Biomaterials 32 (2011) 8593–8604

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Review

Strategies for the nanoencapsulation of hydrophilic molecules in polymer-based nanoparticles

Sandy Vrignaud [a,b,c,*], Jean-Pierre Benoit [a,b,c,d], Patrick Saulnier [a,b]

[a] LUNAM Université, Ingénierie de la Vectorisation Particulaire, F-49933 Angers, France
[b] INSERM, U646, F-49933 Angers, France
[c] Pharmacie Centrale, CHU Angers, 4 rue Larrey, F-49100 Angers, France
[d] Ecole Pratique des Hautes Etudes (EPHE), 12 rue Cuvier, F-75005, Paris, France

ARTICLE INFO

Article history:
Received 5 July 2011
Accepted 17 July 2011
Available online 9 August 2011

Keywords:
Nanoparticle
Polymer
Hydrophilic drug
Aqueous-core nanocapsule
Macromolecule

ABSTRACT

Hydrophilic drug delivery still remains a challenge; this either being attributed to the fragility and poor cellular penetration of macromolecules, or to the unsuitable pharmacokinetics and toxicity of small drugs, for instance anticancer agents. By offering more favourable pharmacokinetics and protection of the drug, encapsulation in polymer nanoparticles constitutes an attractive possibility to overcome these problems. This review provides an overview of the strategies that have been developed for encapsulating hydrophilic molecules in polymer-containing nanoparticles, e.g. nanospheres and nanocapsules. Polymer nanospheres are loaded either by drug entrapment (by pH modification, use of reverse micelles or the addition of a polyanion) and generally produce a poor level of entrapment efficiency, or molecule sorption onto the nanosphere surface (by pH modification, use of high drug concentration, or ion-pair formation) with the drawbacks of a less-well protected drug from degradation and a faster drug release. Another strategy consists of the use of aqueous-core nanocapsules, generally surrounded by a thin polymer layer, in which hydrophilic molecules are directly solubilised in internal water, and are thus entrapped within the nanocapsule core, assuring drug protection and sustained release. Nanocapsules require less polymer compared to nanospheres; on the other hand, when the drug is entrapped, it has to be added before or during the formulation process, and is thus likely to be degraded. Overall, drug encapsulation in polymer nanoparticles provides a better pharmacokinetic profile and bioavailability, enhanced anticancer activity, reduced drug toxicity and modified drug distribution as compared to free drugs.

1. Introduction: on the interests of targeting hydrophilic drugs

Developing strategies for the delivery of hydrophilic drugs is emerging as an important research field for many reasons: (i) the increasing interest in macromolecules, such as nucleic acids, peptides or proteins, for the treatment of a wide range of diseases such as cancer, infectious and inflammatory diseases [1], and (ii) the importance of small, hydrophilic drugs currently under development [2]. It is obvious that the problem is different when delivering macromolecules and small drugs. Hence, even if the discovery of macromolecules has opened up many perspectives in therapeutics, their use is often limited by low bioavailability due to their poor stability against proteolytic and hydrolytic degradation, low permeability across barriers, and a short biological half-life in the circulatory system [1,3–6], whereas the use of small, hydrophilic drugs such as anticancer agents often involves toxic side effects, or unsuitable biodistribution [7].

To get round these critical points, nanomedicines have been used for many years to encapsulate and target drugs. Drug encapsulation in colloidal systems offers many advantages, as for instance: (i) the protection of a drug against *in vivo* degradation, (ii) the reduction of potentially toxic side effects that occur with the direct administration of the solution, (iii) the increase of patient comfort by avoiding repetitive bolus injections or the use of perfusion pumps, and (iv) the achievement of more favourable drug pharmacokinetics [8].

Abbreviations: ACN, Aqueous Core Nanocapsules; BCA, PolyButyl CyanoAcrylate; ECA, PolyEthyl CyanoAcrylate; HDol, 1,6-hexanediol; PACA, PolyAlkylCyanoAcrylate; PCL, Poly(ε-CaproLactone); PEG-PCL/MA, PolyEthyleneGlycol-ε-PolyCaproLactone/Malic Acid; PEG-PLGA, PolyEthyleneGlycol-PolyLactic-co-Glycolic Acid; PEI, Poly(EthyleneImine); PIBCA, PolyIsoButylCyanoAcrylate; PIHCA, PolyIsoHexylCyanoAcrylate; PIT method, Phase-Inversion Temperature method; PLA, PolyLactic Acid; PMA, Poly(MethylAcrylate); PMMA, Poly(MethylMethAcrylate); POCA, PolyOctylCyanoAcrylate; PVA, Poly(Vinyl Alcohol); PVP, Poly(VinylPyrrolidone); VA-060, 2,20-Azobis{2-[1-(2-hydroxyethyl)-2-imidazolin-2-yl] propane} dihydrochloride.

* Corresponding author. LUNAM Université, Ingénierie de la Vectorisation Particulaire, F-49933 Angers, France. Tel.: +33 244 688568; fax: +33 244 688546.
E-mail addresses: sandy.vrignaud@etud.univ-angers.fr, sandy-vrignaud@hotmail.fr (S. Vrignaud).

0142-9612/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biomaterials.2011.07.057

In the field of oncology, because of the tumour's particular physical properties, namely hypervascularisation and an aberrant vascular architecture, the carriers' (in the nanometre range) accumulation and retention is enhanced at the tumour site. This Enhanced Permeation and Retention effect (EPR) is observed only when the drug is nano-encapsulated, and has been shown to increase drug efficacy [9].

About twenty nanocarriers are currently marketed [10]. For instance, liposomal forms of doxorubicin hydrochloride (DOXIL® and CAELYX®), or Daunorubicin citrate (DAUNOXOME®) have led to reductions of the related drug toxicity [11,12]. Many others are under clinical trials, such as CALAA-01, the first nanoparticle, composed of cyclodextrin-containig polymer and polyethylene glycol, containing siRNA and administrated to humans for the treatment of solid tumours [13].

Among the different nanocarriers, nanoparticles have emerged as a promising strategy. Nanoparticles are solid, sub-micronic drug carriers of natural, semi-synthetic or synthetic polymer types in the nanometre range [14]. The term nanoparticles includes both nanocapsules and nanospheres. Nanospheres consist of (homogenous) matrix systems in which the drug is dispersed within the polymer throughout the particle, whereas nanocapsules are (heterogeneous) vesicular systems in which the drug is confined to a cavity surrounded by a single polymeric membrane. Nanocapsules may thus be considered as a reservoir system [15].

This review aims to perform a state-of-the-art summary of the strategies for delivering hydrophilic molecules. We have considered hydrophilic molecules to be those that are soluble or freely dispersible in water. This review devotes special attention to polymers containing nanoparticles. It is obvious that other nanocarriers are available for encapsulating hydrophilic drugs: liposomes (for which reviews have already been published [16], or even lipid nanoparticles [17,18]). Polymer-containing nanoparticles are attractive because of their process feasibility and repeatability, their controlled physicochemical properties, their low cost, the large panel of biodegradable polymers that can be used for their generation, and the knowledge of these polymers.

In the present review, we focus on strategies developed for hydrophilic drug encapsulation in the nanocarrier, the drug possibly being entrapped within the nanocapsules core, dispersed in the nanosphere matrix, or adsorbed on the nanoparticle surface. The nature of the polymer and the encapsulation method advantages and drawbacks are also discussed.

2. Polymer nanoparticles

Polymer nanospheres have been extensively used for the encapsulation and drug delivery of lipophilic and hydrophilic drugs for several years. The aim of this review is not to sum up all these studies, but to present and discuss the main available strategies for encapsulating hydrophilic drugs.

As seen in Table 1, many processes have been described to produce polymer nanoparticles, involving different monomers or polymers. Conventionally, polymer nanoparticles are prepared by two methods: (i) the dispersion of preformed polymers and (ii) the polymerisation of monomers [27]. For instance, the dispersion of preformed polymers is performed by the solvent evaporation method, or the spontaneous emulsification/solvent diffusion method. It concerns polymers such as polylactic acid, polylactic-co-glycolic acid, chitosan or alginate. Polymerisation methods essentially deal with the anionic polymerisation of alkylcyanoacrylate monomers (ACA).

The main strategies for drug loading in polymer nanospheres are either by drug entrapment within the bulk polymer matrix or by drug adsorption onto the nanoparticles. In the first case, the drug encapsulation is achieved by adding the drug during the nanoparticle fabrication process. Drug sorption at the nanoparticle surface requires the nanoparticles to be processed, and simply occurs by incubating the drug with the nanoparticle suspension.

The loading method, consisting of drug chemical conjugation with, for instance, the polymer composing the nanoparticles, will not be developed in this review [28]. This strategy induces chemical modifications of the drug, possibly leading to a loss of its activity.

Entrapment Efficiency (EE, in percent) represents the ratio of the amount of drug entrapped within the nanocapsules to the drug amount initially introduced in the formulation. According to the authors, drug loading is a more representative and pertinent parameter, but this data is often not available in the studies.

2.1. Drug entrapment within the polymer matrix

Drug entrapment within a nanosphere matrix, with the advantages of both ensuring drug protection and providing the possibility of sustained release, is performed by adding the drug to the reaction medium before or at the same time as the polymer during the generation process of the nanoparticles [29].

Table 1
Examples of strategies for enhancing hydrophilic molecule encapsulation in polymer nanoparticles.

Drug	Nature of the nanoparticle	Preparation method	Strategy	Result	Ref.
DRUG LOADING BY ENTRAPMENT					
5-FU	PACA	Monomer emulsion polymerisation	pH increase	Enhancement of the polymerisation rate	[19]
methylene blue, congo red, methyl orange or vasopressin	PLA	Emulsion-solvent evaporation	Reverse micelles	Enhancement of drug solubility in the polymer network	[20]
doxorubicin hydrochloride	chitosan	Chitosan ionic gelation	Polyanion (dextran sulphate)	2-fold increase of EE	[21]
DRUG LOADING BY ADSORPTION					
doxorubicin hydrochloride fluorescein and daunorubicin	PACA	Emulsion polymerisation	pH increase	Increase of drug/polymer interactions and of nanoparticle loading	[22,23]
gemcitabine	PACA	Emulsion polymerisation	High drug concentration	Increase of nanoparticle loading	[24]
Oligonucleotides (ON)	PACA	Emulsion polymerisation	Ion-pairing cation (CTAB)	Ionic interaction between ON and CTAB and increase of nanoparticle loading	[25]
SiRNA	PACA	Redox radical emulsion polymerisation	Chitosan/Ion pair formation	Ionic interaction between SiRNA and chitosan and increase of nanoparticle loading	[26]