UNIVERSITI PUTRA MALAYSIA

PREPARATION AND CONTROLLED RELEASE PROPERTIES OF ZINC-LAYERED HYDROXIDES-CINNAMALDEHYDE AND GELLAN GUM CINNAMALDEHYDE HYDROGEL BEADS

NURUL JANNAH BINTI JAMALUDDIN

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By

NURUL JANNAH BINTI JAMALUDDIN

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October 2017

Chairman: Adila Mohamad Jaafar, PhD
Faculty : Science

Mosquitoes are giving threat and responsible for the transmission of many deadly diseases such as malaria, dengue, chikungunya and the latest outbreak disease, the zika virus. Insecticides and larvicides are one of the solutions to lower down the mosquitoes population but most of the products in the current market are synthetic and are not environmental friendly. Cinnamaldehyde (CN) is the main constituent of cinnamon oils has been reported to possess excellent inhibitory effects in killing mosquito larvaes. Looking at the interesting properties of CN, has brought the idea to intercalate and encapsulate CN into two different nano host materials; zinc layered hydroxides (ZLH) and gellan gum hydrogel. The two hosts are chosen due to their eco-friendly material, low cost and easy to prepare. Controlled release study is better than using the anion directly as the hosts will protect the anions and the anions can be release in sustained and longer time. Intercalation of CN into ZLH was done via ion exchange method forming the zinc-layered hydroxides-cinnamaldehyde (ZCN) nanocomposites. X-ray diffraction pattern indicated a successful intercalation of CN into the interlayer galleries of ZLHs matrix when 1g of ZnO with 0.08M concentration of CN was used. Considering with the X-Ray diffraction and FTIR analyses, successful formation of ZCN was further confirmed. Further physico-chemical characterisations of the resulting materials including thermal analysis, elemental analysis and surface morphology, were also carried out. Encapsulation of cinnamaldehyde into gellan gum hydrogel was done via ionotropic gelation method forming gellan gum cinnamaldehyde hydrogel beads (CNB). FTIR analysis shows that functional groups of both CN and gellan gum appeared in all CNB (cinnamaldehyde concentrations 0.01M to 0.32M). The samples were then further characterised by elemental analysis and surface morphology analysis. The swelling study of CNB was done in tap water and lake water which are the common breeding media for mosquito larvae. As CN concentration increases, the swelling percentage decreases ranging 544% to 484% for tap water (pH 6.7) and 628% to 544% for lake water (pH 7). In the degradation study, CNB were exposed at room temperature until day 8 and showed decrease in weight percentage. The controlled release study of CN was done in three

media that resemble the mosquito breeding condition which are tap water (pH 6.7), MARDI lake water (pH 7.0) and Sri Serdang lake water (pH 7.5). Controlled release of CN from both ZCN and CNB was rapid intially and slow thereafter. The release percentage of CN into the media for both ZCN and CNB can be arranged in the order of pH 7.0 > pH 7.5 > pH 6.7. The highest release percentage recorded was 90.7% for ZCN while 70.4% for CNB. It was found that the release is slow and highly in sustained manner over 40 hours. The kinetic model of pseudo-second order fits well with most of the release profile with $r^2 > 0.9$ for both ZCN and CNB. Two new host-anion materials has been successfully prepared. This highlighted the potential of both hosts that can be prepared using simple, direct reaction of CN and two hosts; gellan gum and ZLH in the application of controlled release formulations for mosquito control.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENYEDIAAN DAN PENCIRIAN PENGELUARAN TERKAWAL HIDROKSIDA BERLAPIS ZINK-CINNAMALDEHID DAN HIDROGEL GUM GELAN CINNAMALDEHID MANIK

Oleh

NURUL JANNAH BINTI JAMALUDDIN

Oktober 2017

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Nyamuk memberi ancaman dan bertanggungjawab untuk penyebaran pelbagai penyakit yang membawa maut seperti malaria, denggi, chikungunya dan penyakit terbaru iaitu virus zika. Racun serangga dan racun larva merupakan salah satu penyelesaian untuk mengurangkan populasi nyamuk tetapi kebanyakan produk dalam pasaran semasa adalah sintetik dan tidak mesra alam. Cinnamaldehid (CN) adalah konstituen utama dalam minyak kulit kayu manis telah dilaporkan mengandungi kesan penghalang yang sangat baik dalam membunuh larva nyamuk. Dengan melihat kepada ciri-ciri yang menarik dari CN telah membawa idea untuk menginterkalasi dan mengkapsulkan CN ke dalam dua bahan perumah nano yang berbeza; zink hidroksida berlapis (ZHB) dan hidro gel gum gellan. Kedua-dua perumah telah dipilih kerana mereka mesra alam, rendah kos dan mudah disediakan. Kajian pelepasan terkawal lebih baik daripada pelepasan langsungan kerana perumah akan melindungi anion dan anion dapat dilepaskan secara berterusan dan pada masa yang lebih lama. Interkelasi CN ke dalam ZHB dilakukan melalui kaedah pertukaran ion dan menghasilkan komposit hidroksida berlapis zink-cinnamaldehid (ZCN). Corak pembelauan sinar-X menunjukkan interkalasi CN telah berjaya dilakukan ke dalam inter lapisan ZHB matrik apabila menggunakan 1g zink oksida dengan 0.08M kepekatan CN. Gabungan analisis pembelauan sinar-X dan FTIR mengesahkan lagi pembentukan nanokomposit ZCN. Pencirian lain terhadap bahan yang dihasilkan telah dilakukan adalah seperti analisis therma, analisis kandungan organik-tak organik dan morfologi permukaan. Pengkapsulan cinnamaldehid ke dalam gel hidro gum gellan telah dilakukan melalui kaedah gel ionotropik menghasilkan gel hidro gum gellan cinnamaldehid (CNB) dalam bentuk manik. Analisis FTIR menunjukkan kedua-dua kumpulan berfungsi daripada CN dan gum gellan hadir dalam kesemua CNB (kepekatan cinnamaldehid 0.01M ke 0.32M). Pencirian lain telah dilakukan ke atas semua sampel seperti analisis kandungan organik-tak organik dan analisis morfologi permukaan. Kajian pembengkakkan CNB telah dilakukan dalam air paip dan air tasik yang merupakan media pembiakan yang biasa untuk larva nyamuk. Semakin tinggi kepekatan cinnamaldehid, peratusan pembengkakkan menurun dari 544% ke 484% untuk air paip (pH 6.7) dan 628% ke 544% untuk air tasik (pH 7). Dalam kajian degradasi, CNB telah didedahkan dalam suhu bilik sehingga hari ke 8 dan menunjukkan keputusan menurun dalam peratusan berat. Kajian pelepasan terkawal oleh CN telah dijalankan dalam tiga media yang menyerupai media pembiakan nyamuk iaitu air paip (pH 6.7), air tasik MARDI (pH 7.0) dan juga air tasik Sri Serdang (pH 7.5). Pelepasan CN yang terkawal oleh ZCN dan CNB laju pada permulaannya tetapi kemudiannya semakin perlahan. Peratusan pelepasan CN ke dalam media oleh kedua-dua ZCN dan CNB boleh disusun dalam susunan pH 7.0 > pH 7.5 > pH 6.7. Peratusan pelepasan paling tinggi direkodkan iaitu 90.7% oleh ZCN dan 70.4% oleh CNB. Didapati daripada keputusan, pelepasan adalah dalam keadaan perlahan dan sangat berterusan. Model kinetik pseudo-kedua telah didapati sesuai dengan semua profil perlepasan dengan $r^2 > 0.9$ untuk kedua-dua ZCN dan CNB. Dua bahan anion yang baru telah berjaya sediakan. Ini menonjolkan potensi kedua-dua perumah yang boleh disediakan secara mudah, menggunakan reaksi langsung bersama CN dan dua perumah; gum gellan dan ZLH dalam penggunaan formulasi pelepasan terkawal untuk mengawal nyamuk.

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I certify that a Thesis Examination Committee has met on 12 October 2017 to conduct the final examination of Nurul Jannah binti Jamaluddin on her thesis entitled "Preparation and Controlled Release Properties of Zinc-Layered Hydroxides-Cinnamaldehyde and Gellan Gum Cinnamaldehyde Hydrogel Beads" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

CHNS	Carbon, Hydrogen, Nitrogen and Sulphur
CN	Cinnamaldehyde
CNB	Cinnamaldehyde Gellan Gum Hydrogel Beads
CRF	Controlled Release Formulations
FESEM	Fourier Emission Scanning Electron Microscope
FTIR	Fourier Transform Infrared Spectrophotometer
GG	Gellan Gum
HDS	Hydroxyl Double Salts
ICP-OES	Inductively Coupled Plasma Optical Emission Spectrophotometer
LDH	Layered Double Hydroxides
LHS	Layered Hydroxide Salt
PXRD	Powder X-Ray Diffraction
TGA-DTG	Thermogravimetric Analysis-Derivatives Thermogravimteric
SEM	Scanning Electron Microscope
UV-Vis	Ultraviolet-visible Spectrophotometer
VPSEM	Variable Pressure Scanning Electron Microscope
ZCN	Zinc Layered Hydroxides-Cinnamaldehyde
ZLH	Zinc Layered Hydroxides

CHAPTER 1

INTRODUCTION

1.1 Research background

Controlled release study of drugs or anions is one of the most interesting areas of current research with the increasing growth and importance in all kinds of research fields including medicine (Vithani *et al.*, 2017), agrochemical (Tejada *et al.*, 2017), food industry (Ghaderi-Ghahfarokhi *et al.*, 2017) and etc. Controlled release can be defined by a method of which one or more anions or drugs are made available at a desired site and time and at specific rate (Pothakamury & Barbosa-Canovas, 1995). There are countless of drugs and anions that can be incorporated into various kinds of materials or can be called as hosts based on the needs and applications that been desired. Different types of hosts and materials governed different types of release mechanisms. Figure 1.1 below shows the common release mechanisms:

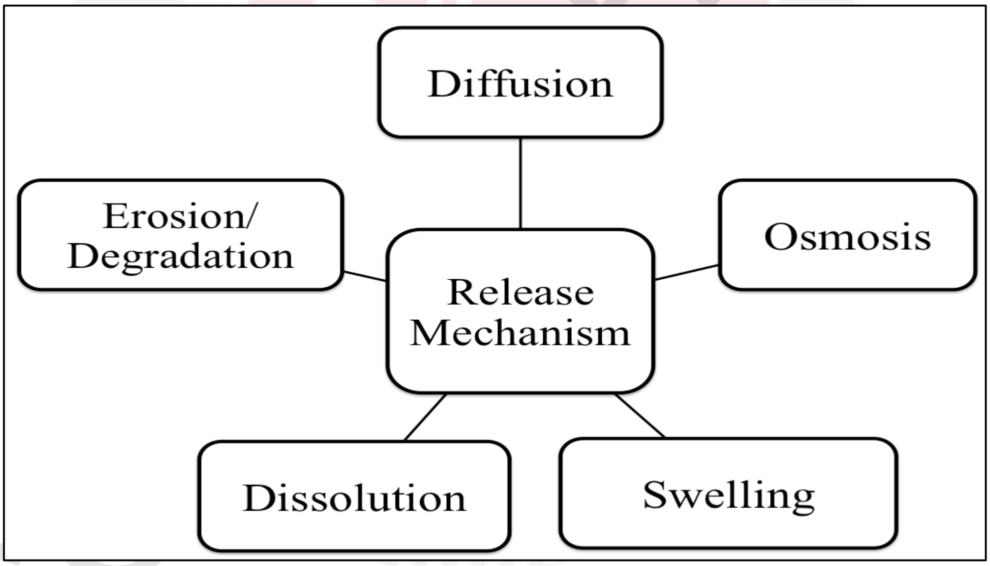

Figure 1.1: Release mechanism for controlled release study.

Dissolution involves in the transfer of drug or anion in its solid phase to the surrounding medium (Bhaskar *et al.*, 1986). Dissolution rate increases with the solubility and decrease with drug size. The dissolution rate is commonly controlled by diffusion. Diffusion is when the drugs move from higher concentration to lower concentration; move down to its concentration gradient (Siepmann *et al.*, 2011). Release of drug or anion usually occurs by dissolution followed by diffusion through the matrix. This is because particles at the surface dissolve quickly, leading to a burst. Thus, the particles inside dissolve more slowly as dissolution rate is controlled by diffusion in time. At some time, barrier that separating a central core containing solid drug or anion from a periphery containing completely dissolved drug. Thus, the drug will diffuse into the surrounding medium and been released.

Swelling refers to the uptake of water by a polymer system, with lead to increase in volume (Shaikh *et al*., 2015). According to Pundir *et al*. (2017) swelling is accompanied by a glass-to-rubber transition. If drug is trapped inside the glass, it will be liberated when the polymer swells, and if it can diffuse through the softened matrix faster than water can invade, then the release process is swelling in control. As for erosion and degradation mechanisms are mainly popular for drug delivery systems particularly for implantable or injectable therapies, since they do not require retrieval after drug is fully released (Tzur-Balter *et al*., 2015). Each system that consisted of drug or anion with the hosts governed with different kind of mechanisms of release as it depends on each properties of materials and how each of the materials react with its media.

1.2 Problem statement

Mosquito species has been widely known playing a predominant role in the transmission of various deadly diseases such as dengue fever, malaria and yellow fever which not only affects Malaysian but also to the world population (Cheng *et al*., 2004; Hemingway, 2004; Kuo *et al*., 2007). Tropical countries such as Malaysia are more prone to the transmission of mosquito diseases due to the climate. During rainy seasons, the presence of ponds, lakes, stagnant water and poor irrigated drains provide more mosquito breeding places.

There are so many methods to control mosquito population such as repellent, fogging, insecticides and etc. Often, prevention against adult mosquitoes is deficient, even in temporary time, leads to environmental pollution. Treatment and prevention in larvae stage of mosquitoes is much more affective in managing mosquito population because at this stage, larvae are localised and restricted to small area due to low level of mobility (Howard *et al*., 2007). 1% temophos and sand granules (Grisales *et al*., 2013), insect growth regulator metoprene in the form of briquettes (Lawler, 2017) and BTI (*Bacillus thuringiensis* H-14) (Narkhede *et al*., 2016) are some examples of current larvicides been used. Nowadays, public awareness on how synthetic larvicides could help in managing environment is increased. This has leads to the investigations and explorations of the scientists and researchers to find better combination of materials in order to create more environmental friendly and efficient larvicides. For example, plant essential oils are one of the best approaches for better environmentally larvicides.

Essential oils from plants have been recognized as important natural resources of insecticides and larvicides because some are selective, biodegrade to non-toxic products and have few effects on non-target organisms and environment (Rehman *et al.*, 2014). Cinnamaldehyde (CN) is the main constituent of cinnamon oils has proven in various applications such as food industry, pesticides, antibacterial activities and also can be use as larvicides. Before been proven by scientific research, cinnamon oil has been conventionally used as home remedies for mosquito repellent, and also used as larvicides. Adding one part of cinnamon oils with one part of water into the ponds of any water that contained mosquito larvaes is one of the examples of home remedies been suggested by elders (Nice, 2005). According to Cheng *et al.* (2004), CN has the ability of excellent inhibitory effect in killing mosquito larvae. Other properties of CN are as good anti-inflammatory, anti-oxidant, anti-ulcer, anti-microbial, hypoglycaemic and hypolipidemic (Lee at al., 2005; Wang et al., 2005; Chao et al., 2005;2008).

Due to the interesting properties of CN as discussed above has brought the idea to intercalate and encapsulate CN into two different hosts; zinc layered hydroxides (ZLH) and gellan gum hydrogel. ZLH and gellan gum hydrogel have been chosen for the hosts because both of the hosts are biodegradable materials (Barahuie *et al*., 2014) and they are both easy to prepare (Mohsin *et al*., 2013; Mohd Sebri & Mat Amin, 2015). Besides that, both of the hosts are commonly been used for controlled release study (Section 2.3.3 & 2.4.4). The main reason on the needs to encapsulate and intercalate CN into the hosts are because the hosts will enable superior control of drug exposure over time, to assist drug in crossing physiological barriers and to minimize drug exposure elsewhere the related media (Siepmann *et al*., 2012). The samples of both hosts were tested for further use as controlled release formulations (CRF) on mosquito larvicides control. It is interesting to investigate and discover how well CN can be intercalated and encapsulated into two different hosts showing different properties. It is clear that there are many applications which could be brought to reality from the intercalation of key anionic species into the nano hosts, particularly if the guest anion can then be released in a controlled manner.

In this research, we report on the intercalation of cinnamaldehyde into ZLHs layer, named as ZLH-cinnamaldehyde (ZCN) nanocomposites and also the encapsulation of CN into gellan gum hydrogel beads, named as cinnamaldehyde gellan gum hydrogel beads (CNB). To date, there are no intercalation of cinnamaldehyde (CN) into both nano-hosts have been reported. Controlled release study of CN from both nano hosts were done into various resembling mosquitoes breeding media. Few kinetic models were tested in order to understand the release behavior of CN in different media. The controlled release of CN in the formed of nanocomposites is hoped to be effective and environmental friendly CRF of larvicides.

1.3 Objectives

The objectives of this study are outlined as listed below:

1. To prepare zinc-layered-hydroxides-cinnamaldehyde (ZCN) and gellan gum cinnamaldehyde hydrogel beads (CNB) with various CN concentrationsranging from 0.01M to 0.32M.

2. To study the physico-chemical properties of ZCN and CNB.

3. To study the release behavior of CN from both ZCN and CNB in the release media of larvae breeding solution; tap water, MARDI lake and Sri Serdang lake.

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