FLOATING KAPPA CARRAGEENAN BASED HYDROGEL WITH GRAPHENE OXIDE NANOPARTICLES

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ABSTRACT

Incorporation of nanoparticles in drug vehicle has attracted much attention in the area of drug delivery application due to its unique properties. It is hypothesised graphene oxide (GO) nanoparticles incorporation can provide excellent hydrogel properties with effective drug vehicle. In this work, GO nanoparticles are used in the formulation of floating hydrogel prepared using κ-carrageenan, sodium carboxymethyl cellulose and calcium carbonates. Calcium carbonate is added as effervescent agents to promote the buoyancy effect. Floating hydrogel without GO nanoparticle and floating hydrogel with GO nanoparticle act as controls. The analyses were carried out on swelling degree, antibacterial study, floating properties and *in vitro* methylene blue released as modelled drug. The properties of drug carrier were analysed using Fourier transform infrared spectroscopy (FTIR), TGA and Variable Pressure Scanning Electron Microscope (VPSEM). GO-loaded floating nanocomposite hydrogels showed significant effect on swelling ratio which is reduced more than 50% but did not much effect on kinetic reaction with acidic pH1.2 buffer solution. Antibacterial properties were proved based on positive result that inhibited spore growth within 96hours. *In vitro* released profile with additional 0.01% GO was slower (5.4%) compared to the controls. In summary, GO nanoparticles-loaded κ-carrageenan based floating nanocomposite hydrogel has a significant floating potential that could be used as prospective drug carrier in gastrointestinal tract.

ABSTRAK

Campuran nanopartikel dalam sistem penyampaian dadah telah menarik banyak perhatian dalam bidang aplikasi penghantaran ubat kerana sifatnya yang unik. Ia adalah hipotesis graphene oxide (GO) nanopartikel yang dicampur boleh memberikan sifat hidrogel yang sangat baik dengan penyampaian ubat yang berkesan. Dalam kerja ini, nanopartikel GO digunakan dalam perumusan hidrogel terapung yang disediakan menggunakan κ-carrageenan, natrium karboksimetil selulosa dan kalsium karbonat. Kalsium karbonat ditambah sebagai ejen ampungan untuk mempromosikan kesan keapungan. Hidrogel terapung tanpa GO nanoparticle dan hydrogel terapung dengan GO nanoparticle bertindak sebagai kawalan. Analisis dilakukan pada tahap serapan air, kajian antibakteria, sifat-sifat terapung dan in vitro metilene biru dilepaskan sebagai ubat model. Ciri-ciri pembawa dadah dianalisa menggunakan spektroskopi inframerah transformasi Fourier (FTIR), TGA dan Mikroskop Pengimbasan Tekanan Pembolehubah (VPSEM). Hidrogel nanocomposit terapung yang dicampur GO menunjukkan kesan yang ketara terhadap nisbah serapan air yang berkurang lebih daripada 50% tetapi tidak banyak memberi kesan kepada tindak balas kinetik dengan redaman pH1.2 berasid. Sifat antibakteria terbukti berdasarkan hasil positif yang menghalang pertumbuhan spora dalam tempoh 96 jam. Profil in vitro yang dikeluarkan dengan tambahan 0.01% GO adalah perlahan (5.4%) berbanding dengan kawalan. Ringkasnya, GO nanopartikel yang dimuatkan κ-carrageenan berasaskan nanocomposite terapung hidrogel mempunyai potensi terapung yang besar yang boleh digunakan sebagai pembawa dadah prospektif dalam saluran gastrointestinal.

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LIST OF ABBREVIATION

Ca^{2+}	Calcium ion
$CaCO_3$	Calcium carbonate
CO_2	Carbon dioxide
CO_3^{2-}	Carbonate ion
F	Floating
FTIR	Fourier transforms infrared spectra
GO	Graphene Oxide
H^+	Hydrogen ion
H_2O	Water
HCl	Hydrochloric acid
κ-carrageenan	Kappa-carrageenan
NaCMC	Sodium carboxymethyl cellulose
MB	Methylene blue
SEM	Scanning electron microscope
SD	Swelling degree
-OH	Hydroxyl bonding

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CHAPTER 1

INTRODUCTION

1.1 Research Background

Hydrogel is a macromolecular polymer gel that was constructed of network of crosslinked polymer chain. Due to their properties like hydrophilic, biocompatibility and three dimensional structures, hydrogel especially “smart” hydrogel became the great interest to biomaterials scientists. According to Ebara and co-workers(2014),“Smart hydrogel” has the remarkable ability to respond to stimuli in a variety of ways. It has enormous potential in various biomedical applications because some environmental variables, such as low pH and elevated temperatures are found in the human body which is important factor need to consider in designing drug delivery system (Jingquan*et al*., 2014). The fascinating properties of the stimuli-sensitive polymers are promising for many future applications and offer possible use as the next generation of materials in biological, biomedical and pharmaceutical products.

The hydrogel can be classified in various physical form including solid model form (e.g. soft contact lenses), pressed powder matrices (e.g. pills or capsules for oral ingestion), microparticles (e.g. as bioadhesivecarriersfor wound treatments),coating

(e.g. on implants or catheters on pills or capsule or coating on the inside capillaryelectrophoresis), membranes or sheets (e.g. as reservoir in a transdermal drug delivery patch), encapsulated solids (e.g. osmotic pumps) and liquids form (e.g. gels upon heating or cooling) (Ebara*et al.*, 2014; Hoffman, 2002).

Despite considerable advancements in drug delivery, the oral route remains the preferred route due to ease of administration and a cheaper therapy compare to other route. However, the main important is to achieve the high level of patient compliance.

Recently, there are many researches on the development of new materials and these partly are the innovative combination of known components. The structural combination of a polymer hydrogel network with nanoparticles (metals, non-metals and metal oxides) promising of providing superior functionality to the composite materials with various applications (Praveen*et al*,. 2015) The new components could be applied in diverse fields including catalysis, electronics, bio-sensing, drug delivery, nano-medicine, and environmental remediation. Today, incorporation with nanoparticle hydrogel finds their applications in common consumer products and appliances due to their differences in properties compared to bulk materials. However, Praveen and his coworker (2015) stated that, the hydrogel with nanoparticles still have challenges to decrease risks to human health and environment.

1.2 Problem Statement

Recently, many people are aware and concern about their health. The modern lifestyle such as over taking junk food, fast food and the food that contain high percentage of saturated fats are the major factors of unhealthy lifestyle. These imbalance diets will cause the body prone to diseases such as diabetes, heart problem and cancer (Rajgopal*et al.,* 2002). Therefore the patient will seekthe most effective medicine that can reduce pain and heal as fastas possible.

In conventional dosage form, oral drugs delivery are easily absorbed into gastrointestinal tract and have a short-lives due to quickly eliminated from systemic circulation. Frequent dosing is required to achieve suitable therapeutic activity. Sometime, the drugs carried by drug vehicle could not deliver directly to specific target of action to achieve and maintain the desired drug concentration in the body.

By taking conventional oral dosage, patients need to follow the instruction and advice from doctor or medical expertisein hospital. Sometimes the patients forget to follow the schedule by taking the medicine on time or lazy to consume it frequently per day. This is because the conventional oral dosage forms suffer from inability of drug to reside in stomach or proximal part of the small intestine for a prolonged period (Singh and Chauhan.,2011). These will result incomplete drug release in the absorption zone and reducing its bioavailability and therapeutic efficacy (Gadad*et al*., 2009). In another words, the conventional dosage form is very wasting because of incomplete absorption and reduce patient's compliance to consume it (Sing *et al.,* 2011).

Other factors that lead to unhealthy styles are poor sleeping habit, smoking and alcoholic addiction. These bad habits contribute stress to the body and may reduce the absorption nutrient into the body (Nicklas*et al.,* 2000). Insufficient nutrient in the body may cause the person to easily feel tired, inactive and promote

sickness and diseases (Nicklas*et al.*, 2001). To overcome this problem, many people take some dietary supplements of essential nutrient such as vitamin, calcium, iron and probiotics to replenishthe lack of nutrient in the body (Nicklas*et al.*, 2001).

Oral controlled-release drug delivery system provide drug release at a predetermined, predictable, and controlled rate and have drawn considerable attention. Moreover, some drugs have demonstrated poor bioavailability and biocompatibility due to incomplete absorption or degradation in gastrointestinal tract. Biocompatibility is the major concern in development of biomaterial (Ying *et al.*, 2013).

Based onthese problems, more effective way of therapeutic drug or functional food deliveryinto the body has to be studied. To achieve the desired concentration of drug or essential nutrient absorbs into the blood or tissue, designing drug delivery system need to be improved (Singh *et al.*, 2011). Floating deliveryis one of the systems than could potentiallyachieve longer retention time of capsulated bioactive drug or functional food in the gastrointestinal tract (Rajinikhanth and Mishra, 2008). This system will enhance the absorbance of drug or functional food. At the same time, the patient can reduce uptake of oral drug dose per day due the longer pharmacotherapy per dose intake (Patil*et al.*, 2011).

To avoid this limitation, extensive research need to be carried out in designing of sustained drug delivery system that can highly control the drug release, so the drug could be supplied continuously to its absorption site in gastrointestinal tract.Efficient drug delivery system is crucial to ensure optimum dosage of medicine necessary to treat a certain disease. Taking over dosage or drug that is wasted in the digestive system will reduce the benefit to the patients. Hence, a more effective design of delivery system will help patient to heal in a comfortable and practical way.

To improve targeted delivery of drug, the bioavailability and stability of therapeutic agents against degradation and extending drug effect in target tissue, applying nanoparticles seemsto offer much benefit in pharmaceutical studies (Hezaveh and Muhammad, 2012). Besides, applied nanotechnology in drug delivery system offers a suitable method for site-specific and time-controlled delivery of bioactive agents. Many biomaterial researchers showed interests to develop hydrogel incorporated with nanoparticles like gold nanoparticle, graphene, graphene oxide and magnesium oxide for this purpose.

1.3 Objectives of Study

To develop carrageenan based floating hydrogel incorporated with graphene oxide and evaluateits performance in drug delivery system.

1.4 Scope of Study

To achieve the objective, three scopes have been identified in this study

(1) Formulations of carrageenan based floating hydrogel with graphene oxide and examinethe effect of blend ratio by measuringthe swelling degree of hydrogel.

(2) Determination of drug release properties by evaluatingdrug release profilesoffloating hydrogel incorporated with graphene oxide and floating hydrogel withoutgraphene oxide.

(3) Study of the properties offloating carrageenan based hydrogel incorporated with graphene oxide based on antimicrobialeffect, surface morphology thermal stability.

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