Polymeric nanocarriers for polymyxin B delivery

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Abstract
Biodegradable polymeric nanoparticles have high biocompatibility, encapsulate various therapeutic agents, permit prolonged drug release, and can also be functionalized or modified in order to change and improve their biodistribution properties. This work aimed at comparing two nanoparticle formulations for polymyxin B.

Key words:
Nanoparticles, PBCA, Gelatin, Polymyxin B.

Introduction
Polymyxin B (polB) is an antibiotic, usually prescribed for skin and mucosal infections, especially against *Pseudomonas* species 1. Gelatin type B is a biopolymer obtained by alkaline hydrolysis of bovine collagen. Extraction can hydrolyze amide groups from asparagine and glutamine, transforming them into carboxyl groups and converting them to aspartate and glutamate 2. Poly-butylcyanoacrylate (PBCA), a syntetic polymer, has been prominent in recent years as a release system for various drugs. PBCA NPs are formed by anionic polymerization in aqueous media from monomers of n-butylcyanoacrylate, a compound used as a biological tissue adhesive applied in surgical incision occlusion 3,4. Nanostructures make it possible to overcome challenges associated with drug delivery such as low solubility, low permeability, toxicity, degradation and delivery to specific cells/tissues. Like any ideal drug delivery system, they must be biocompatible, biodegradable, and physically and chemically stable 5. This work aims to produce and compare the physicochemical characteristics of nanoparticles of gelatin and PBCA with polB.

**Results and Discussion**
Gelatin NPs were prepared according to previous studies 6. Addition of polB 1 mg/ mL was done in a ratio of 1: 1 (gelatin: polB). The positively charged polB was adsorbed onto the surface of the negatively charged gelatin NPs. The resulting solution was stable and cloudy, the particle size increased and potential ζ decrease with the addition of polB (chart 1, 1st and 2nd lines). The samples were analyzed by dynamic light scattering (DLS), Zetasizer Nano ZS, Malvern Instruments Ltd, Malvern, England).

**Chart 1. Medium size and ζ potential, measured by DLS, and encapsulation efficiency (EE) of formulated NPs.**

<table>
<thead>
<tr>
<th></th>
<th>Medium size (nm)</th>
<th>PDI</th>
<th>ζ potential (mV)</th>
<th>EE (%)</th>
<th>Amount of encapsulated drug (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelatin, empty</td>
<td>256.4</td>
<td>0.130</td>
<td>-94.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelatin-polB 0.5 mg/mL</td>
<td>347.3</td>
<td>0.140</td>
<td>11.0</td>
<td>40.2</td>
<td>241</td>
</tr>
<tr>
<td>PBCAnp-b</td>
<td>216.9</td>
<td>0.167</td>
<td>-18.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBCAnp-p1</td>
<td>207.4</td>
<td>0.182</td>
<td>3.16</td>
<td>21.6</td>
<td>216</td>
</tr>
<tr>
<td>PBCAnp-p5</td>
<td>216.5</td>
<td>0.172</td>
<td>1.70</td>
<td>17.5</td>
<td>885</td>
</tr>
<tr>
<td>PBCAnp-p10</td>
<td>203.7</td>
<td>0.152</td>
<td>2.91</td>
<td>10.5</td>
<td>1550</td>
</tr>
</tbody>
</table>

For the synthesis of PBCA NP, the anionic emulsion polymerization method was used, according literature 3. The addition of polB was carried out after NP formation. Four types of PBCA NPs were formulated: empty NP (PBCAnp-b); NP with 1 mg/ mL of polB (PBCAnp-p1), NP with 5 mg/ mL of polB (PBCAnp-p5), and NP with 10 mg/ mL of polB (PBCAnp-p10).

The different formulations of PBCA NPs were reproducible with respect to size when measured by DLS, and it was possible to observe that the addition of polB did not significantly alter the size of NPs (p = 0.51) (Chart 1, 2nd column). The observed size distribution was monomodal, with a polydispersity index of less than 0.2, forming a moderately polydispersed solution (Chart 1, 3rd column).

The mean ζ potential changes from negative (PBCAnp-b) to positive (NPs with polB) (chart 1, 4th column), due to the adsorption of the cationic drug on the anionic surface of the NPs and the presence of its free form in solution. PolB was incorporated in the nanostructures by electrostatic adsorption. In this case, the more drug in the external medium the greater the adsorption, the relation observed with PBCA (chart 1, 5th column). The encapsulation efficiency was inversely proportional to the increase of polB (chart 1, 6th column), a result probably due to the drug concentration being close to the maximum adsorption capacity of the polymer structure.

**Conclusions**
Gelatin and PBCA NPs were successfully produced for subsequent drug uptake. The incorporation of polB in different types of polymeric NPs varied, with PBCA formulations incorporating the highest amount of drug. PBCA formulations had the lowest polydispersity index (0.167), and maintained a reproducible and stable size. Therefore, PBCA NPs are a better carrier than gelatin NPs for higher antimicrobial loads.


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