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RESEARCH PAPER

A Review of Poly Butyl Cyanoacrylate Nanoparticles as a Cancer Drug Delivery and Targeting

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ABSTRACT

Cancer is recognized as a one of the major health hazards worldwide and also accounts for one in eight deaths globally. Chemotherapy, which is considered a principal treatment in cancer, is plagued by significant limitations because of its imminent drug resistance. Our focus should be in providing effective and long lasting treatment procedures without compromising longevity and quality of life of cancer patients. Resistance to chemotherapeutics and designing an effective means of drug delivery system, to overcome cancer treatment failure, remain a challenging task for researchers and scientists. Nanoparticles (NPs) are broadly being applied to improve the therapeutic index, because of their higher bioavailability, solubility and retention time. Apart from that, several studies have used poly butyl cyanoacrylate (PBCA) as one of the most common carriers in drug delivery purpose for the treatment of cancer .PBCA and its co-polymers are important in designing NPs with desired characteristics such as biocompatibility, biodegradation, smaller particle size, unique surface properties, facile drug release and target specificity. In this article. We aim to review and summarize the literature behind the use of PBCA nanoparticles as an effective drug carrier in the treatment of different cancers.

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INTRODUCTION

Cancer is a major health hazard and one of the leading causes of high morbidity [1]. Cancer is characterized by the explosive growth and differentiation of anomalous cells in the living body [2]. Over 200 different types of cancers have been reported so far for humans, [3] and environmental factors have known to be responsible for 80-90% cancers, [4] followed by heredity, which has been linked to about 3-10% [3].

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Chemotherapy is one of procedures for treatment of cancer, although the most popular, have limited application because of its eventual drug resistance [5, 6]. Patients in whom the tumour has already metastized, are usually resistant to drug administration[7].

Lu et al. divided resistance to chemotherapy into two categories, namely, intrinsic and acquired and associated intrinsic immunity to heterogeneous nature of tumours [5]. On the other hand, acquired resistance which had been linked to genetic and epigenetic causes can result in changing the sensitivity of the drug [8]. Chemotherapeutic agents which are conventional are also known to be vague in their delivery in human body; as a result, they may affect cells which are both cancerous and normal, thus limiting their use due to excessive toxicities [9].

In most recent years, nanotechnology is being extensively applied in medical therapeutics [10]. Nanoparticles (NPs) are being used to boost the medical benefit for treatment of cancer because of their enhanced biocompatible and soluble nature and improved time of retention [11]. Drug-nanoparticle combination is known to be less toxic and more economical [12]. The concept of nano-medicine can be traced back to 1980s and had been used for nano-encapsulation in augmented drug effect, selectivity, efficacy, and clinical level of the drugs in question [13]. It is known that nano-medicines have many tangible benefits, which includes: interaction with the surrounding biological environment, increased absorption into an intended tissue, bioavailability, utilization time and increased intracellular dispersion [14]. These vesicles like components made from lipids were used as possible drug distributors because of the secure sheath that they develop around encapsulating different drugs in their centre.

Also, liposomes have demonstrated poorer encapsulation capacity, weak stability in storage and accelerated escape of water-soluble medications in the blood, hence their ability to regulate the release of several drugs might not be sufficient. Therefore, biodegradable and biocompatible polymeric NPs have been recognized as an alternative in transportation of particulate matter in the clinical and pharmaceutical sectors [15]. Due to their higher encapsulation performance, better bioavailability and retention period, polymeric NPs have proven advantageous in a variety of ways over micro particles [16].

Poly butyl cyanoacrylate (PBCA) is one such unique nanosized polymer which is wholly synthetic, that has biodegradable properties and exhibits much lower cellular toxicity. PBCA nanocarriers (NCs) are considered to have such compelling properties as: small size, simplistic synthesizing procedure, ease in levelling up and hassle free purification, exhibiting stability in vitro and rapid body elimination [17]. One big benefit of this NP is its capacity to resolve multidrug resistance in tumour cells [18].

There are two methods for synthesizing PBCA NPs, namely, polymerization reaction using anionic components and mini-emulsion polymerization methods [19]. In vitro studies have shown that mini-emulsion polymerization mode being the most suitable mode for the preparation of cisplatin-PBCA NPs in ovarian cancer, [20] but results in past studies have shown polymerization via mini emulsion could not be deemed an appropriate method for loading drugs into PBCA NPs [21]. Principal questions that need to be addressed are: which method of PBCA is appropriate for delivery of drugs, and which mode is more efficient in what type of cancers. Thus, this review sheds light on the preparation methods of polymer synthesis of PBCA NP and its efficiency as an effective drug source in cancer therapeutics.

Furthermore to PBCA, there are other poly (alkyl cyanoacrylate) NPs for example poly (2-ethyl-butyl cyanoacrylate) PEBCA, poly (ethyl 2-cyanoacrylate) PECA, and poly (octyl cyanoacrylate) POCA that have attracted the interest of numerous researchers [22, 23].

Introduction to preparation methods of polymeric PBCA NPs

Latest studies on the PBCA synthesis process exhibit that there are several preparation approaches for these nanoparticles [24]. . Surface parameters may be adjusted to regulate the interaction between NPs and living systems, which facilitates the in vivo management of NPs [25]. Introduction via the surface of NPs during the period of emulsification or adsorption is the most common approach of preparing drug-laden PBCA-NPs [26, 27]. Production factors such as the stabilizing agent, the medium pH and the volume and duration of the addition of the drug are perceived to be as advantageous considerations to increase the carrying capacity. The drug launching and encapsulation efficiency may be enhanced by

selection of suitable drug and nanoparticle matrix with ligands where hydrophilic/hydrophobic properties of poly (BCAco-OCA) can be modulated [28]. Poly (BCAC-OCA) is a matrix material for nanoparticles that is a synthetic copolymer of made of n-butyl cyanoacrylate (BCA) and 2-octyl cyanoacrylate (OCA) monomers. The physicochemical properties of this structure specify that it is appropriate for encapsulating hydrophilic drug materials and promote the drug loading efficiency [28, 29].

The first NPs for pharmaceutical uses were produced in the 1970s by polymerization method.

Types of PBCA nanoparticles

Based on preparation methods of NCs, nanospheres or nano capsules can be produced. Nanospheres own a single unified (matrix) framework in which drugs are either deposited or adsorbed superficially or embedded within the particles [30]. Capsules of nano dimension (NC's) are vesicular structures serving as a storage system and liquids having a fluid centre (i.e. oil or water) enclosed by a rigid material framework [31] are restricted to the cavity. Schematic diagram images of polymer NPs, presented in Fig. 1.

Methods for preparation of polymer nanoparticles

Various methods for preparing polymer NPs are present. Two of the most frequently used methods are: (1) nanoprecipitation-based; (2) polymerization-based [32]. Fig. 2 represents strategies for processing PBCA-NCs, where biodegradable NCs are graded as nanocapsule and nanosphere according to complex structure organization,

Nanoprecipitation-based method

This method is necessary for PCBA-NC preparation beginning from polymer which has been synthesized previously. In brief, sufficient volume of stabilizer is administered in water or PBS to receive the water phase and its pH is then gradually modified to an acceptable value. The acetone solution comprising previously-synthesized PBCA is then transferred in drops in the water phase, the solution is kept under continuous stirring, and the resultant suspension is nullified with a solution of 0.1 N of sodium hydroxide to conclude the polymerization process. The excess acetone will eventually be extracted by rotating evaporation. Depending on the solubility, the drug can either be added to the aqueous phase (ie, water) or organic phase (ie, acetone) [33, 34].

Organic solvents, such as acetone, ethanol, hexane, methylene chloride or dioxane which are satisfyingly soluble in water and extract via evaporation easily, are often used as polymer solvents. Among these organic solvents, acetone is often used. This is generally prepared from mixed solvents, for example acetone with nominal

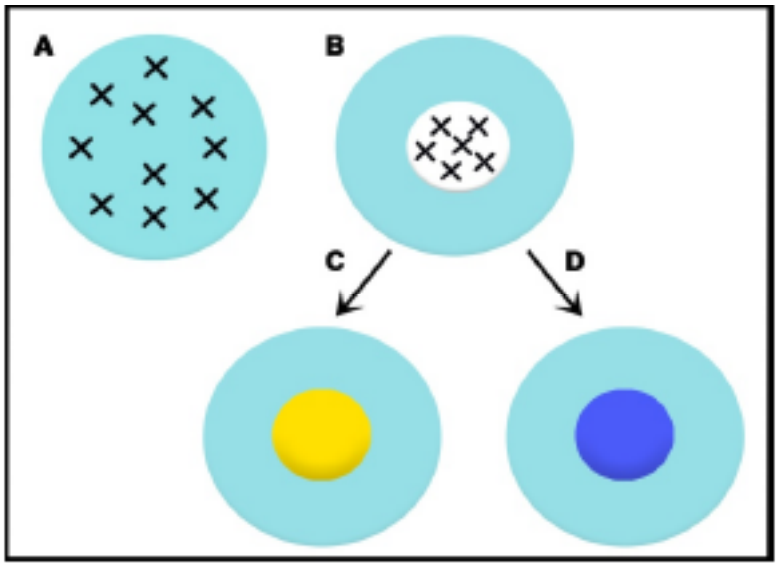

Fig. 1. Classification of NPs having drug (A & B) in nanocapsules containing oil (C) and nanocapsules containing water (D).

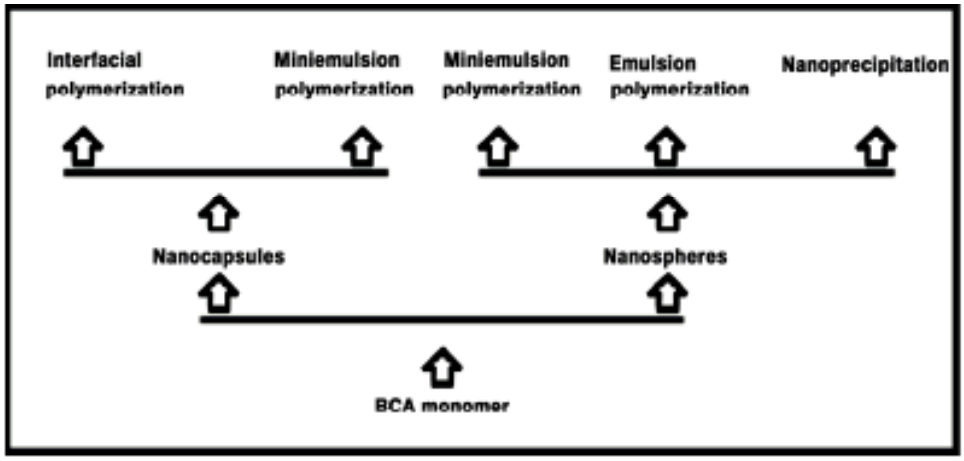

Fig. 2. Techniques for preparation of PBCA- NPs, (all methods being based on BCA monomer, except for nanoprecipitation which based on presynthesized PBCA polymer)

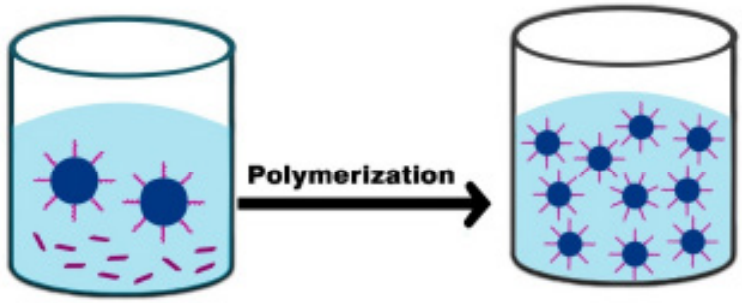

Fig. 3. The process of direct emulsion polymerization, adopted from [36].

amounts of water, acetone mixture of acetone with methanol and ethanol. Apart from that, the phase lacking of solvent comprises a non-solvent, or a mixed form containing of non-solvents, supplemented by one or several synthetic or natural surfactants.

Polymerization-based method

In this method, polymerization of monomer occurs in an aqueous solution to form NPs. Upon polymerization completion the drug is adsorbed either by submerging in the medium or by diffusion onto the nanoparticles [35]. The polymerization-based approach is characterized as BCA monomer polymerization activated by an anion (anion initiated polymerization) or radical (radical initiated polymerization) at room temperature (Fig. 5), which also involves polymerization using emulsions, polymerization of the interfaces and polymerization of mini-emulsions [32] (Fig. 2).

Emulsion polymerization, where an emulsification of monomer occurs into a non-solvent surfactant, the formation of monomer-swollen micelles and stable monomer droplets occurs. The polymerization is achieved in presence of an initiator [36] (Fig. 3).

This method includes polymerization via emulsion in presence of an organic phase, which is continuous, and emulsion polymerization in an aqueous continuous phase [36]. Since PBCA can be extensively produced via mini-emulsion and anionic polymerization, our focus will be on the stated methods. Several studies have been reported which describe the preparation of PBCA loaded with paclitaxel NPs via mini-emulsion procedures or polymerization which is anionic in nature [29, 37].

Mini-emulsion is a method of generating small, robust droplets continuously utilizing high shear stress[38]. The droplet sizes particularly rely on the nature and the volume of applied emulsifier,

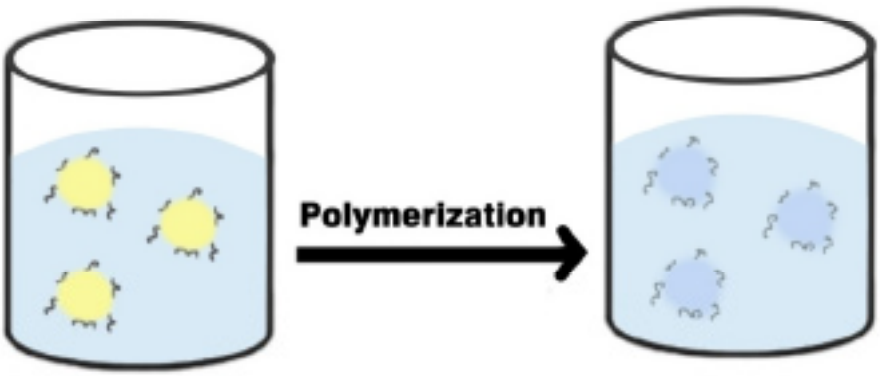

Fig. 4. The process of direct (oil-in-water) mini-emulsion polymerization, adopted from.

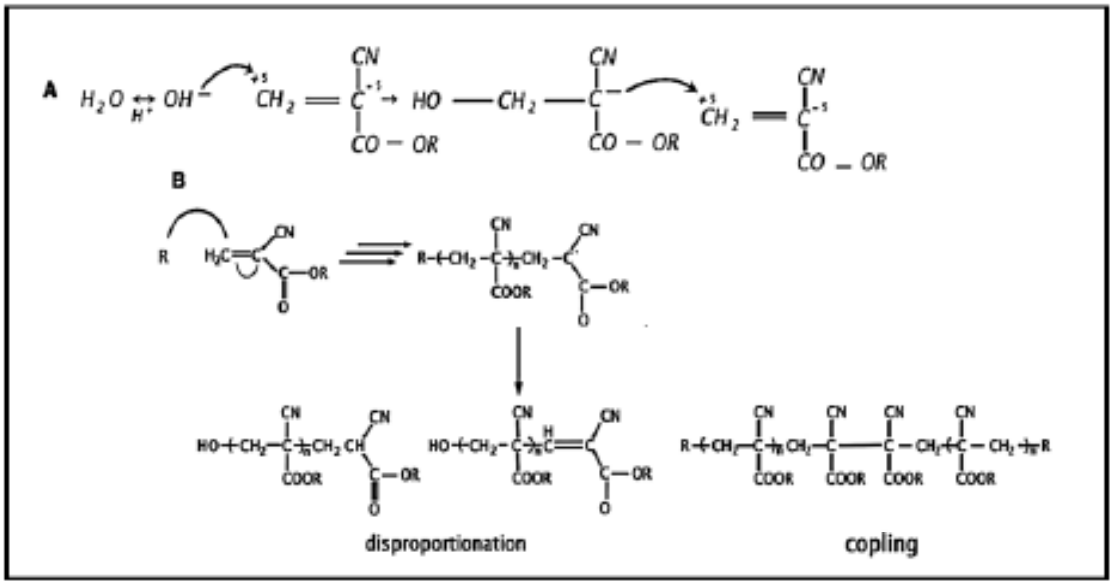

Fig. 5. The mechanism of PBCA polymerization applied during polymerization via encapsulation method. (A) Anion; (B) Radical, Adapted from [32].

varying from system to system. Mini-emulsion polymerization uses small stabilized droplets to initiate polymerization, i.e. polymerization occurs in small nanodroplets. Long-chain alkanes have been applied as stabilizers for direct mini-emulsion (oil-in-water). Fig. 4 presents the process of direct (oil-in-water) mini-emulsion polymerization [39]. This method, in contrast to emulsion polymerization, does not need monomers or other compounds that have less affinity towards water from one tank into a polymerization place [40]. For this reason, mini-emulsion polymerization is considered as a one-step nano-encapsulation procedure for the encapsulation of hydrophobic compounds [41].

The majority of poly(alkyl cyanoacrylate) NP are a result of anionic polymerization [42]. The cyanoacrylate monomers are synthesized in aqueous medium through anionic polymerization [20]. Anionic polymerization happens when the butyl cyanoacrylate monomer is dispersed on the aqueous medium to forms particles as shown in Fig. 5. Previously it was shown that dsDNA molecules have been encapsulated successfully into nanocapsules containing PCBA through polymerization of anionic nature, which interacts between the mini-emulsion droplets and the continuous phase [43].

BCA polymerization can happen both via anions, as well as radicals, polymerization through

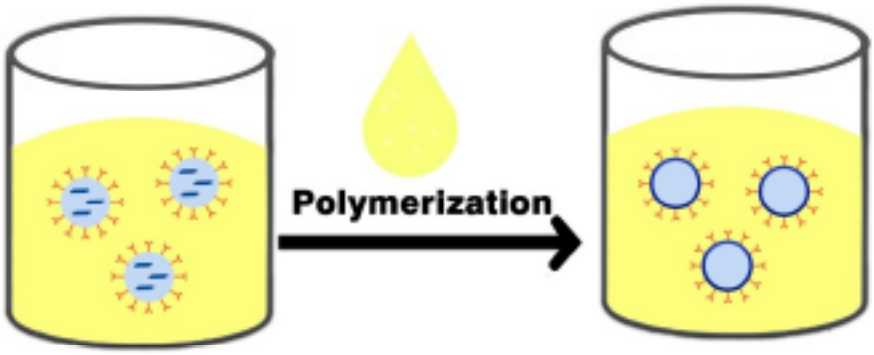

Fig. 6. Schematic description of interfacial interactions in inverse emulsion; one monomer (violet) is given in the aqueous droplets, the other (light green) is inserted, dissolved in solvent. The reaction ends in a polymer shell like shielded structure that encloses the droplets of water. Adapted from [97].

emulsion and miniemulsion polymerization processes initiated via radicals, have recently been explained [32]. Polymerization generated through radicals is similar to the polymerization process induced by anion except that it involves a far reduced pH in medium (almost(>1.0) including the introduction of radical originator, e.g. 2,2-azobis(2-methylpropionitrile) with cerium ions, before adding BCA monomer. Consecutively, disproportionation and coupling methods hinder radical polymerization (Fig. 5).

Another method which needs to be mentioned is interfacial polymerization where monomers polymerization occurs at the junction of two phases which are immiscible. This method is done in an environment which is water based and in presence of organic phase that has been emulated and homogenized at micro-fluidized volume by severe mechanical shakings. This cycle dissolves the drug and monomer in a combination of oil and ethanol followed by gradual addition to the aqueous phase containing surfactant through a small tube or syringe [44] (Fig. 6).

Effect of nanoparticles characteristics regarding drug delivery mechanism

Characterization of Nanoparticles (based on particle morphology such as size, distributions, charge on its surface, Drug loading, Entrapment efficiency and ease of Drug release)

Distribution of particle size is the most significant characterization parameters in NPs. The primary use of NPs is in drug discharge and drug targeting. Particulate size has been shown to influence product production and ever after that. Smaller particles have a larger range. As a consequence, much of the drug installed into them would be released to the surface of particles contributing to its accelerated release. Smaller particles have a broader surface; as a consequence, much of the drug mounted into them would be revealed to the surface of particles contributing to accelerated release of the drug. Alternatively, there is a gradual diffusion of drugs within larger particles. As a limitation, smaller particles appear to accumulate during nanoparticular dispersion, storage and transport. Hence, a contrast occurs between a smaller size and the maximized stability of NPs [30]. The size distributions of NPs are known as important factors affecting the cell membrane and also their penetration as physiological drug barriers. Studies have considered NPs size is dependent on the type of tissue, its target site and circulation [45]. Temperature and pH are perhaps the two triggers used most commonly and have gained further consideration from researchers. Solution pH plays a crucial function in the NCs' scale and polydispersity measure. PH=1, A pH of 1 has been found to be ideal for average size of NP, since higher pH values improve the NC scale [46]. Temperature promotes the polymerization rate and nanoparticle production, but it in no way alters the molecular weight of the synthesized nanoparticles [47]. High temperatures tend to improve the stability of PBCA NPs below the PBCA polymer's glass stage, which is around 100 °C. Buffers affect the size of nanoparticles, as shown by Kamaly et al. Therefore, the H_3PO_4 medium (which is acidic in nature) initiates the formation of smaller nanoparticles with higher molecular weight [48]. In fact, the stabilizer has a major impact on the volume, polydispersity index and

Table 1. The physical and chemical properties of PBCA-NPs and its different preparation physicochemical properties of drug loaded PBCA-NPs prepared by different methods.

Drug	Method (A-E)	DLE%/EE%/PDI/ Zeta potential (mv)	Nanoparticle size (nm)	Target sites	Ref
Paclitaxel	E	1.07/99.23/0.27/–	224.5±5.7	Ovarian	[51]
Cisplatin	B	5/25/0.429/-20	489.3	Ovarian	[20]
Carboplatin	B	3.6/40/0.384/-10.3	360±30	Ovarian	[40]
Cisplatinum and Carboplatinum	A	4/–/0.21/-8 6/–/0.24/-7.2	287 319	Breast	[21]
doxorubicin and curcumin	A/E	0.619/49.98/–/+32.23 1.17/94.52/–/+32.23	133±5.34	Breast	[52]
Doxorubicin	A	–/46.8/–/+23.14	~174 ± 8.23	Breast/Liver	[53]
Cisplatin	B	6/30/–/-19.5	451±11	Brain	[54]
Cisplatin	C	–/–/0.470/+5.1	222	Brain	[55]
Doxorubicin	A	10.58/ 87.43/-/-	120.5 ± 30.8	Brain	[56]
Doxorubicin	C	71.10-73.38/-/-/-	210-215	Brain	[57]
Doxorubicin	C	80/-/-/-	270	Brain	[58]
Cisplatin	C	14–19/–/0.25–0.44/-7–-11	355–386	Lung	[59]
Paclitaxel	D	–/73.8–90.8/–/-32.58–-44.50	291–325	Sarcoma	[60]
Curcumin	A	–/90.04/–/+29.11	~250	Liver	[61]

A: polymerization through emulsification; B: polymerization through mini emulsion; C: Anionic-Emulsion; D: polymerization through radicals; E: polymerization via interfaces; DLE: efficiency of drug loading; EE: efficiency of entrapment; PDI: polydispersity index; ''–'' not mentioned.

physical and chemical properties of synthesized NPs. The disparity in the impact of stabilizers, such as dextran 40 and poloxamer 188, on the size of nanoparticles was discovered by Pons et al., who found that if there was a decrease in the average size of stabilizers, NP mean size decreases [49].

The stability of colloids is evaluated by zeta potential of NPs. Large zeta potential figures, whether positive or negative, should be obtained and preserved to ensure equilibrium and to prevent particle aggregation [50]. Theoretically, an effective network of nanoparticles would have a large drug-loading potential thus decreasing the amount of matrix materials for distribution. Drug loading efficiency (DLE) and entrapment efficiency (EE) greatly rely on solid-state solubility of drug in matrix substrate or polymer (solid dissolution or diffusion) relevant to the structure of the product, interaction between polymer and drug molecular weight and functional groups present at the end [30]. Table 1 represents the physical and chemical properties of PBCA-NPs and its different preparation methods.

Biodegradability and release mechanisms of PBCA-NPs

Drug discharge based on carrier of particulate network relies on the cross-linking, shape, volume, particle density and chemical and physical properties of the drug as well as adjuvant's presence. In vitro drug release from nanoparticles depend on several factors namely, temperature, pH, drug solubility, surface-binding property or ease of desorption of adsorbed drug, drug dissemination through the swelling and erosion of nanoparticles matrix and the convergence of diffusion and erosion processes [62]. There are three basic models for drug release; in Phase I of a triphasic escape profile is attributed to the impact of burst release, that is the sudden launch of drug molecules nearby or at the surface of water. The release profile phase II is a controlled release process governed by gradual drug dissemination through the polymer matrix or via existing pores, which is parallel to hydrolysis and degradation of polymers. Phase III may be a more rapid release process, when erosion begins [48] (Fig. 7). Table 2 presents different studies reported using PBCA-NPs for drug release. Diffusion coefficient and rate of biodegradability are the main factors affecting drug release, apart from the importance of biological environment. There are two major biodegradation pathways for PBCA NPs; the main pathway being enzymatic breakage of butyl ester group from the polymer followed by production of an acidic polymer and butanol. In another pathway, the polymeric chain is degraded and formaldehyde is formed, where its amount is too low to physiologically cause any risk to the body. Both metabolites formed are water-soluble and

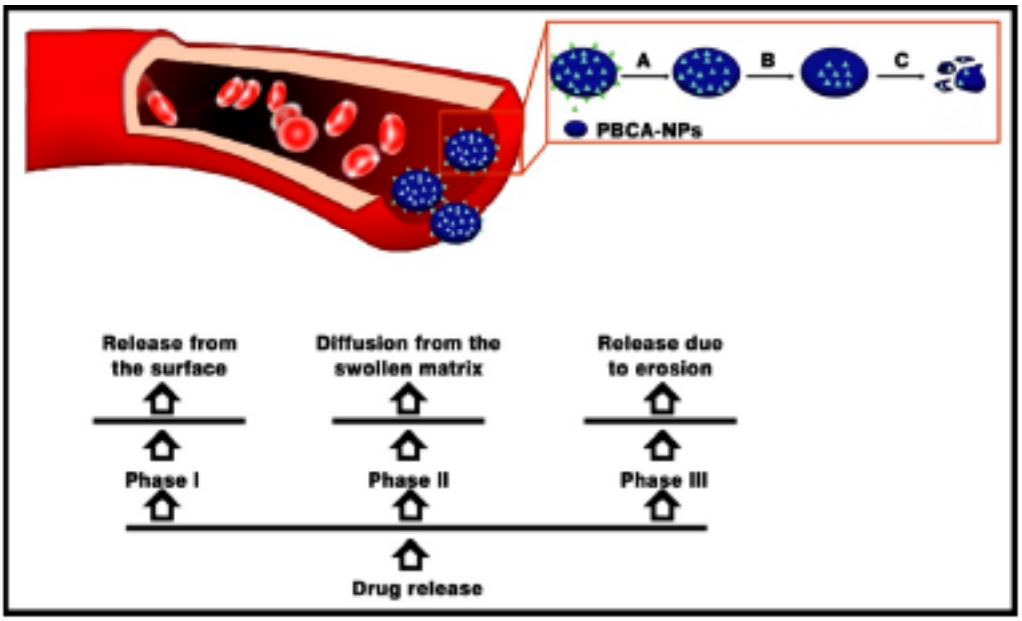

Fig. 7. The schematic view of fast drug desorption from NPs surface(A), and Diffusion due to two nanoparticle erosion process; Drug dissemination through diffusion via polymeric matrix and the shell (B),diffusion of drug through nanoparticle biodegradation (C).

Table 2. The reported different studies using PBCA-NPs for drug release.

Drug	Method	Phase	PH (PBCA-NCs)	Ref
Paclitaxel	Dialysis	Phase I	7.4	[51]
Cisplatin	ICP-EOS	Phase II*	Neutralized withNaOH	[20]
Carboplatin	ICP-EOS	Phase II*	Neutralized withNaOH	[40]
Temozolomide	Dialysis	Phase II**	5.0	[69]
Cisplatin	ICP-EOS	Phase II***	Neutralized withNaOH	[54]
Cisplatin	–	–	Neutralized withNaOH	[55]
Cisplatin	Dialysis	Phase I	7.0	[59]
Paclitaxel	Dialysis	Phase I	7.4	[60]

Model drug release profiles (Phase II); II*: burst and zero-order release; II**: releasethrough triple phase; II***: triphasic dissemination with short phase II; ''–'' not mentioned

excreted through kidneys [44].

In recent years, nanoparticles as one of the potential components in the treatment of patients have attracted the attention of many researchers. However, due to limited research on toxicity and safety, insufficient success has been made in the pharmaceutical use of nanoparticles [63]. Nanoparticle toxicity may be evaluated on three levels: molecular, cellular, and tissue. By interacting with diverse biological environments such as organelles, cytoplasm, extracellular matrix, and blood, nanoparticles induce changes in biomolecules, cellular components, and tissue structures [64]. One of the most important challenges in the use of nanoparticles is the immune response to these structures. Nanoparticles can interact with various components of the immune system and alter the functioning of the immune system. When this shift in immune response is not related to nanoparticles' specific function, it is termed a side effect of nanoparticles, and nanoparticle immunotoxicity is addressed. Cytokines, particularly proinflammatory cytokines, serve as biomarkers for detecting nanoparticle immunotoxicity. High levels of inflammatory cytokines are associated with toxicity adverse reactions and low therapeutic efficacy when using nanoparticles [65]. A growing body of evidence

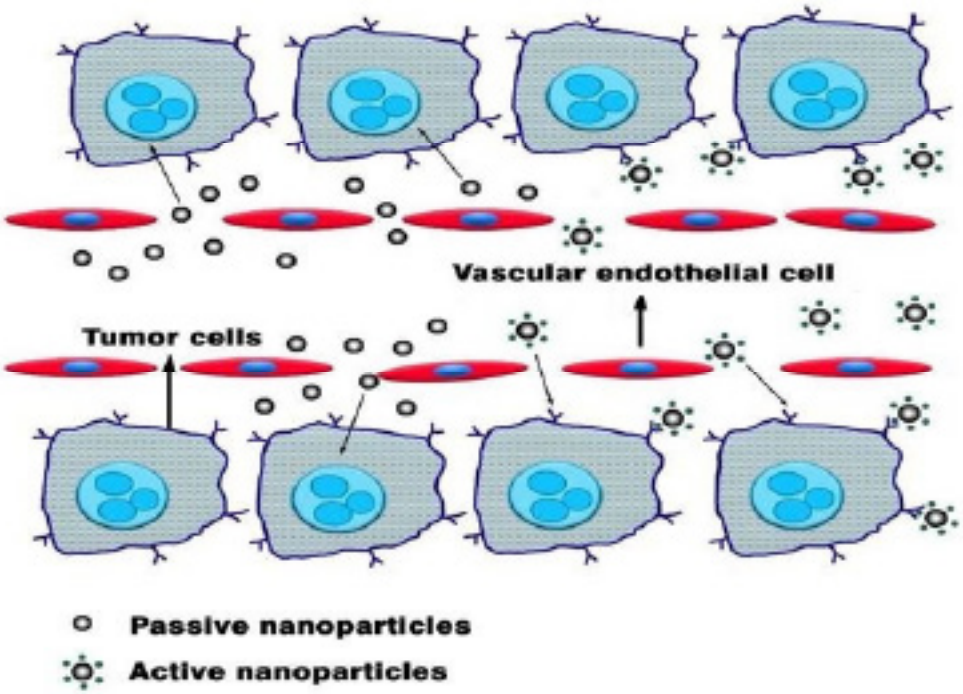

Fig. 8. PBCA-NCs accomplish tumor targeting typically in two ways: namely by passive targeting system as well as by active targeting approach.

suggested that nanoparticles have the potential to polarize the balance of TH1 and TH2 cytokines towards a specific pathway. This evidence suggests that some nanoparticles raised serum levels of TH1 cytokines such as IL-2, IFN-γ and TNF-α, while decreasing TH2 cytokines such as IL-4, IL-5 and IL-6 and others did the reverse[66, 67]. Another concern with nanoparticle application is the abnormal generation of reactive oxygen species (ROS). These structures have a high oxidant capacity and can generate high level of ROS. ROS through interactions with proteins, lipid peroxidation, DNA and RNA damage, and genomic mutations can all impair cell membrane integrity and lead to apoptosis and necrosis [68]. However, more study is needed to improve researchers' understanding of the toxicity of nanoparticles, particularly polymeric nanoparticles.

Surface properties of nanoparticles and targeted drug delivery

The reticuloendothelial system (RES), primarily the spleen and liver, are significant carrier for efficient targeting, owing to their capacity to detect these processes; eliminate them from systemic circulation and by doing so restrict the optimal distribution of NPs to organs other than belonging to RES [70].

PBCA-NCs accomplish tumour targeting typically in two ways: by passive targeting system as well as by active targeting approach respectively (Fig. 8). According to the unique structural properties of the tumour vasculature, active PBCA-NCs continue to be stored and preserved in tumour tissues. The lymphatic channels, identified as the efflux network, are often defective in tumours, contributing to inadequate drainage [71], hence to achieve active targeting, ligands are attached to the exterior of NCs to target endothelial cancer tumour cells which provide the tumour with oxygen and nutrients. Carcinoma cells tracking ligands incorporate: folate receptor, glycoprotein transferrin receptor, receptor epidermal growth factor (EGFR); and component of vascular endothelial formation for tumour endothelial cell targeting. Ligands are attached to the surfaces of the nanocarriers to attack carcinogenic endothelial cells, which supply the tumour cells with nutrients and oxygen. To invade the tumour cells, the ligands include: the EGFR and glycoproteins, the folate receptor, the transferrin receptor, and the matrix metalloprotein

integrins in endothelial cells of cancer, vascular cells adhesion molecule, the vascular endothelial growth factor receptors [32, 72]. Many alteration techniques have been developed to disguise or mask NPs from MPs. PBCA-based NCs provide complex surface modification to realize active targeting by changing pharmacokinetic variables such as PEG (a water-soluble polymer with reduced immunogenicity and antigenicity, safe in blood circulation and capable of increasing drug launch time simultaneously) [73] such as chitosan (because of its desirable biological properties such as ease of degradation in biological systems, biocompatible and non-toxic nature) [32]. Antibodies, such as Hyaluronic acid, Folic acid (one of the most effective targeting agents in cancer therapeutic purposes), [32] Tween 20/80 (drugs that work effectively against diseases associated with the central nervous system, must travel through the blood–brain barrier (BBB) to make its way to the brain , through the blood compartment) (Fig. 9) [32]. Table 3 presents the reported studies using surface-modified PBCA-NPs and performance of drug-loaded PBCA-NCs against cancer.

Applying PBCA to drug delivery in different cancers

In following sections, the literature is reviewed and summarized for the applicability of PBCA in the delivery of different drugs by various procedures and their mechanisms have been the extensively discussed.

Using PBCA in ovarian cancer treatment

Paclitaxel is an effective drug against different cancers and especially ovarian cancer [74]. Although it has insufficient aqueous solubility, its commercial formulation faces major challenges [75]. In addition, it has been studied previously that the difficulty in overcoming multidrug resistance (MDR) may be a result of NPs adsorption on the cell surface. [53] In the past, studies have reported providing paclitaxel-loaded PBCA NPs through mini-emulsion procedures or anionic polymerization [31].

Ren, Chen et al. studied to analyze the capability of PBCA NPs loaded with paclitaxel to alleviate the MDR in ovarian resistant cells in humans (A2780/T) and also to investigate the probable mechanism [51]. Paclitaxel-loaded PBCA NPs were formulated through interfacial polymerization procedure which resulted in their spherical form having an average diameter of 224.5±5.7 nm. Their results showed NPs formulated with paclitaxel could increase cellular toxicity and also alleviation of MDR by the inhibition of P-glycoprotein action created by the NPs system was observed. The researchers also compared emulsion polymerization with interfacial polymerization and stated that interfacial polymerization resulted in high encapsulation and drug loading amounts because of introduction via lecithin and dextran 70 like surfactants [76]. Another research assessed the cytotoxicity effects of cisplatin-charged PBCA NPs on cisplatin-resistant ovarian cancer cell line A2780cp [20]. Cisplatin, one of the most important drugs in treatment of ovarian cancer and their effect, is attributed to DNA binding and apoptosis initiation. They synthesized NPs through mini-emulsion polymerization procedure.

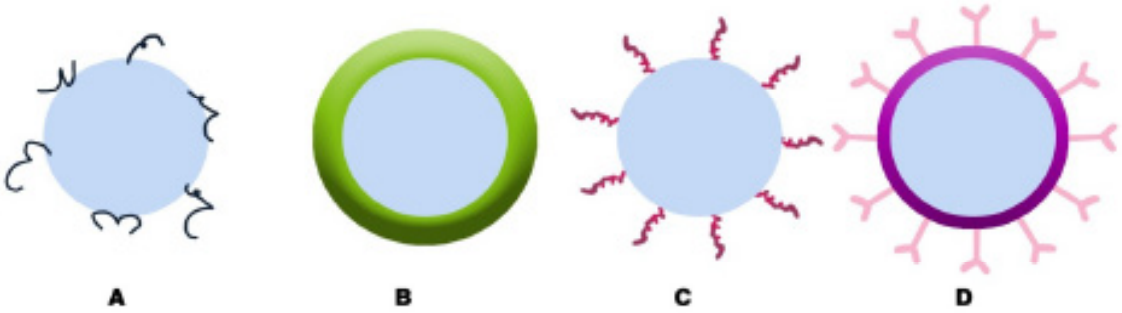

Fig. 9. PBCA-NCs modified with different materials (A) molecules having longer chain as PEG or Dextran, one moleculecular terminal is embedded into PBCA-NCs and another is available in the medium; (B) For Tween 80 like surfactants , materials are adsorbed to the outer most layer of PBCA-NCs; (C) shows hyaluronic acid HA) ligand-modified surface and packing of chemotherapy agents, relatively large-linear molecules such as targeting ligands, linear molecules are needed to form a link between the NC and the targets; (D) Surface modified drug loaded PBCA NPs with FA-Chitosan, enhancing the relative bioavailability of NPs and a targeting agent.

Table 3. The reported studies using surface-modified PBCA-NPs and relevance of PBCA-NCs armed with anti-cancer medications.

Drug	Additive used	*In vitro* investigation	*In vivo* investigation	Ref
Paclitaxel	Lecithin/ Dextran 70	PBCA NPs loaded with Paclitaxel can increase cytotoxicity and resolve MDR via the inhibition mechanism of P-gp activity of NP induced system.	–	[51]
Cisplatin	Dextran/ PEG400	PEGylated NPs demonstrated enhanced medication effects involving increased stability, antitumor impact and decreased nano-drug release levels, compared tostandard drug.	–	[20]
Carboplatin	Dextran 70/PEG3350	PEGylated NPs showed improvement of cytotoxicity, size, EE% and DLE% compared with non- PEGylated NPs.	–	[40]
Cisplatinum and Carboplatinum	Dextran 70/PEG600	PEGylated nanodrugs (both drugs) resulted in enhanced cytotoxicity in MCF-7 cell line than their unbound counterparts free drugs.	–	[21]
doxorubicin and curcumin	Chitosan/Antibody/Tween 20	The analysis indicate that the dual-agent mounted PBCA NPs system had comparable systemic toxicity to co-administer 2 individual-agent mounted PBCA-NPs, marginally higher than the free combination of drugs, to single free drug / another stacked PBCA-NPs combination.	–	[52]
Doxorubicin	Folic acid/ Chitosan	DOX-PBCA NPs redardless of folate groups displayed comparable cytotoxicity in case of both MCF-7 cells and HepG2cell types, while folate-when conjugated with DOX-PBCA NPs displayed increased cell utilization, increased targeting efficiency and increased cytotoxicity to MCF-7 cells that overexpress folate receptors.	–	[53]
Cisplatin	Dextran/PEG400	In addition, it can enhance the stability of the tumor cell and increase its chances of drug delivery.	–	[54]
Cisplatin	Dextran	IC50 on C6 cells of drug solution, blank PBCA NPs and drug-loaded NPs were 99.5, 164 and 67 µM, respectively.	–	[55]
Cisplatin	Dextran 70/PEG2000	Increasing the concentration of PEG improved the efficiency of drug loading, drug release profile and cytotoxicity impacts of drug-loaded NPs.	Cisplatin conjugated PCBA nanoparticles lead to the decrease in tumor volume unlike its unbound form and the control under consideration.	[59]
Paclitaxel	Hyaluronic acid/ Tween 80/ Dextran	The profiles of the in vitro release showed that the HA adjustment will delay the release of the drug and that the initial burst will be lowered in the first 10h.	PTX- embedded HA-PBCA NPs were primarily of higher potency for suppressing tumour growth than PTX-loaded PBCA NPs or PTX injection.	[60]
Curcumin	Antibody/Chitosan/Tween 20/	Enhanced therapeutic efficacy of Antibody-NPs cytotoxicity in HepG2 cells compared to PBCA-NPs and free drug.	The elimination half-life and the average time of residenceof complex formed with PBCA NP were higher than that of free curcumin. Nano-drug reduced hepatocellular carcinoma growth in murine xenograft models and controlled r angiogenesis. of tumour	[61]

DLE: Drug loading efficiency; EE: Entrapment efficiency; "–" not mentioned.

Size, size distribution and zeta potential of NPs were evaluated as 489 nm, 0.429, and -20 mV, respectively. This research shed light on the efficacy of cisplatin-PBCA NPs and their usage in in vivo ovarian cancer studies.

Kanaani, Ebrahimi Far et al. recently reviewed the basic properties and cellular effects of nano-poly (butyl cyanoacrylate) on ovarian cancer cells with carboplatin. The non-PEGylated and PEGylated nano particles were prepared by polymerizing PBCA NPs with mini-emulsions. The cytotoxicity findings showed both of these nano drugs are of higher toxicity than that of unloaded drug. This can be explained with drug

accumulation in loaded form which is remarkably higher than free form and thus increases drug delivery to tumor as compared to free drug. However PEGylated carboplatin PBCA was more toxic on the cells than no-PEGylated nano drug, because of the presence of PEG which could augment the stability and increase drug delivery to tumor, and also was able to prolong the period of drug release. These researchers concluded that both NPs are suitable for carrying carboplatin to ovarian cancer cell line A2780CIS [40].

Other study showed, the introduction of cisplatinum and carboplatinum drugs on PBCA NPs by means of emulsion polymerization method in varied types of cancer treatment, one of them is/ would be on ovarian cancer cells [21]. It was showed a loading efficiency of ~5 % that agreed with the value reported by Egea Mas [77]. It was studied that, in spite of administration in equal doses, cisplatinum exhibited higher toxic property toxicity in comparison to its counterpart carboplatinum, both as free and loaded on nanocarrier [78]. Both theses nano drugs exhibited lower cytotoxicity on MCF-7 cell line owing to its lower loading capacity, which was more evident in for carboplatinum nanoparticles. The authors concluded other approaches such as miniemulsion polymerization were more favourable in loading such drugs onto PCBA nanoparticles, unlike only emulsion polymerization.

Using PBCA in gastric cancer treatment

Drugs that are magnetically responsive show promising results for treating solid tumours, as they can be smoothly transported via intravenous system to any systemic position. The impact of magnetic poly butyl cyanoacrylate NPs charged with aclacinomycin A on the growth of gastric cancer under in vivo and in vitro conditions was previously investigated [79]. Aclacinomycin A along with magnetic PBCA nanospheres was encapsulated through interfacial polymerization. The content of aclacinomycin A into magnetic PBCA nanospheres was 12.0% and the mean particle size was 210 nm. Aclacinomycin A exhibited PBCA-NCs accomplish tumour targeting typically in two ways: by passive targeting system as well as by active targeting approach. Inhibitory rates of (8 mg/kg bm), high dosage of magnetic PBCA nanospheres entrapped with aclacinomycin A (8 mg/kg bm); low amount of magnetic PBCA nanospheres entrapped with aclacinomycin A (1.6 mg/kg bm) and magnetic PBCA nanospheres regarding study on human gastric carcinoma in nude mice amounted to 22.63%, 52.55%, 30.66% and 10.22%, respectively.

In vitro study showed that the effect of aclacinomycin-MPNS-PBCA-NCs on gastric cancer cell line was less differences in comparison with that of the physical blend of blank MPNs-NPs with aclacinomycin solution, without any external magnetic field. When the magnetic field with surface field strength of 2.5 T was implanted into the core of the cancer cells, the inhibitory rate of aclacinomycin-MPNS-PBCA-NCs on human gastric carcinoma (52.55%) was relatively twice higher than that of the aclacinomycin solution (22.63%).

In spite of the remarkable targeting capability of magnetic NCs in animal tests, there is still some difficulties in its use to humans, for example insignificant targeting at a depth of 42 cm within the body, poor preservation of the magnetic carriers upon the removal of magnet and also poor drug binding and release capacity of the carriers [32].

The researchers concluded that the magnetically targeted chemotherapy using aclacinomycin a conjugated magnetic PBCA nanospheres showed improved tumour targeting, lower toxicity and therapeutic efficiency.

Applying PBCA in breast cancer treatment

Anticancer property of cisplatin was well entrapped into dextran NPs which showed considerable effect on treatment for breast cancer, was studied by Li et al. Studies have also shown the improvement the efficacy of cisplatin is related to various NPs [80] Farhat, Ibrahim et al. assessed that lipoplatin in combination with liposomal cisplatin and vinorelbine has the potential to act positively and with good tolerability in the treatment of HER2/neu negative metastatic breast cancer, and such a combination show promising results in first line of treatment [81].

Koohi Moftakhari Esfahani, Alavi et al. evaluated the effectiveness of cisplatin-conjugated PBCA NPs in treating breast cancer and employed an orthotopic model of this tumour. They synthesized PBCA NPs in conjugation with cisplatin through mini-emulsion polymerization procedure and concluded that cisplatin-conjugated PBCA NPs had the potential to enhance the effectiveness of cisplatin and lower the toxicity of the drug. Cisplatin -PCBA nanoparticles lead to the reduction in tumor

size dissimilar its free form and the control sample [17]. Cabeza, Ortiz et al. evaluated the activity of doxorubicin as an antitumour agent in breast cancer, with the application of PBCA-NPs. NPs was synthesized through emulsion/polymerization technique. Size and size distribution of NPs were assessed as 135 nm and 0.071, respectively. It was showed that doxorubicin-encapsulated PBCA-NPs is of importance in decreasing the amount of doxorubicin required in achieving an appropriate result as an anticancer agent but with negligible toxicity in other tissues, because of two features including biodegradability and size. Small size of NPs makes them appropriate candidates for easy penetration via tiny capillaries into the target tissues and when constructed using biodegradable materials, they can easily remain in the body for several days and lead to proper drug discharge [82].

In another study, co-encapsulation of doxorubicin (DOX) and curcumin (CUR) were done on PBCA-NPs using polymerization through emulsion and via interfacial approaches. The prepared nanoparticles were used for in vitro anticancer evolution on breast cancer cells. CUR–DOX–PBCA-NPs had average particle size and zeta potential of 133±5.34 nm and +32.23±4.56 mV respectively. The dual incorporation of curcumin along with doxorubicin gained maximum reversal effectiveness and unequivocally down regulated in P-glycoprotein in an MCF-7 breast cancer cell line which shows resistance to Adriamycin [52].

Duan et al [53] prepared chitosan coated PBCA NPs loaded doxorubicin and after which folic acid was subsequently conjugated to fabricate a folate-targeted drug conveyer in drug delivery against cancer. The average size and zeta potential of synthesized DOX-PBCA-NPs (DOX-PBCA NPs) were ~174 ± 8.23 nm and 23.14 ± 4.25 mV, respectively with 46.8 ± 3.32% encapsulation capacity. Folate-doped DOX-PBCA NPs presented improved cellular intake, enhanced aiming capacity, and augmented cell toxicity toward MCF-7 cells which overexpress folate receptor compared to DOX-PBCA-NPs lacking folate groups.

Applying PBCA in prostate cancer treatment

A study was conducted to investigate the prostate cancer cells incubated with PBCA regarding free Nile Red solubilized in growth medium [83]. They investigated the consumption and distribution throughout cells, using flow cytometry and confocal laser scanning microscopy. They concluded that delivery of antitumour drugs into the cytosol via a contact-induced mechanism is not possible directly to the intracellular targets. They also stated that contact-dependent transfer mechanism and enhanced consumption of bound drugs compared to non-bound ones could be successful in delivering of hydrophobic anticancer drugs as a therapeutic means for cancer therapy.

Applying PBCA in glioblastoma cancer treatment

Glioblastoma stands among one of the fiercest and most aggressive of known human cancers. In treating glioblastoma, pharmaceutical agents should be able to cross blood-brain barrier (BBB). Ebrahimi, Movahedi et al. studied the efficacy of cisplatin-loaded PBCA prepared by miniemulsion polymerization on the glioblastoma. Size and zeta potential of NPs were evaluated as 489 nm and −20 mV, respectively. Polysorbate 80 (surface structure) was used as a coating agent to amiably pass BBB in glioblastoma-bearing rats. Polysorbate 80 was used by one of them as endocytosis receptor via brain endothelial cells, where absorption of apolipoprotein E in plasma was preferred. NPs functionalized with apolipoprotein E, absorbed into brain, are notified as LDL. The researchers concluded that nano drugs show low efficacy rather than free drug, because of mean survival time in nanodrug receivers was 17.5 days, while it was 19.6 days for free drug receivers. In addition decreasing side effects in vivo, this indicates their favourable applicability in treatment against other tumours. It was suggested that lowering the size and altering the surface structure and properties may be effective in smooth passing of BBB [35, 84].

Applying PBCA in brain cancer treatment

Studies have confirmed PBCA in conjugation with non-ionic surfactant polysorbate-80 appropriately delivered various small molecule drugs of polar nature into the central nervous system (CNS) [85, 86]. Drugs ranging from doxorubicin to loperamide to tubocurarine, and dalargin were readily targeted to CNS, by adsorbing onto PBCA-NPs, its site for showing pharmacological activity ,[85] by creating a specific disruption of the BBB. Studies have proposed that NPs nonspecifically permeabilize BBB, which negates their effectiveness in brain intake [87]. It has been reported that PBCA-NPs are capable of drug delivery in BBB impenetrable

fluorophores of a variety of sizes ranging from 500-Da targeted polar molecules to 150,000-Da marked immunoglobulins into living mouse brain [88]. However, high doses of PBCA-NPs with polysorbate-80 can cause damage to the BBB. Other studies have reported that PBCA-NPs only have pharmacological effects after administration of drugs. It is shown that LDL uptake system plays vital role in initiating polysorbate 80 absorbing of plasmatic apolipoprotein E (Apo-E) and NPs coated with Apo-E [89]. Conducting investigative studies on rats, unlike non targeted NPs, poly-lactic-co-glycolic acid NPs decorated with polysorbate 80 and charged with methotrexate-transferrin, displayed higher penetrability, lower toxicity effects on organs, and better activity against tumour [90]. Kreuter and Gelperina showed that PCBA-NPs charged polysorbate 80 / poloxamer 188 was able to transfer doxorubicin across the BBB and significantly lowered to PBCA-NCs accomplish tumour targeting typically in two ways: by passive targeting and by active targeting approach [91]. Apart from that, the importance of magnetic nanoparticles in treatment of brain cancer is of utmost consideration since, brain cells are particularly sensitive to its administration and leading to their ease of diffusion across BBB, unlike cells in liver and heart[92, 93]. Reimold, Domke et al. used fluorescence microscopy to evaluate brain-NP delivery through mini-emulsion technique to produce PBCA particles of high reproducibility and yield, in an efficient manner. The NPs were loaded with 1.5% (w/v) fluorescein-isothio-cyanate-dextran (FITC-dextran), 1.5% rhodamine-123 or 7.3% doxorubicin. 10% w/v of polysorbate 80 was used to coat the NPs, and injected into rats. Their results indicated that surface-coupled PBCA-NPs could pass the BBB and additionally mediate in drug-delivery to the CNS. It was concluded that polymeric systems of colloidal nature show an encouraging pathway to surpass BBB [94]. Tian, Lin et al. conducted a study to evaluate PBCA-NPs covered by polysorbate-80 to carry drugs into the animal brain. NPs were prepared by emulsion polymerization. Higher concentration of polysorbate-80-coated PBCA NPs coupled with temozolomide was discovered in the brain compared to unbound drug. They concluded that delivery of temozolomide to the brain can possibly be accomplished using polysorbate-80 coated PBCA-NPs delivery [69].

In another study, cisplatin loaded PBCA NPs (Cisplt-PBCA-NPs) were synthesized by polymerization using by mimi-emulsion technique for treating A172 brain cancer cell line. The average size and zeta potential of cisplatin conjugated-PBCA-NPs were 451.2±11.1 nm and 0.452± 0.09 mV, respectively. Cisplatin was physically administered and only 4.7% of cisplatin was released after 68 h. Cisplt-PBCA-NPs showed more cytotoxic effects on the cancer cells in comparison to free cisplatin by enhanced apoptosis rate in tumours. The results were at par with the research on Cispt-PBCA-NPs showing enhanced number of apoptotic and necrotic cells in comparison to unbound cisplatin [95]. The authors concluded that Cisplt-PBCA-NPs were more effective in treatment of A172 brain cancer cells compared to cisplatin in free/unbound form [54].

In a similar study, PBCA NPs coupled with cisplatin were synthesized by anionic polymerization method, and their cytotoxic effect was evaluated on the rat glioma cell line C6. The synthesized nanoparticles were of optimum size (222 nm) and zeta/surface potential was (5.1 ± 0.2 mV) suitable for drug delivery. The results presented that nanoconjugates of cisplatin have more cytotoxic effect (IC50 of 67 μM) on brain cell line than that of the free drug (IC50 of 99 μM) [55]. Nanoparticles were efficiently passed through the barrier cells and cisplatin added an alkyl group to DNA molecules, thus DNA replication is inhibited in this manner which stimulates apoptosis induction in cancer cells.

Applying PBCA in other cancer treatment

Cisplatin-loaded PBCANPs were prepared by means of an anionic polymerization procedure for the cure of lung cancer cells. It was displayed that the size and the drug binding capacity of the spherically synthesized NPs were 355–386 nm and 14–19%, respectively, and the drug escape profile was a slow and controlled, around 10% release over 48 h. Furthermore, the PBCANPs importantly enhanced the cellular toxicity twice to that of cisplatin in in vitro and increased the healing property of the drug in vivo by increasing the survival by 20%, in case of lung-cancer-containg mice, unlike the standardized drug receiver group. They presented that the prepared formulation with 1.0% (w/v) PEG stabilizer at the temperature of 65 °C had the maximum ease of drug loading, cytotoxicity effects, and anticancer efficacy in vivo

[59].

He et al. described preparation of hyaluronic acid (HA) coated PBCA NPs using radical polymerization method [60]. The NPs sizes ranged from of 291–325nm. HA coating could considerably decrease the cytotoxicity. It was found that consumption of HA-PBCA NPs were nine and a half time higher in Sarcoma-180 (S-180) cells that of PBCA NPs, because of HA has specific receptors in various tumours, thus gaining active targeting and more absorb by tumour's cells. It was showed that paclitaxel (PTX)-bound HA-PBCA NPs were of higher effectiveness in growth suppression of cancer cells compared to PTX-conjugated PBCA NPs or PTX administered intravenously to S-180 tumour containing mice. The author claimed that the HA-PBCA NPs could were a potent as well as safe for carrying hydrophobic antitumour drugs of systemic nature.

Evangelatov was successful in synthesizing epirubicin-conjugated PBCA NPs via the pre-polymerization procedure and used this to treat cervical carcinoma cells. It was showed that cytotoxicity of the epirubicin-loaded PBCA decreased as compared to the free drug .They demonstrated that epirubicin and epirubicin-loaded NPs as well as the free drug initiated cell death, but showed innumerable cell responses along with dissimilar cellular localization [96] [82]. Epirubicin-loaded NPs were consumed /up taken through endocytosis, showed endosomal aggregation and resulted in twice the stronger pro-apoptotic signal in comparison to unbound drug.

PBCA-NPs coupled with chitosan synthesized, using encapsulated formulation of curcumin via, emulsion polymerization were synthesized by Duan and co-workers [61]. The spherical curcumin conjugated PBCA NPs had a mean particle size of ~ 250nm, making them suitable carriers in drug delivery. A positive charge of 29.11±1.69mV on the surface was successful in enhancing their interaction with negatively charged biological membranes and also stability as biological cations and for targeted in-vivo delivery. Curcumin-PBCA-NPs suppressed both COX-2 and VEGF expression simultaneously inhibiting abnormal growth of human hepatocellular carcinoma cell lines in vitro. The cell viability of the HepG2, Bel7402 and Huh7 cell decreased from 87.35% to 8.5%, 92.47% to 4.84% and 94.57% to 0.99%, respectively, as the curcurmin NPs concentration augments from 5 to 50µg/mL after 24 h incubation at 37 ◦C. In vivo study showed that curcumin NPs inhibited cancer cell growth in liver in murine xenograft models and these effects were accompanied via a potent antiangiogenic response.

CONCLUSION

This review article aimed to summarize the studies conducted on PBCA technique in drug delivery, with some studies on cancer models of higher significance, while several others require further investigation. It is indeed a thorough task to sum up and represent the drug delivery efficiency of PCBA entirely. The review has mostly focused on beneficial effects of PBCA as successful drug delivery system. Considering the preparation method, mini-emulsion polymerization looks promising, and as its therapeutic applicability, PCBA, showed positive results in suppressing brain cancer in in vivo models. Overall, further investigation is required to confirm the clinical efficiency of PCBA.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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