Nanoparticle – Based Drug Delivery for Stomach Cancer

Supriya Kumari., Ritik Nishad., Ritikesh., Mohd. Moinuddin., Deepak Verma

Department of Biotechnology, Kanpur Institute of Technology, Kanpur, 208001, India

***Corresponding Author**

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ABSTRACT

Stomach cancer, or gastric cancer, continues to be a major global health challenge, largely because it is often detected late and responds poorly to standard treatments. Traditional therapies like chemotherapy and radiotherapy frequently struggle with issues such as high toxicity, low drug solubility, and the development of multidrug resistance. In recent years, nanoparticle-based drug delivery systems have emerged as a promising way to overcome these barriers. By designing nanoparticles that can carry drugs directly to the tumour, researchers are able to achieve better targeting, controlled drug release, and enhanced drug accumulation at the cancer site through the enhanced permeability and retention (EPR) effect. When nanoparticles are further modified with specific ligands, they can actively recognize tumour markers, improving, treatment precision while reducing harm to healthy tissues. Innovations in polymeric nanoparticles, liposomes, dendrimers, metallic nanoparticles, and nano-micelles have significantly improved drug stability, bioavailability, and overall patient comfort. As this review highlights, the integration of nanotechnology into gastric cancer therapy represents an exciting step toward personalized medicine and may open the door to more effective clinical treatments in the future.

Keywords: Stomach cancer, gastric cancer, nanoparticle-based drug delivery, targeted therapy, Nano medicine, controlled release, EPR effect, chemotherapy

INTRODUCTION

Gastric cancer (GC), commonly known as stomach cancer, remains a serious global health issue and continues to rank among the leading causes of cancer-related deaths. Despite improvements in diagnostic tools and treatment options, the outlook for many patients is still poor. This is largely because the disease is often detected at an advanced stage, shows significant tumour heterogeneity, and frequently develops multidrug resistance (MDR) to standard chemotherapy drugs (Zou et al., 2025). Conventional treatments-including surgery, chemotherapy, and radiotherapy-are further limited by non-specific drug distribution, high systemic toxicity, and low overall therapeutic efficiency. Nanotechnology has therefore emerged as a promising way to overcome these challenges. Nanoparticle-based drug delivery systems (Nano-DDS) offer unique advantages such as improved drug solubility, longer circulation time in the bloodstream, and targeted accumulation at the tumour site through the enhanced permeability and retention (EPR) effect. When nanoparticles are functionalized with specific ligands or antibodies, they can actively recognize tumour-associated markers, achieving more precise targeting. These systems can also be engineered to provide controlled or stimuli-responsive drug release, which helps maximize treatment effectiveness while reducing harmful side effects. A wide range of nanoparticles—including liposomes, polymeric nanoparticles, metallic nanoparticles, dendrimers, and biomimetic carriers—are currently being explored for their potential in GC therapy. Recent research not only shows improvements in conventional chemotherapy but also demonstrates possibilities for combining nanoparticle systems with gene therapy, immunotherapy, and imaging-guided treatments. While the transition to clinical use remains challenging, these advancements indicate that Nano-DDS could significantly transform personalized treatment for gastric cancer in the future.

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Classes Of Nanoparticles in Stomach Cancer Therapy

Nanoparticle-based drug delivery systems include a wide variety of materials, each offering unique structural and functional benefits for treating gastric cancer. These carriers help improve the solubility and stability of therapeutic agents, enhance targeted delivery, minimize systemic toxicity, and allow for controlled or sustained drug release. The major classes of nanoparticles studied for GC treatment include the following:

Lipid-Based Nanoparticles

This group includes liposomes, Solid Lipid Nanoparticles (SLNs), and Nanostructured Lipid Carriers (NLCs). Lipid-based nanoparticles are highly versatile and biocompatible, making them suitable for delivering both water-soluble and poorly soluble drugs. Liposomes, for example, have been used to deliver chemotherapeutic agents such as doxorubicin and paclitaxel, increasing drug accumulation in tumour tissues through both passive and active targeting approaches (Zou et al., 2025).

Polymeric Nanoparticles

Made from natural or synthetic polymers such as PLGA, chitosan, and PEG, polymeric nanoparticles provide controlled and sustained drug release. Their surfaces can be easily modified with targeting molecules—like folic acid or antibodies—to direct the nanoparticles specifically to gastric cancer cells. Chitosan-based nanoparticles, for instance, have been investigated for co-delivering 5-fluorouracil and siRNA, helping to overcome multidrug resistance (Liu et al., 2023).

Metallic and Inorganic Nanoparticles

Metal-based nanoparticles, including gold, silver, selenium, and iron oxide, have gained attention due to their unique physical and optical properties. They can be used not only for therapy but also for diagnosis, making them powerful theranostic tools. Selenium nanoparticles have shown promising anticancer effects by inducing apoptosis in gastric cancer cells through the PI3K/Akt/mTOR pathway (Liu et al., 2023). Gold nanoparticles, meanwhile, are being studied as radiosensitizers and targeted drug carriers.

Dendrimers

Dendrimers are highly branched, tree-like molecules with numerous surface sites for attaching drugs, imaging agents, or targeting ligands. Their precise structure allows efficient drug loading and controlled release. In gastric cancer models, dendrimers have been shown to improve the solubility and bioavailability of drugs that typically dissolve poorly (Zhang et al., 2022).

Protein and Peptide-Based Nanoparticles:

Nanoparticles made from natural proteins—such as albumin—are particularly attractive because they are biocompatible and can naturally target tumors. Albumin-bound paclitaxel formulations, for example, take advantage of albumin receptors on cancer cells to improve drug uptake. Additionally, peptide-modified nanoparticles are being explored to enhance penetration into dense gastric tumour tissues.

Biomimetic and Cell-Derived Nanoparticles

Biomimetic systems such as exosomes and cell membrane-coated nanoparticles have become an emerging area of interest. These carriers can evade immune detection and imitate natural biological processes. Tumour cell membrane-coated nanoparticles, in particular, show promise for gastric cancer therapy by improving tumour-specific targeting while reducing immune clearance (Zou et al., 2025).

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Stages Of Stomach Cancer

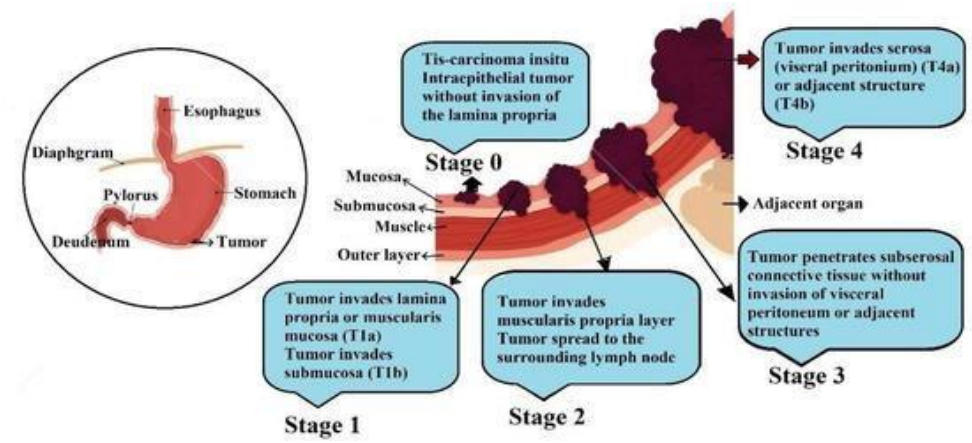

Figure 1. The stages of stomach cancer, from the earliest stage to the most advanced. It explains how deeply the tumor grows into the layers of the stomach and nearby areas.(Umme Hani ,et al 2022)

Stage 0 (Carcinoma in situ): The tumour is only on the surface of the inner lining of the stomach (mucosa). It has not invaded deeper layers. Not any lymph nodes involved in it. It is highly curable stage for the stomach cancer

Stage 1: Early stage Cancer

Stage 1A – cancer spread to mucosa to submucosa Lining but then no lymph nodes involved to it.

Stage 1B- Tumour spread slightly deeper into submucosa or muscular layer. It spread to 1-2 nearly lymph nodes.

Stage 2: The tumour reaches the muscular wall of the stomach (muscularis). At this stage, it may also spread to 1-6 nearby lymph nodes.

Stage 3: The tumour grows further and penetrates the tissue under the stomach's outer covering (subserosa), it spread to more than 7 lymph nodes , or includes the all nearby organ like liver , spleen, pancreas.

But till this stage Cancer can cure with different therapy, treatment or combination therapy.

Intensive Treatment – chemotherapy , surgery, combination therapy (surgery- chemo – radiation)

Stage 4: The cancer becomes advanced it spread the all distant organs , not it have no chance to cure it is the last stage where death happened.

Mechanisms Of Stomach Cancer Treatment Using Nanoparticles

Nanoparticle-based drug delivery systems (Nano-DDS) enhance the therapeutic efficacy of anticancer agents by altering their pharmacokinetics, biodistribution, and cellular interactions. In Gastric Cancer (GC), nanoparticles improve drug targeting, overcome resistance, and enable multimodal therapy.

Enhanced Permeability and Retention (EPR) Effect – Passive Targeting:

It is a biological effect that allow nanoparticles and macromocular drugs to accumulate more in tumour tissue than normal tissue. Cancer grows very fast and require new blood vessels , they formed abnormal , leaky vessel have a large gaps between endothelial cells. Allow nanoparticles (usually 10-200 nm) to easily pass through into the tumour cells . Retention – Nanoparticles stay longer in the tumour .

Importance – Reduce systemic toxicity (less damage to healthy tissue). Improve the effectiveness of chemotherapy and gene therapy .

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Active Targeting via Surface Functionalization:

It attached to the specific ligand that binds selectively to receptors present on the target cells . Nanoparticles attached to the ligand, ligand recognise the binding site to the specific receptor on the target cells. Nanoparticles accumulate at the target cells (stomach cells). Drug enter to the cells released inside the High therapeutic effects.(Lu,X., et al 2020)

Receptor which frequently used in it EGFR receptor –

Epidermal growth factor receptor found on the surface of skin Cells, gastrointestinal Cells.

It is cell surface receptors that control the growth, division, repair to the tissue.

Working mechanism –

Ligand bind with epidermal growth factor receptor (EGFR). EGFR dimerizes (2 receptor come together for binding). Tyrosine kinase domain become active for controlling the cancer cells.

HER2 -

Human Epidermal growth factor receptor 2, It is a Receptor tyrosine kinase. It does not have no known natural ligand. It is always in a ready to activate confirmation, making it very powerful in signaling. Over expression of HER2 (15-20%) causes aggressive tumour growth.

Ph- Responsive Drugs Delivery:

pH-responsive drug delivery systems are engineered to release their therapeutic drug, when they encounter a specific pH environment. Because many pathological sites (tumours, inflamed tissue, endosomes/lysosomes) and particular body compartments (stomach, tumour extracellular space, end lysosomal vesicles) have pH values different from normal blood (≈7.4), pH-sensitive carriers enable site-selective release, improving efficacy and reducing systemic toxicity. pH-responsive nanoparticles are designed using smart materials—such as pH-sensitive polymers, acid-cleavable linkers, or proton-reactive groups—that stay stable in the body's normal physiological pH but change their structure in acidic environments. While circulating in the bloodstream, these nanoparticles remain intact, preventing any early or unwanted drug release. However, once they reach the acidic surroundings of a tumour, the polymer chains become protonated or the acidsensitive bonds (such as hydrazone, Schiff-base, acetal, or cis-aconitic linkages) begin to break. This triggers the nanoparticle to swell, degrade, or fall apart, leading to a rapid and targeted release of the anticancer drug directly at the tumour site. After entering cancer cells through endocytosis, the even lower pH inside endosomes accelerates drug release further. This multi-stage, pHtriggered process helps concentrate the drug within the tumour, enhances treatment effectiveness, and minimizes damage to healthy tissues.. (Parodi, et al 2021)

Combination Therapy and Theragnostics

Nanoparticles also offer the advantage of delivering more than one type of therapy at the same time—for example, combining chemotherapy with gene therapy, or pairing a drug with a photothermal agent to strengthen the overall treatment effect. Certain metallic nanoparticles, such as gold and iron oxide, can act as imaging contrast agents as well, making it possible to diagnose and treat the tumour simultaneously, a concept known as theranostics. For instance, gold nanoparticles have been used as radiosensitizers in gastric cancer models, improving the impact of radiotherapy while also enabling clearer tumour imaging. (Varzandeh M, sabouri et al. 2021)

Global Data of Different Cases of Stomach Cancer:

The number of new stomach cancer cases has increased over the past 30 year – from about 980,899 cases in 1990 to 1.23 millions cases in 2021. Total number of cases grown up, the rate of stomach cancer per 100,000 people decreased from 24.76 in 1990 to 14.33 in 2021. (Zhou, et al 2025)

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Table 1 Regional distribution of newly diagnosed stomach cancer cases: (Inoue, M. 2024)

S. No.	Region	Number Cases Of	Total Percentage
1.	Eastern Asia	520,975	53.8%
2.	South central Asia	109,794	11.3%
3.	Eastern Europe	66,400	6.9%
4.	South America	55,313	5.7%
5.	South-eastern Asia	38,700(approx.)	4.0%
6.	Southern Europe	31,000(approx.)	3.2%
7.	Northern America	30,000(approx.)	3.1%

According to the global cancer data from 2022, stomach cancer in India had about 64,611 new cases in 2022, placed India among the top three countries by total stomach cancer cases- Number of cases in male(approx.) ~ 43,060, Number of cases in female (approx.) ~ 21,551.

There are different state where stomach cancer has higher rate of cases-

Table 2. Stomach cancer cases in India:(shanker N, et al 2021)

State	Observation	Sources
Aizawl district, Mizoram	Highest recorded gastric cancer incidence in men age adjusted rate 269.4 per 1000,000	Risk linked to the regional diet and lifestyle.
Papumpare district, Arunachal Pradesh	Incidence in women age adjusted rate 27.1 per 100,000 for stomach cancer	Based on regional cancer registry
Manipur	Gastric cancer is among the common cancer, it is the 2nd most common among males 6.1%, female 2%	Hospital based cancer registry 2012
Meghalaya	Highest overall cancer rates, stomach cancer contributes significantly	North-eastern lifestyle but consistent trends

Challenges

Nanoparticle-based drug delivery systems (Nano-DDS) hold great potential for improving stomach cancer therapy, several major challenges still limit their widespread clinical adoption. One of the key concerns is toxicity and biocompatibility. Some metallic or inorganic nanoparticles can accumulate in healthy organs, and their long-term clearance from the body remains uncertain. They may also trigger immune responses or display unpredictable biodistribution, leading to unwanted side effects. Another critical issue involves biological and physiological delivery barriers. The gastric environment is highly acidic and rich in digestive enzymes, (parodi, A. et al. 2021), while the thick mucosal layer can degrade or alter nanoparticles, particularly when they are administered orally. Moreover, the tumour microenvironment itself is complex and heterogeneous - variations in blood vessel density, interstitial pressure, and tissue architecture can limit deep nanoparticle penetration and reduce treatment uniformity. Maintaining nanoparticle stability and achieving controlled drug release present additional difficulties. Problems such as premature drug leakage, nanoparticle aggregation in the bloodstream, opsonization, and rapid clearance by the mononuclear phagocyte system can significantly decrease therapeutic efficacy. On an industrial level, largescale manufacturing and regulatory challenges also persist. Achieving precise control over nanoparticle size, surface chemistry, and drug-loading capacity is essential for reproducibility and safety, but these requirements make mass production complex and costly. Ensuring high

targeting specificity remains another obstacle. Selecting ligands that bind selectively to gastric tumour markers while avoiding healthy tissues is crucial, yet balancing ligand density without provoking immune detection or altering pharmacokinetics is difficult. Furthermore, issues such as MultiDrug Resistance (MDR) and tumour heterogeneity continue to hinder progress. Gastric tumours can develop multiple resistance mechanisms, and genetic variations among patients make it challenging to design a universal Nano-DDS. These challenges highlight the need for continued research, optimization, and clinical validation before nanoparticle-based systems can become fully established in gastric cancer therapy.

Future Aspects

Nanoparticle-based drug delivery systems hold great promise for transforming stomach cancer treatment. Future research is expected to focus on developing smarter and more precise nanoparticles that can target tumour cells with greater accuracy. Scientists are exploring multifunctional nanoparticles capable of detecting, treating, and monitoring tumours simultaneously, which could significantly enhance early diagnosis and enable more personalized therapy. Another exciting direction involves stimuli-responsive systems that release their drug cargo only under specific tumour conditions - such as low pH, high enzyme activity, or unique redox environments. These “smart” systems could minimize side effects and improve treatment outcomes. Moreover, integrating nanotechnology with immunotherapy and gene therapy may open new possibilities for patients who do not respond well to traditional treatments, offering a more comprehensive and adaptive therapeutic strategy.

CONCLUSION

Nanoparticle-based drug delivery represents a powerful and innovative approach to overcoming many of the limitations associated with conventional stomach cancer therapies. By improving drug targeting, enhancing cellular uptake, and reducing systemic toxicity, Nano-DDS have the potential to make treatments more effective and less harmful. While challenges such as patient variability, long-term safety, and high production costs still remain, ongoing progress in nanotechnology and biomedical engineering offers strong hope for the future. With continued research and clinical validation, nanoparticle-based therapies may soon become a standard and more effective option for managing gastric cancer.

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