PLGA-g-PVP -based nanocapsules for the controlled delivery of antimalarials

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Introduction

Amphiphilic PLGA-*g*-PVP copolymers with different PLGA and PVP content were recently obtained by the radical polymerization of 1-vinylpyrrolidin-2-one (VP) in liquid poly(lactic-*co*-glycolic acid) (PLGA) (50:50) at 100°C [1]. Saponification of the PLGA portion allowed isolating the PVP side chains and measuring their molecular weight, which turned to be lower than the threshold for glomerular filtration. The orthogonal solvent pair ethyl acetate-methanol gave PLGA-*g*-PVP fractions with different PLGA and PVP content. Furthermore, PLGA/PVP blends gave the two homopolymers. PLGA-*g*-PVP and PLGA/PLGA-*g*-PVP blends, but not PLGA/PVP blends, gave long-term stable nanodispersions in water [1].

AIM

PLGA-*g*-PVP copolymers were employed to obtain novel artemisinin and curcumin formulations. Both drugs are endowed with potential and pitfalls for malaria treatment. Artemisinin is a potent *Plasmodium falciparum* malaria parasite inhibitor (IC_{50} = 10^{-8} - 10^{-7} M) but with low bioavailability, poor pharmacokinetic properties and high cost [2]. Curcumin inhibits the growth of *P. falciparum* with a dose dependent trend and IC_{50} = 5 mM. Despite the absence of secondary effects in humans, the use of curcumin is limited by the low solubility in water, the high chemical instability and photosensitivity, resulting in low bioavailability [3,4]. To increase bioavailability, artemisinin and curcumin were loaded into nanocapsules consisting of a biocompatible oily core acting as drug solvents, and a PLGA-*g*-PVP shell. Hereafter, the study of these formulations is presented.

PLGA-*g*-PVP copolymers

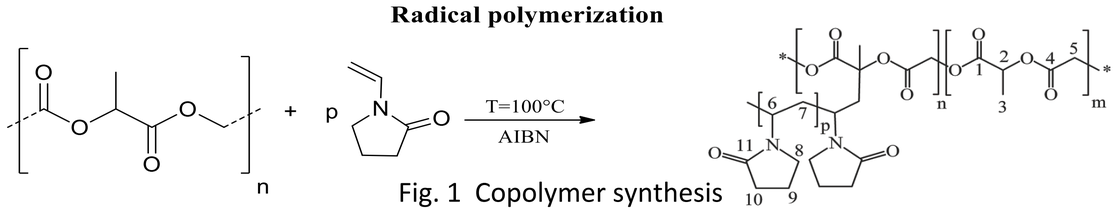

Fig. 1 Copolymer synthesis

PLGA-*g*-PVP copolymers were prepared by adding VP to PLGA 50:50 with three different di PLGA/VP weight ratio, namely, 10:1 (PLGA-*g*-PVP_{01}), 10:2 (PLGA-g-PVP_{02}) e 10:3 (PLGA-*g*-PVP_{03}), in the presence of AIBN as radical initiator (1% w/w on VP content) at 100°C

✓ Chemical characterization has been carried out by ^{1}H-NMR, SEC and MALDI

Table 1. Yield, PVP side chain M_W and M_n, PLGA C_T average for repeating unit (a) and PLGA unit (b)

Sample	Yield (%)	PVP	PVP	C_T x 10^{3} (a)	C_T x 10^{5} (b)
PLGA-*g*-PVP_{01}	98.6	2 700	5 600	1.25	1.46
PLGA-*g*-PVP_{02}	99.8	12 100	31 000	5.58	0.65
PLGA-*g*-PVP_{03}	95.0	28 000	49 500	3.62	0.42

Drug formulations

Table 2. ζ and nanocapsule size

Formulation	Potential ζ	Size (nm)	PDI
Epikuron[a] DOSS[b] Mygliol[c]	+20.04±3.93	133.1±16.1	0.30±0.04
Epikuron Pluronics[d] Mygliol	+20.18±1.50	123.3±1.2	0.29±0.01
Epikuron Tween 80 Mygliol	+24.75±1.85	118.2±2.2	0.34±0.01
Epikuron Tween 80 i-pr-myristate[e]	+23.57±1.19	94.7±4.0	0.21±0.02

a) Epikuron 200; [b] DOSS= dioctyl sulfoccinate; [c]Mygliol 810; [d] Pluronic F68; [e] isopropyl myristate

Table 3. Nanocapsule core size

Alcohol	Size (nm)	PDI
Butanol	39.9 ± 3.0	0.308 ± 0.017
Hexanol	43.2 ± 3.3	0.211 ± 0.024
Heptanol	53.8 ± 2.2	0.237 ± 0.014
Decanol	28.9 ± 0.5	0.231 ± 0.012
Benzyl alcohol	84.7 ± 3.9	0.344 ± 0.005

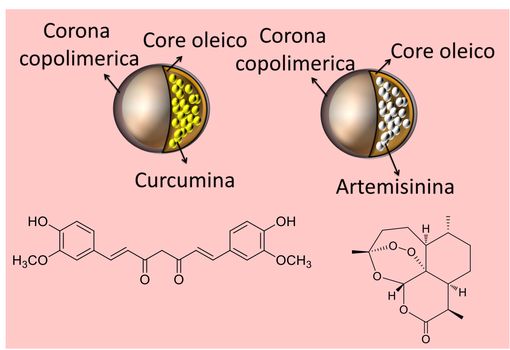

Fig. 2 Nanocapsule and drug structures

Table 4. Nanocapsule core size for artemisinin and curcumin

Curcumin (mg/mL)	Size (nm)	PDI
0.4	54.8 ± 0.7	0.21 ± 0.01
0.7	34.1 ± 0.2	0.13 ± 0.03
1.0	42.5 ± 0.5	0.20 ± 0.00

Artemisinin (mg/mL)	Size (nm)	PDI
0.4	59.6 ± 0.3	0.19 ± 0.01
0.7	33.2 ± 0.5	0.19 ± 0.01
1.0	31.7 ± 0.5	0.22± 0.01

Table 5. Unloaded and drug-loaded nanocapsule size

PLGA-g-$PVP_{10:1}$	Size (nm)	PDI
Reference	57.1 ± 0.8	0.27 ± 0.01
Curcumin	67.6 ± 0.6	0.17 ± 0.03
Artemisinin	74.7 ± 0.7	0.20 ± 0.02
PLGA-g-$PVP_{10:2}$	Size (nm)	PDI
Reference	69.5 ± 1.0	0.30 ± 0.01
Curcumin	54.7 ± 0.1	0.20 ± 0.01
Artemisinin	94.6 ± 0.7	0.26 ± 0.01

Table 7. ζ and osmolarity

PLGA-g-$PVP_{10:1}$	Potenziale (mV)	Osmolarity (mOsmol)
Reference	-11.54 ± 4.05	145
Curcumin	-12.37 ± 4.66	241
Artemisinin	-14.07 ± 2.94	200
PLGA-g-$PVP_{10:2}$	Potenziale (mV)	Osmolarity (mOsmol)
Reference	-7.56 ± 1.82	130
Curcumin	-10.78 ± 4.93	204
Artemisinin	-13.03 ± 2.39	160

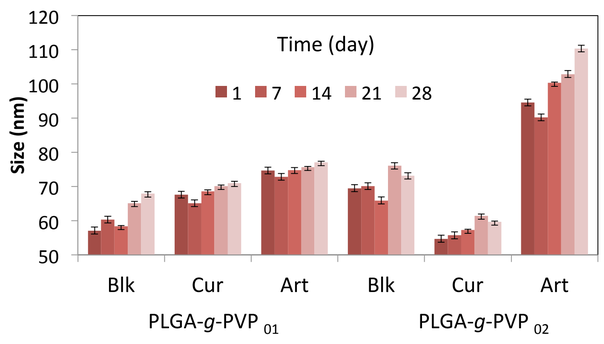

Fig 3. Dimensional stability of unloaded and drug-loaded nanocapsules

Table 6. Drug concentration in nanocapsule and Encapsulation Efficiency: E.E.=(mg_{final}/ $mg_{initial}$)×100 (%)

Drug	Drug concentration (mM)	E.E. (%)
Curcumin	1.42	74
Artemisinin	2.46	99

Conclusions

- ✓ PLGA-g-PVP copolymers allowed for preparing nanocapsules with 50-100 nm size (by DLS) loaded with curcumin and artemisinin,
- ✓ Very high encapsulation efficiency was achieved (74 and 99% for curcumin and artemisinin, respectively),
- ✓ *In vitro* tests revealed high efficiency of curcumin against *Plasmodium Falciparum (3D7)* parasite.

References

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in vitro TEST

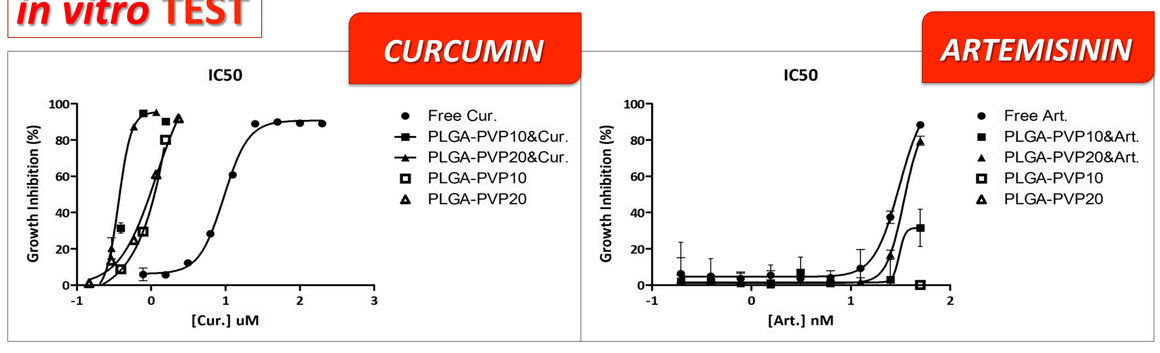

Fig. 4 IC_{50} of free Cur and Art (curcumin and artemisinin), references (PLGA-PVP 10 and PLGA-PVP 20) and drug-loaded nanocapsules *vs. Plasmodium falciparum* (3D7)

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