

Polymeric Nanoparticles for cancer treatment:

Introduction

After cardiovascular diseases, cancer will be the largest killing disease in the upcoming years. Therefore, effective steps are required to stop this enormous threat to human life. Developments of chemotherapy technique that uses NPs drugs can offer significant advantages. Researchers are focusing to improve the properties of chemotherapeutic agents (CTX) using NPs and decrease their side effects on cancer chemotherapy. This review article describes the developments of polymeric NPs (PNPs) applications used in cancer chemotherapy. Cancer kills 1 in 6 of its patients and will kill more than 27000 people around the world per day. Because of continuous increase in population, cancer patients are increasing and treatment of cancer is too expensive.

Cancer cause of about 70% of deaths in low- and middle-income countries, but this might be related to poorer access to health care rather than risk factors.

Chemotherapy is the main treatment for cancer that involved treatments with high toxicity. Many factors are involved in determining successful chemotherapy including, the drugs types, dosage, form, pharmacokinetics, resistance and toxicity. Traditional chemotherapy drugs indicate two effects, the cytotoxic that interfere with cell division by killing the cancer cells, or cytostatic effect through decreasing their replication. The therapeutics discriminate between normal and malignant cells and therefore damage normal cells as well as malignant cells. It uses CTX including synthetic chemicals and natural extracts in the treatment of metastatic cancer but they cause high toxicity. Most CTX are highly hydrophobic and require adjuvants, thus this may cause severe side effects. The sufficiently high concentrations of drugs for enough time is necessary to kill cancer cells, and the usage of more effective anti-cancer drugs will be more toxic.

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

Drug resistance is a problem in drug adsorption, distribution, metabolism, and excretion at various physiological levels. Because of low concentration of drug in tumour pharmacokinetic resistance, kinetic resistance for the few cells in a susceptible 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 nerve system and the gastrointestinal barrier for oral chemotherapy. However, patients with advanced disease need combination therapy or newer treatment options because available chemotherapy is not effective.

NPs drugs with diverse sizes (from a few tenths to a few hundreds of nanometres), and a specific architectures and surface properties efficiently increase the target diseased areas and selective destruction of the cancer cells with controlled and targeted drug delivery and can enhance treatment efficacy with reduction in side effects.

We aimed to develop NPs applications in cancer chemotherapy. It also provides some background information about drug nanocarriers, fabrication, and characterization of PNPs cancer chemotherapy.

Methods

We performed a search for published manuscripts about nanotechnology applications on the cancer therapy. We collected data from research papers, on PubMed, and Google Scholar.

Results and Discussion

Different forms of polymeric chemotherapy were also explored and discussed to understand better the effects of NPs on cancer chemotherapy.

Characteristics of NPs and Nanocarriers

NPs are typically small to administer systemically (intravenous) or local (mucosal), to diffuse into cancer cells. They can carry drugs, and cytotoxic properties. The properties of the CTX NPs can significantly change by their size, shapes, surface charge and hydrophobicity. Furthermore, biological formation on their intravascular flow and organ accumulation. Particles size smaller than the width 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 show high ability to incorporate both hydrophilic and hydrophobic substances and improved diffusing in the tissues, high effective surface areas, compatibility with different administration routes, and long sedimentation.

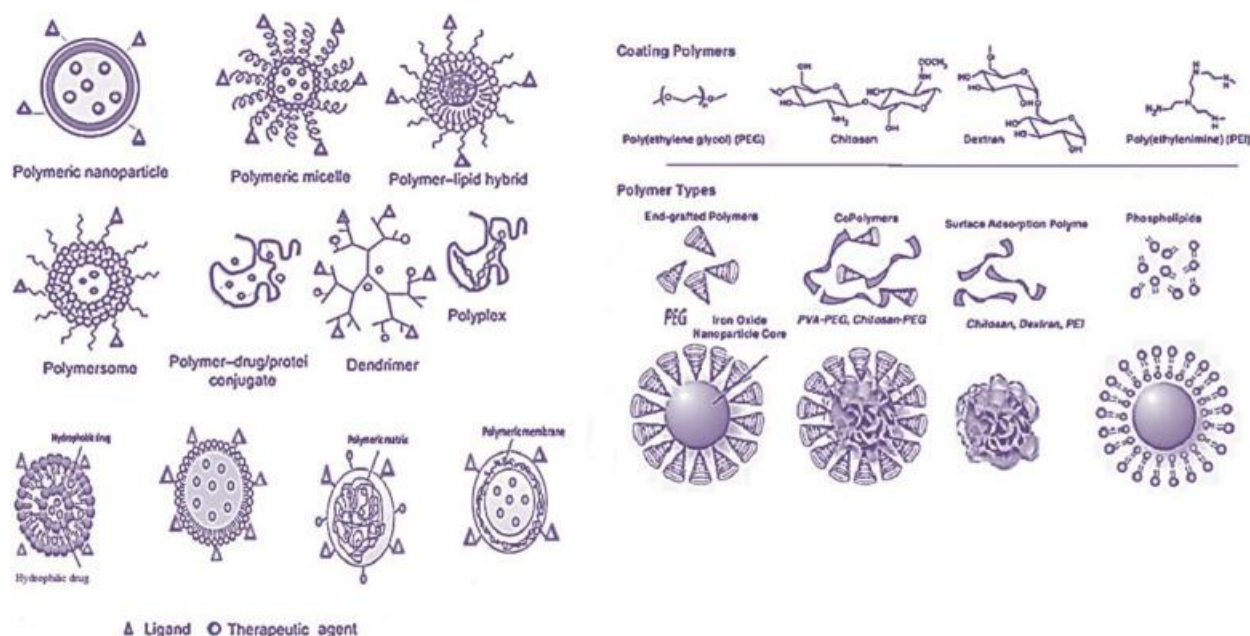
NPs properties were depending on the size and morphology, zeta potential, drug loading, and surface functionality with ligands. The NPs zeta potential affects their distribution and up-take. Cationic particles bound to negatively charged plasma proteins, that have shorter circulation time, insufficiently accumulate within tumors.

The CTX attacks targeted cancer cells, which only kill tumour cells without adversely affecting healthy tissues. The ability of NPs is specifically target tumour cells, depending on their type and formulation additives used, making them a useful delivery system, also improving the drug-loaded ligand-conjugated Nanocarriers.

NPs play a passive role in tumours (as a target) rather than normal tissues because of their size limiting nonspecific leakage. And so they are unable to exit the intravascular space in normal tissues, limiting their volume of distribution. Moreover, NPs is active drug or dissolved as drug agents, encapsulated, entangled, particles are adsorbed physically, or chemically on the surface of NPs with more tumours targeted and activating cellular uptake.

Some NPs and biodegradable polymers (PNPs) include metal oxide particles, nanoclusters, carbon nanotubes, cytotoxic liposomes, biodegradable micelles; polymer/drug-protein conjugates, etc. (Fig. 1).

Fig. 1:



Morphology of some biodegradable Nano polymers

Various biodegradable polymers have been approved with zero toxicity and good pharmacokinetics. However, there are undoubtedly toxicities

Polymeric chemotherapy

Polymer-based NPs are naturally derived polymers, and synthetic polymeric conjugates (Table 1 and 2). Their advantages are good biocompatibility, high stability, and biodegradability, used for RNA delivery (Fig. 2). In addition to their low production cost.

Table 1:

Biodegradable natural polymers and Synthetics usage for drug delivery in cancer therapy

Synthetics polymers

Polyglycolic acid (PGA)
 Polylactic acid (PLA)
 poly-l-lactic acid (PLLA), PGA-PLA
 Polycaprolactone (PCL)
 PGA- PCL
 PLA-poly lactic actone Pluronics
 Polydioxanone (PDO)

Natural or naturally derived polymers

Hyaluronic acid
 Heamoglobine
 Alginate
 Chitosan, is composed of N-acetyl-d-glucosamine
 Dextran, Elastin
 Collagen blends
 d-glucosamine

Synthetics polymers

polyethylene glycol (PEG)

Polyethyleneimine (PEI)

Polylactide-co-glycolide (PLGA)

Polyvinyl alcohol (PVA),

Natural or naturally derived polymers

Fibrinogen, Fibrillar collagen

Gelatin, Gelatin collagen

Poly-L-lysine, consists of repeating units of lysine, and atelo

Collagen

Table 2:

Comparison of some advantages and disadvantages of the techniques applied formation to *PNPs* (23,24)

<i>Method</i>	<i>Advantages</i>	<i>Disadvantages</i>
NPs, obtained using colloidal mill	Production of well-characterized emulsions, uniform size, Easy to scale-up	High energy for the emulsification process
Emulsification, solvent evaporation	Possibility to encapsulate both hydrophilic and lipophilic drugs	Possible coalescence of the nanodroplets during the evaporation process
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
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
Gelation of the emulsion droplets	Possibility to use natural macromolecules, hydrophilic and biocompatible	Limited to the encapsulation of hydrophilic drugs
Polymerization of alkylcyanoacrylates	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
Interfacial poly-condensation reactions	Low concentrations of surfactants, Modulation of the nanocapsules thickness by varying the monomer concentration	Limited to the encapsulation of lipophilic drugs Purification
Nanoprecipitation of a polymer	High simplicity, fast and reproducible, Low concentrations of surfactants, Easy to scale-up	Low polymer concentration in the organic phase
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

Method

Formation of NPs from neutral nanogels

One step procedure based on ionic gelation

Advantages

Organic solvent-free method
Controlled release of the drug

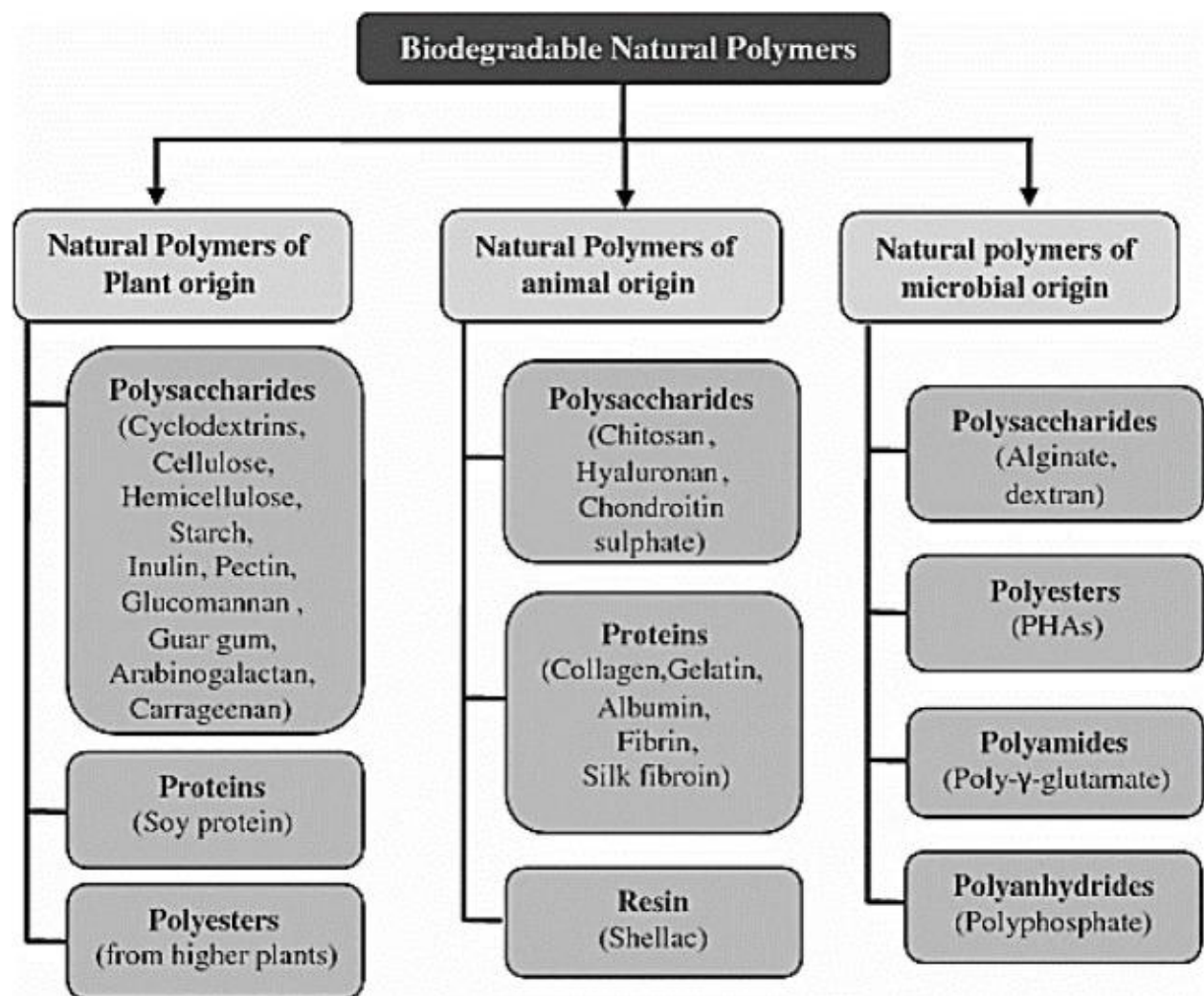
Organic solvent free method controls the release of a drug encapsulated in the NPs upon the action of a pH or an ion concentration variation stimulus

Disadvantages

Is not yet applicable to hydrophilic drugs

Possible particle disintegration due to the weakness of the ionic interactions

Fig. 2:



The types of Nano based biodegradable natural polymers

Moreover, precise core-shell nanostructures of cationic dendrimers, with properties such as interior encapsulation, surface adsorption, and chemical conjugation represent the incorporation of drug into polymer. Furthermore, Carbon nanotubes as nanohybrids with specific polymeric properties functionalize 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 minimizes the unwanted side effects in the body. Some techniques can be used to synthesize biocompatible polymers with well-defined nanometres to a few micrometres structures.

Opportunities and challenges of nanocarriers in cancer treatment

For treatment, prevention, and elimination of metastases, specific 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. Nanocarriers as tools to deliver drugs, offer several advantages such as enhancing the solubility of hydrophobic drugs, sustaining their release, and prolonging their circulation time.

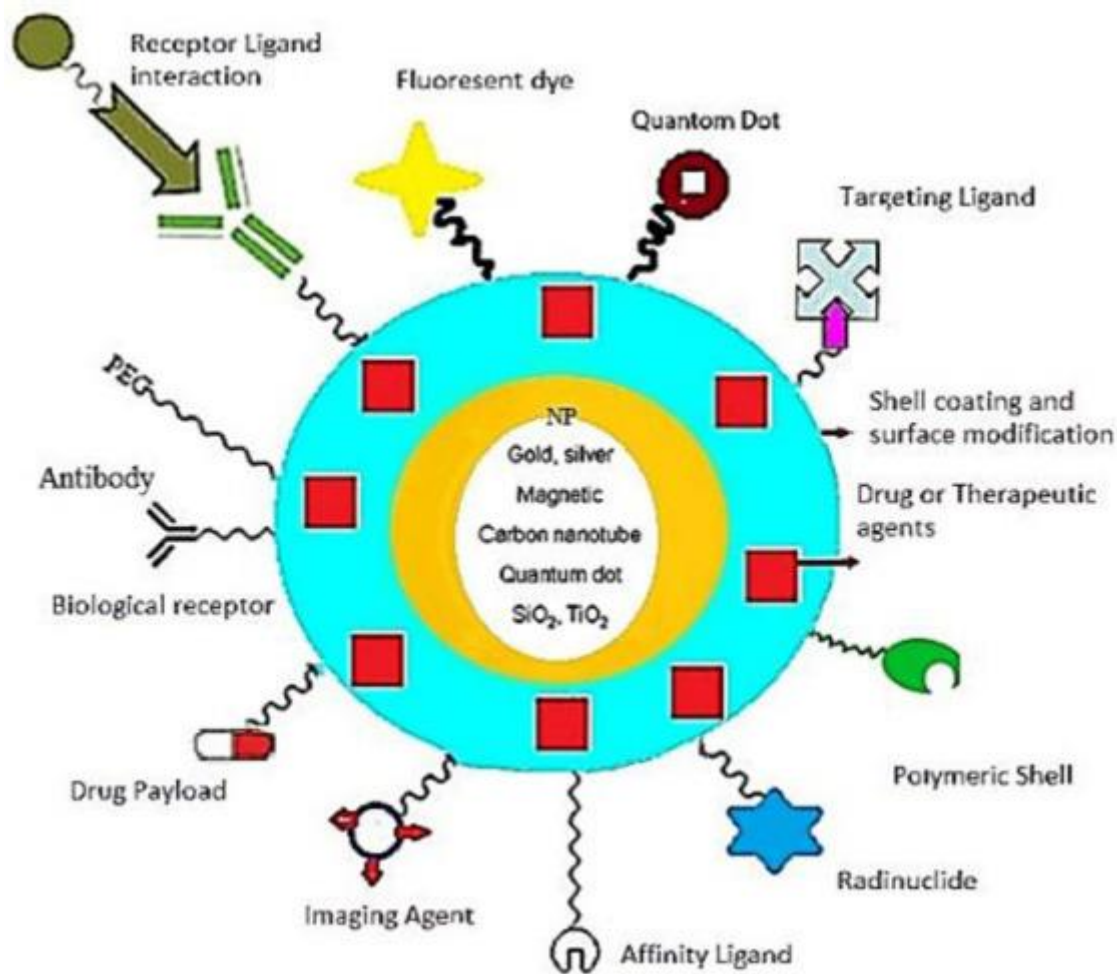
The properties of nanocarriers are ideal drug delivery ways, that include optimal physicochemical properties designed for superior drug loading, capable of effective homing, biodegradable and biocompatible; cost-effective, circulation half-life, and sustained drug release between administration times.

The ideal NPs should possess for drug delivery, physicochemical properties and biological activity such as absorption, distribution, and metabolism. Besides, these possess the possibility to deliver into cells, enhancing permeability and retention effect of passage through the endothelium of inflammatory tissues. Nanocarriers administrate in the treatment of drug-resistant cancers, have been designed based on polymer micelles, dendrimers, surface-modified PNPs, polymer nanocapsules, polymer-modified liposomes, polymer-modified silica, gold nanopolymers and Graphene. Control delivery and release mechanism provide an effective dose to the target site and avoids normal cells and tissues.

Further NPs are antibody-functionalized quantum dots, gold nanoshells 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 make drug delivery in cancer therapy less toxic. Nano size drug carriers increase the half-life of an active part by protecting it and avoid its interaction with normal tissues.

Cancer-specific ligands, therapeutic genes (small interfering RNA, or siRNA), and optical reporting dyes are hybrid nanostructures, made by combining magnetic NPs with other nanocomponents, ([Fig. 3](#)). They offer controlled sizes and the ability to be manipulated externally, biocompatibility and provide less toxic drug delivery ways.

Fig. 3:



The various type of multifunctional nanocarriers for cancer therapy include diagnostics, imaging, reporter molecules, humoral marker, targeting molecules, therapeutic radionuclide, CTX drugs delivery

Advantage of NPs usage in chemotherapy

NPs properties are related to shape, size, and particle material, surface charge, surface (PEGylation) or another coating, and targeting ligand.

Use of NPs have following advantages (A to H) over traditional CTX techniques.

- A. Special surface coating on NPs (have large surface area to mass ratio) allowing them to escape from macrophage uptake hence half-life increases.
- B. Small size NPs have larger surface area that also increases their efficiency. Small size particles easily flowing in the circulatory system.
- C. Smaller particles easily penetrate the cell membrane and can also easily penetrate targeted organelle in the body.
- D. For brain cancer treatment, to enhance brain delivery across the BBB nanocarriers have the potential to increase the therapeutic effects of drugs and to reduce their side effects.
- E. Bioavailability of drug oligonucleotides is seriously reduced due to their fast degradation by enzymes exonucleases, and endonucleases after intratumoral injection.

These types of drugs must be encapsulated in NPs, giving them much more stability until they strike their target.

- F. NPs can be changed in to target specified particles by applying some special ligands on their surface (Fig. 3). Thus preventing loss to neighbouring normal cells.
- G. Overexpression of P-glycoprotein (P-gp) in cell membrane (P-gp), which cause drug resistance. NPs can be coated with some new polymer to solve this problem.

With the time-lapse, cancer cells can develop drug resistance up to some extent; hence, high dosage is required to get excellent results.

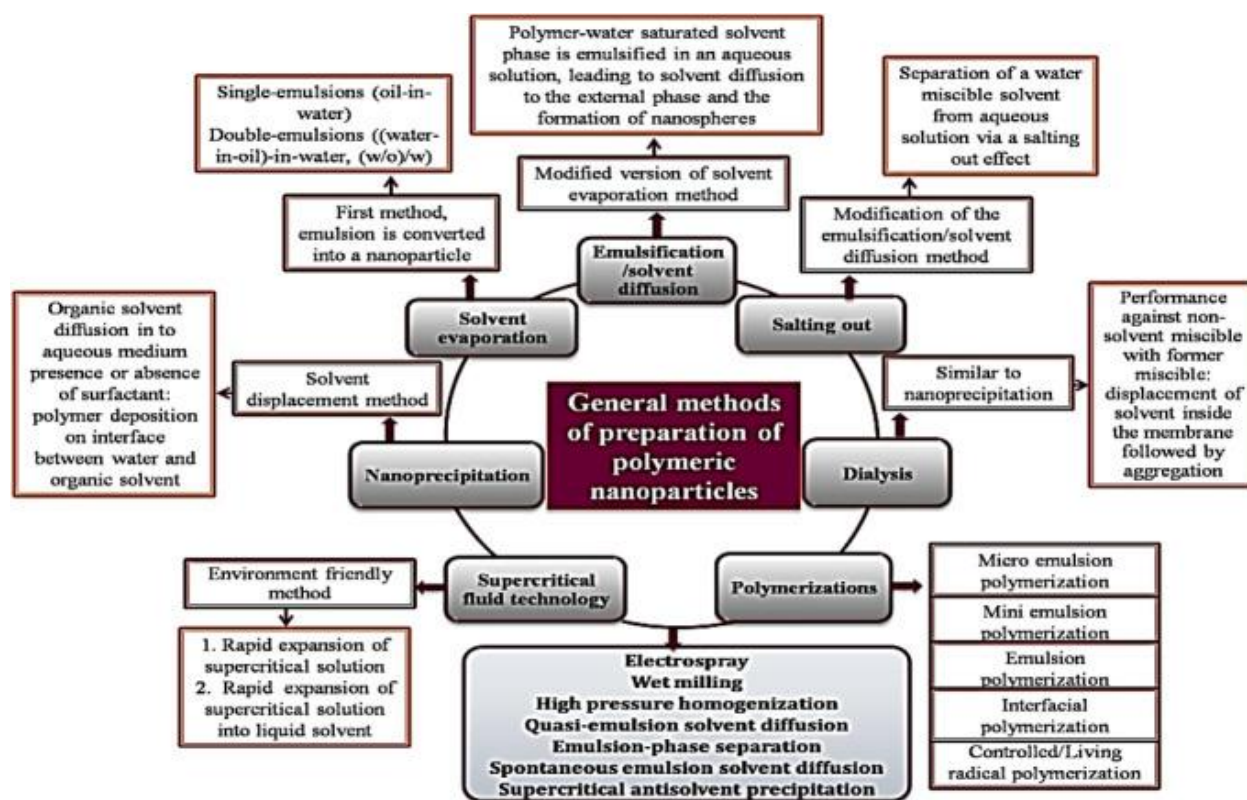
Fabrication

In designing of NPs, the natural or synthetic materials were selected based on size, charge, biocompatibility, drug release, and degradation rate of polymers.

There are two strategies to fabricate NP-based multifunctional nanostructures. The first is molecular functionalization, consisting of attachment of antibody, proteins, and dyes to the NPs. secondly, it is an integration with other functional nanocomponents, such as quantum dots (QDs) or metallic NPs to exhibit several features and deliver more than one function simultaneously.

Their main methods for preparation of PNPs, include the dispersion of preformed polymers or ionic gelation, concertation of hydrophilic polymers, monomers polymerization, supercritical fluid technology, solvent displacement, evaporation/extraction and nanoprecipitation (Fig. 4. and Table 2). To achieve the special properties of PNPs depending on several factors, such as particle size, their distribution, and area of application.

Fig. 4:



Schematic showing various techniques for the preparation of PNPs

NPs production by supercritical fluid spraying is becoming popular because no toxic organic compounds are required in the synthesis and hence it is environment friendly.

The synthetic polymer-based nanomaterials are bound by ligand for targeting, and the controllable release of carriers. Nevertheless, it may increase potential toxicity because most cationic units and polymers are non-degradable.

Developed method

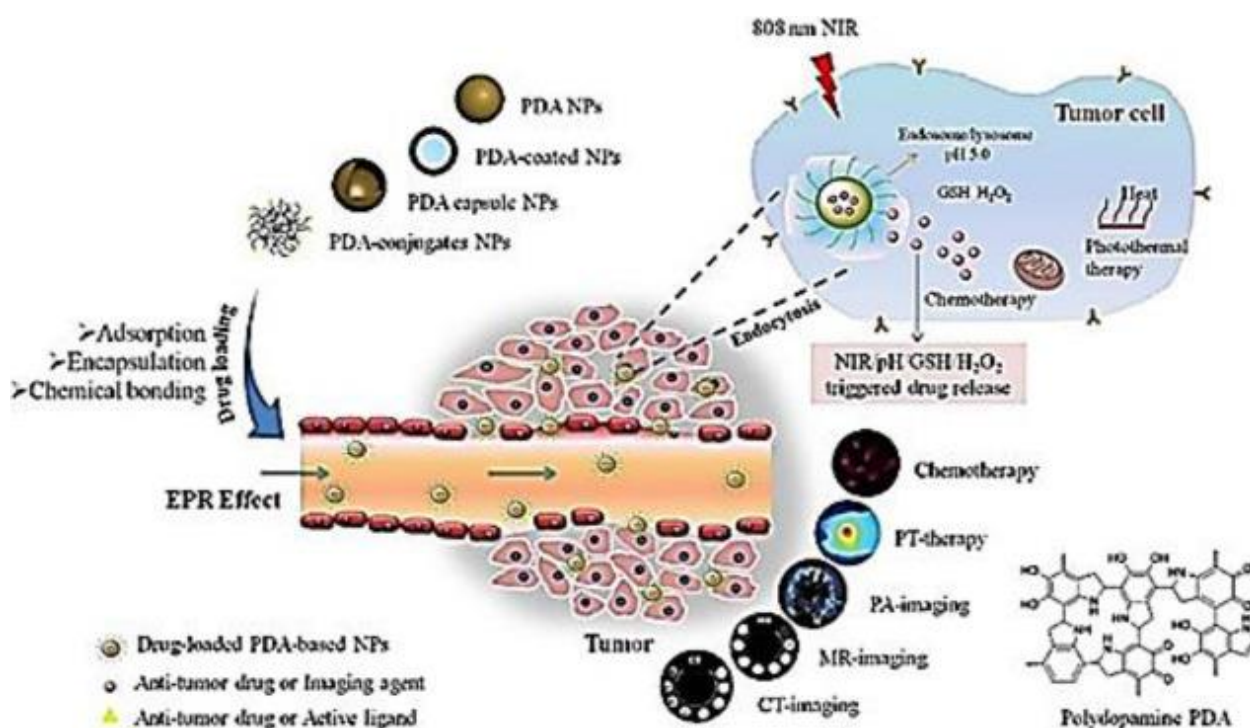
The optimization of the properties of PNPs, including Nanospheres and nanocapsules, improves drug-loading efficiency and prolong drug release. Depending on the application, preparation method, the nature of polymer-drug interactions, as well as the polymer type and their physicochemical characteristics. The physico-chemical parameter of the nanocarriers need to be adjusted biofunctionally to obtain, stability at the point of delivery and, clearance after the delivery and drugs are attached to the substrate and controlled release in cancer site. Concentration and type of the stabilizer, surfactant and the pH of the polymerization medium determines the particle size, the molecular mass of NPs, the Speed of stirring and concentration of monomer.

PNPs can be developed by numerous methods as follows:

- A. Preparation of NPs using a polymer method: The NPs are obtained from a polymer, according to a very independent method (Fig. 4),

- B. Solvent evaporation method: The polymer is dissolved in an organic solvent for dissolving the hydrophobic drug (Fig. 5).
- C. Spontaneous emulsification or solvent diffusion method: It is a modified edition of solvent evaporation method for hydrophobic or hydrophilic drugs.
- D. Coacervation or ionic gelation method: Using biodegradable hydrophilic polymers by ionic gelation.
- E. mixture of two aqueous phase's method: The positively charged amino group of chitosan combined with negative charged triphosphosphate to make a Coacervates with a range of size of nanometres.
- F. Conventional methods

Fig. 5:



The representation of different polymers being used as carriers of anticancer drugs to the target tissue

Organic solvents, used in conventional methods are toxic.

Characterization of drug delivery system

The delivery of CTX to the target cancer tissue by NPs is a passive and ligand-based targeting that either prolongs the duration of systemic therapy or focuses drug therapy on a particular tissue region. However, there are several barriers to reaching their site of action within cancer cells. The CTX must cross through capillary walls, and diffuse through the extracellular space, to reach the proper intracellular targets to overpass the cancer cell membrane.

Important factors of ligand-mediated active tumor-targeting treatment modality, is particle shape and size, type and density of ligands. The effect of the attached ligand orientation, which blocks the recognition sites, needs density optimization.

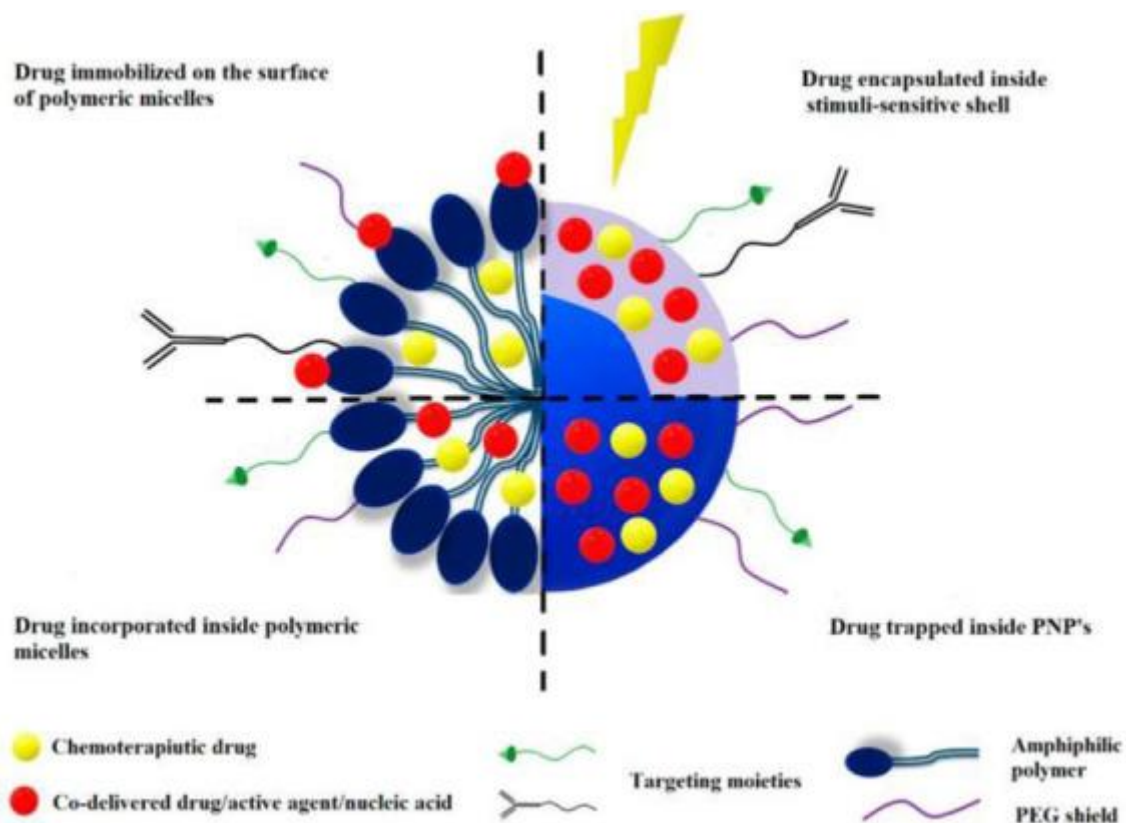
The NPs surface is coated with appropriate bioadhesive materials, and the emulsifier if loaded with CTX can significantly decrease systemic toxicity and increase therapeutic efficacy against drug-resistant and by their fast clearance by lymphatic drainage. Different coating surfaces (Fig. 3) result in different assembly of polymers.

For the treatment of drug-resistant cancers, the anticancer drugs and siRNAs are delivered into cancer cells to stop the gene's resistance, decreasing the drug efflux pumps and activating the apoptosis pathways of cancer cells, especially inaccessible solid tumours.

After the encapsulation process, an important question is whether the drugs released from the NPs still have their original structure and bioactivity.

Implant drug delivery system and colloidal solid materials provided for targeted and controlled release of drugs to tissue, by responsive and biodegradable polymer, pump, and a typical system . The improved drug carriers (Fig.6) for the application of different drugs via different routes to the various treatment .

Fig. 6:



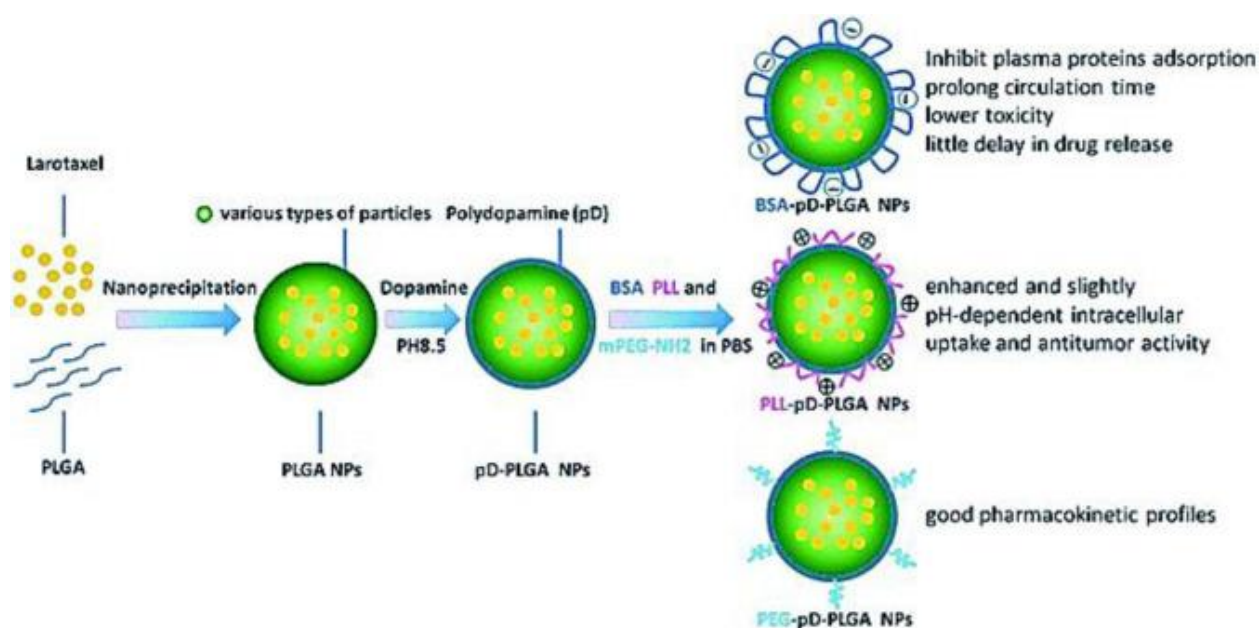
Co-delivery system of PNPs drug loading

Whereas applications of conventional drug delivery methods, including eye drop solutions, injections and implants, cause ocular adverse effects.

Recent progress in drug delivery systems in colorectal cancer, are pH sensitive smart polymers.

The various polymer coating conjugated to NPs using polydopamine (Fig. 7) as drug carriers with combined Chemo- and Photothermal modalities to enhance treatment efficacy and reduce side effects

Fig. 7:



A general schematic showing administration of different coating polymers being used as Polydopamine nanocarriers.

Using SLN (solid lipid NPs) prevents normal tissue toxicity, poor specificity and stability and a high incidence of drug-resistant tumor cells by further improving delivery to anticancer compounds in a more efficient, specific and safer manner.

Most anticancer drugs are stable. Although more research is needed on physicochemical properties of the drugs encapsulated in the nanocarriers polymers.

The efficacy of targeted polymeric drug delivery system depends on the greater bioavailability and biocompatibility, toxicity, the doses required, and the effect on healthy body tissues. The future study requires to provide access to variations of new functions and properties of PNPs and a combination of stimuli their responsive with biological systems.

Conclusion

NPs and various forms of polymeric being used in cancer chemotherapy have significant advantages compared to the conventional drug in terms of controlled mode of action, different administration methods to the tumor site, both organic and inorganic drug delivery. Conventional methods did not reach an effective concentration of drugs the target sites of cancer. NPs have shown their capability to manipulate particles, target malignant tissues, control the release of drugs, and minimize the uptake of the drug by normal cells. Besides, they may enhance the treatment efficacy of chemotherapy medicine and reduce their toxic effects.

NPs as therapeutic agents improved delivering activities of the CTX biomolecules. The best polymer to achieve an efficient frame of drug-loaded NPs depends on their physicochemical characteristics. The use of PNPs showed potential, which facilitates targeting of cancer cells, demonstrating its efficacy to enhance local drug concentration and improving chemotherapy. However, drug resistance limited the clinical benefits of PNPs, therefore necessary to develop multifunctional characters of different CTX; with the capability to deliver two or more therapeutic agents, lower systemic doses, and less toxicity.