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Inorganic nanoparticle empowered biomaterial hybrids: Engineered payload release

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There are many challenges in delivering active pharmaceutical ingredients from biomaterials, including retention of payload activity, accurate temporal release, and precise spatial administration, to name only a few. With our constantly increasing knowledge of biology and physiology, pathologies that require therapeutic interventions are becoming more understood. While the desired temporal and spatial administration of a therapy might be theorized, the ability to deliver an active therapeutic in a precise location during a specific time frame is often challenging. This has led researchers to develop hybrid biomaterials containing inorganic nanoparticles in order to combine the advantages of both inorganics and organics in payload delivery applications. Organic materials have many beneficial properties, including the ability to form networks and matrices to create three-dimensional structures from the nanometer to centimeter scale, biodegradability, the versatility to use both synthetic and natural precursors, and ease of chemical modifications, while inorganic materials offer highly controllable nanoscale features, can entrap and protect therapeutics, and have degradation properties that can be tightly regulated. Here in, we discuss the current state-of-the-art in active pharmaceutical ingredient delivery from biomaterial hybrids, demonstrate the added levels of control that these hybrid biomaterials offer, and give our perspective on future innovations in the field.

KEYWORDS

hybrid biomaterials, inorganic nanoparticles, drug delivery, hydrogels, polymer scaffolds, silica nanoparticles, tissue engineering

Introduction

Innovations in biomaterial design have accelerated greatly over the last decades, expanding from materials that have limited interactions with the body to current designs where natural, synthetic, composite, living, stimuli responsive and/or actuable biomaterials not only interact with cells and tissues but can also instruct specific outcomes post implantation (Dos Santos et al., 2020; Lavrador et al., 2021). Implanted organic biomaterials are most commonly in the form of hydrogels or polymer scaffolds, and can either be injected into tissues or preformed structures can

be surgically placed into an exposed area (Pawelec et al., 2018; Babu et al., 2021). One important property engineered into biomaterials is the capability to release active pharmaceutical ingredients (APIs) for applications ranging from cancer therapeutics to nervous system repair (Fadia et al., 2020; Yang et al., 2020; Ciciriello et al., 2021). Releasing APIs from implantable biomaterials has several advantages, including on site release with tunable kinetics, administration of multiple APIs from the same biomaterial, and actuable payload release (Dumont et al., 2015; Rambhia and Ma, 2015; Gayet et al., 2020). As a way to more precisely regulate API release kinetics from biomaterials, inorganic nanoparticles have begun to be incorporated into their structure to form nanoparticle-laden composites. These composites allow for the advantages of organic biomaterials, formation of 3D architectures, biodegradability, cellular adhesion, and diverse material selections, to be combined with the advantages of inorganic nanoparticles, including designed degradability, tunable nanoscale sizes, the capability to include mesopores into the nanoparticles, and, importantly, entrapment and protection of APIs.

Inorganic nanoparticles used in biomedical applications are derived from many different materials, including gold, silver, iron oxide, clay, silicon, and silica (Park et al., 2009; Mousa et al., 2018; Dutz et al., 2020; Kankala et al., 2020; Mitchell et al., 2021; Morillas-Becerill et al., 2021). Gold nanoparticles are inert and nontoxic, can be synthesized with diameters ranging from 1–150 nm, and offer photophysical properties as well as the ability for drugs to be incorporated onto their surface (Ghosh et al., 2008). Silver nanoparticles are readily fabricated below 100 nm, and show the most promise in biomedical applications as anti-bacterial and anti-fungals (Nene et al., 2021). Super paramagnetic iron oxide nanoparticles can be fabricated in a range of sizes from >10 nm to more than 200 nm and their magnetic properties allow them to be contrasting agents in biomedical imaging (Dadfar et al., 2019). It is difficult to make these three classes of nanoparticles porous, limiting the potential to trap APIs within these particles. Clay nanoparticles are layered silicate structures that crystalize into nanoparticles, and their interactions with biologics make them intriguing carriers for drug delivery, but their variability and solubility may be problematic (Dawson and Oreffo, 2013). Silicon nanoparticles, especially porous silicon nanoparticles (pSiNPs), are most commonly created through electrochemical etching of crystalline silicon in sizes ranging from ~70 nm to multiple micrometers, and their large pore volume, biodegradability, and ease of surface functionalization make them excellent API carriers (Canham, 1995; Li et al., 2018). Fabrication of these particles predominately requires hydrofluoric acid and there is variability in their size distribution. Mesoporous silica nanoparticles (MSNs) are most commonly synthesized through the surfactant templating approach, and their large pore volume, tunable sizes and shapes, and ease of surface

functionalization give them exceptional properties for API delivery (Manzano and Vallet-Regi, 2020). However, controlling their biodegradation properties can be difficult. While the main research thrust in particle development for applications in health has been towards nanomedicine, the unique properties of inorganic nanoparticles have begun to lead researchers to incorporate them into biomaterials to create multifunctional hybrid materials with a greater level of control of API release.

Inorganic nanoparticles incorporated into three-dimensional biomaterials

There are many different strategies that have been used to incorporate inorganic nanoparticles into biomaterials, and these procedures are selected based on several factors, including the desired material properties, the fabrication processes of both the inorganic nanoparticles and the biomaterial, and the desired application. Hydrogels, polymer networks that have the ability to retain water and form a swollen gel, are used extensively as biomaterials due to their biocompatibility, resemblance to native tissues in mechanical properties and water content, ease of fabrication, injectability, and their versatility to be readily modified to induce cell adhesion and growth (Kim et al., 1992; Mandal et al., 2020). Inorganic nanoparticles have been incorporated into hydrogels through three general design principles: 1) micro or nano-gels that stabilize nanoparticles, 2) nanoparticles non-covalently incorporated into the hydrogel network, and 3) nanoparticles covalently crosslinked in a hydrogel matrix (Thoniyot et al., 2015). One straightforward fabrication approach is the formation of a hydrogel in a nanoparticle suspension that non-covalently incorporates nanoparticles into the hydrogel structure (Sershen et al., 2002). Nanoparticles have also been incorporated into hydrogels after gelation, either through addition of nanoparticles during hydrogel swelling or through various centrifugation steps with a preformed hydrogel (Pardo-Yissar et al., 2001; Jones and Lyon, 2003). Another approach loads nanoparticle precursors into crosslinked hydrogels with the addition of reducing agents forming nanoparticles throughout the hydrogel network (Wang et al., 2004). Nanoparticles themselves have been used as crosslinkers for hydrogels, incorporating them directly into the hydrogel network to impact the hydrogel mechanical properties and gelation rate (Skelton et al., 2013; Rose et al., 2014; Fiorini et al., 2016). By applying these techniques, inorganic nanoparticles can be incorporated into hydrogels in order to capitalize on the advantages of both material types. This has allowed researchers to create hydrogels with unique characteristics, including self-healing (Wu et al., 2020), photothermal activity (Sershen et al., 2005), magnetically induced hydrogel disruption (Qin et al., 2009), anti-bacterial effects (Urzedo et al., 2020), and

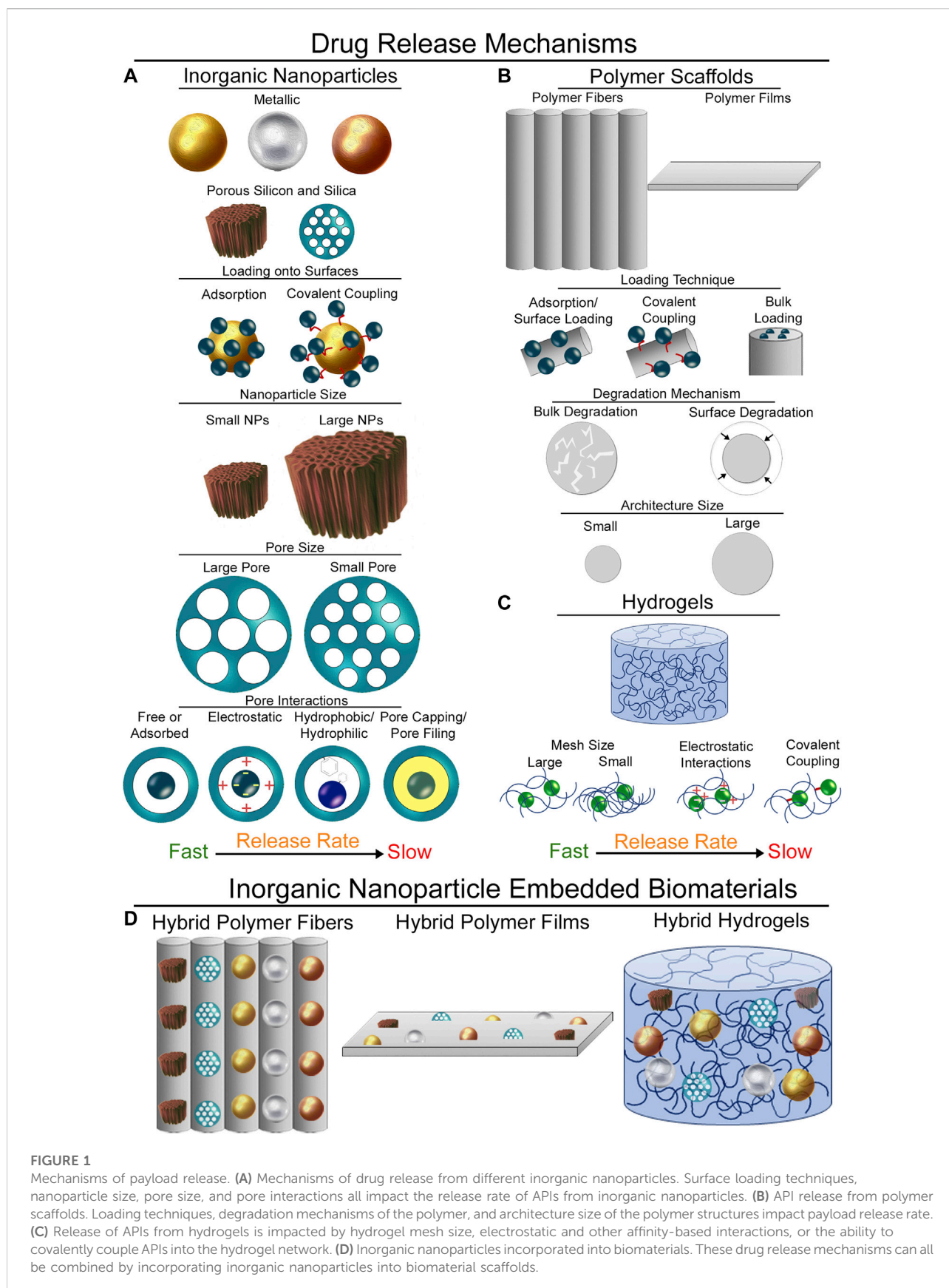


FIGURE 1

Mechanisms of payload release. **(A)** Mechanisms of drug release from different inorganic nanoparticles. Surface loading techniques, nanoparticle size, pore size, and pore interactions all impact the release rate of APIs from inorganic nanoparticles. **(B)** API release from polymer scaffolds. Loading techniques, degradation mechanisms of the polymer, and architecture size of the polymer structures impact payload release rate. **(C)** Release of APIs from hydrogels is impacted by hydrogel mesh size, electrostatic and other affinity-based interactions, or the ability to covalently couple APIs into the hydrogel network. **(D)** Inorganic nanoparticles incorporated into biomaterials. These drug release mechanisms can all be combined by incorporating inorganic nanoparticles into biomaterial scaffolds.

electrical conductivity (Koppes A.N et al., 2016), demonstrating the various functions that these materials may possess.

Biodegradable polymers represent a class of biomaterial scaffolds that are used extensively in tissue engineering (Zhang and King, 2020). They can be fabricated into a variety of structures, including films (Lyu et al., 2019), tissue engineering scaffolds (Daly et al., 2012; Shahriari et al., 2017; Pawelec et al., 2018), microneedles (Sullivan et al., 2010), and micro- and nano-fibers (Venugopal and Ramakrishna, 2005). Polymer films are readily fabricated via casting or spin coating, and porosity can be incorporated into scaffolds through particulate leaching from the polymer films (Suntornnond et al., 2015). Microneedles are commonly fabricated through creation of a master mold followed by filling molds with polymers of interest (Park et al., 2005). Micro- and nano-fibers are made predominately *via* electrospinning, but other techniques, including blow spinning, centrifugal or force spinning, or thermal drawing, have also been applied to make these structures (Coffer et al., 2005; Padron et al., 2013; Behrens et al., 2014; Canales et al., 2015; Koppes R.A et al., 2016; Dos Santos et al., 2020; Rihova et al., 2021). Because most of these polymer structures are made from a polymer melt or from polymers dissolved in an organic solvent, inorganic nanoparticles can be readily mixed into the melt or polymer solution prior to creation of the 3D structure and incorporated throughout the formed architectures (Fan et al., 2009; Kashanian et al., 2010; Kim et al., 2010; Johnson et al., 2019; Yadid et al., 2019). Inorganic nanoparticles can also be coupled onto the surface of these materials, creating polymer structures that have surfaces composed of inorganic nanoparticles (Demir et al., 2018; Funnell et al., 2021). One other approach is pressing inorganic particles into polymer structures via heating of the polymers near their melt temperatures, pressing dried particles onto the structures, and then cooling the polymers back below their melt temperature (Irani et al., 2015; Bodiford et al., 2018). 3D printing of polymer solutions and melts containing inorganic nanoparticles is another more recent advance in this field, allowing for tightly controlled three-dimensional architectures with nanoparticles embedded throughout (dos Santos et al., 2021). Using these approaches, inorganic nanoparticles are incorporated into biomaterials to capitalize on the advantageous properties of both materials.

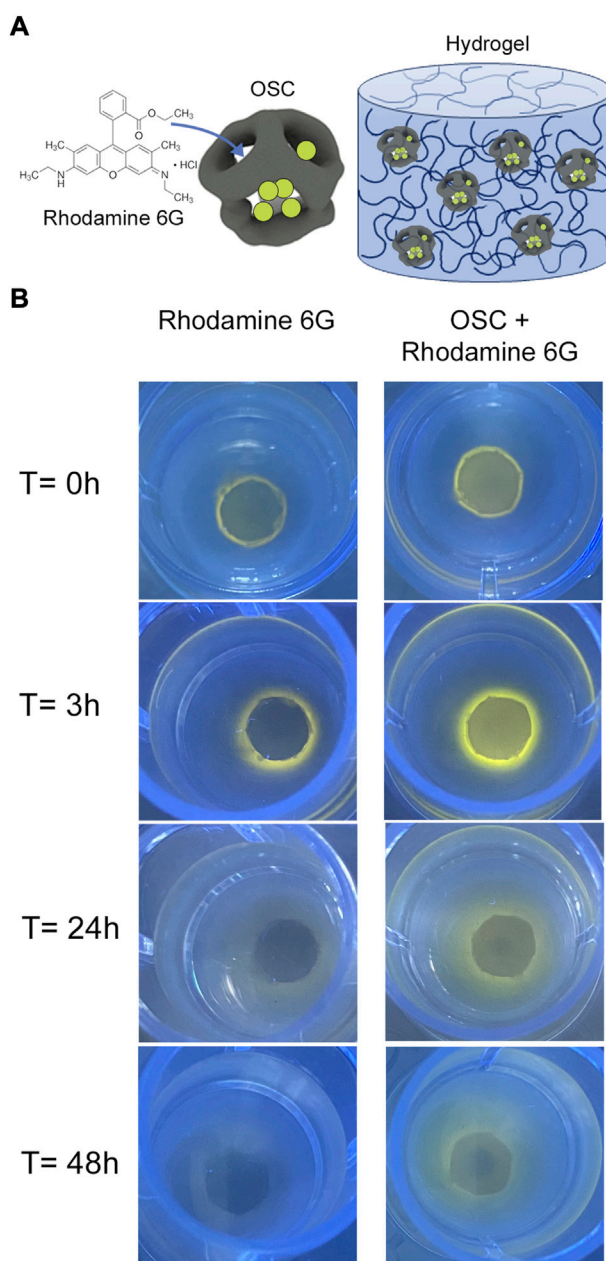
Drug delivery from inorganic nanoparticles

Inorganic nanoparticles are being extensively explored in nanomedicine due to their capability to load APIs and target them to tissues of interest. There are several strategies that can be used to incorporate payloads within metal nanoparticles, including covalent attachment of the API to the surface of the nanoparticles (Gibson et al., 2007) (Figure 1A). There are also non-covalent interactions that have been applied by

modifying the surface of gold nanoparticles to create electrostatic affinity towards nucleic acids and anionic proteins (Sandhu et al., 2002). Modifying iron oxide NP surfaces (Hola et al., 2015) allows drugs to be loaded into the interspace of nanoparticle clusters (Bakandritsos et al., 2012) or linked to an activated nanoparticle surface (Magro et al., 2014). Porous inorganic nanoparticles are especially attractive for applications in API delivery because of the large pore volume they offer to load APIs inside the structure of the nanoparticle. Pores allow for an added control of drug release kinetics, where pore size, surface chemistry, and pore capping or filling strategies can be used to tailor API release from these structures (Figure 1A). pSiNPs and MSNs have been studied extensively as API carriers because of these properties (Anglin et al., 2008; Slowing et al., 2008). APIs can be loaded using a variety of techniques, including covalent attachment to the surface (Secret et al., 2013; Zhang et al., 2019), affinity adsorption (Liu et al., 2013; Kaasalainen et al., 2015; Kwon et al., 2017; Zilony et al., 2017), oxidation trapping (Fry et al., 2014; Kim et al., 2016), calcium and magnesium silicate trapping (Kang et al., 2016; Wang et al., 2018), during synthesis (Prasetyanto et al., 2016), post-synthesis adsorption (Wang et al., 2014), adsorption and subsequent rapid solvent evaporation (Mellaerts et al., 2008), and pore-capping following drug incorporation (Lai et al., 2003; Giri et al., 2005; Aznar et al., 2009; Zhao et al., 2009).

Polymer scaffolds in drug delivery

Polymer scaffolds, especially those composed of polycaprolactone, polylactic acid, polyglycolide, and copolymers such as poly (lactic-*co*-glycolic acid), have been used extensively in tissue engineering due to their biocompatibility, biodegradability, and ease of manufacturing (Liu and Ma, 2004; Place et al., 2009). These advantageous properties have led researchers to develop techniques to release APIs from polymers. The most commonly employed strategy is to blend the polymer and drug together either in solution or in a polymer melt prior to formation of the scaffold. Drug release is governed by several factors, including polymer degradation (bulk vs. surface) and the scale of the polymer architecture (Figure 1B) (Xu et al., 2017). While this method works well for hydrophobic APIs with commonly employed synthetic polymers, blending does not work well for hydrophilic APIs. Soak loading is one technique that can be used to overcome this limitation (Cho et al., 2015), but this technique can lead to burst release of the drug from the surface. In order to extend the release timeframe, APIs have been covalently linked to the polymer surface (Seifu and Nath, 2019). Fabrication specific techniques have also been employed to incorporate APIs into polymer scaffolds. Specifically, electrospinning allows for the formation of core-

**FIGURE 2**

Rhodamine 6G release from OSC incorporated polyacrylamide hydrogels. **(A)** Schematic depicting hydrogel design. Rhodamine 6G was loaded into OSCs, following by physical entrapment in UV crosslinked polyacrylamide hydrogels. **(B)** Release of rhodamine 6G from hydrogels. Rhodamine 6G control hydrogels are compared to rhodamine 6G-loaded OSC incorporated hydrogels. At $t = 0$, rhodamine 6G control and OSC hydrogels are crosslinked into the center of the molds. At $t = 3$ h, the release of rhodamine 6G from control hydrogels is obvious as the dye can diffuse out of the gel through the network mesh and as the gel swells. In the OSC-rhodamine hydrogels, very little diffusion is evident. 24 h after crosslinking control hydrogels have very low amounts of rhodamine visible, while the OSC-rhodamine hydrogels still have rhodamine in the center and around the crosslinked hydrogel. At 48 h, there is nearly no rhodamine visible in the control hydrogels, while rhodamine 6G is still visible in the center the OSC-rhodamine crosslinked hydrogels and throughout the hydrogel mold.

sheath fibers, where the inner core can be hydrophilic and the outer polymer sheath can be formed to be hydrophobic (Sill and von Recum, 2008; Hu et al., 2014), and centrifugal spinning has been used to incorporate water soluble vitamins into fibers

(Rihova et al., 2022). However, hydrophilic APIs may not be homogeneously distributed throughout the polymer structures and fabrication techniques need to be optimized for each API type.

Hydrogels in drug delivery

Hydrogels offer many beneficial properties in API delivery, providing spatial control of API release in their site of implantation, temporal control through polymer network interactions, and protection of APIs from the native tissue environment (Li and Mooney, 2016). The most straightforward approach for incorporation of APIs is through mixing the payload with the hydrogel precursors prior to gel formation (Leach and Schmidt, 2005). The mesh size plays an important role in API release rates with this technique (Figure 1C) (Amsden, 1998). Hydrogels have also been designed to electrostatically interact with charged APIs to modulate their release (Tabata and Ikada, 1998). Other affinity-based mechanisms have been exploited to control API release (Delplace et al., 2016) including covalent attachment of aptamers into hydrogel networks (Soontornworajit et al., 2010), extracellular matrix-protein interactions (Sakiyama-Elbert and Hubbell, 2000), protein-protein interactions (Pakulska et al., 2013), and co-polymers containing hydrophobic domains (Thatiparti et al., 2010). Covalently binding of desired payloads to the hydrogel backbone represents a highly stable incorporation strategy that can greatly extend API release (Mann et al., 2001). The difficulty in loading hydrophobic drugs, the relatively quick release of hydrophilic APIs, and the problems associated with covalently crosslinking APIs into hydrogel networks leave areas for further innovation in the design of drug eluting hydrogels.

Payload delivery from hybrid biomaterials

Hybrid biomaterials offer diverse mechanisms to control API release kinetics. These biomaterials create complex drug interactions with the implanted scaffolds, first through the API loading strategy employed, then the choice of material and architecture, and finally through affinities to the biomaterial network. Polymeric nano- and micro-fibers have been created with drug loaded inorganic nanoparticles embedded throughout (Figure 1D) (Elsherbini and Sabra, 2022). API loaded MSNs have been used extensively to create these hybrid materials using electrospinning techniques (Qiu et al., 2013; Zhou et al., 2015; Lim et al., 2016; Yuan et al., 2016; Chen et al., 2019; Lian et al., 2019; Wang et al., 2019; Sun et al., 2020; Mohebian et al., 2021; Xu et al., 2021; Batista et al., 2022). This approach can be used to extend release of loaded APIs since the nanoparticles act to protect their payloads. They also provide a versatile platform, where different classes of APIs can be loaded into the MSNs while the fabrication procedure of the hybrid fibers remains largely unchanged. Importantly, APIs can be incorporated both throughout the polymer network and within loaded nanoparticles to have two different drug release profiles (Yuan et al., 2016; Samadzadeh et al., 2021; Xu et al.,

2021). This allows for quick release of the incorporated API followed by a long-term sustained release due to loading into the nanoparticles. Other nanoparticles have also been used in these strategies, including amorphous calcium phosphate (Fu et al., 2016), graphene oxide (Rezaei et al., 2021), and zinc oxide (Fazli et al., 2016). Further control of drug release from these scaffolds can be added by incorporating magnetic nanoparticles into scaffolds (Kim et al., 2013). Through application of an alternating magnetic field, magnetic nanoparticles in the scaffolds generate heat to induce swelling of the polymers and release incorporated payloads. Similar strategies can be used to incorporate pSiNPs into fibrous scaffolds. Spray nebulization techniques have been used to create nanofibrous scaffolds containing API loaded porous silicon nanoparticles (Zuidema et al., 2018; Zuidema et al., 2020a; Zuidema et al., 2020b). These platforms are highly versatile, and by simply changing the approach to load APIs into nanoparticles, the same fabrication technique was used for prolonged release of active proteins, nucleic acid-based devices and aptamers, and hydrophilic APIs. API loaded porous silicon particles have also been incorporated into poly (ϵ -caprolactone) films to slow release kinetics (Irani et al., 2015; Bodiford et al., 2018).

There are several mechanisms with which to control drug release from hybrid hydrogels, and the most elementary is through passive diffusion out of the nanoparticle and through the hydrogel matrix. Silica nanoparticles loaded with ibuprofen (Zhao et al., 2014), antibiotics (Alvarez et al., 2014), and proteins (Lee et al., 2013; Fiorini et al., 2016) have been embedded into hydrogels to prolong their release compared to loading the APIs directly into a hydrogel. We demonstrate this concept here to provide an obvious visual to show the power of these hybrid materials. Rhodamine 6G was loaded into poly (ethylene glycol) conjugated, cage-like organosilica nanoparticles (OSCs) following a previously reported two-step bottom-up protocol (Supplementary Material) (Talamini et al., 2021). The OSCs have a relatively small diameter (44 ± 4 nm, Supplementary Figure S1A), that allows them to be uniformly distributed throughout the precursor solution without forming aggregates. Their cage-like structure provides space for API loading while protecting the payload inside the cage. While these properties are beneficial for applications in nanomedicine, they can also be employed to control payload release from hybrid materials. OSCs were then non-covalently incorporated into a polyacrylamide hydrogel (Figure 2A). As a control, free rhodamine 6G was dispersed in the hydrogel precursor solution prior to gelation. Qualitative release of rhodamine 6G was then visualized over time from the hydrogels (Figure 2B). Rhodamine 6G hydrogels were placed in the center of a hydrogel mold so visualization of the release could be monitored. After only 3 h of incubation in PBS, it is apparent that the control hydrogels have begun to release rhodamine 6G from the hydrogel network, while only a

small amount of the rhodamine can be seen outside the original area of gelation in the OSC hydrogels. The rhodamine could freely diffuse into the solution when no nanoparticles were present. Even after 48 h, rhodamine 6G can be visualized in the nanoparticle containing gels where there is only a small amount of rhodamine 6G in the surrounding hydrogel from the controls at this time frame. This experiment demonstrates how inorganic nanoparticles can be used to control the release of small molecules out of hydrogel networks. While this model system provides a visual of the advantages of these hybrids, more advanced designs are easily envisioned. Engineering the particle degradation timeline can be used to precisely release payloads instead of the elementary release kinetics demonstrated here, while incorporation of API-loaded nanoparticles into hydrogels that biodegrade on-demand may provide a means to release a nanoparticle from hours, to days, to even weeks after a hydrogel is implanted. Beyond nanoparticle loading, there are several other mechanisms with which to control drug release from hybrid hydrogels which include electro-responsive, magnetically responsive, and light responsive mechanisms (Liu et al., 2006; Giri et al., 2011; Yan et al., 2012; Merino et al., 2015). As an example, pSiNPs combined with gold nanorods have been incorporated into alginate hydrogels, and near infrared light can be used to trigger release from these materials (Zhang et al., 2018).

Discussion

There are many unexplored research avenues that may elicit even further control of API release from inorganic nanoparticle biomaterial hybrids. In hybrid hydrogels, many different drug interactions can be foreseen that will improve control of API release timelines. API release first can be governed by loading into inorganic nanoparticles, and the rate can be controlled through applying adsorption loading, adding electrostatic interactions, adjusting the pore size, covalent attachment, or capping/filling the pores after loading. Once an API leaves the nanoparticle, release can be further controlled by interactions with the hydrogel network. This may be through affinity with the hydrogel itself, either through controlling the mesh size of the hydrogel or electrostatic interactions. More advanced affinities can be envisioned, such as releasing an API from an inorganic nanoparticle with affinity to an aptamer coupled to the hydrogel, as previous studies have demonstrated the ability of aptamers to sequester chemokines inside a hydrogel (Enam et al., 2017). Recent advances in hydrogel design explore injectable microparticle hydrogels that can assemble to form granular hydrogels (Daly et al., 2020; Darling et al., 2020; Muir et al., 2022). Incorporating API-loaded inorganic nanoparticles into

hydrogel microparticles could be used to further control the release characteristics from these biomaterials. 3D printing strategies can also be used, where API-loaded inorganic nanoparticles are printed into hydrogels during fabrication. Within polymeric scaffolds, new pathways to control API release can also be envisioned. The ability to load and protect different categories of APIs into pSiNPs and fabricate nanofibers from solutions of polymers in organic solvents can be exploited in many different ways. One clear advancement would be to incorporate multiple therapeutics into the same scaffold. This could be done by loading different APIs into inorganic nanoparticles, and incorporating all the nanoparticles together into polymer solutions prior to fabrication. Through this process, there are possibilities to release proteins, nucleic acids, and small molecule drugs all from the same scaffold. Release rates can be controlled by selection of the polymer used to create the scaffolds and the API loading technique (Zuidema et al., 2020a).

The field of API delivery from inorganic nanoparticle incorporated biomaterials is still relatively young, and as advances to both inorganic nanoparticles and biomaterial scaffolds are realized, further complexities can be engineered into these hybrids. Currently, one of the major limitations in the field is incorporating nanoparticles only into specific regions of biomaterials. Nanoparticle location impacts API release over time, and can be important at tissue interfaces and for creating API gradients. If a pathology can be improved by releasing two APIs, location of the nanoparticles also plays a key role in their release profiles. 3D printing will play a role in selective placement of different NPs throughout biomaterial regions, however, this becomes more complicated for applications that require injectable materials. Other limitations are in optimizing biomaterial mechanical properties, since most inorganic nanoparticles will create stiff nanoregions throughout biomaterials that may impact cellular growth. Nonetheless, as nanotechnology fabrication techniques become more ubiquitous and costs decrease, combining nanoparticles with biomaterials will be a common research thrust for control of API release from biomaterials. It can be envisioned that precise API release paradigms can be achieved using biomaterial hybrids that traditional biomaterials cannot realize. With applications foreseen in diverse areas- ranging from cancer therapy, wound healing, bone repair, and nervous system regeneration- research into biomaterials that exploit the advantages of nanotechnology will continue to evolve towards applications in the clinic.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

LM-B and JZ conceived the experiments. LD provided laboratory support. LM-B synthesized nanoparticles, performed the experiments, and collected the data. JZ and LM-B wrote the manuscript. LM-B, LD, and JZ discussed the results and commented on the manuscript. This project was coordinated by JZ.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnano.2022.999923/full#supplementary-material>

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