Publications

1. Sarita Rani, **Rakesh K. Sahoo**, Ashutosh Mahale, Kanan Panchal, Akash Chaurasiya, Onkar Kulkarni, Kaushik Kuche, Sanyog Jain, Kartik T. Nakhate, Ajazuddin, and Umesh Gupta. Sialic Acid Engineered Prodrug Nanoparticles for Co-delivery of Bortezomib and Selenium in Tumor Bearing Mice. **Bioconjugate Chemistry.** 2023, doi: https://doi.org/10.1021/acs.bioconjchem.3c00210 **(Accepted) (IF: 4.7)**
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1. Sanya Batheja, Remya K M, Vinay Kumar, **Rakesh K. Sahoo**, Umesh Gupta (2023), Chapter 8: Drug Delivery to Central Nervous System. *In* **Controlled and Novel Drug Delivery,** 2nd edition, *Edited by* NK Jain. **CBS Publishers & Distributers Pvt. Ltd.** 265-295 (ISBN: 978-9-35-466727-5)
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Article

Angiopep-2 Grafted PAMAM Dendrimers for the Targeted Delivery of Temozolomide: *In Vitro* and *In Vivo* Effects of PEGylation in the Management of Glioblastoma Multiforme

Rakesh Kumar Sahoo, Hitesh Kumar, Vikas Jain, Sonal Sinha, Ajazuddin, and Umesh Gupta*

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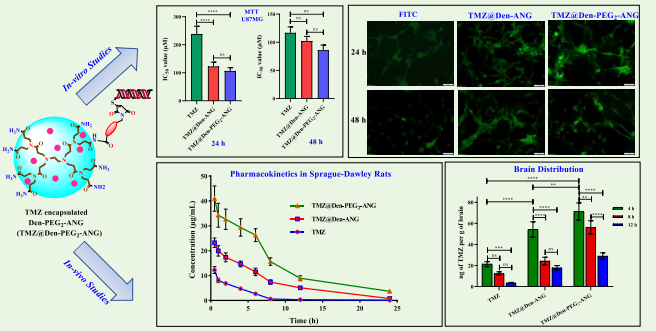
ABSTRACT: The present study was aimed to synthesize, characterize, and evaluate the angiopep-2 grafted PAMAM dendrimers (Den, G 3.0 NH_2) with and without PEGylation for the targeted and better delivery approach of temozolomide (TMZ) for the management of glioblastoma multiforme (GBM). Den-ANG and Den-PEG_2-ANG conjugates were synthesized and characterized by ^{1}H NMR spectroscopy. The PEGylated (TMZ@Den-PEG_2-ANG) and non-PEGylated (TMZ@Den-ANG) drug loaded formulations were prepared and characterized for particle size, zeta potential, entrapment efficiency, and drug loading. An *in vitro* release study at physiological (pH 7.4) and acidic pH (pH 5.0) was performed. Preliminary toxicity studies were performed through hemolytic assay in human RBCs. MTT assay, cell uptake, and cell cycle analysis were performed to evaluate the *in vitro* efficacy against GBM cell lines (U87MG). Finally, the formulations were evaluated *in vivo* in a Sprague–Dawley rat model for pharmacokinetics and organ distribution analysis. The ^{1}H NMR spectra confirmed the conjugation of angiopep-2 to both PAMAM and PEGylated PAMAM dendrimers, as the characteristic chemical shifts were observed in the range of 2.1 to 3.9 ppm. AFM results revealed that the surface of Den-ANG and Den-PEG_2-ANG conjugates were rough. The particle size and zeta potential of TMZ@Den-ANG were observed to be 229.0 ± 17.8 nm and 9.06 ± 0.4 mV, respectively, whereas the same for TMZ@Den-PEG_2-ANG were found to be 249.6 ± 12.9 nm and 10.9 ± 0.6 mV, respectively. The entrapment efficiency of TMZ@Den-ANG and TMZ@Den-PEG_2-ANG were calculated to be 63.27 ± 5.1% and 71.48 ± 4.3%, respectively. Moreover, TMZ@Den-PEG_2-ANG showed a better drug release profile with a controlled and sustained pattern at PBS pH 5.0 than at pH 7.4. The *ex vivo* hemolytic study revealed that TMZ@Den-PEG_2-ANG was biocompatible in nature as it showed 2.78 ± 0.1% hemolysis compared to 4.12 ± 0.2% hemolysis displayed by TMZ@Den-ANG. The outcomes of the MTT assay inferred that TMZ@Den-PEG_2-ANG possessed maximum cytotoxic effects against U87MG cells with IC_{50} values of 106.62 ± 11.43 μM (24 h) and 85.90 ± 9.12 μM (48 h). In the case of TMZ@Den-PEG_2-ANG, the IC_{50} values were reduced by 2.23-fold (24 h) and 1.36-fold (48 h) in comparison to pure TMZ. The cytotoxicity findings were further confirmed by significantly higher cellular uptake of TMZ@Den-PEG_2-ANG. Cell cycle analysis of the formulations suggested that the PEGylated formulation halts the cell cycle at G2/M phase with S-phase inhibition. In the *in vivo* studies, the half-life ($t_{1/2}$) values of TMZ@Den-ANG and TMZ@Den-PEG_2-ANG were enhanced by 2.22 and 2.76 times, respectively, than the pure TMZ. After 4 h of administration, the brain uptake values of TMZ@Den-ANG and TMZ@Den-PEG_2-ANG were found to be 2.55 and 3.35 times, respectively, higher than that of pure TMZ. The outcomes of various *in vitro* and *ex vivo* experiments promoted the use of PEGylated nanocarriers for the management of GBM. Angiopep-2 grafted PEGylated PAMAM dendrimers can be potential and promising drug carriers for the targeted delivery of antiglioma drugs directly to the brain.



KEYWORDS: *PAMAM, temozolomide, angiopep-2, glioblastoma, PEGylation, in vivo*

1. INTRODUCTION

Glioblastoma multiforme (GBM) is the most abundant type of all primary brain tumors of the central nervous system.[1] Based on the profoundness of the disease, glial tumors are classified from grade I (benign) to IV (highly malignant). The benign tumors usually progress into malignant GBM.[2] The primary grade tumors exhibit high infiltrative evolvement characteristics, with the glial tissues traveling apart from the central into the nearby normal brain tissues. Hence, higher-grade glial

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Sialic Acid Engineered Prodrug Nanoparticles for Codelivery of Bortezomib and Selenium in Tumor Bearing Mice

Sarita Rani, Rakesh K Sahoo, Ashutosh Mahale, Kanan Panchal, Akash Chaurasiya, Onkar Kulkarni, Kaushik Kuche, Sanyog Jain, Kartik T. Nakhate, Ajazuddin, and Umesh Gupta*

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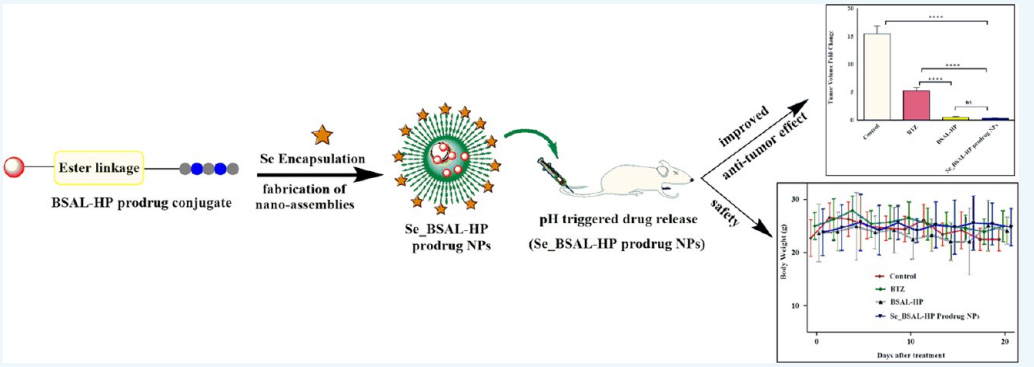

ABSTRACT: Most cancer patients rarely benefit from monodrug therapy because of both cancer complexity and tumor environment. One of the main reasons for this failure is insufficient accumulation of the optimal dose at the tumorous site. Our investigation implies a promising strategy to engineer prodrug nanoparticles (NPs) of bortezomib (BTZ) and selenium (Se) using sialic acid (SAL) as a ligand to improve breast cancer therapy. BTZ was conjugated with SAL and HPMA (*N*-2-hydroxypropyl methacrylamide) to prepare a prodrug conjugate; BTZ-SAL-HPMA (BSAL-HP) and then fabricated into prodrug NPs with Se (Se_BSAL-HP prodrug NPs). The self-assembly of prodrug NPs functionalized with Se showed size (204.13 ± 0.02 nm) and zeta potential (−31.0 ± 0.11 mV) in dynamic light scattering (DLS) experiments and spherical shape in TEM and SEM analysis. Good stability and low pH drug release profile were characterized by Se_BSAL-HP prodrug NPs. The tumor-selective boronate-ester-based prodrug NPs of BTZ in combination with Se endowed a synergistic effect against cancer cells. Compared to prodrug conjugate, Se_BSAL-HP prodrug NPs exhibited higher cell cytotoxicity and enhanced cellular internalization with significant changes in mitochondria membrane potential (MMP). Elevated apoptosis was observed in the (G2/M) phase of the cell cycle for Se_BSAL-HP prodrug NPs (2.7-fold) higher than BTZ. *In vivo* studies were performed on Sprague−Dawley rats and resulted in positive trends. The increased therapeutic activity of Se_BSAL-HP prodrug NPs inhibited primary tumor growth and showed 43.05 fold decrease in tumor volume than the control in 4T1 tumor bearing mice. The surprising and remarkable outcomes for Se_BSAL-HP prodrug NPs were probably due to the ROS triggering effect of boronate ester and selenium given together.

1. INTRODUCTION

Breast cancer is a global health concern among women accounting for almost one-third of three major types of cancers (lung, breast, and colorectal).[1] It is a highly complex type of cancer with five major subtypes; out of those estrogen receptor (ER) type is a highly aggressive subtype accounting for more than 80% of breast cancer cases. The standard drugs used for breast cancer treatment are anthracycline-, taxane-, and platinum-based derivatives as a single agent or in combination. Unfortunately, metastasis, drug resistance, and chronic toxicity of existing medications have become new paradigms and hurdles. Therefore, the search for novel drug candidates as single or combination is a need for urgent attention.

Targeted nanotherapeutics showed a steep increase in cancer therapeutics with the ability to improve solubility, pharmacokinetics, and release of drug selectively at the targeted site. Enormous progress in nanomedicine is still addressing certain challenges which point out the need to amalgamate the prodrug approach with NPs.[2] Prodrug NPs leveraged the strength of the drug delivery platform by releasing active molecules on demand, avoiding premature loss of drug, improving drug circulation time, and reducing toxicity.[3] Esterification is the most common

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