PREPARATION AND CHARACTERIZATION OF CARRAGEENAN/ HALLOYSITE NANOTUBE NANOCOMPOSITE FILMS FOR POTENTIAL TRANSDERMAL DRUG DELIVERY APPLICATION

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DEDICATION

This thesis is dedicated to my mother, Rosna Osman, and father, Wahab Musa for their unending support and prayers since the beginning of my study till now. To my husband, Muhammad Akmal Hizami Gapar, who continuously motivates and supports me under all conditions, no matter how challenging and difficult it has been. I would also like to dedicate this thesis to my parent- in- laws, Fatimah Zainudin and Gapar Saleh, whose encouragement and assistance have also helped me to complete this thesis.

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ABSTRACT

The attention of using synthetic polymers in medical and pharmaceutical purposes has been drawn towards polysaccharide-based materials due to their inertness, non-toxicity, biocompatibility, biodegradability, low cost and abundant availability. Among polysaccharides, there has been very little work on carrageenan (CRG) as a candidate for transdermal drug delivery patches. Carrageenan is a sulphated polysaccharide with simple gelation mechanism, thermo-reversible ability and tunable viscoelastic properties. Despite its interesting properties and potential, CRG has low mechanical strength and possesses fast drug release rate which lead to fast disintegration of polymer matrix. In this study, a CRG film was prepared by solution casting with the addition of halloysite nanotube (HNT) as reinforcing filler. Significant mechanical improvement of CRG film was achieved at 3 pph loading of HNT with increased tensile strength and elongation at break, and decreasing modulus; optimum strength of 8.54 MPa, elongation percentage of 53.72% and modulus of 13.76 MPa. The CRG/HNT film with 3 pph HNT also showed high swelling capacity (~97%) with longer disintegration time of more than 20 minutes. The morphological observations and Fourier transform infrared (FTIR) spectra confirmed that good dispersion and interactions were achieved between CRG and HNT. The nanocomposite film has better moisture repellent and thermal stability compared to the pure CRG film. The X-ray diffraction (XRD) of the nanocomposite film revealed preferential orientation of the HNT in CRG matrix and increase in the level of crystallinity. The loading of diclofenac sodium (DS) and benzalkonium chloride (BKC) to the HNT separately showed that the position of drug in the HNT was charge dependent. The DS was found to entrap inside the HNT lumen and has better sustainable release than the BKC which deposited mostly onto the external surface of HNT. The Franz diffusion study revealed that the inclusion of HNT minimized the burst effect of both drug models, sustained the release of DS by ~23% after 12 hours and prolonged the complete release of BKC for more than 7 hours. The nanocomposite film with DS possessed a flux (J) of 0.0117 $mg/cm^2/h$ and a permeability coefficient (P) of 5.91×10^{-3} cm/h, while the film patch with BKC possessed a J value of 0.0489 $mg/cm^2/h$ and a P value of 24.7×10^{-3} cm/h. The release of DS from the patches follows first order kinetic model while the BKC follows zero order kinetic model. The cytotoxicity study indicated improved patch biocompatibility by the HNT addition and the drugs loading induced certain toxicity towards the film patches. Based on these results, the addition of HNT has improved the performance of CRG film as a matrix patch. Therefore, the CRG/HNT film presents potential and feasibility as a material for transdermal drug delivery system.

ABSTRAK

Tumpuan terhadap penggunaan polimer sintetik dalam kegunaan perubatan dan farmasi telah berubah ke arah bahan berasaskan polisakarida disebabkan kelebihannya yang inert, tidak toksik, bioserasi, bioterurai, berkos rendah dan tersedia banyak. Antara kumpulan polisakarida tersebut, terdapat sedikit kajian ke atas karaginan (CRG) sebagai calon pelekat berubat transdermal. Karaginan merupakan polisakarida bersulfat yang mempunyai mekanisma menjadi gel yang ringkas, keupayaan haba boleh diterbalikkan dan ciri-ciri elastik likat yang boleh diubah. Walaupun mempunyai ciri-ciri dan potensi yang menarik, karaginan menghadapi masalah kekuatan mekanikal yang rendah dan kadar pelepasan ubat yang terlalu cepat sehingga membawa kepada penguraian matriks polimer dalam masa yang singkat. Dalam kajian ini, filem karaginan telah disediakan menggunakan teknik acuan larutan beserta penambahan tiub nano halosit (HNT) sebagai pengisi pengukuhan. Peningkatan kekuatan mekanikal filem CRG yang nyata dapat dilihat pada kepekatan 3 pph HNT dengan kenaikan kekuatan tarik dan pemanjangan pada waktu putus dan penurunan modulus; kekuatan optima ialah 8.54 MPa, peratus pemanjangan ialah 53.72%, dan modulus ialah 13.76 MPa. Filem komposit nano dengan 3 pph HNT juga menunjukkan kapasiti pembengkakan yang tinggi (~97%) dengan masa terurai yang lebih panjang melebihi 20 minit. Pemerhatian ke atas morfologi dan inframerah Fourier (FTIR) mengesahkan pengedaran seragam dan interaksi yang bagus telah dicapai di antara CRG dan HNT. Filem komposit nano mempunyai penghindar kelembapan dan kestabilan haba yang lebih baik berbanding filem CRG tulen. Pembelauan sinar-X (XRD) mendedahkan keutamaan orentasi HNT di dalam matrik CRG dan peningkatan tahap pengkristalan. Muatan ubat natrium diklofenak (DS) dan klorida benzalkonium (BKC) ke dalam HNT secara berasingan telah menunjukkan kedudukan ubat di dalam HNT bergantung kepada cas yang dimiliki. DS dijumpai terperangkap di dalam lubang HNT dan mempunyai pelepasan mampan yang lebih baik berbanding BKC yang terletak di kawasan permukaan luar HNT. Kajian penyerapan Franz mendedahkan kemasukan HNT dapat meminimumkan kesan letusan model-model ubat, memampan pelepasan DS sebanyak ~23% selepas 12 jam dan memanjangkan pelepasan BKC sepenuhnya melebihi 7 jam. Komposit nano CRG/HNT-DS mempunyai fluks (J) bernilai 0.0117 $mg/cm^2/h$ dan pekali kebolehtelapan (P) bernilai 5.91 x 10^{-3} cm/h, manakala CRG/HNT-BKC mempunyai nilai J sebanyak 0.0489 $mg/cm^2/h$ dan nilai P sebanyak 24.7 cm/h. Pelepasan DS daripada pelekat berubat mengikut model kinetik pertama manakala BKC mengikut model kinetik sifar. Kajian toksik sel mengesahkan peningkatan bioserasi pelekap berubat yang mengandungi HNT dan kemasukan ubat ke dalam pelekap tersebut menimbulkan kesan toksik tertentu. Berdasarkan keputusan-keputusan ini, penambahan HNT telah menambahbaik prestasi filem CRG sebagai bahan pelekap berubat matriks. Oleh itu, filem komposit CRG/HNT mempamerkan potensi dan kesesuaian sebagai bahan dalam sistem penghantaran ubatan transdermal.

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LIST OF ABBREVIATIONS

2D	-	Two dimensional
3D	-	Three dimensional
AFM	-	Atomic force microscopy
BC	-	Bacterial cellulose
BKC	-	Benzalkonium chloride
CNT	-	Carbon nanotube
CRG	-	Carrageenan
CS	-	Chitosan
DS	-	Dilofenac sodium
EVA	-	Ethyl vinyl acetate
FTIR	-	Fourier transform infrared
GIT	-	Gastrointestinal tract
HA	-	Hyaluronic acid
HCl	-	Hydrochloride
HNT	-	Halloysite nanotube
HPMC	-	Hydroxypropylmethylcellulose
MMT	-	Montmorillonite
MTT	-	(3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide)
PBS	-	Phosphate buffered saline
PCL	-	Poly(ε-caprolactone)
PE	-	Polyethylene
PEG	-	Poly(ethylene glycol)
PET	-	Polyethylene terephthalate
PIB	-	Polyisobutylene
PP	-	Polypropylene
PS	-	Polystyrene
PVA	-	Poly(vinyl alcohol)
SC	-	Stratum corneum
SEM	-	Scanning electron microscopy

TEM	-	Transmission electron microscopy
TGA	-	Thermogravimetric analysis
XG	-	Xyloglucan
XRD	-	X-ray diffraction

LIST OF SYMBOLS

κ	-	Kappa
t	-	Time
%	-	Percentage
wt.	-	Weightage
pph	-	Parts per hundred of base polymer
R^2	-	Linear regression coefficient
>	-	More than
<	-	Less than
±	-	Plus minus
μ	-	Micro
λ	-	Wavelength
Ɵ	-	Angle
J	-	Steady-state flux
P	-	Permeability coefficient
˚C	-	Degree Celsius

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

Drug delivery system aims to heals, suppress, or maintain certain activity inside the body by introducing any formulation or device containing active substance that enables therapeutic effects (Jain, 2008). Numerous methods of drug transportation have been developed such as oral extended-release pills and tablets, injection, inhalers, transdermal patches, and various implants to meet this purpose. Traditional method of delivering drug often favours oral route as it is easy to consume. Then, parenteral route (injection) was established to accommodate the transport of low bioavailability drug which failed to be accomplished by the oral route. However, this parenteral route is least selected by patients since it is painful. Owing to that, transdermal route of drug delivery captures wide attention to be explored and applied in pharmaceutical and health care area (Jain, 2008; Yewale *et al.*, 2014).

Transdermal or dermal route of drug delivery makes use of skin as the place of transporting drug topically or into the systemic circulation. Skin is readily accessible for drug delivery with large surface absorption. The advantage of implementing transdermal drug delivery is that it avoids the first pass metabolism and allows sustained release. Skin patch, compared to other transdermal drug dosage form, can control the period of administration easily by simply apply and remove the patch and is not easy to get wash off by unintended touching like most semi-solid form. In addition, since the patch has defined area and drug loading, the rate and amount of drug delivered is controllable (Ranade and Cannon, 2011; Xi *et al.*, 2013).

There are several commercialized skin patch for different treatment purposes available on the market. Most of them were made from synthetic polymers and

synthetic elastomers (Kandavilli *et al.*, 2002; Yewale *et al.*, 2014). These have later bring up concern on environmental side-effects which have created a priority in using natural-derived polymers in manufacturing of any biomedical and pharmaceutical devices (Ojeda, 2013; Erni-Cassola *et al.*, 2019). Even natural polymers like hydroxypropyl cellulose used in current patches were not made to stand alone in layer but as a gel-like drug reservoir which needs other synthetic polymer membrane to support. Whereas hydroxypropyl methylcellulose (HPMC) matrices without rate-controlling membranes, eventhough was able to yield clear films because of the enough solubility of the drug in the polymer, exhibited a burst effect during dissolution testing because the polymer was hydrated easily and swelled, leading to the fast release of the drug (Kandavilli *et al.*, 2002). The preferences on synthetic polymers to construct good biomedical devices and transdermal drug delivery patches were because they provided excellent combination of physical and mechanical properties (Kandavilli *et al.*, 2002; Maitz, 2015). Thus, initiatives to provide more feasible natural polymer films with adequate characteristics are crucial so that it meets the latest global interest.

Among numerous natural biomaterials, polysaccharide-based materials have created massive interest in biomedical and pharmaceutical purposes through versatile chemical and physical modifications of carrageenan (CRG) for the past two decades with good compatibility and consolidating behavior (Liu *et al.*, 2015). CRG is a sulphated polysaccharide and has the ability to form a thermo-reversible gel upon cooling. Being derived from certain red seaweeds, CRG poses as promising excipient with anticoagulant, antihyperlipidemic, antioxidant, anticancer, antiviral, and immunomodulating effects (Campo *et al.*, 2009; Necas and Bartosikova, 2013; Li *et al.*, 2014). The uniqueness of CRG lies on its ester sulphate group and the existence of 3,6-anhydro-bridge. However, like other natural biodegradable polymers, CRGs suffer from weak mechanical strength (Yu *et al.*, 2006). A comparison study has revealed that κ-CRG tablets eroded very fast, resulting in short drug release (Liu *et al.*, 2015). Furthermore, there are limited reports exploring the effects of nanofillers toward CRG. Gold (Au) nanoparticle, iron (III) oxide (Fe_3O_4), and carbon nanotube (CNT) are examples of nanomaterial used to facilitate interesting functions to CRG (Estrada *et al.*, 2013; Liu *et al.*, 2015).

This decade has witnessed escalating interest in the use of halloysite nanotubes (HNTs) clay mineral in drug delivery application. Its special tubular structure and high surface area are comparable to that of CNTs (Erpek *et al.*, 2015b) . HNTs are at an advantage because they are nontoxic, biocompatible, cheaper and easier to disperse (Kamble *et al.*, 2012). There are several HNTs-polymer nanocomposites reported in previous researches (Pasbakhsh *et al.*, 2013; Saif and Asif, 2015). A polymer-coated HNT exhibited reduced drug release and displayed potentially prolonged drug release. The ultrasmall lumen of HNT is practical for active agents loading and control release. HNTs also may serve as reinforcement in polymer composites to effectively enhance mechanical and overall properties of polymers (Mousa *et al.*, 2016). The inclusion of nano-sized material such as HNT in the CRG might open many interesting properties mainly for drug delivery applications.

Therefore, this study aims to develop a nanocomposite film used as drug–polymer matrix film for transdermal delivery systems. Here, we improved the mechanical properties and disintegration time of CRG film by adding HNT as the reinforcement. Series of evaluation and testing was conducted to evaluate the nanocomposite potential for transdermal drug delivery. After confirming the potential of CRG/HNT as transdermal patch, two drug models namely, diclofenac sodium (DS) and benzalkonium chloride (BKC) were first loaded to the HNT. DS is a non-steroidal anti-inflammatory drug that always been an anionic drug candidate for transdermal drug delivery because of its low bioavailability (Willis *et al.*, 1979). Meanwhile, BKC antimicrobial agent is a good candidate for cationic drug model in this study because it has shown high affinity towards negatively charged clay minerals (Zanini *et al.*, 2013). The best feed ratio for the drugs and halloysite was determined before HNT-drug was incorporated into CRG matrix. Then, pure CRG and its nanocomposite films were taken to Franz diffusion test and cytotoxicity study as these two studies are very crucial in investigating the important properties of a matrix forming polymer.

1.2 Problem Statement

Material selection and design are of prime importance in formulating various criteria of new transdermal patch. Back then, the trend of material choice was towards synthetic polymers. Nevertheless, this has later brings up concern on environmental side-effects which have created a priority in using natural-derived polymers in manufacturing of any biomedical and pharmaceutical devices (Ojeda, 2013; Erni-Cassola *et al.*, 2019). Previous studies have shown CRG as a potential candidate for drug delivery application such as oral extended-release tablets, microcapsules, microspheres, beads, nanoparticles, and film dressing (Li *et al.*, 2014). However, there is hardly any report on CRG as transdermal patch. This is due to the low mechanical strength and fast disintegration of polymer matrix (Yu *et al.*, 2006; Ghanam and Kleinebudde, 2011; Liu *et al.*, 2015). These resulted in fast drug release rate and thus the system failed to sustain. This is the main challenge faced by many natural polymers which forced for incorporation of other synthetic polymers or non-economic and not eco-friendly fillers (Kandavilli *et al.*, 2002; Yewale *et al.*, 2014). In view of the aforementioned conditions, CRG needs some kind of eco-friendly reinforcement to improve the mechanical properties and increase the disintegration time of polymer matrix. Estrada *et al.* (2013) and Liu *et al.* (2015) suggested this issue to be resolved by adding nano-sized materials within the CRG matrix(Estrada *et al.*, 2013; Liu *et al.*, 2015). In this study, nanocomposite CRG films were prepared with HNT as interesting non-toxic filler to achieve an ideal sustainable delivery system of anionic and cationic drug models.

1.3 Research Objectives

This study aims to achieve the following objectives:

(a) To optimize the mechanical properties and disintegration time of CRG film by adding HNT

(b) To characterize the optimized CRG/HNT films in compare to the pure CRG film through morphological, structural , and thermal analyses

(c) To investigate the loading and release of benzalkonium chloride and diclofenac sodium as drug models in HNT

(d) To evaluate the drug-loaded CRG/HNT films for transdermal drug delivery by Franz diffusion and cytotoxicity studies

1.4 Scope of Study

In order to achieve the listed objectives, nanocomposite films of CRG with HNT as the reinforcement were prepared. In this study, κ-CRG was incorporated with HNT at filler contents of 1, 2, 3, and 4 pph. Pre-observation of film preparation showed the sample with HNT content of more than 4 pph resulting in agglomeration of HNT caused by over saturation. Effects of HNT loading on the mechanical and swelling properties of CRG were studied. An optimized nanocomposite film was selected according to these testings and was further characterized. Morphological and physicochemical studies of the composite films were carried out by means of scanning electron microscopy (SEM), transmission electron microscopy (TEM), water contact angle measurement, moisture absorption, Fourier transform infrared (FTIR), thermogravimetric analysis (TGA) and x-ray diffraction (XRD). Next, the loading of two drugs into HNT were analysed in terms of entrapment efficiency, loading capacity and adsorption capacity. N_2 sorption isotherms and FTIR confirmed the loading. Release of both drugs was investigated in buffer solution. At final stage, the drug-loaded HNT was added into CRG films and tested for mechanical properties to confirm the films integrity after drug loading. The evaluation of the film potential in transdermal drug delivery was conducted by Franz diffusion test. Lastly, the prepared films were also evaluated on kinetic model calculation, MTT assay, fluorescent microscopy and SEM.

1.5 Significance of Study

Transdermal drug delivery represents one of the most rapidly advancing areas in pharmaceutical technology, catalyzed by the developments in the field of polymer science. Natural-derived polymers offer non-toxic, biodegradable, and many unique properties that can be manipulated to occupy the industry needs. CRG, being a thermoreversible gel-forming material, hydrophilic, and having tunable viscoelastic properties make it an ideal polymer for sustainable drug delivery applications. The presence of functional groups has allowed CRG to be easily modified and improved. This new exploration may open up more variety of material choices for transdermal patch in future. Incorporation of HNT into CRG film may not only provides good reinforcing properties, but also consumer-safe and eco-friendly material option. Current material used for transdermal patch is very limited and are very dependent on synthetic polymers. For instance, Alza Corporation (Mountain View, CA) mainly concentrates on using ethylene vinyl acetate (EVA) copolymers or microporous polypropylene, and Searle Pharmacia (Barceloneta, PR) company concentrates on silicone rubber. By far, the researches on new materials for transdermal patches are still repeatedly growing and relevant.

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