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Research Paper

Amphiphilic polylactic acid-hyperbranched polyglycerol nanoparticles as a controlled release system for poorly water-soluble drugs: physicochemical characterization

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Abstract

Objectives Quercetin was applied as a model drug to evaluate the potential application of amphiphilic polylactic acid-hyperbranched polyglycerol (HPG-PLA) nanoparticles as carriers for poorly water-soluble drugs.

Methods The drug delivery systems were characterized by dynamic light scattering, powder X-ray diffraction (XRD) and Fourier-transform infrared spectroscopy (FTIR) and so forth.

Key findings The results showed the particle sizes ranged from 205.3 to 433.3 nm with low polydispersity index. XRD and FTIR demonstrated that the crystal of the drug was converted to an amorphous state in the matrices and formed intermolecular interaction with carriers. The drug encapsulation efficiency and drug loading could reach 91.8% and 21.0%, respectively. Cell viability assay suggested the nanoparticles had good cytocompatibility. The in-vitro drug release profiles showed a sustained quercetin release up to 192 h, indicating the suitability of nanoparticles in sustained drug release. Furthermore, the influence of many factors on release profiles could also be evaluated for the potential of using nanoparticles as controlled release systems.

Conclusions This system may be of clinical importance in both stabilizing and delivering hydrophobic drugs for the treatment of many diseases.

Keywords amphiphilic copolymer; biodegradation; controlled release; cytocompatibility; hydrophobic drug

Introduction

Flavonoids are a large group of natural polyphenols that are almost ubiquitously distributed in plants and thus present in vegetables normally consumed by humans. Among the flavonoids, quercetin is the major representative of the flavonol subclass.[1] It has been extensively investigated for its pharmacological effects that include antitumour, anti-inflammatory and antioxidant.[2–5] Recently, there has been a growing interest in the potentially beneficial effects on the chemical prophylaxis and therapeutic effects of quercetin for treatment of organ inflammation.[6–10] Furthermore, it can reverse multi-drug resistance in cancer cells and enhance the anticancer effects of other drugs.[11–15]

In spite of the wide spectrum of pharmacological properties, the use of quercetin in the pharmaceutical field is limited by its low aqueous solubility and chemical instability.[16] Many researchers have attempted to improve its solubility and chemical stability. To overcome this problem, polymer nanoparticles have been widely investigated as a delivery system for poorly water-soluble drugs. The nanoparticles were used as nanocarriers with the drug enveloped or dispersed to obtain the drug-loaded matrices with several advantages.[15–17] Many materials, such as chitosan, polylactic acid and poly (lactic-co-glycolic acid) have been used for biomedical and pharmaceutical formulations.[18–20] However, surfactants are always used in those matrices, which will make the systems more complicated and the safety of surfactants is still questionable. Accordingly, many amphiphilic block copolymers have been synthesized and used as nanocarriers for encapsulating guest molecules.[21–23] Due to the amphiphilicity of the copolymers, a more moderate condition was employed and sonication could be avoided in the formation process of nanoparticles.

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Dendritic polymers and their amphiphilic derivatives with a core-shell architecture have been applied in encapsulation and release of hydrophobic compounds, water-soluble dyes and metal colloids.[24–28] Hyperbranched polyglycerol (HPG) is a flexible hydrophilic aliphatic polyether polyol with well defined dendritic structure, which can be obtained by controlled anionic polymerization of glycidol.[29] Due to its structural similarity with polyethylene glycol (PEG), it has low toxicity and high hydrophilicity; and has high biocompatibility.[30]

Polylactic acid (PLA), a biodegradable polyester, has been widely used as one of the most prominent bioabsorbable polymers with good biocompatibility and nontoxicity.[31–34] An amphiphilic polymer has been synthesized by a coupling reaction of PLA chains onto HPG, as described previously.[22] Here, HPG with a molecular weight of 14 kDa (M_w/M_n = 1.73) was synthesized and used to obtain block copolymer nanoparticles with different properties.

This study has investigated the application of amphiphilic HPG-PLA copolymer nanoparticles as a drug delivery vehicle for quercetin. The copolymer nanoparticles were prepared by the nanoprecipitation method and characterized in detail with regard to its physicochemical characterization.

Materials and Methods

Materials

Quercetin was kindly donated from Xi'an Xiao Cao Botanical Development Co. Ltd (Xi'an, China) and was used as received. PLA was purchased from Shenzhen Bright China Industrial Co., Ltd (Shenzhen, China). Glycidol, 1-ethyl-(3-3-dimethylaminopropyl) carbodiimide hydrochloride (EDC·HCl) and 1-hydroxybenzotrizole (HOBt) were purchased from J&K-Acros Chemical Ltd (Tianjin, China) without further purification. All other chemicals were of analytical grade.

Synthesis and characterization of amphiphilic HPG-PLA copolymers

HPG was synthesized by the anionic polymerization of glycidol in the presence of alkoxides as described by Sunder *et al*.[29] The molecular weight of the resulting product was 14 kDa (M_w/M_n = 1.73), with a degree of branching of 0.56. Amino-hyperbranched polyglycerol (HPG-NH_2) was prepared by a two-step reaction according to the reported synthetic method.[22] The copolymer was synthesized following the coupling reaction procedure. Briefly, EDC (134 mg, 0.7 mmol) in N,N-Dimethylformamide (DMF) (5 ml) was added dropwise to a solution of PLA (14 g, 0.7 mmol), HPG-NH_2 (1.1 g, 0.35 mmol) and HOBt (95 mg, 0.7 mmol) in cooled DMF (15 ml) with six drops of triethylamine at 0°C. The solution was stirred at 0°C for 4 h and allowed to warm to room temperature. After five days reaction under N_2, the product was poured into 200 ml cold diethyl ether under vigorous stirring. The precipitate was filtered out and washed with methanol three times. The filtrate was dissolved in DMF at a concentration of 1% (w/w) and carefully fractioned with methanol. The structure of the copolymer was analysed by ^{1}H NMR (Varian Unity-plus 400 NMR spectrometer) and Fourier-transform infrared spectroscopy (FTIR) (FTS-6000, Bio-Rad Co.). The molecular weight and the polydispersity of HPG-PLA were measured by gel permeation chromatography.[22]

Preparation of HPG-PLA nanoparticles

Drug-loaded nanoparticles were prepared by the nanoprecipitation method.[35–38] Briefly, 10 mg HPG-PLA and a predetermined amount of quercetin were dissolved in 2 ml tetrahydrofuran. The obtained organic solution was added dropwise under stirring to 16 ml water, at room temperature overnight to allow the evaporation of tetrahydrofuran. The resulting aqueous dispersion was filtered through a 1.0-μm syringe filter to remove the unincorporated drug. Nanoparticles were obtained by centrifugation (15 000 rev/min, 1 h, 4°C), washed with distilled water at least three times and freeze-dried to prepare the powdered nanoparticles. Drug-free nanoparticles were prepared according to the same procedure omitting the drug.

Characterization of HPG-PLA nanoparticles

Water absorption

Copolymer (or nanoparticles), 20 mg dried *in vacuo*, was immersed in phosphate buffered saline (0.1 M PBS, pH 7.4) at 37°C. After 24 h, the sample was taken out, washed rapidly with distilled water and put in a stream of nitrogen gas until the surface was dry.[34] The percentage of equilibrium water uptake was calculated as follows:

$$\text{Water uptake } (\%) = (W_w - W_d)/W_d \times 100\% \qquad (1)$$

where W_w was the weight of the wet sample and W_d was the initial weight of the sample. All samples were analysed in triplicate and the error bar in the plot was the standard deviation.

In-vitro degradation experiment

Copolymers (or nanoparticles), 20 mg dried *in vacuo* was immersed in 0.1 M PBS (pH 7.4) at 37°C. At predetermined intervals, the sample was washed with distilled water and dried *in vacuo*. The residual mass was calculated according to the following formula:

$$\text{Weight loss } (\%) = (W_i - W_c)/W_i \times 100\% \qquad (2)$$

where W_i and W_c represented the initial weight of the sample and that of the constant weight after being dried on the predetermined day, respectively. All samples were analysed in triplicate and the error bar in the plot was the standard deviation. To qualitatively investigate the degradation of HPG-PLA 40 versus time, ^{1}H NMR (Varian Unity-plus 400) measurement was carried out.

X-ray diffraction analysis

The X-ray diffraction (XRD) diagrams of pure quercetin, quercetin free nanoparticles and the quercetin-loaded nanoparticles were determined with a Rigaku D/max-2500 X type

X-ray diffractometer (Ni-filtered, CuKa radiation with a wavelength of 0.154 nm). The result was recorded using diffraction angles (2θ) from 2° to 60° with steps of 0.02°, at a scanning speed of 4°/min (2θ).

Nanoparticle size measurement

The mean diameter and polydispersity index (PDI) of the nanoparticles were determined by a dynamic light scattering particle size analyser (Brookhaven, INNDVO300/BI900AT). The analysis was performed at a scattering angle of 90° and at a temperature of 37°C. All samples were analysed in triplicate and the error bar in the plot was the standard deviation.

Drug encapsulation efficiency and drug loading

The encapsulation efficiency (EE) and drug loading (DL) of the nanoparticles was conducted according to the modified procedure described previously.[39] The amount of quercetin entrapped in the nanoparticles was determined by dissolving the nanoparticles (20 mg) in anhydrous ethanol under sonication (10 min). The resulting solution was determined with UV spectrometer (Shimadzu UV-2550) at 373 nm and the total amount of quercetin was obtained. The drug encapsulation efficiency and drug loading could be achieved by the following equations:

$$\text{EE}\ (\%) = W_{LQ}/W_{TQ} \times 100\% \quad (3)$$

$$\text{DL}\ (\%) = W_{LQ}/W_{NP} \times 100\% \quad (4)$$

where W_{LQ} was the amount of quercetin loaded in the nanoparticles, W_{TQ} was the total quercetin amount used initially, and W_{NP} was the weight of the nanoparticles. All samples were analysed in triplicate and the error bar in the plot was the standard deviation.

Cell toxicity assay

Cell viability was evaluated by using NIH 3T3 cells in Dulbecco's modified Eagle's medium (DMEM, ph 7.4) under a range of concentrations (25, 50, 100 and 200 μg/ml) of blank nanoparticles as demonstrated in a previous study.[22] Cells untreated with the blank nanoparticle solution were used as the control group and their viability was set at 100%. The cell viability in each well was calculated as follows:

$$\text{Cell viability} = (\text{average optical density values in experimental groups}/\text{average optical density values in the control groups}) \times 100\% \quad (5)$$

Each experiment was performed in triplicate and the results were reported as means ± standard deviation.

In-vitro drug release

The drug release experiment was performed in 0.1 M PBS (pH 7.4) using the dialysis bag method.[15,40] A 20-mg sample of drug-loaded nanoparticles was put into a dialysis bag and 4 ml release medium was added to the dialysis bag. The bag was then placed in a conical flask, the flask was filled with 400 ml PBS (0.1 M, pH 7.4) and incubated at 37°C under horizontal shaking. At predetermined time points, 4 ml dissolution medium was withdrawn and the same volume of fresh medium was added.[41] Quercetin in the sample solution was measured using a UV spectrometer (Shimadzu UV-2550) at 373 nm. All samples were analysed in triplicate and the error bar in the plot was the standard deviation.

Statistical analysis

Statistical analysis of the effects of variance on the diameter, drug loading and encapsulation efficiency of the nanoparticles and release profiles was performed by one-way analysis of variance. The effect of various factors on the water uptake, weight loss and cell viability of the materials was statistically examined by the Kruskal–Wallis test. All data were presented as mean values with standard deviations indicated (mean ± SD). Differences were considered to be statistically significant when the P values were less than 0.05.

Results and Discussion

Synthesis and characterization of the copolymers

The copolymers were synthesized according to the modified procedures described by Gao *et al.*[22] With the feeding ratio of PLA/HPG at 1 : 3, HPG-PLA had approximately 14 kDa larger M_n than the original PLA. This proved that we had obtained the coupled products as one PLA chain grafting onto one HPG.[22,23] The characterization data of the products are summarized in Table 1.

Table 1 The characterization data of the copolymers

Material	PLA (kDa)	M_n (kDa)	M_w/M_n	Yield (%)	T_g (°C)
HPG-PLA12	12	27	1.7	64	–
HPG-PLA21	21	36	1.8	61	48.9
HPG-PLA40	40	52	1.7	65	55.6
HPG-PLA80	80	94	1.9	67	59.1

HPG-PLA, hyperbranched polyglycerol-polylactic acid; PLA, polylactic acid; T_g, glass transition temperature.

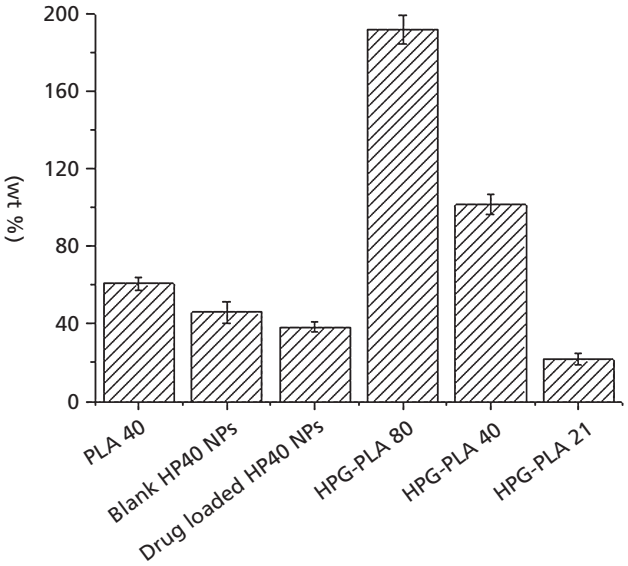

Figure 1 Water uptake of HPG-PLA 40 nanoparticles, PLA and HPG-PLA copolymers.
HPG-PLA, hyperbranched polyglycerol-polylactic acid; NPs, nanoparticles; PLA, polylactic acid.

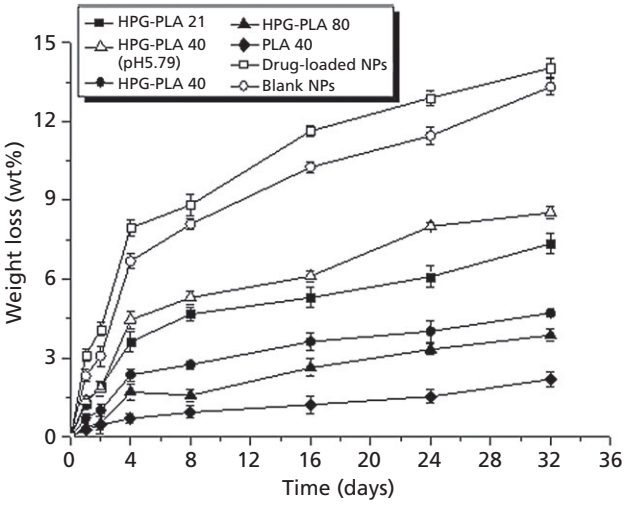

Figure 2 Weight loss of HPG-PLA 40 nanoparticles, PLA 40 and HPG-PLA copolymers.
HPG-PLA, hyperbranched polyglycerol-polylactic acid; NPs, nanoparticles; PLA, polylactic acid. Triplicates for each sample were analysed and each datum point represents the mean ± SD ($n = 3$).

Water absorption

Results in Figure 1 shows the water absorption by PLA, HPG-PLA and corresponding nanoparticles. The water uptake of HPG-PLA 40 was 45.8%, which was higher than that of PLA 40 (21.5%). The introduction of HPG on the end group of the PLA block resulted in an increase of water absorption because HPG was hydrophilic. Furthermore, the hyperbranched structure of HPG could provide more channels for water molecules. The water absorption of the copolymers increased from 38.3% to 60.6% when HPG content in HPG-PLA increased from 14.9% to 41.2%, which was due to the hydrophilicity of the copolymer increasing as the content of HPG in the copolymer increased. Both nanoparticles exhibited higher water absorption than that of the copolymers as shown in Figure 2. The reason for this phenomenon could be considered from two aspects. Firstly, the formed micelles had a hydrophobic core coated with a hydrophilic shell, which was in favour of enhancing water absorption capacity.[22] Secondly, the crystallinity of HPG-PLA nanoparticles was less than that of HPG-PLA, thus nanoparticles had a looser structure (Figure 3) and water molecules could easily permeate into the nanoparticles. Moreover, water absorption capacity of drug-loaded nanoparticles was up to 192.0% compared with that of blank nanoparticles (101.5%).

In-vitro degradation experiment

Under physiological conditions HPG is fairly stable and can be metabolized after HPG breaks away from the conjugate. The plots of weight loss vs time are demonstrated in Figure 2. The degradation rate of PLA 40 was quite low due to its high hydrophobicity and crystallization. The hydrophilicity of the HPG moiety was attributed to HPG-PLA 40 biodegrading much faster than PLA 40. The copolymer with low molecular weight was degraded faster than those with high molecular

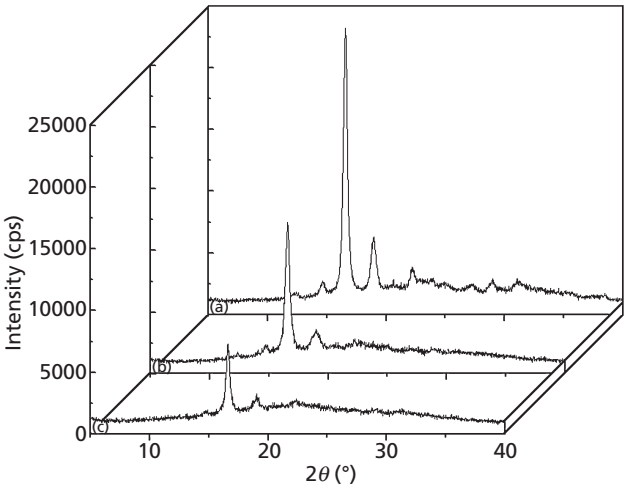

Figure 3 The X-ray diffraction diagrams of (a) PLA 40, (b) HPG-PLA 40 and (c) blank HPG-PLA 40 nanoparticles.
HPG-PLA, hyperbranched polyglycerol-polylactic acid.

weight. This was because the polymeric chains of small molecular weight possessed better mobility and more hydrophilicity so that the water penetrated into the polymer matrix more easily.[38,42] In addition, the degradation of the copolymer was highly susceptible to pH change. HPG-PLA 40 degraded faster at pH 5.8 than pH 7.4 as shown in Figure 2. Additionally, nanoparticles exhibited a faster biodegradation rate than the copolymers. This was because nanoparticles possessed larger water absorption capacity, facilitating the copolymer biodegradation. More importantly, drug-loaded nanoparticles presented a faster degradation rate than blank nanoparticles, which was also due to the larger water absorption capacity of drug-loaded nanoparticles.

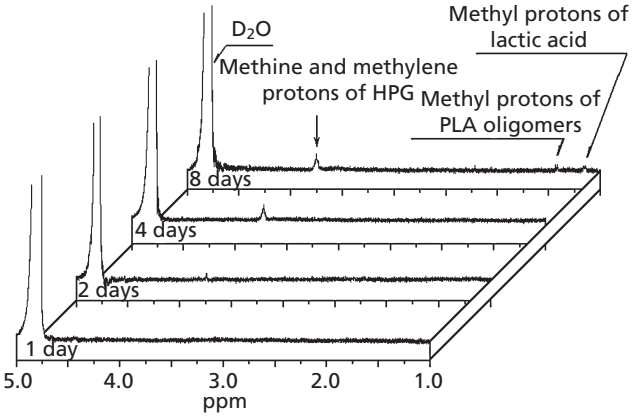

Figure 4 Degradation measurement of HPG-PLA 40 by ^{1}H NMR.
HPG, hyperbranched polyglycerol-polylactic acid; PLA, polylactic acid.

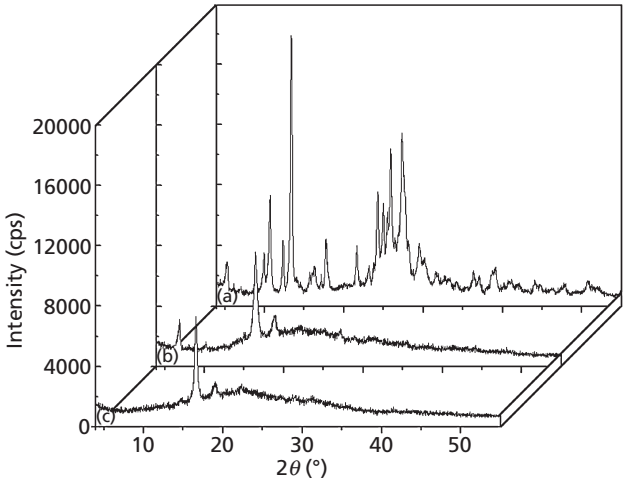

Figure 5 The X-ray diffraction diagrams of (a) quercetin, (b) quercetin-loaded nanoparticles (HPG-PLA 40) and (c) blank nanoparticles (HPG-PLA 40).
HPG-PLA, hyperbranched polyglycerol-polylactic acid.

Interestingly, there was a steep phase of the degradation curve after two days (Figure 2), which could be explained by the separation of HPG from the copolymer due to hydrolysis. As shown in Figure 4, ^{1}H NMR measurement was performed to qualitatively investigate HPG-PLA 40 degradation versus time. In the first two days, there was no obvious peak observed in the spectrum, suggesting that no significant degradation took place. However, on the fourth day, peaks at δ 3.7 ppm were observed clearly, which were assigned to the methane and methylene protons of HPG block.

X-ray diffraction and FTIR analysis

The XRD patterns for quercetin, quercetin-loaded nanoparticles (HPG-PLA 40) and blank nanoparticles (HPG-PLA 40) are shown in Figure 5. The characteristic peaks of quercetin exhibited at a diffraction angle of 2θ, 10.68°, 12.34°, 15.72°, 24.26° and 27.32° could be inferred to traits of a high crystalline structure.[43] However, the diffraction peaks relevant to crystalline quercetin were no longer detectable in the quercetin-loaded nanoparticles, indicating that quercetin dispersed in the hydrophobic core region and was in the amorphous state.[18,19,43,44]

Figure 3 shows the XRD diagrams of drug free nanoparticles (HPG-PLA 40), HPG-PLA 40 and PLA 40 independently. The results showed the degree of crystallization in the order PLA 40 > HPG-PLA 40 > blank nanoparticles (HPG-PLA 40). The introduction of HPG on the end group of the PLA block could be unfavourable for the crystallinity of the copolymer. Moreover, the steric hindrance effect between PLA blocks in the hydrophobic core of the nanoparticle might decrease the crystallinity of the nanoparticles.

The intermolecular interaction between nanoparticles and quercetin was established by FTIR. The results showed quercetin presenting the characteristic intensities of C = O absorption band at 1671 cm^{-1} and the OH stretch at 3361 cm^{-1}.[43] The spectrum from drug-loaded nanoparticles showed that the C = O absorption band of quercetin was shifted toward lower wave numbers and the OH stretch of quercetin completely disappeared. These results suggested that intermolecular interaction existed between quercetin and nanoparticles.

Nanoparticle morphology and size

The freshly prepared nanoparticles appeared to be well dispersed with regularly spherical shape. Degradation of drug-loaded nanoparticles after 32 days was measured by SEM (data not shown). Serious collapse of the nanoparticles was observed and the particles were mainly irregular with uneven surfaces. Such a degradation character of drug-loaded nanoparticles would have a great effect on the release profile.

The mean particle size and size distribution of nanoparticles are shown in Table 2. Nanoparticles had sizes in the range 205.3–433.3 nm with a narrow distribution. Increasing the molecular weight of PLA in the copolymers led to a larger particle size. A similar phenomenon had been observed in a previous study.[45] As shown in Table 2, the average particle size was approximately 380.6 nm for the blank and 402.0 nm for quercetin-loaded HPG-PLA 40 nanoparticles, respectively. The results indicated that loading of quercetin led to an increase of particle size.

Drug encapsulation efficiency and drug loading

Drug encapsulation efficiency and drug loading are presented in Table 2. Both encapsulation efficiency and drug loading in HPG-PLA 40 nanoparticles increased in comparison with those in the PLA 40 nanoparticles. The reasons for the high encapsulation efficiency and drug loading could be considered as follows: the crystallization ability of the copolymer nanoparticles was decreased in the presence of HPG, that is, HPG-PLA 40 nanoparticles fabricated had a looser structure, which facilitated more quercetin into nanoparticles during the formation process of nanoparticles.

As shown in Table 2, encapsulation efficiency and drug loading increased with an increase in the copolymer molecular weight. This was because the amount of quercetin that interacted with the PLA backbone increased as the content of the hydrophobic block increased, leading to the increase of encapsulation efficiency and drug loading. Furthermore, the

Table 2 Drug loading, encapsulation efficiency and particle size of different nanoparticles

Nanoparticles made with	QUI (mg)	DL (%)	EE (%)	AD (nm)	PDI
HPG-PLA 21	2	17.1 ± 0.5	79.3 ± 2.8	205 ± 2.1	0.107
HPG-PLA 40	0	–	–	381 ± 2.3	0.114
	1	8.1 ± 0.2	93.7 ± 3.9	333 ± 1.9	0.055
	2	21.0 ± 0.6	91.8 ± 2.7	402 ± 1.5	0.110
HPG-PLA 80	2	25.2 ± 0.8	92.3 ± 2.4	433 ± 2.9	0.065
PLA 40	0	–	–	321 ± 3.1	0.102
	2	16.8 ± 0.4	74.4 ± 2.1	361 ± 3.3	0.133

AD, average diameter; DL; drug loading; EE, encapsulation efficiency; HPG-PLA, hyperbranched polyglycerol-polylactic acid; PDI, polydispersity index; QUI, quercetin used initially. HPG-PLA used initially: 10 mg; aqueous phase: 16 ml; organic phase: 1 ml.

molecule of quercetin dispersed into the HPG-PLA copolymer during the preparation process of nanoparticles, thus forming an amorphous complex with intermolecular interaction occurring within the matrix.

Cell toxicity assay

In this work, HPG with a molecular weight of 14 kDa was used to synthesize HPG-PLA copolymer. Therefore, it was important to verify the harmless nature of the copolymer nanoparticles. Samples were analysed using the MTT method in the NIH 3T3 cell line to investigate cytotoxicity. For HPG-PLA 40, the cell viability kept stable as the concentration increased. High cell viability (approximately 100%) in the presence of HPG-PLA 40 nanoparticles was obtained. The viability of the cells treated with different sample solutions (HPG-PLA 12, HPG-PLA 21, HPG-PLA 40 and HPG-PLA 80) with the same concentration (50 μg/ml) was evaluated. For all materials, the viability of cells was approximately 100%, which indicated that the materials had no cytotoxicity. No significant difference ($P > 0.05$) between groups was observed on the fourth day. The results suggested that the materials had good cytocompatibility.

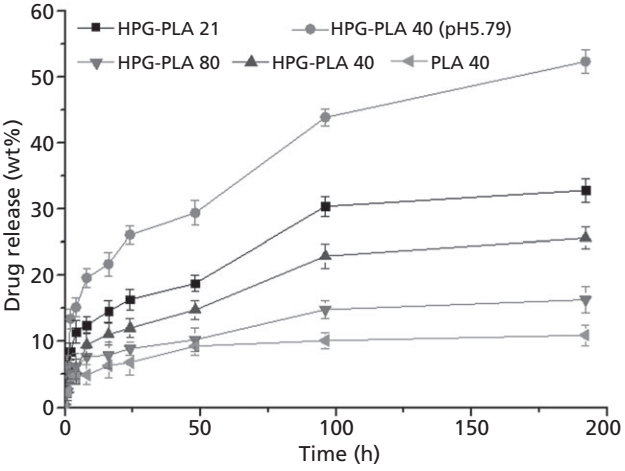

Figure 6 In-vitro cumulative percentage of quercetin released from HPG-PLA and PLA nanoparticles in phosphate buffered saline at pH 7.4. HPG-PLA, hyperbranched polyglycerol-polylactic acid; PLA, polylactic acid. Triplicates for each sample were analysed and each datum point represents the mean ± SD ($n = 3$).

In-vitro drug release

Figure 6 shows the cumulative release percentage of quercetin from the copolymer nanoparticles and that from PLA 40 nanoparticles as a function of time. In both curves a burst effect was observed followed by a slow continuous release phase. Both nanoparticles exhibited burst release properties and the drug released during the first 24 h was approximately 10%. This indicated that a certain amount of quercetin was located on the surface of nanoparticles. However, quercetin released from the copolymer nanoparticles was much faster than that released from PLA 40 nanoparticles. PLA nanoparticles are hydrophobic and the hydrophobic interaction between quercetin and PLA 40 nanoparticles is stronger than the interaction between quercetin and HPG-PLA nanoparticles. Therefore, it was easier for quercetin to penetrate out from HPG-PLA nanoparticles than from PLA 40 nanoparticles, which would induce the faster release rate. Furthermore, there was a steep phase after two days only for the copolymer nanoparticles. This could be explained by HPG separation from HPG-PLA due to hydrolysis. The drug released from nanoparticles could be controlled by both drug diffusion and polymer degradation.[38] Since there is a significant interaction occurring between the drug and nanoparticles, as demonstrated by FITR and XRD, it would be difficult for quercetin interacting with the hydrophobic block in the matrix to diffuse out of the nanoparticles before the degradation of HPG-PLA. Therefore, the drug release might mainly depend on the biodegradation of the polymeric nanoparticles. A high degradation rate after two days resulted in a fast release of quercetin at the same time. Without the steric hindrance of HPG on the surface of the copolymer nanoparticles, the drug release rate would increase obviously. In the same physical condition, the order of the biodegradation rate for HPG-PLA copolymers and PLA homopolymer was: HPG-PLA 21 > HPG-PLA 40 > HPG-PLA 80 > PLA 40. The drug release rates from the prepared nanoparticles were in the same order. The results implied that biodegradation could play an important role in drug release. In addition, drug release from the copolymer nanoparticles was highly susceptible to changes in pH as shown in Figure 6. This might also have been induced by the faster degradation rate of samples at low pH.

It is known that the degradation rate of the samples is influenced by many factors (polymer composition, molecular weight, particle size and pH). Those factors that affected biodegradation could also play an important role in drug release. A unique drug delivery system with an exclusively

defined release property could be exploited by adjusting the characteristics of the nanoparticles.

Conclusions

It has been demonstrated that quercetin, a poorly soluble drug, could be easily packed into HPG-PLA nanoparticles with high drug encapsulation efficiency and drug loading. The copolymer nanoparticles possessed no cytotoxicity and had high biodegradability. The formulated drug-loaded nanoparticles exhibited spherical structure in the nanometer range with a sustained release profile, which could be affected by many factors. In general, HPG-PLA nanoparticles may be considered as a promising carrier system for controlled release for possible clinical applications.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

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