ENCAPSULATION OF *Acalypha Indica* EXTRACT IN CHITOSAN-POLYCAPROLACTONE BLEND

BY

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ABSTRACT

Polymer encapsulation is commonly adopted in drug delivery systems to form encapsulation that can assist in delivering active compound to the targeted area. *Acalypha indica* (AI) crude extract was obtained from AI plants through ultrasound assisted extraction, is naturally unstable in external environment, thus need to be encapsulated to protect against volatility. Chitosan has promising properties good for drug carriers. Physically blending of chitosan with PCL via physical during encapsulation process can benefit to immobilize the AI extracts against any interactions with the external environment through encapsulation. Herein, this study emphasized the development of the encapsulations of AI extracts using chitosan-polycaprolactone (PCL) blend by emulsion-solvent evaporation and then freeze-dried methods. In the beginning, the sonication time was studied to find the best time. Later, 5 minutes time was chosen and being used throughout the study. Three (3) parameters (ratio of chitosan: PCL concentration, PVA concentration , and Concentration of chitosan-PCL blend) for Al encapsulation were studied by fixing a parameter at a time (OFAT). The percentage of encapsulation efficiency (EE%) was recorded as a response for each parameter. To study the interactions between the factors, the study proceeded with central composite design (CCD) as the optimization tools of response surface methodology (RSM). Central points were taken from the preliminary data obtained in one-parameter experiments. The validation was carried out with two data of highest and lowest EE% suggested by CCD. Fourier Transform Infrared Spectroscopy (FTIR), scanning electron microscopy (SEM), particle size analyzer, and zeta potential were used to analyze the properties of selected microencapsulated samples. The highest EE% recorded was 98.70% and the lowest EE% was 87.80%. The results showed the difference of predicted and experimental values at percentage lower than 7.5%. The SEM images revealed the formation of smooth sphrerical shapes. The zeta potential for the highest and lowst EE% recorded were not so significant difference (-24.0 and -26 mV). Whereas the particle size obtained were 2.631 ± 0.14 and 3.568 ± 1.35 respectively. Overall, the encapsulation of (AI) extracts was successful and has the potential to be applied in drug delivery.

ملخص البحث

يتم اعتماد التغليف البوليميري الحيوي بشكل شائع في أنظمة توصيل الأدوية لتشكيل تغليف يمنع انحلال المركبات النشطة قبل الوصول إلى موقع معين. على الرغم من وجود اهتمام بحثي كبير بالعقاقير الاصطناعية ، إلا أن تغليفها بمركبات نشطة طبيعية يبدو أقل دراسة بشكل ملحوظ. نظرًا لأن المركبات النشطة بيولوجيًا *Acalypha indica* غير مستقرة في البيئة الخارجية وأثناء النقل ، فإن التغليف ضروري كحامل لتقليل فقد الأدوية. Chitosan لها خصائص واعدة جيدة لشركات الأدوية.يمكن أن يفيد المزج الفيزيائي Chitosan مع PCL عبر عملية التغليف الفيزيائية في شل حركة مقتطفات AI ضد أي تفاعلات مع البيئة الخارجية من خلال التغليف. تركز هذه الدراسة على تطوير تغليفات مستخلص *Acalypha indica* لتوصيل الدواء. في هذا البحث ، تم مزج Chitosan مع polycaprolactone (PCL) بطريقة تبخير المستحلب والمذيب والتجفيف بالتجميد كأسلوب تجفيف لتقوية تشكيل كبسولات دقيقة. في البداية ، تمت دراسة وقت الصوتنة للعثور على أفضل وقت. اولا اجريت التجربة لايجاد افضل زمن صوتنة والذي تراوح من 3، 5، 7 الى 10 دقائق. تمت دراسة ثلاثة (3) معلمات (نسبة Chitosan: تركيز PCL ، تركيز PVA ، وتركيز مزيج PCL -Chitosan) لتغليف Al عن طريق تثبيت معامل في وقت واحد (OFAT). تم تسجيل النسبة المئوية لكفاءة التغليف (EE٪) كاستجابة لكل متغير. شرعت الدراسة في التصميم المركب المركزي (CCD) كأداة لتحسين منهجية سطح الاستجابة (RSM) ، باستخدام البيانات الأولية التي تم الحصول عليها من OFAT كنقاط مركزية. تم إجراء المصادقة وتم اختيار معطيات من أعلى نسبة (98.70٪) وأدنى (87.80٪) من كفاءة الطاقة (EE٪) مقترحة من قبل وزارة الطاقة. تم استخدام مطيافية فوريه لتحويل الأشعة تحت الحمراء (FTIR) وحجم الجسيمات وإمكانات زيتا لتحليل عينات الكبسلة الدقيقة المختارة. أظهرت النتائج اختلاف القيم المتوقعة والتجريبية بنسبة أقل من 7.5٪. كشفت صور SEM عن تشكيل أشكال كروية ناعمة. لم تكن إمكانات زيتا لأعلى وأدنى نسبة EE% مسجلة فرقًا كبيرًا (24.0- و 26- mV). بينما كان حجم الحبيبات التي تم الحصول عليها 2.631 ± 0.14 و 3.568 ± 1.35 على التوالي. بشكل عام ، كان تغليف مستخلصات (AI) ناجحًا ولديه إمكانية تطبيقه في توصيل الدواء.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master of Science in Engineering

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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Signature Date

This thesis is dedicated to my parents for turning on my dream into reality and my fiancé for his endless support.

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At first glance, my utmost pleasure to dedicate this work to my dear parents and my family, who granted me the gift of their unwavering belief in my ability to accomplish this goal. Thank you for your support and patience.

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LIST OF ABBREVIATIONS

AI	*Acalypha indica* Linn
CCD	Central composite design
Ch	Chitosan
DOE	Design of Experiment
EE	Encapsulation efficiency
FTIR	Fourier Transform Infrared Spectroscopy
OFAT	One-factor-at-a-time
PCL	Polycaprolactone
PEG	Poly(ethylene) glycol
PLGA	Poly Lactic-co-Glycolic Acid
PVA	Polyvinyl alcohol
RSM	Response surface methodology
SEM	Scanning electron microscope
UV-Vis	Ultraviolet-visible

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Over the past decades, a lot of research and invention has been done and keeps growing to enhance the current drug delivery system (Yusuf et al., 2023). In developing a good controlled-release drug delivery system, selecting a good drug carrier is the most challenging in the sense that the side effects of the drugs and the drug carriers on human can be minimized (Adepu & Ramakrishna, 2021). Recently, encapsulation studies are focusing more on synthetic pharmaceutical drugs. However, encapsulations of certain plant extracts somehow are less explored. The challenges of maintaining stable *Acalypha indica* (AI) extracts are related to the fact that the active compounds are naturally volatile, light and temperature sensitive and susceptible to degradation (Bazana et al., 2019). AI is a herbaceous species plant. Yet it gets less attention due to its habitat mostly grow in the yards and often treated as weed. However, AI can be found only at in certain geographical regions (Zahidin et al., 2017). Interestingly, there is a fascinating fact of this plant and highly potential for commercialization. Previously, it was reported that the leaf extracts of AI have several bioactive compounds that can treat respiratory problems such as bronchitis, asthma, and pneumonia (Martin, & Ashokkumar, 2017; Taurozzi, Hackley, & Wiesner, 2012).

Chitosan has been proven as an effective polymeric drug carrier. Chitosan is found naturally from aquatic shell wastes and exists as one of the most abundant polymers occurring in nature, thus providing a vast potential of commercial value. Due to good mucoadhesive properties and biodegradability, chitosan is safe for consumption (Roy & Sahoo, 2016; Szymańska & Winnicka, 2015). However, chitosan needs modification to improve its stability and solubility to form an excellent polymer matrix for microencapsulation. By blending chitosan with other polymers during encapsulation process, the limitations of homopolymer encapsulation can be improved while maintaining the structure of the chitosan and preserves the good physicochemical properties. Physically blending with another polymer is one of many ways to improve the characteristics of chitosan.

Poly-ε-caprolactone (PCL) is a biodegradable aliphatic polyester that has better viscoelastic and allowing a large range of structures such as microspheres. Due to its property, PCL can be easily blended with other polymers such as chitosan for microencapsulations (Christen & Vercesi, 2020). Physically blending of chitosan with PCL via physical during encapsulation process can benefit to immobilize the AI extracts against any interactions with the external environment through encapsulation (Rivas et al., 2019). Encapsulation is very vital as without encapsulation, the uncontrolled environmental condition has tendency to breakdown certain types of beneficial bioactive compounds of the AI extracts.

The emulsion-solvent evaporation method is identified as the most suitable method to encapsulate the ethanolic AI extracts. This method is suitable for the mixing of insoluble materials and polymer assisted by different phase of surfactants (Iqbal et al., 2015). This method followed by hardening and finally produced a sphere shaped particles with the active materials enclosed inside the sphere (Luo et al., 2023). Encapsulation efficiency is one of the most potential indicators of accomplishment in encapsulation. The encapsulation efficiency through this method is affected by several factors, including sonication time, the ratio of chitosan:PCL PVA concentration, and the concentration of chitosan-PCL blends.

The purpose of identifying the best sonication time is the most crucial as the microtip of the ultrasonic homogenization device is sensitive towards erosion (Taurozzi et al., 2012). Considering each brand and size of the microtips have different time of sonication depending on the input power, finding the different sonication time is the most important parameter in this study.

So, the change of these factors gave valuable findings, and this knowledge contributes to the next encapsulation studies.

1.2 STATEMENT OF THE PROBLEM

It is known that chitosan is a weak base, and insoluble in water and organic solvents which limits the encapsulation (Garg et al., 2019). Physically blending of chitosan with other polymers during encapsulation process are promising. To the best of author's knowledge, stabilization study of AI extracts through encapsulation are still less explored. In 2013, an encapsulation study of AI extract done by Amarnath et al. need improvement in terms of the microparticles stability. In conjunction of that, a study of AI extract loaded into the biodegradable chitosan-PCL was proposed to preserve the active compounds against degradations due to the interactions with the environment (Bilia et al., 2018). This blended material is very promising due to non-toxic thus safe for the human body system.

Besides, chitosan-PCL copolymer was capable to microencapsulate the hydrophobic behaviour of AI extracts by emulsion-solvent evaporation method using ultrasonic homogenizer modified by El Hady et al. (2019) methods. The ultrasonic homogenization has several parameters need to be optimized. One of the most important parameters are homogenization time since each ultrasonic homogenization devices possessed different output. Concerning of finding the applicable homogenization time, the sonication time was proposed in the beginning of this research by identifying the highest encapsulation efficiency (EE%) and the morphological characteristic of the microencapsulations. Anwar et al. (2022) reported the optimized sonication time for the encapsulation of lycopene was 6 minutes.

Other than that, the previous reported parameters are less applicable for different types of active compounds used and the polymer matrix due to the behaviour of the drugs and the polymer (El Hady et al., 2019). To overcome this drawbacks, pre-optimizations have been done by one-factor-at-a-time (OFAT) method and followed central composite design (CCD) model to study the interactions among the parameters. There are numerous studies on the chitosan copolymer encapsulation on the hydrophobic and hydrophilic drugs (Kim et al., 2019). Yet to the best of our knowledge, no studies reported on the chitosan-PCL modification encapsulated AI extract. The previous study only focusing the encapsulation for wound healing (Nezhad-Mokhtari et al., 2023). Combining two types of polymers create a new blended biomaterials

give synergistic effects for the better encapsulation. Hence, this study is motivated to produce a stable microencapsulation of AI extracts through the chitosan modification as a polymer matrix to maximize the amount of extract being encapsulated. This is because of the challenges of maintaining a stable *Acalypha indica* (AI) extract are related to the fact that the active compounds are volatile, light and temperature sensitive and degradations (Bazana et al., 2019).

1.3 PURPOSE OF THE STUDY

The *Acalypha indica* (AI) has been acknowledged as medicinal plants traditionally and scientifically proven even though they are often classified as weeds. AI has several beneficial active compounds that can be found abundantly in this plant such as quercetin, gallic acid and rosmarinic acid (Zahidin et al., 2017).

Encapsulation is highly necessary due to the instability of the bioactive compounds in external environment. According to the previous study, chitosan is a promising natural biopolymer obtained by partial deacetylation of chitin which can be naturally found in marine wastes (Kurita, 2006). Chitosan is one of the excellent types of a versatile polymer as it has numerous advantages including non-toxic. Thus, chitosan is safe for oral consumption. Additionally, chitosan is also a biomaterial which can be blended easily to encapsulate the active compound and applied in drug delivery (Wang et al., 2011). The study on the chitosan modification is a topic of interest as it is not altering the fundamental backbone of chitosan and preserve its physicochemical properties. The encapsulation process was successfully done by emulsion-solvent evaporation method with Poly(ε-caprolactone) (PCL). Towards the end of the steps, the microemulsion AI extracts were dried by freeze drying technique and turned into microparticles which in powder form.

1.4 RESEARCH OBJECTIVES

This study aims to achieve the following objectives:

1- To investigate the best sonication time for the formation of chitosan-PCL microencapsulation.

2- To analyse the optimum encapsulation parameter of *Acalypha indica* in the selected chitosan modification for maximum encapsulation efficiency.
3- To examine the characterizations of the chitosan-PCL microencapsulation.

1.5 RESEARCH SCOPES

This study is focusing on the encapsulation of *Acalypha indica* (AI) extracts by emulsion-solvent evaporation method. To be specific, the scopes of this study were further explained according to the objectives as follows:

- Sonication time was the first parameter studied in objective 1 to find the best time to form encapsulations. The time chosen was 3, 5, 7 and 10 minutes. The best sonication time was chosen based on the highest percentage of encapsulation efficiency (EE%) and supported by surface morphology characterization using scanning electron microscope (SEM).

- In objective 2, the ratio of chitosan and PCL as a polymer matrix, PVA concentrations and the polymer matrix concentrations were the other factors optimized by OFAT. Polyvinyl alcohol (PVA) was selected as the non-ionic surfactant for further improving dispersion stability. The chitosan solution with concentrations ranging 0.2-1.0 %w/v were properly diluted in 0.2% w/v acetic acid, PCL solution (0.2-1.0 %w/v) were diluted in dichloromethane (DCM), PVA solution (0.05-1.0 %w/v) were diluted in deionized water under 60 °C and the AI extracts (0.02% w/v) were diluted in ethanol absolute. These solutions were blended ultrasonically later forming the emulsions. The emulsions were stirred gently for 24 hours. The microparticles were dispersed in the deionized water and keep in the -81°C before freeze dried.

- In objective 3, the encapsulated chitosan-PCL loaded AI extract was analysed using FTIR and the morphological structure was observed under SEM. Ultraviolet-visible (UV-Vis) spectrophotometer was used to determine the percentage of encapsulation efficiency (EE%). The microparticles were further characterized with Fourier Transform Infrared (FTIR), particle size analysis and zeta potential.

1.6 THESIS ORGANIZATION

This thesis consists of five chapters which covers all the introduction, literature reviews on the chitosan biopolymers and the selection of methods, methodology, results, and discussion and finally conclusion and recommendations. The abstract briefly summarizes the whole study in this thesis.

Chapter 1 introduced the background of study which is the importance of chitosan blended with synthetic polymer for better encapsulation towards the potential applications of AI extracts. This chapter also briefly introduced the importance of finding the best sonication time and optimized the other three parameters with OFAT and RSM. Then followed by the problem statements, purpose of study, research objectives, and the research scopes.

Chapter 2 discussed details on the introduction of chitosan and its origins. Previous studies of chitosan and the need of modifications were further explained. Numerous types of chitosan copolymer that has been studied in past 10 years and the selection of methodology are also well explained in this chapter. Next, another interesting subchapter is the exploration of encapsulation technology as well as to rediscover the lack of knowledge. The study on encapsulation for drug delivery has been extensively studied not only for the modern medical drugs but also the encapsulation of plant extract. End of this chapter, briefly description of *Acalypha indica* plant and its benefits were reported.

Chapter 3 reports in detail the methodological approach in this study illustrated by flowchart of methodology to give a clear figure. The method of microencapsulation, the optimizations by OFAT and RSM, and analysis has been discussed thoroughly in this chapter. The design of experiment (DOE) of RSM were assisted by Design-Expert v.12. The zeta potential, particle size analysis and SEM are the analysis conducted in this study.

Chapter 4 discusses all the results and analysis obtained from this study. The results from OFAT were used in RSM. Two (2) data of validations suggested by DOE were selected

for the analysis in objective 3. Thus, the importance and the selection of each data were discussed thoroughly.

Chapter 5 concludes all the numerical data obtained from this research work and answered all the objectives. This chapter also includes the future outlook as well as suggestions to improve this research for the next continuation.

CHAPTER TWO

LITERATURE REVIEW

2.1 INTRODUCTION

Encapsulation is a great topic to be explored in the polymer science, and the applications are most promising in pharmaceutical and medicinal fields. Encapsulation is defined as the process of enclosing the plant extracts or drugs in a sphere of capsules to improve its stability (Castro-Enríquez et al., 2020). Encapsulation is very important for every bioactive material to protect from the external environment until reaching the targeted sites in the body system. Besides, encapsulation is important to mask the odour and taste during consuming. In conjunction of that, selection of the carriers (polymer matrix) is promising as to maximise the quantity of drugs being encapsulated and maintain stable while delivery. Moreover, encapsulation can optimize the use of raw materials as well as minimize the production cost.

There are numerous encapsulation materials studied in past years. Mostly focuses on the biopolymer-based in order to maintain stability and bioavailability. Chitosan is one of the encapsulating materials used to encapsulate various kinds of hydrophobic drugs and some bioactive compounds which obtained from plant constituents. Chitosan is not only having biocompatibility properties but also has antimicrobial properties that may kill some harmful microbes in the body system. Due to some limitations on the chitosan, it is needed to blend with other biopolymers or synthetic polymers. Instead of blending with other polymers, recent studies reported by modifying the chitosan with fatty acid-based materials for instance oleic acid (Méndez et al., 2017).

Drying is the most important steps to turn the emulsions into particles. The method of drying also depends on the solubility, sensitivity of the bioactive materials and applications. Spray drying and freeze drying are among the common methods of drying. Spray drying was used mainly for emulsion encapsulation like the encapsulations of *Boswellia carterii* essential oil (Barre et al., 2020) whereas freeze drying usually for drying of insoluble encapsulations like encapsulation of diosmin with chitosan-PLGA (El Hady et al., 2019).

Acalypha indica (AI) somehow was known as cat attractants by some rural regions due to the fresh roots attract cats for their remediation. A study done by Zahidin et al (2018) found out the potential benefits of AI. Interestingly, research also found that AI extracts have numerous good properties of antibacterial (Nikmah et al., 2019). Research and development keep on going from the scratch until ways to stabilize the active compounds of the AI. Further elaborations are given in the next subchapter of the literature review.

2.2 THE POLYMER MATRICES FOR ENCAPSULATIONS

Polymer matrix is defined as the layers consisting of multiple polymer chains (homopolymer or copolymer) which capable to entrap the hydrophilic or hydrophobic drugs. In other words, polymer matrix is the outer layer of the encapsulations (Uhrich & Abdelhamid, 2016). There are many types of polymers which classifies according to the nature of the polymers and chitosan is one of the natural polymers.

2.2.1 Chitosan

Chitosan is a biopolymer derives from chitin. Chitin is the second most important natural polymer of carbohydrates (polysaccharides) in the world. Chitin undergoes deacetylation to form a chitosan biopolymer. Chitosan or linear (1-4) linked 2-amino-2-deoxy-β-d-glucan (i.e., β-d-glucosamine) is a natural polymer which is a linear polysaccharide derived from partial deacetylation of chitins that soluble in acidic aqueous media but insoluble in higher pH media (Rinaudo, 2006). Each unit of chitosan monomer consists of two functional groups which are OH- and NH_3- as illustrates in Figure 2.1

The source of chitosan can be found abundantly from shrimp and crab shell containing chitin which is an N-acetyl glucosamine polymer (Ahmed & Ikram, 2015). Other than that, chitosan also can be obtained from the extraction of chitin from fungi, algae, Echiruda, Annelida, Mollusca, Cnidaria, Aschelminthes, Entoprocta, Bryozoa, Brachiopoda, Arthropoda, Ponogophora and the epidermal cuticle of the vertebrates (Ho et al., 2015).

2.2.2 Chemical structure of chitosan

Chitosan comprises of three reactive groups, which are primary (C-6) and secondary (C-3) hydroxyl groups on each repeat unit and amino (C-2) group on each deacetylated unit. Structurally, chitosan is a linear-chain of copolymer that composed of D-glucosamine and N-acetyl-D-glucosamine that has been synthesized by the partial deacetylation (removal of acetyl group) of chitin (Figure 2. 1). The presence of -NH_2 and -OH groups allow chitosan to interact with other polymers as well as improving the drug properties. Drug solubility, adsorption and biocompatibility are among the improvements in drug properties (Kaur et al., 2023).

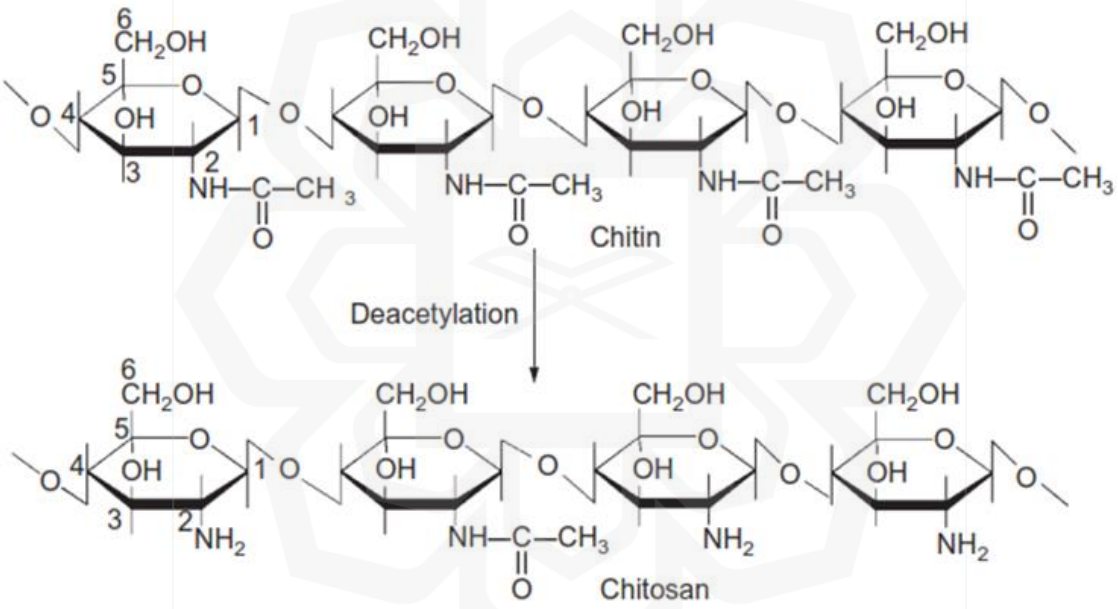

Figure 2.1 Chitin and chitosan's (linear (1-4) linked 2-amino-2-deoxy-β-d-glucan) chemical structure (Lv, 2016)

Chitosan is a non-toxic and biocompatible polymer. Hence, the viscosity of chitosan can influence the biological properties such as wound-healing properties as well as biodegradation by lysozyme. This is because chitosan also has antibacterial properties (El-Hefian et al., 2014). Next, the swelling property of the chitosan decreases with an increase in the concentration of

the cross-linking agent. The summary of physical, chemical and biological properties as tabulated in Table 2.1.

Table 2.1 Physical, chemical, and biological properties of chitosan (El-Hefian et al., 2014)

Physical properties	**Chemical properties**	**Biological properties**
White-yellow in colour	Degree of deacetylation range 70-95%	Biocompatibility
Flakes, bead or powder	Cationic polyamine	Antibacterial
High molecular weight (1.2 X 10^5 $gmol^{-1}$)	High charge density at pHs < 6.5	Safe and non-toxic
High to low viscosity	Forms gels with polyanions	Haemostatic
Intermolecular hydrogen bonding	Linear weak polyelectrolyte	Biodegradable to normal body constituents
Amorphous solid	Adheres to negatively charged surfaces	Bacteriostatic/ Fungistatic
Density range 0.18 to 0.33 g cm^{-3}	Chelates certain transitional metals	Spermicidal
Soluble in diluted aqueous acid solution (i.e.,acetic acid)	Amiable to chemical modification	Anticancerogen
Insoluble in water	Reactive amino/hydroxyl groups	Anticholestermic

According to the Table 2.1 above by El-Hefian et al. (2014), the biodegradability of the chitosan catches more attention among drug delivery researchers as the polymer matrix. Besides, chitosan only needs the diluted aqueous acid (0.1-0.2 %w/v) to dissolve thus promote better degradations in the body digestive system (El Hady et al., 2019).