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Poly(1,4,5-oxadithiepan-2-one)-based Redox and pH Dual-responsive Polyzwitterionic Micelles for Tumor Cell-targeted Drug Delivery

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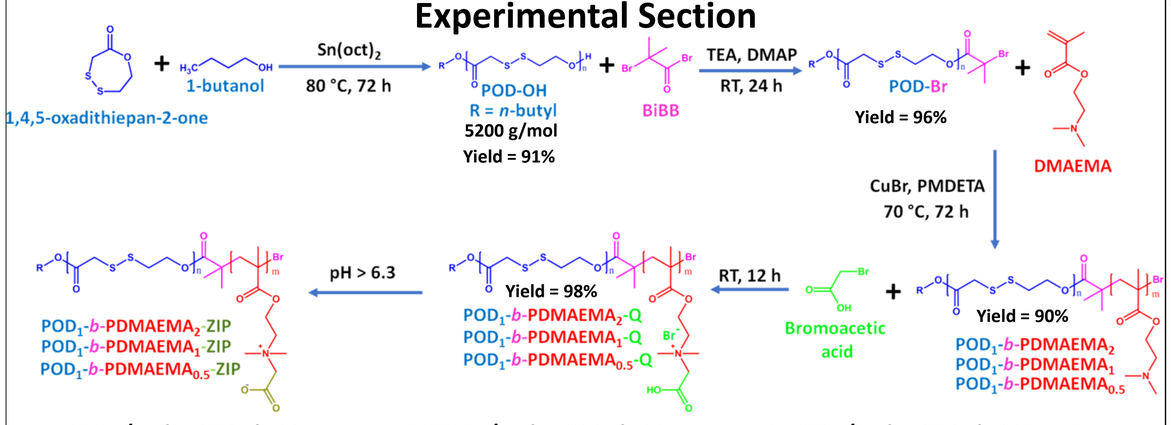
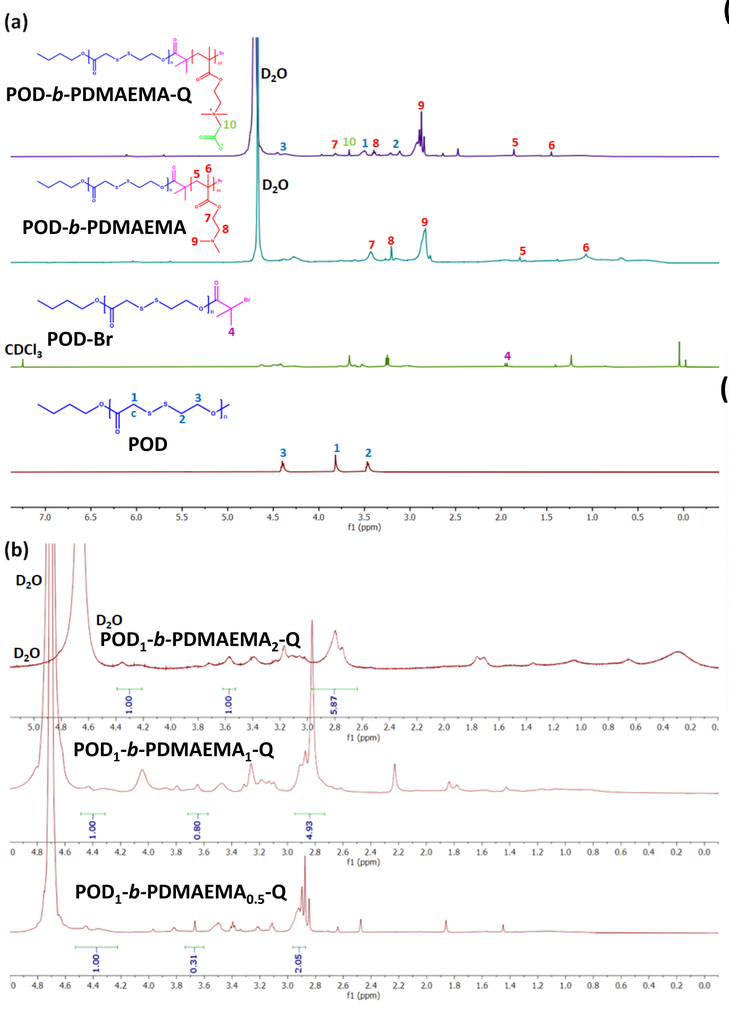
- Polyzwitterionic shell of the micellar particle imparted antifouling property during blood circulation and prevent unwanted biological molecule adhesion on the particle surface
- pH-responsive outer shell of the micelle converted from polyzwitterion to polycation in the tumor environment and accumulated inside the tumor cell
- Due to the redox-responsiveness, disulfide-based core degraded in presence of high concentration of glutathione inside the tumor cell and release the drug to the targeted position

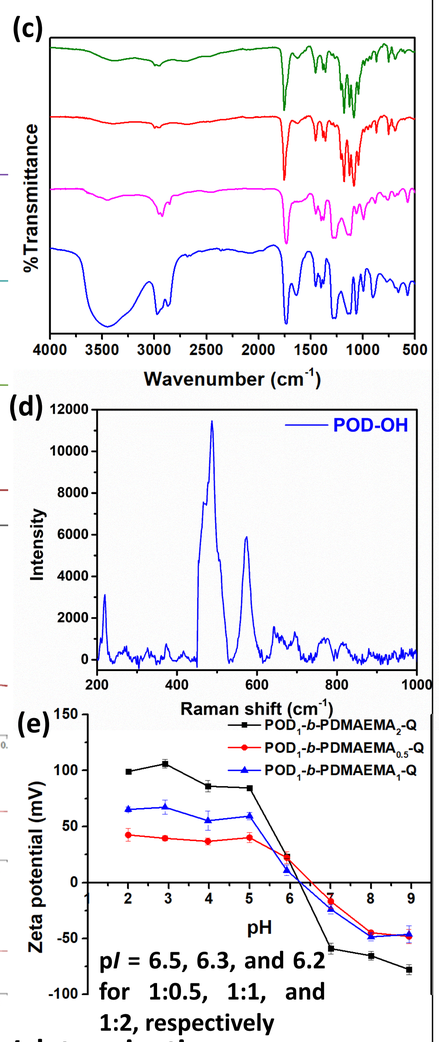
Experimental Section



7100 g/mol – POD_1-*b*-$PDMAEMA_{0.5}$, 10200 g/mol – POD_1-*b*-$PDMAEMA_1$, 14900 g/mol – POD_1-*b*-$PDMAEMA_2$

Synthesis of POD-*b*-PDMAEMA-ZIP from 1,4,5-Oxadithiepan-2-One

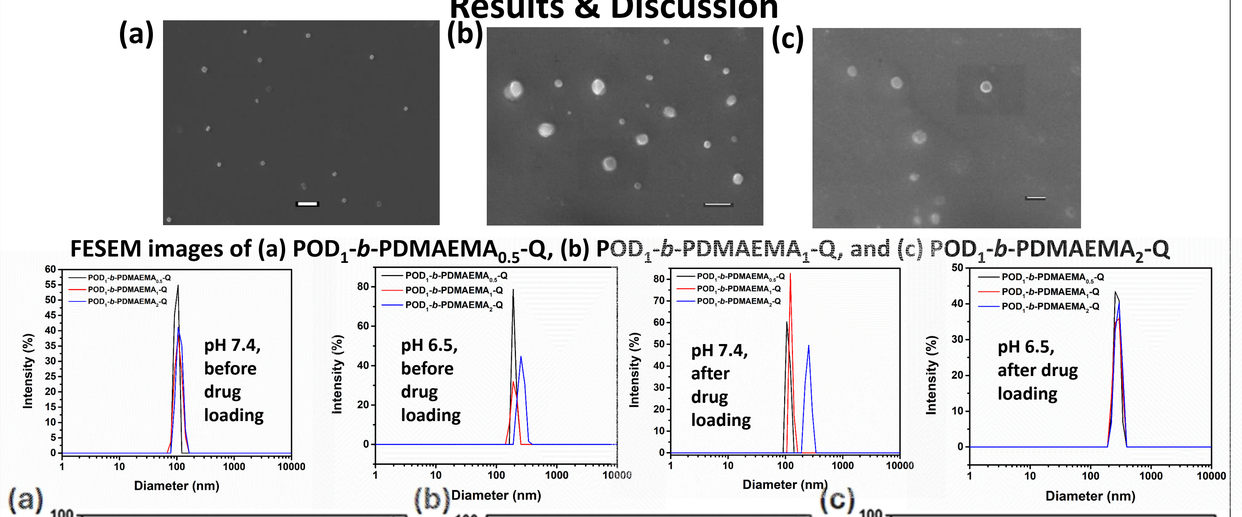




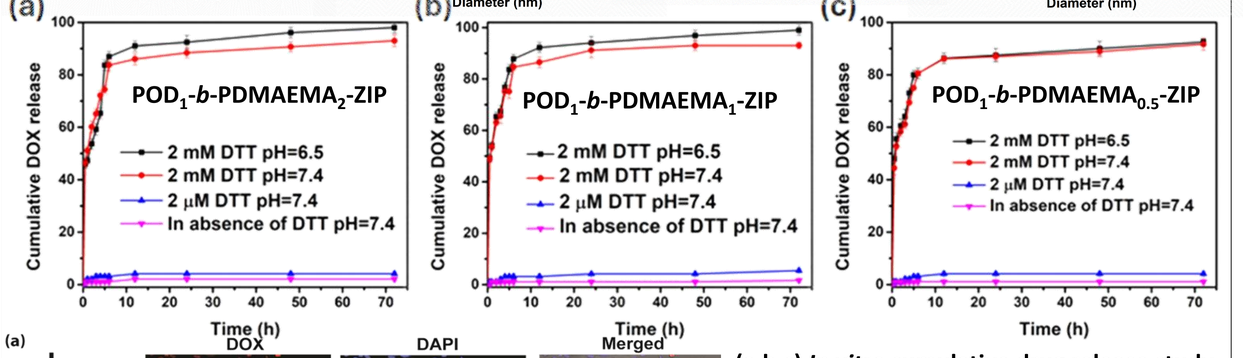
pI = 6.5, 6.3, and 6.2 for 1:0.5, 1:1, and 1:2, respectively

(a,b) ^{1}H NMR, (c) FTIR, (d) Raman, (e) p*I* determination

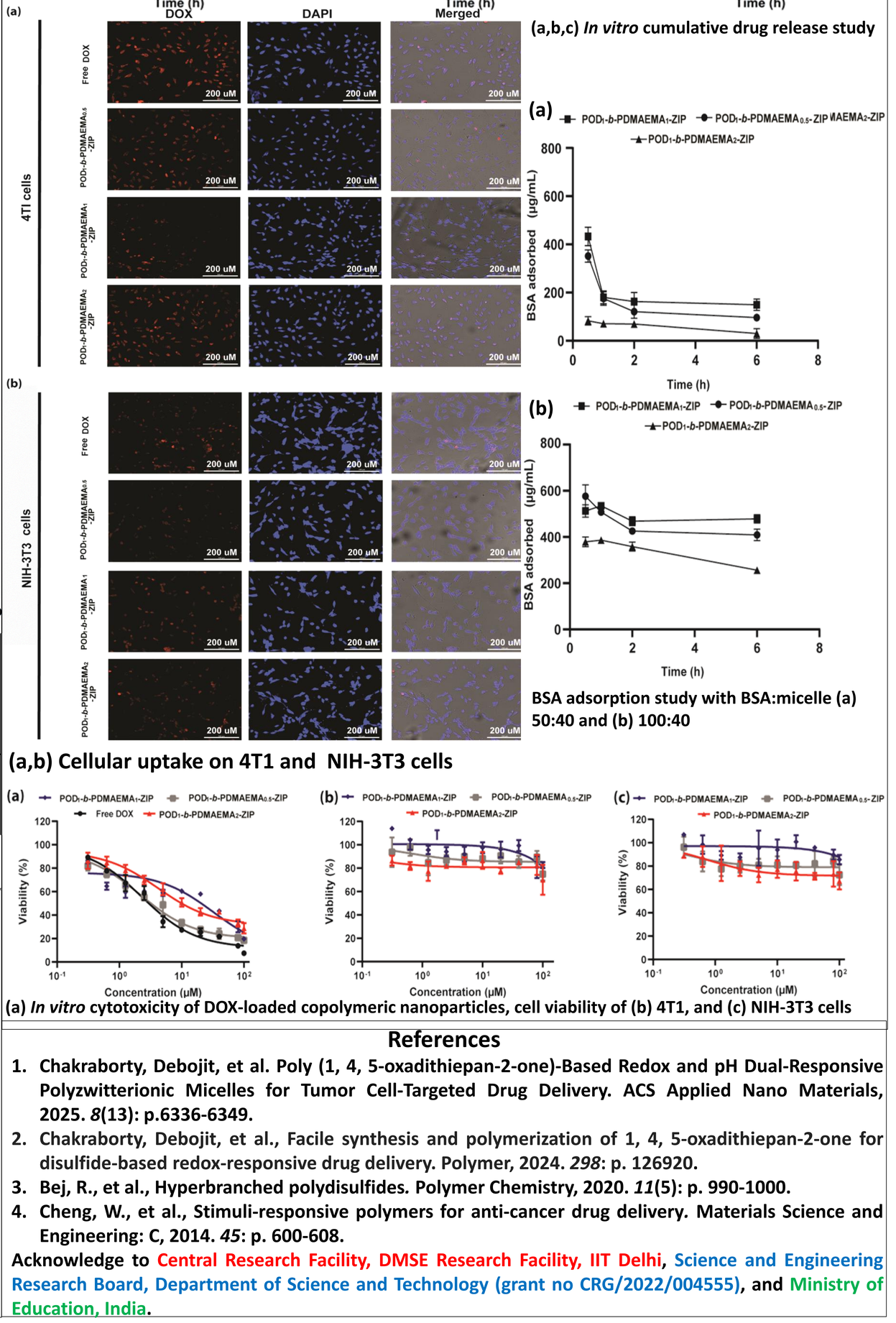
Results & Discussion



FESEM images of (a) POD_1-*b*-$PDMAEMA_{0.5}$-Q, (b) POD_1-*b*-$PDMAEMA_1$-Q, and (c) POD_1-*b*-$PDMAEMA_2$-Q



(a,b,c) *In vitro* cumulative drug release study



BSA adsorption study with BSA:micelle (a) 50:40 and (b) 100:40

(a,b) Cellular uptake on 4T1 and NIH-3T3 cells

(a) *In vitro* cytotoxicity of DOX-loaded copolymeric nanoparticles, cell viability of (b) 4T1, and (c) NIH-3T3 cells

Conclusions

- Polydisulfide-based polyzwitterionic block copolymer POD-*b*-PDMAEMA-ZIP was synthesized using ROP of 1,4,5-oxadithiepan-2-one and ATRP of DMAEMA.
- Three different compositions of block copolymers POD_1-*b*$PDMAEMA_{0.5}$, POD_1-*b*-$PDMAEMA_1$, and POD_1-*b*-$PDMAEMA_2$ were prepared by varying the ratio of mol. wt. of two blocks POD:PDMAEMA.
- Average diameter of the particles were ~ 137, 164, and 182 nm for POD_1-*b*-$PDMAEMA_1$-Q, POD_1-*b*-$PDMAEMA_2$-Q, and POD_1-*b*-$PDMAEMA_{0.5}$-Q, respectively measured by FESEM.
- Reduction responsive DOX release was studied in presence of 2 mM and 2μM DTT. In absence of DTT and in presence of 2μM DTT, DOX release was very low. Whereas in presence of 2 mM DTT at pH 6.5, the DOX release percent from three types particles was ~99% after 72 hours.
- All the drug loaded micelle is showing very low BSA protein absorption. POD_1-*b*-$PDMAEMA_2$-ZIP is showing lowest amount of protein absorption, with the increase of PDMAEMA block.
- Including all these studies, it can be concluded that the synthesized disulfide based reduction responsive micellear drug delivery system is the perfect example for targeted stimuli responsive drug delivery system.

References

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