Carbohydrate Polymers xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

# Radiation synthesis and characterization of hyaluronan capped gold nanoparticles

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ARTICLE INFO

*Article history:*
Received 5 July 2011
Received in revised form 6 March 2012
Accepted 13 March 2012
Available online xxx

*Keywords:*
Gold nanoparticles
Hyaluronan
γ-ray

ABSTRACT

Gold nanoparticles (AuNPs) with diameter from 4 to 10 nm, capping by hyaluronan (HA) were synthesized using a γ-irradiation method. The maximum absorption wavelengths at 517–525 nm of colloidal AuNPs/HA solutions were measured by UV–vis spectroscopy. The size and size distribution of AuNPs were determined from TEM images. The influence of various factors on the size of AuNPs particularly the concentration of $Au^{3+}$ and HA, and dose rate were also investigated. Results indicated that higher dose rate and HA concentration favor smaller sizes of AuNPs whereas the size increases with $Au^{3+}$ concentration. The colloidal AuNPs/HA solution was fairly stable more than 6 months under storage at ambient condition. The AuNPs stabilized by biocompatible HA with the size less than 10 nm as prepared can potentially be applied in biomedicines and cosmetics.



## 1. Introduction

Gold nanoparticles (AuNPs) with diameter less than 100 nm exhibits new characteristics such as a catalytic property for conversion of CO to $CO_2$ at low temperature (35 K) (Kim, Dohnálek, & Kay, 2005), enhancement of free radical scavenging for antioxidation in cosmetics (Nie et al., 2007), acceleration of reaction speed in highly sensitive bio-sensor (Ramanavicienne et al., 2009) and cancer diagnosis and therapy assistances (Huang & El-Sayed, 2010). In addition, AuNPs can be used to modify pharmaceuticals for targeted therapy purpose (Yang, Wang, Hwu, & Je, 2006). Results of the study performed by Kattumuri et al. (2007) revealed that AuNPs stabilized by gum arabic can be used for X-ray contrast imaging enhancement. More details of the application of AuNPs in medicine can be found in the studies reviewed by Baptista et al. (2008), and Boisselier and Astruc (2009). Furthermore, Esumi, Takei, and Yoshimura (2003) reported that the antioxidant activity of AuNPs-chitosan was 80 times higher than that of ascorbic acid, which is well-known as an antioxidant substance. Recently, Fathi-Azarbayjani, Qun, Chan, and Chan (2010) studied the use of AuNPs in the formulation of facial mask owing to AuNPs help to improve blood circulation, skin elasticity, and can rejuvenate the skin and reduce the formation of wrinkles.

Different methods such as laser treatment of bulk gold (top-down) (Amendola, Polizzi, & Meneghetti, 2006), reduction of $Au^{3+}$ ion in solution (bottom-up) by chemical reductants (Anderson, Torres-Chavolla, Castro, & Alocilja, 2011; Hussain et al., 2005; Hussain, Iqbal, & Mazhar, 2009; Ramanavicienne et al., 2009), UV (Huang et al., 2007), X-ray (Yang et al., 2006), gamma Co-60 ray (Akhavan, Kalhor, Kassaee, Sheikh, & Hassanlou, 2010; Anh, Phu, Duy, Du, & Hien, 2010; Li, Park, & Choi, 2007; Meyre, Dlapierre, & Faure, 2008; Treguer et al., 1998) have been studied to synthesize AuNPs. Compared with other methods, gamma Co-60 ray irradiation is considered as an effective method with several advantages such as: (1) the reaction is carried out at room temperature; (2) yield of AuNPs is high; (3) AuNPs can be purely prepared without contamination of excessive chemical reductant and $Au^{3+}$ ions residue; (4) the size of AuNPs is easily controlled by varying $Au^{3+}$ ions or seed enlargement approaches; (5) mass production can be carried out and (6) processing is satisfied to requirement of clean production (Meyre et al., 2008; Treguer et al., 1998). Furthermore, according to Meyre et al. (2008), the size of AuNPs (~2 nm) prepared by gamma Co-60 irradiation method was smaller compared to that by UV (~6 nm) and by chemical reduction (~10 nm) from the same $Au^{3+}$ concentration. Therefore, gamma Co-60 radiation is a useful tool for the preparation of AuNPs with suitably controllable size for application in different fields especially in biomedicines (Yang et al., 2006). Characteristics of AuNPs depend on morphology, size of particles and surface ligands (Amendola et al., 2006; Aryal, Remant, Khil, Dharmaraj, & Kim, 2007; Huang & El-Sayed, 2010). For instance, chemical inertness of AuNPs with particles size bigger than 5 nm is comparable to bulk gold (Alkilany & Murphy, 2010). AuNPs of ~2 nm with positive surface charged ligand is toxic for cells while it is non-toxic with negative ones (Alkilany & Murphy, 2010). AuNPs with particles size less than 3 nm have no maximum absorption wavelength in the visible region (Hussain et al.,

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doi:10.1016/j.carbpol.2012.03.041

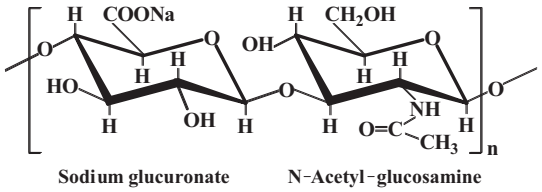


**Fig. 1.** Chemical structure of hyaluronan.

2005). Stabilizers such as PVA (Aryal et al., 2007; Treguer et al., 1998), PVP (Li et al., 2007), PA (Aryal et al., 2007; Hussain et al., 2005), citric (Yang, Wang, Wang, Zhang, & Ding, 2007), had to be used for protection from agglomeration among AuNPs. Recently, natural polymers such as CM-chitosan (Huang et al., 2007), gum arabic (Kattumuri et al., 2007), starch (Hussain et al., 2009), chitosan (Sun et al., 2008), glycosaminoglycan (Kemp et al., 2009), protein (Akhavan et al., 2010), alginate (Anh et al., 2010) and dextrin (Anderson et al., 2011) have been studied as a stabilizer for capping of AuNPs instead of synthetic polymers. AuNPs stabilized by natural polymers are considered to be safe and biocompatible for application in biomedical, cosmetic and pharmaceutical field (Akhavan et al., 2010; Huang & El-Sayed, 2010; Kemp et al., 2009). In our previous research, alginate has been used as stabilizer for preparation of AuNPs with particles sizes of 8–40 nm (Anh et al., 2010). In this study, we present the results of the synthesis of AuNPs with 4–10 nm by gamma Co-60 irradiation using hyaluronan (HA) as a stabilizer. The factors affecting on particle size, such as $Au^{3+}$ and HA concentrations and dose rate have been also investigated. Moreover, HA an anionic polysaccharide which consists of two types of saccharide monomer plays an important role in many biological processes and is one of the main components of the extracellar matrices found in many tissues of the body such as skin, cartilage, and the vitreous humor (Kemp et al., 2009). Chemical structure of HA with a repeat unit of D-sodium glucuronate and N-acetyl-glucosamine is shown in Fig. 1. HA is used as lubricant and shock absorber in the intracellular matrix of cartilage to treat osteoarthritis by injection into the knee joint to supplement the viscosity of the joint fluid, thereby lubricating and cushioning the joint (Lohmander, Dalen, Hamalainen, Jensen, & Karlsson, 1996). For normal development in eukaryotes, HA regulates cell proliferation, migration and tissue architecture at multiple levels (Lee & Spicer, 2000). HA can be crosslinked to produce hydrogels for tissue engineering (Shu, Liu, Palumbo, Luo, & Prestwich, 2004). More recently, HA and its derivatives have been used as target-specific drug delivery systems for various therapeutic agents (Larsen & Balazs, 1991; Lee, Mok, Lee, Oh, & Park, 2007). HA is a common ingredient in skin care products. Further information about biological properties of HA can be referred to the article reviewed by Morra (2005). Nowadays, HA is recognized as a valuable polymer which can be applied in both biomedical and cosmetic industries. According to Morra (2005), HA is emerging more and more as a key molecule in the regulation of many cellular and biological processes. Therefore, the resultant AuNPs/HA composite may be useful for application in biomedicine and cosmetics due to the biocompatible properties of HA as well as the unique properties of Au core nanoparticles.

## 2. Materials and methods

### 2.1. Chemicals

Hydrogen tetrachloroaurate trihydrate ($HAuCl_4{\cdot}3H_2O$) and pure water from Merck and pure hyaluronan (sodium HA) from Sigma were used as received. Glasswares were treated with regia solution (1 V $HNO_3$:3 V HCl), washed with pure water and dried.

### 2.2. Preparation of $Au^{3+}$/HA solution and irradiation

Two stock solutions particularly 10 mM $Au^{3+}$ and 1% HA were prepared by dissolving $HAuCl_4{\cdot}3H_2O$ and HA into water. $Au^{3+}$/HA solutions were prepared by pouring $Au^{3+}$ solution into HA solution with desired different concentrations while stirring of about 5 min. And then, the prepared $Au^{3+}$/HA solutions of 20 ml were put into glass bottles with plastic cap. Irradiation was carried out using a gamma Co-60 irradiator STSVCo-60/B (Hungary) with dose rate of 1.25 kGy/h at VINAGAMMA Center (Ho Chi Minh City) and the Gamma Chamber 5000, BRIT (India) with dose rate of 0.5–5.0 kGy/h at the Nuclear Research Institute (Da Lat City).

### 2.3. Characterization of AuNPs/HA

The absorption spectra of AuNPs solutions which were diluted by water to 0.05 mM calculated as $Au^{3+}$ concentration were taken on an UV–vis spectrophotometer model UV-2401PC (Shimadzu, Japan). The size and size distribution of the AuNPs were characterized by TEM images on transmission electron microscope (TEM) model JEM1010 (JEOL, Japan) and statistically calculated from about 500 particles (Aryal et al., 2007). The AuNPs/HA solution from 0.1 mM $Au^{3+}$/0.2% HA solution was dried by spray drying with Spray dryer model ADL311 (Yamato, Japan) to obtain AuNPs/HA powder. X-ray diffraction (XRD) measurement of AuNPs/HA powder was taken on an X'Pert Pro X-ray diffractometer (PANalytical, Netherlands) operated at 45 kV–40 mA and in the 10–90° ($2\theta$) range. The stability of colloidal AuNPs/HA solution from 0.1 mM $Au^{3+}$/0.2% HA sample was investigated with storage time under ambient condition by measurement of optical density (OD), maximum absorption wavelength ($\lambda_{max}$) and particles size by TEM.

## 3. Results and discussion

The results of UV–vis absorption spectra in Fig. 2a indicated that $Au^{3+}$, HA and $Au^{3+}$/HA solution have no absorption peaks in visible region. However, in UV region $Au^{3+}$, HA and $Au^{3+}$/HA solutions have maximum absorption wavelengths ($\lambda_{max}$) at 290, 259 and 280 nm, respectively. Absorption peak of $Au^{3+}$/ligand solution depends on ligand type forming complex with $AuCl_4^-$, for example $AuCl_4^-$/citric: $\lambda_{max}$ at 310 nm (Yang et al., 2007), $AuCl_4^-$/PVA: $\lambda_{max}$ at 259 nm (Aryal et al., 2007). After irradiation, the color of $Au^{3+}$/HA solution turned from yellow to purple with $\lambda_{max}$ at ~520 nm which is surface plasmon resonance characteristic of AuNPs (Boisselier & Astruc, 2009; Henglein, 1999). Results of UV–vis absorption spectra of irradiated 0.4 mM $Au^{3+}$/0.2% HA solution in Fig. 2b indicated that optical density (OD) at $\lambda_{max}$ increased with the increasing of dose and attained stable value at 3 kGy. Thus, when solution of 0.4 mM $Au^{3+}$/0.2% HA is irradiated at 3 kGy, the $Au^{3+}$ is reduced completely to $Au^0$ by $e^-_{aq}$, $^\bullet H$ and $^\bullet HA$ occurred during irradiation and this dose is referred to as saturated conversion dose (Akhavan et al., 2010; Anh et al., 2010). This value of dose (3 kGy) is consistent with theoretical calculation on reduction of $Au^{3+}$ to $Au^0$ by gamma radiation, the dose of about 6 kGy is needed for complete reduction of 1 mM $Au^{3+}$ (Treguer et al., 1998). The mechanism of $Au^{3+}$ reduction by γ-irradiation method was described by Belloni, Mostafavi, Remita, Marignier, and Delcourt (1998) and Henglein (1999) as follows:

$$H_2O \xrightarrow{\gamma\text{-radiation}} e^-_{aq}, H^\bullet, OH^\bullet, H_2O_2, H_2, H_3O^+, \ldots \quad (1)$$

$$Au^{3+} + \text{reducing radicals}\,(e^-_{aq}, H^\bullet) \rightarrow Au^{2+} \quad (2)$$

$$Au^{2+} + \text{reducing radicals} \rightarrow Au^{1+} \quad (3)$$

$$2Au^{2+} \rightarrow Au^{3+} + Au^{1+} \quad (4)$$

$$Au^{1+} + \text{reducing radicals} \rightarrow Au^0 \quad (5)$$

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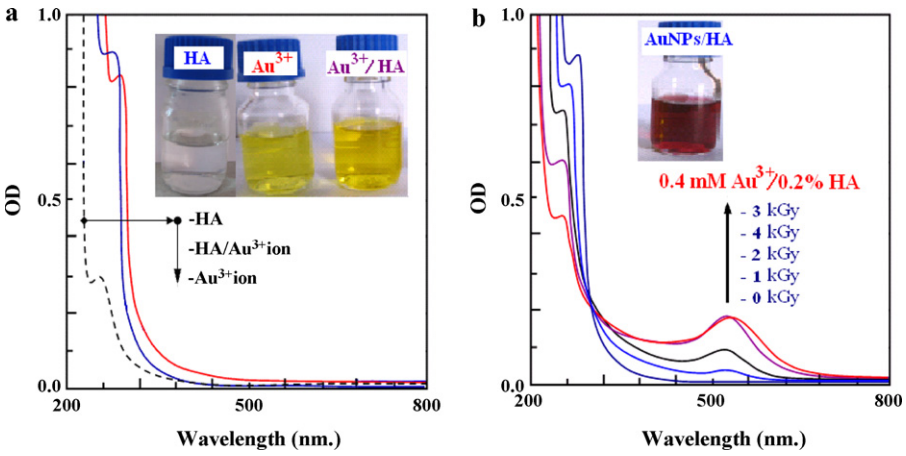


**Fig. 2.** UV–vis spectra of HA, $Au^{3+}$, $Au^{3+}$/HA solutions (a) and irradiated $Au^{3+}$/HA solution (b).

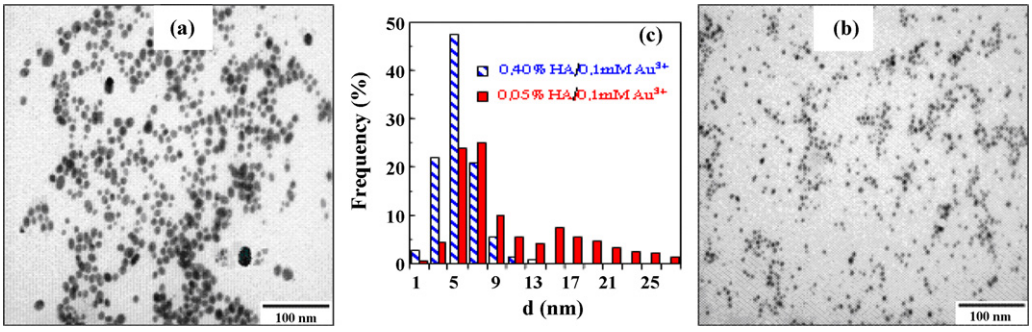


**Fig. 3.** TEM images of AuNPs from 0.1 mM $Au^{3+}$/0.05% HA (a) and 0.4% HA (b), and size distribution (c).

$$n\mathrm{Au}^0 \rightarrow \mathrm{Au}^0{}_n\,(\mathrm{AuNPs}) \quad (6)$$

where Eqs. (2), (3) and (5) correspond to the reduction of gold ions and Eq. (4) is the disproportionation, respectively.

Results in Table 1 indicated that $\lambda_{max}$ of AuNPs solution shifted from 517 nm (0.05 mM $Au^{3+}$) to 523 nm (0.4 mM $Au^{3+}$) and particles size of AuNPs also increased from ~4 nm (0.05 mM $Au^{3+}$) to ~9 nm (0.2 and 0.4 mM $Au^{3+}$). The tendency of the increase of AuNPs size with the increasing $Au^{3+}$ was also reported in our previous article for AuNPs/alginate (Anh et al., 2010). The AuNPs were prepared by γ-irradiation from solutions containing 0.5% (w/v) alginate with different of $Au^{3+}$ concentrations particularly 0.25, 0.5 and 1 mM. The results also indicated that as the $Au^{3+}$ concentration increased while the concentration of alginate stabilizer was kept as 0.5% then the ratio of alginate/$Au^{3+}$ will be smaller and that resulted bigger AuNPs particularly 5, 8 and 20 nm for $Au^{3+}$ concentration of 0.25, 0.5 and 1 mM, respectively. The main reason for this phenomenon is due the development of clusters and the agglomeration among AuNPs when the ratio of stabilizer and $Au^{3+}$ concentration is not appropriately high enough. For instance, the critical concentration of alginate for obtaining smallest AuNPs (~8 nm) prepared by γ-irradiation method was 0.5% for 0.5 mM $Au^{3+}$ concentration (Anh et al., 2010).

**Table 1**
OD, $\lambda_{max}$ and the size of AuNPs ($d$) from solution of 0.2% HA/$Au^{3+}$ (0.05–0.4 mM) irradiated 4 kGy (dose rate: 1.25 kGy/h).

| $Au^{3+}$ conc. (mM) | OD | $\lambda_{max}$ (nm) | $d$ (nm) |
|---|---|---|---|
| 0.05 | 0.17 | 517.0 | 4.3 ± 1.7 |
| 0.1 | 0.17 | 518.5 | 6.0 ± 2.6 |
| 0.2 | 0.19 | 521.0 | 9.0 ± 3.2 |
| 0.4 | 0.18 | 523.0 | 9.2 ± 3.6 |

The effect of HA concentrations has been studied at 0.1 mM $Au^{3+}$ concentration. The average diameters of AuNPs were of 10.2, 7.0, 6.0 and 5.5 nm for HA concentrations of 0.05, 0.1, 0.2 and 0.4%, respectively. Results in Fig. 3c indicated that the size distribution of AuNPs was Gaussian type and narrow for 0.1 mM $Au^{3+}$/0.4% HA and while for 0.1 mM $Au^{3+}$/0.05% HA the quadratic equation form was

**Table 2**
OD, $\lambda_{max}$ and d of AuNPs from solution of 0.1 mM $Au^{3+}$/0.2% HA with different dose rates (dose: 4 kGy).

| Dose rate (kGy/h) | OD | $\lambda_{max}$ (nm) | $d$ (nm) |
|---|---|---|---|
| 0.5 | 0.14 | 532.5 | 9.5 ± 2.3 |
| 1.25 | 0.17 | 518.5 | 6.0 ± 2.6 |
| 2.5 | 0.18 | 517.5 | 5.6 ± 2.1 |
| 5 | 0.16 | 516.5 | 5.0 ± 1.9 |

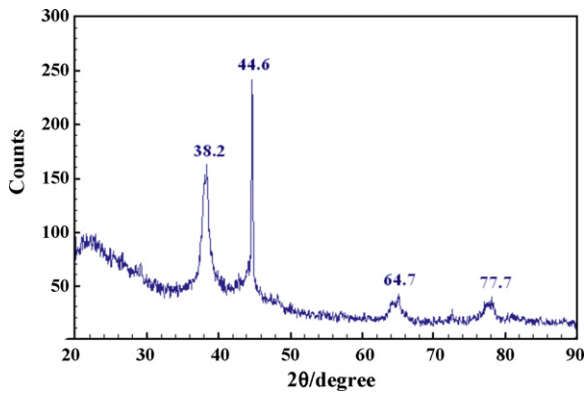


**Fig. 4.** XRD pattern of AuNPs from 0.1 mM $Au^{3+}$/0.2% HA.

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**Table 3**
OD, $\lambda_{max}$ and d of AuNPs from 0.1 mM $Au^{3+}$/0.2% HA on storage time.

| Storage time (day) | 1 | 10 | 20 | 30 | 60 | 120 | 180 |
|---|---|---|---|---|---|---|---|
| OD | 0.168 | 0.168 | 0.167 | 0.166 | 0.167 | 0.164 | 0.160 |
| $\lambda_{max}$ (nm) | 518.5 | 519.0 | 518.5 | 518.0 | 519.5 | 520.0 | 520.5 |
| $d$ (nm) | 6.0 ± 0.5 | – | – | – | – | – | 6.8 ± 3.3 |

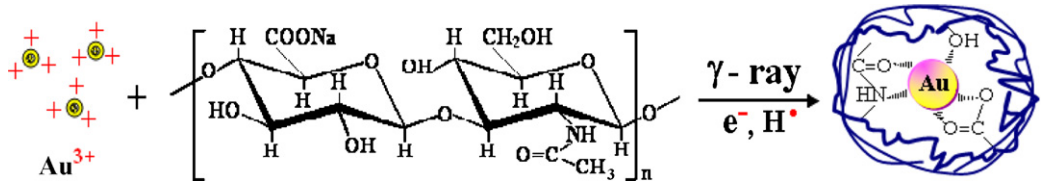


**Fig. 5.** Schematic diagram of HA capped AuNPs prepared γ-irradiation.

almost appropriate. Thus, the concentration of 0.2–0.4% HA is suitable for 0.1 mM $Au^{3+}$ to prepare AuNPs with smallest size (~5 nm). The effect of stabilizers concentration in the synthesis of AuNPs has been studied for PVA (Aryal et al., 2007), citric (Yang et al., 2007), polymer-thiol (Hussain et al., 2005) and protein BSA (Akhavan et al., 2010). Results also indicated that AuNPs size decreased with the increasing of stabilizer concentration. For instance, the smallest AuNPs size was of about 8 nm obtained from the samples of 0.5 mM $Au^{3+}$ containing alginate of 0.5–1% (Anh et al., 2010). HA has good ability to stabilize AuNPs due to the chain of HA consists of —OH, $-COO^-$ groups which have affinity with $Au^{3+}$ (Anh et al., 2010; Huang et al., 2007; Yang et al., 2007). And simultaneously HA is a free radical scavenger via hydrogen abstraction by $^{\bullet}H$ and $^{\bullet}OH$ occurred during radiolysis of water (Kim et al., 2008), therefore the $^{\bullet}OH$ scavenger such as alcohols is not necessary to add into $Au^{3+}$/HA solution as in the case of $Au^{3+}$/PVA (Treguer et al., 1998) and $Au^{3+}$/PVP (Li et al., 2007) to prepare colloidal AuNPs solution by gamma irradiation. Results in Table 2 indicated that the characteristics of AuNPs are also affected by dose rate particularly when dose rate increased from 0.5 to 5 kGy/h, the AuNPs size decreased from 9.5 to 5 nm and $\lambda_{max}$ shifted from 533 to 517 nm. The reason for this phenomenon is due to the competition between the adsorption $Au^{3+}$ onto the resultant gold clusters and the reduction reaction of $Au^{3+} \rightarrow Au^{2+} \rightarrow Au^{1+} \rightarrow Au^0$ to form new clusters (Meyre et al., 2008; Treguer et al., 1998). At high dose rate, the reduction reaction is predominant, therefore there are many new clusters allowing smaller AuNPs to be formed. In contrast, at low dose rate the adsorption of $Au^{3+}$ onto clusters is predominant, therefore AuNPs will be larger. This phenomenon is almost similar as in the cases of chemical reduction (Hussain et al., 2009) and ultrasonic irradiation (Okitsu, Yue, Tanabe, Matsumoto, & Yobiko, 2001). The diameter of AuNPs decreased exponentially with the increase of the hydrazine reductant concentration (Hussain et al., 2009). Okitsu et al. (2001) recognized that the smaller the intensity of the ultrasound, the slower the rate of $Au^{3+}$ reduction and, furthermore, the size of the AuNPs decreased with the increase in the rate of reduction.

The XRD pattern in Fig. 4 indicated that AuNPs have 4 peaks at $2\theta = 38.2^\circ$, $44.6^\circ$, $64.7^\circ$ and $77.7^\circ$ corresponding to the (1 1 1), (2 0 0), (2 2 0) and (3 1 1) facets of gold. The peaks demonstrated that the AuNPs/HA obtained is crystalline gold with face-centered cubic (fcc) structure (Lee, Kamada, Enomoto, & Hojo, 2007; Tseng, Liao, Huang, Tien, & Tsung, 2008).

The stability of colloidal AuNPs solution depends on various factors such as pH, dielectric constant, concentration of ligand around the particles (Akhavan et al., 2010; Yang et al., 2006). Tseng et al. (2008) reported that AuNPs dispersed in ethanol was more stable than in water due to dielectric constant of ethanol (24.3) is lower than that of water (80). Hamaguchi, Kawasaki, and Arakawa (2010) studied the stability of AuNPs/glycine in aqueous solution with different pHs. Results indicated that at pH 6–9, the stability of colloidal AuNPs solution was better compared to that at pH 3. Furthermore, colloidal AuNPs solution was more stable at low temperature compared to that at high ones (Balasubramania, Yang, Yung, Ong, & Ong, 2010). Results in Table 3 indicated that colloidal AuNPs/HA solution was relatively stable during 6 months storage under ambient condition based on the value of OD and $\lambda_{max}$. Furthermore, the size of AuNPs was almost unchanged (Table 3). Therefore, it can be concluded that the colloidal AuNPs/HA solution prepared by gamma irradiation was stable over long periods which could be suitable for applications. In addition, Cui et al. (2008) also explained the stabilization effect of HA for silver nanoparticles induced by hydrolysis inhibition of carboxyl groups due to irradiation. Polysaccharides such as chitosan, HA, alginate, with oxygen-rich structures in hydroxyl and ether groups, which lead to a tightly bind with metals clusters and nanoparticles via electrostatic interactions (Huang et al., 2007). On the basis of these ideas, a schematic diagram of HA capped AuNPs prepared γ-irradiation was proposed as in Fig. 5. And more importantly, spherical AuNPs of different sizes (5–70 nm) are not inherently toxic to human skin cells (Wang et al., 2008). Thus, hyaluronan capped AuNPs hold great promise for several biomedical and cosmetic applications.

## 4. Conclusions

AuNPs with diameter of AuNPs from 4 to 10 nm was synthesized by gamma Co-60 ray irradiation. The AuNPs size can be controlled by varying the concentration of $Au^{3+}$ and HA, and dose rate. Due to the biocompatibility of HA, the stability of AuNPs colloid as well as the unique attributes of AuNPs, colloidal dispersions of AuNPs/HA solutions can potentially be applied in biomedicines and cosmetics.

## Acknowledgement

The authors wish to thank VINAGAMMA Center, VAEI for financial support (CS/10/07-02).

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Please cite this article in press as: Hien, N. Q., et al. Radiation synthesis and characterization of hyaluronan capped gold nanoparticles. *Carbohydrate Polymers* (2012), doi:10.1016/j.carbpol.2012.03.041