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Communication

Synthesis of Polymeric Janus Superstructures via a Facile Synthesis Method

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Abstract

Polymeric Janus particles can be exploited for myriad of applications. Through the understanding of interfacial tensions, theragnostic agents such as drugs or nanomaterials can be successfully encapsulated into Janus particles without losing their anisotropic structure. In this work, we report how Janus superstructures, as a further extension of the Janus morphology, can be obtained by blending other synthesis parameters into the solvent emulsion process, while maintaining to the requirements of the Harkin's Spreading Coefficient (HSC) theory. Designing such unique structures for drug delivery can provide a broader range of possibilities and applications, beyond just the conventional Janus particles.

1 Introduction

Janus particles are anisotropic particulate entities that comprise of two co-joint components. Each component or ‘face’ can be functionalized to achieve anisotropic properties via methods like sputtering and Pickering emulsions¹⁻³. For instance, Janus particles of amphiphilic nature can possess hydrophilic properties on one face and hydrophobic properties on the other, and can thus function as surfactants⁴⁻⁶. While sputtering and Pickering emulsions are primarily used for the synthesis of inorganic Janus particles, microfluidics is the predominant technique for the fabrication of polymer-based Janus particles. With microfluidics, two polymer solutions are extruded from two channels, and this co-jetting action forms Janus particles at the junction where the channels meet⁷⁻⁹. Through this, dual-drug loaded polymeric Janus particles and Janus particles comprising of multiple components can be fabricated¹⁰⁻¹².

Despite advancements in Janus particle fabrication, several hurdles still exist in preparing these anisotropic particles. For instance, the harsh conditions used in sputtering and for Pickering emulsions are generally not suitable for polymers^{6, 13-14}. While microfluidics is a popular fabrication technique for polymeric Janus particles, it suffers from low throughputs and requires complex fabrication infrastructure. In addition, polymer choices are usually limited as high

1 intrinsic viscosity polymers are challenging to extrude¹⁵⁻¹⁷. In 2014, Romanski et al. reported
2 an alternative fabrication technique for polymeric Janus particles via solvent emulsion¹⁸. Here,
3 a polymer solution is first prepared before emulsifying in an aqueous surfactant solution,
4 making it a simple, scalable and economical approach. However, the inclusion of encapsulates,
5 i.e. drugs or diagnostic nanomaterials, often result in a loss of the original anisotropic structure.
6
7 Based on a review by Ge et al., the role of interfacial thermodynamics of multiple emulsions,
8 particularly the formation of Janus emulsions, was making progress with reports of one-step
9 formations of Janus emulsions. However, the formation of solid polymeric Janus particles via
10 these methods still required an additional step for solidification, such as UV treatments or
11 polymerization reactions. Furthermore, the effect of drug addition into these systems was still
12 in question¹⁹. Fan et al. subsequently documented the mechanistic effect of drug addition to
13 Janus particles, reporting how drugs can affect polymer interfacial tensions thereby shaping the
14 final particle morphology²⁰. Using data on interfacial tensions, a broad range of polymeric Janus
15 particles (i.e. drug-loaded, surface functionalized, etc.) can now be produced through solvent
16 emulsion²¹.
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39 As a furtherance of our previous work, we hereby report how Janus superstructures can be
40 obtained through solvent emulsion, based on extensions from the conventional Harkin's
41 Spreading Coefficient (HSC) theory. Janus superstructures are Janus particles with additional
42 structural features, such as a hollow core, core-shell, etc. (*see TOC Figure*). We hypothesized
43 that by blending other synthesis parameters into the solvent emulsion process, while
44 maintaining to the requirements of HSC theory, a range of Janus superstructures can be
45 achieved. Designing such unique particulate structures for drug delivery purposes can provide
46 a broader range of possibilities and applications, beyond just the plain Janus particle
47 morphology. Here, we aim to report how interfacial tensions can influence the formation of
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Janus superstructures, when blended with other synthesis conditions, to achieve a range of superstructures (*see TOC Figure*).

2 Results and Discussion

Previous reports have systematically shown that thermodynamics is the main driving force for the formation of Janus particles via the solvent emulsion method^{9, 20-21}. In solvent emulsion, there are three interfaces arising from the three phases (phases one & three are polymer solutions, and phase two is the aqueous solution). These interfaces are with respect to the individual polymers and the aqueous solution (γ_{12} and γ_{23}), as well as the interface between both polymers (γ_{13}) (**Figure S1a**). These interfacial values can then be applied to HSC theory to obtain the respective spreading coefficients (S_1 , S_2 and S_3). From the spreading coefficients, three possible scenarios can be achieved that would result in three different morphologies, i.e. Janus, core-shell or no-engulfment (**Figure S1b**). To investigate how interfacial tensions can influence spreading coefficients, and ultimately the nature and structure of Janus superstructures, we have chosen to work on three different polymer combinations, i.e. EVA/PLGA, PMMA/PLGA and PCL/PLGA, as models for comparison. They were also chosen because of their biocompatibility and potential for biomedical and pharmaceutical applications²²⁻²⁵. To begin, their baseline interfacial tension values (γ_{12} , γ_{13} , γ_{23}) at their optimal weight ratios were first measured, and these values are summarized in **Table S1**. These three polymer combinations have also been shown to be able to form Janus particles by varying weight ratios²⁰⁻²¹, and are also documented in **Table S2**.

2.1 Janus Hollow-Core Superstructure (JHC)

The structural features of JHCs involves a traditional Janus structure where both polymer faces meet at the bifurcation while maintaining a hollow-core within the particle (**Figure 1**). Previously, Kharel et al²⁶ reported how hollow-core microparticles can be obtained through the addition of an osmogen, such as sodium chloride (NaCl). With the addition of NaCl into the polymer solution, the emulsified polymer micelle would entrap a proportion of the salt that results in an osmotic pressure gradient. This causes water influx into the core that coalesce into a water pocket within the particles that subsequently dries into a hollow-core structure.

Through this concept, we aimed to fabricate hollow-core Janus particles using NaCl as the osmogen, while maintaining the Janus morphology. **Figure 1a** shows optical images of EVA/PLGA Janus particles presenting a hollow-core (~100% yield), whereas PCL/PLGA (**Figure 1b**) particles appeared to have partially lost their anisotropic structures, resulting in less well-defined Janus structures. Based on Fan et al., the authors proposed an additional requirement, $|\gamma_{12} - \gamma_{23}| < \gamma_{13}$, as a possible extension to the HSC theory to achieve Janus particles²⁰. Thus, to favour the formation of Janus particles, the polymer-to-polymer interfacial tension (γ_{13}) value would have to be as high as possible. A high γ_{13} value can buffer changes to the interfacial tensions, while still keeping to the above criteria, and thus favouring Janus particles formation²¹. From γ_{13} measurements of EVA/PLGA and PCL/PLGA, a much higher value was observed for the former ($\gamma_{13} = 15.32$ mN/m) as compared to the latter ($\gamma_{13} = 0.65$ mN/m)²⁰, therefore favoring the formation of JHC for EVA/PLGA (**Table S1**).

The optimal amount of osmogen to achieve JHC particles was also investigated (**Figure S2a-c**). At lower % w/w of NaCl (10 and 15%), it was observed that JHC particles were also formed but with a less well-defined single core. At 20% w/w, a clearly well-defined core within the Janus particle was observed. It is postulated that a higher NaCl content would increase osmotic

pressure. This allows for a larger influx of water that could coalesce into a larger single water core, rather than multiple smaller cores that was observed for lower NaCl %.

These results therefore establish that a single-step solvent emulsion, with the introduction of an osmogen, can form JHCs, as opposed to a multi-step microfluidic approach²⁷. Secondly, relatively high values of γ_{13} , like those measured for EVA/PLGA, is an important parameter to maintain the Janus morphology.

2.2 Janus Core-shell Superstructure (JCS)

The fabrication of core-shell particles has been an area of keen interest particularly in the field of drug delivery. Core-shell and multi-layered particles are usually comprised of one material in the core and preceding outer shell layers in tandem.²⁸⁻³². Lee et al. previously reported how a triple-layer ternary system was shown to improve the sustained-release of Doxorubicin due to the encapsulation of Doxorubicin within the core²⁸. We define JCS particles as Janus particles with a core-shell structure at the center of each Janus particle (**Figure S3a**). While various authors have reported in detail the structural transitions of emulsions through interfacial tension data, the meta-state of a JCS has not yet been observed in their studies³³⁻³⁴. Such multi-compartment structures can allow for the encapsulation of multiple drugs in separate compartments within a JCS.

Figure 2 shows the fabrication of EVA/PLGA in decreasing concentrations of PVA. Above 1% of PVA concentration, Janus particles were obtained as observed through light microscope images (**Figure 2d-e**). At 0.5% PVA, JCS particles were obtained at a near 100% yield (**Figure 2f**, close-up in **Figure S3c**), which is against the prediction based on HSC theory that normal Janus particles should be expected (**Table S3**). This is further confirmed by selective dissolution of EVA to verify that the core was PLGA (**Figure 2i**), similar to what is schematically shown

in **Figure S3b**. To explain this phenomenon, the interfacial data measurements were obtained for decreasing concentrations of PVA and are shown in **Table S3**. From **Table S3**, it was observed that the interfacial tension values of γ_{12} and γ_{23} gradually increased as the concentration of surfactants decreased. It was hypothesized that as the interfacial tensions of γ_{12} and γ_{23} increased upon the reduction of the surfactant concentration to 0.5%, it gradually became less energetically favorable for the droplet to maintain a Janus morphology. To compensate for this increase in interfacial tension, some of the polymer was driven into the core of the opposing polymer (i.e. PLGA in EVA) as it is energetically more favorable to form a surface with the opposing polymer as compared to forming a surface with the external aqueous phase ($\gamma_{13} \ll \gamma_{12} \text{ \& } \gamma_{23}$)(**Table S3**). The resultant structure is therefore a JCS particle, where both the Janus and core-shell morphology were observed. However, the reasons why PLGA forms the core, rather than EVA, is still not fully understood.

2.3 Encapsulating Sub-micron Particles into Janus Superstructures (JEM)

Sub-micron particles encapsulated within larger particles have been shown to have potential as pay-load delivery vehicles. Khung et al.³⁵ reported the encapsulation of sub-micron drug-loaded particles into larger microcapsules to achieve controlled release. In addition to sub-micron particle encapsulation, we demonstrated that the understanding of γ_{13} of the respective polymers could add a new dimension to the release of these sub-micron payloads. Based on the γ_{13} values of EVA/PLGA and PMMA/PLGA in **Table S1**, the interfacial tension values of EVA/PLGA ($\gamma_{13} = 15.32 \text{ mN/m}$) was observed to be significantly higher than that of PMMA/PLGA ($\gamma_{13} = 3.34 \text{ mN/m}$). This infers that as more energy is needed to form a surface between EVA and PLGA, the strength of this adhesion at the interface of EVA and PLGA would likely be weaker than that of PMMA/PLGA. As such, we hypothesized that EVA/PLGA would dissociate at its bifurcation, releasing its payloads earlier than PMMA/PLGA, creating another dimension of time-based release of payloads from these Janus particles.

To confirm our hypothesis, a 14-day degradation study of both neat PMMA/PLGA and EVA/PLGA Janus particles was conducted (**Figure S4**). From these results it was shown that the polymer combination with a higher γ_{13} (EVA/PLGA) dissociates significantly quicker at its bifurcation than the polymer combination with a lower γ_{13} (PMMA/PLGA). For EVA/PLGA, it was observed that upon reaching day 7 of the degradation study, a significant proportion of the particles had dissociated, leaving behind the half-crescent faces of the Janus particle. Meanwhile, the PMMA/PLGA particles still exhibited Janus structural integrity well beyond day 7, even up till day 14. These observations further confirmed the hypothesis that the lower the γ_{13} , the stronger the adhesion between both faces as concluded by how much quicker EVA/PLGA Janus particles dissociate as compared to PMMA/PLGA.

Traditionally, Janus particles have been fabricated via a solvent emulsion step using an oil-in-water configuration. To encapsulate sub-micron particles within Janus particles, a water-in-oil-in-water (W/O/W) configuration was used, where the payload particles were suspended in the water phases inside the polymer solution, and then subsequently emulsified. PLLA sub-micron particles loaded with C6 were fabricated and found to be in the size range of $\sim 2\mu\text{m}$ (results not shown). These sub-micron particles were used as model payloads and were encapsulated within EVA/PLGA and PMMA/PLGA Janus particles as seen in **Figure 3a** and **Figure 3b** respectively. A cross-sectional SEM image of each respective particle was carried out, as shown in **Figure 3c** and **Figure 3d** respectively.

The EVA/PLGA and PMMA/PLGA JEM particles were subjected to normal sink conditions and its dissociation behavior was studied. For the EVA/PLGA JEM particles, it was observed that almost 50% of the particles were found to be dissociated and finally almost 100% dissociated by day 2. For the PMMA/PLGA JEM particles, almost all the particles were still

co-joined at day 1. Only at day 3 was it observed that some of the particles (~64%) started to dissociate. Finally, on day 5, almost all particles dissociated and released the payload into the media (**Figure 4**). These findings were congruent with the degradation study shown in **Figure S4** with regards to particle dissociation at the bifurcation. This establishes a proof-of-concept model where payload particles can be housed within Janus particles and designed to release at specific time points. All this would be made possible through the understanding of γ_{13} and how it can be a predictive model to design Janus particles with different time-based payload release behaviors.

3 Conclusions

In conclusion, Janus superstructures can be achieved through a scalable, facile, one-step solvent emulsion technique. By blending other synthesis parameters, different Janus superstructures can be achieved at both a high yield and efficiency. γ_{13} was shown to be an important parameter in the formation of JHCs as well as the time-based dissociation of JEM particles. The lowering of surfactant concentration gave rise to the formation of JCS particles, which is presently not predicted nor shown in the HSC theory. All this is facilitated through the understanding of interfacial tension data and its role in allowing manipulation of Janus particles in creating new Janus superstructures.

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Supporting Information

Supporting Information is available from the Wiley Online Library or from the author ((delete if necessary))

Figure 1 Light microscope images of (a) EVA/PLGA JC particles with 20% w/w of NaCl and (b) PLGA/PCL particles with 20% w/w of NaCl. Scale bar = 100 μ m.

Figure 2 SEM images of (a-c) EVA/PLGA Janus particles fabricated with 2.5%, 1.0% and 0.5% PVA respectively. (d-f) Corresponding light microscope images of particles in (a-c) and (g-i) light microscope images of particles of each respective concentration selectively dissolved in cyclohexane, leaving behind pink PLGA components. Scale bar = 100μm.

Figure 3 **Light microscope images** of (a) EVA/PLGA and (b) PMMA/PLGA JSH particles loaded with C6-loaded PLLA particles as model payloads. The corresponding cross-sectional **SEM** images for (c) EVA/PLGA and (d) PMMA/PLGA shows the encased payloads within the particles. **Scale bar = 100μm.**

Figure 4 Graph of % dissociation of EVA/PLGA and PMMA/PLGA Janus particles encapsulated with sub-micron particle payloads

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