Analysing intracellular deformation of polymer capsules using structured illumination microscopy†

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Understanding the behaviour of therapeutic carriers is important in elucidating their mechanism of action and how they are processed inside cells. Herein we examine the intracellular deformation of layer-by-layer assembled polymer capsules using super-resolution structured illumination microscopy (SIM). Spherical- and cylindrical-shaped capsules were studied in three different cell lines, namely HeLa (human epithelial cell line), RAW264.7 (mouse macrophage cell line) and differentiated THP-1 (human monocyte-derived macrophage cell line). We observed that the deformation of capsules was dependent on cell line, but independent of capsule shape. This suggests that the mechanical forces, which induce capsule deformation during cell uptake, vary between cell lines, indicating that capsules are exposed to higher mechanical forces in HeLa cells, followed by RAW264.7 and then differentiated THP-1 cells. Our study demonstrates the use of super-resolution SIM in analysing intracellular capsule deformation, offering important insights into the cellular processing of drug carriers in cells and providing fundamental knowledge of intracellular mechanobiology. Furthermore, this study may aid in the design of novel drug carriers that are sensitive to deformation for enhanced drug release properties.

1 Introduction

Over the past two decades, polymer capsules have evolved from hollow polyelectrolyte constructs to promising tailor-made nanoreactors and drug delivery systems.1,2 In particular, nanoengineered polymer capsules fabricated through layer-by-layer (LbL) assembly are promising candidates for the intracellular delivery of therapeutics due to the control that can be exerted over their surface chemistry, size, shape, and cargo loading/release.3,4 Given their versatile properties, such polymer capsules have been engineered to be readily internalised by a wide range of cell lines, including epithelial cells and various immune cells.3 The potential application of LbL capsules in drug delivery and other biological applications highlights the importance of elucidating a fundamental understanding of their interaction with biological systems.6 To this end, the intracellular processing and intracellular fate of the capsules are important aspects.7

The deformation of polymer capsules upon internalisation process provides insight into their stability and potential mechanism of action inside the cells.8-11 Confocal laser scanning microscopy (CLSM) revealed that 5 µm polymer capsules are internalised by human breast cancer cells (MDA-MB-435s), but the shape of internalised capsules differs significantly from those remaining outside the cells.8 The change in shape is believed to be caused by force-driven deformation within the endocytic compartments in which the capsules are trapped. A study on the deformation of polymer capsules of 2.0 to 3.5 µm diameter upon intracellular uptake by HeLa cells, investigated by atomic force microscopy (AFM), suggested that the tracking of polymer capsules can be used to examine the mechanical properties of living cells through their uptake process.12 These results revealed that polymer capsules deformed upon internalisation, and that this was caused by a mechanical deformation process that exhibits intracellular forces that the polymer capsules cannot withstand during internalisation.13 This is in agreement with our previous transmission electron microscopy (TEM) study where 850 nm polymer capsules appeared distorted in the late endosomes or lysosomes of a human colon cancer derived cell line (LIM 1899).14 These deformation-based studies indicate that intracellular processes can vary dramatically for different polymer capsules due to differences in their physicochemical properties, as well as the cell physiology.15,16 Therefore, in this work, we investigate the intracellular deformation of polymer capsules of size more applicable for intracellular drug delivery.
(less than 500 nm), and examine the effect of shape and cell line on capsule deformation.

Most cellular events are highly dynamic, therefore, tracking them under biological conditions requires high temporal resolution of the analytical procedure employed. Live cell imaging may be used; however, determining subtle changes in the morphology of nanostructures upon interaction with biological systems is often challenging using conventional microscopy, such as confocal or deconvolution microscopy. We have previously reported the deformation of spherical polymer capsules (diameter \( D = 390 \pm 850 \) nm) in different cell lines, including human cervical cancer cell line HeLa (HeLa), mouse leukemia cell line RAW264.7 (RAW), and differentiated human leukemia cell line THP-1 (dTHP-1). However, given the resolution limits of conventional microscopy, any differences in the intracellular deformation of polymer capsules were not able to be resolved. Recently, stochastic optical reconstruction microscopy (STORM) and structured illumination microscopy (SIM) techniques have been applied for imaging the internalisation and intracellular processing of particles.

Herein we examine the intracellular deformation of polymer capsules in different cell lines using a super high resolution microscopy technique, SIM. SIM provides more than a two-fold increase in resolution by collecting information from frequency space outside the observable region, which is able to clearly identify nanostructures (ca. 110 nm in X/Y resolution) compared with other conventional microscopes (ca. 250 nm in X/Y resolution). Thiolated poly(methacrylic acid) \( \text{PMA}_{\text{SH}} \) capsules with two different shapes (spherical: \( D = 390 \) nm and cylindrical: \( \max = 390 - 850 \) nm, \( \min = 235 \) nm) were purchased from Life Technologies. Mouse anti-human LAMP-1 antibody (CD107a) was obtained from BD Pharmingen (USA). For all experiments, high-purity water with a resistivity greater than 18.0 MΩ cm (Milli-Q) was obtained from an in-line Millipore ROIs/Synergy purification system.

2.2 Synthesis of PMA\(_{\text{SH}}\)

Poly(methacrylic acid) with 12% thiol group modification was synthesised as reported elsewhere. Briefly, a PMA solution (187.15 mg) was diluted with 3 mL of phosphate buffer (50 mM, pH 7.4). The resulting solution was activated with 43 mg of EDC and the mixture was stirred at ambient temperature for 30 min. Subsequently, 28.36 mg of \( \text{PDA-HCl} \) was added to the mixture and the reaction was allowed to proceed for 24 h. The resulting solution was purified via dialysis for 3 days against Milli-Q water and subsequently freeze dried for 48 h to obtain PMA–PDA as a powder. The degree of PMA modification of PMA was quantified using a NanoDrop 1000 spectrophotometer (Thermo Scientific). For all experiments, high-purity water with a resistivity greater than 18.0 MΩ cm (Milli-Q) was obtained from an in-line Millipore ROIs/Synergy purification system.

2.3 Synthesis of SiO\(_2\) particles with cylindrical shapes

SiO\(_2\) particles with cylindrical shapes were fabricated according to the method reported by Kuijk et al. Briefly, 3 g of PVFON \( (M_w = 40 \text{ kDa}) \) was dissolved in 30 mL of 1-pentanol by sonication for 4 h. Then, 0.8 mL of Milli-Q water, 0.2 mL of sodium citrate dihydrate solution (0.18 M in water), 3 mL of ethanol, and 0.7 mL of ammonia (28 wt%) were separately added to the mixture. The solution was mixed by hand for 1 min and then kept static for 5 min, followed by the addition of 0.3 mL of TEOS (99%). After gentle shaking by hand for 1 min, the bottle was kept static to allow the reaction to proceed at 37 °C for 60 min to obtain the cylindrical SiO\(_2\) particles. To
purify the as-synthesised rods, the middle layer of reaction mixture was collected and centrifuged at 3000 g for 30 min. The pellet was washed twice with ethanol, then twice with Milli-Q water and finally suspended in Milli-Q water. The SiO₂ particles with cylindrical shape obtained were characterised using TEM, as shown in Fig. S1†.

2.4 Assembly of PMA₅₄ capsules

SiO₂ particles (5 mg) were washed three times with NaOAc buffer (50 mM, pH 4) by centrifugation for two min at 1000 g. The particles were then suspended in 50 µL NaOAc buffer by vortexing and sonication for 5 min. PVPON solution (50 µL, 4 g L⁻¹ in 50 mM NaOAc buffer) was then added to the SiO₂ particles and incubated with mixing for 10 min to allow polymer adsorption. After incubation, the PVPON-coated particles were washed three times with NaOAc buffer and finally suspended in 50 µL NaOAc buffer. The adsorption of PVPON then PMA SH constituted the assembly of a single bilayer. The layering process was repeated until four bilayers were deposited with PVPON as the outermost layer. The polymer multilayers were crosslinked by disulfide bridging through oxidation of the thiol groups of PMA SH. In brief, PVPON/PMA₅₄ core-shell particles were incubated in MES buffer (50 mM, pH 6) with gentle shaking overnight in the presence of 2.8 mM CaT (reversible crosslinking) or BM(PEG)₂ (irreversible crosslinking). The crosslinked core-shell particles were collected and centrifuged at 3000 g for 30 min. The pellet was washed twice with ethanol, then twice with NaOAc buffer. Capsules were obtained by dissolving the SiO₂ templates using 5 M HF for 5 min (Caution! HF is corrosive and highly toxic! Extreme care must be taken when handling!), followed by three washing and redispersion cycles with PBS buffer. The capsules were then fluorescently labelled by mixing the capsules with 5 µL of AF633 hydrazide and 1 mg of DMTMM in 200 µL PBS for 12 h. Fluorescently labelled capsules were obtained using centrifugation and washing with PBS for four times.

2.5 Characterisation of PMA₅₄ Capsules

TEM (Philips CM120 BioTWIN, operated at 120 kV) was used to determine the capsule size and morphology (at least 100 capsules were imaged and analysed). Fluorescently labelled PMA₅₄ capsules were imaged with SIM (DeltaVision OMX Blaze 3D-SIM from Applied Precision). Film thicknesses of PMA₅₄ capsules were measured by AFM using an MFP-3D atomic force microscope (Asylum Research). Imaging was performed using ultrasharp SiN gold-coated cantilevers (NT-MDT). Capsule counting was performed using an Apogee A50-Micro flow cytometer (Apogee Flow Systems Ltd.) with a laser excitation wavelength of 638 nm.

2.6 Cell culture

HeLa and RAW cells were cultured in DMEM GlutaMAX supplemented with 10% FBS at 37 °C in a 5% CO₂-humidified atmosphere and subcultured prior to confluence using trypsin. Macrophage-like THP-1 (dTHP-1) cells were differentiated from THP-1 cells by incubation with 200 nM TPA for 48 h in complete RPMI medium (RPMI contain 10% FBS, termed as cRPMI) at 37 °C in a 5% CO₂-humidified atmosphere.

2.7 Cellular association

HeLa, RAW and dTHP-1 cells were plated in 12-well plates at a density of 1 × 10⁵ cells per well and allowed to adhere overnight. Cells were then incubated with PMA SH capsules at a capsule-to-cell ratio of 100:1 for a 24 h period at 37 °C in 5% CO₂. After incubation, the cells were gently washed three times with DPBS and then harvested by trypsinization at 37 °C. At least 10 000 cells were analysed by flow cytometry.

2.8 Intracellular deformation of PMA₅₄ capsules

HeLa, RAW and dTHP-1 cells were plated in 8-well Lab-Tek I chambered coverglass slides (Thermo Fisher Scientific, Rochester) at a density of 3 × 10² cells per well. Cells were then treated with PMA₅₄ capsules at a capsule-to-cell ratio of 100:1 for 24 h at 37 °C in 5% CO₂. After incubation, cells were fixed with 4% PFA for 10 min at 25 °C and the membrane stained by incubation with AF488 WGA (0.5 µg mL⁻¹) for 10 min at 25 °C, followed by washing with DPBS three times. For actin staining, the cells were fixed and then 500 µL of Triton X-100 (0.1% in PBS buffer) was used to permeabilise cells for 5 min at 25 °C. Subsequently, the actin was stained by incubation with AF488 phalloidin (0.5 µg mL⁻¹) for 20 min at room temperature. Fluorescence images and optical sections were collected using a SIM equipped with a 60×1.24 NA oil objective under a FITC/CY5 filter set. Images were processed with Imaris 6.3.1 (Bitplane).

2.9 Intracellular fate

HeLa, RAW or dTHP-1 cells (3 × 10⁴) were plated per well in 8-well Lab-Tek I chambered coverglass slides, and incubated with PMA₅₄ capsules at a capsule-to-cell ratio of 100:1 at 37 °C in 5% CO₂. After 24 h incubation, cells were fixed with 4% PFA for 10 min at 25 °C. To permeabilise the cells for immunostaining, fixed cells were incubated with 500 µL Triton X-100 (0.1% in PBS buffer) for 5 min at 25 °C. Late endosomes and lysosomes were then immunostained with 200 µL of mouse anti-human antibody (LAMP1, 2.5 μg mL⁻¹) followed by 200 µL of AF488 goat anti-mouse IgG (2 µg mL⁻¹) for 45 min at 25 °C. Fluorescence images and optical sections were collected using SIM equipped with a 60×1.24 NA oil objective under a FITC/CY5 filter set. Images were processed with Imaris 6.3.1 (Bitplane).

3 Results and discussion

3.1 Preparation and characterisation of PMA₅₄ capsules with spherical and cylindrical shapes

PMA₅₄ capsules were prepared according to the protocol reported previously.¹⁸ Briefly, spherical and cylindrical SiO₂
templates were sequentially coated with PVPON/PMA$_{SH}$ via hydrogen bonding-mediated LbL assembly, followed by oxidative crosslinking of thiol groups on PMA$_{SH}$ layers. Upon removal of the sacrificial SiO$_2$ templates and PVPON layers, homogeneous and well-dispersed PMA$_{SH}$ capsules were obtained. The dimensions of the obtained PMA$_{SH}$ capsules were examined by TEM, revealing spherical (390 × 390 nm, Fig. 1A) and cylindrical capsules (2020 × 310 nm, Fig. 1D). The size increase of the capsules compared with the corresponding templates is due to swelling of the capsule wall after removal of the template support. Both types of capsules retained their original morphology after template removal. AFM was used to determine the wall thickness of the PMA$_{SH}$ capsules. The measured height profile was consistent across all capsules, indicating a homogenous LbL build-up (Fig. 1C, F), with an average thickness of 3.5 nm per polymer layer (Fig. S2†).

3.2 Cell association kinetics

The association, which encompasses binding and/or internalisation, of PMA$_{SH}$ capsules with various cell lines (HeLa, RAW and dTHP-1) was investigated using flow cytometry. The cells were incubated with either spherical or cylindrical capsules at a capsule-to-cell ratio of 100:1 for 24 h at 37 °C. Our data show that cylindrical capsules exhibit decreased association with HeLa cells (54%) compared with their spherical counterparts (81%) after 24 h incubation (Fig. 2A). This is consistent with our previous study on shape dependent cellular association of polymer capsules in HeLa cells, where a lower internalisation was observed for higher aspect ratio (AR) capsules. This is likely attributed to the larger average radius or surface area the cells may endure during endocytosis. However, in murine macrophage RAW cells, cylindrical capsules appeared to have an enhanced association (97%) after 24 h incubation compared with spherical capsules (86%) (Fig. 2B), which indicates bigger capsules were phagocytized more readily than smaller ones by RAW cells. Meanwhile, for dTHP-1 cells, cellular association appeared independent of PMA$_{SH}$ capsule shape, as different shapes did not result in a significant difference in cellular association after 24 h (Fig. 2C). Spherical capsules (D = 390 nm) were associated with RAW and dTHP-1 cells to a similar degree. This is consistent with a recent report where fluoromica nanoparticles with different diameters (D = 250, 600 and 1000 nm) showed comparable uptake in RAW and dTHP-1 cells. However, cylindrical capsules associated to RAW cells to a greater degree than dTHP-1 cells for all time points. This was particularly obvious in the first 2 h of incubation, when cellular association of cylindrical PMA$_{SH}$ capsules with RAW cells already reached 75%. In contrast, it took approximately 6 h for the same capsules to reach the same level of association with dTHP-1 cells. This suggests that RAW cells exhibit a stronger affinity to associate with the dimensionally larger cylindrical PMA$_{SH}$ capsules compared to dTHP-1 cells. Taken together, these data demonstrate that the effect of PMA$_{SH}$ capsule shape on cellular association is cell line-dependent. Moreover, spherical capsules experienced similar cellular association in all three cell lines (HeLa, RAW and dTHP-1 cells after 24 h incubation), while the cellular association differed in all cases for cylindrical PMA$_{SH}$ capsules (Fig. 2D).

3.3 Intracellular deformation of spherical PMA$_{SH}$ capsules

Next, we investigated the intracellular deformation of PMA$_{SH}$ capsules in different cell lines. PMA$_{SH}$ Capsules were incubated with HeLa, RAW or dTHP-1 cells at 37 °C for 24 h. Subsequently, the cells were fixed, and the cell membranes were stained with AF488 WGA followed by super high resolution imaging using SIM. After incubation with cells, spherical PMA$_{SH}$ capsules were found to be both internalised and surface bound for all three different types of cells (Fig. 3). In the case of HeLa cells, the internalised capsules appeared to be highly compressed, morphologically changing from the original hollow spheres to dense particle structures, and showing increased fluorescence intensity (Fig. 3A). In contrast, the internalised capsules were less deformed in RAW cells, appearing as hollow crescent-like and ellipsoid-like structures (Fig. 3B). In dTHP-1 cells, almost all internalised capsules maintained their hollow spherical structures (Fig. 3C). This is
consistent with previous reports that polyelectrolyte multilayer capsules gradually buckle and deform during internalisation into human breast cell lines, indicating that only polymer capsules with reinforced stiffness were able to withstand cell-generated mechanical forces during the uptake process.\(^8\) Notably, the deformation of capsules outside but already attached to the cell membrane was also observed with HeLa cells (Fig. 3A, inset). This suggests that deformation starts to occur at the engagement between capsules and the cell membrane during the early stages of internalisation. The intracellular deformation of capsules was quantified using a deformation percentage defined as the number of deformed capsules divided by the number of total (deformed and non-deformed) capsules after internalisation. Hence, intracellular capsule deformation levels of 96%, 56% and 29% were observed for HeLa, RAW and dTHP-1 cells, respectively (analysing at least 300 internalised capsules). Due to the differing deformation exhibited by identical spherical capsules, we propose that HeLa cells generate higher mechanical forces, followed by RAW cells and dTHP-1 cells during their internalisation processes. Our previous study demonstrated that at pH below the pKa of PMA (pH = 6.5), the stiffness of PMA\(_{SH}\) films increased dramatically due to protonation of the carboxyl group on the polymer backbone.\(^{31}\) Thus, pH differences that exist between the extracellular and intracellular environment may also contribute to the deformation of PMA\(_{SH}\) capsules after internalisation. We examined the intracellular localisation of the spherical PMA\(_{SH}\) capsules in different cells. The internalised capsules appeared to be mainly located in the late endosomes and lysosomes (pH = 4.5 – 5.5) in all cell types (Fig. S3†). Since the capsules had the same intracellular fate, it appears that pH is an unlikely factor in the intracellular deformation of capsules in different cells. Next, we investigated if the redox-triggered (bio)degradability of disulfide crosslinked PMA\(_{SH}\) capsules influenced the intracellular deformation of PMA\(_{SH}\) capsules. Disulfide crosslinked PMA\(_{SH}\) capsules degrade in the presence of GSH, an abundant reductive agent found inside cells including endosomes and lysosomes.\(^{32}\) We compared the deformation of non-degradable and degradable PMA\(_{SH}\) capsules after internalisation by cells. Non-degradable PMA\(_{SH}\) capsules were prepared using (1,8-bismaleimido)diethyleneglycol (BM(PEG)\(_2\)), a linker that induces a noncleavable covalent bond when reacted with thiol groups (as shown in Fig. S4†). It was observed that non-degradable spherical PMA\(_{SH}\) capsules are also deformed (92%) in HeLa cells after 24 h incubation, with levels comparable to that of degradable PMA\(_{SH}\) capsules (Fig. S5A†). Meanwhile, we observed that 59% and 21% of non-degradable capsules deformed in RAW and dTHP-1 cells, respectively (Fig. S5B†, 5C). Despite the slight differences (4% in HeLa, 3% in RAW and 8% in dTHP-1 cells) in the percentage of deformation of degradable and non-degradable PMA\(_{SH}\) capsules in all cell lines studied, these differences are not significant enough to suggest that the deformation of PMA\(_{SH}\) capsules during internalisation is dominated by destabilisation of the PMA\(_{SH}\) polymer layers. Rather, the intracellular deformation of the PMA\(_{SH}\) capsules suggests that the capsules are subjected to differing magnitudes of mechanical force during internalisation by HeLa, RAW and dTHP-1 cells, which is consistent with the literature that suggests cell mechanical forces can differ significantly for different cells types.\(^{33}\) Although techniques to quantify mechanical stress in living cells during dynamic uptake processes are not yet available, the intracellular forces exerted by a cell upon internalisation of particulates is believed to be one of the key parameters to successful delivery.\(^{34}\)

### 3.4 Intracellular deformation of cylindrical PMA\(_{SH}\) capsules

To investigate the possible effect of shape on capsule deformation, we treated the cells with cylindrical PMA\(_{SH}\) capsules for 24 h to allow significant internalisation (see Fig. 4). It was observed that cylindrical PMA\(_{SH}\) capsules were compressed and lost their cylindrical shapes inside HeLa cells (Fig. 4A, D), whereas they were partially deformed after internalisation by RAW cells (Fig. 4B, E), and largely retained their dimensions and hollow morphology within dTHP-1 cells (Fig. 4C, F). The intracellular deformation of these cylindrical capsules is in line with that of spherical capsules, where we found that HeLa cells subjected capsules to the highest mechanical forces during their uptake process, followed by RAW cells, then dTHP-1 cells.

### 3.5 Actin-mediated intracellular deformation of PMA\(_{SH}\) capsules

Previous studies have speculated that polymer capsules are engulfed into cells through the formation of large cytoplasmic protrusions regulated by actin movement.\(^{13,35}\) Actin filaments are particularly abundant beneath the plasma membrane, where they form a network that provides mechanical support for the cell and facilitates the movement that leads to the engulfment of external particles.\(^{36}\) In addition, actin filaments play a role in the process of endocytosis, which may contribute to cellular osmotic pressure.\(^{35}\) Therefore, to elucidate the
influence of cell-generated mechanical forces on intracellular deformation, the role of actin was investigated. Spherical PMA
SH capsules were incubated with all cell types for 24 h. Subsequently, the cells were fixed and the actin was fluorescently stained with AF488 phalloidin to allow imaging using SIM. Long and thick horizontal actin filaments were observed in HeLa cells (Fig. 5A). Short strands of thick actin filaments were observed in RAW cells (Fig. 5B) and a meshwork pattern of thin actin filaments were observed in dTHP-1 cells (Fig. 5C). Different actin patterns arise from the assembly of actin filaments, which is governed by a variety of actin-binding proteins that crosslink actin filaments in distinct structures in different cell lines.37 By staining the actin filaments, protrusions that surround the PMA
SH capsules were observed for all three types of cells (Fig. 5D-F). Importantly, the actin filaments surrounding capsules showed different morphologies with each cell lines. In the case of HeLa cells, the capsules are largely compressed after being surrounded by the actin filament protrusions (Fig. 5D). However, the actin appears to have little effect on the morphology of the capsules in RAW and dTHP-1 cells (Fig. 5E, F). These observations indicate that PMA
SH capsules undergo a greater deformation as a result of the higher mechanical forces enforced by the denser actin filaments of HeLa cells compared with RAW and dTHP-1 cells. This is in agreement with previous studies that actin filament movement requires mechanical forces in the range of tens of piconewtons to hundreds of nanonewtons that vary among different cell types.38 We believe this is likely due to the different endocytic pathways between epithelial cells (HeLa) and phagocytic cells (RAW and dTHP-1), which regulate cells with differential abilities to internalise polymer capsules, resulting in the different deformation of the capsules.

4 Conclusions
We investigated the intracellular deformation of spherical and cylindrical polymer capsules in HeLa, RAW and dTHP-1 cells using super high resolution microscopy. Our data showed similar association of spherical PMA
SH capsules between the three cell lines, but revealed that the intracellular deformation of capsules was cell line-dependent, which may arise from the different degrees of mechanical forces generated by cells during the internalisation process. Spherical capsule deformation was highest in HeLa cells (96%), followed by RAW (56%), then dTHP-1 cells (29%). A similar trend of cell line-dependent deformation was also observed with cylindrical capsules, despite the higher association of the cylindrical capsules to the RAW/dTHP-1 cells compared with HeLa cells. The detailed measurement of mechanical forces of cells during their dynamic uptake processes warrants further investigation. However, our findings reveal that intracellular processing based on capsule deformation is cell line-dependent given the identical physicochemical properties of the capsules studied. The use of SIM to image intracellular deformation provides a means to explore the interactions between polymer capsules and biological systems, which in turn can guide the design of polymer capsules for effective drug delivery, as well as drive the fundamental understanding of cell mechanobiology.

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