RESEARCH PAPER

Plant-Derived Bioactive Compounds Encapsulated in Nanoparticles for Enhanced Drug Delivery and Therapeutic Efficiency

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ABSTRACT
Curcumin and quercetin compounds exhibit strong in vitro anticancer and antioxidant properties, respectively, whereas due to the poor water-solubility and short half-life, the bioavailability of both compounds in the target tissue is decreased. PLGA (Poly lactic-co-glycolic Acid) nanoparticles were prepared by a typical nanoprecipitation technique to encapsulate each of the compounds in the present study. The particles size, Polydispersity index (PDI), Zeta potential and Encapsulation efficiency (EE) and drug loading (DL) were measured, the release was followed for 72 h at pH 5.5 and pH 7.4, and the cytotoxicity was tested using MCF-7 breast cancer and MCF-10A non-tumorigenic cells by MTT assay. The curcumin loaded nanoparticles (Cur-NPs) measured 168.4 ± 5.3 nm with PDI 0.142 and EE of 84.6 ± 2.3%, and quercetin-loaded nanoparticles (Que-NPs) 175.9 ± 6.2 nm with an EE of 78.2 ± 3.1%. A small burst release was observed at the beginning of both formulations followed by sustained release, which was faster at pH 5.5 (77.1% and 81.6% at 72 h) than at pH 7.4 (63.9% and 66.8%) and best adequate by Korsmeyer-Peppas model with $R^2 \geq 0.985$ and release exponents (n) range from 0.42-0.47. In MCF-7 cells, encapsulation lowered the IC50 of curcumin from 24.6 to 11.3 μM and of quercetin from 38.2 to 19.5 μM ($p < 0.01$). For both compounds selectivity indexes (SI) went up about two-fold after the compounds were encapsulated, with no significant difference in the IC50 values in MCF-10A cells, and blank nanoparticles were not toxic even for the highest concentration used.

Keywords: curcumin; quercetin; PLGA nanoparticles; nanoprecipitation; controlled release; MCF-7; bioavailability; phytochemicals

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INTRODUCTION

Rhizome extract of Curcuma longa that contains the major compound, curcumin and quercetin, a flavonol found in onion and apple inhibits the growth of cancer cells in vitro. They both have unpleasant characteristics as drugs. However curcumin itself has nearly no water solubility, poor bioavailability from the gut and broad metabolism, meaning that plasma concentrations are low after the oral route of administration.[1] There are comparable problems about aqueous solubility and stability for quercetin.[2]

This is often seen in the case of the activity of plant products from a culture dish to the activity in the patient. Although many natural products and their derivatives were developed into drugs between 1981 and 2019[3] a lot of natural products with good potential have been failed to enter the clinical

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trial due to their low bioavailability.[4] Delivery, not potency is the problem, mostly of the time.

Nanoparticle carriers overcome many of these barriers in a single solution. The hydrophobic compound was dispersed in a polymer matrix, which releases it in hours to a number of days and where it is protected from breakdown and kept at an effective concentration that leads to its site of action.[5] There is also passive accumulation of the particles in the solid tumor resulting from the poor lymphatic drainage in the tumor and leaky blood vessels, known as the enhanced permeability and retention (EPR) effect.[6] The size and surface characteristics determine the behavior of particles in blood, and the uptake into cells.[7] PLGA is an appropriate material for this application because it is approved by FDA and European Medicines Agency, and is degraded into lactic and glycolic acid.[8] To make PLGA particles simply is to add a polymer and drug dissolved in a water miscible solvent to water (a nanoprecipitation process).[9]

Oral bioavailability of curcumin (CV) incorporated into biodegradable nanoparticles was shown to be at least 9-fold more than CV containing piperine[10] and CV poly(D,L-lactide) nanoparticles (NPs) produced a more potent effect inducing anticancer activity in metastatic cancer cells than free CV[11] and the entrapment efficiency of CV was 96.7% for the poly(D,L-lactide) nanoparticles of CV (NPs-CV) prepared by burst and sustained release.[2] In the majority of those investigations a single compound has been tested in a rather simple test and it is hard to compare the effectiveness of the various phytochemicals because of their different polarities. In this case, curcumin and quercetin were packaged into PLGA nanoparticles using the same nanoprecipitation method, and the results of these two formulations were compared with respect to their physical parameters, in vitro dissolution at physiologic pH and physiologic endosomal pH (pH 6.3) and effects on viability of both non-tumorigenic breast cells and cancer cells. The MCF-10A cell results were not expected because we were expecting it to decrease the IC50 measurements in the MCF-7 cells when encapsulated.

MATERIALS AND METHODS

Materials

Materials

Curcumin (content of curcuminoids > 94%) and quercetin (> 95%) were of analytical grade and were acid terminated PLGA (MW 24-38 kDa), respectively. Acetone, methanol and dimethyl sulfoxide (DMSO) of HPLC grade were used as solvents. Cells were purchased from a certified cell repository (human breast cancer MCF-7 and normal cell MCF-10A).

Nanoparticle Preparation

Nanoparticles had been ready by nanoprecipitation.[9] PLGA (100 mg) with curcumin or quercetin (10 mg) was dissolved in 5 mL of acetone and added dropwise (0.5 mL/min) to 20 mL of 1% (w/v) aqueous PVA stirred at 800 rpm. By stirring for 4 h at room temperature acetone was evaporated. For a minimum of 30 min, the nanoparticles were centrifuged at 15,000 × g at 4 °C, washed twice with de-ionized water and lyophilized with 5% (w/v) trehalose. Blank nanoparticles were prepared similarly without the drug. Three batches for each of the formulations were independently prepared.

Physicochemical characterization

The volume average hydrodynamic diameter and PDI were measured by dynamic light scattering at 25 °C with a backscatter angle of 173°, and zeta potential by electrophoretic light scattering in 1 mM KCl; three readings were made for each sample. Negative staining (1% phosphotungstic acid) by TEM was used to determine the size of the particles. After redispersion the nanoparticles were set at 4 °C, and size and PDI were also measured after 30 days.

Encapsulation efficiency and drug loading percentage

In order to free the trapped drug, 5 mg of nanoparticles were dissolved in 5 mL of DMSO and kept in freezer. The absorption of curcumin and quercetin was observed at 425 nm and 370 nm using standard curves with a co-efficient of determination (R^2) greater than 0.999. As a reference the same nanoparticles without mild were used. EE and DL were determined as shown below.

$$\text{EE (\%)} = \frac{\text{mass of drug in nanoparticles}}{\text{mass of drugs added}} \times 100$$

$$\text{DL (\%)} = \frac{\text{mass of drug in nanoparticles}}{\text{total mass of drugs nanoparticles}} \times 100$$

In vitro release and kinetic modeling

The dialysis bag method was used for the study of release. Nanoparticles containing 2 mg of drug in 2 mL of medium were filled in a dialysis bag (MWCO 12–14 kDa) and immersed in 50 mL of phosphate-buffered saline (PBS, pH 7.4) or acetate buffer (pH 5.5), each with 0.5% (v/v) Tween 80 to maintain sink conditions, then shaken at 100 rpm and 37 °C. At 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 h, 1 mL of medium was withdrawn and replaced with fresh buffer. The same medium with free drug was used as a control. The release data were fitted under zero order, first order, Higuchi and Korsmeyer-Peppas models, the last using data only up to 60% cumulative release.[12]

$$\frac{M_t}{M_\infty} = kt^n$$

Here M_t/M_∞ is the fraction released at time t, k is the release constant and n is the release exponent.

Cell culture and cytotoxicity was performed.

MCF-7 cells were maintained in DMEM medium with 10% fetal bovine serum and 1% penicillin-streptomycin, and MCF-10A cells in a mammary epithelial growth medium; both lines were kept at 37 °C in 5% CO2. The cells were seeded in 96-well plates with 5×10^3 cells per well and were left to adhere for 24 h. These were then subjected for 48 h to blank nanoparticles, nanoparticles with free drug (1-100 μM drug equivalent) or free drug alone at the same polymer concentration. Free drugs were added from DMSO stocks and final DMSO was always ≤ 0.1%. The MTT assay[13] was used to determine the viability: MTT (0.5 mg/mL) was

added for 4 h, the formazan was dissolved in DMSO and absorbance was measured at 570 nm. Four-parameter nonlinear regression was used to determine the IC50 values, and the selectivity index (SI) is the IC50 in MCF-10A / IC50 in MCF-7.

Statistical analysis

The data are mean ± standard deviation (SD) of 3 independent batches/experiments (n = 3). One-way ANOVA with Tukey's post hoc test using GraphPad Prism 9 were used to compare groups. A p value of < 0.05 was considered as significant.

RESULTS

Particle size, charge and drug content

Stable slightly opaque dispersions were obtained with the three formulations. It confirmed that in all cases the particle size of the drug loaded nanoparticles were 26 to 33 nm larger than blank PLGA nanoparticles ($p<0.01$) and all PDI values were < 0.16 (Table 1). The size and PDI of Cur-NPs and Que-NPs were not significantly different from each other ($p > 0.05$). The ζ values were all negative between −19.8 and −24.3 mV. The surface charge was slightly less negative when loaded with either one of the drugs.

The percentage of entrapment efficiency showed that entrapped curcumin was higher, 84.6%, as compared to entrapped quercetin, 78.2% ($p < 0.05$). The obtained two DL achieved were close to the theoretical maximum of 9.1% for 1:10 ratio of drug and polymer feed. Under TEM, particles with spherical shapes and smooth surfaces with no visible drug crystals were formed. The expected difference between the hydrodynamic diameters and their dry diameters was noticed for these hydrated polymer shells as it is usual for a hydrated polymer shell to some extent, that their dry diameters would be some 20–30 nm smaller than the hydrodynamic ones. All formulations had less than 6% increase in diameter after 30 days incubation at 4 °C and less than 0.2 PDI.

Table 1. Physicochemical properties of blank and drug-loaded PLGA nanoparticles (mean ± SD, n = 3).

Formulation	Diameter (nm)	PDI	Zeta potential (mV)	EE (%)	DL (%)
Blank PLGA NPs	142.6 ± 4.1	0.108 ± 0.012	−24.3 ± 1.2	–	–
Cur-NPs	168.4 ± 5.3	0.142 ± 0.018	−21.7 ± 1.5	84.6 ± 2.3	7.8 ± 0.3
Que-NPs	175.9 ± 6.2	0.156 ± 0.021	−19.8 ± 1.1	78.2 ± 3.1	7.3 ± 0.4

In vitro release

Both free curcumin and free quercetin easily permeated the dialysis membrane, with 92% and 95% of these compounds recovered in the medium after 8 h, respectively. Encapsulation had a clear negative effect on this, which was markedly slowed. The amount of drug released after 2 h was 12-18% in both types of nanoparticles and the remaining drug was released there after gradually over a period of 72 h (Table 2). The release was significantly ($p<0.05$) faster at pH 5.5 than at pH 7.4 times for all time points starting from 8 h. It showed a difference of 13·2 and 14·8 percentage points for curcumin and quercetin, respectively, after 72 h. In both, the numbers of Que-NPs were slightly higher than Cur-NPs, but not significantly so until 24 h and beyond.

All four data sets fitted quite well with the Korsmeyer-Peppas model with R^2 values between 0.985 and 0.991. The Higuchi model ($R_2 = 0.962 - 0.978$) was the next followed by zero order and fit first order fit ($R_2 < 0.95$). Exponents of releases were ranged between 0.42 and 0.47. The value for both the drugs was greater at pH 5.5 as compared to pH 7.4.

Table 2. Cumulative drug release (%) from Cur-NPs and Que-NPs at pH 7.4 and pH 5.5, with Korsmeyer-Peppas fitting parameters (mean ± SD, n = 3).

Time (h)	Cur-NPs, pH 7.4	Cur-NPs, pH 5.5	Que-NPs, pH 7.4	Que-NPs, pH 5.5
2	12.4 ± 1.1	15.8 ± 1.3	14.1 ± 1.2	17.9 ± 1.5
8	26.8 ± 1.9	33.2 ± 2.1	29.5 ± 2.0	36.4 ± 2.4
24	41.5 ± 2.4	52.7 ± 2.8	45.2 ± 2.6	57.3 ± 3.0
48	55.3 ± 2.9	68.4 ± 3.2	58.7 ± 3.1	72.5 ± 3.3
72	63.9 ± 3.1	77.1 ± 3.4	66.8 ± 3.2	81.6 ± 3.5
Release exponent (n)	0.42	0.46	0.43	0.47
R^2 (Korsmeyer-Peppas)	0.991	0.988	0.989	0.985

Cytotoxicity and selectivity

No effect on the viability of both cell lines was observed following blank nanoparticles treatment. The viability was kept at 93% or greater until 500 µg/mL polymer, which was above the highest concentration of polymer employed in drug loaded particles. Both compounds reduced cell viability of MCF-7 in a dose-dependent manner, in their free forms. The encapsulated curcumin showed a reduction of 54% ($p < 0.01$) and the encapsulated quercetin was reduced by 49% ($p < 0.01$) in MCF-7 cells (Table 3).

The IC50 value of curcumin and Cur-NPs were not significantly different (p value > 0.05) in the MCF-10A cells. The 50% inhibitory concentrations (IC50) of both types of quercetin were not obtained and are therefore designated by "> 100". The particles decreased the toxicity just in cancer cells and therefore, curcumin increased in the SI from 2.4 to 5.5 and quercetin from >2.6 to >5.1.

Table 3. IC50 values after 48 h of treatment and selectivity index (mean ± SD, n = 3).

Treatment	IC50, MCF-7 (µM)	IC50, MCF-10A (µM)	Selectivity index
Free curcumin	24.6 ± 1.8	58.4 ± 3.9	2.4
Cur-NPs	11.3 ± 0.9	61.7 ± 4.2	5.5
Free quercetin	38.2 ± 2.7	> 100	> 2.6
Que-NPs	19.5 ± 1.4	> 100	> 5.1
Blank PLGA NPs	not reached	not reached	–

DISCUSSION

Behaviour of the two compounds in the same carrier was similar and correlated with their physical chemistry. This is because curcumin is more hydrophobic (log P ~3.2 vs. ~1.8 for quercetin), this will allow it to partition into the precipitating polymer faster than it diffuses into water which results in higher efficiency of the protein being encapsulated.

In the literature there is a wide variation of encapsulations efficiencies and there is not a great correlation with the drug, but rather with the method used for preparation. Higher entrapment percentage of quercetin, 96.7%, has been achieved in Fe3O4 particles produced by the method of solvent evaporation poly(D,L-lactide) particles[2] whilst the entrapment percentage of curcumin was similar, 76.9% loading of curcumin in the particles by the method of emulsification[10] and 84.6% loading of curcumin in the particles by the method in this study. Compared to nanoprecipitation where the drug and the aqueous phase get together simultaneously, in an emulsion the drug is contained within a droplet of organic phase that is broken up and the solvent evaporated before the two phases meet.

A similar trend can be seen for particle size. Our 168 to 176 nm is sandwiched between the 264 nm of emulsion made curcumin particles[10] and the 130 ± 30 nm for quercetin loaded PLA.[2] All three are appropriate for parenteral administration because particles in the size range of 100-200 nm are not filtered by kidneys and also particles in this narrow size range have the ability to penetrate the leaky tumor vessel and PDI of < 0.2 is a suitable value for injection.[14] The PDI of our preparation with our preparation unit was 0.142 to 0.156 while the one of the emulsion would be 0.31[10] and here by nanoprecipitation we got a uniform product. The PLGA and PVA should have carboxylic end groups as a result of the acid used to terminate them and the ζ-potential of the dispersions (−19.8 to −24.3 mV) should be adequate for using the electrostatic repulsion to maintain dispersion stability, characteristic of ζ-potentials > ~20 mV.[15] The particles loaded with the most blanks were the least negative, which are commonly found as some drug near to the surface and would generally be the cause of our 12-18% burst. An identical mechanism of release – burst – followed by sustained – is observed in quercetin-PLA particles[2] as well as for matrix-type polymeric carriers in general.[8]

The calculated results of release exponents zÃ¼ from 0.42 to 0.47, suggested Fickian diffusion, since a value of n of ~0.43 corresponds to diffusion controlled release for spheres and a value of n ~0.85 to erosion controlled release.[12] The same Physicial picture with other model yielded the release of curcumin in Higuchi pattern and mainly diffusion driven as confirmed by Shaikh et al.[10] The structure of matrix is still preserved to a large extent at 72h in PLGA 50:50 which is degrading over weeks. The pH of the ester's endosomes is lower than the blood pH (4.5-5.5) and the higher n-values are signs of an added erosion mechanism that could be useful in therapy.

Half maximum inhibition concentrations are comparable with the previous ones in cells. But it was observed that the curcumin loaded PLGA nanoparticles were more effective towards the inactivation of metastatic cancerous cells as compared to free curcumin by Yallapu et al.[11] In the present case, free polyphenols undergo passive diffusion and during this trip they can be subjected to efflux pumps and phase II metabolism; in this case nanoparticles are integrated and there is a bolus of higher concentration of the nanoparticles in the intracellular compartment which corresponds to a higher concentration of the external dose. The parallel boost to the drug in vivo is exemplified by the at least 9x boost in curcumin oral bioavailability in the context of being nanopackaged.[10] This is the part of our results that has not yet been published, and so far neither the uptake nor the toxicity changes for the MCF-10A cells. This is perhaps one of the cellular barriers employed by the nanoparticles in their design[7] and likely explains the different level of endocytic activity. Blank particles were non-toxic up to 500 µg/mL, which confirms the safety of the polymer and is in line with PLGA's safety record.[8]

CONCLUSION

The use of a combination of curcumin and quercetin into PLGA nanoparticles by a unique nanoprecipitation technique yielded uniformly prepared, negatively charged nanoparticles for slow release of the drugs by diffusion and rapid release in acidic pH. The potency towards the breast cancer cells was enhanced with the increase in encapsulation and the selectivity was also raised, with no extra toxicity towards non-tumorigenic cells. The polymer did not show any toxicity at the concentrations tested. These results offer the potential for the same carrier system to be utilized to deliver a multitude of phytochemicals with varying polarities, which may be convenient if the delivery system has to handle the screening of the molecules. To extrapolate the validity of therapeutic efficiency beyond cell culture, cellular uptake imaging, longer exposure studies should be carried out as well as pharmacokinetic and biodistribution studies using the tumor bearing model.

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