Nanotechnology Based Drug Delivery Systems for Ovarian Cancer

Chandni Sawlani[1], Pooja Sharma[2]

[1]Assistant Professor, Department of CS & IT, Kalinga University, Raipur, India.
[2]Research Scholar, Department of CS & IT, Kalinga University, Raipur, India.

Drug resistance continues to be a barrier to successful chemotherapy for ovarian cancer. A potential delivery strategy for circumventing drug resistance and locating a combination of strong medications has been developed by nanoparticulate drug delivery. Using solvent evaporation techniques, we developed albendazole & Paclitaxel dual drug loaded D-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS)-soluplus folic acid conjugated nanomicelles. First, we used molecular docking and molecular dynamics simulation study to establish the anticancer potential of ABZ. Albendazole binding affinity towards VEGFR-2 was checked by molecular docking and dynamics study, which revealed a potent binding energy ΔG = -7.12 kcal/mol, inhibitory concentration (Ki) = 6.04 µM, and as a positive control comparison with standard drug (42Q1170A) showed ΔG = -12.35 kcal/mol and Ki = 881 µM. The binding energy is significantly high for greater stability of the complex. Therefore, the current work suggests the role of Albendazole as a potent angiogenesis inhibitor as ascertained by its potential interaction with VEGFR-2.

Keywords: Nano technology, drug delivery system, Health.

1. Introduction

Because more people are using oral contraceptives, there has been a decrease in the incidence of ovarian cancer diagnoses in recent years [1]. among 2018, more than 240,000 women received an ovarian cancer diagnosis, making it the sixth most frequent malignancy among women globally [4]. Ovarian cancer is the second most prevalent cancer worldwide, especially in industrialised nations, after breast cancer, which is the most common type of cancer in women over 40 [3]. As mentioned earlier, the most deadly kind of gynecologic cancer is ovarian cancer, which also happens to be the tenth most frequent disease in women [5]. It is also the fifth most common cause of cancer-related deaths among females [7]. The survival and cure rates for ovarian cancer have not significantly changed over time, despite the fact that we now know more about the disease [6]. This is a result of the disease's ongoing difficulty with early diagnosis [9]. This is caused, in part, by unclear screening tools not being available and by symptoms and indicators that might be misleading and "masquerade" as other illnesses that are not malignant [2]. Approximately 22,000 new cases of ovarian cancer are found in the

US each year, and 14,000 women pass away from the disease directly [8]. The encapsulation efficiency can be calculated by dividing the amount of drug loading by the theoretical feed [10]. Because it helps determine medicine or active medicinal component intake (API), this statistic is important [13]. The dose is determined using this parameter [15]. High-pressure liquid chromatography (HPLC), an efficient drug analysis technique, is widely used to evaluate both of these attributes.

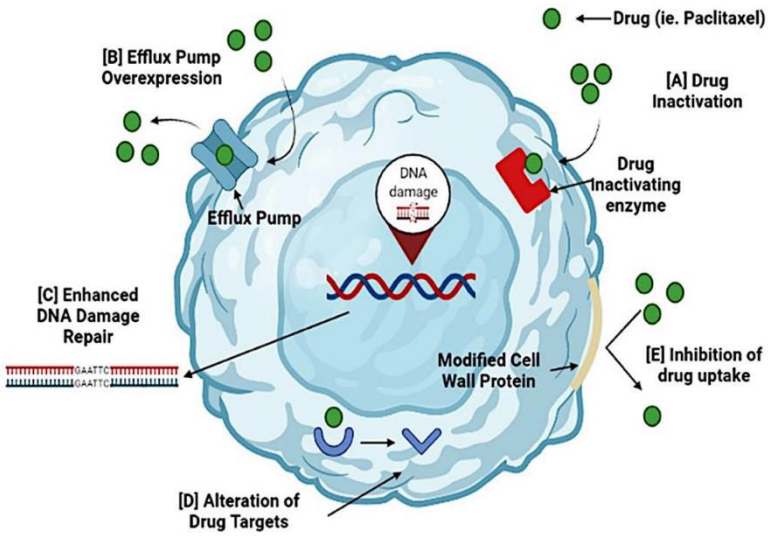

Figure 1: Entry and movement of nano-enabled anticancer drugs in a ovarian cancer cell.

Despite significant advancements in research, issues including low drug loading and poor stability have hindered the creation of these better drug carriers, especially for hydrophilic medications. Notwithstanding these challenges, polymeric micelles have achieved notable advancements [11]. Despite this, the chemical flexibility provided by amphiphilic block co-polymers makes it possible to construct polymeric micelles that can overcome these difficulties [14]. Despite significant advancements in research, issues including low drug loading and poor stability have hindered the creation of these better drug carriers, especially for hydrophilic medications [12]. Notwithstanding these challenges, polymeric micelles have achieved notable advancements. Despite this, the chemical flexibility provided by amphiphilic block co-polymers makes it possible to construct polymeric micelles that can overcome these difficulties..

The rest of the paper is organized as follows: Section 2 provides the classification scheme for the survey; Section 3 provides an overview of proposed architecture. Section 4 provides a summary and comparison of the results of the various papers discussed in this taxonomy. Finally, Section 5 concludes the paper.

2. Literature Review

The evaluation of the literature includes a detailed analysis of drug delivery systems that use TPGS as a carrier for ovarian cancer as well as dual drug loading micelles for ovarian cancer

therapy. When compared to single drug loaded delivery systems, dual drug loaded delivery systems may show to be superior drug delivery systems since they can get beyond the drawbacks of convectional drug delivery systems.

Reference	Drug	Composition	Result
[4]	Paclitaxel	MPEG-SS-2SA and TPGS Polymeric mixed micelles	Potential carrier for anti-cancer drugs
[5]	Albendazole	Bovine serum albumin nanoparticles	Effective in tumor therapy
[6]	Doxorubicin and vinorelbine	DSPE-PEG-2000	Higher therapeutic efficiency in breast cancer treatment
[7]	Paclitaxel & doxorubicin	Immunomicelles decorated with CD147ab	Proved to be better line of treatment in various cancer cell lines
[8]	Paclitaxel and Gemcitabine	N-(2-hydroxypropyl)-methacrylamide (HPMA) copolymer with drug conjugation	HPMA copolymer was prove as a promising carrier for dual drug delivery
[9]	Curcumin and platinum	Triblock polycaprolactum (PCL) polymeric micelles	Dual drug loaded polymeric micelles shows good synergistic effect as compared to single loaded micelles
[10]	Paclitaxel & doxorubicin	TPGS & DTDPA contain linker disulfide bond	Synergistic anticancer efficacy & reduced systemic toxicity

3. Materials and Methods

A gift sample of Paclitaxel was supplied by Cipla Pvt Ltd, whereas a gift sample of albendazole was obtained from Sequent Pharma, Mumbai. Acetonitrile and water of HPLC grade were purchased from Merck Pharmaceuticals. Every substance used was of AR grade.

- Instrumentation

The analysis was conducted using a Shimadzu HPLC model prominence LC-2030C 3D system. A High-Performance Liquid Chromatography system with quaternary gradient pumps,

a variable wavelength PDI detector linked to a data recorder, and integrator software were used for method development and data processing.

- Preparation of Mobile phase:

500 cc of Milli-Q Water and 100 cc of TFA were dissolved in the 1000 mL measuring container to create mobile phase A (0.1% TFA + water). Milli-Q Water was used to make up the final volume, which was subsequently filtered and degassed using 0.45 µ membrane filter paper. Phase B mobile phase was acetonitrile.

Selection of drug and polymer

An anti-cancer medication called paclitaxel is used to treat different types of cancer. BCS class IV medication paclitaxel has poor permeability and solubility. Albendazole is usually used as an anti-helminthic medication, however studies have shown that it also acts through the depolymerization of microtubules. Using molecular docking, it is found that ABZ has a binding affinity for VEGF receptor, which is crucial for the development of new blood vessels. Because it is overexpressed in a lot of cancers, the folate receptor (FR) is a known biomarker for tumour cells. Additionally, Pgp efflux of pharmaceuticals is inhibited by vitamin E (TPGS), which promotes drug accumulation within cells. A solubilizing compound called Soluplus aids in the creation of micelles. Micelles of PTX and ABZ combined with soluplus and TPGS-Fol have never been made before. Therefore, these particular drug and polymer combinations were chosen in order to prepare polymeric micelles.

3.1 Characterization of Albendazole and Paclitaxel

- FCMC determination

Using the UV technique, the critical micelle concentration of TPGS was determined. To prepare a standard KI/I2 solution, precisely weighed 1 gramme of iodine and 2 grammes of potassium iodide were dissolved in 100 millilitres of distilled water, following the previously described procedure. For the purpose of determining the CMC, samples with varying concentrations of polymer solution (from 0.001% to 0.1%), each containing precisely 25 µl of iodine solution, were created. All of the samples were stored in the dark for 12 hours before to analysis. Using a UV spectrophotometer, the absorbance of various polymer solution concentrations was determined at 366 nm. By displaying the graph of absorbance vs. log of polymer mass concentration, the CMC value of micelles was determined.

- Molecular docking

The purpose of this work is to investigate the binding characteristics of the 3VHE protein by means of geometrically optimised compounds such as standard 42Q and ABZ. Proteins were screened for missing sidechain residues using the open Molecular Mechanics (MM) simulation tool (https://openmm.org/) before to use in molecular interaction investigations. Investigations on molecular docking were conducted using Autodock v4.2.6.

- Molecular dynamics simulation

Using Schrödinger's Desmond software Vs 2020.1, MD simulations of docked complexes of ABZ and 42Q with protein were carried out (PDB ID: 3VHE). Triplicate sampling was carried out under the same conditions for every MD run in order to obtain more accurate results. The

force field of OPLS-2005.

4. Results and Discussions

The time and financial savings associated with drug repurposing make it a very viable substitute for the conventional approach to anticancer drug research and development. Albendazole is a benzimidazole carbamate that has been used for a long time to treat parasitic worms in both humans and animals. It is generally used as an anti-helmintic medication, but it has also been used as an anti-cancer medication in recent times. By inhibiting VEGFR-2, ABZ stops angiogenesis. The development of new blood vessels, or angiogenesis, is what causes tumours to grow. The well-known anti-cancer medication paclitaxel is used to treat a variety of cancers. There has also been reports of albedazole action in paclitaxel-resistant cells. Its low water solubility and cytotoxicity are still thought to be significant obstacles to creating formulations that would effectively treat the condition. Enhancing antitumor efficaciousness is one of vitamin E TPGS's important roles. It also blocks the Pgp channel, which prevents drug efflux. Patients with ovarian cancer have overexpressed folate receptors. Therefore, folic acid can increase micelles' targeted efficacy. Developing targeted polymeric mixed micelles with ABZ-PTX codelivery to increase therapeutic potential was the main goal of this effort. Moreover, the target and synergistic effect of polymeric mixed micelles were improved by the concurrent administration of TPGS-Fol and ABZ-PTX.

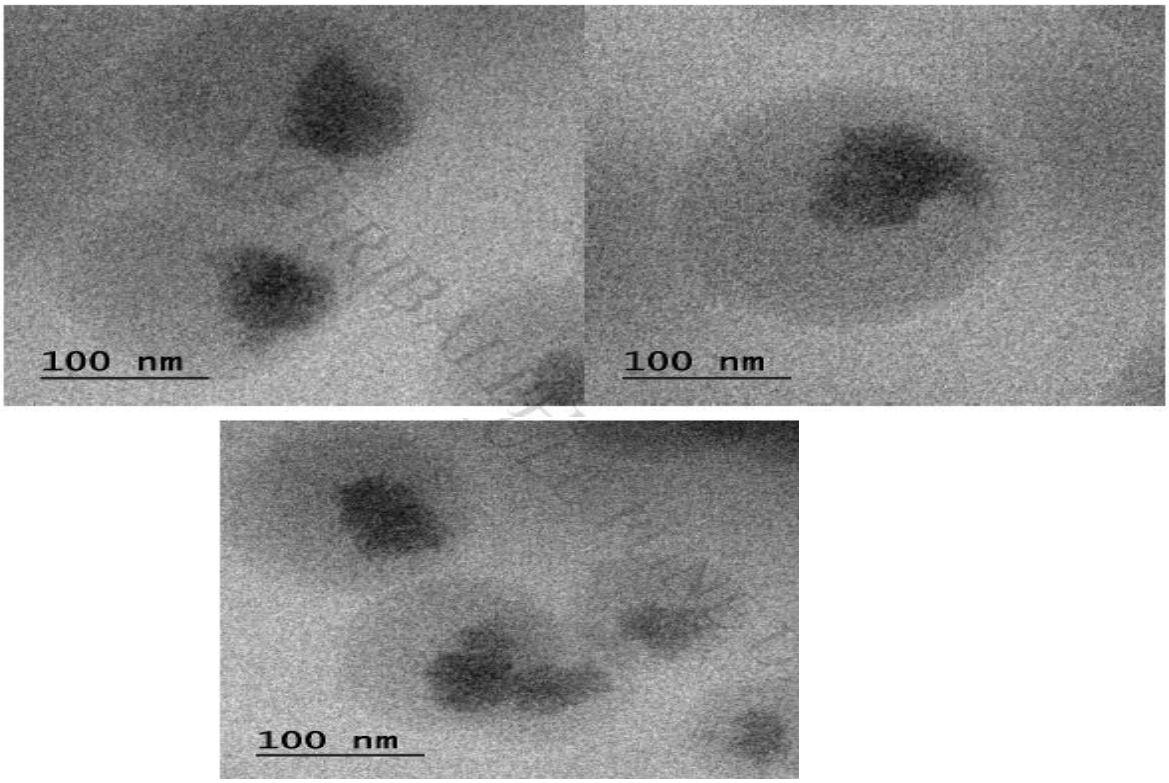

Figure 2: TEM of APSTFM

Using TEM, the surface morphology of the final optimised formulation of APSTFM was studied. The micelles' morphology from TEM images revealed a homogeneous, smooth surface area and spherical shape (fig 2).

5. Conclusion

The goal of the study was to strengthen PTX and ABZ's combined therapeutic efficacy while also stabilising ABZ's anticancer potential. The ABZ is a good candidate for an anticancer drug, as demonstrated by simulation research and molecular docking. Additionally, TPGS-Fol-soluplus polymeric mixed micelles loaded with ABZ PTX were effectively synthesised and characterised. The superior entrapment efficiency and target specificity of the ABZ-PTX-Soluplus-TPGS-Fol micellar system allowed it to outperform traditional polymeric micelles. The synthesised soluplus & TPGS-FOL conjugated polymeric micelles loaded with PTX and ABZ showed reduced size, strong encapsulation, increased stability at dilution, prolonged release, and biocompatibility. The MTT experiment and research on animals verified the formed micelles' higher cytotoxicity. The investigation concluded that PTX and ABZ distribution was aided by the nanosystem TPGS-SOL-FA polymeric mixed micelles. There is room for more research on the whole release profile in animals as well as acute and long-term toxicity assessments.

References

1. Li, Shiding, Liangbo Chen, and Yao Fu. "Nanotechnology-based ocular drug delivery systems: recent advances and future prospects." Journal of Nanobiotechnology 21, no. 1 (2023): 232.
2. Wen, Ming Ming, Noha S. El-Salamouni, Wessam M. El-Refaie, Heba A. Hazzah, Mai M. Ali, Giovanni Tosi, Ragwa M. Farid, Maria J. Blanco-Prieto, Nashiru Billa, and Amira S. Hanafy. "Nanotechnology-based drug delivery systems for Alzheimer's disease management: Technical, industrial, and clinical challenges." Journal of controlled release 245 (2017): 95-107.
3. Ramakrishnan, J., Ravi Sankar, G., & Thavamani, K. (2019). Publication Growth and Research in India on Lung Cancer Literature: A Bibliometric Study. Indian Journal of Information Sources and Services, 9(S1), 44–47.
4. Dos Santos Ramos, Matheus Aparecido, Patrícia Bento Da Silva, Larissa Spósito, Luciani Gaspar De Toledo, Bruna Vidal Bonifacio, Camila Fernanda Rodero, Karen Cristina Dos Santos, Marlus Chorilli, and Tais Maria Bauab. "Nanotechnology-based drug delivery systems for control of microbial biofilms: a review." International journal of nanomedicine (2018): 1179-1213.
5. Bhatia, Saurabh, and Saurabh Bhatia. "Nanotechnology and its drug delivery applications." Natural Polymer Drug Delivery Systems: Nanoparticles, Plants, and Algae (2016): 1-32.
6. Alamer, L., Alqahtani, I. M., & Shadadi, E. (2023). Intelligent Health Risk and Disease Prediction Using Optimized Naive Bayes Classifier. Journal of Internet Services and Information Security, 13(1), 01-10.
7. Calixto, Giovana Maria Fioramonti, Jéssica Bernegossi, Laura Marise De Freitas, Carla Raquel Fontana, and Marlus Chorilli. "Nanotechnology-based drug delivery systems for photodynamic therapy of cancer: a review." Molecules 21, no. 3 (2016): 342.

8. Luo, Ming-Xin, Shan Hua, and Qi-Yun Shang. "Application of nanotechnology in drug delivery systems for respiratory diseases." Molecular Medicine Reports 23, no. 5 (2021): 1-17.
9. George, Reny, et al. "Some existential fixed point results in metric spaces equipped with a Graph and it's application." Results in Nonlinear Analysis 7.1 (2024): 122-141.
10. Ramana, R.H.V., & Ravisankar, V. (2024). Precision in Prostate Cancer Diagnosis: A Comprehensive Study on Neural Networks. Journal of Wireless Mobile Networks, Ubiquitous Computing, and Dependable Applications (JoWUA), 15(2), 109-122. https://doi.org/10.58346/JOWUA.2024.I2.008
11. Sahu, Tarun, Yashwant Kumar Ratre, Sushma Chauhan, L. V. K. S. Bhaskar, Maya P. Nair, and Henu Kumar Verma. "Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science." Journal of Drug Delivery Science and Technology 63 (2021): 102487.
12. Saeedi, Majid, Masoumeh Eslamifar, Khadijeh Khezri, and Solmaz Maleki Dizaj. "Applications of nanotechnology in drug delivery to the central nervous system." Biomedicine & pharmacotherapy 111 (2019): 666-675
13. Bobir, A.O., Askariy, M., Otabek, Y.Y., Nodir, R.K., Rakhima, A., Zukhra, Z.Y., Sherzod, A.A. (2024). Utilizing Deep Learning and the Internet of Things to Monitor the Health of Aquatic Ecosystems to Conserve Biodiversity. Natural and Engineering Sciences, 9(1), 72-83.
14. Oroojalian, Fatemeh, Fahimeh Charbgoo, Maryam Hashemi, Amir Amani, Rezvan Yazdian-Robati, Ahad Mokhtarzadeh, Mohammad Ramezani, and Michael R. Hamblin. "Recent advances in nanotechnology-based drug delivery systems for the kidney." Journal of controlled release 321 (2020): 442-462.
15. Ho, Benjamin N., Claire M. Pfeffer, and Amareshwar TK Singh. "Update on nanotechnology-based drug delivery systems in cancer treatment." Anticancer research 37, no. 11 (2017): 5975-5981.
16. Jahangirian, Hossein, Ensieh Ghasemian Lemraski, Thomas J. Webster, Roshanak Rafiee-Moghaddam, and Yadollah Abdollahi. "A review of drug delivery systems based on nanotechnology and green chemistry: green nanomedicine." International journal of nanomedicine (2017): 2957-2978.