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POLYCAPROLACTONE NANOPARTICLES AS DELIVERY VEHICLE IN COMBATING DISEASES

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ABSTRACT Conventional chemotherapy against various diseases causes severe side effects in the biological system. To overcome drug toxicity, insolubility and resistance, and to get greater therapeutic efficacies, vesicular biodegradable and biocompatible polymeric nanoparticles have attracted attention as drug delivery vehicle. Polycaprolactone (PCL) nanoparticles owing to their nanosizes, spherical shapes and easy surface functionalization capability with drug encapsulation characteristics are utilized as drug carrier for targeted biomedical applications. This review is mainly focused on the preparation of polycaprolactone nanoparticles with their surface functionalization and their usages in different targeted drug delivery applications.

KEYWORDS : Diseases; Chemotherapy; Side effects; Polycaprolactone nanoparticles; Targeted drug delivery applications

INTRODUCTION

Pharmaceutical drugs used as chemotherapeutics against various diseases, encounters several limitations such as biological barriers, non-specificity, instability, fast degradation, insolubility and resistance before transporting to the targeted site/s.[1-3] To conquer these barriers, it is needed to administer high drug dosage for achieving the preferred concentration at the targeted zone/s leading to cytotoxicity and other unwanted pathological side effects.[4] These adverse effects may be overcome through the employment of polymeric cargo delivery systems for getting desired concentration of cargo to the specific targeted area/s.[1,5-8] FDA-approved biodegradable and biocompatible polycaprolactone nanoparticles (PCL NPs) have been attracted attention not only as delivery system but also as vaccine carrier for their nanosize, cell penetrating capability, non-immunogenic characteristics and sustained cargo-release property to the targeted site/s of interest.[9-14] PCLs, the semi-crystalline hydrophobic polymers having relatively polar ester groups with five non-polar methylene groups in the repeating units, are produced by ring-opening polymerizations of ε-caprolactone monomers, while the high olefin contents provide poly-olefin-like features to PCL.[13,15] By virtue of the high degree of hydrophobicity and crystallinity, PCLs generally degrade slowly and are less biocompatible with biological cells leading to restricted long term bioavailable treatment against diseases as drug delivery system or vaccine carrier.[16,14] Therefore, surface-modification of PCL by copolymers and / or ligands may be suitable to get greater biological efficacies associated with their improved hydrophilicity, non-toxicity, non-antigenicity, non-immunogenicity and biodegradability.[17-19] The synthetic biodegradable polymers are very suitable for biomedical application against diseases as they are biologically inert, having lot to lot homogeneity and their composition and structure are easily functionalized for specific application.[20,21] The hydrophilic, non-toxic and non-immunogenic polyethylene glycol (PEG) has great effects on cargo adsorption, prevention and escape from capture of the reticuloendothelial system increasing blood circulation time of PEGylated PCL NPs to get maximum delivery to targeted region/s.[22,23] In addition, PEG side chains further enable functionalization of NPs utilizing well designed specific bio-ligands to get greater targeting of the encapsulated cargo through the transportation to the zone/s of the intended liberation.[24] Moreover, restricted smaller nanosized PCL particles coupled with targeting ligand can specifically bind to target cells after administration for internalizing the NPs to release cargos inside the cells with higher affinity and specificity.[25-27] Furthermore, as traditional vaccines have susceptibility to degradation, short duration of action, side effects and inflammatory reactions, polymeric nanoparticles have attracted attention to overcome these barriers. PCL NPs as carrier / adjuvant may promote and induce strong cellular Th1, humoral Th2 and mucosal immune responses to enhance the vaccines immune efficacy and achieve controlled release and mucosal immunities.[28-32] This review elucidates the therapeutic efficiencies of PCL NPs against various diseases to consider as favorable delivery carrier.

Preparation and functionalization of polycaprolactone nanoparticles

The nanoprecipitation / solvent displacement method may be utilized to prepare the PCL NPs with the requirements of organic phase (solvent phase) and aqueous phase (non-solvent phase).[10,33,34] In brief, PCL is liquefied in an suitable organic solvent, while the organic phase is added gently into a surfactant containing watery phase under continual magnetic stirring. The organic solvent is then evaporated out at ambient temperature with continuous stirring or by using a rotary evaporator. Afterthat, the solution is centrifuged and lyophilized to prepare PCL NPs.[33,35-38] In general, aqueous phase containing various hydrophilic surfactants such as polysorbate 80 / tween®80 / polyvinyl alcohol is used for preventing the aggregation of the NPs. In this context, different operating conditions such as polymer molecular weight and amount, surfactant amount and stirring rate in this method may influence the size of the NPs.[33] For encapsulation of cargos in the NPs, various hydrophobic drugs / bioactive molecules are dissolved in appropriate solvent and adjoined to the prepared PCL solution prior to the inclusion of the organic phase into the watery phase.[39,10,38] On the other hand, several hydrophilic molecules / drugs may also be encapsulated effectively into the PEGylated PCL NPs by dissolving the cargos in an external watery phase or usages of co-solvent or suspension in minimum quantity of cargos in the organic phase.[10,33,40,41] Coupling of PCL and the amino-aptamer is made with N-hydroxysuccinamide (NHS) and dicyclohexylcarbodiimide (DCC) reagents. In brief, an amount of 2.5 nmol S15-aptamer is amalgamated with 34.4 µL 70 mM carbonate buffer (sodium carbonate and sodium hydrogen carbonate, pH 10). Afterthat, 12.5 µmol NHS and DCC, and 250 nmol $PCL_{5.4}$ dissolved in 100 µL di-methylsulfoxide (DMSO) at 70°C, is adjoined into the aptamer. After ultrasonication for 2 min, the reaction mixture is incubated at 500 rpm for 6 h at 20°C. Each 1 h new NHS and DCC (each 12.5 µmol in 40 µL DMSO) are adjoinded following ultrasonication for 2 min. The solvents are then removed under reduced pressure to get solid conjugates, while the water-resuspended aptamer-$PCL_{5.4}$ NPs are refined with reversed phase high performance liquid chromatography (RP-HPLC).

Determination of encapsulation efficiency and drug loading

The drug loading and encapsulation efficiency of nanoparticulated formulations are assayed quantifically by RP-HPLC. The prepared drug loaded nanoparticles are dissolved in 2 mL methanol for 24 hrs at 4°C. The supernatant suspension containing drug is collected by centrifugation. The drug loading and encapsulation efficiency of PCL NPs are estimated by the following formulas:

Encapsulation efficiency (%) = [(Total amount of formulated drug – Amount of supernatant drug) / Total amount of formulated drug] x 100.
Drug loading (%) = [(Total amount of formulated drug – Amount of supernatant drug) / Polymeric mass] x 100.

Characterization of nanoparticles-conjugates

Transmission electron microscope and scanning electron microscope are used to determine the shape, size and surface morphology of the NPs. The average particle sizes and polydispersity index are measured by dynamic light scattering utilizing zetasizer nano-ZS. The zeta potential of the aqueous NPs dispersion is determined by zetasizer nano-ZS at 25◦C. The interactions of drug and polymer are investigated by Fourier transform infrared spectrometer. The interactions among different ingredients in the NPs-conjugates are estimated by differential scanning calorimeter.

Polycaprolactone nanoparticles in delivery applications

PCL NPs have been used in different drug delivery applications for achieving better therapeutic efficiencies with sustained targeting to specific site of interests.[42-44] Curcumin-loaded PCL NPs have shown their high impact in therapeutic efficacies.[45] Carboplatin-loaded PCL NPs have been utilized for treating glioma through nasal route having no severe damage on the nasal mucosal integrity.[46] Hydrophobic tamoxifen-loaded polyethylene oxide -modified PCL NPs have shown their enhanced level of drug accumulation within tumor for anticancer therapy.[47] Biodegradable PCL and non-biodegradable polycationic acrylic polymer blended NPs have been used to deliver orally insulin for the treatment of diabetes.[48] Hydrophobic clonazepam -loaded poly(N-isopropylacrylamide)-b-poly(ε-caprolactone) NPs have been utilized to achieve desired drug release motif having additional diffusion barrier to the encapsulated drug by the poly(N-isopropylacrylamide) layer on the surfaces of NPs.[49] Curcumin encapsulated polycaprolactone-montmorillonite nanoclay -functionalized n-cetyl-N,N,N,-trimethylammonium bromide NPs have been delivered for enhancing their antitumor activities.[50] Vinblastine-loaded PCL-grafted dextran NPs have been used to treat breast cancer cells for getting efficient cellular uptake of NPs.[51] Mucoadhesive chitosan-PCL NPs have been utilized to combat H1N1 influenza virus as a vehicle for nasal vaccines for getting effective humoral and cellular immune responses and mucosal antibodies.[30,31] Methoxy PEG-PCL has been used as ecotropic diblock copolymer for the hydrophobic drugs-deliveries.[32] Quercetin-biapigenin encapsulated PCL NPs have been applied as synergistic actions of antioxidants to get effective hepatoprotective effects.[52] A lot of studies have indicated that mPEG-PCL NPs have been utilized as vehicles for protein, genes and vaccines cargos specifically in a sustained liberation drug delivery system for their specific targeting to cells to get higher biological effectiveness.[53]

Biodegradation of polycaprolactone

Polycaprolactone is degraded through two discrete stages in physiological conditions: (i) Non-enzymatic hydrolysis of ester linkage of PCL attributing to haphazard chain scission and resulting reduced molecular weight, (ii) Intracellular degradation of highly crystalline and low molecular weight (<3000) –PCL.[42,54-56] Generally, PCL is degraded from few months to several years depending on the starting molecular weight.[42,21]

Conclusions and future perspectives

As biodegradation rate of PCL NPs is slower, it may be utilized to overcome biological barriers as drug delivery vehicle for long term treatment against chronic diseases. Moreover, PCL NPs may be copolymerized with PEG and / or conjugated with ligands and loaded with cargos to deliver drugs to targeted site/s with sustained release and accumulation for achieving higher efficacies at lower dosages against various diseases. However, this delivery system needs more explorations regarding their thorough systemic long term studies on biodistribution, pharmacokinetics, cytotoxicity, elimination, immune responses, appropriate size, shape and suitable surface functionalizations with surfactants, cargos, ligands and polymer coating, administrative routes specially oral and intravenous, and efficacies for the specific targeting to diseased cells before going to clinics to consider as suitable nanoparticulated delivery system for biomedical applications in combating different diseases.

Conflict of interest

None.

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