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Polymer based Drug Delivery Systems- benchtop to Bedside Transition

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ABSTRACT

Research in the field of polymers and polymeric materials has garnered immense attention in the past few decades due to the versatile functional and structural capabilities of polymers which often can be manipulated for applications in the field of therapy and diagnosis for a host of diseases and disorders. Polymer therapeutics comprises polymer-drug and polymer-protein conjugates as well as supramolecular systems used as drug delivery systems. Although the pharmacological industry invests immensely in the design and discovery of novel drug molecules, small molecular drugs are often inefficient in targeting many diseases like deep seated low vasculature tumours, metastasized cancers and various autoimmune diseases. Coupled with a rapid clearance rate, low solubility, drug resistance and high off target toxicity these small molecular drugs often present modest benefits for a host of common diseases. In order to improve the therapeutic index of pre-existing drugs and shortening the translation from preclinical validation to clinical approval, a vast area of drug delivery research focuses on the improvement of drug carriers by various alterations. The major challenges currently faced by drug delivery systems include a low payload, transition through the desmoplastic barrier for solid tumours and high hepatic and renal clearance. In order to address these issues numerous polymer-protein and polymer-drug conjugates have been engineered and have reported to enhance the stability and pharmacokinetic properties of the active drugs. Highly toxic anticancer drugs like doxorubicin, cis-platin and gemcitabine have successfully been coupled with high molecular weight polymers to formulate targeted drug delivery agents, some of which have undergone successful clinical trials. Apart from PEGylated polymers, dendritic polymers and polyplexes with DNA or RNA moieties have also been considered as candidates for improving the therapeutic index of various drugs. Ongoing efforts in the development of polymer-based therapeutics are promising and open new horizons for personalized medicine for effective cure of various life-threatening diseases.

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Polymer therapeutics comprises a vast field of materials including polymer-drug, polymer-protein conjugates as well as supramolecular assemblies. The application of polymers, both synthetic and natural, is usually in the form of carriers of low molecular weight compounds. Nanomaterials derived from such polymers which can be micelles, polymersomes or vesicles offer attractive chemical and physiologically modifiable features harnessed for drug delivery applications. While small molecular drugs have demonstrated promising results throughout history, these agents are usually associated with limitations to combat several complex diseases including but not limited to cancer, various autoimmune and rheumatic diseases and diabetes. Not only do such diseases exhibit aggressive resistance against small molecular drugs, but these drug molecules exhibit high hydrophobicity, rapid renal, hepatic and splenic clearance, off-target toxicity, high dosage and low penetration and accumulation across the desmoplastic barrier in low vasculature tumor tissues [1-22]. To overcome these challenges extensive research has been carried out to develop and enhance targeted delivery of active therapeutic agents, thereby resulting in phenomenal achievements in nanotechnology drug delivery approaches such as improved solubility, controlled and sustained release of drugs, higher circulation times, lower clearance rates, adaptable release profile and reduced off-target toxicity [1,2,4,5]. Variation of surface functionalities and use of biomolecules and ligands enhance the targeting capacity of these nanocarriers. The use of passive (pH,

hypoxia, temperature, enzyme, ROS) and active (targeting ligands, aptamers etc.) stimuli can selectively deliver the therapeutic cargo at the intended site with least collateral damage (Figure 1).

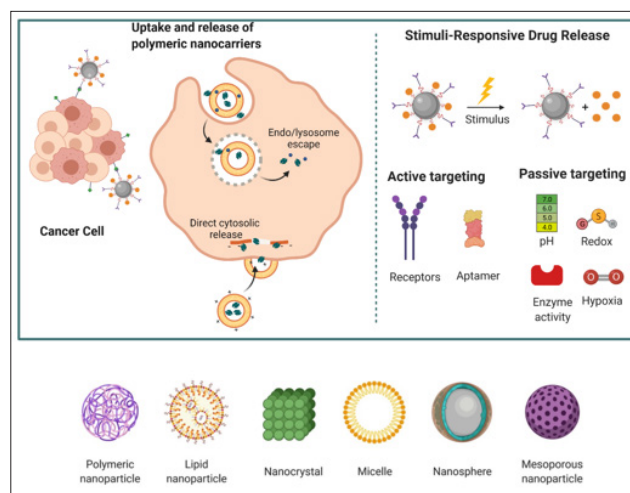


Figure 1: The various stimuli used for release of drug into cancer cells along with the uptake mechanism in cancer cells and (below) some varieties of nanoparticles used for drug delivery (Created using BioRender)

Currently most drug delivery systems rely on small molecular drugs to address a disease and thus still face a drug's inherent limitations. Despite the fact that these delivery systems are efficient to sustain a desired concentration of drugs at a targeted location, cellular barriers and resistance mechanisms of targeted tissues may still reduce the overall efficiency of a drug [22-33]. Additionally, such systems are prone to other drawbacks such as burst release that raises safety concerns for a drug, enzymatic drug degradation, and activation of the immune system [6,5]. To address safety concerns, complex strategies have been utilized involving simultaneous-loading of several small molecular drugs and multifunctional nanoparticles [31,34,35]. As a result, design of a simple effective delivery system remains a challenge, considering the stringent biocompatibility requirement of nanoscale drug delivery systems.

The inherent ability of polymers to interact with a target at multiple sites locations simultaneously grants them a distinguishable property. Multivalent interactions, concurrent binding between multiple ligands and receptors of two molecular entities, is the key characteristics of many biological processes, such as adhesion of bacteria to the surface of a host cell, cell-cell interactions, or binding between transcription proteins and DNA (deoxyribonucleic acid). The multivalent interactions are reversible and play a role in activation/inhibition of biological processes. While small molecular drugs are typically monovalent, the multivalent interaction of macromolecules offers unprecedented benefits that are not reachable by the small drugs. The inherent benefits result from the repeating units of polymers that allows multivalent interaction, generating enhanced affinity, favorable entropy, and cooperativity [7,11]. The multivalent interactions opens the door for simple applications like polymeric sequesters. Further, the use of nanoparticles offers a wide range of size and shape tunability to adapt for desired use [36-49].

The potential of polymers as therapeutic agents is highly underestimated. Polymers possess a multi-ligand property allowing them to mimic the natural multi-ligand processes and bind simultaneously to multiple binding-sites [12,13]. Binding to receptors is a reversible process, meaning when a receptor disconnects, another ligand of a polymeric drug is situated in a position to rebound, offering a statistical rebounding mechanism [8,16]. This process is more energy efficient than recruiting another small molecule following each release and macromolecular drugs establish a hindrance stabilizing effect which prevents association of the surrounding medium with the targeted detrimental biological agents like viruses [17,18].

Polymeric drugs are promising candidates to fight against many diseases. The discoveries in the past few decades have resulted in multiple FDA approved polymeric drugs which offer commercial viability and feasibility to be produced in large quantities in comparison to labor-extensive preparation of small drugs or conjugated peptide-polymeric agents. Recent research strongly supports the potential of polymers as drugs where the target cells are killed while the constructs themselves did not demonstrate multidrug resistance behavior. As the field of polymeric drugs field is relatively new, there is a huge potential of investigating their properties and tuning them for personalized medicine.

References

1. Tannock IF (1998) Conventional cancer therapy: promise broken or promise delayed? *The Lancet* 351: SII9-SII16.
2. Haag R, Kratz F (2006) Polymer Therapeutics: Concepts and Applications. *Angewandte Chemie International Edition* 45: 1198-1215.

3. Chitkara D, Mittal A, Behrman SW, Kumar N, Mahato RI (2013) Self-Assembling, Amphiphilic Polymer-Gemcitabine Conjugate Shows Enhanced Antitumor Efficacy Against Human Pancreatic Adenocarcinoma. *Bioconjugate Chemistry* 24: 1161-1173.
4. Rosenblum MD, Gratz IK, Paw JS, Abbas AK (2012) Treating human autoimmunity: current practice and future prospects. *Science translational medicine* 4: 125sr1-125sr1.
5. Mócsai A, Kovács L, Gergely P (2014) What is the future of targeted therapy in rheumatology: biologics or small molecules? *BMC Medicine* 12: 43.
6. Milne JC, Lambert PD, Schenk S, Carney DP, Smith JJ, et al. (2007) Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. *Nature* 450: 712-716.
7. Sena CM, Bento CF, Pereira P, Seica R (2010) Diabetes mellitus: new challenges and innovative therapies. *The EPMA journal* 1: 138-163.
8. Kokil GR, Veedu RN, Ramm GA, Prins JB, Parekh HS (2015) Type 2 Diabetes Mellitus: Limitations of Conventional Therapies and Intervention with Nucleic Acid-Based Therapeutics. *Chemical Reviews* 115: 4719-4743.
9. Satchi-Fainaro R (2002) Targeting Tumor Vasculature: Reality or a Dream? *Journal of Drug Targeting* 10: 529-533.
10. Duncan R, Izzo L (2005) Dendrimer biocompatibility and toxicity. *Advanced Drug Delivery Reviews* 57: 2215-2237.
11. Lategahn J, Keul M, Rauh D (2018) Lessons To Be Learned: The Molecular Basis of Kinase-Targeted Therapies and Drug Resistance in Non-Small Cell Lung Cancer. *Angewandte Chemie International Edition* 57: 2307-2313.
12. Ringsdorf H (1975) Structure and properties of pharmacologically active polymers. *Journal of Polymer Science: Polymer Symposia* 51: 135-153.
13. Gros L, Ringsdorf H, Schupp H (1981) Polymeric Antitumor Agents on a Molecular and on a Cellular Level? *Angewandte Chemie International Edition in English* 20: 305-325.
14. Ringsdorf H (2004) Hermann Staudinger and the future of polymer research jubilees - Beloved occasions for cultural piety. *Angewandte Chemie-International Edition* 43: 1064-1076.
15. Caliceti P, Veronese FM (2003) Pharmacokinetic and biodistribution properties of poly(ethylene glycol)-protein conjugates. *Adv Drug Deliv Rev* 55: 1261-1277.
16. Vasey PA, Kaye SB, Morrison R, Twelves C, Wilson P, et al. (1999) Phase I clinical and pharmacokinetic study of PK1 [N-(2-hydroxypropyl)methacrylamide copolymer doxorubicin]: first member of a new class of chemotherapeutic agents-drug-polymer conjugates. *Cancer Research Campaign Phase I/II Committee. Clin Cancer Res* 5: 83-94.
17. Duncan R (2003) The dawning era of polymer therapeutics. *Nature Reviews Drug Discovery* 2: 347.
18. Köhler G, Milstein C (1975) Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 256: 495-497.
19. Senapati S, Mahanta AK, Kumar S, Maiti P (2018) Controlled drug delivery vehicles for cancer treatment and their performance. *Signal Transduction and Targeted Therapy* 3: 7.
20. Jain RK (1987) Transport of molecules in the tumor interstitium: a review. *Cancer Res* 47: 3039-3051.
21. Fukumura D, Jain RK (2007) Tumor microvasculature and microenvironment: Targets for anti-angiogenesis and normalization. *Microvascular Research* 74: 72-84.
22. Chauhan VP, Jain RK (2013) Strategies for advancing cancer nanomedicine. *Nat Mater* 12: 958-962.
23. Ray P, Dutta D, Haque I, Nair G, Mohammed J, et al. (2021) pH-Sensitive Nanodrug Carriers for Codelivery of ERK

- Inhibitor and Gemcitabine Enhance the Inhibition of Tumor Growth in Pancreatic Cancer. *Molecular Pharmaceutics* 18: 87-100.
24. Ray P, Kale N, Quadir M (2021) New side chain design for pH-responsive block copolymers for drug delivery. *Colloids and Surfaces B: Biointerfaces* 200: 111563.
 25. Abdullah CS, Ray P, Alam S, Kale N, Aishwarya R, et al. (2020) Chemical Architecture of Block Copolymers Differentially Abrogate Cardiotoxicity and Maintain the Anticancer Efficacy of Doxorubicin. *Molecular Pharmaceutics* 17: 4676-4690.
 26. Confeld MI, Mamnoon B, Feng L, Jensen-Smith H, Ray P, et al. (2020) Targeting the tumor core: hypoxia-responsive nanoparticles for delivery of chemotherapy to pancreatic tumors. *Molecular Pharmaceutics*.
 27. Sarker NC, Ray P, Pfau C, Kalavacharla V, Hossain K, et al. (2020) Development of Functional Nanomaterials from Wheat Bran Derived Arabinoside for Nucleic Acid Delivery. *Journal of Agricultural and Food Chemistry* 68: 4367-4373.
 28. Ray P, Nair G, Ghosh A, Banerjee S, Golovko MY, et al. (2019) Microenvironment-sensing, nanocarrier-mediated delivery of combination chemotherapy for pancreatic cancer. *Journal of Cell Communication and Signaling*.
 29. Ray P, Alhalhooly L, Ghosh A, Choi Y, Banerjee S, et al. (2019) Size-Transformable, Multifunctional Nanoparticles from Hyperbranched Polymers for Environment-Specific Therapeutic Delivery. *ACS Biomaterials Science & Engineering* 5: 1354-1365.
 30. Ghosh A, Sarkar S, Ghosh S, Ray P, Quadir M, et al. (2019) Abstract 1234: Zoledronic acid-induced suppression of invasive phenotypes of pancreatic cancer cells is mediated through downregulation of CYR61/CCN1. *Cancer Research* 79: 1234.
 31. Ray P, Confeld M, Borowicz P, Wang T, Mallik S, et al. (2019) PEG-b-poly (carbonate)-derived nanocarrier platform with pH-responsive properties for pancreatic cancer combination therapy. *Colloids and Surfaces B: Biointerfaces* 174: 126-135.
 32. Ray P, Ferraro M, Haag R, Quadir M (2019) Dendritic Polyglycerol-Derived Nano-Architectures as Delivery Platforms of Gemcitabine for Pancreatic Cancer. *Macromol Biosci* 19: e1900073.
 33. Das A, Haque I, Ray P, Ghosh A, Dutta D, et al. (2021) CCN5 activation by free or encapsulated EGCG is required to render triple-negative breast cancer cell viability and tumor progression. *Pharmacol Res Perspect* 9: e00753.
 34. Karaca M, Dutta R, Ozsoy Y, Mahato RI (2016) Micelle Mixtures for Coadministration of Gemcitabine and GDC-0449 To Treat Pancreatic Cancer. *Molecular Pharmaceutics* 13: 1822-1832.
 35. Ray P, Haideri N, Haque I, Mohammed O, Chakraborty S, et al. (2021) The Impact of Nanoparticles on the Immune System: A Gray Zone of Nanomedicine. *Journal of Immunological Sciences* 5.
 36. Ray P, Gidley D, Badding JV, Lueking AD (2019) UV and chemical modifications of polymer of Intrinsic Microporosity 1 to develop vibrational spectroscopic probes of surface chemistry and porosity. *Microporous and Mesoporous Materials* 277: 29-35.
 37. Ray JK, Singha R, Ray D, Ray P, Rao DY, Anoop A (2019) Palladium-catalyzed expedient Heck annulations in 1-bromo-1,5-dien-3-ols: Exceptional formation of fused bicycles. *Tetrahedron Letters* 60: 931-935.
 38. Ray P, Xu E, Crespi VH, Badding JV, Lueking AD (2018) In situ vibrational spectroscopy of adsorbed nitrogen in porous carbon materials. *Physical Chemistry Chemical Physics* 20: 15411-15418.
 39. Ray JK, Paul S, Ray P, Singha R, Rao DY, et al. (2017) Pd-catalyzed intramolecular sequential Heck cyclization and oxidation reactions: a facile pathway for the synthesis of substituted cycloheptenone evaluated using computational studies. *New Journal of Chemistry* 41: 278-284.
 40. Chaudhuri S, Maity S, Roy M, Ray P, Ray JK (2016) A Vinyl Radical Cyclization Route to Hydroxycyclohexene Fused Carbocycles. *Asian Journal of Chemistry* 28.
 41. Ray P, Gray JL, Badding JV, Lueking AD (2016) High-Pressure Reactivity of Triptycene Probed by Raman Spectroscopy. *The Journal of Physical Chemistry B* 120: 11035-11042.
 42. Ray P (2016) Interactions of nitrogen and hydrogen with various 1D and 3D carbon materials probed via in-situ vibrational spectroscopy. Ph. D. Thesis.
 43. Wang CY, Ray P, Gong Q, Zhao Y, Li J, Lueking AD (2015) Influence of gas packing and orientation on FTIR activity for CO chemisorption to the Cu paddlewheel. *Physical Chemistry Chemical Physics* 17: 26766-26776.
 44. Clément M, Abdellah I, Ray P, Martini C, Coppel Y, et al. (2020) Synthesis and NMR study of trimethylphosphine gold(i)-appended calix[8]arenes as precursors of gold nanoparticles. *Inorganic Chemistry Frontiers*.
 45. Ray P, Clément M, Martini C, Abdellah I, Beaunier P, et al. (2018) Stabilisation of small mono- and bimetallic gold-silver nanoparticles using calix[8]arene derivatives. *New Journal of Chemistry* 42: 14128-14137.
 46. Brahma S, Ray P, Singha R, Ray JK (2016) Visible Colourimetric and Ratiometric Fluorescent Chemosensors for Cu (II) and Ni (II) Ions. *Asian Journal of Chemistry* 28: 1035.
 47. André E, Boutonnet B, Charles P, Martini C, Aguiar-Hualde JM, et al. (2016) A New, Simple and Versatile Strategy for the Synthesis of Short Segments of Zigzag-Type Carbon Nanotubes. *Chemistry* 22: 3105-3114.
 48. Singha R, Roy S, Nandi S, Ray P, Ray JK (2013) Palladium-catalyzed one-pot Suzuki-Miyaura cross coupling followed by oxidative lactonization: a novel and efficient route for the one-pot synthesis of benzo[c]chromene-6-ones. *Tetrahedron Letters*, 54: 657-660.
 49. Ray D, Nasima Y, Sajal MK, Ray P, Urinda S, et al. (2013) Palladium-Catalyzed Intramolecular Oxidative Heck Cyclization and Its Application toward a Synthesis of (\pm)- β -Cuparenone Derivatives Supported by Computational Studies. *Synthesis* 45: 1261-1269.

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