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THE ROLE POLYMERIC NANOPARTICLES IN CANCER CHEMOTHERAPY: A NARRATIVE SYNTHESIS OF THE EVIDENCE

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ABSTRACT: Chemotherapy is a familiar treatment technique that uses chemical drugs to kill cancer cells. This technique affects normal healthy tissues because it is unspecific and has toxic side effects. Now a days, nano technology application in chemotherapy have helped to solve uncontrolled problems of drug delivery and other side effects. Nanoparticles (NPs) can provide outstanding advantages over conventional drug delivery by having excellent properties such as controlled mode of action, different methods administration, and the ability to transport organic and inorganic molecules. Special ligands attached to polymeric NPs target the tumour site because of their chemical affinity to the malignant tissues. This article reviews the characterization, fabrication and application of NPs used in cancer chemotherapy. Moreover, different forms of polymeric chemotherapy was explored and analysed to better understand the effects of nano particles on cancer chemotherapy.

INTRODUCTION: After cardiovascular diseases, cancer will be the largest killing disease in the upcoming years. Therefore, effective steps are required to stop this huge threat to human life. Development of chemotherapy technique that uses NP drugs can offer significant advantages [1, 2]. Researchers are focusing on improving the characteristics of cancer chemotherapeutic agents (CTX) using NPs and reducing their side effects on cancer chemotherapy. This review article describes the developments of polymeric NP (PNP) applications used in cancer chemotherapy.

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Cancer kills 1 in 6 of its patients and will kill more than 27000 people worldwide per day. Because of the continuous increase in population, cancer patients are increasing, and treatment of cancer is too expensive [3, 5]. Cancer causes around 70% of deaths in low- and middle-income countries, but this could be related to poorer access to health care rather than risk factors [6, 7].

Chemotherapy is the main treatment for cancer that involves drugs with high toxicity. Many factors are involved in determining effective chemotherapy including, the types of drugs, dosage form, pharmacokinetics, resistance, and toxicity [8]. Conventional chemotherapy drugs show two effects, the cytocidal that interferes with cell division by killing the cancer cells, or cytostatic effect by reducing their replication. The drugs do not differentiate between normal and malignant cells and therefore damage normal cells as well as

cancerous cells. They use CTX including synthetic chemicals and natural extracts in the treatment of metastatic cancer, but they cause high toxicity [9]. Most CTX are highly hydrophobic and require adjuvants, thus this may cause serious side effects. The sufficiently high concentrations of drugs for adequate time are essential to kill cancer cells, and the use of more effective anti-cancer drugs will be more toxic [10].

In conventional chemotherapy, drugs flood the whole body with poor pharmacokinetic properties. The CTX have different efficacy, possible side effects, and are still expensive because of their limited supply. The side effects of the anticancer drugs reduce effective chemotherapy and the quality of life of patients. Another problem with chemotherapy is that, with the time-lapse, cancer cells can develop drug resistance up to some extent, therefore high dosage is required to get excellent results [11].

Drug resistance is a problem in drug absorption, distribution, metabolism, and excretion at different physiological levels. Because of low concentration of drug in tumour pharmacokinetic resistance, active resistance for the few cells in a vulnerable state, and genetic resistance by cause of the biochemical resistance of the tumour cells to the CTX. There are some physiological drug barriers including the blood–brain barrier (BBB) for the central nervous system and the gastrointestinal barrier for oral chemotherapy [11, 13]. However, patients with advanced disease need combination therapy or newer treatment options since available chemotherapy is not effective [9]. NP drugs with different sizes (from a few tens to a few hundreds of nanometres), and specific structures and surface properties efficiently increase the targeting of diseased areas and specific destruction of the cancer cells with controlled and targeted drug delivery and can enhance treatment effectiveness with reduction in side effects [14].

Nanoparticles and Nanocarriers:

A New Frontier in Nanotechnology: NPs are usually small enough to administer systemically (intravenous) or locally (mucosal), to diffuse into cancer cells. They can carry drugs and have cytotoxic properties [15]. The properties of the CTX NPs can significantly change by their size, shape, surface charge and hydrophobicity. Moreover, biological factors affect their intravascular flow and organ accumulation. Particles smaller than the diameter of microcapillaries (200 nm) are used in therapeutics, diagnostics, and imaging. However, for cancer treatment, the optimal size is in the range of 20–50 nm.

The anticancer efficacy of the particles shows high ability to incorporate both hydrophilic and hydrophobic substances and improved diffusion in the tissues, high effective surface areas, compatibility with different administration routes, and long sedimentation [14, 16]. NPs properties depend on the size and morphology, zeta potential, drug loading, and surface functionality with ligands [17]. The NPs zeta potential affects their distribution and uptake. Cationic particles bind to negatively charged plasma proteins, that have shorter circulation time, and accumulate inside tumours [18].

The CTX attacks targeted cancer cells, which only kill tumour cells without adversely affecting healthy tissues. The ability of NPs is to specifically target tumour cells, depending on their type and formulation additives used, making them a useful delivery system, and advancing the drug-loaded ligand-conjugated nanocarriers [19, 20]. NPs play a passive role in tumours (as a target) rather than normal tissues because of their size limiting nonspecific leakage. Therefore, they are unable to exit the intravascular space in normal tissues, limiting their volume of distribution [21]. Moreover, NPs are active drugs or dissolved as drug agents, encapsulated, entrapped, particles are adsorbed physically, or chemically on the surface of NPs with more tumours targeted and activating cellular uptake [22]. Some NPs and biodegradable polymers (PNPs) include metal oxide particles, nanoclusters, carbon nanotubes, cytotoxic liposomes, biodegradable micelles; polymer/drug-protein conjugates, *etc*.

How Polymeric Chemotherapy can Revolutionize Cancer Treatment: Polymer-based NPs are usually natural polymers, and synthetic polymeric Conjugates discussed **Table 1** and **Fig. 1** Their advantages are good biocompatibility, high stability, and biodegradability, used for RNA delivery. In addition to their low production cost [29-31].

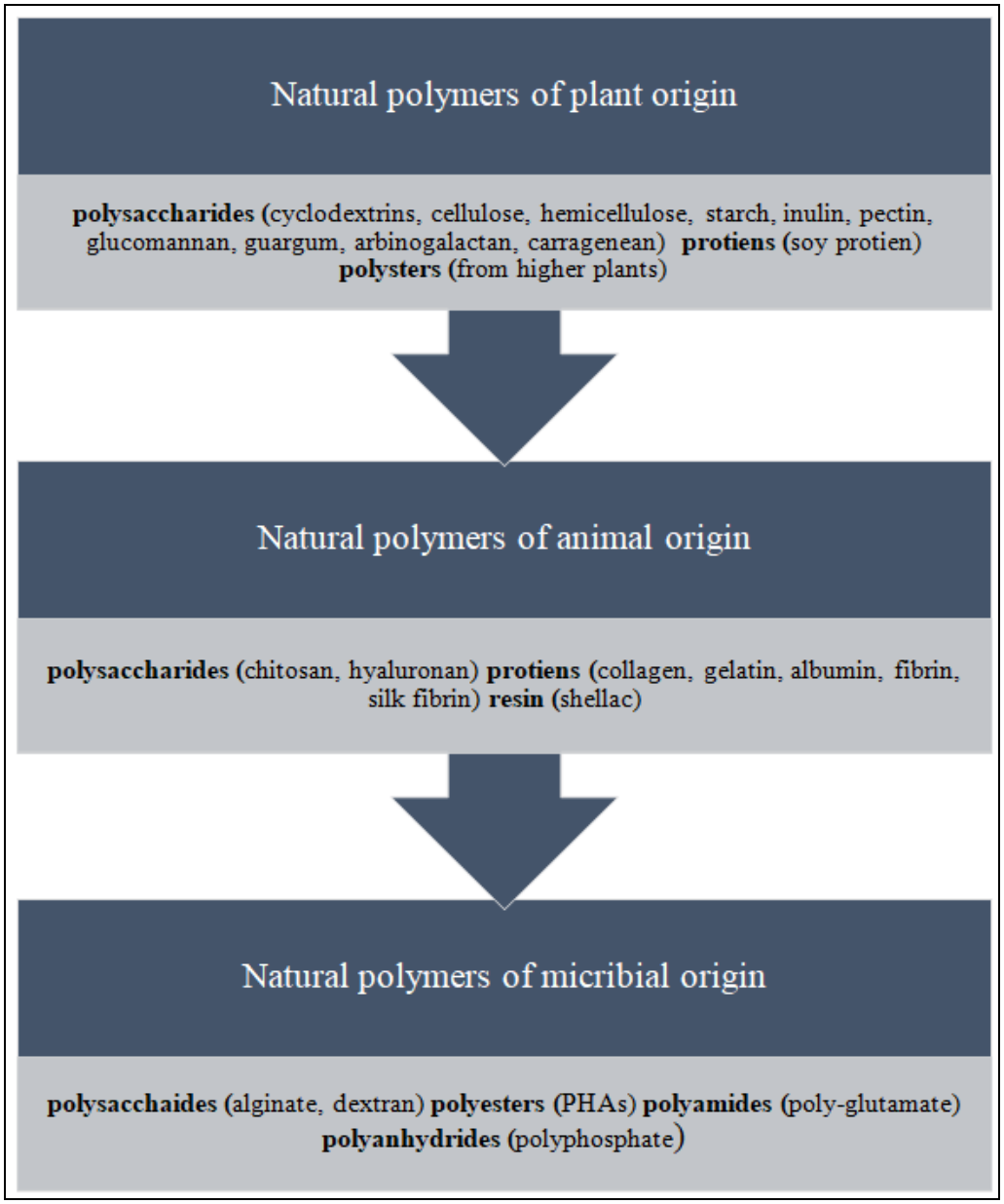

FIG. 1: BIODEGRADABLE NANOPARTICLES: A PROMISING VEHICLE FOR DRUG DELIVERY

The types of nano based biodegradable natural polymers [27, 28, 32]. That gives information about the natural polymers of plant origin, the natural polymers of animal origin, the natural polymers of microbial origin.

TABLE 1: BIODEGRADABLE POLYMERS AND SYNTHETIC MATERIALS: HOW THEY CAN ENHANCE DRUG DELIVERY IN CANCER THERAPY

Sl. no.	Synthetic polymers	Natural polymers
1	Polyglycolic acid (PGA)	Hyaluronic acid
2	Polylactic acid (PLA)	Haemoglobin
3	poly-l-lactic acid (PLLA), PGA-PLA	Alginate
4	Polycaprolactone (PCL)	Chitosan, is composed of N-acetyl-d-glucosamine
5	PGA- PCL	Dextran, Elastin
6	PLA-poly lactic acetone Pluronic's	Collagen blends
7	Nhyju7Polydioxanone (PDO)	d-glucosamine
8	Polyethylene glycol (PEG)	Fibrinogen, Fibrillar collagen
9	Polyethyleneimine (PEI)	Gelatine, Gelatine collagen
10	Polylactide-co-glycolide (PLGA)	Poly-l-lysine, consists of repeating units of lysine,
11	Polyvinyl alcohol (PVA),	Collagen

Additionally, exact core-shell nanostructures of cationic dendrimers, with properties such as inside epitaxy, surface adsorption, and chemical conjugation, represent the incorporation of drugs into polymers. Moreover, carbon nanotubes as nanohybrids with polymeric properties can be functionalized for delivery carriers of cancer therapeutics. The release of both hydrophilic and hydrophobic drugs over a long period is possible by using drug loaded PNP systems. This minimises the undesirable side effects within the body. Several methods can be used to synthesise biocompatible polymers with well-defined structures ranging from nanometres to micrometres.

TABLE 2: COMPARISON OF SOME ADVANTAGES AND DISADVANTAGES OF THE TECHNIQUES APPLIED FORMATION TO PNPS [23, 24]

Sl. no.	Methods	advantages	Disadvantages
1	NPs, obtained using colloidal mill	Production of well-characterized emulsions, uniform size, Easy to scale-up	High energy for the emulsification process
2	Emulsification, solvent evaporation	Possibility to encapsulate both hydrophilic and lipophilic drugs	Possible coalescence of the nanodroplets during the evaporation process
3	Emulsification, solvent diffusion	Possibility to control the size of the NPs, Easy to scale-up	High volumes of water to be eliminated Leakage of water-soluble drug into the saturated-aqueous external phase
4	Emulsification, reverse salting-out	Minimization of the stress to fragile drugs, High loading efficiency, Easy to scale-up	Possible incompatibility between the salts and the drugs. Purification is needed to remove electrolytes
5	Gelation of the emulsion droplets	Possibility to use natural macromolecules, hydrophilic and biocompatible	Limited to the encapsulation of hydrophilic drugs
6	Polymerization of alkyl cyanoacrylates	Easy method to obtaining core-shell tuned NPs, c and control the size of them by using surfactant	Possible reaction between the drug and CeVI in the case of radical emulsion polymerization Purification
7	Interfacial poly-condensation reactions	Low concentrations of surfactants, Modulation of the nano capsules thickness by varying the monomer concentration	Limited to the encapsulation of lipophilic drugs Purification
8	Nanoprecipitation of a polymer	High simplicity, fast and reproducible, Low concentrations of surfactants, Easy to scale-up	Low polymer concentration in the organic phase
9	Formation of polyelectrolyte complexes	Easy to achieve According to the nature of the polyelectrolyte used in advance, either positively or negatively charged NPs can be synthesized	The necessity to optimize the ratio between negatively and positively charged molecules
10	Formation of NPs from neutral nanogels	Organic solvent-free method Controlled release of the drug	Is not yet applicable to hydrophilic drugs
11	One step procedure based on ionic gelation	Organic solvent free method controls the release of a drug encapsulated in the NPs upon the action of a pH or an ion concentration variation stimulus	Possible particle disintegration due to the weakness of the ionic interactions
12	NPs, obtained using colloidal mill	Production of well-characterized emulsions, uniform size, Easy to scale-up	High energy for the emulsification process

The Promise and Pitfalls of Nano-Carrier in Cancer Therapy: For prevention, avoidance, and elimination of metastases, NP-based CTX is delivered to targeted tissues and cancer cells with a lower toxicity and higher efficacy. However, there are still toxicities, not yet fully explained [38]. Nano-carriers as a tool to deliver drugs, offer several advantages such as improving the solubility of hydrophobic drugs, maintaining their release, and prolonging their circulation time [39]. The properties of nano-carriers are ideal drug delivery methods, that include optimal physicochemical properties designed for superior drug loading, capable of effective Drug loading, biodegradable and biocompatible and sustained drug release between administration times [38]. The ideal nanoparticles (NPs) for drug delivery should possess appropriate physicochemical properties and exhibite biological activities such as absorption, distribution, and metabolism [10, 39]. Besides, these have the possibility to deliver into cells, enhancing permeability and retention effect of penetration through the endothelium of inflamed tissues [28, 40].

Nanocarriers administered in the treatment of drug-resistant cancers, have been designed based on polymer micelles, dendrimers, surface-modified PNPs, polymer nano capsules, polymer-modified liposomes, polymer-modified silica, gold nanoparticles and grapheme [19, 20].

Controlled delivery and release mechanism provide an effective dose to the targeted site and avoid normal cells and tissues [27]. Additionally, NPs are antibody-functionalized quantum dots, gold nano shells with silica cores, inorganic ceramic-layered double hydroxide (LDH) and drug-loaded gold. The polymeric form of pulmonary drugs with poor solubility used in inhalers, nebulizers, and dry powder inhalers makes drug delivery in cancer treatment less toxic [41-44]. Nano-sized drug carriers increase the half-life of an active dose by protecting it and avoiding its interaction with normal tissues [45]. Cancer-specific ligands, therapeutic genes (small interfering RNA, or sRNA), and optical imaging agents are hybrid nanostructures, created by combining magnetic NPs with other Nanoprecipitation discussed in **Fig. 2.**

They offer controlled sizes and the ability to be controlled remotely, biocompatibility and provide less toxic drug delivery methods [46-49].

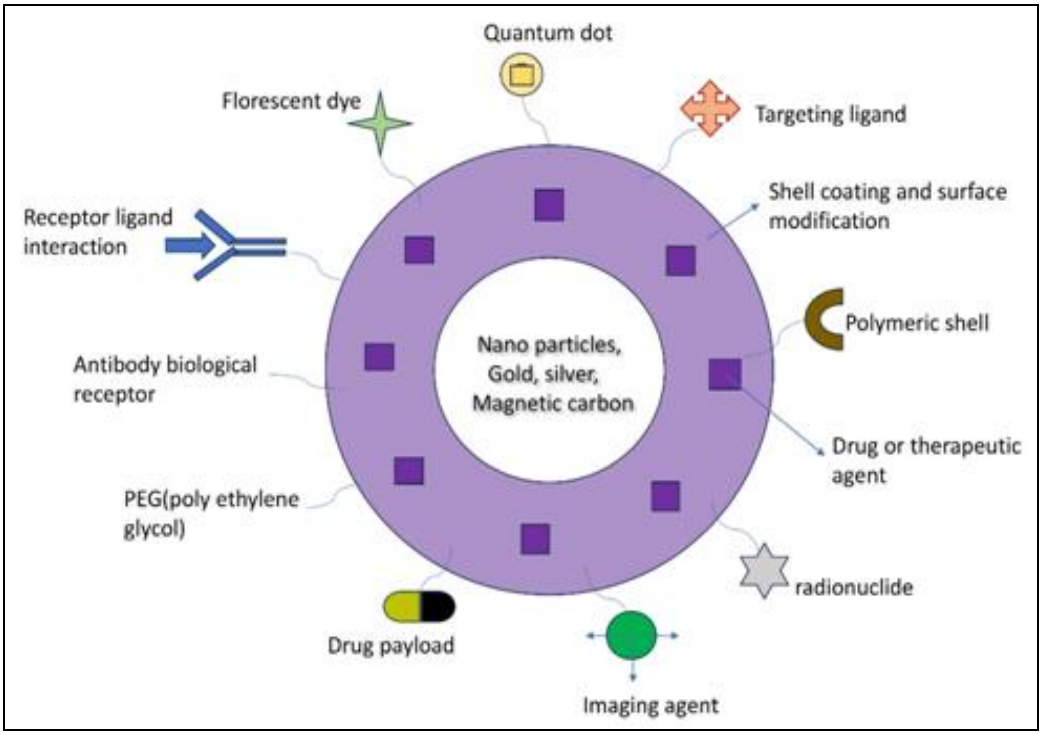

FIG. 2: NANO-CARRIERS AS DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT

How Nanoparticles Enhance Chemotherapy Outcomes: NPs properties are related to shape, size, and molecular structure, surface charge, surface (PEGylation) or other coating, and targeting ligand [28, 50]. Use of NPs has the following advantages (1 to 7) over conventional CTX methods.

1. Unique surface coating on NPs (have large surface area to mass ratio) allowing them to evade from macrophage uptake and thus half-life increases [14, 51].
2. Small size NPs have larger surface area that also increases their efficiency. Small size particles flow easily in the circulatory system [14, 16].
3. Smaller particles easily enter the cell membrane and can also easily penetrate targeted organelle in the body [14, 16].
4. For brain cancer treatment, to improve brain delivery across the BBB nanocarriers have the potential to enhance the beneficial effects of drugs and to reduce their side effects [52].
5. Bioavailability of medicated oligonucleotides truly diminished due to their quick corruption by chemicals, exonucleases, and endonucleases

after intratumoral infusion. These types of drugs must be typified in NPs, giving them much more steadiness until they strike their target [21].

6. NPs can be changed into target-indicated particles by applying a few uncommon ligands on their surface **Fig. 2**. Hence, anticipating misfortune to neighbouring ordinary cells [21].

7. Overexpression of P-glycoprotein (P-gp) in cell layer (P-gp), which causes drug resistance. NPs can be coated with a few modern polymers to solve this issue [9, 53].

With the time-lapse, cancer cells can create drug resistance up to a few degrees; thus, a high dosage is required to achieve fabulous results.

Fabrication: In planning of NPs, the characteristic or engineered materials were chosen based on measure, charge, biocompatibility, drug discharge, and debasement rate of polymers [10, 30]. There are two techniques to manufacture NP-based multifunctional nano structures. The primary is atomic functionalization, comprising of connection of counter acting agent, proteins, and colours to the NPs. The second is an integration with other utilitarian nano-components, such as Quantum dots specks (QDs) or metallic NPs to display a few highlights and provide more than one work at the same. Their primary strategies for planning of PNPs incorporate the scattering of preformed polymers or ionic gelation, concentration of hydrophilic polymers, monomers polymerization, supercritical liquid innovation, dissolvable relocation, evaporation/extraction, and nano-precipitation **Table 2**. To realise the extraordinary properties of PNPs depending on a few variables, such as molecule measure, their dissemination, and range of application [40, 55-59].

Polymeric Nanoparticles: A Novel Method For Developing Nano Particles With Enhanced Properties And Functions: The optimization of the properties of PNPs, counting Nanospheres and nano capsules, progresses drug-loading effectiveness and draw out sedate discharge. Depending on the application, planning strategy, the nature of polymer-drug intelligent, as well as the polymer chain and their physico-chemical characteristics [10, 39].

Drug Delivery Patterns: The delivery of CTX (a chemotherapy drug) to target cancer tissue using NPs (nanoparticles) can occur through either passive or ligand-based targeting. In passive targeting, NPs exploit the enhanced permeability and retention effect to accumulate in tumour tissues. Ligand-based targeting involves attaching specific ligands to NPs, allowing them to actively recognize and bind to cancer cells. However, several barriers must be overcome for effective drug delivery within cancer cells.

Barriers to NP Delivery:

Capillary Walls: NPs must cross capillary walls to reach tumour tissues.

Extracellular Space: NPs need to diffuse through the extracellular space to access intra-cellular targets.

Cell Membrane: To bridge the cancer cell membrane, NPs must reach the right intra-cellular targets.

Ligand-mediated Active Targeting:

Molecule Shape and Size: The shape, size, and density of ligands play a crucial role in active tumour targeting.

Ligand Density Optimization: The ligand Presented on NPs should optimize density to block recognition sites effectively.

Surface Coating and Bio adhesive Materials: Coating NPs with appropriate bio adhesive materials and emulsifiers can reduce systemic toxicity and enhance therapeutic efficacy. Different coating surfaces involve various groups of polymers.

Combating Drug-Resistant Cancers: NPs can deliver anticancer drugs and siRNAs to halt gene resistance, reduce drug efflux pumps, and activate apoptosis pathways in cancer cells, especially in solid tumours.

Drug Release and Bio-activity: After encapsulation, it's essential to ensure that drugs released from NPs maintain their original structure and bio activity. NPs hold promise for targeted drug delivery, overcoming drug resistance, and improving cancer therapy outcomes. Their unique

properties, combined with ligated-mediated strategies, offer exciting possibilities for personalized medicine and effective cancer treatment. Critical components of ligand-mediated dynamic tumour-targeting treatment methodology are molecule shape and size, type, and density of ligands. The effect of the attached ligand orientation, which blocks the recognition sites, requires density optimization. The NPs surface is coated with suitable bio adhesive materials, and the emulsifier if loaded with CTX can significantly reduce systemic toxicity and increase therapeutic efficacy against drug-resistant cancers and by their rapid clearance by lymphatic drainage. Different coating surfaces of polymer resulted discussed in **Fig. 3.**

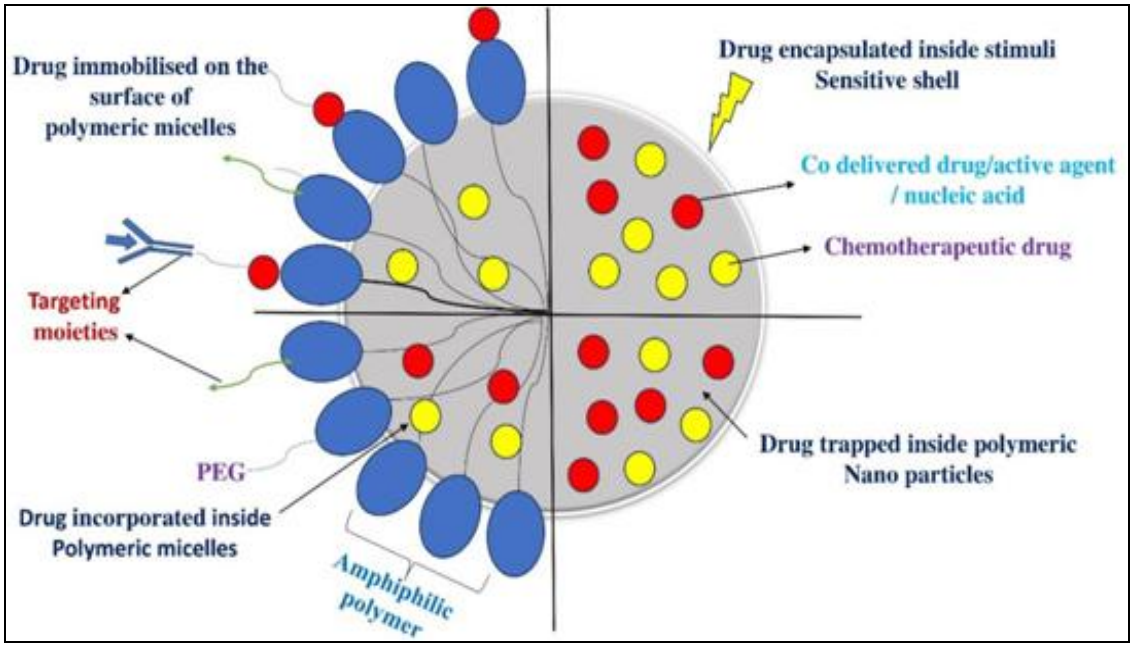

FIG. 3: DELIVERY PATTERN OF POLYMERIC NANO PARTICLES

CONCLUSION: NPs and different shapes of polymeric materials being utilized in cancer chemotherapy have significant advantages compared to the conventional drugs in terms of controlled mode of action, diverse administration methods to the tumour site, both organic and inorganic drug delivery.

Conventional methods did not reach a sufficient concentration of drugs at the target sites of cancer. NPs have shown their ability to control particles, target malignant tissues, control the release of drugs, and minimize the uptake of the drug by normal cells. Besides, they may improve the treatment effectiveness of chemotherapy drugs and reduce their toxic effects. The best polymer to achieve a efficient design of drug-loaded NPs depends on their physicochemical properties. The use of PNPs showed potential, which facilitates targeting of cancer cells.

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