# MODELING OF HYALURONIC ACID CONTAINING CURCUMIN-LOADED POLYLACTIC-CO-GLYCOLIC ACID BIOCONJUGATES FOR TARGETED DELIVERY TO CANCER CELLS

by

Abeedin Adulphakdee

Dissertation submitted in partial fulfillment of
the requirement for the
Bachelor of Engineering (Hons)
(Chemical Engineering)

SEPTEMBER 2011

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CERTIFICATION OF APPROVAL

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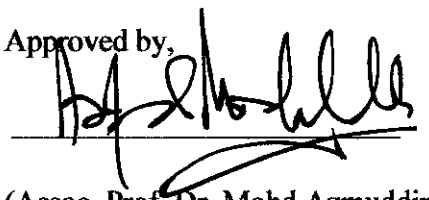
Approved by,



(Assoc. Prof. Dr. Mohd Azmuddin Abdullah)

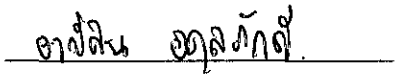
UNIVERSITI TEKNOLOGI PETRONAS

TRONOH, PERAK

SEPTEMBER 2011

CERTIFICATION OF ORIGINALITY

This is to certify that I am responsible for the work submitted in this project, that the original work is my own except as specified in the references and acknowledgements, and that the original work contained herein have not been undertaken or done by unspecified sources or persons.



ABEEDIN ADULPHAKDEE

## ABSTRACT

This project investigates the 3D molecular modeling of hyaluronic acid (HA), curcumin, polylactic-co-glycolic acid (PLGA) and polyethylene glycol bis amine (PEG-bis amine) and all the possible conjugated forms between the compounds as bioconjugates for targeted delivery to cancer cells. Modeling work had been done using Discovery Studios 2.5 from Accelrys Inc. USA. The study focuses on targeted delivery of curcumin to colorectal cancer cells. The generated model will be used in the studies of drug delivery to cancer cells.

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## ABBREVIATION AND NOMENCLATURE

| | |
|---|---|
| 3D | Three Dimensional |
| DCC/DMAP | Dicyclohexylcarbodiimide/(dimethyl)aminopyridine |
| DNA | Deoxyribonucleic Acid |
| DS | Discovery Studio 2.5 |
| ECM | Extracellular Matrix |
| EDAC | 1-ethyl-3-dimethylamino-propyl carbodiimide |
| FAO | Food and Agriculture Organization |
| FDA | Food and Drug Administration |
| GRAS | Generally Recognized As Safe |
| HA | Hyaluronic Acid/Hyaluronan |
| KDa | Kilo Dalton |
| NHS | N-hydroxyl succinamide |
| PEG | Poly(ethylene glycol) |
| PEO | Polyethylene oxide |
| PLGA | Polylactic-co-glycolic Acid |
| USA | United States of America |
| WHO | World Health Organization |

# CHAPTER 1

# INTRODUCTION

## 1.1 BACKGROUND OF STUDY

Cancer is one of the major diseases that cause 13% of all human deaths in 2007 (Gul-e-Saba et al., 2010). Cancer is a result of rapid growth of normal cells, which can harm human body (Pal & Nayak, 2010). Drugs such as cisplatin, doxorubicin have been developed for chemotherapy but most have side effects towards particular tissues or cells which are not the cancer cells or tumors. Curcumin, a natural polyphenolic compound, has shown promising chemopreventive and chemotherapeutic activities in cancer (Yallapu, et al., 2010) but couldn't achieve its optimum therapeutic outcome in the past clinical trials, largely due to its low solubility and poor bioavailability (Basnet & Basnet, 2011). Targeted drug delivery to cancer cells is of utmost important to selectively target diseased tissue while leaving healthy tissue untouched (Sutton et al., 2007). Hyaluronan (HA) is a major component of extracellular matrix (ECM) and main ligand of CD44 receptor cells (Gul-e-Saba, et al., 2010). HA-CD44 binding will play major role in development of targeted control drug delivery to cancer cells. One of the advanced tools that could help drug developers is the computational modeling for designing, testing and simulating the molecular structure of the drugs. The need for drug modeling assists better understanding of the interactions of the drug with microenvironment in the body at the disease sites. In this study, hyaluronic acid containing curcumin-loaded polylactic-co-glycolic acid bioconjugates as a potential anticancer drug will be modeled and discussed for targeted delivery.

## 1.2 PROBLEM STATEMENT

When any new type of drugs is to be used in human body, the process of design and development of drug will involve many trial and error experiments based on previous research. This method is time consuming, costly and fraught with uncertainties. Computational modeling to design the molecular structure to see the

behavior of a drug reacting once injected or consumed in human cells, is a rational approach in drug design and modification which is economical and saves time with limited risk of failures as far as screening for lead compounds is concerned and it is also reduce the limitations of potent anticancer agents.

## 1.3 OBJECTIVES

1.3.1 To model the molecular structure of Hyaluronic Acid (HA) containing curcumin-loaded PLGA bioconjugates by using Discovery Studio 2.5.

1.3.2 To demonstrate the application of controlled, targeted drug delivery system based on 3D molecular model developed.

## 1.4 SCOPE OF STUDY

In this project, the 3D molecular structure of Hyaluronic Acid (HA) containing curcumin-loaded PLGA bioconjugates as potential anticancer drug for controlled, targeted delivery to cancer cell will be modeled using Discovery Studio 2.5 (Accelrys Inc., USA).

## 1.5 FEASIBILITY STUDY

Discovery Studio 2.5 (Accelrys Inc., USA) is available in UTP computer lab for students to use at all time and together with the project itself involves the compounds that have been known its molecular structure, therefore computational modeling of them is possible to generate and complete within project timeframe. Drug design using computational modeling is one of the advanced tools yet that could help drug developers and could play a key role in the pharmaceutical industry (Kumar et al., 2006).

# CHAPTER 2

# LITERATURE REVIEW

## 2.1 COLORECTAL CANCER

Colorectal cancer is one of the most common tumors and a major cause of cancer death worldwide (Fiore et al., 2007). It is a disease in which malignant (cancer) cells form in the inner lining of the colon or rectum (Rex & Liangpunsakul, 2007). Fig. 2.1 shows developmental phases of colorectal cancer. The risk is increased with low fiber intake, high fat diet, and low calcium/micronutrient intake (Johnson & Mukhtar, 2007). Epidemiologic studies have revealed a number of risk factors for colorectal cancer including age, family history of colon cancer or inflammatory bowel disease, smoking, alcohol consumption, obesity, and diet (Byrne, 2008). Regular colorectal cancer screening which is the process of looking for cancer or symptoms or pre-cancer in people who show no symptoms is one of the ways for preventing colorectal cancer.

## 2.2 CURCUMIN AS ANTI-CANCER COMPOUND

Curcumin [(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a natural extract from *Curcuma longa* herb or normally known as turmeric (Fig. 2.2) commonly used in India and Eastern Asia. It is an orange-yellow, crystalline powder with melting point of 183°C, molecular formula of $C_{21}H_{20}O_6$ and molecular weight of 368.37 g/mol (Lin & Lin, 2008). There are three major curcuminoids in turmeric, namely curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin (Fig. 2.3) (Basnet & Basnet, 2011). Curcumin has shown anti-inflammatory and anti-cancer properties (Sharma et al., 2005), highly hydrophobic agent (Anand et al., 2007), prevent the transformation, proliferation, and invasion of tumor cells (Shishodia et al., 2007). Turmeric is Generally Recognized As Safe (GRAS) by the US FDA, and curcumin has been granted an acceptable daily intake level of 0.1-3 mg/kg-BW by the Joint FAO/WHO Expert Committee o Food Additives, 1996 (Institute, 1996). Based on the safety and toxicity profile in several clinical studies shows that the targeted doses for curcumin can be

recommended in between 4,000-8,000 mg to obtain the maximum therapeutic effects (Basnet & Basnet, 2011). The only factor that limits the use of free curcumin for cancer therapy is its poor solubility in water, which in turn limits its systemic bioavailability when administered orally (Dinarvand, et al., 2011). Utilization of nanotechnology has proven to be very effective in solving this problem (Bharali, et al., 2011). Some studies demonstrated that curcumin encapsulation in PLGA nanoparticles produced a very stable nanoformulation and also enhanced cellular drug uptake and retention, as well as sustained release of curcumin (Dinarvand, et al., 2011).

Anti-cancer agent refers to a compound capable of negatively affecting cancer in a subject, for example, by killing, inducing apoptosis, reducing the growth rate of one or more cancer cells, reducing the incidence or number of metastases, reducing a tumor's size, inhibiting a tumor's growth, reducing the blood supply to a tumor or one or more cancer cells, promoting an immune response against one or more cancer cells or a tumor, preventing or inhibiting the progression of a cancer, or increasing the lifespan of a subject with a cancer (Klostergaard, et al., 2010).

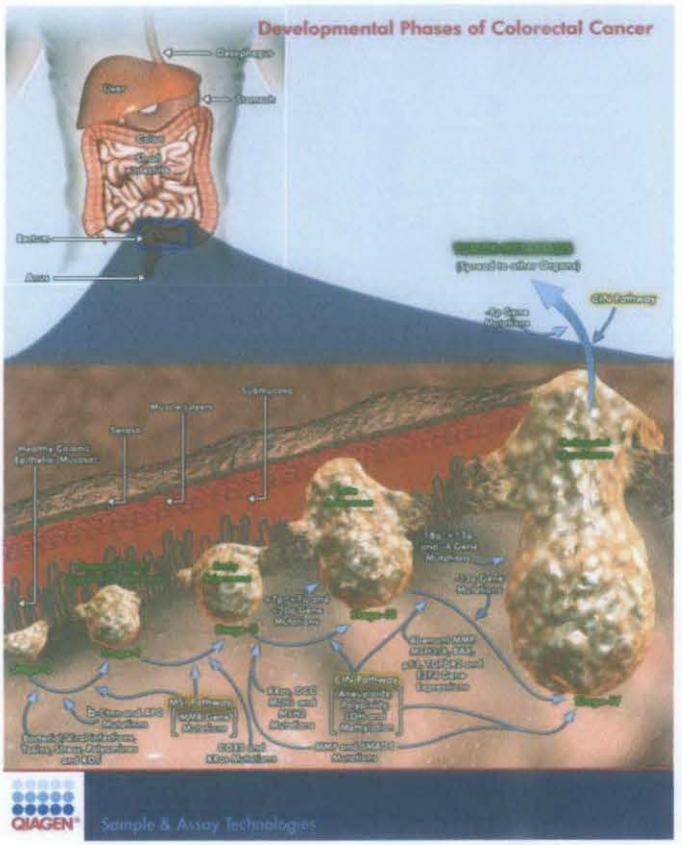



**Figure 2.1** Developmental phases of colorectal cancer (QIAGEN, 2011).

**Figure 2.2** *Curcuma longa* (Duvoix et al., 2005).

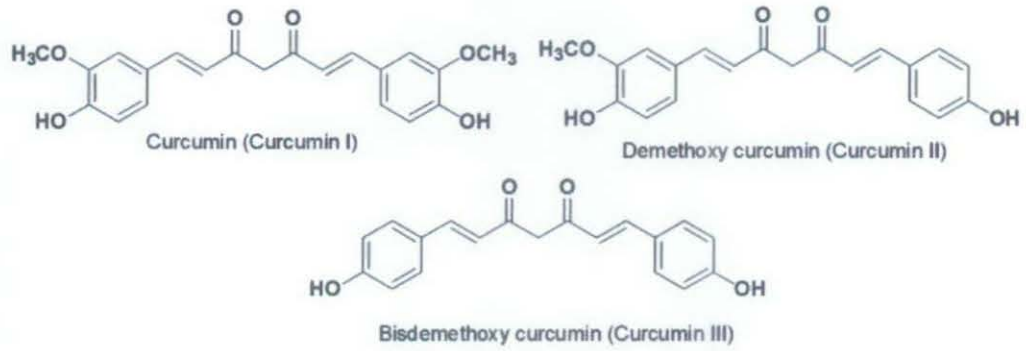



**Figure 2.3** Fractions of turmeric known as curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) (Basnet & Basnet, 2011).

## 2.3 PLGA AS A DRUG-DELIVERY AGENT

Drug-delivery agent or drug-carrier nanoparticles are defined as submicroscopic colloidal systems that may act as drug vehicles, either as nanospheres (matrix system in which the drug is dispersed) or nanocapsules (reservoirs in which the drug is confined in a hydrophobic or hydrophilic core surrounded by a single polymeric membrane) (Jeanneret, 2008). Figure 2.4 shows two major loading models—Liposome and Micelle—for effectively loading water soluble and water insoluble natural chemopreventive agents, respectively (Muqbil, et al., 2011). Figure 2.6 shows how nanoparticles do interact with immune system; a) The effect of nanoparticle size, charge, hydrophobicity and targeting or immunotoxicity and b) Some nanoparticles (shown schematically) can trigger certain immune responses as listed there, a characterization scheme for nanoparticles intended for biomedical

applications must include testing for these responses, such tests may exclude a potentially harmful drug candidate from the development pipeline and inform future studies relevant to the immunomodulatory properties of nanoparticles (Dobrovolskaia & McNeil, 2007).

Polylactic-co-glycolic acid (PLGA) has been developed to be one of the carrier molecules for targeted delivery of the anticancer drug (Yadav et al., 2010). It is one of the most studied diblock copolymer biomaterials for drug encapsulation and is present in several commercially available pharmaceutical products (Mansour et al., 2010). Schematic representation of PLGA molecular structure is shown in Fig. 2.5. In a study to test for the quality of the curcumin-loaded PLGA nanospheres as potential anticancer drug, PLGA grade of Poly(D,L-lactide-co-glycolide) 50:50 has been used, having inherent viscosity 1.13 dl/g and MW 50000 (Mukerjee & Vishwanatha, 2009). A unified atomic mass unit of PLGA of 40-75KDa has been reported (Yadav et al., 2010). Studies have shown the possibility of having PLGA nano-formulation of curcumin as anticancer agent (Basnet & Basnet, 2011).

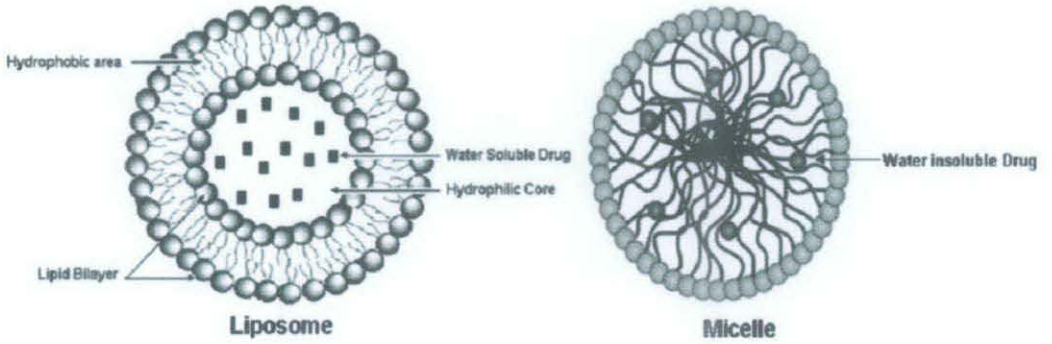
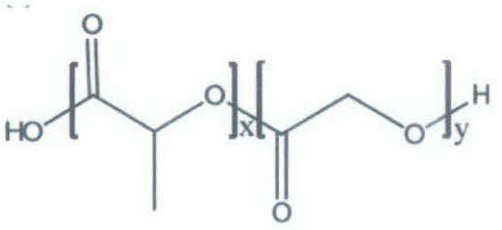



**Figure 2.4** Two major loading models - Liposome and Micelle (Muqbil, et al., 2011).




x - Number of units of Lactic Acid
y - Number of units of Glycolic Acid

Poly(lactide-co-glycolide)

**Figure 2.5** Structure of PLGA (Mansour et al., 2010).

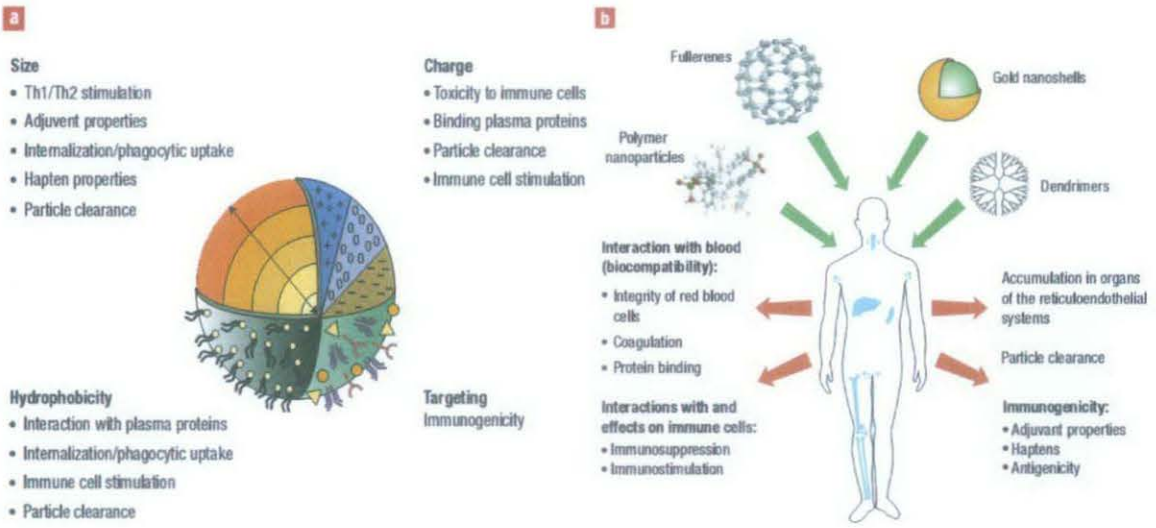



**Figure 2.6** Nanoparticle properties determine their interaction with the immune system (Dobrovolskaia & McNeil, 2007).

## 2.4 HYALURONIC ACID CONTAINING BIOCONJUGATES

Hyaluronic acid (HA) is a repeating disaccharide units composed of D-glucuronic acid and N-acetyl-D-glucosamine and can be considered as the main component of the extracellular matrix of the cell membrane. It plays an important role in the mechanical support of the cell of many tissues, such as skin, tendons, muscles and cartilage (Mohapatra et al., 2008). HA can interact with CD44, its receptor at the cell surface which can lead to the site-specific delivery or targeted delivery of drug (Yadav et al., 2010), which later on degraded inside the cells (Luo et al., 2009). Nanoparticles composed of HA, can be encapsulated and formulated with various peptide, DNA and drugs (curcumin) for cell specific drug delivery. The nanoparticles are natural polymers, biocompatibles and biodegradables such as PLGA. PLGA allows controlled release of the active molecules such as anti-cancer drug and their orientation towards the target tissues (Mohapatra et al., 2008). Targeting anti-cancer agents to tumor cells and tumor metastases can be accomplished by receptor-mediated uptake of bioconjugates such as anti-cancer agents conjugated to HA, followed by the release of free drugs through the degradation of HA in cell compartments (Luo et al., 2009). Fig. 2.7 shows the structure of HA-curcumin conjugates and Fig. 2.8 shows CD-44 receptor on cell membrane.

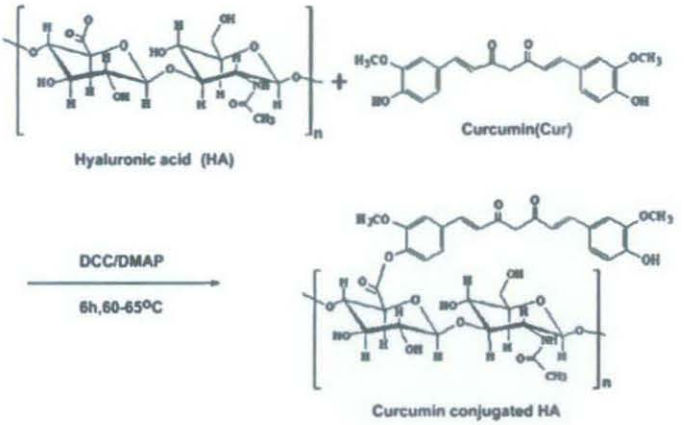



**Figure 2.7** Structure of hyaluronic acid (HA)-curcumin conjugate.

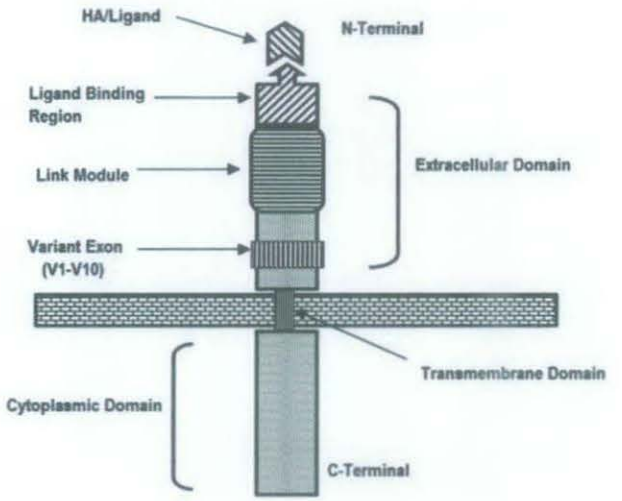



**Figure 2.8** Schematic representation of CD44 molecule (Gul-e-Saba et al., 2010).

## 2.5 POLYETHYLENE GLYCOL BIS AMINE AS CROSSLINKING AGENT

Poly(ethylene glycol) (PEG), also known as polyethylene oxide (PEO), is a largely exploited polymer for advanced physical and chemical stability of drugs and its "stealth" properties (Mansour, et al., 2010). When PEG is properly linked to a polypeptide, it modifies many of its features while the main biological functions, such as enzymatic activity or receptor recognition maybe maintained (Veronese, 2001). Addition of PEG or PEG-containing copolymers to the nanoparticle surface results in an increase of half-life in the blood circulation by several orders of magnitude (Dinarvand, et al., 2011).

Polyethylene glycol-bis amine (PEG-bis amine) is used as an intermediate in the synthesis of crosslinking agents for polymerization and surface modification of

hemoglobin or other proteins for pharmacological use (Hai, et al., 2003). A two step mechanism for the preparation of PEG-bis amine comprising a first step of reacting the terminal hydroxyl groups of PEG with a halogen substituted aromatic sulfonyl halide in a solvent to form a disubstituted sulfonyl activated polyethylene glycol intermediate and in a second step the intermediate is directly aminated with ammonia to give PEG-bis amine (Fig. 2.9) (Hai, et al., 2003).

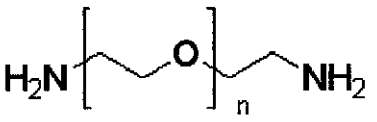



**Figure 2.9** Structure of polyethylene glycol bis amine (Sigma-Aldrich, 2011).

# CHAPTER 3

# METHODOLOGY

## 3.1 RESEARCH METHODOLOGY

The study has been divided into 2 stages for molecular modeling as follows:

### 3.1.1 Uni-molecular Modeling

All of the following main molecules will be modeled separately using Discovery Studios 2.5 (Accelrys Inc., USA):

3.1.1.1 An anticancer agent (curcumin)

3.1.1.2 A carrier molecule (PLGA)

3.1.1.3 Hyaluronic acid (HA)

3.1.1.4 Spacer Arm (PEG-bis amine)

### 3.1.2 Multi-molecular Modeling

The following conjugates will be modeled using Discovery Studios 2.5 (Accelrys Inc., USA):

3.1.2.1 PLGA-HA

3.1.2.2 Curcumin-HA

3.1.2.3 PLGA-PEG-HA

3.1.2.4 Curcumin-PLGA-PEG-HA

## 3.2 PROJECT ACTIVITIES

The following shows the instruction of molecular modeling for each of the molecules according to previous session which will be described in details using Discovery Studios 2.5 (Accelrys Inc., USA).

The molecular modeling has been divided into 2 stages:

### 3.2.1 Uni-molecular Modeling

All of the following main molecules had been modeled separately using Discovery Studios 2.5 (Accelrys Inc., USA) together with their instruction step-by-step for each of the modeled molecule:

#### 3.2.1.1 An anticancer agent (curcumin)

The study chose curcumin I to be modeled (refer to Fig.2.3) and the following shows its modeling instruction:

1) Discovery Studios 2.5 was opened by using its software icon on the desktop.
2) Molecule window was opened from menu File | New | Molecule Window.
3) The Ring Tool was selected from Sketching Toolbar.
4) The 2 rings with 6 carbon atoms each was created by clicking in molecular window for 2 times on left and right of the screen.
5) The Draw Tool was selected from Sketching Toolbar.
6) For the 1st ring on the left of the screen, the lower left atom was clicked then the mouse was dragged to lower left and single click was pressed after that to make a new atom and by clicking on the new atom, it released the cursor. Then, the upper left atom of the ring was clicked and the mouse was dragged to upper left side with single clicking to make 1 atom and one more clicking to the left to add another 1 atom. The cursor was released by clicking on the new atom just added. Since both of the 1st atoms added and attached to the ring is oxygen atom so that changing of the atom was needed. This was successfully done by choosing Select Tool from View Toolbar then right mouse button was clicked to show the pull-down menu then option Element > O was selected for both of the atoms.

Note: Releasing the cursor can be done also by dragging the mouse out of document window.

7) For the 2nd ring on the right of the screen, the lower right atom was clicked then the mouse was dragged to lower right and single click was

pressed after that to make a new atom and by clicking on the new atom, it released the cursor. Then, the upper right atom of the ring was clicked and the mouse was dragged to upper right side with single clicking to make 1 atom and one more clicking to the right to add another 1 atom. The cursor was released by clicking on the new atom just added. Since both of the 1st atoms added and attached to the ring is oxygen atom so that changing of the atom was needed. This was successfully done by the same method as previous step 6).

8) The Chain Tool was selected from Sketching Toolbar.
9) The upper right atom of the 1st ring was clicked and the new atom appeared then it was clicked while holding the left mouse button down. The mouse was dragged across to make the side chain of totally 9 atoms; it was the number appearing to show the number of atom in the chain while dragging the mouse.
10) The whole 2nd ring was selected using the Select Tool then the mouse was clicked and dragged to draw a region covering the whole 2nd ring and once it had been done, the selected ring will be highlighted with yellow color. Next, the whole 2nd ring was moved and placed nearby another side of the chain drew in previous step and by selecting Draw Tool, the atom of the chain at the end was clicked and then the link between this atom and the upper left corner atom of the 2nd ring was created by clicking on that atom on the ring. The cursor was released with the same method as previously mentioned.
11) The single atom was added on the side chain at atom number 3 and 5 using Draw Tool. These atoms were changed into oxygen atoms by the same method as mentioned before in step 6).
12) The Select Tool was chose and all the single bonds that need to be converted to double bond had been selected. Then by pressing number 2 on the keyboard or by clicking on Double Bond in Chemistry Toolbar, it automatically changed into double bond.
13) The Show Hydrogen was selected from Chemistry Toolbar. This made the hydrogen appeared on each of the atoms that available on the modeled structure.

14) Optimizing the geometry of the structure was needed since the drawing model was not yet precise and accurate in terms of standard bond length, bond angles and Van der Waals radii for close contact. The Clean Geometry was chose from Chemistry Toolbar; this can be clicked repeatedly until there's no longer changing in the model.
15) Annotation to the model was needed by choosing Annotation Tool in Sketching Toolbar and left clicking on the place where to put the annotation then the word 'Curcumin' was typed in the dialog box and finally the 'OK' button was pressed. The completed model of curcumin has illustrated in the next chapter (Fig. 4.1).

#### 3.2.1.2 A carrier molecule (PLGA)

The current study choose to model only some portion of PLGA molecular structure as shown in previous chapter (refer to Fig. 2.5). PLGA modeling instruction has been illustrated as follow:

1) The Chain Tool was chosen from Sketching Toolbar to draw the chain total of 7 atoms.
2) The single atom was added on the side chain at atom number 2, 3 and 5 using Draw Tool. The atom added at number 2 and 5 were changed into oxygen atom together with atoms on the chain number 1, 4 and 7 by the same method used in previous curcumin model.
3) The Select Tool was chose and all the single bonds that need to be converted to double bond had been selected. Then by pressing number 2 on the keyboard or by clicking on Double Bond in Chemistry Toolbar, it automatically changed into double bond.
4) The Show Hydrogen was selected from Chemistry Toolbar. This made the hydrogen appeared on each of the atoms that available on the modeled structure.
5) Optimizing the geometry of the structure was needed using the same method mentioned in previous model.
6) The annotation of PLGA was added using the same method explained in curcumin model. The complete model structure of PLGA has been illustrated in the next chapter (Fig. 4.2).

### 3.2.1.3 Hyaluronic acid (HA)

The modeling of HA refers to the structure in Fig. 2.7 and the following is its modeling instruction:

1) The Ring Tool was selected from Sketching Toolbar in order to draw the two rings with the size of 6 atoms each.
2) The Draw Tool was selected to add all the chain to both 2 rings.
3) Some of the atoms have changed into oxygen atom and nitrogen atom by the same method used for curcumin.
4) All the double bond had been located using Double Bond button in Chemistry Toolbar.
5) The 2 rings had been connected using Draw Tool to draw the bond between these two structures at the atom according to Fig. 2.7.
6) The Show Hydrogen was selected from Chemistry Toolbar. This made the hydrogen appeared on each of the atoms that available on the modeled structure.
7) The modeling of HA had been optimized by clicking on Clean Geometry button in Chemistry Toolbar until there's no changing in the model.
8) The annotation of HA was added using the same method explained in curcumin model. The complete model structure of HA has been illustrated in the next chapter (Fig. 4.3).

### 3.2.1.4 Spacer arm (PEG-bis amine)

The modeling of PEG-bis amine refers to the structure in Fig. 2.9 and the following is its modeling instruction:

1) The Chain Tool was chosen from Sketching Toolbar to draw the chain total of 7 atoms.
2) The Select Tool was chosen from View Toolbar then right mouse button was clicked on atom number 1 to show the pull-down menu then option Element > N was selected for nitrogen. The same procedure was done for atom number 7 as well but it was difference for atom number 4 which has been changed into oxygen atom.

3) The Show Hydrogen was selected from Chemistry Toolbar. This made the hydrogen appeared on each of the atoms that available on the modeled structure.
4) The modeling of PEG had been optimized by clicking on Clean Geometry button in Chemistry Toolbar until there's no changing in the model.
5) The annotation of PEG was added using the same method explained in curcumin model. The complete model structure of PEG has been illustrated in the next chapter (Fig. 4.4).

### 3.2.2 Multi-molecular Modeling

The following conjugates have been modeled using Discovery Studios 2.5 (Accelrys Inc., USA):

#### 3.2.2.1 PLGA-HA

The structure of these conjugated molecules has shown in Fig. 3.1.

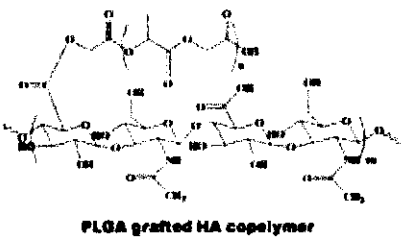



**Figure 3.1** PLGA grafted HA copolymer (Lee, Ahn, & Park, 2009).

The modeling structure of these conjugated molecule had been completed for only one HA molecule which is smaller than structure shown in Fig 3.1 which contains two HA molecules. The modeling instructions of these conjugated structure is simply take the uni-molecule that we have in previous modeling and make a link bond between these two molecules as illustrated in Fig. 3.1. The completed modeling of this conjugated structure will be shown in the next chapter (Fig. 4.5).

#### 3.2.2.2 Curcumin-HA

This modeling structure refers to Fig. 2.7. The modeling instruction of curcumin conjugated HA had been done by taking those two uni-structures and then make a

link bond between them as illustrated in Fig. 2.7. Clean Geometry tool had used to optimize the conjugated molecule and the completed modeling structure will be shown in the next chapter (Fig. 4.6).

### 3.2.2.3 PLGA-PEG-HA

The structure of these conjugated molecules has shown in Fig. 3.2.

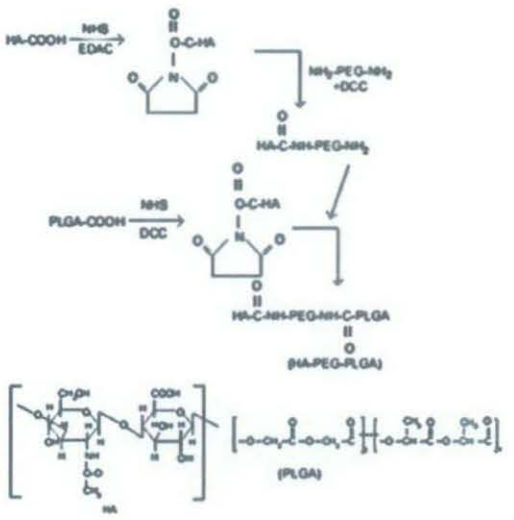


**Figure 3.2** Schematic representation of synthesis of HA-PEG-PLGA polymer (Yadav, et al., 2010).

The modeling instruction of HA-PEG-PLGA polymer had been done by taking those three uni-structures and then makes a link bond between them as illustrated in Fig. 3.2. Clean Geometry tool had used to optimize the conjugated molecule and the completed modeling structure will be shown in the next chapter (Fig. 4.7).

### 3.2.2.4 Curcumin-PLGA-PEG-HA

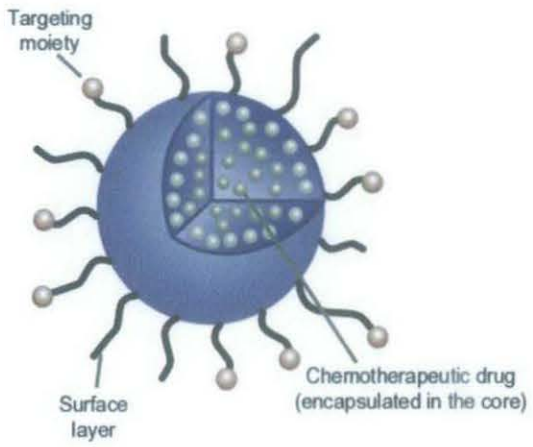



**Figure 3.3** Targeted PLGA nanoparticle carrying the chemotherapeutic drug (Dinarvand, et al., 2011)

This modeling structure refers to Fig. 2.4 and Fig. 3.3. The modeling instruction of curcumin-PLGA-PEG-HA had been done by taking one molecule of curcumin and those PLGA-PEG-HA polymers in previous result and then makes a spherical shape over curcumin by selecting the curcumin molecule and the option under Tools Tab which is 'Define and Edit Binding Site' category followed by selecting 'Create Sphere'. The spherical shape appeared covering curcumin inside. Then covering the sphere by selecting PLGA-PEG-HA polymer and copying it and pasting it at the surface of sphere but need to make sure that only PLGA molecule would touch the sphere as inner with the outer of HA molecule. The completed modeling structure will be shown in the next chapter (Fig. 4.8).

## 3.3 TOOLS REQUIREMENT

Tools requirement as for development of the molecular modeling are shown below.

### 3.3.1 Hardware

- Computer

### 3.3.2 Software

- Discovery Studios 2.5 (Accelrys Inc., USA)

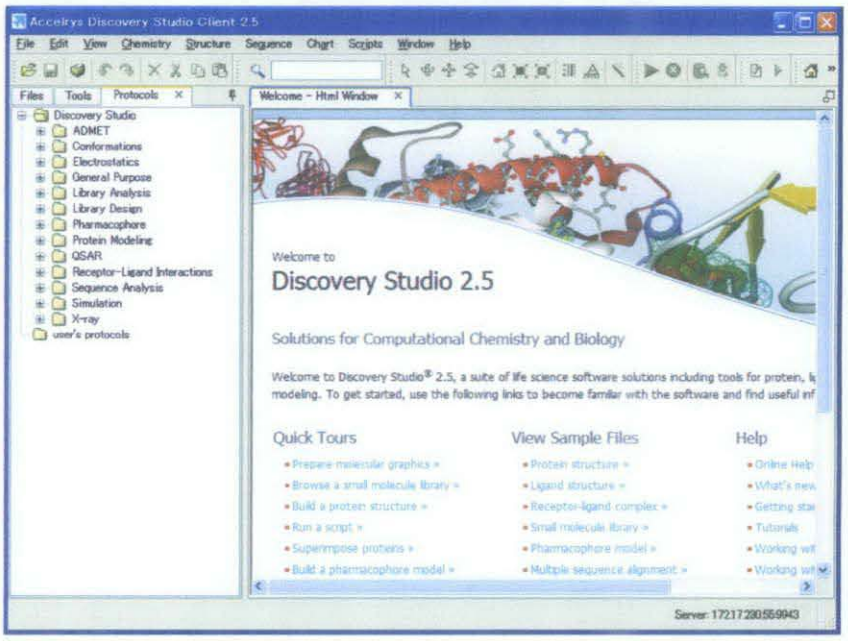



**Figure 3.4** User interface of Discovery Studios 2.5 (Accelrys Inc., USA).

### 3.4 PROJECT TIMELINE

| Activities in FYP I | W1 15/5 | W2 22/5 | W3 29/5 | W4 5/6 | W5 12/6 | W6 19/6 | W7 26/6 | W8 3/7 | W9 17/7 | W 10 24/7 | W 11 31/7 | W 12 7/8 | W 13 14/8 | W 14 21/8 | W 15 28/8 | W 16 4/9 | W 17 11/9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Selection of project topic | | | | | | | | | | | | | | | Study week | Final Examination Week | Final Examination Week |
| Preliminary research work | | | | | | | | | | | | | | | | | |
| a) Literature review: Modeling of HA containing curcumin-loaded PLGA nanosphere bioconjugates for targeted delivery to cancer cells | | | | | | | | | | | | | | | | | |
| Submission of extended proposal | | | | | | | | | | | | | | | | | |
| Proposal defense | | | | | | | | | | | | | | | | | |
| Project work continues | | | | | | | | | | | | | | | | | |
| b) Execute the uni-molecular modeling | | | | | | | | | | | | | | | | | |
| c) Execute the multi-molecular modeling | | | | | | | | | | | | | | | | | |
| Submission of Interim Draft Report | | | | | | | | | | | | | | | | | |
| Submission of Interim Report | | | | | | | | | | | | | | | | | |

**Table 3.1**: Final Year Project I (May 2011) proposed activities timeline.

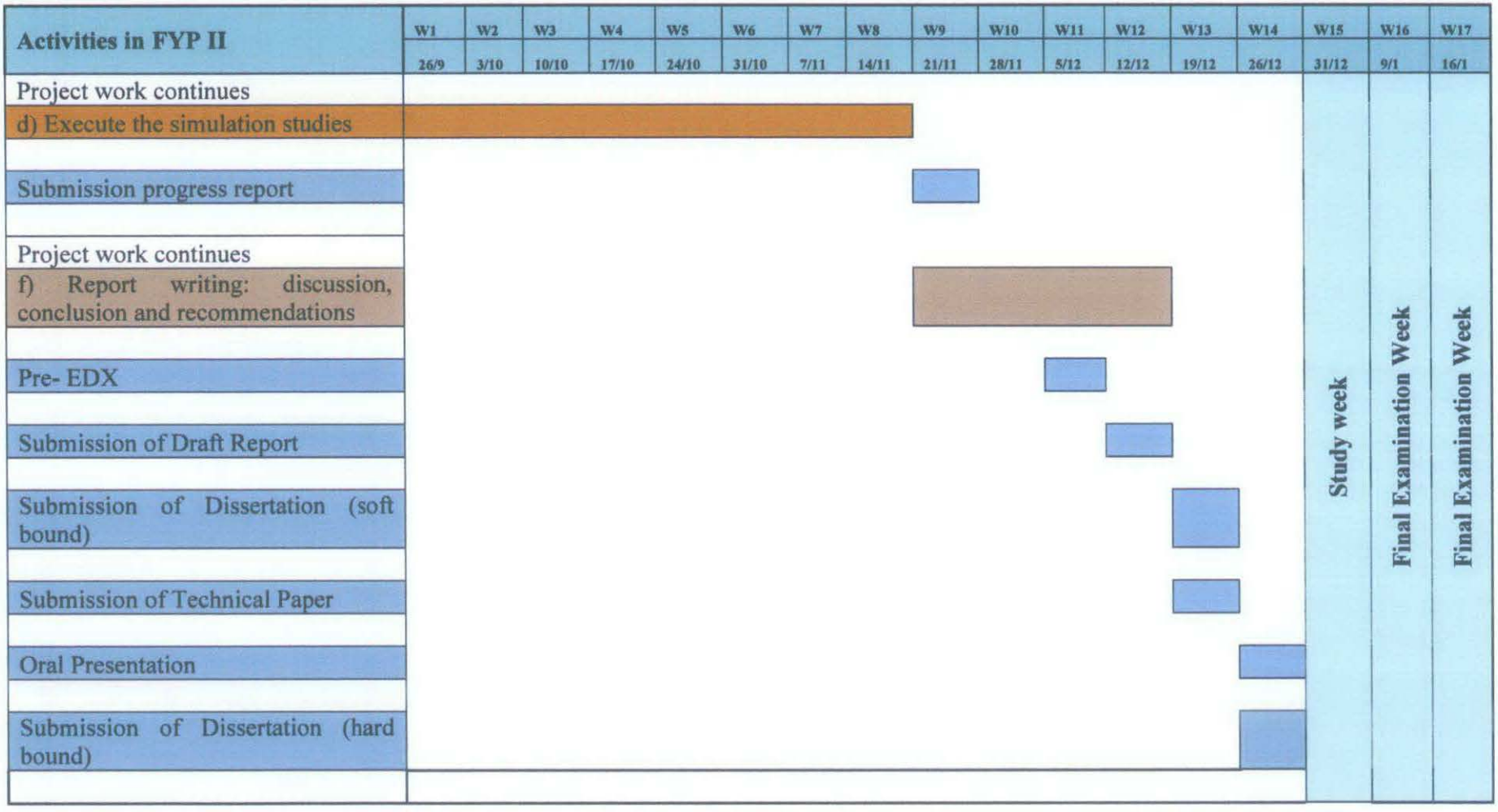



**Table 3.2**: Final Year Project II (September 2011) proposed activities timeline.

# CHAPTER 4

# RESULTS AND DISCUSSION

## 4.1 MOLECULAR MODELING

The following content illustrate the molecular modeling developed by using Discovery Studios 2.5 (Accelrys Inc., USA).

### 4.1.1 Uni-molecular Modeling

#### 4.1.1.1 An anticancer agent (curcumin)

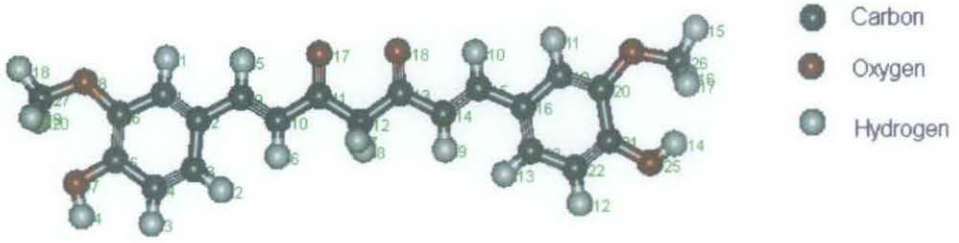



**Figure 4.1** Molecular modeling of curcumin (with atom number).

The modeling of curcumin has been shown in Fig. 4.1. The red atom indicates oxygen atom, the dark grey atom indicates carbon atom and the light grey atom indicates hydrogen atom. The bond length between each atom has also been calculated using function in the software together with its basic properties as shown in Table 4.1 and 4.2, respectively.

**Table 4.1** Bond and bond length of curcumin.

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 1 | C1 - C2 | Curcumin | 2 | Double | 1.32923 |
| 2 | C2 - C3 | Curcumin | 1 | Single | 1.46169 |
| 3 | C3 - C4 | Curcumin | 2 | Double | 1.32782 |
| 4 | C4 - C5 | Curcumin | 1 | Single | 1.4662 |
| 5 | C5 - C6 | Curcumin | 2 | Double | 1.35625 |
| 6 | C6 - C1 | Curcumin | 1 | Single | 1.47053 |
| 7 | C5 - O7 | Curcumin | 1 | Single | 1.39542 |
| 8 | C6 - O8 | Curcumin | 1 | Single | 1.45342 |

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 9 | C9 - C10 | Curcumin | 2 | Double | 1.33412 |
| 10 | C10 - C11 | Curcumin | 1 | Single | 1.45658 |
| 11 | C11 - C12 | Curcumin | 1 | Single | 1.50271 |
| 12 | C12 - C13 | Curcumin | 1 | Single | 1.5026 |
| 13 | C13 - C14 | Curcumin | 1 | Single | 1.45672 |
| 14 | C14 - C15 | Curcumin | 2 | Double | 1.33515 |
| 15 | C15 - C16 | Curcumin | 1 | Single | 1.48623 |
| 16 | C2 - C9 | Curcumin | 1 | Single | 1.47967 |
| 17 | C11 - O17 | Curcumin | 2 | Double | 1.23582 |
| 18 | C13 - O18 | Curcumin | 2 | Double | 1.23587 |
| 19 | C19 - C20 | Curcumin | 2 | Double | 1.33295 |
| 20 | C20 - C21 | Curcumin | 1 | Single | 1.55536 |
| 21 | C21 - C22 | Curcumin | 2 | Double | 1.33191 |
| 22 | C22 - C23 | Curcumin | 1 | Single | 1.45423 |
| 23 | C16 - C19 | Curcumin | 1 | Single | 1.45691 |
| 24 | C16 - C23 | Curcumin | 2 | Double | 1.33304 |
| 25 | C20 - O24 | Curcumin | 1 | Single | 1.45352 |
| 26 | C21 - O25 | Curcumin | 1 | Single | 1.42368 |
| 27 | O24 - C26 | Curcumin | 1 | Single | 1.41594 |
| 28 | O8 - C27 | Curcumin | 1 | Single | 1.43531 |
| 29 | C1 - H1 | Curcumin | 1 | Single | 1.06021 |
| 30 | C3 - H2 | Curcumin | 1 | Single | 1.05826 |
| 31 | C4 - H3 | Curcumin | 1 | Single | 1.06032 |
| 32 | O7 - H4 | Curcumin | 1 | Single | 0.988694 |
| 33 | C9 - H5 | Curcumin | 1 | Single | 1.06027 |
| 34 | C10 - H6 | Curcumin | 1 | Single | 1.05684 |
| 35 | C12 - H7 | Curcumin | 1 | Single | 1.09892 |
| 36 | C12 - H8 | Curcumin | 1 | Single | 1.0992 |
| 37 | C14 - H9 | Curcumin | 1 | Single | 1.05716 |
| 38 | C15 - H10 | Curcumin | 1 | Single | 1.06027 |
| 39 | C19 - H11 | Curcumin | 1 | Single | 1.0602 |
| 40 | C22 - H12 | Curcumin | 1 | Single | 1.0603 |
| 41 | C23 - H13 | Curcumin | 1 | Single | 1.05659 |
| 42 | O25 - H14 | Curcumin | 1 | Single | 0.941025 |
| 43 | C26 - H15 | Curcumin | 1 | Single | 1.0993 |
| 44 | C26 - H16 | Curcumin | 1 | Single | 1.09957 |
| 45 | C26 - H17 | Curcumin | 1 | Single | 1.09965 |
| 46 | C27 - H18 | Curcumin | 1 | Single | 1.09929 |
| 47 | C27 - H19 | Curcumin | 1 | Single | 1.09989 |
| 48 | C27 - H20 | Curcumin | 1 | Single | 1.09983 |

The curcumin structure shows the total measurement of 48 bond length with average bond length of 1.266556 Å.

**Table 4.2** Basic properties of curcumin.

| Properties | Curcumin |
|---|---|
| Number of Atoms | 47 |
| Molecular Formula | C21 H20 O6 |
| Molecular Composition | C: 0.685, H: 0.055, O: 0.261 |
| Molecular Weight | 368.391 |
| Exact Molecular Weight | 368.126 |
| Net Formal Charge | 0 |

According to Table 4.2, the exact molecular weight of curcumin is slightly lower than its molecular weight because exact molecular weight is the mass of a molecule calculated with only the most abundant isotopes present which are usually the lightest isotopes (University of Colorado, 2011). Since curcumin is the neutral molecule therefore the net formal charge is equal to zero.

#### 4.1.1.2 A carrier molecule (PLGA)

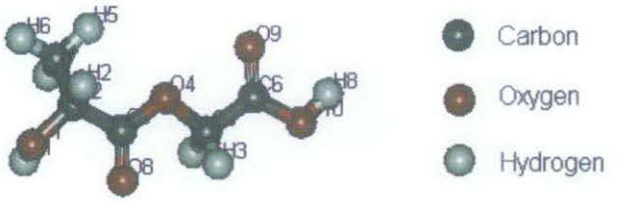



**Figure 4.2** Molecular modeling of PLGA (with atom number).

The molecular modeling of PLGA has been demonstrated in Fig. 4.2. The color of atoms indicates the same element as in previous modeling. The bond length of PLGA and its basic properties has also been evaluated as appeared in Table 4.3 and 4.4, respectively.

**Table 4.3** Bond and bond length of PLGA.

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 1 | O1 - C2 | PLGA | 1 | Single | 1.42944 |
| 2 | C2 - C3 | PLGA | 1 | Single | 1.50007 |
| 3 | C3 - O4 | PLGA | 1 | Single | 1.40999 |
| 4 | O4 - C5 | PLGA | 1 | Single | 1.44509 |
| 5 | C5 - C6 | PLGA | 1 | Single | 1.5004 |
| 6 | C3 - O7 | PLGA | 2 | Double | 1.23722 |
| 7 | C5 - C8 | PLGA | 1 | Single | 1.55092 |
| 8 | C6 - O9 | PLGA | 2 | Double | 1.23615 |

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 9 | O1 - H1 | PLGA | 1 | Single | 1.05003 |
| 10 | C2 - H2 | PLGA | 1 | Single | 1.09 |
| 11 | C2 - H3 | PLGA | 1 | Single | 1.09 |
| 12 | C5 - H4 | PLGA | 1 | Single | 1.09 |
| 13 | C6 - H5 | PLGA | 1 | Single | 1.09 |
| 14 | C8 - H6 | PLGA | 1 | Single | 1.08996 |
| 15 | C8 - H7 | PLGA | 1 | Single | 1.09003 |
| 16 | C8 - H8 | PLGA | 1 | Single | 1.09003 |

The PLGA structure shows the total measurement of 16 bond length with average bond length of 1.249333 Å.

**Table 4.4** Basic properties of PLGA.

| Properties | PLGA |
|---|---|
| Number of Atoms | 18 |
| Molecular Formula | C5 H8 O5 |
| Molecular Composition | C: 0.405, H: 0.054, O: 0.540 |
| Molecular Weight | 148.119 |
| Exact Molecular Weight | 148.037 |
| Net Formal Charge | 0 |

#### 4.1.1.3 Hyaluronic acid (HA)

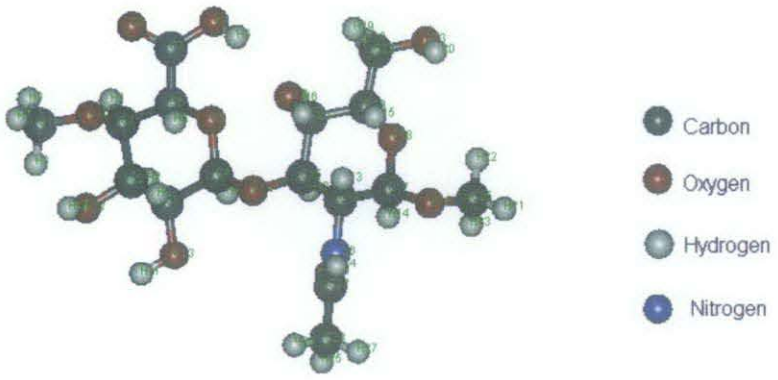



**Figure 4.3** Molecular modeling of HA (with atom number).

The molecular structure of HA contains nitrogen atom which indicates in blue color of modeling in Fig. 4.3. Detail bond length between atoms of HA and its basic properties are shown in Table 4.5 and 4.6, respectively.

**Table 4.5** Bond and bond length of HA.

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 1 | C1 - C2 | Hyaluronic Acid | 1 | Single | 1.59635 |
| 2 | C2 - C3 | Hyaluronic Acid | 1 | Single | 1.4931 |
| 3 | C3 - C4 | Hyaluronic Acid | 1 | Single | 1.59474 |
| 4 | C4 - O5 | Hyaluronic Acid | 1 | Single | 1.48098 |
| 5 | O5 - C6 | Hyaluronic Acid | 1 | Single | 1.38242 |
| 6 | C6 - C1 | Hyaluronic Acid | 1 | Single | 1.55595 |
| 7 | C6 - C7 | Hyaluronic Acid | 1 | Single | 1.50029 |
| 8 | C7 - O8 | Hyaluronic Acid | 2 | Double | 1.23601 |
| 9 | C7 - O9 | Hyaluronic Acid | 1 | Single | 1.39077 |
| 10 | C1 - O10 | Hyaluronic Acid | 1 | Single | 1.4566 |
| 11 | O10 - C11 | Hyaluronic Acid | 1 | Single | 1.43783 |
| 12 | C2 - O12 | Hyaluronic Acid | 1 | Single | 1.42998 |
| 13 | C3 - O13 | Hyaluronic Acid | 1 | Single | 1.42868 |
| 14 | C4 - O14 | Hyaluronic Acid | 1 | Single | 1.45673 |
| 15 | O14 - C15 | Hyaluronic Acid | 1 | Single | 1.45659 |
| 16 | C15 - C16 | Hyaluronic Acid | 1 | Single | 1.49247 |
| 17 | C16 - C17 | Hyaluronic Acid | 1 | Single | 1.60289 |
| 18 | C17 - O18 | Hyaluronic Acid | 1 | Single | 1.4804 |
| 19 | O18 - C19 | Hyaluronic Acid | 1 | Single | 1.37854 |
| 20 | C19 - C20 | Hyaluronic Acid | 1 | Single | 1.56016 |
| 21 | C20 - C15 | Hyaluronic Acid | 1 | Single | 1.57294 |
| 22 | C20 - O21 | Hyaluronic Acid | 1 | Single | 1.42935 |
| 23 | C19 - C22 | Hyaluronic Acid | 1 | Single | 1.53752 |
| 24 | C22 - O23 | Hyaluronic Acid | 1 | Single | 1.42903 |
| 25 | C17 - O24 | Hyaluronic Acid | 1 | Single | 1.43032 |
| 26 | O24 - C25 | Hyaluronic Acid | 1 | Single | 1.43136 |
| 27 | C16 - N26 | Hyaluronic Acid | 1 | Single | 1.45817 |
| 28 | N26 - C27 | Hyaluronic Acid | 1 | Single | 1.34361 |
| 29 | C27 - C28 | Hyaluronic Acid | 1 | Single | 1.49999 |
| 30 | C27 - O29 | Hyaluronic Acid | 2 | Double | 1.23771 |
| 31 | C1 - H1 | Hyaluronic Acid | 1 | Single | 1.09 |
| 32 | C2 - H2 | Hyaluronic Acid | 1 | Single | 1.09 |
| 33 | C3 - H3 | Hyaluronic Acid | 1 | Single | 1.09 |
| 34 | C4 - H4 | Hyaluronic Acid | 1 | Single | 1.09 |
| 35 | C6 - H5 | Hyaluronic Acid | 1 | Single | 1.09 |
| 36 | O9 - H6 | Hyaluronic Acid | 1 | Single | 1.05003 |
| 37 | C11 - H7 | Hyaluronic Acid | 1 | Single | 1.08996 |
| 38 | C11 - H8 | Hyaluronic Acid | 1 | Single | 1.09003 |
| 39 | C11 - H9 | Hyaluronic Acid | 1 | Single | 1.09003 |
| 40 | O12 - H10 | Hyaluronic Acid | 1 | Single | 1.05003 |
| 41 | O13 - H11 | Hyaluronic Acid | 1 | Single | 1.05003 |
| 42 | C15 - H12 | Hyaluronic Acid | 1 | Single | 1.09 |
| 43 | C16 - H13 | Hyaluronic Acid | 1 | Single | 1.09 |
| 44 | C17 - H14 | Hyaluronic Acid | 1 | Single | 1.09 |
| 45 | C19 - H15 | Hyaluronic Acid | 1 | Single | 1.09 |

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 46 | C20 - H16 | Hyaluronic Acid | 1 | Single | 1.09 |
| 47 | O21 - H17 | Hyaluronic Acid | 1 | Single | 1.05003 |
| 48 | C22 - H18 | Hyaluronic Acid | 1 | Single | 1.09 |
| 49 | C22 - H19 | Hyaluronic Acid | 1 | Single | 1.09 |
| 50 | O23 - H20 | Hyaluronic Acid | 1 | Single | 1.05003 |
| 51 | C25 - H21 | Hyaluronic Acid | 1 | Single | 1.08996 |
| 52 | C25 - H22 | Hyaluronic Acid | 1 | Single | 1.09003 |
| 53 | C25 - H23 | Hyaluronic Acid | 1 | Single | 1.09003 |
| 54 | N26 - H24 | Hyaluronic Acid | 1 | Single | 1.07 |
| 55 | C28 - H25 | Hyaluronic Acid | 1 | Single | 1.08996 |
| 56 | C28 - H26 | Hyaluronic Acid | 1 | Single | 1.09003 |
| 57 | C28 - H27 | Hyaluronic Acid | 1 | Single | 1.09003 |

The HA structure shows the total measurement of 57 bond length with average bond length of 1.280556 Å.

**Table 4.6** Basic properties of HA.

| Properties | HA |
|---|---|
| Number of Atoms | 56 |
| Molecular Formula | C16 H27 O12 N1 |
| Molecular Composition | C: 0.452, H: 0.064, O: 0.451, N: 0.033 |
| Molecular Weight | 425.399 |
| Exact Molecular Weight | 425.153 |
| Net Formal Charge | 0 |

Since some specific HA receptors (CD44) are overexpressed in various malignant cell types, linking an antitumor drug to HA might improve targeting to cancerous cells and overcome the problem of low drug hydrosolubility (Leonelli et al., 2008).

#### 4.1.1.4 PEG-bis amine

**Figure 4.4** Molecular modeling of PEG-bis amine (with atom number).

The molecular structure of PEG-bis amine contains carbon, hydrogen, oxygen and nitrogen atom which indicates in dark grey, light grey, red and blue color

respectively of modeling in Fig. 4.4. Detail bond length between atoms of PEG-bis amine and its basic properties are shown in Table 4.7 and 4.8, respectively.

**Table 4.7** Bond and bond length of PEG-bis amine.

| No. | Name | Parent | Order | Type | Length |
|---|---|---|---|---|---|
| 1 | N1 - C2 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.46616 |
| 2 | C2 - C3 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.53352 |
| 3 | C3 - O4 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.42302 |
| 4 | O4 - C5 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.42302 |
| 5 | C5 - C6 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.53352 |
| 6 | C6 - N7 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.46616 |
| 7 | N1 - H1 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.02949 |
| 8 | N1 - H2 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.02949 |
| 9 | C2 - H3 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.09939 |
| 10 | C2 - H4 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.09939 |
| 11 | C3 - H5 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.09913 |
| 12 | C3 - H6 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.09913 |
| 13 | C5 - H7 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.09913 |
| 14 | C5 - H8 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.09913 |
| 15 | C6 - H9 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.09939 |
| 16 | C6 - H10 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.09939 |
| 17 | N7 - H11 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.02949 |
| 18 | N7 - H12 | Poly(ethylene glycol) bis(amine) | 1 | Single | 1.02949 |

The PEG-bis amine structure shows the total measurement of 18 bond length with average bond length of 1.208747 Å.

**Table 4.8** Basic properties of PEG-bis amine.

| Properties | PEG-bis amine |
|---|---|
| Number of Atoms | 19 |
| Molecular Formula | C4 H12 O1 N2 |
| Molecular Composition | C: 0.461, H: 0.116, O: 0.154, N: 0.269 |
| Molecular Weight | 104.154 |
| Exact Molecular Weight | 104.095 |
| Net Formal Charge | 0 |

### 4.1.2 Multi-molecular Modeling

#### 4.1.2.1 PLGA-HA

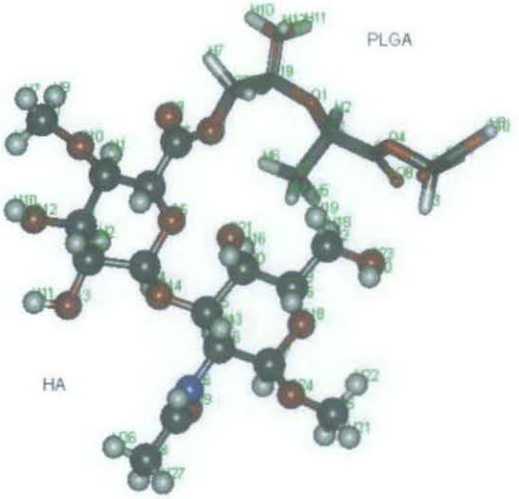



**Figure 4.5** Molecular modeling of PLGA-HA conjugate (with atom number).

The PLGA-HA conjugate contains only one of each molecule as illustrated in Fig. 4.5 whereas PLGA is in stick representation. PLGA acts as a drug carrier while HA is the tumor-specific targeting vehicle to interact with CD44 receptor at tumor cell. Table 4.9 shows PLGA-HA bond length while Table 4.10 shows its basic properties.

**Table 4.9** Bond and bond length of PLGA-HA conjugate.

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 1 | O1 - C2 | PLGA | 1 | Single | 1.45449 |
| 2 | C2 - C3 | PLGA | 1 | Single | 1.4912 |
| 3 | C3 - O4 | PLGA | 1 | Single | 1.38889 |
| 4 | O4 - C5 | PLGA | 1 | Single | 1.42627 |
| 5 | C5 - C6 | PLGA | 1 | Single | 1.49706 |
| 6 | C2 - C7 | PLGA | 1 | Single | 1.55577 |
| 7 | C3 - O8 | PLGA | 2 | Double | 1.23613 |
| 8 | C6 - O9 | PLGA | 2 | Double | 1.23605 |
| 9 | C6 - O10 | PLGA | 1 | Single | 1.38972 |
| 10 | C2 - H2 | PLGA | 1 | Single | 1.09863 |
| 11 | C5 - H3 | PLGA | 1 | Single | 1.10014 |
| 12 | C5 - H4 | PLGA | 1 | Single | 1.09925 |
| 13 | C7 - H5 | PLGA | 1 | Single | 1.09859 |
| 14 | C7 - H6 | PLGA | 1 | Single | 1.09911 |
| 15 | C7 - H7 | PLGA | 1 | Single | 1.09946 |
| 16 | O10 - H8 | PLGA | 1 | Single | 0.989376 |
| 17 | O1 - C19 | HA | 1 | Single | 1.40638 |

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 18 | C19 - C22 | HA | 1 | Single | 1.5023 |
| 19 | C22 - H6 | HA | 1 | Single | 1.09869 |
| 20 | C22 - H7 | HA | 1 | Single | 1.09861 |
| 21 | C19 - O25 | HA | 2 | Double | 1.23636 |
| 22 | C19 - H9 | HA | 1 | Single | 1.05814 |
| 23 | O25 - H10 | HA | 1 | Single | 0.956449 |
| 24 | O25 - H11 | HA | 1 | Single | 0.955898 |
| 25 | O25 - H12 | HA | 1 | Single | 0.957543 |
| 26 | C1 - C2 | HA | 1 | Single | 1.65527 |
| 27 | C2 - C3 | HA | 1 | Single | 1.43775 |
| 28 | C3 - C4 | HA | 1 | Single | 1.64816 |
| 29 | C4 - O5 | HA | 1 | Single | 1.5115 |
| 30 | O5 - C6 | HA | 1 | Single | 1.31797 |
| 31 | C6 - C1 | HA | 1 | Single | 1.58321 |
| 32 | C6 - C7 | HA | 1 | Single | 1.48369 |
| 33 | C7 - O8 | HA | 2 | Double | 1.23591 |
| 34 | C7 - O9 | HA | 1 | Single | 1.3794 |
| 35 | C1 - O10 | HA | 1 | Single | 1.45766 |
| 36 | O10 - C11 | HA | 1 | Single | 1.44215 |
| 37 | C2 - O12 | HA | 1 | Single | 1.4279 |
| 38 | C3 - O13 | HA | 1 | Single | 1.42559 |
| 39 | C4 - O14 | HA | 1 | Single | 1.455 |
| 40 | O14 - C15 | HA | 1 | Single | 1.462 |
| 41 | C15 - C16 | HA | 1 | Single | 1.45104 |
| 42 | C16 - C17 | HA | 1 | Single | 1.66827 |
| 43 | C17 - O18 | HA | 1 | Single | 1.52245 |
| 44 | O18 - C19 | HA | 1 | Single | 1.31818 |
| 45 | C19 - C20 | HA | 1 | Single | 1.57756 |
| 46 | C20 - C15 | HA | 1 | Single | 1.6257 |
| 47 | C20 - O21 | HA | 1 | Single | 1.4359 |
| 48 | C19 - C22 | HA | 1 | Single | 1.52833 |
| 49 | C22 - O23 | HA | 1 | Single | 1.42626 |
| 50 | C17 - O24 | HA | 1 | Single | 1.42995 |
| 51 | O24 - C25 | HA | 1 | Single | 1.42988 |
| 52 | C16 - N26 | HA | 1 | Single | 1.4666 |
| 53 | N26 - C27 | HA | 1 | Single | 1.34458 |
| 54 | C27 - C28 | HA | 1 | Single | 1.4954 |
| 55 | C27 - O29 | HA | 2 | Double | 1.23692 |
| 56 | C1 - H1 | HA | 1 | Single | 1.09839 |
| 57 | C2 - H2 | HA | 1 | Single | 1.09906 |
| 58 | C3 - H3 | HA | 1 | Single | 1.10303 |
| 59 | C4 - H4 | HA | 1 | Single | 1.09817 |
| 60 | C6 - H5 | HA | 1 | Single | 1.10296 |
| 61 | C11 - H7 | HA | 1 | Single | 1.0989 |
| 62 | C11 - H8 | HA | 1 | Single | 1.08647 |
| 63 | C11 - H9 | HA | 1 | Single | 1.09904 |
| 64 | O12 - H10 | HA | 1 | Single | 0.979453 |

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 65 | O13 - H11 | HA | 1 | Single | 0.988772 |
| 66 | C15 - H12 | HA | 1 | Single | 1.09629 |
| 67 | C16 - H13 | HA | 1 | Single | 1.10109 |
| 68 | C17 - H14 | HA | 1 | Single | 1.09631 |
| 69 | C19 - H15 | HA | 1 | Single | 1.10263 |
| 70 | C20 - H16 | HA | 1 | Single | 1.09749 |
| 71 | O21 - H17 | HA | 1 | Single | 0.986586 |
| 72 | C22 - H18 | HA | 1 | Single | 1.09779 |
| 73 | C22 - H19 | HA | 1 | Single | 1.09873 |
| 74 | O23 - H20 | HA | 1 | Single | 0.988731 |
| 75 | C25 - H21 | HA | 1 | Single | 1.09904 |
| 76 | C25 - H22 | HA | 1 | Single | 1.09957 |
| 77 | C25 - H23 | HA | 1 | Single | 1.09928 |
| 78 | N26 - H24 | HA | 1 | Single | 0.993172 |
| 79 | C28 - H25 | HA | 1 | Single | 1.09945 |
| 80 | C28 - H26 | HA | 1 | Single | 1.09947 |
| 81 | C28 - H27 | HA | 1 | Single | 1.09947 |
| 82 | O9 - C22 | HA | 1 | Single | 1.41757 |

The PLGA-HA conjugate shows the total measurement of 82 bond length with average bond length of 1.266312 Å.

**Table 4.10** Basic properties of PLGA-HA conjugate.

| Properties | PLGA-HA conjugate |
|---|---|
| Number of Atoms | 81 |
| Molecular Formula | C23 H39 O18 N1 |
| Molecular Composition | C: 0.447, H: 0.064, O: 0.466, N: 0.023 |
| Molecular Weight | 617.572 |
| Exact Molecular Weight | 617.217 |
| Net Formal Charge | 0 |

#### 4.1.2.2 Curcumin-HA

One molecule of HA conjugated with one molecule of curcumin appearing in stick representation as illustrated in Fig. 4.5. Table 4.11 shows the bond length of this conjugate structure and Table 4.12 shows its basic properties.

In a study shows another important aspect of HA-Curcumin conjugate micelles is the protection of curcumin from degradation at physiological pH. Almost 90% of curcumin degradation occur within 30 min, but the conjugation has resulted in minimal change in the adsorption maximum even after 8 hr of incubation at 37°C (Manju & Sreenivasan, 2011).

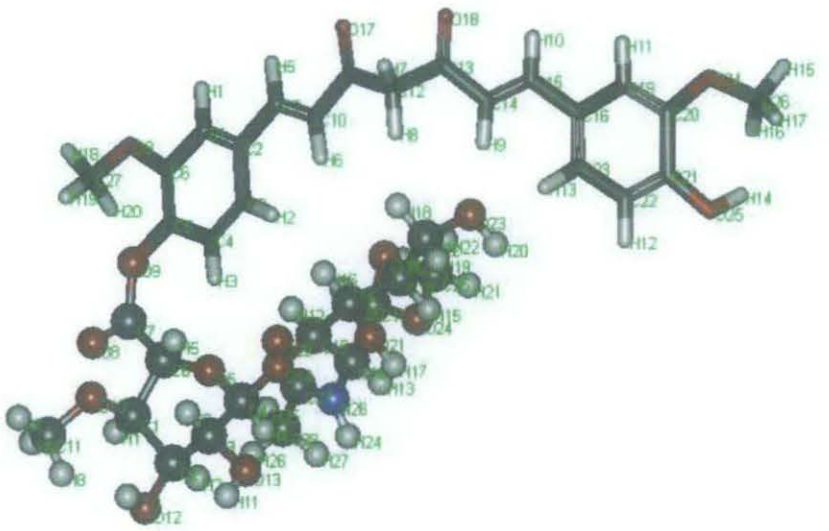


**Figure 4.6** Molecular modeling of Curcumin-HA conjugate (with atom number).

**Table 4.11** Bond and bond length of Curcumin-HA conjugate.

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 1 | C1 - C2 | Curcumin | 2 | Double | 1.32394 |
| 2 | C2 - C3 | Curcumin | 1 | Single | 1.43878 |
| 3 | C3 - C4 | Curcumin | 2 | Double | 1.32559 |
| 4 | C4 - C5 | Curcumin | 1 | Single | 1.48737 |
| 5 | C5 - C6 | Curcumin | 2 | Double | 1.36542 |
| 6 | C6 - C1 | Curcumin | 1 | Single | 1.47133 |
| 7 | C6 - O8 | Curcumin | 1 | Single | 1.46237 |
| 8 | C9 - C10 | Curcumin | 2 | Double | 1.33506 |
| 9 | C10 - C11 | Curcumin | 1 | Single | 1.45425 |
| 10 | C11 - C12 | Curcumin | 1 | Single | 1.49463 |
| 11 | C12 - C13 | Curcumin | 1 | Single | 1.49428 |
| 12 | C13 - C14 | Curcumin | 1 | Single | 1.4547 |
| 13 | C14 - C15 | Curcumin | 2 | Double | 1.33452 |
| 14 | C15 - C16 | Curcumin | 1 | Single | 1.48586 |
| 15 | C2 - C9 | Curcumin | 1 | Single | 1.48015 |
| 16 | C11 - O17 | Curcumin | 2 | Double | 1.23584 |
| 17 | C13 - O18 | Curcumin | 2 | Double | 1.23586 |
| 18 | C19 - C20 | Curcumin | 2 | Double | 1.33284 |
| 19 | C20 - C21 | Curcumin | 1 | Single | 1.55537 |
| 20 | C21 - C22 | Curcumin | 2 | Double | 1.33199 |
| 21 | C22 - C23 | Curcumin | 1 | Single | 1.45335 |
| 22 | C16 - C19 | Curcumin | 1 | Single | 1.4565 |
| 23 | C16 - C23 | Curcumin | 2 | Double | 1.33299 |
| 24 | C20 - O24 | Curcumin | 1 | Single | 1.45357 |
| 25 | C21 - O25 | Curcumin | 1 | Single | 1.42359 |
| 26 | O24 - C26 | Curcumin | 1 | Single | 1.41593 |
| 27 | O8 - C27 | Curcumin | 1 | Single | 1.43541 |

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 28 | C1 - H1 | Curcumin | 1 | Single | 1.06019 |
| 29 | C3 - H2 | Curcumin | 1 | Single | 1.05252 |
| 30 | C4 - H3 | Curcumin | 1 | Single | 1.02923 |
| 31 | C9 - H5 | Curcumin | 1 | Single | 1.06019 |
| 32 | C10 - H6 | Curcumin | 1 | Single | 1.05784 |
| 33 | C12 - H7 | Curcumin | 1 | Single | 1.09886 |
| 34 | C12 - H8 | Curcumin | 1 | Single | 1.10038 |
| 35 | C14 - H9 | Curcumin | 1 | Single | 1.0563 |
| 36 | C15 - H10 | Curcumin | 1 | Single | 1.0602 |
| 37 | C19 - H11 | Curcumin | 1 | Single | 1.06021 |
| 38 | C22 - H12 | Curcumin | 1 | Single | 1.06026 |
| 39 | C23 - H13 | Curcumin | 1 | Single | 1.05705 |
| 40 | O25 - H14 | Curcumin | 1 | Single | 0.941093 |
| 41 | C26 - H15 | Curcumin | 1 | Single | 1.09934 |
| 42 | C26 - H16 | Curcumin | 1 | Single | 1.09958 |
| 43 | C26 - H17 | Curcumin | 1 | Single | 1.09959 |
| 44 | C27 - H18 | Curcumin | 1 | Single | 1.09924 |
| 45 | C27 - H19 | Curcumin | 1 | Single | 1.09991 |
| 46 | C27 - H20 | Curcumin | 1 | Single | 1.09995 |
| 47 | C1 - C2 | HA | 1 | Single | 1.64311 |
| 48 | C2 - C3 | HA | 1 | Single | 1.43863 |
| 49 | C3 - C4 | HA | 1 | Single | 1.63816 |
| 50 | C4 - O5 | HA | 1 | Single | 1.52075 |
| 51 | O5 - C6 | HA | 1 | Single | 1.33557 |
| 52 | C6 - C1 | HA | 1 | Single | 1.58622 |
| 53 | C6 - C7 | HA | 1 | Single | 1.52527 |
| 54 | C7 - O8 | HA | 2 | Double | 1.23583 |
| 55 | C7 - O9 | HA | 1 | Single | 1.46687 |
| 56 | C1 - O10 | HA | 1 | Single | 1.45904 |
| 57 | O10 - C11 | HA | 1 | Single | 1.44321 |
| 58 | C2 - O12 | HA | 1 | Single | 1.42779 |
| 59 | C3 - O13 | HA | 1 | Single | 1.42528 |
| 60 | C4 - O14 | HA | 1 | Single | 1.43113 |
| 61 | O14 - C15 | HA | 1 | Single | 1.46174 |
| 62 | C15 - C16 | HA | 1 | Single | 1.47818 |
| 63 | C16 - C17 | HA | 1 | Single | 1.67568 |
| 64 | C17 - O18 | HA | 1 | Single | 1.52053 |
| 65 | O18 - C19 | HA | 1 | Single | 1.31474 |
| 66 | C19 - C20 | HA | 1 | Single | 1.57355 |
| 67 | C20 - C15 | HA | 1 | Single | 1.61159 |
| 68 | C20 - O21 | HA | 1 | Single | 1.43504 |
| 69 | C19 - C22 | HA | 1 | Single | 1.52861 |
| 70 | C22 - O23 | HA | 1 | Single | 1.42564 |
| 71 | C17 - O24 | HA | 1 | Single | 1.43039 |
| 72 | O24 - C25 | HA | 1 | Single | 1.43002 |
| 73 | C16 - N26 | HA | 1 | Single | 1.47832 |
| 74 | N26 - C27 | HA | 1 | Single | 1.34839 |

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 75 | C27 - C28 | HA | 1 | Single | 1.49404 |
| 76 | C27 - O29 | HA | 2 | Double | 1.23677 |
| 77 | C1 - H1 | HA | 1 | Single | 1.09839 |
| 78 | C2 - H2 | HA | 1 | Single | 1.09929 |
| 79 | C3 - H3 | HA | 1 | Single | 1.10267 |
| 80 | C4 - H4 | HA | 1 | Single | 1.09536 |
| 81 | C6 - H5 | HA | 1 | Single | 1.09457 |
| 82 | C11 - H7 | HA | 1 | Single | 1.09889 |
| 83 | C11 - H8 | HA | 1 | Single | 1.08652 |
| 84 | C11 - H9 | HA | 1 | Single | 1.09909 |
| 85 | O12 - H10 | HA | 1 | Single | 0.979841 |
| 86 | O13 - H11 | HA | 1 | Single | 0.988798 |
| 87 | C15 - H12 | HA | 1 | Single | 1.09834 |
| 88 | C16 - H13 | HA | 1 | Single | 1.10064 |
| 89 | C17 - H14 | HA | 1 | Single | 1.09307 |
| 90 | C19 - H15 | HA | 1 | Single | 1.10252 |
| 91 | C20 - H16 | HA | 1 | Single | 1.09109 |
| 92 | O21 - H17 | HA | 1 | Single | 0.987153 |
| 93 | C22 - H18 | HA | 1 | Single | 1.10075 |
| 94 | C22 - H19 | HA | 1 | Single | 1.09852 |
| 95 | O23 - H20 | HA | 1 | Single | 0.988783 |
| 96 | C25 - H21 | HA | 1 | Single | 1.09902 |
| 97 | C25 - H22 | HA | 1 | Single | 1.09959 |
| 98 | C25 - H23 | HA | 1 | Single | 1.09926 |
| 99 | N26 - H24 | HA | 1 | Single | 0.992856 |
| 100 | C28 - H25 | HA | 1 | Single | 1.09925 |
| 101 | C28 - H26 | HA | 1 | Single | 1.10017 |
| 102 | C28 - H27 | HA | 1 | Single | 1.09939 |
| 103 | O9 - C5 | HA | 1 | Single | 1.46764 |

The Curcumin-HA conjugate shows the total measurement of 103 bond length with average bond length of 1.280048 Å. HA-Curcumin conjugates is amphipilic in nature containing both hydrophobic core by curcumin and the hydrophilic HA protruding outwardly and form shell layer (Gul-e-Saba, et al., 2011).

**Table 4.12** Basic properties of Curcumin-HA conjugate.

| Properties | Curcumin-HA conjugate |
|---|---|
| Number of Atoms | 100 |
| Molecular Formula | C37 H45 O17 N1 |
| Molecular Composition | C: 0.573, H: 0.058, O: 0.351, N: 0.018 |
| Molecular Weight | 775.774 |
| Exact Molecular Weight | 775.269 |
| Net Formal Charge | 0 |

### 4.1.2.3 PLGA-PEG-HA

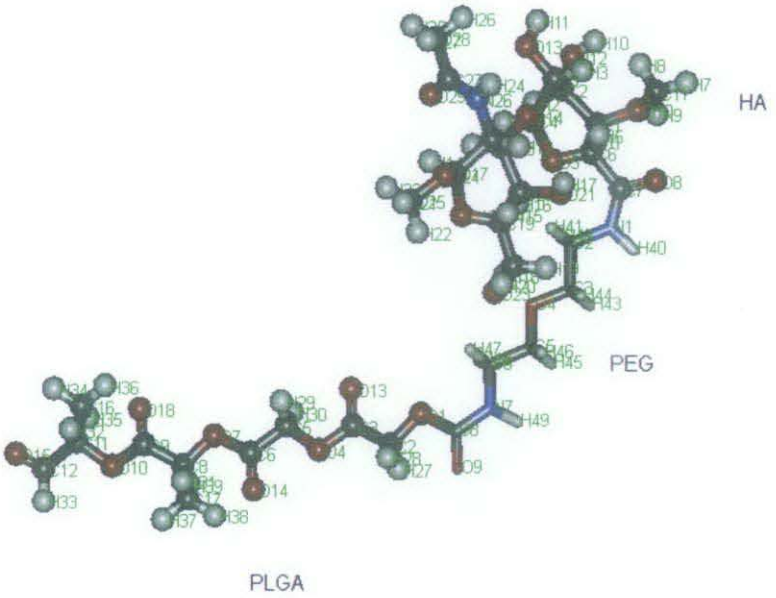



**Figure 4.7** Molecular modeling of PLGA-PEG-HA conjugate (with atom number).

One molecule of HA conjugated with one molecule of PEG-bis amine as a spacer appearing in stick representation and one molecule of PLGA as illustrated in Fig. 4.7. This conjugated structure has been modeled from skeletal structure in Fig.3.2. Table 4.13 shows the bond length of this conjugate structure and Table 4.14 shows its basic properties.

**Table 4.13** Bond and bond length of PLGA-PEG-HA conjugate.

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 1 | C1 - C2 | HA | 1 | Single | 1.65421 |
| 2 | C2 - C3 | HA | 1 | Single | 1.43798 |
| 3 | C3 - C4 | HA | 1 | Single | 1.64219 |
| 4 | C4 - O5 | HA | 1 | Single | 1.51794 |
| 5 | O5 - C6 | HA | 1 | Single | 1.32966 |
| 6 | C6 - C1 | HA | 1 | Single | 1.58803 |
| 7 | C6 - C7 | HA | 1 | Single | 1.54045 |
| 8 | C7 - O8 | HA | 2 | Double | 1.23577 |
| 9 | C1 - O10 | HA | 1 | Single | 1.45877 |
| 10 | O10 - C11 | HA | 1 | Single | 1.44341 |
| 11 | C2 - O12 | HA | 1 | Single | 1.4279 |
| 12 | C3 - O13 | HA | 1 | Single | 1.42562 |
| 13 | C4 - O14 | HA | 1 | Single | 1.45506 |
| 14 | O14 - C15 | HA | 1 | Single | 1.46159 |
| 15 | C15 - C16 | HA | 1 | Single | 1.45083 |

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 16 | C16 - C17 | HA | 1 | Single | 1.66793 |
| 17 | C17 - O18 | HA | 1 | Single | 1.52218 |
| 18 | O18 - C19 | HA | 1 | Single | 1.31802 |
| 19 | C19 - C20 | HA | 1 | Single | 1.57516 |
| 20 | C20 - C15 | HA | 1 | Single | 1.61966 |
| 21 | C20 - O21 | HA | 1 | Single | 1.43594 |
| 22 | C19 - C22 | HA | 1 | Single | 1.53067 |
| 23 | C22 - O23 | HA | 1 | Single | 1.42623 |
| 24 | C17 - O24 | HA | 1 | Single | 1.42983 |
| 25 | O24 - C25 | HA | 1 | Single | 1.42979 |
| 26 | C16 - N26 | HA | 1 | Single | 1.46651 |
| 27 | N26 - C27 | HA | 1 | Single | 1.34448 |
| 28 | C27 - C28 | HA | 1 | Single | 1.49547 |
| 29 | C27 - O29 | HA | 2 | Double | 1.2369 |
| 30 | C1 - H1 | HA | 1 | Single | 1.0983 |
| 31 | C2 - H2 | HA | 1 | Single | 1.09903 |
| 32 | C3 - H3 | HA | 1 | Single | 1.10268 |
| 33 | C4 - H4 | HA | 1 | Single | 1.09819 |
| 34 | C6 - H5 | HA | 1 | Single | 1.10187 |
| 35 | C11 - H7 | HA | 1 | Single | 1.09891 |
| 36 | C11 - H8 | HA | 1 | Single | 1.08611 |
| 37 | C11 - H9 | HA | 1 | Single | 1.099 |
| 38 | O12 - H10 | HA | 1 | Single | 0.979109 |
| 39 | O13 - H11 | HA | 1 | Single | 0.988776 |
| 40 | C15 - H12 | HA | 1 | Single | 1.09638 |
| 41 | C16 - H13 | HA | 1 | Single | 1.10112 |
| 42 | C17 - H14 | HA | 1 | Single | 1.09635 |
| 43 | C19 - H15 | HA | 1 | Single | 1.10271 |
| 44 | C20 - H16 | HA | 1 | Single | 1.09509 |
| 45 | O21 - H17 | HA | 1 | Single | 0.986539 |
| 46 | C22 - H18 | HA | 1 | Single | 1.10032 |
| 47 | C22 - H19 | HA | 1 | Single | 1.09901 |
| 48 | O23 - H20 | HA | 1 | Single | 0.989312 |
| 49 | C25 - H21 | HA | 1 | Single | 1.09903 |
| 50 | C25 - H22 | HA | 1 | Single | 1.09954 |
| 51 | C25 - H23 | HA | 1 | Single | 1.0993 |
| 52 | N26 - H24 | HA | 1 | Single | 0.993187 |
| 53 | C28 - H25 | HA | 1 | Single | 1.09942 |
| 54 | C28 - H26 | HA | 1 | Single | 1.09951 |
| 55 | C28 - H27 | HA | 1 | Single | 1.09947 |
| 56 | N1 - C7 | PEG-HA | 1 | Single | 1.34936 |
| 57 | N1 - C2 | PEG-bis amine | 1 | Single | 1.43977 |
| 58 | C2 - C3 | PEG-bis amine | 1 | Single | 1.53534 |
| 59 | C3 - O4 | PEG-bis amine | 1 | Single | 1.42819 |
| 60 | O4 - C5 | PEG-bis amine | 1 | Single | 1.42779 |
| 61 | C5 - C6 | PEG-bis amine | 1 | Single | 1.53802 |
| 62 | C6 - N7 | PEG-bis amine | 1 | Single | 1.43419 |

| No. | Name | Parent | Order | Type | Length (Å) |
|---|---|---|---|---|---|
| 63 | N7 - C8 | PEG-bis amine | 1 | Single | 1.39519 |
| 64 | C8 - O9 | PEG-bis amine | 2 | Double | 1.23641 |
| 65 | N1 - H40 | PEG-bis amine | 1 | Single | 1.07 |
| 66 | C2 - H41 | PEG-bis amine | 1 | Single | 1.09 |
| 67 | C2 - H42 | PEG-bis amine | 1 | Single | 1.09 |
| 68 | C3 - H43 | PEG-bis amine | 1 | Single | 1.09 |
| 69 | C3 - H44 | PEG-bis amine | 1 | Single | 1.09 |
| 70 | C5 - H45 | PEG-bis amine | 1 | Single | 1.09 |
| 71 | C5 - H46 | PEG-bis amine | 1 | Single | 1.09 |
| 72 | C6 - H47 | PEG-bis amine | 1 | Single | 1.09 |
| 73 | C6 - H48 | PEG-bis amine | 1 | Single | 1.09 |
| 74 | N7 - H49 | PEG-bis amine | 1 | Single | 1.07 |
| 75 | C8 - O1 | PLGA-PEG | 1 | Single | 1.39224 |
| 76 | O1 - C2 | PLGA | 1 | Single | 1.43024 |
| 77 | C2 - C3 | PLGA | 1 | Single | 1.49798 |
| 78 | C3 - O4 | PLGA | 1 | Single | 1.39185 |
| 79 | O4 - C5 | PLGA | 1 | Single | 1.42868 |
| 80 | C5 - C6 | PLGA | 1 | Single | 1.49864 |
| 81 | C6 - O7 | PLGA | 1 | Single | 1.4095 |
| 82 | O7 - C8 | PLGA | 1 | Single | 1.44536 |
| 83 | C8 - C9 | PLGA | 1 | Single | 1.49838 |
| 84 | C9 - O10 | PLGA | 1 | Single | 1.40994 |
| 85 | O10 - C11 | PLGA | 1 | Single | 1.44508 |
| 86 | C11 - C12 | PLGA | 1 | Single | 1.50032 |
| 87 | C3 - O13 | PLGA | 2 | Double | 1.23636 |
| 88 | C6 - O14 | PLGA | 2 | Double | 1.23702 |
| 89 | C12 - O15 | PLGA | 2 | Double | 1.23615 |
| 90 | C11 - C16 | PLGA | 1 | Single | 1.55065 |
| 91 | C8 - C17 | PLGA | 1 | Single | 1.55089 |
| 92 | C9 - O18 | PLGA | 2 | Double | 1.23706 |
| 93 | C2 - H27 | PLGA | 1 | Single | 1.09 |
| 94 | C2 - H28 | PLGA | 1 | Single | 1.09 |
| 95 | C5 - H29 | PLGA | 1 | Single | 1.09 |
| 96 | C5 - H30 | PLGA | 1 | Single | 1.09 |
| 97 | C8 - H31 | PLGA | 1 | Single | 1.09 |
| 98 | C11 - H32 | PLGA | 1 | Single | 1.09 |
| 99 | C12 - H33 | PLGA | 1 | Single | 1.09 |
| 100 | C16 - H34 | PLGA | 1 | Single | 1.08996 |
| 101 | C16 - H35 | PLGA | 1 | Single | 1.09003 |
| 102 | C16 - H36 | PLGA | 1 | Single | 1.09003 |
| 103 | C17 - H37 | PLGA | 1 | Single | 1.08995 |
| 104 | C17 - H38 | PLGA | 1 | Single | 1.09003 |
| 105 | C17 - H39 | PLGA | 1 | Single | 1.09003 |

The PLGA-PEG-HA conjugate shows the total measurement of 105 bond length with average bond length of 1.274163 Å. Considering the bond no. 56 it indicates the bond between N7-C7 atoms where the conjugation between PEG and HA occurred and also at the bond no.75 indicates where the conjugation between PEG and PLGA occurred with C8-O1 atoms.

**Table 4.14** Basic properties of PLGA-PEG-HA conjugate.

| Properties | PLGA-PEG-HA conjugate |
|---|---|
| Number of Atoms | 104 |
| Molecular Formula | C31 H49 O21 N3 |
| Molecular Composition | C: 0.466, H: 0.062, O: 0.420, N: 0.053 |
| Molecular Weight | 799.754 |
| Exact Molecular Weight | 799.286 |
| Net Formal Charge | 0 |

The PLGA-PEG-HA conjugates can successfully prepared via reaction of one of the amino groups of PEG-bis amine with carboxylic group of HA and reacting second free amino group with PLGA (Fig. 3.2) (Yadav, et al., 2010). This conjugate molecule will be used for preparation of nanoparticles as a drug carrier.

#### 4.1.2.4 Curcumin-PLGA-PEG-HA

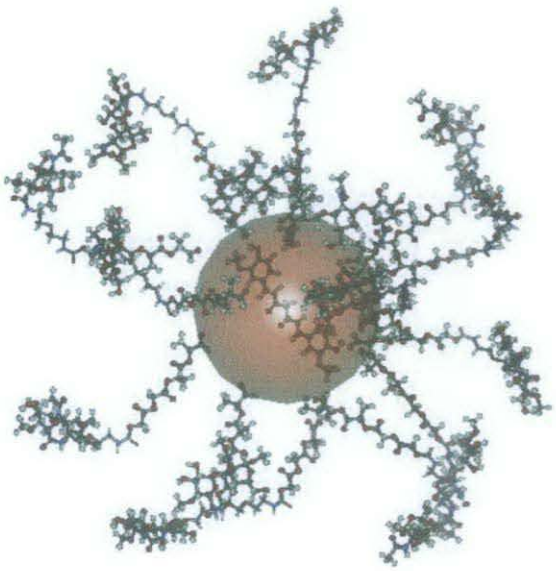


**Figure 4.8** Molecular modeling of Curcumin-PLGA-PEG-HA nanoparticle.

Fig 4.8 shows the PLGA-PEG-HA nanoparticle with one molecule of curcumin as anticancer agent inside the hydrophobic core of spherical shape whereas at the surface of nanoparticle contains hydrophilic micelles of 15 PLGA-PEG-HA molecules. The basic process of synthesizing this nanoparticles is, first is to synthesize the empty nano-conjugates of PLGA-PEG-HA. Secondly, the curcumin is put into it by preparing the curcumin solution formed in water miscible organic solvents and during the synthesis of curcumin containing in nanoparticles, the streams of polymer (PLGA-PEG-HA) will collide with other stream of curcumin. Third, the hydrophobic curcumin and conjugate polymers will precipitate out of solution in an attempt to avoid the water molecules and finally the polymers immediately self-assemble onto the curcumin to form a coating with the hydrophobic portion attached to the nanoparticle core containing curcumin and the hydrophilic portion containing HA stretching out into the water solution.

Since the major roadblocks in curcumin development as a therapeutic for cancer is its poor water solubility and limited bioavailability therefore by using biodegradable nanoparticle like PLGA-PEG would exhibit enhanced cellular uptake and increase its bioavailability (Anand, et al., 2009). It is also been reported that grafting of PEG to the surface of nanoparticle containing PLGA will reduce the interaction between the nanoparticles and digestive enzymes, increases uptake of the encapsulated drug in the bloodstream and lymphatic tissue and also increase its half-life in the blood circulation (Dinarvand, et al., 2011). Conjugation to HA not only further increases the drug solubility but more importantly it enhances the chances to reach the cancer site. CD44 is overexpressed in human cancer cells and it is cell membrane-localized receptors or HA binding proteins therefore HA can bind to the cell surface via interactions with CD44 (Luo, et al., 2009). HA-PEG-PGLA uptake by CD44 receptor via endocytosis. The main advantage of the conjugation of drug to biodegradable polyester like PLGA-PEG is, first to prevent the initial burst and control the sustained release of molecules from nanoparticles (Oh, et al., 2007) and secondly is drug-polymer conjugates are easily formulated into nanoparticles by nano-precipitation method with very high encapsulation efficiency (almost 100%) (Anand, et al., 2009). In the study of Yadav, et al. (2010) has concluded that PLGA-PEG-HA nanoparticles can serve as efficient tools to ferry large doses of anti-cancer drug to tumor sites, with reduced access to non-tumor tissues.

# CHAPTER 5

# CONCLUSION

## 5.1 CONCLUSION

The three dimensional molecular modeling of the following molecule had been successfully developed using Discovery Studio 2.5: Curcumin, PLGA, HA, PEG-bis amine, PLGA conjugated HA, Curcumin conjugated HA, PLGA-PEG-HA conjugates and Curcumin-PLGA-PEG-HA nanoparticles. HA conjugates with nanoparticles molecules have high potential as targeted delivery vehicle to transport the anticancer agent to cancer cells and it also improves the stability, bioavailability of anticancer hydrophobic drug as compared to free curcumin. These molecular modeling might be further used as one of the references regarding the drug development method or molecular modeling study. Furthermore the nanoparticle model can also be modeled for CD44 target and this could possibly pave the way for rational design of target-specific drug delivery.

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