



Covalent nano delivery systems for selective imaging and treatment of brain tumors☆



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ABSTRACT

Nanomedicine is a rapidly evolving form of therapy that holds a great promise for superior drug delivery efficiency and therapeutic efficacy than conventional cancer treatment. In this review, we attempt to cover the benefits and the limitations of current nanomedicines with special attention to covalent nano conjugates for imaging and drug delivery in the brain. The improvement in brain tumor treatment remains dismal despite decades of efforts in drug development and patient care. One of the major obstacles in brain cancer treatment is the poor drug delivery efficiency owing to the unique blood-brain barrier (BBB) in the CNS. Although various anti-cancer agents are available to treat tumors outside of the CNS, the majority fails to cross the BBB. In this regard, nanomedicines have increasingly drawn attention due to their multi-functionality and versatility. Nano drugs can penetrate BBB and other biological barriers, and selectively accumulate in tumor cells, while concurrently decreasing systemic toxicity.

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Contents

1.	Introduction	178
2.	Covalent drug delivery systems (CDS)	179
2.1.	Ringsdorf's vision of therapeutic polymers	179
2.2.	The multimodular architecture of nano conjugates	179
2.3.	Structural and functional diversity of CDS.	179
3.	Intramolecular dynamics and group mobility	180
3.1.	Antibodies and their replacement by affine peptides.	180
3.2.	Prodrugs and cleavable linkers	180
4.	Modular organization of CDS with diverse functions	180
5.	CDS structural coherence	182
6.	Examples of covalent nanodelivery systems based on polymer platform	182
6.1.	Poly(β -L-malic acid)	182
6.2.	Poly(L-amino acid)s	182
6.3.	Poly(α -L-glutamic acid).	182
6.4.	Poly(γ -(DL)-glutamic acid)	183
6.5.	Poly(aspartic acid)	183
6.6.	Polyacrylic acid and its derivative N-(2-hydroxypropyl)methacrylamide copolymer (HPMA).	184
7.	Coherence of polymeric nano drug design.	184

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7.1.	Hydrodynamic shape and size	184
7.2.	High axial ratio in support of CDS environmental interactions and directional mobility	184
7.3.	Coherence and biodegradability	185
7.4.	Examples of modules with specific functions	185
7.5.	Platforms, typical chemical/structural outfit	185
7.6.	Platforms for precision molecular therapy and imaging.	185
8.	Prodrugs	185
9.	Nucleic acids delivery by covalent nano drugs	185
10.	Covalent Nanodelivery Systems for Imaging and treatment of brain tumors	186
10.1.	Nanomedicine overview	186
10.2.	Brain barriers: Blood-brain barrier	186
10.3.	Brain barriers: Blood-CSF barrier (BCSFB)	188
10.4.	Brain cancers	188
11.	Application of nanotechnology for brain cancer imaging	188
11.1.	Magnetic resonance imaging (MRI)	189
11.2.	Fluorescent imaging	190
11.3.	Computed tomography (CT)	190
11.4.	Positron emission tomography (PET)	190
11.5.	Ultrasound (US).	190
12.	Brain cancer treatment	191
12.1.	Primary brain cancer treatment.	191
12.2.	Secondary brain tumor treatment.	191
13.	Designing a nano drug for treating brain tumors	191
13.1.	Choosing an appropriate nanocarrier	192
13.2.	Optimizing circulation time.	192
13.3.	Targeting and crossing the blood-brain barrier	193
13.4.	Penetrating the brain tumor	193
13.5.	Internalization	194
13.6.	Endosomal escape	194
13.7.	Tumor-suppressing activity.	195
14.	Future directions.	195
	Acknowledgements	195
	References.	196

1. Introduction

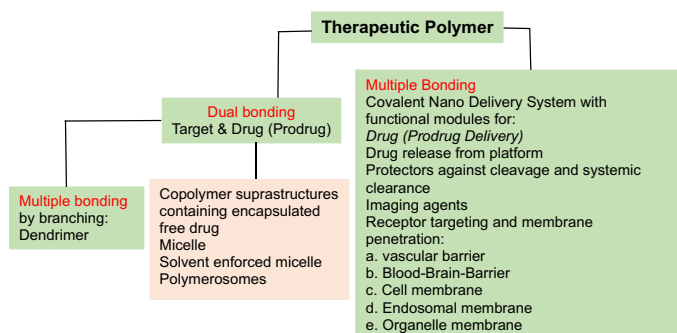
Medicines have been traditionally given to patients in the forms of pills (“small ball or round mass of medicine”), from Middle Dutch or Middle Low German “pille” [1] corresponding to modern encapsulated nano drugs. Or in the form of a drug as in French “drogue” [2], a natural or synthetic soluble chemical, corresponding to covalent nano drug. The fundamental difference between pills and drugs is that the active reagent in the pill or capsule is not immobilized by chemical bonds and thus is free to evade the carrier material (micelle, liposome, suspended water insoluble precipitate), whereas the drug given e.g., in the form of a soluble nano drug contains an active natural or synthetic compound, which is covalently bound to a macromolecular platform and often resembles a prodrug.

The main features of a nano drug are precise targeting and delivery, which are equally important for successful treatment. Addressing safety is of great

importance. Unsecured delivery could cause adverse reactions/side effects that occur when a toxic drug and targeted carrier are disconnected during delivery and the drug becomes available elsewhere. To achieve a rapid transport through the body's vascular system, minimize clearance through kidneys and facilitate high penetration through tissue and membrane barriers, imaging or therapeutic delivery vehicles have been developed that cover a range of nanoscale sizes (5–400 nm) [3,4].

Transported cargo may be both chemically (covalently) bound to the vehicle, and cleaved from the vehicle platform to become the pharmacologically active drug. The bound drugs are not free to diffuse from the carrier, whereas in contrast, encapsulating vehicles transport the drugs in their free unbound form. Encapsulating vehicles are liposomes, micelles, or one of several nanoparticles fabricated by dispersion or precipitation methods. Encapsulating devices release their cargo by spontaneous drug diffusion or after nanoparticle dissolution or capsule erosion. The nano capsules can be designed to “open” at the targeted delivery site in response to the typical environment such as local pH or enzyme cleavage activity. However, because of spontaneous diffusion and capsule-destabilizing environment, release can occur in an uncontrolled fashion and cause harmful damage to healthy tissue. Micelles have a structure, which is in dynamic equilibrium with their parts forming free constituents. They are self-assembled only when the concentration of the free constituents exceeds the so-called critical micelle concentration (CMC). Below CMC the micelles are instable and dissociate into the free constituents [5,6], which may occur with injected micelles when they circulate in the vascular system. Concomitantly with the dissociation, the drug located in the micelle core will be released into plasma. Despite this possibility and uncontrolled drug diffusion out of capsules, micelles and other encapsulating devices are frequently used for targeted drug delivery. In this review, we analyze the best possibility for the drug delivery through the multiple bio-barriers with the special attention to the delivery to the brain.

Table 1
Properties of therapeutic polymers.



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