



Anti-cancer nanoparticulate drug delivery system using biodegradable polymers

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ABSTRACT

Cancer is a hyper proliferative disorder marked by metastasis into the vital organs of the body through invasion and angiogenesis. Biodegradable nanoparticles have been used frequently as anti-cancer drug delivery vehicles due to its splendid bioavailability, better encapsulation, and control release with less toxic properties. Various nanoparticulate systems, general synthesis and encapsulation process, control release and improvement of therapeutic value of nano-encapsulated cancer drugs are covered in this review. We have highlighted the impact of biodegradable polymer such as PLGA, PLA, chitosan, gelatin, polycaprolactone and poly-alkyl-cyanoacrylates in the formulation of nanoparticles for encapsulation of cancer drugs. Hence in the current review a detailed studied has been done for the delivering of cancer drugs effectively using biodegradable polymers.

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Introduction

Cancer is a complicated disease to treat, contain, and identify. There are many different ways for treating cancer such as surgery, chemotherapy and radiation therapy. These methods are effective if the cancer tumor is caught soon enough. However, these treatments are not effective enough because they do not only target the affected cells, they also affect healthy cells. There is new technology that is showing promise in detecting cancer cells along with destroying cancer cells using chemicals found in nature and manmade chemicals. This new technology, which is a subcategory of nanotechnology, is less painful and targets the infected cells. Today Nanoparticles (NPs) are being studied and used for detecting and destroying cancer cells in mice. Hence the particles are so small that they are passing through healthy cells and making them mutate into cancer cells [1]. Nanotechnology has the prospective to impact the treatment of cancer significantly. In the present review will explore how this potential tool of drug delivery used effectively for the delivery and design of polymeric nanoparticle delivery systems. Hence in the recent research work has been focused on developing biocompatible nanoparticles capable of targeting specific cancer drugs and delivering imaging and therapeutic agents for the detection and treatment of cancer, resulting in a number of preclinical and clinical applications. More sophisticated nanoparticle designs are now in development, including particles able to release multiple drugs for enhanced treatment efficacy and targeted, multifunctional particles capable of combining imaging and drug release [2]. The impact of nanotechnology in cancer treatment effectively has a greater potential. In the modern research the development of biodegradable polymeric nanoparticles which had the ability of targeting specific cancer markers and delivering the agents for the detection and treatment of cancer, which improved the pre-clinical and clinical applications. More sophisticated

nanoparticle designs are now in development, including particles able to release multiple drugs for enhanced treatment efficacy and targeted, multifunctional particles capable of combining imaging and drug release. Dr. Ljubimova had demonstrated the use of polymalic polymer nanoparticles which effectively used to target brain tumor, and to a greater extent reduce the extent of cancer cells [3]. The synthesis and nanomedicine formulation of chitosan, PLGA, PLA are well reviewed. However, the present study will review about the different types of biodegradable polymers used for the development of cancer chemotherapy.

Classification of Biodegradable polymer

When working with biodegradable materials, the obvious question is why some polymers biodegrade and others do not? To understand this, one needs to know about the mechanism through which polymeric materials are biodegraded [4-5]. The biodegradable polymer is broadly classified into two categories based on the source from where it is obtained such as natural and synthetic.

I. Natural Polymers

1. Protein-based polymers

▪ Albumin, Collagen, Gelatin, Silk proteins, Fibroin, Sericin, Keratin

2. Polysaccharides

▪ Alginate, Chitosan

II. Synthetic Polymers or semi-synthetic

1. Polyesters: PLGA, Poly (lactic acid) PLA, Poly (caprolactone) PCL, Poly-alkyl-cyano-acrylates (PAC), Poly (glycolic acid) PGA.

2. Ceramic based NPs

3. Miscellaneous

▪ Poly anhydrides, Poly peptides, Poly (ethylene glycol) PEG, Polyamides.

Formulation of polymeric NPs

Based on the need and type of drug to be encapsulated the Polymeric NPs have been synthesized. These NPs are extensively used for the encapsulation of various useful bioactive molecules and medicinal drugs to develop nanomedicine. The uses of Biodegradable polymeric NPs are highly preferred because they show promise in drug delivery system. Such NPs provide controlled/sustained release property, sub-cellular size and biocompatibility with tissue and cells [6]. Apart from this, these NMs are stable in blood, non-toxic, nonthrombogenic, nonimmunogenic, noninflammatory, do not activate neutrophils, biodegradable, avoid reticuloendothelial system and applicable to various molecules such as drugs, proteins, peptides, or nucleic acids[7]. The general synthesis and encapsulation of biodegradable NMs are represented in Fig. 1. The drug molecules either bound to surface as nanosphere or encapsulated inside as nanocapsules. For the past two decades, countless work has been conducted to develop most effective NMs from biocompatible and biodegradable nanopolymers. The role of nano-systems for drug delivery through oral, nasal, ocular administration is reviewed by Alonso reviewed the various methods of synthesis and encapsulation of different bioactive molecules on NPs [9-10]

Bio-polymeric Nanoparticles (Natural polymers)

Biopolymer nanoparticles were first designed using albumin and non-biodegradable synthetic polymers such as polyacrylamide and poly (methylacrylate). The risks of chronic toxicity due to the intracellular and/or tissue overloading of non-degradable polymers were soon considered as a major limitation for the systemic administration of polyacrylamide and poly (methylacrylate) nanoparticles in humans. As a consequence, the type of nanoparticles that received much attention was designed with synthetic biodegradable polymers including polyalkylcyanoacrylate, poly (lactic-co-glycolic acid) and polyanhydride. The need for developing biodegradable nanoparticles (liposome, virus-like particle (VLP), protein, etc) as effective drug delivery devices was felt years ago. The reason being in addition to the general advantages of nanoparticles, biopolymer nanoparticles in particular offer several advantages, which include the ease of their preparation from well-understood biodegradable polymers and their high stability in biological fluids and during storage. Nanoparticles made of biodegradable polymers like proteins and polysaccharides can act as efficient drug delivery vehicles for sustained, controlled and targeted release, aiming to improve the therapeutic effects and also to reduce the side effects of the formulated drugs [11-12].

Protein nanoparticles

The first naturally occurring material used for the preparation of nanoparticles consisted of two proteins, albumin and gelatin. Among the colloidal systems, those based on proteins are very promising because they are biodegradable, less immunogenic and non-toxic; they have greater stability *in vivo* and during storage, are relative easy to prepare and to monitor size distribution, and their manufacture can be scaled up. In addition, because of the defined primary structure of proteins, the protein-based nanoparticles offer various possibilities for surface modification and covalent drug attachment [13].

Albumin

Albumin, a protein found in blood plasma, has always been a remarkable molecule owing to its manifold functions and applications. Albumin is a biodegradable, biocompatible and less-immunogenic protein. The paramount function of albumin is in the circulatory system to aid in transportation, metabolism,

and distribution of exogenous and endogenous ligand. It also has an ability to act as an important extracellular antioxidant and to impart protection from free radicals and other harmful chemical agents. These unique attributes of albumin created a premier place for it in the drug therapy from time immemorial [32-38]. The effect of an albumin polymer during breast cancer surgery on postoperative seroma formation was evaluated. The findings demonstrated that use of albumin polymers during breast cancer surgery lowers postoperative seroma outcome significantly [14].

Collagen

Collagen is the structural building material of vertebrates and the most abundant mammalian protein that accounts for 20–30% of total body proteins. Collagen has a unique structure, size and amino acid sequence which results in the formation of triple helix fiber. Collagen is regarded a useful biomaterial because of its excellent biocompatibility, biodegradation and availability. The biodegradable collagen based nanoparticles are thermally stable, readily sterilizable, can be uptaken by the reticuloendothelial system and enable enhanced uptake of drug molecules into the cells. Current research efforts in several laboratories are aimed at overcoming the barriers that limit the effective tumor delivery and penetration of the nanomedicine candidates as Ac therapeutics, including: [1] heterogeneous tumor circulation caused by abnormal and irregular architecture of the tumor vasculature, [2] intratumoral vascular hyperpermeability contributing to increased interstitial pressure in the targeted tumor that substantially reduces the convective transport of nanoparticles and [3] impaired diffusion in the context of an abnormal and highly dense extracellular collagen matrix in the tumor microenvironment [15-16].

Gelatin

Gelatin is a natural water-soluble macromolecule resulting from the heat dissolution and partial hydrolysis of collagen. There are two types of gelatin: type-A gelatin is obtained by acid treatment of collagen with the isoelectric point (pI) between 7.0 and 9.0, whereas Type-B gelatin is produced via alkaline hydrolysis of collagen with the pI between 4.8 and 5.0. Gelatin offers a number of advantages over other synthetic polymers including non-irritability, biocompatibility and biodegradability, which makes it one of the desirable materials as carrier molecule. It is a natural macromolecule which is non-toxic and non-carcinogenic, and it shows low immunogenicity and antigenicity. Gelatin has large number of functional groups on its surface which aid in chemical cross linking and derivatization. These advantages led to its application for the synthesis of nanoparticles for drug delivery during the last thirty years. Paclitaxel-loaded gelatin NPs have been reported by desolvation method. Entrapped paclitaxel was present in an amorphous state, which has higher water solubility compared with the crystalline state. The paclitaxel-loaded NPs were effective against human bladder transitional cancer cells [17].

Silk proteins

Sericin and fibroin nanoparticles Silk fibers are primarily made of fibroin and sericin where the structural protein, fibroin is enveloped by the gum-like sticky protein, sericin.

Silk Fibers (Cocoons)

The biomedical application of silk fibroin (SF) evaluated to develop a novel silk-based platform for the controlled drug delivery. The fibers are biocompatible, biodegradable and minimal inflammatory reaction, also used as a matrix for enzyme immobilization and mammalian cell culture. The SF containing matrixes are prepared by spray-drying and film

casting. SF containing matrixes and microparticles are prepared from aqueous solutions of the fibroin protein polymer. Crystallinity is induced and controlled by treatment with different solvents and by spray-drying, resulting in a formation of a fine interpenetrating network (IPN) of SF. The *in vitro* release assays have shown that the increase in crystallinity resulted in sustained release of the model drugs from the dehydrated SF containing matrix, proving SF is an interesting polymer for drug delivery of bioactive compounds, particularly for colonic drug delivery. Silk fibroin (SF)-coated liposomal emodin was shown to have higher efficacy against breast cancer cells as compared to the uncoated liposomal emodin due to increased retention of emodin in the presence of SF. Loading the drug into liposomes and then coating them with SF produced particles that were larger in size than 100 nm. Nanoparticles of curcumin encapsulated with pure SF showed the highest curcumin entrapment, release, intracellular uptake, and efficacy towards breast cancer cells.

Fibroin

Fibroin is a hydrophobic glycoprotein and one of the 'core' proteins—constitutes over 70% of the cocoon. This insoluble protein is almost entirely made of the amino acids glycine, alanine, and serine (-Gly-Ala-Gly-Ala-Gly-Ser-) leading to the formation of antiparallel pleated sheet in the fibers. Fibroin is semi-crystalline and consists of two phases: one is the highly crystalline pleated sheet phase and the other is non-crystalline phase. Silk fibroin is also histocompatible, less immunogenic and non-toxic. Silk fibroin can be processed into various forms including gels, fibers, membranes, scaffolds, hydrogels and nanoparticles. Silk fibroin matrices with high specific surface area, high porosity, good biocompatibility and biodegradability have extensive applications in the field of biomaterials and cancer drug delivery. Moreover silk-based biomaterials are highly biocompatible with various cell types and promote cell growth and proliferation [18].

Sericin

Sericins-hydrophilic glycoproteins functioning as 'glue' constitute about 20 to 30% of the cocoon. These hot water soluble proteins comprise different polypeptides ranging in weight from 24 to 400 kDa and have unusually high serine content (40%) along with significant amounts of glycine (16%). Sericin is comprised of 35% sheet and 63% random coil, and has no α -helical content—hence, its partially unfolded state. Sericin nanoparticles, apart from the general advantages of protein nanoparticles, may also offer certain other benefits of the inherent property of sericin. Those include antioxidant and antitumor action; enhancement of the bioavailability of such elements as Zn, Mg, Fe, and Ca; as well as suppression of coagulation when sulfated. Sericin is non-toxic to fibroblast cells. Methionine and cysteine content in silk sericin are important factors to promote cell growth and collagen synthesis. Water-soluble silk sericin has no immunogenicity and is also a biocompatible macromolecular protein like silk fibroin. A study of the macrophage response of silk protein concludes that sericin does not usually manifest inflammatory activity when present in soluble form. It has been proved that sericin promotes wound healing without causing any inflammation [19].

Keratin

Keratins are a group of cysteine-rich structural proteins that exhibit a high mechanical strength owing to a large number of disulfide bonds. Keratin has been used very recently as nanosuspension that results in ultrathin, transparent keratin

coatings to investigate the *in vitro* cell proliferation behavior as a potential coating material for standard cultivation. The keratin nanosuspension coatings may provide an inexpensive alternative to materials like collagen or fibronectin. Keratin nanosuspension may also find applications in tissue engineering if it is explored further [20].

Polysaccharide nanoparticles

Polysaccharide-derived nanoparticles and nanostructured surfaces help to improve biocompatibility of cell toxic material, together with new immobilization approaches, which are currently in development for novel bionanoparticle-derived pharmaceutical formulations. Nanoparticles from naturally occurring polysaccharides were designed for the administration of peptides, proteins, and nucleic acids.

Alginate

Alginate is a naturally occurring, water-soluble, linear unbranched polysaccharide extracted from brown seaweed. Alginate is composed of two types of uronic acids, α -L-guluronic acid and β -D-mannuronic acid. The monomeric units are grouped in three ways: blocks of alternating guluronic and mannuronic residues, blocks of guluronic acids and of mannuronic acids. Alginate has been reported as mucoadhesive, biocompatible, non-immunogenic substance that undergoes dissolution and biodegradation under normal physiological conditions. The solubility of alginate in water depends on the associated cations. Sodium alginate is soluble in water, whereas calcium induces the formation of a gel [21].

Chitosan

Chitosan polymers have emerged as a new class of physiological materials of highly sophisticated functions and to exploit the properties of these versatile polysaccharides, several attempts made to derivatize them. Chemical modifications have done an excellent job for the preparation of chitosan derivatives with higher solubility in water, such as O-N-carboxymethyl-chitosan, N-carboxymethyl-chitosan, O-carboxymethyl-chitosan, N-sulfate-chitosan, O-sulfate chitosan, O-succinyl-chitosan, N-methylene phosphonic chitosan, hydroxypropyl chitosan, N-trimethyl chitosan, and others. The emergence of synthesis strategies for the fabrication of nanosized particles leads to advancements in the nanotechnology, which benefits molecular imaging for understanding of biological processes at the molecular level. In addition, with the added multifunctional features such particles may become an integral part of the development of next generation therapeutic, diagnostic and imaging technologies [22]. Brain tumor treatment employing MTX is limited by the efflux mechanism of P-gp on the blood-brain barrier. We aimed to investigate MTX-loaded chitosan or glycol chitosan (GCS) NPs in the presence and in the absence of a coating layer of Tween 80 for brain delivery of MTX. The results suggest that even a low concentration of Tween 80 is sufficient for enhancing the transport of MTX from the NPs across MDCKII-MDR1 cells. The nano-carriers represent a promising strategy for the administration of MTX to brain tumors [22].

Synthetic Polymers

Polyesters

Poly-D,L-lactide-co-glycolide (PLGA)

The application of PLGA (poly-D,L-lactide-co-glycolide) in the delivery of cancer drugs specifically found to be most successful method of biodegradable nanosystem used for the development of NMs. Hence, it undergoes hydrolysis in the body to produce the biodegradable metabolite such as

monomers, lactic acid and glycolic acid. The rate of elimination of the monomer from the body is found to be effective because of which the systemic toxicity levels are minimal. PLGA NPs have been mostly prepared by emulsification–diffusion, solvent emulsion–evaporation, interfacial deposition and nano-precipitation method. The preparation of PLGA nanoparticles designed specifically to target breast tumour cells [23].

Encapsulation of various Anti-cancer (Ac) drugs on PLGA NPs PLGA is approved by FDA for therapeutic use in humans. Protocols have been optimized for PLGA NPs synthesis and numerous cancer related drugs are incorporated in PLGA. These loaded NPs protect poorly soluble and unstable payloads from the biological milieu and are small enough for capillary penetrations, cellular internalization and endosomal escape. Furthermore, their surface is modified for targeted delivery of molecules to tumor or other tissues. PLGA NPs are frequently used for the encapsulation of various cancer related drugs and their successful delivery *in vivo*. The cancer related drug paclitaxel, doxorubicin, 5-fluorouracil, 9-nitrocamptothecin, cisplatin, triptorelin, dexamethasone, xanthone, etc., have been successfully encapsulated on PLGA NPs. The mechanism of action of these drugs, encapsulation mechanism, encapsulation efficiency are peculiar characteristic for encapsulation and drug release mechanisms of the cancer therapeutics. [24-27]

Poly(lactic acid (PLA)

A modified spontaneous emulsification solvent diffusion method is used to prepare the Oridonin (ORI) loaded lactic poly (D, L-lactic acid) nanoparticles. ORI-PLA-NPs showed greater antitumor efficacy than PLA NPs, as reflected by the decreased tumor growth and the prolonged survival time of mice bearing H22 tumors. The tumor-targeting efficiency and subsequent antitumor efficacy of ORI is increased by incorporation into PLA NPs [28].

PLA-Ethyl Cellulose Copolymer

The PLA-EC copolymer synthesized from lactic acid and ethyl cellulose of by azeotropic dehydration, under reduced pressure, at 140°C for 8 hours and characterized. The prepared PLA-EC copolymer was used for controlled drug release for an anticancer drug namely 6-Thioguanine with gold NPs. Anticancer drug containing PLA-EC copolymer nanocapsules were prepared by solvent evaporation method in the presence and absence of gold NPs [29]. The rate of drug release from the nanocapsules was influenced by the pH of the dissolution medium. Due to prolonged drug release in acidic pH as suggested by the dissolution, PLA-co-EC nanocapsules can be used for delivery of 6-thioguanine drug [30].

Poly-ε-caprolactone (PCL)

Docetaxel-loaded nanoparticles were prepared by modified solvent displacement method using commercial PCL and self-synthesized PCL/Pluronic F68, respectively. PCL/Pluronic F68 nanoparticles were found to be of spherical shape with a rough and porous surface. The nanoparticles had an average size of around 200 nm with a narrow size distribution. The *in vitro* drug release profile of both nanoparticle formulations showed a biphasic release pattern. There was an increased level of uptake of PCL/Pluronic F68 nanoparticles in docetaxel-resistance human breast cancer cell line, MCF-7 TAX30, when compared with PCL nanoparticles. The cytotoxicity of PCL nanoparticles was higher than commercial Taxotere® in the MCF-7 TAX30 cell culture, but the differences were not significant ($p > 0.05$). However, the PCL/Pluronic F68 nanoparticles achieved significantly higher level of cytotoxicity than both of PCL

nanoparticles and Taxotere® ($p < 0.05$), indicating docetaxel-loaded PCL/Pluronic F68 nanoparticles could overcome multidrug resistance in human breast cancer cells and therefore have considerable potential for treatment of breast cancer [30-32].

Poly-alkyl-cyano-acrylates (PAC)

The biodegradable as well as biocompatible poly-alkylcyanoacrylates (PAC) are degraded by esterases in biological fluids and produce some toxic products that will stimulate or damage the central nervous system. Thus this polymer is not authorized for application in human. However, PAC NPs are prepared mostly by emulsion polymerization, interfacial polymerization and nanoprecipitation for drug delivery and nanoformulation [33]. The polybutylcyanoacrylate (PBC) encapsulated doxorubicin NPs have been reported to increase 60-fold in the brain after coated with polysorbate 80. Ftorafur is a type of substance being used in the treatment of cancer. It is a combination of tegafur and uracil. The tegafur is taken up by the cancer cells and breaks down into 5-FU, a substance that kills tumor cells. The uracil causes higher amounts of 5-FU to stay inside the cells and kill them. Poly-ethyl-2-cyanoacrylate (PE-2-CA) and PBC nanospheres were used to encapsulate ftorafur [Tegafur, 5-fluoro-1-(tetrahydro-2-furyl) uracil], a broad spectrum antitumor drugs. With respect to the release profiles, ftorafur surface adsorption onto nanospheres led to a very rapid drug release in sink conditions. However, the drug incorporation into the NPs permitted a larger loading and a slower release [34].

Poly-glycolic acid

Poly-glycolic acid is biocompatible in the body. A needle-shaped long-acting anti-cancer preparation (F-PGA needle) was prepared by compounding polyglycolic acid and the anti-cancer drug 5-Fluorouracil (5-FU). The release of 5-FU from the needle was maintained for about 10 days, and the needle disappeared after one year. A clinical study with the F-PGA needle was made on patients with terminal carcinomas. Shrinkage of tumors and tumor necrosis were observed in two patients with metastatic liver carcinomas. The F-PGA needle supplies high-dose 5-FU locally for a long time with fewer side effects by embedding it into the tumor tissue. Therefore the F-PGA needle can be said to be promising in the treatment of unrespectable (check the spelling and meaning) cancer as a topical application of chemotherapy [48].

Ceramic Based NPs

Ceramic-based NPs are extensively investigated because of their enormous potential in the photodynamic cancer therapy (PCT) field. This is an emerging modality for the treatment of a variety of oncological, cardiovascular, dermatological and ophthalmic diseases. PCT is based on the concept that light-sensitive species or photosensitizers can be preferentially localized in tumor tissues upon systemic administration. Roy *et al.*, [30] have shown that ultra-fine organically modified silica-based NPs, carrying a water-insoluble photosensitizing Ac drug-dye, 2-devinyl-2-(1-hexyloxyethyl) pyropheophorbide (HPPH), were efficiently taken up by tumor cells *in vitro*, and light irradiation of such impregnated cells resulted in significant cell death.

Polyanhydrides

A novel approach to targeted antigen delivery by decorating the surface of polyanhydride nanoparticles with specific carbohydrates to provide “pathogen-like” properties that ensure nanoparticle engage C-type lectin receptors on DCs. The surface

of polyanhydride nanoparticles was functionalized by covalent linkage of dimannose and lactose residues using an amine-carboxylic acid coupling reaction [35].

Polypeptide

Polymeric targeted nanoparticle-polypeptide conjugates that shows cell binding specificity and stealth properties. The targeted nanoparticles binds and are taken up efficiently by Her2 expressing breast cancer cells. These nanoparticles represent a powerful tool for breast cancer treatment [36].

Poly ethelene glycol

Breast cancer treatment drug tamoxifen has been widely administered for more than three decades. This small molecule competes with 17 β - estradiol for binding to estrogen receptor, a hormone receptor unregulated in a majority of breast cancer, subsequently initiated programmed cell death. The thiol-PEGylated Tamoxifen derivatives that can be used to selectively target and deliver plasmonic gold nanoparticles to estrogen receptor positive breast cancer cells with enhanced drug potency [37].

Polyamides

Paclitaxel-loaded formulations using a novel type of self-assembled nanoparticles (P/NPs) composed of block copolymers synthesized by poly (gamma-glutamic acid) and poly(lactide). For the potential of targeting liver cancer cells, galactosamine was conjugated on the prepared nanoparticles (Gal-P/NPs). The biodistribution and anti-tumor efficacy of the prepared nanoparticles were studied in hepatoma-tumor-bearing nude mice. It was found that the groups injected with Phyxol, the P/NPs or the Gal-P/NPs significantly delayed the tumor growth as compared to the control group injected with PBS. Therefore, the prepared Gal-P/NPs may be used as a potential drug delivery system for the targeted delivery to liver cancers [38-42].

Conclusion

Biodegradable anti-Cancer nanoparticulate drug delivery systems seem to be a viable and promising strategy for the treatment of cancer chemotherapy. They have advantages over conventional drug delivery systems. They can increase the bioavailability, solubility and permeability of many potent anti-cancer drugs which are otherwise difficult to deliver orally. Anti-Cancer Nanoparticulate drug delivery systems will also reduce the drug dosage frequency and will increase the patient compliance. In near future biodegradable nanoparticulate drug delivery systems can be used for exploiting many drugs, which have poor aqueous solubility, permeability, and less bioavailability. NPs can minimize some of these drugs unique problems by safeguarding stability and preserving their structure. In addition, NPs provide ingenious treatment by enabling targeted delivery and controlled release.

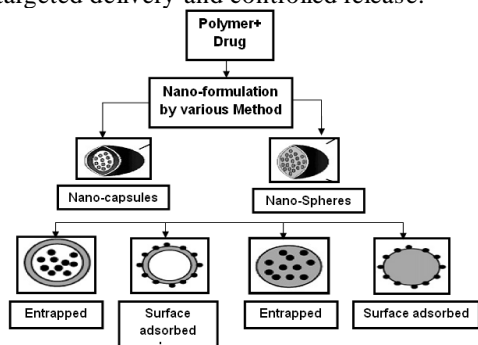


Figure 1 Classification of biodegradable NPs

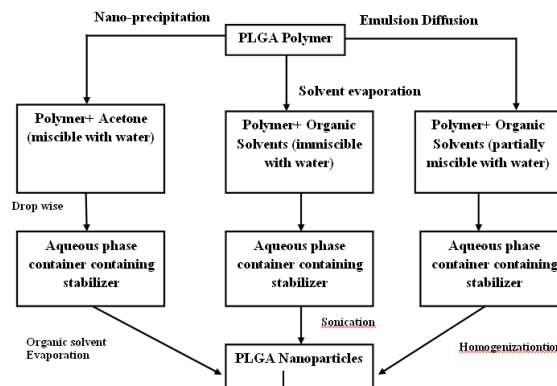


Figure 2 different methods for the synthesis of PLGA nanoparticles

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