidics	Rods, Disks, Ellipsoids		-	[52]
	PEG-DA	Droplet Microfluidics	Hexagonal , Circular, Triangular		-	[53]
	PLA/ Eudragit	Droplet Microfluidics	Crescent shape		Cell trapping	[54]
	PLA+Poly(MMA-*co*-BEMA)	Electrospraying	Cups, discs		-	[23]
	PMMA	Electropsraying	Cups		-	[62]
	Chitosan	Electrospraying	Cell-shaped		Drug delivery, Imaging	[63]
	PFS-b-P2VP	Self-Assembly	Ellipsoid Nanosheets			[67]

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Table 1. continued

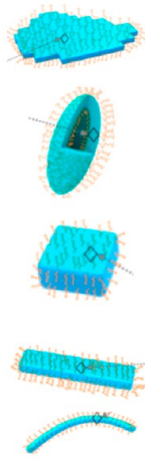
Anisotropy category	Polymer	Method of Fabrication	Shape	Schematic	Application	Reference
	PMAAz-co-PMAA	Self-Assembly	Lamella Ellipsoidal vesicle Cuboid Short belt Worm			[70]
	PLGA	Film stretching	Rods		Cell uptake	[71]
	PLGE	Film stretching	nanorods, nanoellipsoids, circular disks, elliptical nanodisks		Drug delivery carriers	[72]
	PLGA	Film stretching	Elliptical		Cell uptake	[74]
	PVP	Soft lithography	Disks, hemispheres		-	[70]
	poly(ethylene glycol diacrylate)	PRINT	conical/trapezoidal		Drug delivery	[71]
	PLGA	PRINT	Cyllinders, cubes, particles with centre fenestrations		Drug delivery	[72]
	PLGA	PRINT	cyllindrical		Targeted drug delivery	[73]

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Table 1. continued

Anisotropy category	Polymer	Method of Fabrication	Shape	Schematic	Application	Reference
Anisotropic composition	PLA/PLGA	Electrohydrodynamic co-jetting	Discs (biphasic)		Drug Delivery	[82]
	PEO	Electrohydrodynamic co-jetting	Spheres(triphasic)		-	[84]
	PLA/PLGA+PEI	Electrohydrodynamic co-jetting	spheres(biphasic)		SiRNA	[85]
	PLGA/PLGA+gold nanoparticles	Electrohydrodynamic co-jetting	Spheres, microcyllinders		Imaging	[86]
	PLGA/PCL	Emulsion technique	Spheres(biphasic)		Drug Delivery	[93]
	PCL/precirol	Emulsion technique	Spheres(biphasic)		Drug Delivery	[94]
	PLGA/PLLA	Emulsion technique	Spheres(biphasic)		-	[95]
	PAAmicrogel containing PNIPAM nanoparticles	Droplet Microfluidics	Spheres(biphasic)			[97]
	Pectin/Pectin Or Pectin/Alginate	Droplet Microfluidics	Spheres(biphasic)			[98]
	PLGA/PCL	Droplet Microfluidics	Spheres(biphasic)		Drug Delivery	[99]

which was selectively reacted with the compartment containing alkyne group via click reaction. Subsequently, the newly introduced amino groups were reacted with a fluorescence probe to visualize the selective patch formation only onto one compartment (Figure 14a), thus unveiling a new way for the spatioselective attachment of biomolecules such as cell adhesion peptides, antibodies, lectins, etc. They have further explored the click-chemistry-based spatioselective surface modification onto microcylinders (bicompartment, tricompartment, or tertracompartment) obtained by cryosectioning of electrojetted microfibers.[113] For example, the alkyne-functionalized PLGA was introduced in one of the phases of tetracompartmental particle and the surface alkyne groups were reacted with biotin-(ethylene oxide)$_3$ azide to immobilize biotin onto that specific compartment. These biotin-containing microcylinders were further incubated with streptavidin (a protein conjugated with dye, Alexa Fluor 633), which got bounded selectively onto a biotin patch as shown in Figure 14b.

More complex systems were demonstrated by Rahmani and co-workers[114] in their subsequent work. In their study, they have

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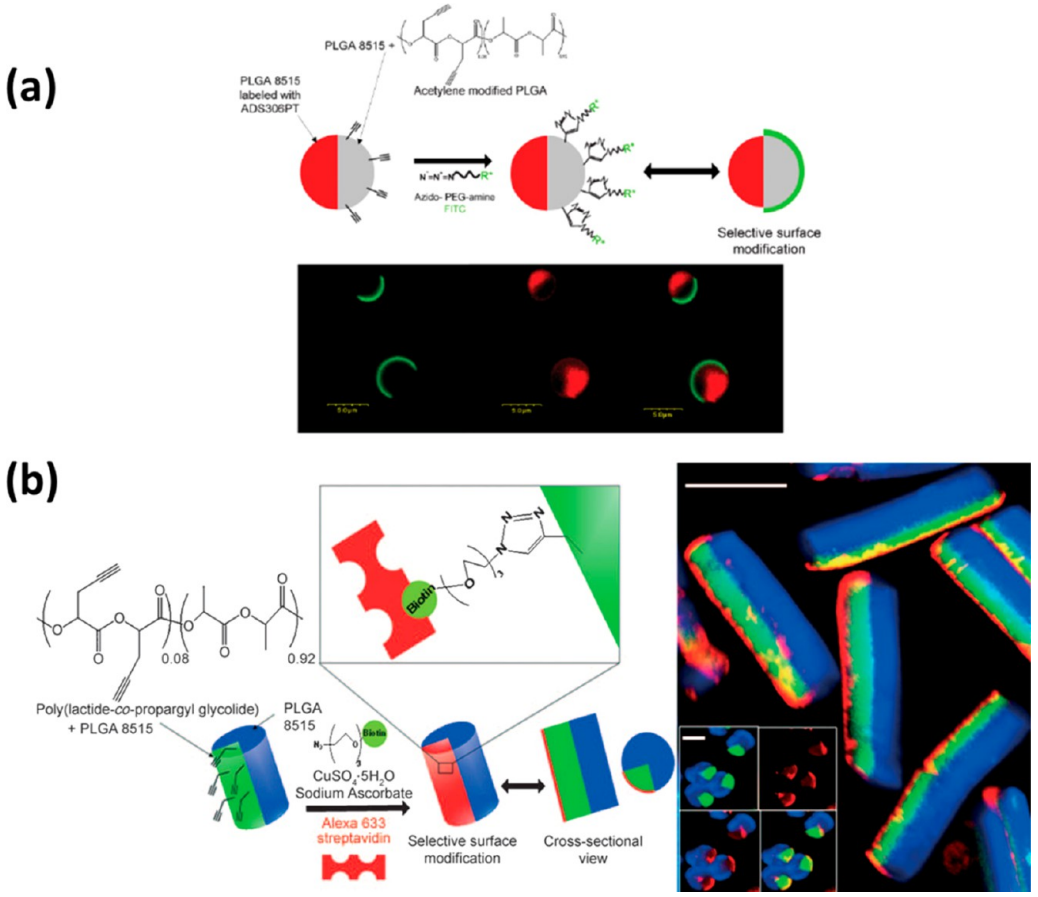

Figure 14. (a) Acetylene−modified containing bicompartmental microparticles which were modified with PEG-amine-FITC. Reproduced with permission from ref 33. Copyright 2008 Wiley−VCH. (b) Tetracompartmental microcylinders containing acetylene functionalized PLGA in one of the compartment and selectively modified with streptadivin. Reproduced with permission from ref 113. Copyright 2009 Wiley−VCH. Scale bars: (a) 5 μm, (b) 50 mm for the main image and 20 mm for the insets.

produced polylactide/PLGA-based two-patch and three patch microparticles, formed by using a combination of electrohydrodynamic cojetting technique and synthetic polymer chemistry. They have synthesized functionalized PLA (Figure 15) containing different types of orthogonal functionalities that were placed in two/three different compartments of disk-shaped particles prepared by electrohydrodynamic cojetting of two or three different polymeric solutions arranged in a side-by-side fashion. First, a hydroxyl-functionalized PLA (polymer 2) was synthesized that was then subjected to post polymerization modifications to yield various derivatives as shown in Figure 15. For example, polymer 2 was treated with 3-(diphenylphosphino)-4-(methoxycarbonyl) benzoic acid in the presence of N,N′-dicyclohexylcarbodiimide (DCC)/4-dimethylaminopyridine (DMAP) to synthesize polymer 3 which may further undergo Staudinger ligation chemistry to immobilize desired surface patch. In another reaction, polymer 2 was treated with 2-(4-benzoylphenyl) acetic acid in the presence of DCC/DMAP to give photoreactive PLA derivative, polymer 4. Also, modification of polymer 2 by 2-(cyclooct-2-yn-l-yloxy) acetic acid was carried out to prepare cyclooctyne modified polymer, polymer 5 which may further be utilized to attach biomolecules using copper free click chemistry. Finally, PLGA-based bicompartmental particles were fabricated with polymer 3 (green dye) in one hemisphere that was further treated with azide-PEG-Biotin followed by the selective conjugation of TRITC (tetramethyl rhodamine isothiocyanate)-streptavidin-labeled red dye on biotin modified compartment. CLSM images confirm the selective surface modification of bicompartmental particle. Similarly, polymer 4 was added during jetting as one of the compartments in bicompartmental particles and the prepared particles were incubated with bovine serum albumin (BSA) tetramethyl rhodamine as indicated by red dye (Figure 15). An exposure to UV light (365 nm) resulted in photo initiated immobilization of BSA selectively onto polymer 4 containing compartment. Incorporation of polymer 5 leads to the azide reactive compartment which resulted in the selective binding of azide-PEG biotin followed by dye-labeled streptavidin onto the compartment comprising polymer 5 using copper free click chemistry. On the basis of these initial results, they have expanded the experiments to fabricate tricompartmental particles by incorporating three PLA derivatives with orthogonal functionalities such as polymer 1 (low-molecular-weight polylactide with end-functionalized with carboxylic acid group) with carboxyl group as end functionality), polymer 4, and polymer 5 in three different compartments via the electrohydrodynamic cojetting technique. Individual compartments were then subjected to a series of orthogonal surface modification reactions such as photochemical attachment of polymer 4 with BSA tetramethylrhodamine (red dye), copper free click chemistry with polymer 5 to conjugate azide-PEG-FITC (green dye) and attachment of amine-PEG-biotin to polymer 1 containing compartment through EDC/sulfo-NHS chemistry which was labeled with Alexa Fluor 647 streptavidin

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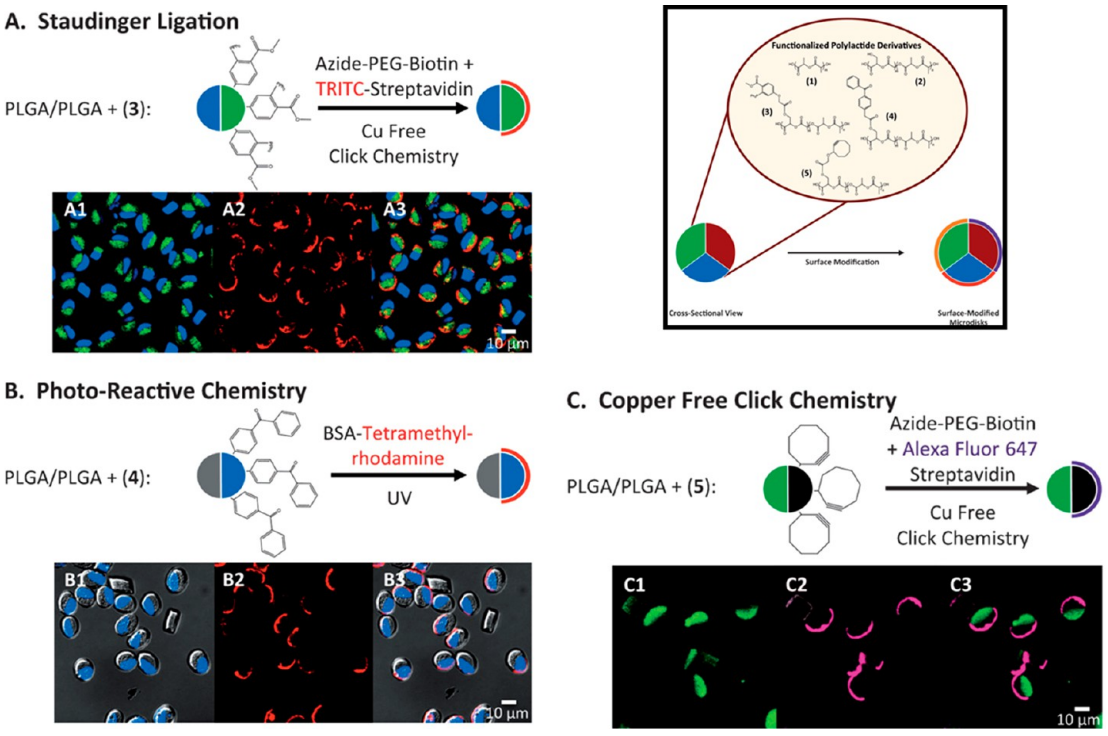

Figure 15. (A–C) Microparticles displaying polymers 3–5 in one hemisphere only are selectively surface functionalized through (A) Staudinger ligation, (B) photoimmobilization, and (C) alkyne/azide click chemistry. Reproduced with permission from ref 114. Copyright 2014 Wiley–VCH.

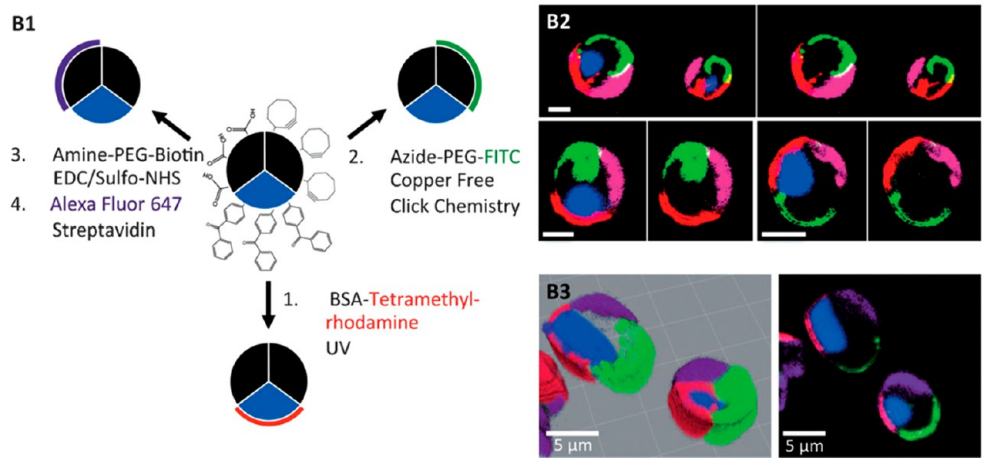

Figure 16. Selective surface functionalization of three-patch microparticles: (B1) Schematic; (B2) CLSM images of surface-modified three patch particles (particles containing poly 1, 4, and 5); (B3) three-dimensional reconstruction of the microparticles collected in the *z*-direction. Reproduced with permission from ref 114. Copyright 2014 Wiley–VCH. Scale bar: (B2) 5 μm.

(magenta dye). Spatioselective attachment of three different dyes in three different compartments is clearly visible from CLSM images, indicating the evolution of anisotropic patchy surfaces (Figure 16).

In another interesting work published by the same group, they have introduced long circulating Janus patchy particles made via electrohydrodynamic cojetting technique.[34] Long circulation of particles inside the body was thought to be originated from the polyethylene glycol (PEG) surface patches immobilized onto the surface of bicompartmental particles. These particles were fabricated by incorporating alkyne functionalized PLGA as one of the compartments, which was then selectively modified with PEG by reacting with PEG azide using click chemistry. To show the wide applicability of the system, we also incorporated an additional polymer (a phenol containing poly(methyl methacrylate) (PMMA)) which could be labeled with I,[125] in the particles for imaging purposes.

4.2. Polymer-Brush-Modified Anisotropic Particles.

Another interesting class of anisotropic patchy particles would be the presence of polymer-brush-modified patches onto the surface of anisotropic/isotropic particles. Recently, various research groups have shown that anisotropy can also be generated onto the particles either by spatioselective attachment of polymer brush or immobilization of polymer brush onto nonspherical (already anisotropic) particles.[23,115,116] The brush-modified particles may undergo nonuniform swelling in water, if the selected brush is hydrophilic in nature, thus bringing anisotropy to the system. Moreover, functionality of polymer

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brushes and their thickness, architectures, geometry of the substrate, etc., are also the crucial factors that directly affect the properties of the modified particle.

Over the past few years, various techniques have been reported for the immobilization of polymer brushes (an assembly of polymer chains tethered to surface via one end) onto the surface of substrates. These brushes can be attached either by a "grafting to" or "grafting from" approach. In "grafting to" approach, polymer brushes are directly attached to the surface either by covalent or noncovalent interactions, whereas in "grafting from approach", polymer brushes start to grow from initiator immobilized substrates via surface-initiated polymerizations techniques such as atom transfer radical polymerization (ATRP), reversible addition−fragmentation chain transfer (RAFT), ring opening metathesis polymerization (ROMP), and nitroxide-mediated polymerization (NMP). Among all these techniques, ATRP is the most commonly used method because of its ease and simplicity.[117] In an interesting example shown by Saha et al., surface initiated ATRP (SIATRP) was carried out onto the surface of one of the compartments of multicompartmental microcylinders obtained by the electrohydrodynamic cojetting technique as previously mentioned. Because only one of the compartments consisted of alkyne-functionalized PLGA, which later clicked with azide-modified ester bromide linker (ATRP initiator), that was finally used to grow hydrophilic poly(PEGMA) (poly(oligo(ethylene glycol) methyl ether methacrylate)) brush selectively from the surface of that particular compartments (Figure 17).[115] Spatio-selective

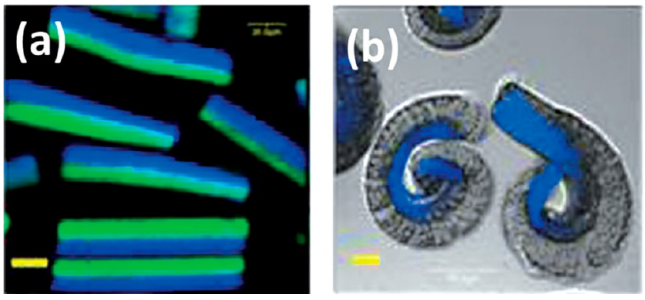

Figure 17. Confocal laser scanning microscopic images of (a) microcylinders having 120 μm length before polymerization, (b) microcylinders having 120 μm length before polymerization. Reproduced with permission from ref 115. Copyright 2012 Wiley−VCH. Scale bar: (a) 20 μm.

attachment of swollen hydrogel brush led to significant bending of the microcylinders, the curvature of which can be tuned by altering cylinder length, grafting density, composition, and architecture of the compartments. The bent microcylinders were thought to originate from the mechanical stress that occurred because of the avoidance of inter polymer chain repulsion faced by the growing polymer brush attached onto a soft polymeric surface (Figure 17).

The structure and conformation of the polymer brush can be regulated by using various external stimuli such as temperature, pH, solvent, light, etc. Hence, the responsive polymer brushes provide a platform to prepare "smart" surfaces suitable for various applications such as controlled cell adhesion, controlled drug delivery, triggered drug delivery, and responsive actuations. As mentioned earlier, Ifra and Saha recently reported the synthesis of cup-shaped particles consisting of PLA and poly(MMA-*co*-BEMA) (poly[methyl methacrylate-*co*-2-(2-bromopropionyloxy) ethyl methacrylate), where BEMA moieties of poly(MMA-*co*-BEMA) were used as an ATRP initiator to further grow pH-responsive poly(DMAEMA) (poly(2-dimethyl amino) ethyl methacrylate) brushes via SIATRP. The pH sensitivity of the polymer brushes was demonstrated by pH-induced adsorption of Rhodamine B dye at pH 4 and 7, where Rhodamine B dye was adsorbed selectively at pH 7 because of electrostatic interaction between dye (negatively charged at pH 7) and polymer brushes (positively charged at pH 7). However, the amount of dye adsorbed onto the brush-modified cup surface was found to be significantly higher than that of its isotropic analogue, citing the benefits of using anisotropic cup shape with larger surface area. The release of adsorbed Rhodamine B in acidic medium was found to be rapid probably because of the swelling of polymer brushes (interchain repulsion between positively charged poly(DMAEMA) brushes) (Figure 18).[23] Later, the applicability of functionalized cup-shaped particles was further explored by the same group by growing self-cross-linkable poly(HEMA) (2-hydroxy ethyl methacrylate) brushes from the surface of cup as well as disc-shaped particles via SIATRP. The controlled polymerization resulted in an interesting shape shifting of cup-shaped particles to spherical balls with one small opening/hole due to the cross-linking of

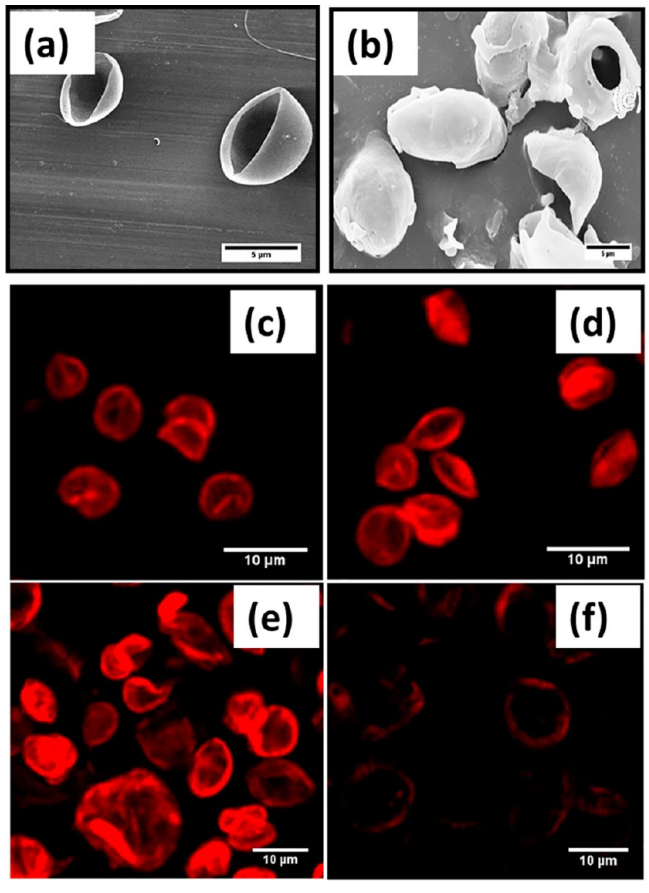

Figure 18. Scanning electron microscopic image of (a) cup-shaped particle before polymerization, (b) cup-shaped particle after growing PDMAEMA brushes. Confocal laser scanning microscopy images of (c, d) Rhodamine B dye adsorption on cup-shaped particles before polymerization at pH 7 and 4, respectively, (e, f) Rhodamine B dye adsorption on cup-shaped particles after polymerization at pH 7 and 4, respectively. Reproduced with permission from ref 23. Copyright 2019 Elsevier.

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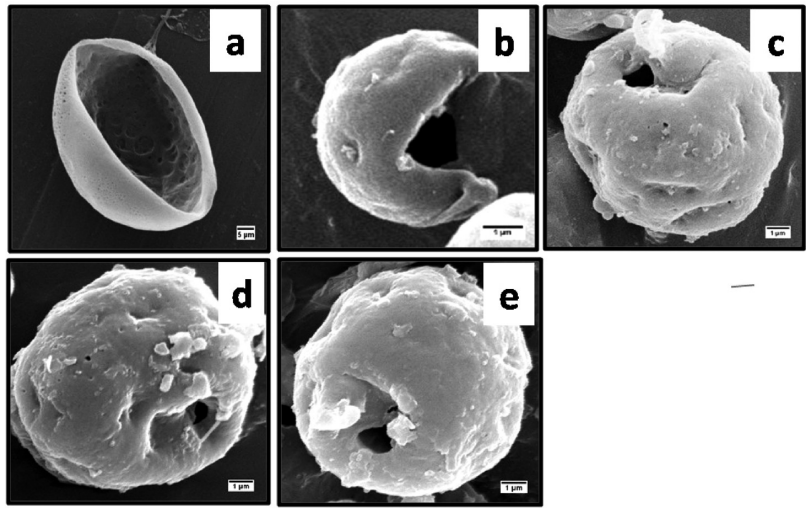
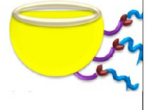


Figure 19. Scanning electron microscope image of cup-shaped particle polymerized at different intervals to grow PHEMA brushes (a) 0 h, (b) 15 min, (c) 1 h, (d) 3 h, and (e) 19 h. Reproduced with permission from ref 116. Copyright 2020 Wiley−VCH.

Table 2. Fabrication Methods, Compositions, Surface Modifications, and Applications of Surface Anisotropic Particles

Anisotropy category	Polymer	Method of Fabrication	Surface modification	Schemetic	Potential applications	Reference
Anisotopic Patchy particles	PLGA/PLGA+acetylene functionalized PLGA	Electrohydrodynamic Co-jetting	spatioselective surface modification (via Huisgen 1,3-dipolar cycloaddition		Imaging	[33]
	PLGA/PLGA+alkyne functionalized PLGA	Electrohydrodynamic Co-jetting	selectively PEG-ylated via copper catalysed click		Drug Delivery	[34]
	PLGA/PLGA+acetylene functionalized PLGA	Electrohydrodynamic Co-jetting	selectively modified with streptadivin.		Drug Delivery	[113]
Anisotopic Polymer Brush Modified particles	PLA+poly(MMA-*co*-BEMA)	Electrospraying	Growth of PDMAEMA brushes from BEMA initiator moities		Triggered/Targeted Drug Delivery	[23]
	PLGA/PLGA+acetylene functionalized PLGA	Electrohydrodynamic Co-jetting	Conversion of acetylene groups to azide modified ester bromide linker (ATRP initiator) and then growth of OEGMA brushes via surface ATRP		Biosensors/shape memory devices	[115]
	PLA+poly(MMA-*co*-BEMA)	Electrospraying	Growth of PHEMA brushes from BEMA initiator moities		Cell/Drug delivery	[116]

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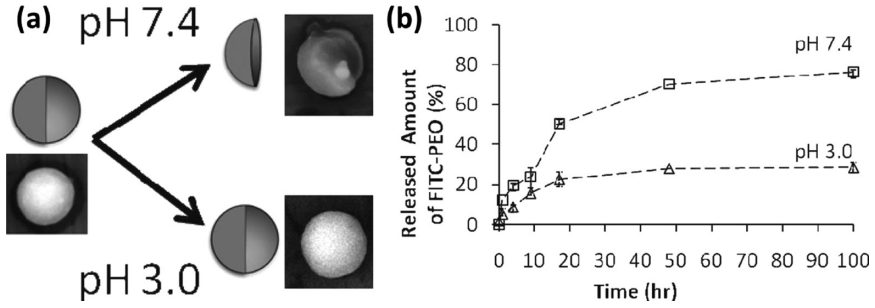

Figure 20. (a) Schematic for the selective degradation of PEO containing poly(AAM-*co*-AA) compartment at pH 7.4 (b) % release of FITC-PEO at different pH. Reproduced with permission from ref 122. Copyright 2012 Wiley−VCH.

poly(HEMA) chains via transesterification (Figure 19). No such shape shifting was observed for disc-shaped particles. This again shows the importance of anisotropy. However, such type of shape shifting did not occur in case of poly(DMAEMA) modified cup-shaped particles. This indicated that the shape shifting process was not only shape driven but also brush selective. The whole shape shifting phenomena was further confirmed by dissipative particle dynamics simulation studies.[116]

A summary table (Table 2) regarding the composition, synthetic technique and applications of surface anisotropic particles has been provided below:

5. APPLICATIONS

As mentioned above, anisotropic particles (shape, composition, or surface anisotropy) can find their potential applications in many areas where their isotropic analogues are being used. A clear advantage of using anisotropic particles over uniform particles is evident in several applications such as targeted as well as triggered drug delivery, biosensors, micro/nanomotors for delivering therapeutics, Pickering emulsion stabilizer, colloidal assembly, antireflection coatings, etc.[16,32,118−120] However, as the primary focus of this paper is on biocompatible particles, a brief account of their various applications in different biomedical areas has been detailed below.

5.1. Drug Delivery. In past decades, various anisotropic particles have been investigated for drug-delivery applications, as drug-release rate is highly affected by the geometry of the carriers. For instance, wormlike micellar particles (d(diameter) = 150 nm and l(length) = 1 mm) composed of PEG−PCL(poly(ethylene glycol)-*b*-poly(caprolactone) block copolymer were prepared to encapsulate anticancer drug such as methotrexate.[121] The wormlike particles were found to show 3.5 ± 0.14% loading efficiency and 65.6 ± 0.12% encapsulation efficiency, which were significantly high as compared to spherical particles (2.1 ± 0.08% loading efficiency and 26 ± 0.10% encapsulation efficiency), when both were synthesized by SORP (self-organization rapid precipitation). However, worm like particles showed comparatively slow release of methotrexate which is again beneficial for sustain release applications. It is noteworthy that many methods such as electrojetting, flash nanoprecipitation, etc., do exist, which also produce spherical particles with high drug-loading efficiency.

Anisotropic composition or compartmentalization has become attractive for many applications, which necessitate the presence of multiple functionalities with orthogonal character in a single particle. For example, single particles may comprise of a combination of acidic/basic, hydrophilic/hydrophobic, adhesive/repellent, conductive/nonconductive, stimuli responsive/stimuli nonresponsive, etc., characteristics. As mentioned earlier, the electrohydrodynamic cojetting technique is a cost-effective technique to prepare such type of systems with various shapes and sizes in one step. Hwang et al. designed and synthesized differentially degradable compositionally anisotropic bicompartmental particles by the electrohydrodynamic cojetting technique.[122] They were composed of an interpenetrating polymer network of PEO (poly(ethylene oxide)) and p(AAm-*co*-AA) (poly(acrylamide-*co*-acrylic acid)) in one compartment and a cross-linked copolymer of poly(acrylamide-*co*-acrylic acid) and dextran segments in the second compartment.[122] The dextran compartment was loaded with Rhodamine B isothiocyanate conjugated with dextran fluorophore, whereas PEO-containing phase was loaded with fluorescein isothiocyanate conjugated PEO (FITC-PEO) to visualize the different compartments, and these dyes have also served as drug surrogates in release studies. Because of the varying cross-linking behavior of both compartments, selective degradation of PEO-containing compartment occurred at pH 7.4, however, both the compartments were stable at pH 3. This happened because, prior to release study, particles were subjected to thermal treatment which accelerated the cross-linking in dextran containing compartment by facilitating imide bond formation between amine and carboxylic acid groups. Further, the carboxylic acid groups from copolymer were also involved to form an ester bond by reacting with free hydroxyl moieties of dextran. However, PEO containing compartment contained only imide groups due to the thermal cross-linking of copolymer, poly(AAM-*co*-AA). The imide bond is susceptible to hydrolysis at pH 7.4, whereas ester bond degrades very slowly at that pH. Hence hydrolytic degradation of PEO-containing compartment occurred very fast (stabilized by only imide bonds); however, both the compartments were stable at pH 3, which made them suitable for oral drug delivery, as particles will maintain their spherical shape at pH 3 (the pH of the stomach) and have the potential to release the drug once it reaches the intestine maintained at physiological pH (pH ∼7.4). This was further confirmed by the release study of fluorophores as shown in Figure 20a, b.

Another example published by Vazquez and co-workers, where they have reported Janus particles composed of poly(vinylpyrrolidone) (PVP) for combined photodynamic therapy−chemotherapy by loading either carmofur (an anticancer drug) or rose Bengal (RB) (photosensitizer) and a combination of both.[123] They have fabricated three sets of particles PVP-C (carmofur-loaded particles), PVP-RB (rose Bengal-loaded particles) and PVP-RBC (carmofur and rose Bengal-loaded bicompartmental particle). First, two were found to have regular spherical shape, whereas PVP-RBC had irregular

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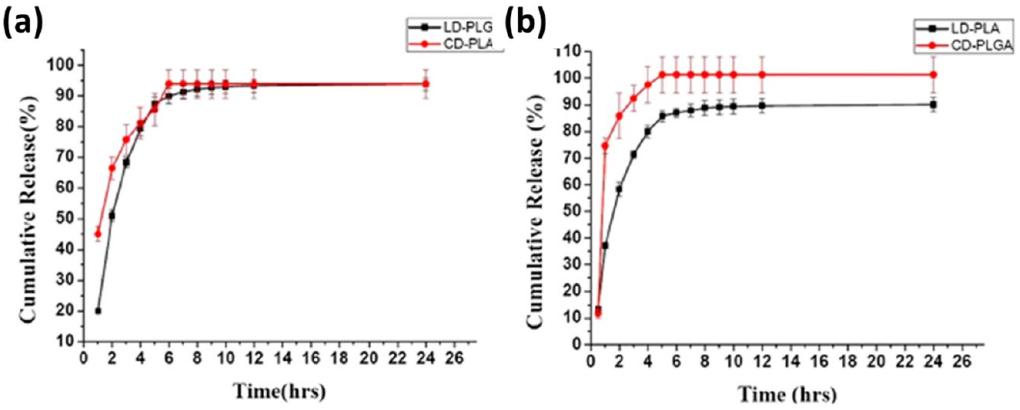

Figure 21. Drug release profile for LD- and CD-encapsulated biphasic PLGA/PLLA particles: (a) when LD is in PLA and CD is in PLGA; (b) when LD is in PLGA and CD is in PLA. Reproduced with permission from ref 91. Copyright 2018 Springer.

shape, the size of all the three sets were also slightly different. The release rate of RB was similar from PVP-RB and PVP-RBC particle system; however, the release rate of carmofur was found to be decreased in the PVP-RBC particle system (Janus particles) in comparison to PVP-C because of the difference in their architecture, thus controlling the release of anticancer drug, often desired to minimize the toxic side effects. Thus, the fabricated Janus particles provide a convenient way to incorporate a photosensitizer along with an anticancer drug whose release can be easily controlled.

As mentioned before,[91] the disk-shaped bicompartmental particles composed of PLA/PLGA were loaded with levodopa (LD) and carbidopa (CD) to treat Parkinson's disease (PD). PD is a neurodegenerative disorder and occurs because of the deficiency of dopamine. Continuous supply of levodopa is effective to treat PD as it gets absorbed in the small intestine area, crosses the blood brain barrier, and then gets converted into dopamine. But a much smaller amount of levodopa is able to reach to the targeted side after each oral dose, as it gets metabolized by 1-amino acid decarboxylase enzyme (AADC), which can be avoided by using carbidopa (an AADC inhibitor). Hence, a continuous delivery of the combination of both LD and CD would certainly help. The dual drug-loaded (LD and CD) disk shaped particles possessing anisotropic roughness are found to be a suitable carrier for both LD and CD placed in different compartments maintaining the required drug ratios, LD/CD = 4:1, similar to the commercially available tablet, Syndopa. The synthesized particles are anisotropic due to their shape (disk) as well as composition (Janus). The disk shape was chosen because it provides a larger surface area for adhesion to the intestine and increases the drug absorption, whereas biphasic character helped to independently tune drug-release rate. Two systems were prepared, having either LD or CD in PLGA or PLA compartments (LD/CD = 4:1) and their release profiles were studied to understand the effect of polymer hydrophilicity/hydrophobicity and crystallinity on the drug-release rate. Both the drugs release at a faster rate from the smooth PLGA compartment because of the more hydrophilic nature of amorphous PLGA as compared to PLA, which was crystalline and hence formed rough surface and retarded the drug release. The bicompartmental particle system containing LD in PLGA and CD in PLA phase was proven to be a potential PD drug carrier which delivers both the drugs at comparable and sustainable rates (release of 80% of drugs in initial 5 h and 90% drugs in 24 h) as shown in Figure 21a, b. Because of the difference in crystallinity between the two different compartments, manipulation of drug-release rates for both the drugs was easily achieved, thus further proving the role of anisotropy in dictating the desired drug-release profile.

Mitragotri et al. have studied the margination (localization toward the blood vessel wall) and adhesion properties of polystyrene particles of different shapes (spheres, oblate, prolate, and rods). The nonspherical shapes were obtained by thermostretching spheres and then particles were coated with biotin. Then, biotin-coated particles were allowed to flow on avidin-coated surfaces (in the presence/absence of RBCs) using a microfluidic setup where nonspherical particles showed high margination as well as adhesion in comparison to spherical particles. The results were further confirmed by computational studies using the large-scale atomic/molecular massively parallel simulator (LAMMPS) package, with dissipative particle dynamics (DPD).[29]

5.2. Biodistribution. Particle shape has found to be a critical parameter affecting the biodistribution. Several studies have been carried out to observe the effect of particle's geometry such as rod, cylinder, quasi-hemispherical, spherical, or many more on its distribution in various organs. In 2013, Chu et al. observed that smaller size features are the most preferable, which decreases the chance of clearance by organs of the mononuclear phagocyte system (MPS) and hence can stay inside the body for a prolonged period of time to serve the purpose. In this regard, they have reported the facile fabrication of docetaxel-loaded (chemotherapeutic agent) monodisperse and shape-specific PLGA (poly(lactide-*co*-glycolide) particles via the PRINT technique.[40] Two different types of cylindrical shapes (d (diameter) = 200, h (height) = 200 nm (PRINT-doc-200 × 200) and d = 80 nm, h = 320 (PRINT-doc-80 × 320)) were prepared because of their superior cellular uptake and inserted into the mice bearing human ovarian carcinoma SKOV-3 flank xenografts. The plasma Doc (docetaxel) exposure for PRINT-doc-200 × 200 and PRINT-doc-80 × 320 was increased to 53 and 76%, respectively, in comparison to free Taxotere (docetaxel) over a time period of 0−168 h. Interestingly, PRINT-doc-80 × 320 showed a higher increase in exposure time in comparison to PRINT-doc-200 × 200 for 0−24 h. Moreover, PRINT-doc-80 × 320 exhibited lower exposure in spleen, lung, and liver in comparison to PRINT-doc-200 × 200 and Taxotere. Because of the smaller diameter of PRINT-doc-80 × 320, it can easily penetrate through the tumor pores, thus preferred for achieving long circulation time. The total concentration of Doc

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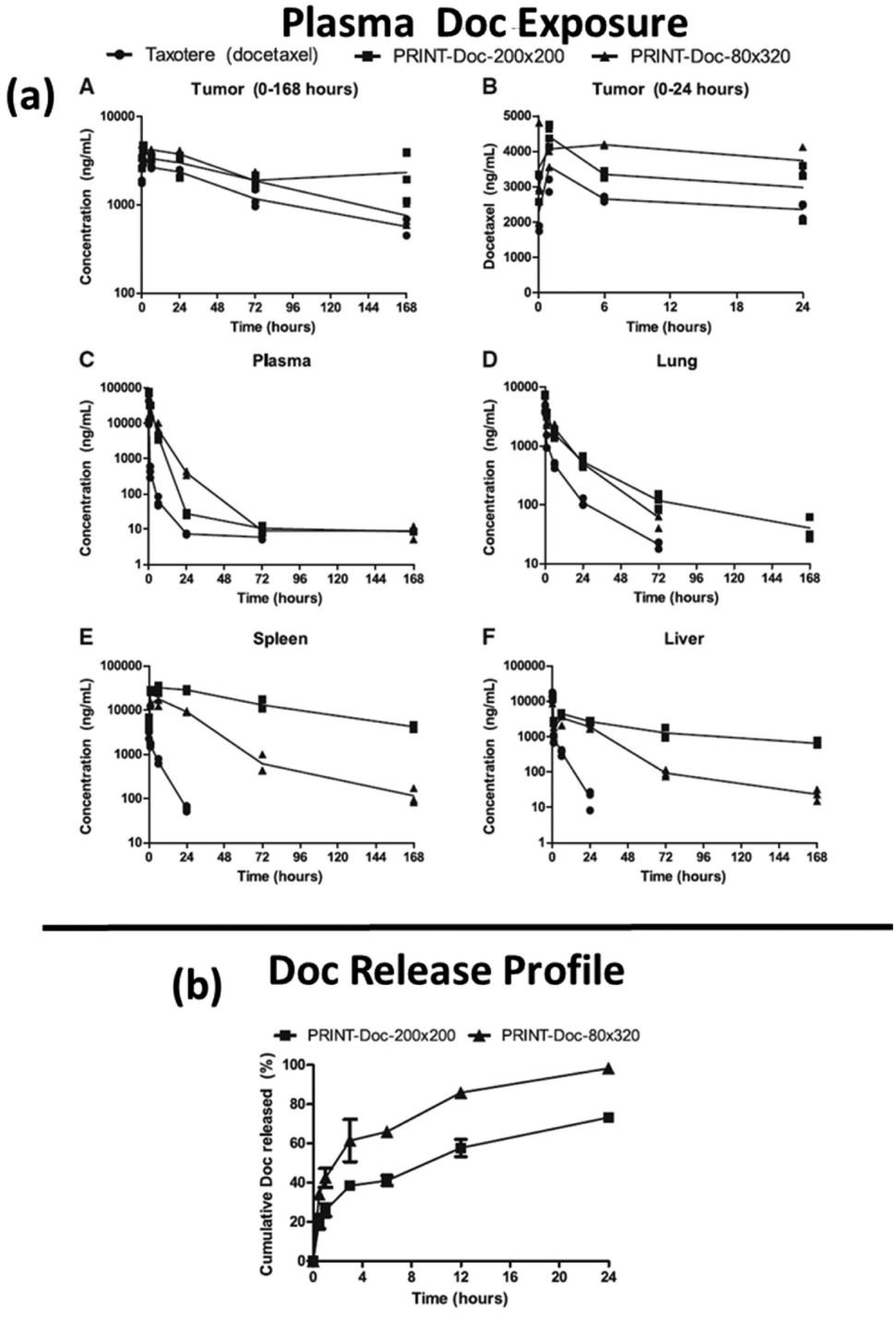

Figure 22. (a) Doc concentration vs time curve at different time intervals and for various organs; (b) % release of Doc with respect to time. Reproduced with permission from ref 40. Copyright 2013 Elsevier.

(encapsulated and released) vs time plots are shown in Figure 22a. PRINT-doc-80 × 320 showed burst release (~60% by 3 h, 100% release in 24 h) of Doc as compared to PRINT-doc-200 × 200 (~38% by 3 h, 73% release in 24 h). This occurs because of the increase in surface to volume ratio for small-sized cylinders that ultimately resulted in faster release (Figure 22b).

As discussed above, the properties of multicompartmental particles with compositional anisotropy can be further tuned by providing some additional surface functionalization to the selective compartments to generate spatioselective surface patches. For example, alkyne-functionalized PLGA-based bicompartmental nanoparticles were fabricated via the electrohydrodynamic cojetting technique by introducing CTAB (cetyltrimethylammonium bromide) to reduce the particle size down to the nanometer level and modified through PEGylation by clicking PEG azide selectively onto the surface of the alkyne-containing compartment. Spatioselective PEGylation helped to enhance the circulation time of the particles, thus prolonging its survival inside the body.[34] In order to find out the distribution of these specially designed compartmentalized nanoparticles in different parts of body, phenol containing poly(methyl methacrylate)(PMMA) was also incorporated in

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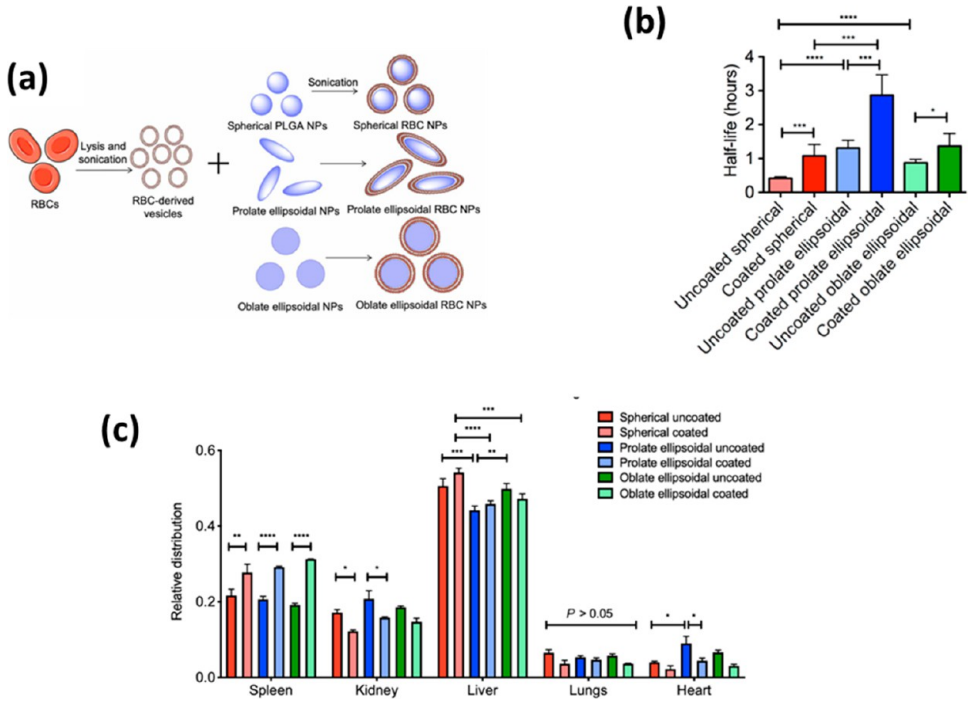

Figure 23. (a) Fabrication scheme of RBC coated spherical, prolate ellipsoid and oblate ellipsoid particles. (b) Half-life of RBC coated and uncoated spherical, prolate ellipsoid, and oblate ellipsoid particles. (c) Biodistribution of RBC coated and uncoated spherical, prolate ellipsoid. and oblate ellipsoid particles. Reproduced with permission from ref 124. Copyright 2020 Science Advances.

one of the compartments to label that specific compartment with radioactive I^{125} using phenol groups. The radioactive-labeled nanoparticles were then injected intravenously into mice and sacrificed after 1, 4, and 24 h. The blood and different organs were collected; organs were weighed and examined via gamma counter. On the basis of amount of radioactive substance, it was concluded that major portion of nanoparticles were accumulated in liver and spleen (35.09 and 29.89% ID (injected dose)/g after 24 h), whereas a significant amount of nanoparticles were found to be present in lungs (2.18% ID/g), kidney (0.95% ID/g), stomach (0.28% ID/g), and bones (1.94% ID/g) after 24 h (Figure 23a). These PEGylated particles can be circulated for more than 24 h and have potential to encapsulate two different therapeutics which can be independently released in desired fashion. Moreover, in addition to PEGylation, one of the compartments can be further functionalized with targeting moieties so that targeted drug delivery along with long circulation time may simultaneously be achieved. This will have a profound effect on the success of the therapy.

More recently, spherical PLGA particles prepared via an emulsion technique were converted to prolate ellipsoidal and oblate ellipsoidal shape via film stretching technique.[124] Later, those particles were coated with RBC to yield a biomimetic lipid membrane. The coated and uncoated particles of various shapes (spherical, prolate ellipsoidal, and oblate ellipsoidal) were injected intravenously into the body of mice. The blood samples collected at frequent time intervals showed that the half-life of all the coated samples increased significantly in comparison to the uncoated one. However, the RBC-coated prolate ellipsoidal shape exhibited superior half-life, when compared with RBC-coated spherical and oblate ellipsoidal shape (Figure 23b). After 24 h of incubation, the distribution of particles was analyzed in different organs and a significant difference in the particle concentrations accumulated in different organs was found with respect to shape of the particles. Uncoated prolate ellipsoidal particles had reduced accumulation in the liver after 24 h as compared to the oblate ellipsoidal and spherical one, whereas there was a high accumulation of uncoated prolate ellipsoidal particles in heart. Moreover, all the coated particles accumulated more in the spleen and uncoated particles in kidney, which this was probably due to the high clearance and degradation of uncoated particles in comparison to coated ones.

5.3. Cellular Uptake. Recently, particle shape has been recognized as an important parameter in biological processes affecting particle cellular uptake and vascular dynamics.[13−16] Cellular uptake of particles is another important biological process that gets affected by the shape of particles. Particle shapes exhibit a high impact on cellular uptake, kinetics of cell uptake and its mechanism, cytotoxicity, and intracellular distribution.[16] For example, Agarwal et al.[125] compared the polyethylene glycol diacrylate (PEGDA)-based hydrogel nanoparticles of various sizes and shapes by their uptake in epithelial, endothelial, and immune cells. They have produced both disc-shaped and rod-shaped particles and carried out their cell uptake study in HeLA and epithelial cell line, HEK 293. They found that disc-shaped particle were internalized more efficiently in comparison to rod-shaped particles; however, particles with a larger volume were more effectively internalized compared to those with smaller volumes. A similar trend was observed when particles were studied in human umbilical vein endothelial cells (HUVECs) and primary mouse bone marrow dendritic cells (BMDCs). Only with HUVEC cells, medium-sized discs (d = 220 nm) could internalize more effectively as compared to either smaller volume discs or larger-volume discs as well as nanorods. This difference in cell uptake behavior could be explained on the basis of a hypothesis that states cell uptake is highly affected by the adhesion force between the nanoparticle surface and the cell membrane (controlled by shape of particles), and strain energy required for membrane deformation (dictated by shape of particles). The contact area of discs and rods are more in

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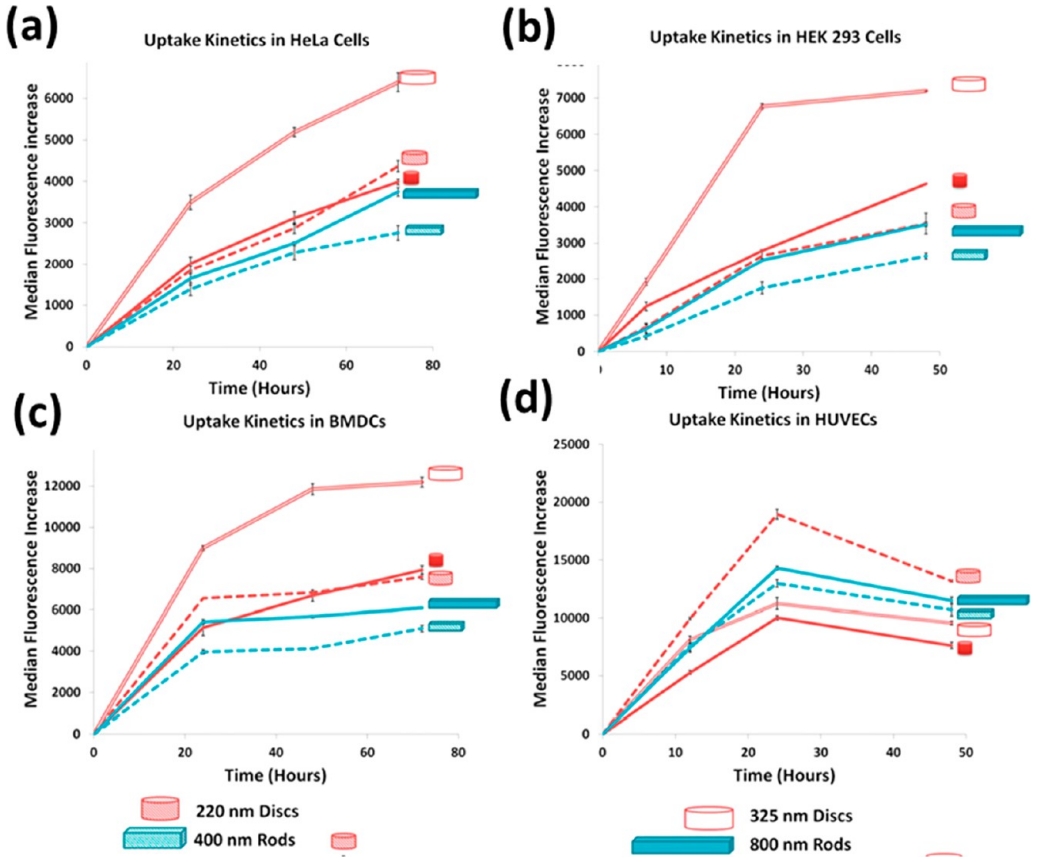

Figure 24. (a) Cellular-uptake kinetics of 200 nm discs, 325 nm discs, 400 nm rods, and 800 nm rods in various cell lines. (a) HeLa cells, (b) HEK 293 cells, (c) BMDCs, and (d) HUVEC cells. Reproduced with permission from ref 125. Copyright 2013 PNAS.

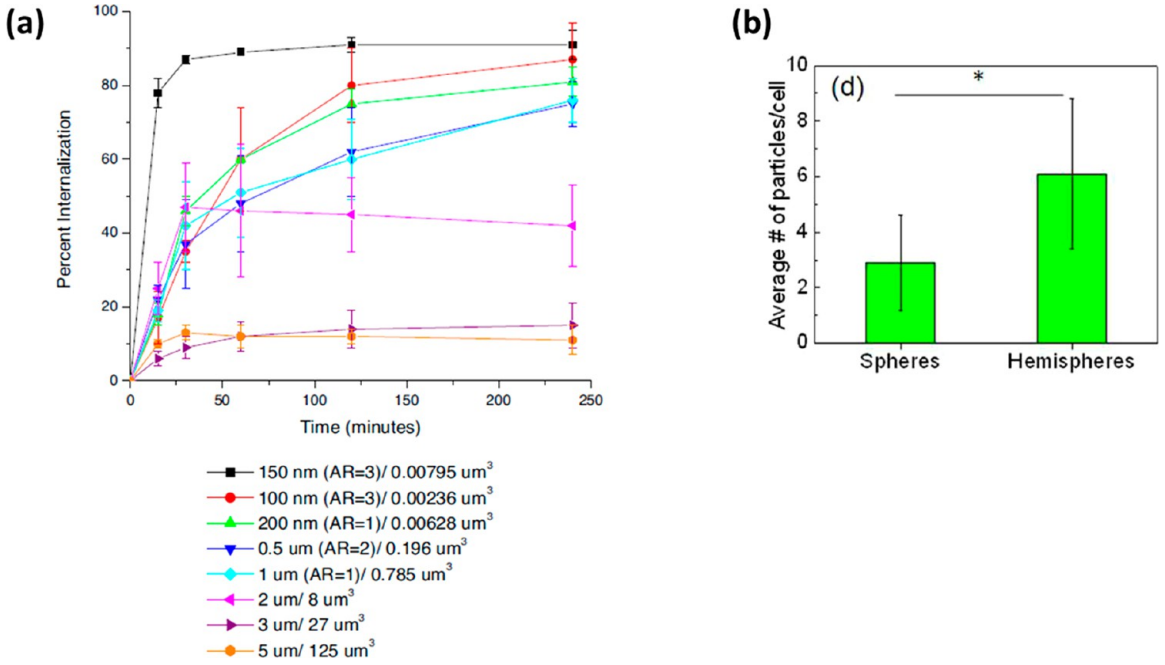

Figure 25. (a) Internalization profile of cubic and cylindrical particles prepared via PRINT technique with HeLa cells over an incubation period of 4 h. Reproduced with permission from ref 31. Copyright 2008 PNAS. (b) PVPON/TA spherical and hemispherical particles internalized per cells. Reproduced with permission from ref 126. Copyright 2013 American Chemical Society.

comparison to spheres, thus enhancing the adhesion and hence cell uptake of anisotropic particles. However, if we compare between the disc and rods of same volume and surface area, strain energy cost for cell uptake is found to be higher in the case of rods, and thus efficient internalization was observed in the case of disc-shaped particles (Figure 24).

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In another interesting example, interaction of anisotropic biocompatible particles with HeLa cells were studied. The particles were made from cationic, cross-linked poly(ethylene glycol) based hydrogels by PRINT technique. A series of anisotropic particles such as micrometer-sized cubic-shaped particles (different sizes) and micrometer-sized cylindrical particles (with various aspect ratios were produced and incubated with cells to study cell uptake behavior. The cell internalization was found to be highly affected by shape and size of the fabricated particles. There was no significant cell internalization for the cubic-shaped particles of 3 and 5 μm size, whereas cubic particles of 2 μm side length could show internalization. However, cylindrical particles were proven to be best for HeLA cell internalization in comparison to cubic shaped particles. The cylindrical particles (d = 150 nm, h = 450 nm) with a high aspect ratio were found to be internalized in HeLA cells four times faster than that of cylindrical particles (d = 200 nm, h = 200 nm) of low aspect ratio (Figure 25a). This was thought to be due to the favorable interaction between multivalent cationic particles and cells. Moreover, the interaction may become stronger for cylindrical particles with high aspect ratio because of the availability of larger surface area to interact with the cells.

In another interesting study, Chen and co-workers[126] have demonstrated the fabrication of spherical, cubical, and hemispherical microparticles by drying multilayer capsules of hydrogen bonded (PVPON(poly(*N*-vinylpyrrolidone)/TA-(tannic acid)). Cell uptake studies showed that spherical and hemispherical particles could be internalized by THP-1 human monocytic leukemia cells; however, efficiency of internalization was two times more for hemispherical particles (Figure 25b), thus further exhibiting the critical role of anisotropic shapes in enhancing cell uptake.

Champion and Mitragotri[127] reported the effect of particle shape on phagocytosis. They have prepared anisotropic-shaped polystyrene particles (nanodisks and nanorods) and observed that macrophages attach to the elliptical disks along a major axis, thus internalizing the particles very quickly, whereas the particles that were attached through a minor axis or flat side could not be internalized well. In another study, Mitragotri and co-workers[30] prepared trastuzumab (antibody)-coated spheres, disk- and rod-shaped nano- and microparticles made from polystyrene, and specific/nonspecific uptake of these particles were studied in three breast cancer cell lines: BT-474, SK-BR-3, and MDA-MB-231. Rods were found to exhibit higher specific cell uptake and lower nonspecific cell uptake as compared to spheres. Later, polystyrene rods were replaced by pure chemotherapeutic drug nanoparticles (rods) made of camptothecin. The dose of trastuzumab-coated camptothecin-based rod-shaped nanoparticles required to inhibit cell growth was found to be 1000-fold lower in comparison to soluble trastuzumab.

6. CONCLUSION AND FUTURE OUTLOOK

In recent years, biocompatible anisotropic polymeric particles have emerged as an irreplaceable tool, especially in biomedical field for their superior biological performance and hence, research in that direction has made a rapid progress. In this review, we presented a summary of fabrication methods describing their theoretical principles that mainly discuss the fabrication process and mechanism of formation, and finally, we discussed several applications (Tables 1 and 2), emphasizing their advantages over spherical particles. Understanding the mechanism of particle formation is crucial to developing particles with various anisotropy, tailored properties, shapes, and sizes. A simple tweaking of parameters in a single method can offer a wide variety of anisotropic particles. This is undoubtedly advantageous for anisotropic particles over spherical ones. Moreover, many difficulties faced by spherical particles can be mitigated by using their anisotropic counterparts that may fall in either of the categories such as shape, composition and surface heterogeneity (patchy surface). These versatile biocompatible anisotropic polymeric particles affect several biological activities such as drug-release profiles, cellular uptake, long circulation times/clearance, biodistribution, etc., through their shape, composition, or surface modification. However, development of anisotropic particles is still at its nascent stage, requiring many refinements to the existing processes to improve the monodispersity, reproducibility, yield, scalability, etc. Moreover, tuning the size and shape of particles within a desirable range is difficult to achieve, unlike the spherical particles, formation of which is always favored by surface tension and hence relatively less challenging. Therefore, a detailed fundamental study to understand their formation would be greatly beneficial for their wide application in various fields.

Among all the methods for the synthesis of particles, the film stretching method is the easiest way to produce shape anisotropic particles, but the shape of the particles fabricated by this method is limited to prolate or oblate shape. PRINT technique overcomes this shape limitation because a wide variety of shape can be produced by this technique, though it faces practical challenges in large-scale implementation. Fabrication techniques such as emulsion solvent evaporation and self-assembly of copolymers always suffer from low drug encapsulation efficiency and high polydispersity; microfluidics is scalable but lacks the ability to produce nanoparticles, whereas electrojetting may produce particles down to nanometer with high drug-encapsulation efficiency but is difficult to scale up. Therefore, enormous scopes for improvements are there to further research on this topic.

A wide variety of polymers with unexplored functionalities and properties can further be investigated in this direction via both simulation and experimental ways to gain insight about their structure−property relationships, thus broadening their application areas. Moreover, organic−inorganic composite particles can be excellent candidates for drug-delivery carriers because of their combined properties. For example, Janus particles may contain dispersed inorganic particles in one of the hemisphere acting as imaging agent, whereas the other hemisphere may act as a drug-releasing compartment, the surface of which may or may not contain a targeting moiety to enable targeted drug delivery. In this way, the fate of the particles can be easily tracked down through the imaging agent in addition to selectively targeting them to a specific organ in which multiple drugs from multiple compartments can be released in predetermined rates. All these innovative particles with fascinating properties require to be developed, optimized, and ultimately transformed from potentiality to reality with the help of a team of researchers including material scientists, physicists, chemists, theoreticians, and biologists. So, research on the anisotropic particles hold great promise in the near future.

AUTHOR INFORMATION

Corresponding Author

Sampa Saha − *Department of Materials Science and Engineering, Indian Institute of Technology Delhi, New Delhi*

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110016, India; orcid.org/0000-0002-6086-317X; Email: ssaha@mse.iitd.ac.in

Author

Ifra Mirza − *Department of Materials Science and Engineering, Indian Institute of Technology Delhi, New Delhi 110016, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsabm.0c01075

Notes

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