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Technology Overview and Current Biomedical Application of Polymeric Nanoparticles

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ABSTRACT

Polymeric nanoparticles are of great importance in the treatment of various diseases, due to the flexibility in the modification of their structures. Recent advances in the field of nanotechnology facilitate the engineering of multifunctional polymeric nanoparticles. All the scientific efforts of the pharmaceuticals companies are mainly focusing on two basic aspects, one is to discover new molecules of potential therapeutic interest and second is to develop of a new drug delivery system. In the last few decades, research and development (R&D) scientists has directed their efforts toward formulating novel drug delivery systems that includes sustained and controlled release, modified release and targeted drug release dosage forms. Application of nanoscience and nanotechnology has opened several new possibilities in development of formulation This review compiles the different preparation methods of polymeric nanoparticles and then briefly explained their current potential applications.

Keywords: Polymeric nanoparticles, PLGA, Biomedical applications, Biodegradable, Dialysis method

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INTRODUCTION

It has been well documented that drugs predicted from *in vitro* studies, fails to reach at target site in adequate quantities *in vivo* studies[1]. Correspondingly, a high amount of the administered drug is left to act on healthy tissues, often to the point of generating dose-limiting side effects[2]. Research related to delivery of drug is clearly moving from the micro to nano size range. Therefore, nanotechnology is evolving as a potential field in medicine that may provide significant therapeutic benefits of existing drugs. The most difficult tasks for pharmaceutical researcher is to develop an effective nano drug delivery system which is capable of carrying drugs, specifically to a desired site of action. Attempts have been made to reformulate the existing conventional formulations into nano delivery systems for better therapeutic use and positive scientific breakthroughs. These systems mainly include polymeric and solid lipid nanoparticles, liposomes and nanoemulsions. The ultimate objective of these nanodelivery systems is to markedly improve the efficacy and reduce the toxic effects of a drug[3].

Recently, nanoparticles based delivery system has been proposed as promising colloidal drug carriers system for such purpose[4]. Nanoparticles (NPs) are a type of colloidal drug delivery system which is comprised of particles in size range from 10 to 1000 nm. Nanoparticles may or may not results size related properties that differ significantly from those observed properties in fine or macro particles[5].

Nowadays, nanoparticles are widely used as carrier system in variety of applications due to their ability to cross organ barriers such as cell membrane and blood brain barrier etc[6]. They are made up from biocompatible polymer and lipids that provide sustained and controlled release effect by either improved dissolution or diffusion mechanism[7,8]. Now a day's nanoparticles are considered as very prolific device for drug delivery system. Dr. Gregory Gregoriad proposed the first liposome's in 1974 as nanoparticulate drug delivery systems which resulted in several breakthrough discoveries by multidisciplinary approaches[3].

The concepts and approaches established in physics, polymer and colloidal chemistry, pharmaceutics, biophysics and molecular biology have described

nanotechnology as a multidisciplinary field. Currently, major research aimed at the development of biocompatible nanocarriers for drugs delivery, cell imaging and for other biomedical applications[9].

POLYMERIC NANOPARTICLES

Polymeric nanoparticles (PNs) are submicron-sized colloidal particles in which therapeutic agent can be encapsulated within their polymeric matrix or adsorbed to the surface of nanoparticles. There are two types of nanoparticles on basis of formulation method i.e., Nanospheres and Nanocapsules[10,11] as depicted in Figure 1. Nanospheres have a matrix system in which drug is uniformly entrapped, dispersed or encapsulated within the particles or attached to their surfaces. Nanocapsules are the liquid-solid core system in which the drug is restricted to a polymer membrane of natural or synthetic polymers[12]. Active moiety is protective by coating and can be used for the controlled release and targeting of drugs[13,14].

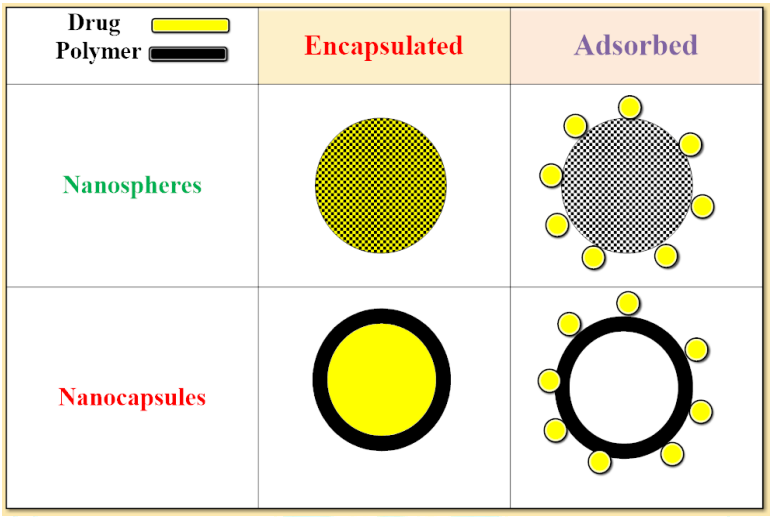

Figure 1: Schematic representation of nanospheres and nanocapsules

Polymeric nanoparticles are prepared from a wide variety of natural or synthetic biodegradable (e.g. albumin, chitosan, alginate, PLGA) and non-biodegradable polymers as describe in Table-1. By the virtue of their nano size, polymeric nanoparticles can also be targeted to specific cells and locations inside the body[15]. Depending on the nature of polymer properties, they are designed in such a way that they can be activated by change in the environmental conditions such as physiological pH, temperature, or chemical stimuli[16]. Macrophages are well recognized phagocytic cells of the reticuloendothelial system and responsible for the uptake and clearance of administered drug loaded nanoparticles. Generally, when drug loaded nanoparticles are opsonized, phagocytosis/ endocytosis may take place and nanoparticles are degraded in a phagolysosome/endolysosome[17]. However, nanoparticles have the capability to escape from the endolysomal compartment which may allows the delivery of drug to the cytoplasm and finally to the nucleus. Thus, NPs are easily taken up by phagocytic cells and that's makes them ideal for intracellular delivery of anti-retroviral drugs. Other applications of NPs include cytoplasmic release of plasmid vectors and therapeutic agents[15,18,19].

Table 1: List of commonly used polymers

Type of polymers	Class of polymers	Examples
Synthetic polymers	Polyamide	Polyamino acids, Polypeptides
	Polyester	Poly(glycolide), Poly(D,L-lactide), Poly(D,L-lactide-co-glycolide), Poly(ε-caprolactone), Poly(dioxanone) Poly(hydroxybutyrate)
	Polyanhydride	Poly[bis(p-carboxyphenoxy) propane-co-sebacic acid], Poly(fatty acid dimmer-co-sebacic acid), Poly(sebacic-co-recinolic acid)
Naturally occurring polymers	Polysaccharides	Dextran, Chitosan, Alginate, Starch, Hyaluronic acid, Gellan
	Proteins	Collagen, Gelatin, Bovine serum albumin (BSA), Human serum albumin (HSA)

BIODEGRADABLE POLYMERS

Biodegradable polymers are polymer that are comprised of monomers linked to each other through a functional group and have unstable linkage in backbone that degrades within the body by enzymatic or chemical degradation as a result of natural biodegradable process[15]. Also when used as drug delivery system it gets eliminated from body and need not to remove the delivery system after complete release of the active ingredients[20]. The release of drug from biodegradable polymers drug delivery system is generally governed by either erosion of surface polymer or swelling of polymer and subsequent release of drug or by diffusion of physically entrapped drug[21].

The major biomedical applications of biodegradable polymers are [15, 21, 22]

- Constructing depot injections
- Biodegradable sutures
- Replacement of bone grafts
- In tissue generation
- For protein drug delivery
- For gene drug delivery for sustain and controlled drug delivery systems

Common characteristics of all biodegradable polymers are[23]

- Stability and compatibility with the drug molecule
- Biocompatible and biodegradable in nature
- Ease of production on a larger scale
- Suitable for sterilization, and
- Flexibility to prepare delivery system with multiple release profiles

The general advantages of nanoparticles includes[24,25]

1. Due to small and narrow particle size distribution of nanoparticles, site specific drug delivery can be achieved
2. Provide a sustained and controlled release of active drug over a long period
3. Protection from chemical and enzymatic degradation of incorporated drug
4. Provide a predefine drug release profile
5. They can be lyophilized and spray dried to resolved stability issues
6. Surface modification can be easily done to achieve both active and passive drug targeting
7. They offer better therapeutic effectiveness response per unit dose as compare to conventional dosages form
8. Biodegradability in blood circulation
9. pH sensitive polymeric nanoparticles can enhanced the oral bioavailability of poorly water soluble drugs[26]
10. Site specific drug can be achieved by surface targeting ligand nanoparticles/magnetic nanoparticles for cancer therapy, vaccine and targeted antibodies[27]

Limitation of Nanoparticles

1. Particle aggregation during storage results in increase the particle size which is difficult in physical handling[28]
2. Limited drug loading and burst release[29]
3. Overall high production cost and scaling up problems[30]
4. Intracellular degradation of nanoparticles due to phagocytosed by cells they may cause cytotoxic effects[31]

METHODS OF PREPARATION OF POLYMERIC NANOPARTICLES

The selection of materials and method of preparation is dependent on following factors:

- Size of desired nanoparticles
- Inherent and physicochemical properties of the drug, e.g., aqueous solubility and stability[32]
- Surface charge properties and permeability[33]
- Degree of biodegradability, biocompatibility, Antigenicity and toxicity[34]
- Desired drug release rate profile[35]

Emulsion and diffusion method

This is the most widely used method of preparation for polymeric nanoparticles. In this method, the encapsulating polymer is dissolved in partially water-miscible organic phase (such as benzyl alcohol, propylene carbonate, ethyl acetate). The organic phase is emulsified by stirring with an aqueous solution of a suitable surfactant i.e., anionic sodium dodecyl sulfate (SDS), non-ionic polyvinyl alcohol (PVA) or cationic didodecyl dimethyl ammonium bromide (DMAB). The diffusion of the organic solvent and the counter diffusion of water into the emulsion droplets induce formation of nanospheres or nanocapsules, according to their oil-to-polymer ratio[36].

This technique presents several advantages, such as high encapsulation efficiency, no need for homogenization, high batch-to-batch reproducibility, ease of scale-up, and narrow size distribution. However, disadvantages includes that are the high volumes of water is to be eliminated from the suspension and less suitable for water-soluble drugs due to leakage into the saturated-aqueous external phase during emulsification, reducing encapsulation efficiency[37]. While, parameters that influenced the size of nanoparticle are: polymer concentration, solvent nature, surfactant/polymer molecular mass, viscosity, stirring rate, nature of solvent, temperature and rate of water addition[36].

Emulsification-solvent evaporation method

Emulsion evaporation is the most popular and oldest method used for preparation of polymeric nanoparticles. The method involves two steps; emulsification of an organic solvent with a polymer in an aqueous solution of surfactant followed by the evaporation of organic phase. Which may leads to polymer precipitation and formation of nanoparticles. Briefly, the organic phase or aqueous phase (internal phase) is poured into an external phase (aqueous or organic phase) in which a surfactant is dissolved and is emulsified. It was furthers subjected to evaporation of organic solvent under vacuum, which leads to polymer precipitation and formation of nanoparticle. The nanoparticles were collected by centrifugation and washed with distilled water to remove surfactant residue or any free drug [38]. Most commonly used organic solvents are ethyl acetate, chloroform and methylene chloride. Biphasic emulsions (o/w or w/o) and multiple emulsions (w/o/w) can be used to accommodate the active drug with variable properties. The o/w emulsion is used for the entrapment of hydrophobic drug, whereas double emulsion (w/o/w) is used for the entrapment of hydrophilic drug. This method is widely used for the preparation of nanoparticles, because it is easy to scale-up, and can be adjusted (by use of the double-emulsion method) to encapsulate water-

soluble drugs[39,40]. This technique has been successfully used for encapsulation of a hydrophobic drug, while in case of hydrophilic drug entrapment was less[41]. Further, modification of this method includes automated batch scale production and is known as high pressure emulsification solvent evaporation process[42]. This method involves preparation of an emulsion (O/W or W/O) which is then subjected to homogenization under high pressure followed by high speed stirring to remove any organic solvent residue[43]. The size of nanoparticles can be controlled by amount and type of polymer, surfactant, viscosity of organic and aqueous phases, temperature and rate of stirring[44]. Commonly used polymers are Polylactic acid, poly (lactic-co-glycolic acid), Ethyl cellulose[15], and Polycaprolactone[45].

Oil in water emulsion technique (single emulsion)

This technique is based on the emulsification of an organic phase, which contains polymer and drug in an aqueous phase, followed by the removal of the organic solvent by evaporation method. A number of hydrophilic surfactants such as polyvinyl alcohol, or Pluronic F68 are generally used in an aqueous phase. For the formation of nanoemulsion, size reduction of emulsion droplet is done by sonication or microfluidization. The evaporation step is required to eliminate the organic solvent present in the organic phase. This leads to the precipitation of the polymer as nanoparticles with a diameter in the nanometric range[46].

There are some considerable variables which effects the preparation of nanoparticles that includes molecular mass and concentration of polymer, co-polymer ratio and end groups, surfactant nature, phase ratio, solvent nature, rate of evaporation, drug entrapment, additives and sterilization[47].

Double-emulsion (w/o/w) method

This method is a modification of emulsification solvent evaporation method and is useful for encapsulation of proteins and hydrophilic drugs. In this method, the primary emulsion (w/o) is prepared by a aqueous solution containing the hydrophilic drug and polymer in the organic phase containing a suitable surfactant, having low HLB value such as Span 80, Pluronic-F68. The primary emulsion is produced by strong shear stress and re-emulsified in an external aqueous phase of a surfactant for formation of water in-oil-in water (w/o/w) emulsion. Further, droplet size reduction of emulsion is achieved with the help of sonication or homogenization. Finally, organic phase residue removed with the help of evaporation under vacuum and nanoparticles can be collected by centrifugation at high speed[48]. The major drawback of this method is the formulation of large sized nanoparticles and the leakage of hydrophilic drugs. Overall production of nanoparticles depends upon polymer/surfactant ratio, polymer concentration, type and nature of surfactant, viscosity, energy input, evaporation and phase ratios[49] .

Solvent displacement/Nanoprecipitation

This technique was first described by Fessi et al. 1989 and is also called as solvent displacement method[50]. This method is commonly used to incorporate lipophilic drugs and involves the precipitation of polymer from an organic phase. In this method, drug, polymer and lipophilic surfactant (e.g., phospholipids) are added in a semi-polar water-miscible solvent (i.e., acetone or ethanol). Under magnetic stirring, this solution is added drop wise into an aqueous phase solution containing a stabilizer. Rapid diffusion of the solvent, facilitate instant formation of colloidal nano suspension. Then organic solvent is removed under reduced pressure from the suspension[51]. This technique is suitable for lipophilic drugs which allow the formation of nanocapsules with high drug loading efficiencies. This method is not suitable for water miscible solvents, in which the diffusion rate is high to produce spontaneous emulsification and may leads to instability when added in water. In some cases, the entrapment efficiency of drugs can be increase by use of acetone/dichloromethane which increases the mean particle size. The particles size and drug entrapment efficiency depend upon the rates of addition of the organic phase into the aqueous phase[52]. This technique has been used for various polymers such as poly(lactic-co-glycolic acid), Poly(lactic acid) and Polycaprolactone etc [41,53].

Dialysis method

This method is a simple and relatively effective method for preparation of polymeric nanoparticles with small and narrow size distribution. Briefly, drug and polymer is dissolved in an organic solvent and are put in the dialysis tube (semi-permeable membranes having a appropriate molecular weight cut off) which is kept in a aqueous phase. The organic phase diffuses out through the pore of dialysis membrane into the aqueous phase which resulted in decrease in interfacial tension between two phase. Subsequently, displacement of organic solvent results in loss of solubility of polymer and may form homogenous suspension of nanoparticles[54]. The mechanism of formation of nanoparticles by dialysis method is similar to that of nanoprecipitation suggested by the Fessi *et al*[50].

Emulsion Polymerization Method

This is *in situ* polymerization of monomers in an aqueous solution containing surfactant which results in formation of nanoparticles. Drug is added during polymerization process or is adsorbed on nanoparticles after completed polymerization. The nanoparticle can be purified and recovered after removal of residues of stabilizers and surfactants by centrifugation and reconstituted in an isotonic medium[55, 56]. One another alternative method is mini-emulsion polymerization method, in which co-stabilizer and high-shear energy (sonication, ultrasound, etc) is used with mixture of monomer, surfactant and a initiator[57]. This method has been reported for the preparation of nanoparticles from organic and inorganic materials and also for hybrid nanoparticles[58].

Salting out method

This method is reported by Ibrahim *et al* and Bindschaedler *et al* and is closely related to solvent-diffusion method. In this method, the polymer is dissolved in water-miscible organic phase, such as acetone or tetrahydrofuran. The ideal choice is acetone because of the high miscibility with water and can be easily removed. The drug and polymer dissolved in organic phase and emulsified in an aqueous phase, under high mechanical staring. The aqueous phase consisted of emulsifying agent with a high concentration of salting out agent. The commonly used salting out agent are magnesium chloride, calcium chloride, or sucrose. In comparison to the emulsion diffusion method, the presence of salts results in no diffusion of the solvent[59]. The rapid addition of water to the o/w emulsion under slow stirring reduces the ionic strength and which leads to the movement of organic solvent to the aqueous phase and resulted in formation of

nanospheres. In final step, salting out agent is removed by centrifugation[60]. The salting out method is suitable for heat sensitive substances. Important variables to be considered includes polymer concentration, nature and concentration of surfactant, molecular mass of polymer, stirring speed and time, and solvent used and cryoprotectants[61,53] .

Coacervation or Ionic Gelation method

Nowadays, much attention of research has been focused on production of biodegradable nanoparticles using polymers such as chitosan, gelatin and sodium alginate having features like biocompatibility and low toxicity. Calvo *et al* introduced a method for preparation of hydrophilic chitosan nanoparticles by ionic gelation[62]. In this method, one aqueous phases consisted of solution of chitosan polymer and a di-block-co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other phase is solution of sodium tripolyphosphate. Nano size coacervates are formed due to an interaction of cationic group of chitosan and anionic tripolyphosphate. Coacervates are produced due to electrostatic interaction between both aqueous phases whereas conversion of material from liquid to gel takes place due to ionic interaction at room temperature. Cross-linking agent such as glutaraldehyde solution (25 %) can be used for hardening of coacervates[63]. Desired property of the nanoparticles can be achieved by concentration of cross linker, temperature, pH, addition rate and agitation speed[64].

Spray drying method

Spray drying has been considered as widely used method for the production of nano/micron-sized particles of heat-sensitive materials. In this method, solution droplet is converted into a dry particle by evaporation of the solvent in a single-step process. Thermo-labile compounds such as proteins and enzymes intended for therapeutic and diagnostic purposes have been successfully developed as spray-dried product. This method is widely used to improve the morphology and particle size of dried powder by varying the process variables and the formulation factors. It is also suitable for protein drugs which are administered as spray dried powders by pulmonary and nasal routes for therapeutic purposes[65]. It has been reported that dried particles of water soluble or water insoluble drugs can be prepared by use of various polymers which resolved the issue of drug leakage[66] and thus, the drug amount in particles can be accurately determined[67]. Innovative advancement in spray drying technology is impact on development of new spray dryers for pharmaceutical industry, which resulted in high product yield with nano size range[68].

Supercritical fluid technology method

In conventional methods, organic solvents used are unsuitable for environment as well as to physiological and biological systems. Therefore, the supercritical fluid technology has been introduced as environmentally safe method for preparation of nanoparticles[69]. Supercritical fluids remains as a single phase without impact of pressure and having intermediate properties of a liquid and a gas. They are commonly used in the production of inorganic and hybrid nanomaterials. Supercritical carbon dioxide ($SCCO_2$) is the most extensively used fluid because of its safe and non-flammable nature. They are commonly employed in supercritical anti-solvent (SAS) and rapid expansion of critical solution (RESS) methods. SAS method, a solid sample is dissolved in an organic or inorganic liquid solvent and which injected into a supercritical fluid under the high pressure. Under these conditions, miscibility of solid solute is reduced in the supercritical fluid which results in the precipitation of the solute and the subsequently formation of nanoparticles[70]. While in RESS method, the solid sample is saturated in a supercritical solvent and is passed through a very fine nozzle at high speed that resulted in precipitation of the solute due to expansion/decompression effect of the system. The overall morphology and size distribution of solute particles are dependent on expansion conditions. Other factors that affect overall production process include nature of solute, supercritical solvent, operating pressure and temperature conditions. Supercritical fluid technology is appropriate for bulk production but costly design of equipment is major limitation[71] .

APPLICATIONS OF POLYMERIC NANOPARTICLES

The extensive advancement in the area of science results in innovative ideas which lead to novel drug delivery systems. Recently reported outcomes of polymeric nanoparticles are summarized in table 2.

Table 2: The research outcomes of polymeric nanoparticle

S. No	Carrier system	Drug /Molecule	Recent applications	Year	Ref.
1	PLGA nanomatrix	Topotecan and Thymoquinone	Co-delivery of topotecan and thymoquinone from PLGA nanomatrix formulated by a modified double emulsion solvent evaporation method. In this topotecan (Hydrophilic moiety) was solubilized in the inner aqueous phase while thymoquinone (lipophilic moiety) was incorporated into the organic phase of the double emulsion. Formulated nanoparticles were characterized by zeta potential, surface morphology, injectability and reconstitution time. The optimized formulation had particle size of 240.7± 8.3 nm and percent entrapment and loading of 62.6± 2.6 % and 6.52 ± 0.25 respectively for thymoquinone and 42.3 ± 1.2% and 3.6 ± 0.26 for topotecan respectively. DSC and XRD results have confirmed the transformation of drug from its crystalline to amorphous form when entrapped in the PLGA nanomatrix. Drug loaded nanoparticles revealed a sustained release pattern of both the drugs with a minimal burst release. The short term accelerated stability analysis showed a minimal variation in the release pattern.	2017	72

2	Biodegradable poly(d,l) lactic acid nanoparticles	Tamoxifen citrate	Biodegradable poly (d,l) lactic acid nanoparticles were prepared by modified spontaneous emulsification solvent diffusion method. *In vitro* studies for cytotoxicity revealed that MCF-7 and MDA-MB-231 cells lines were more sensitive to tamoxifen loaded nanoparticles than tamoxifen citrate alone. DNA ladder and the expression of Bax to Bcl-2 ratio were higher in tamoxifen loaded nanoparticles than that in alone tamoxifen citrate.	2016	73
3	Monomethoxy polyethylene glycol amine-polylactide-co-glycolide (mPEG-PLGA) co-polymer	Gemcitabine	Gemcitabine, a nucleoside analog, has a short half-life in systemic circulation due to its enzymatic degradation.To overcome this problem, monomethoxy polyethylene glycol amine-polylactide-co-glycolide (mPEG-PLGA) co-polymer was synthesized. Gemcitabine loaded mPEG-PLGA nanoparticles (NPs) exhibited sustained drug release profile, compatible with blood and enhanced cellular uptake. The cell cytotoxicity of mPEG-PLGA NPs were observed in MiaPaCa-2 and MCF-7 cells. The half-life of gemcitabine loaded nanoparticles was remarkably enhanced (19 folds) as compared to pure gemcitabine which improved anticancer efficacy in Ehrlich ascites bearing Balb-c mice.	2016	74
4	Poly(d,l-lactide-co-glycolide) (PLGA) nanoparticles nanoprecipitation method	Rapamycin and Piperine	Rapamycin (RPM) with a chemosensitizer (piperine) loaded Poly(d,l-lactide-co-glycolide) (PLGA) nanoparticles were prepared by nanoprecipitation method for improve oral bioavailability and efficacy. Prepared nanoparticles showed sustained *in vitro* drug release and it has been found that the uptake of the Rapamycin (P-gp substrate) increased in the presence of piperine in an everted gut sac method. Pharmacokinetic studies showed improved bioavailability of 4.8 folds in combination with piperine. An *in vitro* cell line studies indicates better efficacy of rapamycin nanoparticles compared to free drug solution which suggests that the use of a combination of rapamycin with piperine nanoparticles would be a effective approach in the treatment of breast cancer.	2016	75
5	PLGA nanoparticles, Emulsified nanoprecipitation technique	Tamoxifen	Tamoxifen loaded PLGA nanoparticles (Tmx-PLGA) were prepared by emulsified nanoprecipitation technique. Tmx-PLGA has been evaluated for its better DNA cleavage potential, cytotoxicity using Dalton's lymphoma ascite cells and MDA-MB231 breast cancer cells. *In vitro* cytotoxicity studies indicate that Tmx-PLGA showed excellent DNA cleavage potential as compared to pure Tmx. Fluorescence imaging of nuclear fragmentation and condensation exhibiting significant increase of apoptosis (70%) in PLGA-Tmx while pure drug (58%). Enhanced DNA cleavage potential, nuclear fragmentation and condensation in apoptotic cells confirm greater bioavailability of PLGA-Tmx as compared to pure Tmx. Tamoxifen loaded PLGA nanoparticles may act as a novel vehicle for the treatment of cancer.	2016	76
6	Biotin-F127-PLA or F127-PLA polymeric nanoparticles	Camptothecin	Camptothecin incorporated into biotin-F127-PLA or F127-PLA polymeric nanoparticles (NPs) prepared by a dialysis method. Results indicate that the targeted CPT NPs exhibited regular spherical shape (mean diameter 180 nm). *In vitro* release exhibited an initial burst (40%) within 12 h, followed by a slow release of camptothecin. The in vitro antitumor effect of the Camptothecin -loaded nanoparticles was determined against H22 cells using an MTT assay which exerted significant antitumor effects as compared to free Camptothecin. The targeted Camptothecin NPs showed increased *in vivo* tumor inhibition.	2016	77
7	PLGA/Solutol HS15 nanoparticles	Docetaxel	Docetaxel loaded PLGA/Solutol HS15 nanoparticles (NPs) were fabricated by a modified emulsification solvent evaporation method. in vitro release studies, indicates that emulsifying property of Solutol HS15 seemed to contribute to the enhanced drug release of Docetaxel from NPs at physiological pH. These NP can be a promising local anticancer drug delivery system for cancer therapy.	2016	78
8	biotinylated chitosan-poly(d,l-	Epirubicin	Surface modification of poly(d,l-lactide-co-glycolide) nanoparticles with biotinylated chitosan of Epirubicin loaded	2016	79

	lactide-co-glycolide) nanoparticles		were prepared for tumor targeted and prolonged delivery system for Epirubicin (EPB). The results revealed encapsulation efficiency (84.1 ± 3.4%), spherical shaped, higher positive zeta potential compared to the unmodfied EPB-loaded PLGA NPs. The *in vitro* drug release studies showed constant drug release kinetics during the first 48 h and the drug burst release significantly decreased in comparison to the unmodified PLGA NPs. The results of MTS assays and the flow cytometry and the confocal microscope showed that Bio-CS-PLGA NPs markedly increased the cytotoxicity and extent of cellular uptake of EPB. In MCF-7 tumor-bearing nude mice, EPB-loaded biotinylated chitosan - PLGA NPs were efficiently accumulated in the tumors which displayed greater potential for application as the carriers of anti-cancer drugs.		
9	Eudragit E 100 nanoparticles, Emulsification diffusion evaporation method	Curcumin	Curcumin loaded Eudragit E 100 nanoparticles were prepared by emulsification diffusion evaporation method to enhance the bioavailability and anti-cancer efficacy. The *in vitro* cytotoxicity sulphorhodamine B assay, showed 19-fold reduction in IC_{50} when treated with curcumin loaded nanoparticles as compared to pure curcumin, Pharmacokinetic studies revealed ~91-fold increase in C_{max} and ~95-fold increase in AUC_0. The *in vivo* anti-cancer activity showed a significant increase in efficacy compared with pure curcumin, as observed by tumor volume, body weight and survival rate. Its offer a great potential to improve bioavailability and efficacy of hydrophobic chemotherapeutic anticancer drug.	2016	80
10	Lipid polymer hybrid nanoparticles	Docetaxel	Docetaxel (DTX) lipid polymer hybrid nanoparticles consist of a pH-responsive PEG layer that gets detached prior to its cellular uptake. Docetaxel was added into the lipid core of the nanoparticles, which was then protected with the pH-responsive block co-polymer polyethylene glycol-b-polyaspartic acid using a modified-emulsion method. Drug release from docetaxel loaded nanoparticles was pH-sensitive, which is helpful in tumor targeting. The negative surface charge and PEG shell of vehicle enhanced the blood circulation time and improved physiological activity of docetaxel loaded nanoparticles as compared to free docetaxel. *In vivo* anticancer effect of Docetaxel lipid polymer hybrid nanoparticles was further confirmed by the elevated levels of poly ADP ribose polymerase and caspase-3 found in the tumors after treatment. Thus, the results indicate that Docetaxel lipid polymer hybrid nanoparticles system could be an effective new treatment for cancer.	2015	81
11	methoxy poly(ethylene glycol)-poly(lactide) polymeric nanoparticles	5-Flurouracil	5-FU loaded methoxy poly (ethylene glycol)-poly (lactide) based polymeric nanoparticles were prepared by nanoprecipitation method in order to increase the efficacy against breast cancer. The prepared nanoparticles were evaluated by DLS, TEM, *in vitro* release kinetics, and *in vivo* parameters. The average particle diameter of 5-FU loaded NP was ~110 nm. The NPs exhibited a pH-dependent drug release pattern and *in vitro* cytotoxicity assay showed the enhanced cytotoxic effect of drug loaded NPs in comparison to free drug. Flow cytometer analysis showed that nanoparticle system remarkably arrested the G2/M phase of cell cycle with significant amount of apoptosis cells in late and early phase. Nanoparticle formulation significantly decreased the tumor burden of mice with minimal signs of adverse effect. The favorable results obtained from this study makes 5-FU loaded methoxy poly(ethylene glycol)-poly(lactide) based polymeric nanoparticles one of the possible alternative for the successful breast cancer therapy.	2015	82
12	poly(lactic-co-glycolic acid)coating on Mg-Al layered double hydroxide (LDH) nanoparticles	Methotrexate	It has been reported that development of methotrexate loaded poly(lactic-co-glycolic acid)coating on Mg-Al layered double hydroxide (LDH) nanoparticles prepared by double and single emulsion-solvent evaporation technique. The optimized nanoparticles were assessed for *in vitro* drug release kinetics,	2015	83

			time and dose dependent *in vitro* cell viability assay and *in vitro* MTX uptake study using MG-63 cell line (human osteosarcoma). The results of *in vivo* pharmacokinetic study revealed the much higher therapeutic efficacy of the optimized PLGA-LDH-MTX and PLGA-MTX nanoparticles in terms of the enhanced half life of the MTX and the slow clearance rate compared to those of the pure drug.		
13	pectin nanoparticles	5-Fluorouracil	5-FU-loaded pectin nanoparticles (5-FU-NPs) with an average diameter of 300 nm are found to posses greater potency in killing cancer cells in HepG2 and A549 cell lines compared to that of the free drug. Pharmacokinetics study using Sprague Dawley rats further confirmed that the 5-FU-loaded nanoparticles showed a longer half life in the circulation fluids than the free 5-fluorouracil.	2014	84
14	poly(d, l-lactide-co-glycolide) nanoparticles	Carboplatin	Carboplatin-loaded poly(d, l-lactide-co-glycolide) nanoparticles were formulated by double emulsion-solvent evaporation technique. Nanoparticles showed sustained release of carboplatin over 7 days. Cellular uptake of carboplatin encapsulated in nanoparticles was several fold higher than that with free carboplatin in A549 (lung) and MA148 (ovarian) tumor cells and reduction in the IC_{50} of carboplatin in several cell lines. Confocal microscopic analysis revealed the existence of carboplatin nanoparticles in lysosomes, cytoplasm, and the nucleus of cells. These results revealed the enhanced Cellular uptake, therapeutic efficacy and reduced toxicity may be achieved with this approach.	2014	85

CONCLUSION

The advantageous effects of polymeric nanoparticles depend on their physicochemical properties such as size, shape, and surface properties. The potential advantages of nanoparticles are improved bioavailability, increased aqueous solubility, increased bio-distribution of drug in the body and targeting the drug to specific location within the body. Emerging technologies and method of preparation play a critical for development of safe and effective drug delivery system. Polymeric nanoparticles based drug delivery system has a promising future in the areas of diagnosis, imaging, and therapeutics

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