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Biodegradable polymeric nanoparticles: The novel carrier for controlled release drug delivery system

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Abstract

In the recent decades, polymers are widely used as biomaterials due to their favourable properties such as good biocompatibility, easy design and preparation, structural varieties and interesting bio-mimetic character. The use of biodegradable polymeric nanoparticles (NPs) for controlled drug delivery has shown significant therapeutic potential. Concurrently, targeted delivery technologies are becoming increasingly important as a scientific area of investigation. The current review entails an in-depth discussion of biodegradable polymeric nanoparticles with respect to types, formulation aspects as well as site-specific drug targeting using various ligands modifying the surface of polymeric nanoparticles with special insights to the field of oncology. Ultimately the goal of polymeric nanoparticle drug delivery is the emergence of a nano-fabricated therapeutic drug release device with the capacity to enough hold and release of various active agents on demand.

Keywords: Biodegradable Polymers; Bio-mimetic; Controlled drug delivery; Targeted delivery; Ligands

1. Introduction

Nanotechnology has been extensively exploited in pharmaceutical and biomedical applications, with significant impact on the therapeutics and diagnosis of diseases such as cancer and cardiovascular diseases[1]. Among several nanoparticulate systems, lipid-based nanocarriers, such as liposomes, solid-lipid nanoparticles, and nanostructured lipid carriers, and biodegradable polymeric nanoparticles are the most widely adopted nanosystems for drug delivery[2]. In general, nanocarriers may protect a drug from degradation, enhance drug absorption by facilitating diffusion through epithelium, modify pharmacokinetic and drug- tissue distribution profile and/or improve intracellular penetration and distribution. Furthermore, by modulating the surface properties, composition and milieu, the desired release pattern of the drug and its biodistribution can be achieved. Additionally, one of the major advantages associated with the nanoparticulate systems is their ability to withstand physiological stress or improved biological stability and possibility of oral delivery which makes them more attractive as a drug delivery strategy than liposomes.

Different types of nano-sized carriers, such as polymeric nanoparticles, solid lipid nanoparticles, ceramic nanoparticles, magnetic nanoparticles, polymeric micelles, polymer-drug conjugates, nanotubes, nanowires, nanocages and dendrimers, etc., are being developed for various drug-delivery applications[3]. Polymeric nanoparticles can be fabricated from polysaccharides, proteins and synthetic polymers. Nanoparticles made from natural hydrophilic polymers have been proved efficient in terms of better drug-loading capacity, biocompatibility and possibly less opsonization by reticuloendothelial system (RES) through an aqueous steric barrier[4].

Polymeric NPs play a significant role because it can deliver therapeutic agents directly into the intended site of action, with superior efficacy. These nanoparticles can enhance the systemic circulation half-life and minimize unwanted

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internalization and prevents the denaturation of the therapeutically active moiety and could use to deliver the target agents. The ideal requirements for designing nano-particulate delivery system are to effectively control particle size, surface character; enhance permeation, flexibility, solubility and release of therapeutically active agents in order to attain the target and specific activity at a predetermined rate and time. Such a drug delivery system has been successfully made by the advances in polymer science in the bio-nanotechnology. Most of the polymeric nanoparticles with surfactants offer stability of various forms of active drugs and have useful release properties. There are numerous biological applications reported for the nano-scale to micro-scale sized particles, such as site-targeted, controlled, and enhanced bioavailability of hydrophobic drugs. Due to the nanoparticles size the drugs have been targeting into various applications, such as, various cancers targeting has been shown to be promising. Moreover, polymeric particles proved their effectiveness in stabilizing and protecting the drug molecules such as proteins, peptides, or DNA molecules from various environmental hazards degradation. So, these polymers are affording the potential for various protein and gene delivery.

Numerous methods had been available to fabricate nanoparticles; it depends on the physical and chemical properties of polymer and active ingredients. Most of the formulation techniques involve different mechanisms such as using organic solvents, temperature, ultra-sonication and mechanical agitation which can degrade the pharmaceutical active ingredients. So, the nano-particulate system can be developed to consider the formulation methodology should not damage the active pharmaceutical ingredients. Several polymer systems are approved by the U.S. Food and Drug Administration (FDA) for human use. It is the belief that when inventions in fabrication can catch up with those in materials; design and development of drug delivery system can enter a new generation of enhancing clinical healthcare[5].

2. Types of Biodegradable Polymers Used in Nanotechnology

2.1. Carbohydrate Based Nanoparticle

Polymers used to form nanoparticles can be two types, hydrophobic and hydrophilic. Nanoparticles based on hydrophilic polymers are appropriate candidates for drug delivery systems, because they have the advantage of prolonged circulation in blood, which could facilitate extravasation and passive targeting. It is worth mentioning that hydrophilic polymer-based nanostructures with particle size less than 100 nm avoid opsonisation[4].

2.1.1. Chitosan

Chitosan, poly [β-(1-4)-linked-2-amino-2-deoxy-d-glucose], is a modified natural carbohydrate polymer similar to cellulose which is obtained from the deacetylation of chitin. It is biologically safe, nontoxic, biocompatible, biodegradable, bioactive, bio adhesive, nontoxic, nonimmunogenic, antibacterial and poly cationic polysaccharide. Chitosan nanoparticles have gained more attention as drug delivery carriers because of their better stability, low toxicity, simple and mild preparation method and providing versatile routes of administration. Their sub-micron size is also suitable for mucosal routes of administration i.e. oral, nasal and ocular mucosa which is non-invasive route. Chitosan nanoparticles showed to be a good adjuvant for vaccine. These properties render chitosan a very attractive material as a drug delivery carrier[6].

Chitosan can be described in general by the following parameters:

- Degree of deacetylation in %
- Dry matter in %
- Ash in %
- Protein in %
- Viscosity in Centipoise
- Intrinsic viscosity in ml/g
- Molecular weight in g/mol
- Turbidity in NTU units.

All of these parameters can be adjusted to the application for which chitosan is being used. The deacetylation is very important to get a soluble product. In general, the solubility of heteroglycans are also influenced by the distribution of the acetyl groups, the polarity and size of the monomers, distribution of the monomers along the chain, the flexibility of the chain, branching, charge density, and molecular weight (50,000 to 2,000,000 Da) of the polymer. Viscosity (10 to 5000 cp) can be adjusted to each application by controlling the process parameters. The pharmaceutical requirements for chitosan include: a white or yellow appearance (powder or flake), particle size < 30 m, density between 1.35 and

1.40 g/cm3, a pH of 6.5 to 7.5, moisture content < 10%, residue on ignition <0.2%, protein content <0.3%, degree of deacetylation 70% to 100%, viscosity <5 cps, insoluble matter <1%, heavy metals (As) <10 ppm, heavy metals (Pb) <10 ppm, and no taste and smell[7].

2.2. Synthetic Nanoparticles

2.2.1. Poly (lactic-co-glycolic acid)

PLGA has attracted great attention in the design of delivery systems because of its excellent biocompatibility and biodegradability, which are the result of its ester linkages undergoing hydrolysis in the presence of water. This produces the original monomers, lactic acid and glycolic acid, which are easily metabolized in the body via the Krebs cycle without any systemic toxicity. The attractive features of PLGA-based nanoparticles, such as small size, high structural integrity, stability, ease of fabrication, tuneable properties, controlled release capability, and surface functionalization characteristics, make them versatile therapeutic delivery vehicles. Besides, FDA has approved PLGA polymeric nanoparticles-based drug delivery for human use and nanomedicines preparation. PLGA of different molecular weights (from 10 kDa to over 100 kDa) and different copolymer molar ratios (50:50, 75:25, and 85:15) is available on the market. Molecular weight and copolymer molar ratio influence the degradation process and release profile of the drug entrapped[8]. Nevertheless, the biodegradable nanoparticles encapsulated various chemotherapeutic agents to improve the compatibility and biodistribution have raised some concerns. The polymeric matrix prevents the degradation of the drug and also allow precise control over the release kinetics of the drug from nanoparticle Moreover, the duration and levels of drug released from the nanoparticles can be easily modulated by altering formulation parameters such as drug: polymer ratio, or polymer molecular weight and composition. Drugs encapsulated in such polymer passively target the tumour tissue through the enhanced permeation and retention (EPR) effect.

However, the limitations of PLGA-based nanoparticles in terms of their physicochemical and biological properties restricting their applications in nanomedicine include poor drug loading, high burst release, uptake by the reticuloendothelial system (RES), less circulation time in the body, aggregation, cost, and manufacturing scale-up. To resolve these constraints of PLGA nanoparticles, the focus has now moved towards the development of hybrid PLGA nanoparticles. To alleviate these limitations, several attempts have also been made to modify the surface properties of PLGA nanoparticles. Hybridization enables the design of novel nanoarchitecture, using two nanostructures, thus imbibing the functionalities of both within one system.

3. Formulation Aspect of Polymeric Nanoparticle

3.1. Chitosan Nanoparticle

3.1.1. Ionotropic Gelation

Chitosan NP prepared by ionotropic gelation technique was first reported by Calvo *et al*[9]. The mechanism of chitosan NP formation is based on electrostatic interaction between amine group of chitosan and negatively charge group of polyanion such as tripolyphosphate. This technique offers a simple and mild preparation method in the aqueous environment. First, chitosan can be dissolved in acetic acid in the absence or presence of stabilizing agent, such as poloxamer, which can be added in the chitosan solution before or after the addition of polyanion. Polyanion or anionic polymers was then added and nanoparticles were spontaneously formed under mechanical stirring at room temperature. The size and surface charge of particles can be modified by varying the ratio of chitosan and stabilizer.

3.1.2. Microemulsion Method

Chitosan NP prepared by microemulsion technique was first developed by Maitra *et al* [10]. This technique is based on formation of chitosan NP in the aqueous core of reverse micellar droplets and subsequently cross-linked through glutaraldehyde. In this method, a surfactant was dissolved in N-hexane. Then, chitosan in acetic solution and glutaraldehyde were added to surfactant/hexane mixture under continuous stirring at room temperature. Nanoparticles were formed in the presence of surfactant. The system was stirred overnight to complete the cross-linking process, which the free amine group of chitosan conjugates with glutaraldehyde. The organic solvent is then removed by evaporation under low pressure. The yields obtained were the cross-linked chitosan NP and excess surfactant. The excess surfactant was then removed by precipitate with $CaCl_2$ and then the precipitant was removed by centrifugation. The final nanoparticles suspension was dialyzed before lyophilization. This technique offers a narrow size distribution of less than 100 nm and the particle size can be controlled by varying the amount of glutaraldehyde that alter the degree of cross-linking. Nevertheless, some disadvantages exist such as the use of organic solvent, time-consuming preparation process, and complexity in the washing step.

3.1.3. Emulsification Solvent Diffusion method

El-Shabouri reported chitosan NP prepared by emulsion solvent diffusion method, (which originally developed by Niwa *et al.* employing PLGA[11]. This method is based on the partial miscibility of an organic solvent with water. An o/w emulsion is obtained upon injection an organic phase into chitosan solution containing a stabilizing agent (i.e. poloxamer) under mechanical stirring, followed by high pressure homogenization. The emulsion is then diluted with a large amount of water to overcome organic solvent miscibility in water. Polymer precipitation occurs as a result of the diffusion of organic solvent into water, leading to the formation of nanoparticles. This method is suitable for hydrophobic drug and showed high percentage of drug entrapment. The major drawbacks of this method include harsh processing conditions (e.g., the use of organic solvents) and the high shear forces used during nanoparticle preparation.

3.1.4. Polyelectrolyte Complex (PEC)

Polyelectrolyte complex or self-assembly polyelectrolyte is a term to describe complexes formed by self-assembly of the cationic charged polymer and plasmid DNA. Mechanism of PEC formation involves charge neutralization between cationic polymer and DNA leading to a fall in hydrophilicity. Several cationic polymers (i.e. gelatin, polyethyleneimine) also possess this property. Generally, this technique offers simple and mild preparation method without harsh conditions involved. The nanoparticles spontaneously formed after addition of DNA solution into chitosan dissolved in acetic acid solution, under mechanical stirring at or under room temperature (Erbacher *et al*., 1998)[12]. The complexes size can be varied from 50 nm to 700 nm.

3.2. PLGA nanoparticles

3.2.1. Emulsion Diffusion Method

In this synthetic scheme, the polymer (PLGA) is dissolved in an organic phase (e.g., benzyl alcohol, propylene carbonate, ethyl acetate), which must be partially miscible in water. The organic phase is emulsified with an aqueous solution of a suitable surfactant (i.e. anionic sodium dodecyl sulfate (SDS), non-ionic polyvinyl alcohol (PVA), or cationic dido decyl dimethyl ammonium bromide (DMAB), under stirring. The diffusion of the organic solvent and the counter diffusion of water into the emulsion droplets induce polymer nanoparticle formation. Important parameters that affect the nanoparticle size synthesized by emulsion evaporation are: PLGA copolymer ratio, polymer concentration, solvent nature, surfactant polymer molecular weight, viscosity, phase ratios, stirring rate, solvent nature, temperature and flow of water added.

3.2.2. Salting Out Method

In this synthesis method, the polymer is dissolved in the organic phase, which should be water-miscible, like acetone or tetrahydrofuran (THF). The organic phase is emulsified in an aqueous phase, under strong mechanical shear stress. The aqueous phase contains the emulsifier and a high concentration of salts which are not soluble in the organic phase. Typically, the salts used are 60% w/w of magnesium chloride hexahydrate or magnesium acetate tetrahydrate in a ratio of 1:3 polymer to salt. Contrary to the emulsion diffusion method, there is no diffusion of the solvent due to the presence of salts. The fast addition of pure water, to the o/w emulsion, under mild stirring, reduces the ionic strength and leads to the migration of the water-soluble organic solvent to the aqueous phase inducing nanosphere formation[14]. The final step is purification by cross flow filtration or centrifugation to remove the salting out agent. Common salting out agents are electrolytes (sodium chloride, magnesium acetate, or magnesium chloride) or non-electrolytes, such as sucrose.

3.2.3. Nanoprecipitation (Solvent Diffusion, or Solvent Displacement) Method

Typically, this method is used for hydrophobic drug entrapment, but it has been adapted for hydrophilic drugs as well. Polymer and drug are dissolved in a polar, water miscible solvent such as acetone, acetonitrile, ethanol, or methanol. The solution is then poured in a controlled manner (i.e. drop-wise addition) into an aqueous solution with surfactant. Nanoparticles are formed instantaneously by rapid solvent diffusion. Finally, the solvent is removed under reduced pressure[15].

The methods detailed above are the main methods extensively employed in the synthesis of PLGA nanoparticles for different purposes. There is a continuous effort to improve the nanoparticle size (size reduction), to reduce the polydispersity index, to better entrap the active components (hydrophilies and hydrophobics), and to reduce the potential toxicity of the different components involved. These efforts stimulated research and discovery of new methods, based on slight modifications of standard methods, and the application of new synthesis steps in the PLGA nanoparticles formation.

3.2.4. Membrane Emulsion Evaporation Method

The aqueous and organic phases are separated by a membrane which has a defined pore diameter and distribution. The organic phase is forced through the pores to form an organic droplet which is detached from the membrane by a certain movement of the aqueous phase. The membrane has a hydrophobic or hydrophilic behaviour as a function of the disperse phase (aqueous or organic solvent). This can lead to very uniform size distribution of nanoparticles, but the main drawback is the bigger size obtained compared to normal emulsion evaporation method. The pore diameter affects the final size of the nanoparticles, and there is a relation pore to droplet diameter of 1:3. There are a number of criteria that have to be met in order to obtain nanoparticles in the nanometer range: the membrane must have a pore diameter between 100 and 200 nm, the applied pressure difference should be slightly greater than the critical pressure, the contact angle should be as small as possible, and the surfactant should be adsorbed fast at the oil water interface. SPG (Shirasu Porous Glass) and PTFE (poly (tetrafluoroethylene)) are the main membranes used in this technique.

3.2.5. Spray Dry Method for Water in Oil

Pamujula et al. developed a method to improve the entrapment efficiency of hydrophilic drugs. An emulsion was formed between the organic phase and water. The organic phase, consisted of a mix of dichloromethane and chloroform, containing the polymer, and lipophilic surfactant L-phosphatidylcholine. The aqueous phase contained the drug (amifostine). The final emulsion was injected in a standard 0.7 mm nozzle blowing into a chamber with hot air (55 °C). The mean size obtained was 257 nm (182- 417 nm) and 240 nm (182-417 nm) for preparations with 40% w/w and 100% of theoretical drug loading, respectively. The main advantage of this method is the high entrapment efficiency for hydrophilic drugs, which were 90.9% ± 0.16% and 100.03% ± 2.01% for the same preparations.

3.2.6. Spryer Solvent Displacement with Dialysis and Freeze Dryer Stabilization

Kim *et al*. modified the solvent displacement as follows. The organic phase was injected into an aqueous solution by a nozzle and the solvent removed by dialysis. The drug addiction (paclitaxel) was done after dialysis, by adsorption onto the nanosphere surface. The system was stabilized by the addition of an aqueous solution of Pluronic F3868 and subsequently freeze dried. The solvent used in the organic phase (discontinuous) was tetra glycol. For the PLGA concentration tested, 0.5 wt% to 5 wt% the nanosphere mean size obtained were in the range of 150 nm to over 1.4 µm. The maximum entrapment efficiency was 28.5% ± 3.3% and loading amount of 9.4% ± 1.4 wt% for PLGA nanospheres formed with 0.05 wt% of paclitaxel-ethanol solution. A limitation of this procedure is the strong dependence of the nanosphere size with respect to the polymer concentration.

3.3. Double Emulsion with Emulsion Diffusion

Cegnar *et al.* Modified the normal emulsion solvent evaporation method. The evaporation step, required for the solvent elimination, was changed by the addition of large amounts of distilled water to promote the diffusion of the solvent from the polymer (organic phase) to the aqueous suspension to improve the energy consumption. PVA was used as surfactant in the emulsion, and it was added to the second aqueous phase, in low concentrations (0.3% w/v), to avoid aggregation. Ethyl acetate was used as the organic solvent. The excess of PVA was reduced by centrifugation and wash steps with distilled water.

3.3.1. Dialysis Method for Modified PLGA

This is a simple method that can be used for the preparation of nanoparticles with block-copolymers, graft copolymers, and amphiphilic materials. Typically, this method consists of using a dialysis device in which the organic solution is placed. The organic solution, containing the polymer and the lipophilic active component is dialyzed for at least 12 hours against distilled water to remove the organic solvent and the free active component.

4. Surface Modification of Polymeric Nanoparticle

4.1. Surface Modified Chitosan Nanoparticles[16]

4.1.1. Thiolated Chitosan

The mucoadhesive and permeation-enhancing properties of chitosan were even significantly further improved by the immobilization of thiol groups on the polymer. These strongly improved mucoadhesive properties are based on the formation of disulphide bonds between the thiolated polymer and cysteine-rich subdomains of the mucus gel layer. Accordingly, thiolated chitosan nanoparticles should display comparatively stronger mucoadhesive properties than unmodified chitosan nanoparticles and should therefore be of advantage for the mucosal administration of various

drugs. Stability of such particles is in most cases provided by the addition of polyanionic excipients such as tripolyphosphate, sulfate, or hyaluronic acid, leading to an ionic cross-linking of chitosan. As a result of the addition of polyanions, however, the positive charges of chitosan are neutralized, resulting in a loss of the mucoadhesive and permeation-enhancing properties of chitosan; furthermore, this may cause oxidation of free thiol groups and lack of mucoadhesion. Several approaches have been developed to preserve the free thiol groups and mucoadhesion during preparation of thiolated chitosan nanoparticles. Recently Bravo-Osuna and co-workers have elaborated thiolated chitosan-coated acrylic nanoparticles by emulsion polymerization method. They also evaluated different promising characters of the nanoparticles such as mucoadhesion, calcium binding capacity, and permeation enhancement.

4.1.2. Biotinylated Chitosan

Because of its biocompatibility and biodegradability, chitosan has been widely used as polymer materials for the modification and delivery of many anticancer drugs, i.e., chitosan nanoparticles (CS-NPs). Biotin is a water-soluble vitamin, having essential roles involving cell growth, signal transduction and many other cellular functions, it is internalized into the cells through binding to the sodium dependent multivitamin transporter (SMVT) in the cell surface. Importantly, many tumor cells highly express this transporter to meet the demand of biotin for rapid tumor growth, and biotinylating is thus a reasonable strategy to enhance the binding/affinity of macromolecular drugs to tumor cells, leading to increasingly effective antitumor therapy. It has been reported that biotinylated nanoparticles selectively bound to breast cancer MCF-7 cells resulting in higher intracellular uptake than non-modified nanoparticles. Therefore, utilization of BCS-NPs would exhibit double tumor-targeting effect, namely, it will selectively accumulate in tumor tissues by EPR effect, and then targetedly bind to and internalized into tumor cells that highly express biotin receptors.

4.1.3. Hydrophobically Modified Glycol Chitosan

Hydrophobically modified glycol chitosan (HGC) nanoparticles is composed of a hydrophilic shell of glycol chitosan and hydrophobic multicores of bile acid analogues. It has been reported that anticancer drug-encapsulated HGC nanoparticles presented a promising therapeutic drug delivery system in cancer therapy. Because of their hydrophobic inner cores, HGC nanoparticles can efficiently imbibe various hydrophobic anticancer drugs, and show a sustained drug release profile. Also, the in vivo characteristics of NIR fluorescence labelled HGC nanoparticles, confirmed by non-invasive and in real-time imaging system in tumor-bearing mice have presented that HGC nanoparticles showed reasonable prolonged blood circulation time and tumor targeting ability, compared to different control nanoparticles. In the study conducted by Kyung Hyun Min et al on Hydrophobically modified glycol chitosan nanoparticles-encapsulated camptothecin enhance the drug stability and tumor targeting in cancer therapy, examined a nano-sized drug delivery system for encapsulating CPT into prolonged circulating and tumor homing HGC nanoparticles.

4.1.4. Thiolated Carboxymethyl Chitosan[17]

There are many reports about the modification studies of chitosan. Among them, the carboxymethyl chitosan (CM-chitosan), obtained by carboxymethylation reaction of chitosan, has been widely applicated. It retains the advantages of chitosan and has greatly improved water solubility, bioactivity, cell compatibility. In addition, most chemical modifications of chitosan are performed at the free amino groups of the glucosamine units, such as thiolated chitosan constituting an integral part of designated thiomers. The thiolated chitosans have mucoadhesive properties and are used as film agents. However, the thiolated chitosans are not amphiphilic molecular and difficult to form nanoparticles for drug release in target cells.

4.1.5. N-Trimethyl Chitosan

A major drawback of chitosan is that it is insoluble at physiological pH, whereas it is soluble and active as an absorption enhancer only in its protonated form in acidic environment. By contrast, N trimethyl chitosan chloride (TMC), a chitosan derivative, obtainable at different degrees of quaternization, has a good water solubility over a wide pH range. Moreover, soluble TMC has mucoadhesive properties and an absorption enhancing effect even at neutral pH. There are some reports about the toxicity of TMC, but only limited toxicity data have been published for particulate TMC systems.

4.2. Surface Modified PLGA Nanoparticle

Several methods and procedures have been utilized for surface modification of PLGA NPs in order to produce PLGA based nanoparticulate systems which are not readily recognized by RES. This goal has been achieved by PLGA NPs surface coating with more hydrophilic agents to cover their hydrophobic surface and provide stealth nanoparticles. Various agents have been used for this purpose including polyethylene glycol (PEG), poloxamers and chitosan molecules to neutralize or reduce the negative zeta potential of PLGA NPs and reduce their phagocytosis by RES. However, surface

modified PLGA NPs have been found to highly localize in liver tissue due to the rigidity of the PLGA core which has triggered many research studies to improve surface modification methods for achieving better outcomes.

4.2.1. Human Serum Albumin (HSA)

Human serum albumin (HSA) seems to be a promising molecule for surface modification of PLGA NPs. HSA is known to be the most abundant native protein in human body which has various advantages including ready availability, biodegradability, and low toxicity and immunogenicity. HSA has received special interest in drug delivery studies due to its ability for passive targeting through enhanced permeation and retention (EPR) effect which is related to both "enhanced permeation" of macromolecules through the fenestrated structure of tumor vasculature in addition to an "enhanced retention" which is considered to be related to the lack of effective lymphatic drainage in tumor tissues. Furthermore, it has been postulated that active targeting of HSA coated nanoparticles occurs through special albumin receptors on tumor cell membranes. Surface modification of PLGA

NPs by grafting protein molecules has been previously reported and various proteins including transferrin and wheat germ agglutinin have been coated on the surface of PLGA NPs through covalent conjugation. The created stealth NPs have successfully increased the cellular uptake of PLGA NPs and have resulted in a greater antiproliferative activity and better cytotoxicity in vitro. In addition, in vivo experiments have confirmed a higher tumor accumulation for the above surface coated NPs. HSA coating by non-covalent interactions have also been studied where protein molecules only saturate the nanoparticles surface and no covalent linking occurs.

4.2.2. Poly (Ɛ-Caprolactone-Co-Ethylene Glycol)[18]

Poly (ε-caprolactone- co-ethylene glycol) (PCL–PEG), an amphiphilic copolymer, was added to take advantage of PEG repulsive properties and to provide a higher stability of nanoparticles in biological fluids.

4.2.3. Cell-Penetrating Peptides (Cpps)[19]

Ligand-modified nanoparticle drug delivery systems are paid much attention for their site-specific targeting capacity. Folic acid as a targeting ligand, is extensively used to immobilize on the surface of nano-sized polymeric carriers to deliver these nanoparticles (NPs) into cells mainly via receptor-mediated endocytosis. However, the selective permeability of the plasma membrane prohibits most exogenous agents from gaining cellular access. A relatively new research direction that addresses this problem is the introduction of cell-penetrating peptides (CPPs) to overcome the permeability barrier and translocate a variety of cargo including small molecules, nucleic acids, antibodies, and NPs across the plasma membrane. Although a complete understanding of the exact mechanism of cellular entry of CPPs remains elusive, its application has been a new avenue for the development of novel drug delivery systems in the past. The application of CPPs including anticancer drug-CPP conjugation is more and more attractive to achieve increased tumor penetration by the CPPs and to enhance cellular uptake in tumor cells of the drug.

5. Conclusion

Biodegradable polymers act as the novel carrier for controlled release of various drugs. They provide effective and convenient delivery of drugs to the site of action. There are various natural and synthetic polymers are widely used due to their various properties like good biocompatibility, easy design and preparation, structural varieties etc. Also, there are various polymers used to deliver the drugs based on formulation aspects. So polymeric nanoparticles have been extensively studied as particulate carriers in the pharmaceutical and medical fields, because they show promise as drug delivery systems as a result of their controlled and sustained release properties, subcellular size, biocompatibility with tissue and cells.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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