Antitumor cytokine DR5-B-conjugated polymeric poly(N-vinylpyrrolidone) nanoparticles with enhanced cytotoxicity in human colon carcinoma 3D cell spheroids

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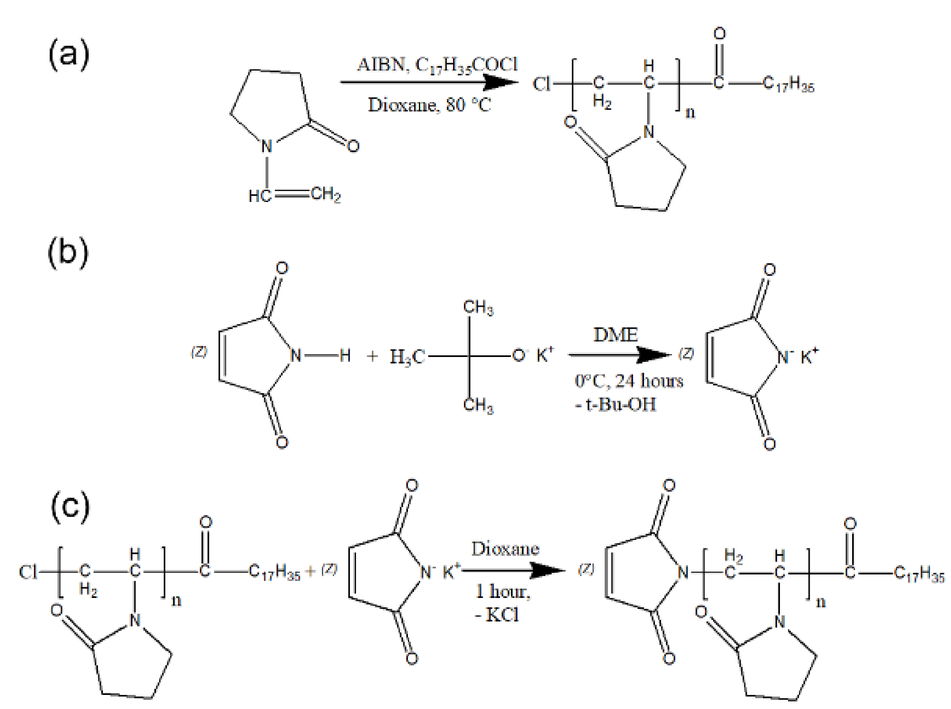
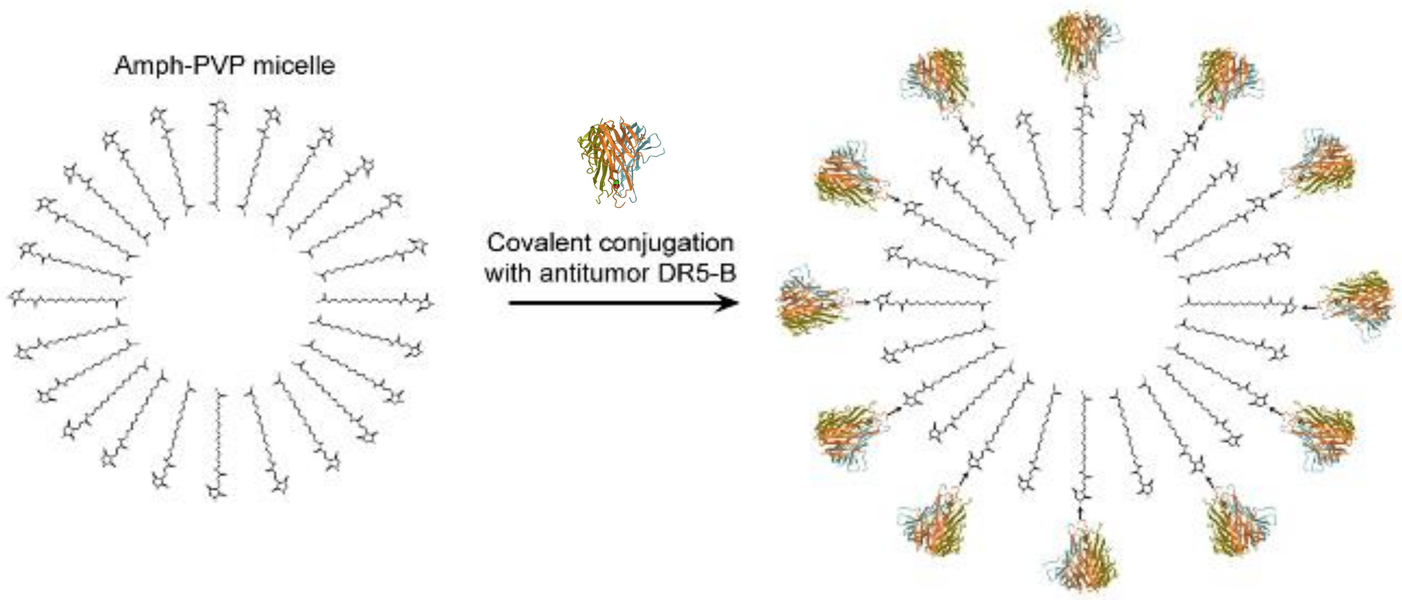
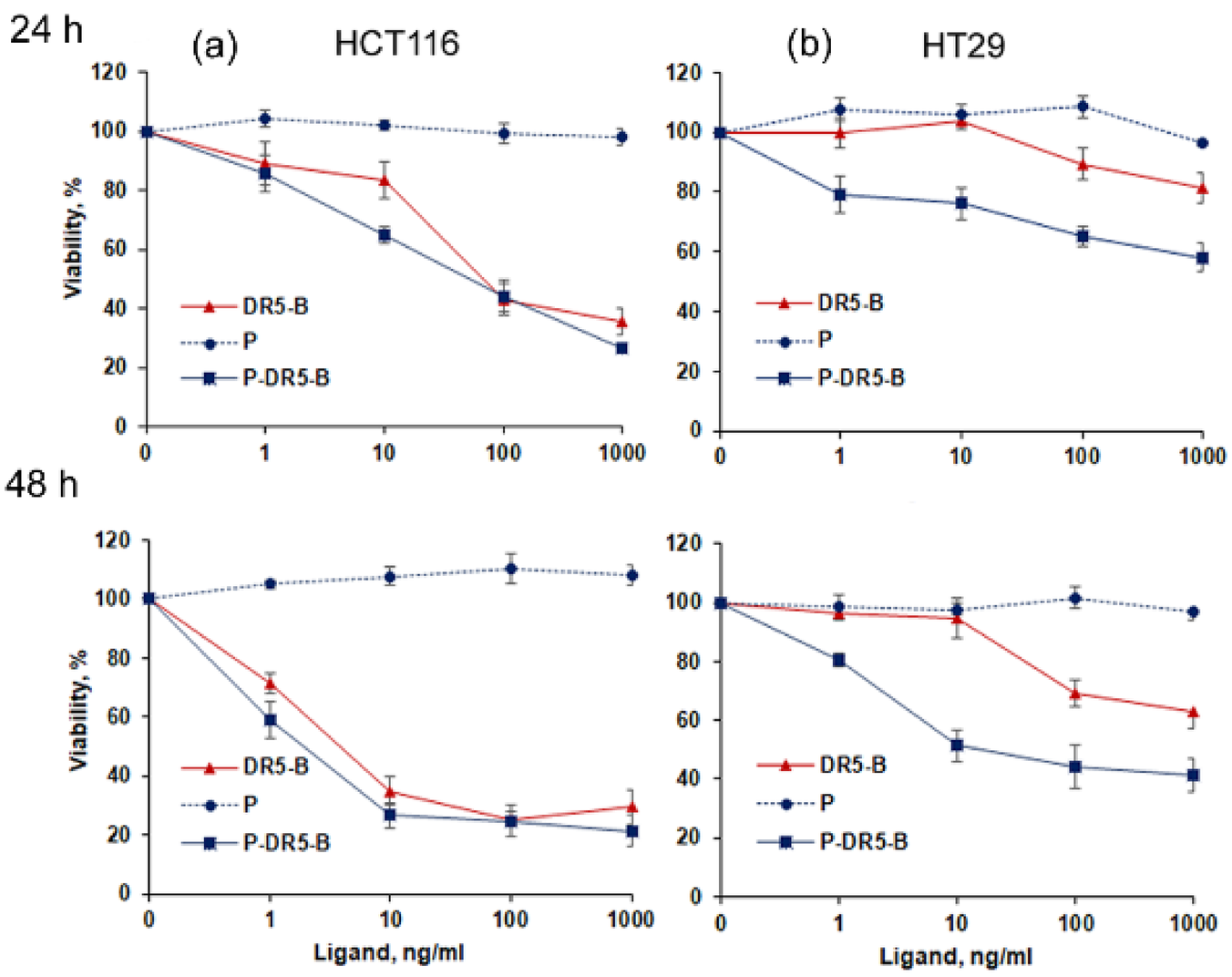
Self-assembled nanoparticles based on amphiphilic poly-N-vinylpyrrolidone (Amph-PVP) were earlier proposed as new drug delivery system [1]. In current work, we studied antitumor activity of Amph-PVP-based self-assembled polymeric micelles covalently conjugated with antitumor receptor-specific TRAIL variant DR5-B (P-DR5-B) [2].



The Amph-PVP polymer was synthesized by earlier developed one-step technique. The synthesis schemes of compounds for further preparation of Amph-PVP nanoparticles: (a) Amph-PVP-Cl polymer; (b) potassium maleimide; (c) Amph-PVP-Cl modification by maleimide group.



DR5-B/V114C was conjugated to the surface of polymeric micelles by selective covalent interaction of N-terminal cysteine residue with maleimide on Amph-PVP. To stabilize Amph-PVP micelles, the hydrophobic core was loaded with model substance prothionamide. For covalent conjugation with DR5-B, hydrophilic ends of polymeric chains were modified with maleimide, and a DR5-B N-terminal amino acid residue Valine was mutated to Cysteine (DR5-B/V114C). The median hydrodynamic size was 220 nm, as measured by DLS. Polydispersity index was about 0.3.



The cytotoxicity of DR5-B-conjugated Amph-PVP polymeric nanoparticles was investigated in 3D multicellular tumor spheroids (MCTS) of colon carcinomas HCT116 (a) and HT29 (b), generated by RGD-induced cell self-assembly technique [3]. Cell viability was determined by MTT test. Mean ± Standard Deviation (n = 3).

- Conjugation of DR5-B to the Amph-PVP nanoparticles enhanced its tumor cell killing capacity both in DR5-B-sensitive HCT116 and in DR5-B-resistant HT29 MCTS. P-DR5-B significantly surpassed DR5-B in the antitumor activity, overcoming DR5-B-resistance of the human colon carcinoma MCTS *in vitro*.
- We obtained a new nano-scaled delivery system based on Amph-PVP self-aggregates coated with covalently conjugated antitumor DR5-specific cytokine DR5-B. Amph-PVP polymeric nanoparticles is a perspective versatile nano-scaled delivery system for the targeted proteins.

References

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2. Yagolovich AV, Artykov AA, Karmakova TA, et al. Genetically Modified DR5-Specific TRAIL Variant DR5-B Revealed Dual Antitumor and Protumoral Effect in Colon Cancer Xenografts and an Improved Pharmacokinetic Profile. Transl Oncol. 2020 Apr;13(4):100762. doi: 10.1016/j.tranon.2020.100762.
3. Akasov, R.; Zaytseva-Zotova, D.; Burov, S.; et al. Formation of Multicellular Tumor Spheroids Induced by Cyclic RGD-Peptides and Use for Anticancer Drug Testing in Vitro. International Journal of Pharmaceutics 2016, 506, 148–157, doi:10.1016/j.ijpharm.2016.04.005.\