Expert Opinion

Poly(alkycyanoacrylate) nanoparticles for enhanced delivery of therapeutics – is there real potential?

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The properties inherent in poly(alkylcyanoacrylate) (PACA) nanoparticles, such as biocompatibility and biodegradability of the polymer, a simple preparation process and particularly the entrapment of bioactives, specifically proteins and peptides, have sparked extensive interest in these nanoparticles as drug delivery systems. Research has focused on the oral route of administration, however ocular, transdermal and delivery across the blood–brain barrier have also been investigated. Despite numerous promising studies, no formulation with this colloidal carrier has been marketed to date. A number of factors have been identified as interfering with the reproducibility of *in vitro* and *in vivo* results, which impedes the comparison of the plethora of experiments done with PACA nanoparticles. This review will highlight the challenges and opportunities of using PACA nanoparticles as drug delivery systems, including polymerisation mechanisms and templates, entrapment, release, nanoparticle uptake and toxicity. *In vitro* and *in vivo* studies, as well as possible surface modifications for targeted delivery in the human field and veterinary applications of PACA nanoparticles are reviewed. Emphasis will be placed on microemulsions as templates for the preparation of PACA nanoparticles and oral delivery of proteins and peptides.

Keywords: alkylcyanoacrylate, microemulsions, nanoparticles, oral delivery, protein delivery

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1. Introduction

Alkylcyanoacrylates, commonly known as Superglue® (Super Glue Corporation, USA/ Henkel Loctite, Germany), have been used as suture materials for more than 40 years [1]. As polymerised nanoparticles they were introduced to the area of drug delivery by Couvreur *et al.* [2] in the 1970s. Nanoparticles are polymeric, spherical structures in the sub-micron size range that can be used as colloidal carriers for therapeutic agents [3]. The properties inherent to poly(alkylcyanoacrylate) (PACA) nanoparticles such as biocompatibility and biodegradability of the polymer, a simple preparation process and particularly the entrapment of bioactives have sparked extensive interest in these nanoparticles as drug delivery systems. Research has focused on the oral route of administration due to the popularity and practicality of oral delivery [4]. However, ocular, transdermal and delivery across the blood–brain barrier have also been investigated. Nanoparticles have the advantages that they are stable in biological fluids, can protect the therapeutic agents from enzymatic degradation and can provide controlled drug release due to their polymeric nature [5,6]. Biodegradable nanoparticles are a versatile system suitable for the delivery of a range of therapeutic agents from small molecular weight drugs to macromolecules (proteins and peptides) and DNA. Since many modern drugs are of peptidic nature and thus prone to degradation upon administration, which results in low bioavailability,

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numerous studies have explored the entrapment of these drugs into PACA nanoparticles to overcome some of the barriers to effective peptide and protein delivery. A prerequisite for systemic absorption is the passage of the intact drug through the epithelium. Epithelial drug absorption can occur either by passive or active mechanisms, through the cells (transcellular) or through the spaces between the cells (paracellular). The transcellular route is predominantly accessible for lipophilic drug molecules; most proteins and peptides, however, are hydrophilic. Furthermore, proteins are macromolecules and thus the paracellular route, despite its hydrophilicity, is usually not feasible due to the small paracellular space. Drug molecules absorbed by random pinocytosis are likely to be degraded by lysosomes. Enzymatic degradation in general is one of the main barriers to effective protein and peptide delivery. With entrapment into PACA nanoparticles, however, these molecules can be protected against enzymatic degradation and the systemic uptake enhanced by transcellular or paracellular translocation of the nanoparticles across the intestinal epithelia (see section 5 on nanoparticle uptake).

Interestingly, despite the plethora of research on PACA nanoparticles as colloidal drug carriers, no product has entered the market to date. A breakthrough was thought to have occurred with the clinical development of Transdrug® (BioAlliance Pharma, France), a formulation containing doxorubicin-loaded poly(isohexylcyanoacrylate) nanoparticles for cancer therapy. Clinical phase II/III trials were announced in 2006 but had to be suspended in July 2008 due to acute pulmonary damage [7].

The focus of this review will be on the challenges and opportunities of using PACA nanoparticles as drug delivery systems. Emphasis will be placed on oral delivery of proteins, peptides and microemulsions as templates for the preparation of PACA nanoparticles.

2. Microemulsions as PACA nanoparticle templates

PACA nanoparticles can be prepared from various templates and the drug can either be encapsulated in the particle core (nanocapsule), dispersed throughout a nanoparticle matrix (nanosphere), or adsorbed to the nanoparticle surface [8]. The type of nanoparticle formed and the preparation mechanism are determined by the type of template used. The formation of nanoparticles from the polymerisation of monomers is achieved using two main methods: polymerisation in an aqueous acidic phase [2] and interfacial polymerisation of (sub-micron) emulsions [2,9,10] or microemulsions [11]. Other terms used in the literature for polymerisation in an aqueous acidic medium are emulsion/dispersion polymerisation and micellar polymerisation. The latter term stems from the theory that polymerisation takes place around micelles formed by surfactants added as formulation stabilisers [12]. However, this has now been found not to be a prerequisite for particle formation [13]. In the process of polymerisation, the monomer is emulsified in water containing a surfactant. Depending on the type of additive, for example dextran [14] or poloxamer [15], one differentiates between dispersion and emulsion polymerisation. Although emulsion polymerisation is a widely used term, the polymerisation medium is by definition an aqueous solution and not an emulsion.

Polymerisation is then started by introducing an initiator into the system. For alkylcyanoacrylate monomers, the initiators are, for example, the hydroxyl ions present in the polymerisation medium from the dissociation of water [2] or other molecules such as alcohols and amino acids. Therefore, polymerisation initiation by nucleophilic molecules, for instance protein and peptide bioactives and excipients present in the formulation, may result in co-polymerisation with the monomer [10,16,17]. Rapid anionic polymerisation initiated by skin proteins resulting in tissue adhesiveness is in fact the underlying mechanism of liquid band aids on the basis of alkylcyanoacrylates [17]. On the one hand co-polymerisation bears a detrimental risk for the protein bioactivity [16,18] and on the other hand it has deliberately been chosen as a strategy to increase drug stabilisation and entrapment [19-21]. It appears that initiation of polymerisation can be competitive, depending on the relative amounts of initiators present. This, for example, has been shown by the addition of excess alcohol to the polymerisation template, effectively preventing the co-polymerisation of insulin with the polymer [22]. Recently, interesting details about the co-polymerisation mechanism were obtained by matrix-assisted laser desorption ionisation time-of-flight (MALDI-TOF) analysis [23]. Poly(ethylcyanoacrylate) (PECA) nanoparticles containing D-Lys6-GnRH showed that the peptide is covalently bound to monomer subunits, resulting in mass shifts of 125 mass units (**Figure 1**). Some of the peptide also persists in its free form, as indicated by the peak at m/z 1253 (**Figure 1**).

Polymerisation in an aqueous acidic medium to prepare PACA nanoparticles was first reported by Couvreur *et al.* [2]. Interfacial polymerisation using an oil-in-water sub-micron emulsion was later established by Al Khouri Fallouh *et al.* [9]. In this preparation method, a monomer-drug-oil mixture is dissolved in a water-miscible organic solvent phase and injected into a surfactant-containing aqueous phase forming the oil-in-water (o/w) sub-micron emulsion. This method was adapted by El-Samaligy *et al.* [24] for a water-in-oil (w/o) sub-micron template. The emulsion system used as a polymerisation template (o/w or w/o) determines the nature of the core of the nanoparticles following polymerisation (lipophilic or hydrophilic respectively) [25] and, in the majority of cases, consequently the type of bioactive that can be entrapped. However, a disadvantage of the use of sub-micron emulsions is that potentially toxic solvents have to be used and so a washing step is required. It is also necessary to include high energy processes, such as vigorous stirring [26] or ultrasonication [24], during their manufacture to form droplets of a sufficiently small size. Microemulsions, which are isotropic mixtures of oil, water, surfactant and co-surfactant, are an improvement on sub-micron emulsions as polymerisation templates because they form spontaneously with a small and uniform droplet

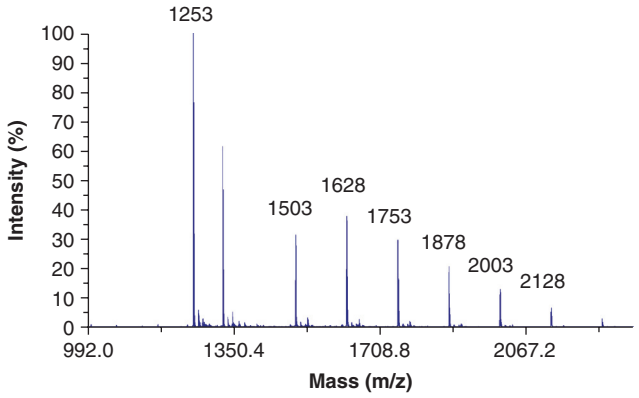

Figure 1. Mass spectrum of PECA nanoparticles polymerised in the presence of D-Lys^6-GnRH peptide. Peak at m/z 1253 is free D-Lys^6-GnRH peptide. Peptide co-polymers with ECA monomers $[M+(125)_n+H]^+$ are present at m/z 1378.7, 1503.8, 1628.8, 1753.9, 1878.9, 2003.0 and 2128.0.

size of approximately 10 – 20 nm. Furthermore, they are thermodynamically stable systems. Microemulsions were introduced as interfacial polymerisation templates by Gasco and Trotta [11], yet still contained organic solvents. Removal of these solvents bears the risk of aggregation and poses problems to method scale-up. To overcome these issues, Watnasirichaikul *et al.* [27] developed a simple, single-step method for preparing PECA nanoparticles by interfacial polymerisation of biocompatible microemulsions. In this system, a w/o microemulsion forms the polymerisation template as a dispersion of swollen micelles with an internal aqueous environment. When monomer (ethyl 2-cyanoacrylate) is added to the microemulsion, it migrates to the interface between the oil and water and the hydroxyl ions from the autoprotolysis of water initiate the polymerisation process (**Figure 2**). In a droplet-type microemulsion, a polymer wall is then formed around micelle clusters which concomitantly collapse and result in nanocapsules with an average size of around 250 nm. Aqueous material, containing the bioactive compound, can be entrapped into these systems [27]. However, interfacial polymerisation can also be applied to other structure-types of microemulsions [28], such as bicontinuous [29], solution-type and water-free systems [30]. An example of PACA nanoparticles prepared from a bicontinuous microemulsion template is shown in **Figure 3**. Using the concept of interfacial polymerisation, Krauel *et al.* [28] hypothesized that following nucleophilic polymerisation initiation, the thermodynamically favoured structure of the forming polymer chains is a sphere, having a minimal surface-to-volume ratio. Therefore, PACAs from these templates also assemble into spherical nanoparticles as in the case of droplet-type templates, and the interface is created *in situ* by the elongating polymer chains. Since biocompatible compounds are used, there is no need to separate the particles from the templates. The nanoparticles can thus be administered dispersed in the microemulsion template. This is beneficial for oral absorption in that permeability enhancing effects of microemulsions can be exploited [31,32]. Watnasirichaikul *et al.* [33] for instance, used poly (isobutyl cyanoacrylate) (PiBCA) nanoparticles (200 nm) and a biocompatible microemulsion to deliver insulin to diabetic rats by intragastric administration. Inclusion of the microemulsion in the formulation significantly reduced blood sugar levels compared with nanoparticles alone. The microemulsion is thought to increase absorption of insulin across the epithelial cell layer by increasing the surface area available for drug release and increasing the viscosity of the formulation so it is retained for a longer time at the surface of the enterocytes [34].

The type of microemulsion template does not seem to affect the properties of the resulting nanoparticles, which makes these templates a flexible formulation option depending on the solubility of the bioactive to be incorporated [35]. However, the entrapment efficiency of bioactives, for instance ovalbumin [28] and insulin [36], was found to change with the type of microemulsion template and the monomer concentration. A variety of bioactives including insulin [27], ovalbumin [37], salmon calcitonin [26] and oligonucleotides [38] have efficiently been entrapped in PACA nanocapsules with an aqueous core for oral peptide and protein delivery. A summary of the different hydrophilic and lipophilic bioactives associated with different types of PACA nanoparticles is given in **Tables 1 – 3**.

3. Entrapment/loading of bioactive molecules

As mentioned above, the entrapment efficiencies of bioactive compounds depend on the method of entrapment used [8]. The entrapment of therapeutic compounds into nanoparticles can be achieved using two different strategies: encapsulation or sorption [8]. Entrapment efficiencies will greatly depend on the drug solubility in the polymerisation medium because the drugs are generally dissolved in the polymerisation medium prior to polymerisation. Entrapment in nanospheres is therefore more suitable for hydrophilic drugs, whereas entrapment in nanocapsules can be modulated by the core material and thus by choosing the appropriate polymerisation template. Entrapment of lipophilic drugs into nanospheres can however be facilitated using cyclodextrins as solubilisers [39]. More details on this specific topic can be found in a review by Duchêne *et al.* [40].

In addition to solubility, molecular weight and polymerisation kinetics are known to influence entrapment. Pitaksuteepong *et al.* [37] entrapped sucrose, fluorescein isothiocyanate (FITC) labelled ovalbumin or dextran in PECA nanoparticles. Encapsulation efficiency increased with the increasing molecular weight of the macromolecule. An encapsulation efficiency of 20% was reported for sucrose (molecular weight 342), 53% for FITC-dextran 10 (molecular weight 10 kDa) and 97% for FITC-dextran 70 (molecular weight 70 kDa). Furthermore, encapsulation efficiency was not influenced by charge of the macromolecule, as shown by the entrapment of ovalbumin below, at and above its isoelectric point [37]. In a number of studies, encapsulation of drug

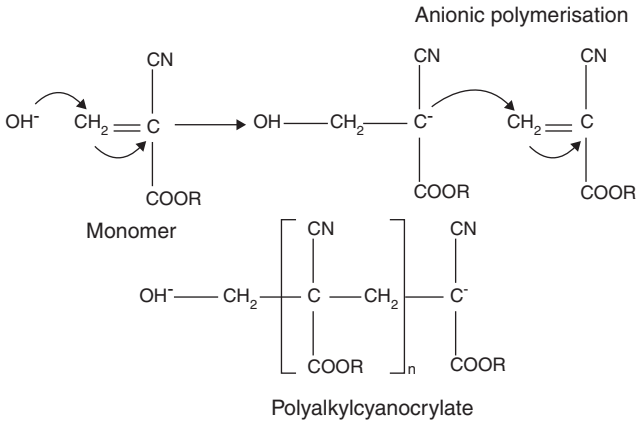

Figure 2. Anionic polymerisation of alkylcyanoacrylates that leads to the formation of nanoparticles. The hydroxyl ions are from the dissociation of water in the swollen, reversed micelles.

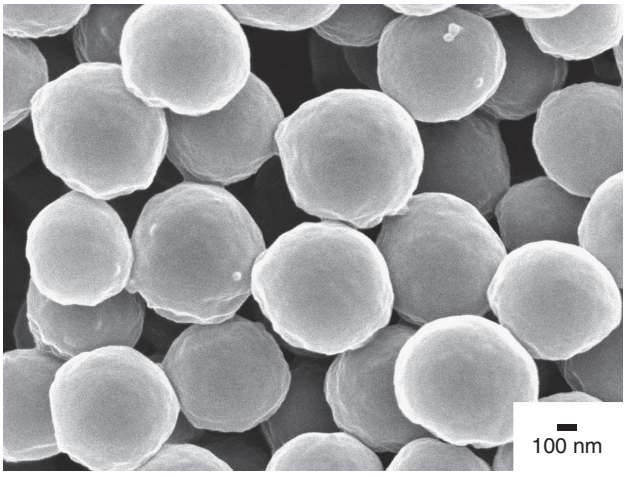

Figure 3. Scanning electron micrograph of poly(butylcyanoacrylate) nanoparticles prepared from a bicontinuous microemulsion template. Bar represents 100 nm.

molecules with a small molecular weight was found to be low due to the drug escaping the forming polymer network, particularly when the drug was soluble in the continuous phase of the polymerisation template [22,35,37,41]. This is potentially problematic for peptide drugs, which are generally hydrophilic. Krauel *et al.* [28] found that a droplet-type polymerisation template generally yields a higher entrapment compared to nanoparticles formed from other microemulsion polymerisation templates, as a result of the drug being confined in the droplet sphere. However, again entrapment is also influenced by the molecular weight of the drug [42,43]. For polymerisation of insulin-containing microemulsion templates, it has recently been shown that if the drug concentration in the continuous aqueous phase is increased, loading capacity can significantly be increased in the nanoparticles, despite a decreased entrapment efficiency [36]. If for instance the amount of insulin in the o/w microemulsion template is fivefold higher than in the w/o microemulsion template, the absolute entrapment is higher for the o/w template, despite an overall lower percentage in entrapment. This is reflected in the loading capacity.

If hydrophilic drugs are to be entrapped, one can also try to exploit the polymerisation kinetics of alkylcyanoacrylates to increase drug entrapment. The polymerisation rate of alkylcyanoacrylates is a function of their alkyl chain length. Entrapment of hydrophilic drugs into PACA nanocapsules from templates with an aqueous continuous phase has been found to be a result of the very fast polymerisation of the shorter alkyl chain monomers, thus essentially being mechanical in nature [22,44-46]. Increasing the monomer concentration generally leads to an improvement in entrapment efficiency [24,28].

Since insulin is the most studied model compound for research into the area of non-invasive delivery of proteins and peptides, there is a wealth of information on entrapment of this bioactive into PACA nanoparticles. In this section we will look at this in more detail. It is remarkable that seemingly similar studies in the literature show controversial results in terms of particle size, molecular weight and entrapment efficiencies of the resulting PACA nanoparticles [14,47,48]. Despite the same nanoparticle preparation method being used, the entrapment efficiency of insulin was 90% in a study by Cournarie *et al.* [49] and Aboubakar *et al.* [50], whereas Damgé *et al.* [44] only yielded 55%. In addition, there was a difference of 200 nm in the average size of the nanoparticles in these preparations. In another study by Cournarie *et al.* [47] the authors identified that the pH of the aqueous insulin solution and the origin of the alkylcyanoacrylate monomer are key parameters that influence entrapment efficiency. Entrapment efficiency not only depends on the alkylcyanoacrylate homologue but also on the compounds that have been added as stabilisers/polymerisation inhibitors to the monomer or synthesis by-products, such as cyanoacrylic acid [14]. The amount of polymerisation inhibitors varies from batch to batch and between suppliers [51]. Moreover, the pH of the polymerisation medium can modulate the efficacy of these compounds in controlling the anionic polymerisation of alkylcyanoacrylates [52,53]. The presence of preservatives in the insulin solution used is another factor that influences entrapment efficiency [47]. Studies in which highly purified insulin preparations were used reported almost complete entrapment efficiencies [22,54-56]. For commercially available insulin solutions, reports of low entrapment due to the additives [44] as well as sufficiently high entrapment can be found [27,49,57]. Further, entrapment and loading of insulin has been suggested to be influenced by the association state of insulin in solution and to depend on the concentration of the monomer species of this drug in the formulation [47]. In conclusion, the multitude of factors affecting entrapment efficiency makes it difficult to compare and contrast individual studies and raises the question of how reliably PACA nanoparticles can serve as drug delivery vehicles in terms of reproducibility of results.

Table 1. Summary of *in vivo* studies on PACA nanoparticles as drug delivery systems.

Polymer	Examples of bioactives	Preparation method/ template	EE (%)	Species	Observations	Ref.
PECA BSA, chitosan	Ganciclovir	Interfacial polymerization w/o emulsion	65	Rabbit	Improved ocular drug concentration	[102]
PECA	Insulin (bovine)	Aqueous acidic medium	85	Rat	Significant glucose reduction with absorption enhancer	[103]
PBCA	Avarol	Alcoholic medium	–	Rat	Eight to ninefold increase in oral bioavailability	[104]
PBCA	BSA	Aqueous acidic medium	70 – 80	Rat	Significantly increased immune response	[105]
PBCA	Insulin (porcine, crystalline, Zn)	Aqueous acidic medium	79	Rat	57.2 % relative pharmacological bioavailability*	[106]
PBCA	LHRH	Aqueous acidic medium	co-polym.	Rat	Significant serum testosterone reduction	[19,107]
PBCA	Calcitonin (salmon)	Interfacial polymerisation w/o emulsion	30 – 50	Rat	hypocalcemic response in the presence of deoxycholic acid as absorption enhancer, 40 – 45% bioavailability*	[26]
PBCA PHCA	HIV-2	Aqueous acidic medium	–	Mouse	Necessity of using vaccines with two or more different adjuvants to induce the required immune response	[108]
PiBCA	ODNs	Interfacial polymerisation w/o emulsion	70	Fetal calf serum	Efficient ODNs protection from degradation by nucleases upon encapsulation	[38]
PiBCA	Darodipine	Interfacial polymerisation o/w emulsion	–	Rat	Reduction in blood pressure	[109]
PiBCA	Indomethacin	Interfacial polymerisatio o/w emulsion	–	Rat	Protection from ulceration, sustained bioactivity of thromboxane blood levels over 24 hours	[110]
PiBCA	Insulin (Zn, Semicrystalline)	Interfacial polymerisation o/w emulsion	≥ 98	Rat/CHO cells	*in vitro* binding of insulin to receptor	[56]
PiBCA	Insulin (Humulin®) Insulin (porcine)	Interfacial polymerisation o/w emulsion	55	Rat	Strong hypoglycaemic response for up to 20 days	[44]
PiBCA	Insulin (bovine, Texas Red®-labelled)	Interfacial polymerisation o/w emulsion	90	Rat	Nanocapsules protect insulin from degradation and are significantly involved in the absorption mechanism	[63]
PiBCA	Insulin (human, Zn) Insulin (^{125}I-labelled)	Aqueous acidic medium	80	Rat	50% decrease of fasted glycaemia for 10 – 13 days, increased/prolonged uptake in GIT, liver, blood	[58]
PiBCA	Insulin (Humulin®)	Interfacial polymerisation w/o microemulsion	> 80	Rat	Significant reduction of glycaemia for 60 hours over control when dispersed in microemulsion	[33]
PiBCA	Insulin (Velosulin®)	Interfacial polymerization o/w emulsion	98	Rat	Intensive and prolonged after ileal administration	[54]

*Pharmacological availability/bioavailability determined based on the extent of hypoglycaemic/hypocalcemic response relative to subcutaneous injection of insulin or salmon calcitonin, respectively.

BSA: Bovine serum albumin; CHO: Chinese hamster ovary; co-polym.: Co-polymerised; DEAE: Diethylaminoethyl; EE: Entrapment efficiency; GIT: Gastrointestinal tract; HIV: Human immunodeficiency virus; I: Iodine; LHRH: Luteinizing hormone releasing hormone; NOD: Non-obese diabetic; ODN: Oligodeoxynucleotides; o/w: Oil-in-water; PACA: Poly(alkylcyanoacrylate); PBCA: Poly(butylcyanoacrylate); PECA: Poly(ethylcyanoacrylate); PiBCA: Poly(isobutylcyanoacrylate); PiHCA: Poly(isohexylcyanoacrylate); rH-G-CSF: Recombinant human-granulocyte-colony stimulating factor; w/o: Water-in-oil; Zn: Zinc.

Table 1. Summary of *in vivo* studies on PACA nanoparticles as drug delivery systems (continued).

Polymer	Examples of bioactives	Preparation method/ template	EE (%)	Species	Observations	Ref.
PiBCA	Insulin	Interfacial polymerisation o/w emulsion	–	Rat	Long-lasting strong hypoglycaemic response reduction of hyperglycaemic peak	[68]
PiBCA	Insulin	Aqueous acidic medium	40	Rat	Prolonged hypoglycaemic effect subcutaneous but not orally	[80]
PiBCA	Insulin (bovine)	Aqueous acidic medium	65 – 95	Rat	Significant reduction of glycaemia for more than 8 hours, pharmacological availability* of 37.6 %	[55]
PiBCA	Insulin (Humalog®)	Interfacial polymerisation o/w emulsion	90	Rat	High variability in the concentration of insulin in plasma, no decrease of glycaemia	[49]
PiBCA	Insulin (Humulin®)	Aqueous acidic medium	59	Rat	Significant reduction of glycaemia over control	[81]
PiBCA	Insulin (human, Zn)	Interfacial polymerisation o/w emulsion	> 98	NOD mouse	Reduced incidence and delayed onset of diabetes, reduced lymphocytic inflammation of endogenous islets	[111]
PiBCA	Insulin/calcitonin (human), (^{125}I-labelled)	Interfacial polymerisation o/w emulsion	90 – 95	Rat	No significant overall enhanced peptide absorption	[45]
PiBCA	Lipiodol	Interfacial polymerisation o/w emulsion	–	Dog	Accelerated, intensified and prolonged passage of iodine through intestinal mucosa	[31]
PiBCA	ODNs	Interfacial polymerisation o/w emulsion	81	Mouse	Inhibition of Ewing sarcoma-related tumour after intratumoural injection of a cumulative dose	[112]
PiBCA	Octreotide	Interfacial polymerisation o/w emulsion	60	Rat	Significant reduction of prolactin secretion	[42]
PiBCA	Pilocarpine	Interfacial polymerisation o/w emulsion	13.5	Rabbit	Significantly increased and prolonged miosis implying an improved ocular bioavailability	[113]
PiBCA PiHCA	rh-G-CSF	Aqueous acidic medium nanoprecipitation	66 90	Mouse	Co-polymerisation, loss of bioactivity	[18]
PHCA PiHCA	ODNs	Aqueous acidic médium DEAE dextran	–	Vero cells, mouse	Protection from degradation, significantly enhanced cellular uptake, improved antisense treatments for tumour and antiviral therapy, liver targeting	[114]

*Pharmacological availability/bioavailability determined based on the extent of hypoglycaemic/hypocalcemic response relative to subcutaneous injection of insulin or salmon calcitonin, respectively.

BSA: Bovine serum albumin; CHO: Chinese hamster ovary; co-polym.: Co-polymerised; DEAE: Diethylaminoethyl; EE: Entrapment efficiency; GIT: Gastrointestinal tract; HIV: Human immunodeficiency virus; I: Iodine; LHRH: Luteinizing hormone releasing hormone; NOD: Non-obese diabetic; ODN: Oligodeoxynucleotides; o/w: Oil-in-water; PACA: Poly(alkylcyanoacrylate); PBCA: Poly(butylcyanoacrylate); PECA: Poly(ethylcyanoacrylate); PiBCA: Poly(isobutylcyanoacrylate); PiHCA: Poly(isohexylcyanoacrylate); rH-G-CSF: Recombinant human-granulocyte-colony stimulating factor; w/o: Water-in-oil; Zn: Zinc.

Table 2. Summary of *in vitro* studies on PACA nanoparticles as drug delivery systems.

Polymer	Examples of bioactives	Preparation method/ template	EE (%)	Observations	Ref.
PMCA PECA PBCA	Fluorescein, doxorubicin	Interfacial polymerisation w/o emulsion	55 – 74	Drug release PMCA > PECA > PBCA, increasing monomer concentration led to retardation of drug release	[24]
PECA	ETS, DPH, CBZ	Interfacial polymerisation o/w emulsion	≤ 12	Controlled drug release by diffusion from oil core through intact polymer wall	[115]
PECA	FITC-OVA	Interfacial polymerisation microemulsions	8 – 92	Nanoparticle morphology determined more by dynamics within template than its microstructure	[28]
PECA PBCA	Insulin (Humulin®)	Interfacial polymerisation microemulsions	86 10 – 50 10 – 20 9 – 18	Effective entrapment decisive release factors different *in vitro* as compared to *in vivo* insulin interference with polymerisation, moderate entrapment due to insulin escaping valuable characterisation with self-diffusion NMR, promising microemulsion templates	[27, 35, 36, 41]
PECA PBCA	$LCMV_{33-41}$	Interfacial polymerisation w/o microemulsion	≥ 90	Functionalised co-polymerisation	[21]
PBCA	Methotrexate	Aqueous acidic medium	42 – 87	Variation in polymerisation technique results in particles with different properties suitable for different drug delivery routes	[15]
PiBCA	Insulin (bovine)	Nanoprecipitation interfacial polymerization o/w emulsion	99 90	Competitive polymerisation initiation by ethanol	[22]
PiBCA PiHCA	GRF saquinavir (HPβCD-complex)	Aqueous acidic medium	74 – 83 45 – 50 (µg/mg)	Co-polymerisation 400-fold increased apparent solubility and 20-fold increased drug loading	[16, 116]

Data referring to loading instead of EE indicated µg/mg.

CBZ: Carbamazepine; DPH: 5,5-Diphenyl hydantoin; EE: Entrapment efficiency; ETS: Ethosuximide; FITC-OVA: Fluorescein isothiocyanate-labelled ovalbumin; GRF: Growth hormone releasing factor; HPβCD: Hydroxylpropyl-[beta]-cyclodextrin; LCMV: Lymphocytic choriomeningitis virus glycoprotein; NMR: Nuclear magnetic resonance; o/w: Oil-in-water; PACA: Poly(alkylcyanoacrylate); PBCA: Poly(butylcyanoacrylate); PECA: Poly(ethylcyanoacrylate); PiBCA: Poly(isobutylcyanoacrylate); w/o: water-in-oil.

Table 3. Summary of surface-modified PACA nanoparticles as drug delivery systems.

Polymer	Examples of bioactives	Preparation method/ template	EE (%)	Species	Observations	Ref.
PEG-PECA	Acyclovir	Aqueous acidic medium	2 (w/w)	Rabbit	25-Fold increase of drug levels in aqueous humour	[117]
PEG-/PS80-PBCA	Dalargin	Aqueous acidic medium	40	Mouse	Significant analgesia due to successful brain targeting	[118]
PEG-PHDCA	Doxorubicin rHuTNF-α	Nanoprecipitation double-emulsion	70 – 85 60	Rat cells, mouse	Unimproved therapeutic response in the gliosarcoma protection of bioactive during preparation, increased anti-tumour potency	[86,119,120]
polysaccharide-PIBCA	Heparin	Aqueous acidic redox radical polymerisation	co-polym.	*in vitro*	Antithrombotic activity preserved	[76]
PS80-PBCA	Dalargin doxorubicin loperamide probenecid tacrine	Aqueous acidic medium	30 80 47 25 – 100 15 (w/w)	Mouse rat	Phagocytic uptake of nanoparticles by the brain blood vessel endothelial cells, high drug concentration in brain, significant analgesic effect prolonged anticonvulsive activity, reduced toxicity	[121-126]

Co-polym.: Co-polymerised; EE: Entrapment efficiency; PACA: Poly(alkylcyanoacrylate); PBCA: Poly(butylcyanoacrylate); PECA: Poly(ethylcyanoacrylate); PEG: Polyethylene glycol; PHDCA: Poly(hexadecylcyanoacrylate); PIBCA: Poly(isobutylcyanoacrylate); PS80: Polysorbate 80; rHuTNF- α: Recombinant human tumour necrosis factor-α.

In addition, the high reactivity of the monomers and competitive polymerisation initiation by any kind of nucleophile leading to possible co-polymerisation adds to the complexity of these studies and their interpretation. Under these circumstances polymerisation may become uncontrollable and often results in polymer aggregates rather than nanoparticles [16,58,59]. Addition of the drug to the polymerisation medium after its initiation or to preformed polymers has been suggested as an alternative to avoid interference of the drug with the polymerisation [22]. In these cases, however, drug entrapment would be via sorption rather than encapsulation. For protein and peptide drugs, the desired protective effect against enzymatic degradation in the gastrointestinal tract upon oral administration provided by the nanoparticle would become questionable (see section 6 on *in vivo* applications).

4. Drug release

The method of entrapment and the distribution of the bioactive within the particulate system determine its release and thus also its degradation characteristics [8]. For nanoparticles where the bioactive has been incorporated by the sorption technique, release of the bioactive is rapid and is controlled by desorption and diffusion characteristics in the continuous phase [8]. Conversely, the release from nanoparticles where the bioactive has been encapsulated by the entrapment method is sustained, as the nanoparticle must degrade and/or the bioactive has to diffuse through the particle wall [5]. Drug release from nanocapsules is often described as zero-order from a reservoir, and matrix kinetics apply to nanospheres [33,60,61]. Release characteristics of nanocapsules can be modified with the amount of monomer used for polymerisation [24,33,36,61]. Diffusion-controlled release is more likely to occur for low molecular weight drugs, as shown by nuclear magnetic resonance (NMR) experiments [62]. Drug release occurring in parallel to PACA nanoparticle degradation was shown by Grangier *et al.* [16] for human growth hormone and for insulin by Aboubakar *et al.* [63]. The shorter the alkyl chain of the homologue, the faster its polymerisation and degradation rate [17] due to a less tightly forming polymer network [24]. Release of insulin from PACA nanoparticles is initiated in hours and can last for several days [33,58]. Furthermore, the release of insulin from these nanoparticles is pH-dependent. In acidic media release is suppressed, but upon increasing the pH release occurs [33,63].

The factors that influence entrapment, including competitive polymerisation initiation by formulation components, possible co-polymerisation and the polymerisation kinetics of alkylcyanoacrylates, will also impact on the release behaviour. Graf *et al.* observed a more variable release profile of insulin from PECA than from poly(butylcyanoacrylate) (PBCA) nanoparticles (**Figure 4**) [36]. It had previously been hypothesized that this was due to a stronger interference of insulin with the faster polymerising monomer ethyl 2-cyanoacrylate [35], yet no signs of co-polymerisation were detected. The authors found no

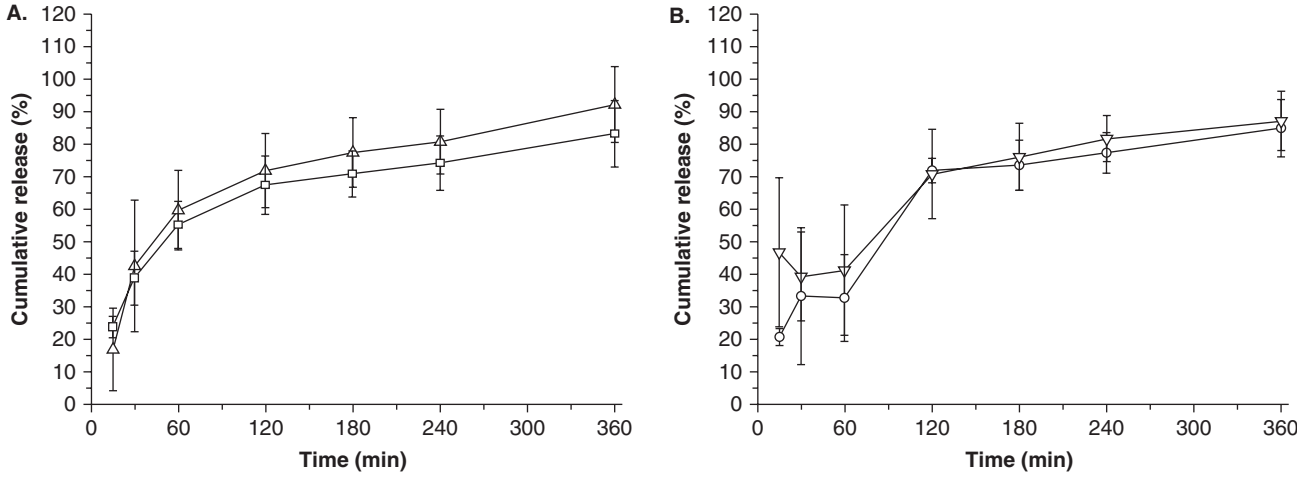

Figure 4. A. Release profile of insulin in phosphate buffer pH 6.8 from poly(butylcyanoacrylate) nanoparticles prepared with 1200 mg monomer in a water-in-oil (□) and oil-in-water (Δ) microemulsion template and **B.** from poly(ethylcyanoacrylate) nanoparticles prepared with 1200 mg monomer in a bicontinuous (○) and oil-in-water (∇) microemulsion template. Values represent mean ± standard deviation, n = 3.

differences in the release of insulin from nanoparticles prepared from different templates. This was attributed to insignificant differences in entrapment or a possible obscuration of differences by a high burst release, which was caused by low entrapment (free insulin was present in the microemulsion template in these experiments). Moreover, mixtures of nanocapsules and nanospheres may result from interfacial polymerisation depending on the type of water-miscible solvent used, whether protic or aprotic [64]. All these factors contribute to the variability in release profiles from PACA nanoparticles and data has to be analysed carefully with consideration of the various aspects mentioned above before general conclusions can be drawn.

5. Nanoparticle uptake

The absorption of nanoparticles following administration is a fundamental prerequisite to achieving a biological response to the bioactive contained in the formulation. The translocation of nanoparticles across intestinal epithelia has been shown to occur in a range of species including pigs, cows and sheep [63,65] and can enhance the systemic uptake of macromolecules [66]. Translocation of nanoparticles can occur either by transcellular transport [65] or via the paracellular pathway [31,66]. The main pathway for absorption of PACA nanoparticles is via the Peyer's patches in the gastrointestinal tract [1,54,67,68]. The small size of nanoparticles is clearly advantageous to enable particulate uptake by epithelial cells [69]. Particulates < 1000 nm in size have been shown to move across the gut epithelium and enter the systemic circulation [63,66,70]. In rats, uptake of nanoparticles from the intestine was up to 250 times greater for 100 nm sized particles compared to 1 μm particles [71]. The size of nanoparticles is a property that can potentially be varied during preparation. For example, the ratio of the mass of monomer added to the microemulsion affects the size of resulting nanoparticles. Larger PECA nanoparticles are produced when more monomer is used [61]. Conversely, high surfactant concentration can reduce the size of nanoparticles [72]. The method of nanoparticle preparation also modulates particle size [72].

Surface characteristics, transit time, interaction of the carrier with luminal contents and transport of the polymeric carrier through the mucus layer of the epithelium, however, are also important for particle uptake and are less easy to control [65,73]. An advantage of PACA nanoparticles is that they exhibit bioadhesive properties that provide intimate contact of the delivery system with mucosal sites [74] and so may enhance absorption.

Surface modification of nanoparticles by coating the outer surface with hydrophilic polymers such as polyethylene glycol (PEG) enhances nanoparticle stability in biological fluids and prolongs circulation times *in vivo* by limiting opsonisation (**Table 3**) [6,75]. Opsonisation is a process in which protein entities capable of interacting with specific plasma membrane receptors on monocytes and various subsets of tissue macrophages adsorb onto the particle surface and thus promote particle recognition by these cells and clearance from the blood (phagocytosis) [6]. Delivery of molecules can also be targeted to specific cells or tissues by the conjugation of nanoparticles to a specific ligand [3,6]. For example, polysaccharides such as dextran and chitosan have been used to coat PACA nanoparticles [76]. Further information on the use of polysaccharide coating for particulate delivery systems is included in a review by Lemarchand *et al.* [77]. The expression of folic acid binding proteins on the surface of human cancer cells has also been utilised to target PEG–PACA nanoparticles. These nanoparticles conjugated with folic acid had a higher affinity for the folate receptor on human cancer cells than free folate [78]. PEGylated PACA nanoparticles have been investigated in the treatment of transmissible prion diseases, including scrapie in sheep and bovine spongiform encephalopathy

(BSE) in cattle by targeting delivery to the spleen and brain of infected mice [79]. Carbon radiolabelled, PEGylated poly(hexadecylcyanoacrylate) nanoparticles improved the systemic circulation time fourfold compared to non-PEGylated particles. Targeting of PEGylated nanoparticles was achieved with greater concentrations of PEG nanoparticles in the brain and spleen compared to non-PEGylated particles [79].

6. *In vivo* applications of PACA nanoparticles

There is a wealth of knowledge on the behaviour of PACA nanoparticles in both isolated biological systems in cell culture and in laboratory animal models, with the aim of developing these delivery systems for the treatment of human disease. A summary of the application of PACA nanoparticles used in animal studies is provided in **Table 1**. Over the years there have been many attempts to deliver insulin with PACA nanoparticles via the oral route. In one of the first studies, Couvreur *et al.* [80] investigated PACA nanoparticles to which insulin was being adsorbed. No hypoglycaemic response was found in this study. This indicated that adsorption of insulin onto nanoparticles did not provide sufficient protection of the peptide from enzymatic degradation in the gastrointestinal tract. Entrapment of insulin into the oily core of PiBCA nanoparticles, however, resulted in a dose-dependent hypoglycaemic response for up to three weeks [44]. This long-term effect was attributed to nanoparticles being progressively transported from the stomach to the gastrointestinal tract and delayed paracellular absorption [54,67]. Lowe and Temple [45], however, were not able to confirm such long-term effects in their study as maximum plasma levels of insulin and calcitonin released from PiBCA nanoparticles appeared in less than 15 min in the blood. The authors hypothesized that insulin may exert local intestinal effects. This has also recently been suggested again in a study on oral delivery of insulin with PACA nanoparticles, in which a hypoglycaemic response was found without any detectable plasma insulin levels [36]. This study also revealed a discrepancy between the factors controlling *in vitro* and *in vivo* release. PECA and PBCA nanoparticles were prepared with different monomer concentrations from structurally different microemulsions and loaded with insulin to investigate the influences of the type of microemulsion and type and amount of monomer on nanoparticle morphology, entrapment and release [36]. *Results* with regards to morphology and entrapment have already been mentioned in the respective sections above. The monomer concentration was found to control insulin release *in vitro*, whereas the type of monomer was decisive for the *in vivo* response [36].

Lowering of blood glucose levels has also been achieved with insulin-loaded PiBCA nanospheres [58]. Insulin was added after polymerisation had been initiated to avoid copolymerisation yielding 80% entrapment efficiency. Upon administration of these nanospheres in an oil-surfactant medium, blood glucose levels could be reduced for almost two weeks. Administration in an aqueous surfactant medium only reduced glucose levels in the short-term. Radwan *et al.* [55] investigated the effect of surfactants on enhancing absorption of insulin from nanospheres and found that they only enhanced the burst release. It was concluded that nanocapsules were better suited for oral protein delivery.

A recent study focused on the absorption of insulin from PiBCA nanocapsules [49]. Particles were prepared in the same manner as in a previous study by Damgé *et al.* [44], but a different type of insulin was used, resulting in nearly twice the entrapment efficiency. In animals in which plasma insulin levels were detectable, they appeared rapidly and very erratically. Parenterally, high insulin concentrations were required to reduce blood glucose levels. This response, however, varied between diabetic and non-diabetic animals, possibly due to an onset of insulin resistance in diabetic animals. This study is another illustration of how results can change simply by choosing a different type of insulin, as discussed in the drug loading section above.

Oral absorption of insulin has also been investigated from PiBCA nanospheres of only 85 nm [81]. The aim of this study was to show a correlation between bioavailability and particle size. However, only one particle size was investigated. Insulin was entrapped to 59% and resulted in a hypoglycaemic response for 60 h without information on plasma insulin levels.

In addition to insulin, other peptides like calcitonin [26,45] and octreotide [42] have also been entrapped into PACA nanoparticles. However, plasma levels were not significantly different from control [45] when administered without a penetration enhancer [26]. Delivery of drugs other than protein and peptides has been found to be more successful (**Table 1**).

In the treatment of human disease, considerable research effort has been invested in PACA nanoparticle formulations suitable for cancer therapies and targeted delivery of drugs to tumours [82]. The vasculature that perfuses tumour tissue has incomplete endothelial walls due to the rapid growth rates of tumours, and thus nanoparticles can passively penetrate into the tumour tissue. This enhanced uptake in tumours is referred to as the enhanced permeability and retention (EPR) effect [83]. In the treatment of brain cancers, the blood–brain barrier (BBB) is a significant boundary of specialised endothelial cells that must be overcome. Although the uptake mechanisms in the brain are not fully understood, the receptors present on the endothelial cells can be utilised to transport drugs into the brain. Surface coating of nanoparticles with the surfactant polysorbate 80 has been the most commonly employed strategy to overcome the BBB by receptor-mediated endocytosis [84]. The endothelial cells of the brain, and other tissues, also have drug efflux transporters (P-glycoprotein) that exclude entry of many compounds into cells. Multi-drug resistance in cancer cells is a problem with many chemotherapeutic drugs used in oncology and the efflux transporters are thought to be responsible for this expulsion of drugs from cells [85]. Entrapment of chemotherapeutics within nanoparticulates reduces the likelihood of multi-drug

resistance because the drugs are not 'recognised' by the cell surface and only released once they have been internalised into tumour cells.

Doxorubicin, one of the most widely used chemotherapy agents, has undesirable side effects including cardiotoxicity, and entrapping doxorubicin within nanoparticles can minimise the unwanted effects of this drug. Brigger *et al.* [86] evaluated PEG-coated poly(hexadecylcyanoacrylate) (PHDCA) nanospheres for *in vivo* brain delivery of doxorubicin in a rat gliosarcoma model. The authors found that while the toxicity of the encapsulated drug was low, the biodistribution was significantly less (approximately 2.5 times) for the PEG-PHDCA nanospheres in tumour tissue compared to unloaded nanospheres [86]. The PEG-PHDCA formulation accumulated in the lungs and spleen, but did not provide improved brain delivery of doxorubicin in this model of 9L gliosarcoma [86]. A list of more successful studies with surface-modified PACA nanoparticles for improved brain delivery is provided in **Table 3**. Koo *et al.* [84], provide a comprehensive review on the use of nanoparticles in brain cancer therapies which the reader may refer to for further information on this topic.

While considerable progress has been made in the understanding of polymeric nanoparticles as carriers of therapeutic agents for the treatment on cancer, to date there are mostly liposomal formulations approved by the American Food and Drug Administration for this purpose [87]. Examples of approved products are a liposome formulation for doxorubicin (Myocet™; Elan Pharmaceuticals, USA) produced by Elan Pharmaceuticals and PEGylated liposomal doxorubicin (Doxil®; Ortho Biotech, USA and Caelyx®; Schering-Plough, USA). There is also one methoxy-PEG-PLGA formulation for delivery of paclitaxel (Genexol-PM™; Samyang, Korea) in the treatment of metastatic breast cancer for i.v. administration that has been clinically approved [84,88].

In the veterinary field, numerous innovative controlled release products for therapeutic agents have been developed [89] and the diversity of animal forms and lifestyle modes requires that delivery to animal patients be tailored to the individual species [90]. An additional consideration for administration of controlled release dosage forms for food-producing animals is the withholding period to prevent transfer of residual medications to the consumer [91,92]. The advantage of biodegradable delivery systems is that they do not require removal at the end of the treatment period, thus reducing labour costs, because a veterinarian is not needed to terminate treatment and there is reduced handling, and so less stress to the animal [91]. For further information on biodegradable polymer use for delivery of therapeutics for animal health see Winzenburg *et al.* for a comprehensive review [91].

Colloidal delivery technology is well developed in the human field and to a smaller extent with farm and companion animals. However, the application of colloidal delivery to a wildlife management situation is largely untested. We have been investigating the application of pharmaceutical delivery technology to administer biocontrol agents to pest wildlife [93]. The common brushtail possum is an introduced species that is New Zealand's most significant vertebrate pest. Development of oral formulations for a free-ranging pest species presents several challenges in addition to those encountered with therapeutic formulations for humans and domestic animals, including environmental stability and species-specificity [94]. While the preferred administration route for bioactive compounds to maintain stability and achieve high systemic concentrations is via injection, the distribution of pest species over large areas and the wild nature of pests mean that injections are not practical. The most prudent route of administration is orally in baits [93]. Nanoparticles were chosen as a potential delivery system for the advantages that have been outlined earlier. In addition, PACA nanoparticulate systems can be made relatively cheaply, which is an important consideration for use in wildlife management.

Consistent with other studies, we have obtained high entrapment of model compounds within PECA nanoparticles of 80%, however data from *in vivo* studies has not been encouraging [95]. The bioavailability of proteins administered orally is typically quoted as < 1% [58,96]. For the brushtail possum, the bioavailability of the model protein insulin in PECA formulations administered by the intracaecal route was particularly low – 0.07% for insulin-loaded nanoparticles – and was highly variable [95].

7. Toxicity

In this section we will look at the potential toxicity of the PACA polymer and possible residual monomer. PACAs are biocompatible and biodegradable [1]. The toxicity profile of the polymer is also a function of the alkyl chain length of the homologues, as it correlates with the polymer degradation. Monomers, however, can elicit an acute inflammatory response in tissues, which decreases with increasing alkyl chain length [17]. Homologues with less than four carbons in the chain are well tolerated by the tissues [17] and two monomers, butyl and octylcyanoacrylate, have received FDA approval for human use.

PACA nanoparticles have first been tested for their toxicity by Kante *et al.* [97] and the authors observed a correlation of toxicity and degradation rate of the homologues. Initially, degradation was believed to occur via a formaldehyde-producing pathway [98], which, however, was later found to be of minor relevance. As a major degradation pathway, Lenaerts *et al.* [99] identified hydrolysis of the ester bond of the alkyl side chain facilitated by enzymes *in vivo*. This leads to alkyl alcohol and poly(cyanoacrylic acid) as degradation products, which are both water soluble and can be renally excreted. An excellent overview on toxicity and cytotoxicity of PACA nanoparticles can be found in a review by Vauthier *et al.* [1]. Generally, the toxicity profile of PACA nanoparticles as colloidal drug delivery systems appears to be low. However more data, particularly on long-term *in vivo* mutagenicity, would be desirable. In addition, more

details of the recent clinical trial suspension of Transdrug would be advantageous for research in the area of drug delivery with PACA nanoparticles.

8. Conclusion

In conclusion, PACA nanoparticles have been considered to be promising polymeric colloidal delivery systems and while there is experimental data to support their potential, to date there is no product available on the human health market that utilises the encapsulation of bioactives into nanoparticulates for therapeutic treatment. This is largely due to the multitude of factors that cannot be easily controlled, leading to highly variable results, particularly for loading and release. Highly variable *in vitro* and *in vivo* responses, toxicity issues and the requirement for surface modifications in order to achieve a targeted response are aspects that still present challenges to effective drug delivery with PACA nanoparticles.

9. Expert opinion

In the treatment of human diseases, PACA nanoparticle formulations have been the focus of attention for various areas of drug delivery, including cancer therapy. Polymeric nanoparticles have also been intensively studied to develop systems for the delivery of modern biopharmaceuticals via the oral route. Insulin-loaded nanoparticle formulations, for example, have been shown to reduce blood glucose concentrations when administered into the lumen of different sections of the gastrointestinal tract, as well as when given orally. Also, for the purpose of overcoming the BBB, PACA nanoparticles have been used with some success. There can be no doubt that these systems have potential as drug delivery carriers. But will they be able to realise this potential? Major challenges remain, including the generally encountered variability in entrapment rate and release profiles, which poses considerable limitations to the effective use of these drug delivery systems. This is of the utmost importance, not least with a view on scaling-up operations that need to be performed, should these delivery systems have a chance to enter the market. Another main challenge will be to detect and subsequently avoid co-polymerisation of the active with the polymer during *in situ* preparation of these nanoparticles. If one was able to optimise and control the factors leading to the high variability upon polymerisation of peptide/protein-containing templates, it is our view that PACA nanoparticles might become promising carriers in drug delivery and provide an alternative to parenteral administration. In our opinion, however, the recent statement by Vauthier *et al.* [60] that the different pharmaceutical characteristics of poly(alkylcyanoacrylate) nanoparticles are perfectly controllable, cannot yet be generalised to all drugs. While PACA nanoparticles might be suitable colloidal carrier systems for some drugs, it appears that they may not be ideal for others. Liposomal formulations in particular have proved more successful for drug delivery, with many more of these products already on the market for the treatment of a number of conditions from fungal infections to cancer. Also PLGA nanoparticles present a strong alternative to PACA nanoparticles for many areas of drug delivery. An excellent review by Mundargi *et al.* [100] highlights the advantages of PLGA as carriers for controlled delivery of macromolecular therapeutics such as proteins and peptides. Recently, the group of Damgé [101] has also changed from PACA to polycaprolactone nanoparticles in their studies to find a suitable oral delivery system for insulin.

We propose that more 'head to head' comparisons between the different polymeric and lipid-based nanoparticle systems are performed. In our view, the usual practice of comparing the performance of a drug in PACA nanoparticles to a drug simply being in some solution or in some cases in the template the nanoparticles have been made from, is not ideal. We think that future work needs to concentrate on a direct comparison, especially *in vivo*, of alternative particulate delivery systems. Experts in the different types of nanoparticulate delivery systems increasingly need to collaborate and compare their systems in similar models, to arrive at the most useful formulation approach for any given bioactive delivery challenge. Doing so will not only result in better formulations for a particular bioactive, but will undoubtedly lead to a better understanding of the general principles underlying the rational choice for the most suitable delivery systems for new drugs.

Declaration of interest

The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

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