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A Novel biodegradable system based on poly (lactic-*co*-glycolic acid) nanoparticles for delivery of a novel anticancer peptide

Samuel M. Girgis[a], Amal A. Elkordy[a], Mohamed El-Tanani[b], Ahmed M. Faheem[a]*

[a]School of Pharmacy and Pharmaceutical Sciences, University of Sunderland, Sunderland SR1 3SD, UK,

[b]Institute of Cancer Therapeutics, University of Bradford, Bradford BD7 1DP , UK

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*Corresponding author.
Tel: +44 (0) 191 515 2229
Fax: +44 (0) 191 515 3405
E-mail: ahmed.faheem@sunderland.ac.uk

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SUMMARY

The main objective of this work was to formulate novel amphiphilic PLGA nanoparticles with improved physicochemical properties for the delivery of the novel peptide (CK-10) to be used for targeting of the cancerous/tumour tissue. This was achieved by blending of various amphiphilic polymers with PLGA, especially by using a novel microfluidic technique which can overcome several problems of the conventional techniques like the double emulsion technique e.g. low peptide loading efficiencies, large sizes and high PDI. Loading efficiency was measured by modified Lowry assay; size and zeta potential were characterized by dynamic light scattering and tuneable pore resistive sensing techniques; images were scanned by scanning and transmission electron microscopes; stability and interaction were confirmed by HPLC-MS, FTIR, DSC and CZE. PLGA/Poloxamer nanoparticles exhibited higher peptide loading than the other types of PLGA nanoparticles [56.13 %m/m for the novel microfluidic technique]. PLGA/Poloxamer prepared by the microfluidics technique had the smallest size with the lowest PDI (208.90 nm, 0.11) which is a vital parameter for targeting. The successful development of better physicochemical properties for the CK-10 loaded PLGA nanoparticles can improve the RAN blocking by CK-10.

INTRODUCTION

PLGA is a copolymer of lactic acid and glycolic acid, having different forms depending on the percentage of lactide to glycolide (e.g., PLGA 50:50 categorizes a copolymer whose composition is 50% lactic acid and 50% glycolic acid). PLGA is one of the greatest, well-known used biodegradable polymers for the advance of nanomedicines because it hydrolyses to produce lactic acid and glycolic acid, which are easily excreted by the body via normal metabolic pathways, resulting in minimal systemic toxicity (Khan et al., 2015). PLGA as a polyester, is a good candidate to design diverse nanoparticles with certain physicochemical properties because its chemical, physical and mechanical properties can be handled by copolymerization or blending or grafting with other polymers (Chan et al., 2016; Kashi et al., 2012).

MATERIALS AND METHODS

All the chemicals were purchased from Sigma Aldrich UK. The novel CK-10 peptide was purchased from GL Biochem in China where it was made by custom synthesis. Nanoparticles were prepared using double emulsion/solvent evaporation (DE/SE) technique and a novel modified microfluidic technique using the NanoAssemblr™. The peptide loading efficiency was analysed by modified Lowry assay method. The particle size and zeta potential were measured by dynamic light scattering (DLS) and tuneable pore resistive sensing technique (TPRS) techniques. The NP morphology was examined using scanning electron microscopy (SEM) and transmission electron microscope (TEM). The degree of interaction and compatibility were confirmed by Fourier Transform Infra-red (FTIR) and (DSC) differential scanning calorimetry whereas the stability of the loaded peptide was

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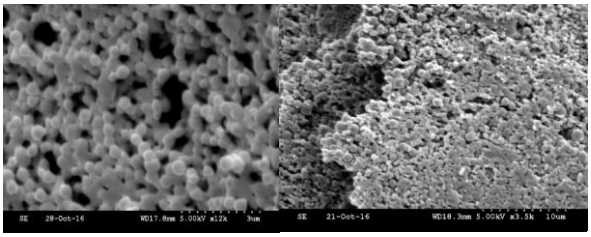
confirmed by HPLC-MS (Applied Biosystems API 4000 LC/MS/MS) and CZE (capillary zone electrophoresis).

RESULTS AND DISCUSSION

PLGA/Poloxomer.N demonstrated the highest loading efficiency (56.13%) on using the NanoAssemblr™ for the nanoparticle formulation (Table.1).



PLGA/Poloxamer NP(s) prepared by DE/SE

PLGA/Poloxamer NP(s) prepared by microfluidics nanoaasembler

Fig 1. *SEM images of PLGA/Poloxamer NP(s)*

The NanoAssemblr™ microfluidic technique succeeded in decreasing the size and narrowing the polydispersivity index (PDI) of the PLGA and PLGA blends (Fig.1, Tables.1 and 2). The droplets and three-dimensional microchannel geometries of the microfluidics device like the NanoAssemblr™ results in composite folding of fluid flows, which can entirely mix two or more streams in milliseconds to enhance the loading and reduce the size with the PDI (Kashi et al., 2012; Khan et al., 2015).

Table 1. *Characterization of PLGA nanoparticles.*

Properties	PLGA. D	PLGA. N	PLGA/PEG. D	PLGA/ PEG.N
z-average, nm (TPRS)	254.33 ± 12.70	238 ± 7.81	229 ± 10.00	214.67 ± 4.04
z-average, nm (DLS)	259.33 ± 2.68	245.4 ± 10.10	238.20 ± 5.56	220.83 ± 10.40
PDI (DLS)	0.26 ± 0.02	0.18 ± 0.06	0.24 ± 0.03	0.17 ± 0.04
Zeta potential, mV (TPRS)	-53.27 ± -4.96	-51.97 ± -1.69	-46.57 ± -2.15	-43.33 ± -2.01
Zeta potential, mV (LAT)	-60.67 ± -7.85	-57.77 ± -7.27	-51.73 ± -4.92	-47.47 ± -6.56
Loading Efficiency %	25.8 ± 3.52	37.14 ± 5.14	38.6 ± 5.81	48.65 ± 9.09

D: double emulsion /solvent evaporation technique. N: novel microfluidic technique.

Table 2. *Characterization of PLGA nanoparticles.*

properties	PLGA /PVP. D	PLGA /PVP. N	PLGA/ Poloxamer..D	PLGA/ Poloxamer. N
z-average, nm (TPRS)	235.33 ± 6.11	219.00 ± 4.58	207.67 ± 5.69	196.00 ± 5.57
z-average, nm (DLS)	240.90 ± 1.91	227.97 ± 3.30	215.70 ± 4.80	208.90 ± 2.75
PDI (DLS)	0.22 ± 0.07	0.20 ± 0.01	0.14 ± 0.01	0.11 ± 0.01
Zeta potential, mV (TPRS)	-44.3 ± -4.55	-41.5 ± -3.40	-40.5 ± -2.25	-39.97 ± -6.67
Zeta potential, mV (LAT)	-50.3 ± -0.64	-44.9 ± -6.29	-43.50 ± -4.92	-41.30 ± -4.70
Loading Efficiency%	39.86 ± 6.46	45.18 ± 6.32	46.53 ± 7.43	56.13 ± 5.68

± s.d n= 3 in all cases. D: double emulsion /solvent evaporation technique. N: novel microfluidic technique.

CONCLUSIONS

Blending of amphiphilic polymers with PLGA produces nanoparticles having improved physicochemical properties compared to PLGA nanoparticles, especially by using the novel microfluidic technique which can overcome several drawbacks of the DE/SE technique.

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