Journal for ReAttach Therapy and Developmental Diversities
eISSN: 2589-7799
2023 September; 6(1): 1974 -1980

Formulation of Biodegradable Polymeric Nanoparticles for Cancer Therapy

Dr. Ramdas Baburao Rode[1*], Deepak Shantaram Borade[2]

[1*]Professor, Shri Swami Samarth Institute of Pharmacy, Malwadi (Bota), District: Ahmednagar Pin: 422602
[2]Assistant Professor, Shri Swami Samarth Institute of Pharmacy, Malwadi (Bota), District: Ahmednagar Pin: 422602

ABSTARCT:

Due to the many, complex treatment choices available for cancer, as well as the adverse effects of chemotherapy, cancer therapy is always crucial. Modern cancer treatment methods require innovative approaches as a result. These days, there is a lot of interest in nanotechnology because of its potential uses as medication delivery systems, theragnostic tools, diagnostic tools, and contrasting agents. The biocompatible and biodegradable polymers that make up nanoparticles (NPs) enhance the pharmacokinetic and pharmacodynamic qualities of medications, lessen adverse effects, increase stability, extend the duration of drug release, and decrease the frequency of dose. The FDA has approved poly (lactic-co-glycolic acid) (PLGA) as a synthetic polymer that can be used to create NPs that are specifically targeted to a particular place for the safe and efficient delivery of medication. Numerous cancer therapies, such as photodynamic therapy, gene therapy, tumor-targeted medication delivery, and hyperthermia, can be implemented with PLGA-based nanoparticles. The preparation, characterization, and encapsulation of chemotherapeutic drugs are covered in this article along with the impact of the physicochemical properties of PLGA-based nanoparticles and how these aspects can be utilized through different preparation techniques for drug loading, biodistribution, target specificity, and cancer therapy.

KEYWORDS: Biodegradable Polymeric nanoparticles, Cancer therapy, PLGA

INTRODUCTION:

As the second largest cause of death globally, after cardiovascular disease, which is the primary cause of mortality globally, cancer poses a serious threat to global public health. Over 1.9 million new cases of cancer were expected to be identified in the United States in 2023, with roughly 609,820 fatalities associated with the disease. The most popular therapeutic techniques for the treatment of cancer involve the combination of chemotherapy with surgery, radiation therapy, and/or both. Small, hazardous chemotherapeutic compounds that can disrupt DNA and affect cellular macromolecular synthesis are frequently used in chemotherapy. However, because of their non-selective and off-target effects, many medicines are known to have side effects. Monoclonal antibodies (mAbs) have emerged as prospective cancer therapies thanks to advances in our understanding of cancer biology. Notably, the first mAb therapies to be licensed for the treatment of lymphoma and breast cancer, respectively, were rituximab and trastuzumab. mAbs possess the exceptional capacity to directly target tumor cells while also boosting the immune system's ability to combat cancer. Additionally, mAbs are being investigated for use in a variety of cancer therapy techniques, such as anti-PD-L1 immunotherapy and polymer-based methods for enhancing T-cell infiltration. With their potential therapeutic benefits and minimal side effects, these novel polymer-based methods to cancer treatment represent a substantial advancement in the field. [1-3]

Compared to other non-biodegradable polymers and lipids utilized for gene/drug delivery, biodegradable polymeric nanoparticles (NPs) and nanosystems (NSs) are thought to be very effective drug delivery systems (DDSs) that are also quite safe. Due to their bioactivity, the biodegradable polymers can also be employed as polymer therapies, which can be leveraged to deliver a variety of small and big compounds in a targeted, sustained, or pulsatile way. It is important to emphasize that the concentration of the medication in the target site is kept within the therapeutic window and that the release of integrated or encapsulated pharmaceuticals from these polymers can be precisely regulated. Biodegradable polymers are regarded as the best biomaterials for the creation of therapeutic devices such biodegradable implants, temporary prostheses, and biodegradable 3-D scaffolds for tissue engineering, as well as controlled- or sustained-release DDSs. In order to create therapeutic devices that work, the best biodegradable polymers must be used, taking into account the biological endpoints and their unique physicochemical, biomechanical, and enzymatic/hydrolytic breakdown capabilities.18 It actually takes a lot of work, time, and money to engineer biomaterial with special qualities in order to develop complex biotherapeutics. In addition, a review of the biomaterials that are currently being used in different clinical contexts is necessary to address all of the problems related to the application of biopolymers in vivo. The majority of these problems are closely related to how the applied biopolymers interact physicochemically with the target tissue or cells. For example, accidental immunologic reactions can severely restrict their applications, but these side effects can be advantageous if the ultimate goal is immune system activation by immunization or vaccination. Furthermore, it appears that strong proof of these materials' long-term safety is required. [4–8] In addition to enhancing their therapeutic effect in a synergistic or additive manner, nanocarriers can hold numerous therapeutic medicines in

order to overcome developed resistance to individual chemotherapeutic medications. Chemoresistance in many malignancies arises from a variety of processes, such as downregulation of absorption mechanisms or elevation of the drug efflux rate. By offering a different route for cellular uptake, nanoparticulate formulations are able to get around this restriction. A number of therapeutic nanoparticle platforms, including lipid-based, polymer-based, inorganic, viral, and polymer-drug conjugated systems, are now being researched for the purpose of treating targeted cancer. More than 20 medicinal items based on nanotechnology have been given the go-ahead for clinical usage in the last 20 years. The two most significant categories of these products are liposomal systems and polymer-drug conjugates; numerous other formulations, such as those for radiation therapy, chemotherapy, hyperthermia, gene or RNA interference (RNAi) therapy, and immunotherapy, are being studied clinically. [9]

The nanometric scale, high surface area-to-volume ratio, attractive drug release profiles, and targeting qualities of nanocarriers are unique characteristics that can facilitate their preferential accumulation in tumor tissues. Since leaky tumor vasculature and inadequate lymphatic drainage are usually believed to be the cause of the enhanced permeability and retention (EPR) effect, the majority of nanosystems used to treat solid tumors are delivered systemically and accumulate in the tumor tissues. This interpretation of EPR-dependence, however, is oversimplified because a variety of biological factors, such as interactions with plasma proteins, blood circulation time, extravasation, tumor tissue penetration, and cancer cell uptake, can affect the biodistribution of systemically administered nano systems. Alterations to the surfaces of nano-systems that can bestow particular targeting attributes or stimuli-sensitive reactions also impact the systems' general distribution. [10]

Importances of Biodegradable Polymer Nanoparticles:

Biodegradable nanoparticles can be arranged based on how they are produced and utilized, just like their non-biodegradable counterparts. This can be achieved by either combining the components of interest into nanospheres or encasing them in nanocapsules. One example of a nanosphere is a dendrimer; other effective nano capsules include liposomes and micelles.

The application of biodegradable nanoparticles bolsters the general advantages of nanomedicine, including targeted administration and controlled and moderated load delivery, which enhance restorative effects and reduce consequences, especially for some cytotoxic drugs. Another advantage of biodegradable nanoparticles is that they lessen cytotoxicity in the body. Other surface modifications should also be permitted in order to improve the drug release profile even more and concentrate on proficiency.

Good biocompatibility and biosafety have been shown by polymers in the production of biodegradable nanoparticles. It is also feasible to alter the size and surface of the molecules to control medication release. Strong polymeric nanoparticles with a size range of 10-500 nm can be used to implant or encapsulate beneficial species inside their polymeric gride in order to bring them to the surface. Polymeric nanomaterials can be classified into two main categories based on the basic ingredients utilized to create the nanoparticles: blended compounds such as poly-D-L-lactide-coglycolide (PLGA), polylactic acid (PLA), and poly-ε-caprolactone (PCL); and common compounds such as chitosan. This group of polymers has the ability to undergo a cycle of deterioration and turn into materials that are safe to use within the body. The size and form of polymeric nanoparticles, in addition to internal factors like pH and temperature, all influence the pace of reactivity of these particles, which in turn affects the payload delivery profile. A relatively longer drug discharge interval is generally a benefit when comparing designed polymers to their ordinary polymer counterparts. [11–13]

Formulation of Polymeric Nano Particles:

It is possible to construct biodegradable polymer nanoparticles into a wide range of formulations, including solid nanoparticles, polymeric micelles, core-shell structures, and polyplexes. The ideal technique for creating and synthesizing nanoparticles relies on the characteristics of the selected polymer and payload; nonetheless, self-assembly or emulsion are the most common ways for creating polymeric nanoparticles. In summary, the methods of self-assembly encompass both intra- and intermolecular interactions between the polymer and its cargo. These include the complexation of cationic polymers with anionic nucleic acids to form polyplexes, as well as spontaneous micelle assembly, which occurs when amphiphilic block co-polymers reach a critical micelle concentration (CMC) and form particles as a result of hydrophobic interactions. Moreover, techniques like emulsification can be used to create nanoparticles, which are created as droplets of one phase scattered over a second phase. To create nano-droplets, the polymer is usually dissolved in an organic phase, combined with a surfactant, and sonicated vigorously in an aqueous phase. Hardened polymer nanoparticles are left behind after the solvent evaporates from the emulsion by stirring it. To create core-shell nanoparticles with advantageous surface characteristics, these hard nanoparticles can also be coated with a different substance. [14]

Synthetic Polymers:

In order to optimize specific cargos, delivery channels, and disease targets, synthetic polymers are created with desired features including charge, hydrophobicity, and degradation profile. Below are a few synthetic polymers.

Poly(Lactide-co-Glycolide) (PLGA):
The utilization of PLGA-based nanoparticles as drug delivery vehicles for different medicinal agents is a possibility. One such application is the targeted medicine delivery they provide in oncology. In order to ensure precise control over pharmacological activity, drug release characteristics, target specificity, and drug degradation, it is imperative that the physicochemical features such as particle size, surface charge, and others align with the intended usage. However, this is a very complex topic since maximizing one NPs characteristic may jeopardize other parameters because modifying a physicochemical activity, such as the size of the nanoparticle, depends on the size, charge, coiling, and other features of the polymers utilized. The hydrophobicity and crystallinity of the product may also be affected by adjusting the ratio of the component polymers employed, such as lactic acid and glycolic acid. Accordingly, we might have to change our targeting strategy due to the polymer's features and characteristics, and vice versa. Hence, creating a nanoparticle with the ideal characteristics is comparable to figuring out a challenging puzzle in which every piece is interconnected such that altering or eliminating one piece affects the puzzle's overall dynamics. An external stimuli-based targeting technique, for example, might improve tumor retention, but because of the larger size of the nanoparticles, it might also trigger phagocytosis.

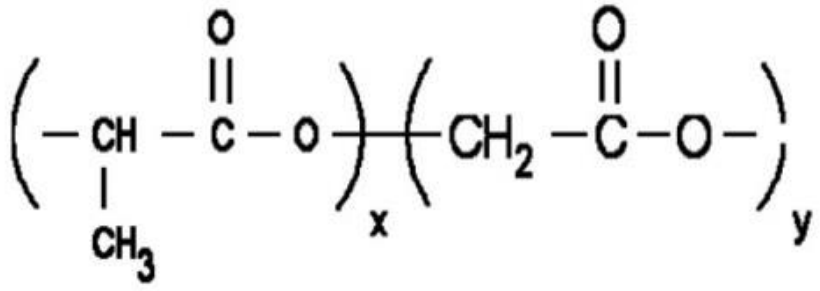

Figure 1: The PLGA's Structure: x: lactic acid and y: glycolic acid

In Figure 1, PLG is one of the most often used biodegradable polymers. as it enters the body, get hydrolyzed to produce monomers of biodegradable metabolites, like lactic and glycolic acid. Since the body already contains lactic acid and glycolic acid, which participate in distinct routes, using PLG to successfully transport medications is practically risk-free. PLG NPs are primarily made using emulsification-dissemination, dissolvable dissipation, and nanoprecipitation techniques. PLG nanoparticles have been applied to in vivo delivery systems as well as the creation of protein- and peptide-based nanomedicines.[15]

Polylactideacid (PLA):
Because of its great biocompatibility, low immunogenicity, low toxicity, and biodegradability, PLA is a polymer that has received FDA approval. Lactic acid, which is employed in other metabolic pathways, is produced when PLA is broken down. According to several PLA NPs research, lactic acid was quickly converted into H2O and CO2, making it simple for the body to get rid of. Ring-opening polymerization (ROP) of the cyclic ester or a polycondensation reaction of lactic acid are the two processes that yield PLA.[16]

Polyglycolicacid (PGA):
Glycolide ROP yields PGA, a polymer recognized by the FDA. In the 1970s, PGA was utilized to create the first bioresorbable suture. PGA is a thermoplastic that breaks down naturally and releases glycolic acid, which is subsequently eliminated through urine. The usage of PGA in the creation of nanoparticles was restricted due to its rapid enzymatic degradability, low stability in water, and low solubility in organic solvent. In fact, the main application of PGA is in tissue engineering for the regeneration of teeth, tendons, cartilage, and bone. [17]

Natural Polymers:
Chemotherapy, often necessary for cancer patients, has many disadvantages, including damage to healthy tissues, lack of medication efficacy because of multi-drug resistance, and financial implications. Natural polysaccharides are preferred over polymer-based DDSs because of their renewability and abundance in the natural world. Compared to synthetic polymers, their non-toxic, water-soluble, biodegradable, and biocompatible qualities provide clear advantages. Below are a few of the most popular natural polymers.

Chitosan: The natural process of N-deacetylation of chitin yields chitosan, a biocompatible and biodegradable polymer. It is most commonly found in fungi and the exoskeleton of crustaceans. Its structure is closely linked to that of cellulose. Chitosan is a widely used cationic linear polymer in biomedical research, agriculture, and the food industry. It is composed of repeated D-glucosamine and N-acetyl D-glucosamine subunits connected by 1-4 glycosidiclinkages.[18]

Gelatin: The partial hydrolysis of animal collagen yields a combination of proteins and peptides known as gelatin. It is frequently utilized in food and cosmetic products and is biocompatible and non-immunogenic. Gelatin, which comes from collagen, is a naturally occurring polymer valued for its biodegradability, biocompatibility, and low toxicity. Collagen is present in the human body in a variety of forms, including fibrous tissues, blood vessels, GI tract, and bones. It makes up around 30% of the major structural proteins in the body.[19]

Cellulose: The most prevalent structural polymer found in nature is undoubtedly cellulose. It is a linear polysaccharide made up of hundreds to thousands of D-glucose monomer subunits joined by β (1-4) glycosidic bonds. Cellulose nanocrystals, also known as cellulose nano whiskers, are crystalline materials with hydrophilic qualities, mucoadhesive qualities, and pH sensitivity. Because of intra- and intermolecular hydrogen bonding, cellulose is insoluble in the majority of organic solvents as well as in water. [20]

Alginate: Alginate is a naturally occurring polysaccharide that may be found in many different brown sea weed species, including Macrocystispyrifera, Ascophyllumnodosum, Laminaria digitate, Laminariahyperborea, and Laminaria japonica. Since alginate is anionic, gelation is caused by the addition of divalent cations like calcium. Since its backbone contains carboxyl and hydroxyl groups, it is easily functionalized, allowing for the tuning of its chemical and biological properties.[21]

Dextran: Made up of basic repeat units of α-d-glycose connected by glycosidic linkages, dextran is a branching polymer (32). Although dextran is water soluble and hydrophilic, it can be acetylated to produce AcDex, a hydrophobic polymer. Neutral polysaccharide dextran is produced by catalyzing the conversion of sucrose, which is found in anaerobic bacterial species like Leuconostoc and Streptococcus. This hydrophilic, branched biopolymer is made up of branched glucose subunits that form α-1,2, α-1,3, and α-1,4 glycosidic links, as well as a linear chain of repeated glucose monomers connected by α-1,6 glycosidiclinkages.[22]

Formulation techniques of PLGA-based NPs:
NPs can be prepared using a variety of methods, and the preparation process has a big influence on the final product's stability, shape, and size. Emulsification, spray drying, nanoprecipitation, and microfluidics are some of these methods.

Nanoprecipitation technique:
One technique comprises adding a drug, polymer, and water miscible organic solvent solution dropwise into an aqueous solution containing stabilizer. At the end, precipitation occurs, forming NPs, and the solvent is removed by applying reduced pressure. The properties of the resulting particles are determined by the molecular weight of the polymer, the concentration of the solvent, the ratio of polymer utilized, and the mixing force.

Salting out/emulsification reverse salting out technique:
A water-soluble polar solvent, such as acetone, is combined with the drug and polymer. This mixture is then added to another aqueous solution containing a salt, like MgCl2 or CaCl2, and a stabilizing agent, like polyvinyl pyrrolidone. The mixture is vigorously agitated to create a uniform emulsion. When enough water is added to the resulting emulsion, the organic solvent diffuses in the water and forms nanoparticles (NPs). For thermolabile materials and preparations with high polymer concentrations, this approach has advantages. A significant problem of this process is that removing the stabilizer necessitates thorough washing, which takes a lot of time and is only appropriate for hydrophilic medicines.

Emulsion solvent evaporation technique:
Emulsification is the most widely utilized technique for PLGA-NP formulation. The medication is dissolved in the organic solvent before being added to a large-volume aqueous phase containing an appropriate surfactant or emulsifier (often PVA). After that, it is constantly swirled to create a uniform emulsion. The oil in the water emulsion is formed by the evaporation of the organic solvent. To create the final formulation, the resulting particles are freeze-dried and then cleaned. [23][24]

REVIEW OF LITERATURE:

Biodegradable chitosan nanoparticles were created by Kim et al., as a vaccine delivery mechanism for hepatitis B. The intramuscular delivery of licenced Hepatitis B vaccines involves the use of needles, which can be uncomfortable and painful. As a result, a trial using a novel vaccine delivery method was carried out. The rats' nasal mucosa was injected with the nanoparticle formulation during the trial. One very bio-absorptive polymer is chitosan. As a result, it entered the nasal mucosa and gave the body a steady supply of antigens. [25]
Black Phosphorous Quantum Dots (BPQD) were encapsulated in PLGA to create nanoparticles as part of a light-triggered photothermal treatment system developed by Shao et al. The BPQDs produce heat when they come into

contact with a near-IR laser, which kills the nearby tumor cells. By employing PLGA nanoparticles to localize BPQDs in the tumor and irradiating the tumor area, this approach takes advantage of the increased penetration and retention (EPR) effect. Tumors in mice treated with PLGA and BPQD photothermal therapy gradually shrank and vanished totally in 16 days, with no signs of recurrence at the tumor location for 40 days. Therefore, in situations when there is local dissemination and metastasis and the locations of the tumor sites are unclear, the medicines are irrelevant. [26]
In this study, José et al. show how biodegradable nanoparticles can target specific areas of the brain. They made and altered PLGA nanoparticles filled with Bacosid-A. A medication called bacosid-A is used to treat neurodegenerative conditions including Alzheimer's disease. Polysorbate 80, a surfactant, was added to the produced nanoparticles to enable them to pass across the blood-brain barrier. Rats were used in the study of the nanoparticles' brain targeting. High amounts of Bacosid-A were able to pass across the blood-brain barrier when the nanoparticle formulation was given intraperitoneally to the rats. [27]

OBJECTIVES:
1. To study of Biodegradable Polymeric nanoparticles.
2. To analysis of formulation of biodegradable NPs.
3. To study application of PLGA nanoparticles.

RESEARCH METHODOLOGY:

The overall design of this study was exploratory. The research paper is an effort that is based on secondary data that was gathered from credible publications, the internet, articles, textbooks, and newspapers.

RESULT AND DISCUSSION:

As seen in Table 1, biodegradable polymer nanoparticles have undergone clinical testing with some encouraging outcomes.

Table 1: Clinical trials of biodegradable polymeric nanoparticle cancer drug delivery systems

Name	Nanoparticles	stage	Cancer	Result
NC-6004	PEG-poly (amino acid) Block co-polymer	I	Pancreatic, head and neck, solid tumors.	Significant toxicity was not observed
NK 105	PEG-Polyaspartate	II	Breast, gastric	Significant toxicity was not observed, 25% overall response rate
BIND-014	PLGAwith PSMA targeting ligand	I	Prostate	Significant toxicity was not observed, 12% overall response rate

Table 1 above shows that NC-6004, a polymeric micelle composed of PEG-poly (amino acid) block copolymers, has successfully completed phase I clinical trials at Nanocarrier. Clinical trials have evaluated the delivery of cisplatin for head and neck, pancreas, lung, bladder, and bile duct malignancies using these particles. Using the nanocarrier in Phase I trials resulted in a 34-fold increase in the dose-limiting toxicity of cisplatin, and seven out of 17 patients with solid tumors treated with NC-6004 showed stable illness for more than four weeks. [28]
Nippon Kayaku Co. created NK105, a micellar paclitaxel formulation made of PEG-polyaspartate block copolymers. The preclinical results of this nanoparticle formulation showed improvement in the anti-tumor efficacy of paclitaxel, decreased off-target toxicity, and lengthened circulation time. [29]
A potential targeted and controlled release polymeric nanoparticle was designed by Dr. Robert Langer of MIT and Dr.Omid Farokhzad of Harvard Medical School and tested on humans. Their product, BIND-014, a prostate-specific membrane antigen (PSMA) targeted PLGA nanoparticle carrying docetaxel, is the foundation of their company, BIND Therapeutics. [30]

Table 2: Applications of PLGA-NPs in cancer therapy

Delivery System	Drug	Methods	Inference
PLGA-NPs	Raloxifene hydrochloride (RAL)	Emulsion solvent diffusion evaporation	Improvement in stability at different temperatures and increase the in vitro efficacy at a lower concentration.
PLGA-NPs	Afatinib	Emulsification followed by solvent evaporation	Localized inhalational drug delivery

			for small lung cancer significantly improved cytotoxicity and cellular uptake.
PEG-coated PLGA-NPs	Curcumin	Solvent displacement method, PEGylation, and ligand conjugation	The ligands HA or FA conjugated with PLGA-PEG showed better in vitro efficacy and target ability.

Table 2 displays the most recent PLGA NPs for combined delivery. Numerous anticancer medications, including as 5-FU, DTX, DOX, PTX, and dexamethasone, have been effectively encapsulated in PLGA NPs; in fact, some of the formulations have received FDA approval for clinical use. Human growth hormones, peptides, and genes are just a few of the macromolecules that have recently been added to PLGA NPs and successfully transported to tumor tissue. Additionally, PLGA NPs provide an appropriate platform for the co-administration of chemotherapeutics with other synergistic medicines, which have been extensively employed for the successful targeting of a variety of cancers. [31]

CONCLUSION:

To get beyond the drawbacks of free therapies for the treatment of cancer, biodegradable polymeric NPs have been developed. Although the pharmacokinetic profile of polymeric nanoparticles (NPs) has proven to be more favorable than that of free chemotherapeutics, further formulation modification is required to maximize the NPs' size and polydispersity. Similar to this, a variety of polymers created especially for that purpose allow for more exact control over drug release from polymeric nanoparticles (NPs). This is how therapeutic polymers are defined: they are polymers having potential uses in cancer research as well as pharmaceutical and biological applications. However, by specifically targeting tumor cells, it is possible to increase the permeability and penetration of the polymeric NPs inside the tumor, reducing toxicity and preventing side effects from long-term therapy. Better, less hazardous medication development is more likely with the advent of nanomedicine, especially in cancer therapy. Cancer treatments may be more successful with the use of PLGA NPs, an FDA-approved biodegradable drug delivery system, because of the possibility of targeting cancer cells and a decrease in harmful side effects, which would eventually improve a patient's quality of life. PLGA NPs have the potential to increase patient prognosis and treatments due to their small size, flexibility in content loading, surface functionalization, biodegradability and biocompatibility, and enhanced absorption by cancer cells.

REFERENCES:

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2021, 71, 209–249.
2. Lin, A.; Giuliano, C.J.; Palladino, A.; John, K.M.; Abramowicz, C.; Yuan, M.L.; Sausville, E.L.; Lukow, D.A.; Liu, L.; Chait, A.R.; et al. Off-target Toxicity is A Common Mechanism of Action of Cancer Drugs Undergoing Clinical Trials. Sci. Transl. Med. 2019, 11, 509.
3. Zahavi, D.; Weiner, L. Monoclonal antibodies in cancer therapy. Antibodies 2020, 9, 34.
4. Kafil V, Omidi Y. Cytotoxic impacts of linear and branched polyethylenimine nanostructures in a431 cells. Bioimpacts 2011; 1: 23-30. doi:10.5681/bi.2011.004
5. Omidi Y, Barar J, Heidari HR, Ahmadian S, Yazdi HA, Akhtar S. Microarray analysis of the toxicogenomics and the genotoxic potential of a cationic lipid-based gene delivery nanosystem in human alveolar epithelial a549 cells. ToxicolMech Methods 2008; 18: 369-78. doi:10.1080/15376510801891286
6. Duncan R. Polymer therapeutics as nanomedicines: new perspectives. CurrOpinBiotechnol 2011; 22: 492-501. doi:10.1016/j.copbio.2011.05.507
7. Khosroushahi AY, Naderi-Manesh H, Yeganeh H, Barar J, Omidi Y. Novel water-soluble polyurethane nanomicelles for cancer chemotherapy: physicochemical characterization and cellular activities. J Nanobiotechnology 2012; 10: 2. doi:10.1186/1477-3155-10-2
8. Jackanicz TM, Nash HA, Wise DL, Gregory JB. Polylactic acid as a biodegradable carrier for contraceptive steroids. Contraception 1973; 8: 227-34. doi:10.1016/0010-7824(73)90033-4
9. Mansoori, B., Mohammadi, A., Davudian, S., Shirjang, S., and Baradaran, B. (2017). The different mechanisms of cancer drug resistance: a brief review. Adv. Pharmaceut. Bull. 7, 339.
10. Wicki, A., Witzigmann, D., Balasubramanian, V., and Huwyler, J. (2015). Nanomedicine in cancer therapy: challenges, opportunities, and clinical applications. J. Contr. Release 200, 138–157.
11. Villemin, E.; Ong, Y. C.; Thomas, C. M.; Gasser, G. Polymer Encapsulation of Ruthenium Complexes for Biological and Medicinal Applications. Nat. Rev. Chem. 2019, 3 (4), 261–282.

12. Panyam, J.; Labhasetwar, V. Biodegradable Nanoparticles for Drug and Gene Delivery to Cells and Tissue. Adv. Drug Deliv. Rev. 2003, 55 (3), 329–347.
13. Carrasquillo, K. G.; Stanley, A. M.; Aponte-Carro, J. C.; De Jésus, P.; Costantino, H. R.; Bosques, C. J.; Griebenow, K. Non-Aqueous Encapsulation of Excipient-Stabilized Spray-Freeze Dried BSA into Poly (Lactide-Co-Glycolide) Microspheres Results in Release of Native Protein. J. Control. Release 2001, 76 (3), 199–208.
14. Chan JM, Zhang L, Yuet KP, Liao G, Rhee J-W, et al. 2009. PLGA–lecithin–PEG core–shell nanoparticles for controlled drug delivery. Biomaterials 30: 1627–34
15. Kumari, A.; Yadav, S. K.; Yadav, S. C. Biodegradable Polymeric Nanoparticles Based Drug Delivery Systems. Colloids surfaces B biointerfaces 2010, 75 (1), 1–18.
16. Feng, C.; Yuan, X.; Chu, K.; Zhang, H.; Ji, W.; Rui, M. Preparation and Optimization of Poly (Lactic Acid) Nanoparticles Loaded with Fisetin to Improve Anti-Cancer Therapy. Int. J. Biol. Macromol. 2019, 125, 700–710.
17. A New Absorbable Suture—Frazza—1971—Journal of Biomedical Materials Research—Wiley Online Library. Available online: https://onlinelibrary.wiley.com/doi/abs/10.1002/jbm.820050207 (accessed on 28 May 2021).
18. Rampino A, Borgogna M, Blasi P, Bellich B, Cesàro A. 2013. Chitosan nanoparticles: Preparation, size evolution and stability. Int. J. Pharm 455: 219–28
19. Santoro M, Tatara AM, Mikos AG. 2014. Gelatin carriers for drug and cell delivery in tissue engineering. J. Control. Release 0: 210–8
20. Lugoloobi, I.; Maniriho, H.; Jia, L.; Namulinda, T.; Shi, X.; Zhao, Y. Cellulose nanocrystals in cancer diagnostics and treatment. J. Control. Release 2021, 336, 207–232.
21. Hudson D, Margaritis A. 2014. Biopolymer nanoparticle production for controlled release of biopharmaceuticals. Crit. Rev. Biotechnol 34: 161–79
22. Chen, F.; Huang, G.; Huang, H. Preparation and application of dextran and its derivatives as carriers. Int. J. Biol. Macromol. 2020, 145, 827–834.
23. Danhier F, Preat V (2015) Strategies to improve the EPR effect for the delivery of anti-cancer nanomedicines. Cancer Cell Microenviron2:e808
24. Ramazani F et al (2016) Strategies for encapsulation of small hydrophilic and amphiphilic drugs in PLGA microspheres: state-of-the-art and challenges. Int J Pharm 499(1-2):358–367
25. Kim BG, Kang IJ. Evaluation of the effects of biodegradable nanoparticles on a vaccine delivery system using AFM, SEM, and TEM. Ultramicroscopy 108: 1168-1173, 2008.
26. Shao J, Xie H, Huang H, Li Z, Sun Z, et al. 2016. Biodegradable black phosphorus-based nanospheres for in vivo photothermal cancer therapy. Nat. Commun 7: 12967.
27. Jose S, Sowmya S, Cinu TA, Aleykutty NA, Thomas S, Souto EB. Surface modified plga nanoparticles for brain targeting of Bacoside-A. Eur J Pharm Sci 63: 29-35, 2014.
28. Plummer R, Wilson RH, Calvert H, Boddy AV, Griffin M, et al. 2011. A Phase I clinical study of cisplatin-incorporated polymeric micelles (NC-6004) in patients with solid tumours. Br. J. Cancer 104: 593–8
29. Hamaguchi T, Kato K, Yasui H, Morizane C, Ikeda M, et al. 2007. A phase I and pharmacokinetic study of NK105, a paclitaxel-incorporating micellar nanoparticle formulation. Br. J. Cancer 97: 170–76
30. Hrkach J, Von Hoff D, Ali MM, Andrianova E, Auer J, et al. 2012. Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. Sci. Transl. Med 4: 12839–39
31. Suk, J.S.; Xu, Q.; Kim, N.; Hanes, J.; Ensign, L.M. PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. Adv. Drug Deliv. Rev. 2016, 99, 28–51.