SYNTHESIS AND CHARACTERIZATION OF POLYACRYLAMIDE/SODIUM CARBOXYMETHYL CELLULOSE/MONTMORILLONITE NANOCOMPOSITE HYDROGEL VAGINAL RING FOR DRUG DELIVERY SYSTEMS

GHORBANALI SHARIFZADEH

A dissertation submitted in partial fulfillment of the
requirements for the award of the degree of
Master of Science (Polymer Technology)

Faculty of Chemical Engineering
Universiti Teknologi Malaysia

AUGUST 2013

To my beloved family

ACKNOWLEDGEMENT

Praises to Allah for giving me the strength, perseverance and intention to go through and complete my study.

I would like to express my sincere gratitude to my respected supervisor Assoc. Prof. Dr. Shahrir Hashim for his help, support, and guidance. I owe him a lot for what he taught me during these years.

Last but not least, I am grateful to my loving family for their loves and supports.

ABSTRACT

This research developed a hydrogel vaginal ring consisting of polyacrylamide (AAm), sodium carboxymethylcellulose (NaCMC) for vaginal drug delivery. To improve the swelling behaviour of vaginal ring, different concentrations of NaCMC were utilized. The results indicated that 0.1 g NaCMC had the highest amount of swelling. However, by increasing the swelling characteristic of vaginal ring, a low strength hydrogel was obtained. Therefore, N,N'-methylenebisacrylamide (MBA) was applied to the hydrogel in order to study the effect of cross-linker on prepared polymer efficiency and swelling properties. By adding of MBA within vaginal ring network, sufficient stability as well as proper swelling properties was obtained. It was found that vaginal ring composed of 0.1 g NaCMC and 0.02 g MBA showed the optimum swelling and suitable structure stability. In addition, montmorillonite (MMT) was added to the blank hydrogel (AAm/NaCMC) to investigate its effect on drug delivery in the simulated vaginal environment (pH= 4-4.5). Both blank and nanocomposite vaginal rings were loaded with methylene blue (MB) as a modelled drug. The vaginal rings were characterized by Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscope (SEM), X-ray Diffraction (XRD) and Nuclear Magnetic Resonance (NMR). *In vitro* release behavior of MB illustrated that incorporation of MMT into vaginal ring controlled the drug delivery. It was found that by changing the concentration of MMT from 0.007 g to 0.01 gr, the drug release was prolonged for 15 days by reducing the initial drug release. According to the results, AAm/NaCMC/MMT nanocomposite hydrogel vaginal rings can be considered as good candidates for the vaginal drug delivery.

ABSTRAK

Kajian ini membangunkan cincin hidrogel faraj yang terdiri daripada polyacrylamide (AAM), carboxymethylcellulose natrium (NaCMC) untuk penghantaran dadah ke faraj. Untuk memperbaiki tingkah laku "swelling" cincin faraj, kepekatan berbeza NaCMC telah digunakan. Keputusan menunjukkan bahawa 0.1 g NaCMC mempunyai jumlah "swelling" tertinggi. Walau bagaimanapun, dengan meningkatkan ciri-ciri "swelling" cincin faraj, hidrogel dengan kekuatan yang rendah telah diperolehi. Oleh itu, MBA telah digunakan ke atas hidrogel untuk mengkaji kesan "cross-linker" ke atas kecekapan polimer tersedia dan sifat-sifat "swelling". Dengan penambahan MBA di dalam rangkaian cincin faraj, kestabilan yang mencukupi serta sifat-sifat "swelling" yang betul telah diperolehi. Didapati bahawa cincin faraj terdiri daripada 0.1 g NaCMC dan 0.02 g MBA menunjukkan "swelling" yang optimum dan struktur kestabilan yang sesuai. Di samping itu, montmorilonit (MMT) telah ditambah kepada hidrogel kosong (AAM /NaCMC) untuk mengenalpasti kesan penghantaran ubat dalam simulasi persekitaran faraj (pH = 4 - 4.5). Kedua-dua hidrogel kosong dan cincin hidrogel faraj berKomposit nano telah ditambah dengan metilena biru (MB) dimodelkan sebagai dadah. Cincin faraj telah dicirikan oleh Spektroskopi inframerah transformasi Fourier (FTIR), Mikroskop Elektron Imbasan (SEM), pembelauan sinar-X (XRD) dan Getaran Magnetik Nuklear (NMR). Sifat pelepasan MB secara "in vitro" mununjukkan bahawa penambahan MMT ke cincin faraj dapat mengawal penghantaran dadah. Didapati bahawa dengan mengubah kepekatan MMT, pelepasan dadah telah berpanjangan selama 15 hari dengan pengurangan pembebasan dadah awal. Berdasarkan keputusan, AAM / NaCMC / MMT cincin faraj hidrogel berkomposit nano boleh dianggap sebagai pilihan yang baik untuk penghantaran ubat faraj.

TABLE OF CONTENTS

LISTS OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AA	-	Acrylic acid
AAm	-	Acrylamide
ACE	-	Angiotensin-converting-enzyme
BSA	-	Bovine serum albumin
CD	-	Cyclodextrin
DDSs	-	Drug delivery systems
DS	-	Degree of substitution
EG	-	Ethylene glycol
EGDMA	-	Ethylene glycol dimethacrylate
FTIR	-	Fourier Transform Infrared
GC	-	Gas chromatography
HA	-	Hyaluronic acid
HDEEMA	-	Hydroxydiethoxyethyl methacrylate
HEEMA	-	Hydroxyethoxyethyl methacrylate
HEMA	-	Hydroxyethyl methacrylate
HIV	-	Human immunodeficiency virus
HPLC	-	High-performance liquid-chromatography
HPMA	-	N-(2-hydroxypropyl) methacrylamide
KBR	-	Potassium bromide
MAA	-	Methacrylic acid
MBA	-	N,N'-Methylenebisacrylamide

MDEEMA	-	Methoxydiethoxyethyl methacrylate
MEEMA	-	Methoxyethoxyethyl methacrylate
MEMA	-	Methoxyethyl methacrylate
MS	-	Mass spectrometry
NIPAAM	-	N-isopropylacrylamide
NVP	-	N-vinyl-2-pyrrolidone
PAAm	-	Polyacrylamide
PBO	-	Poly(butylene oxide)
PCL	-	Polycaprolactone
PCM	-	Phase change material
PEGA	-	PEG acrylate
PEG	-	Poly(ethylene glyol)
PEGDA	-	PEG diacrylate
PEGDMA	-	PEG dimethacrylate
PEGMA	-	PEG methacrylate
PF	-	Propylene fumarate
PHB	-	Poly(hydroxy butyrate)
PLA	-	Poly(lactic acid);
PLGA	-	Poly (lactic-co-glycolic acid)
PNIPAAm	-	Poly(N-isopropyl acrylamide)
PNVP	-	Poly(N-vinyl pyrrolidone)
PVA	-	Poly(vinyl alcohol)
PV amine	-	Poly(vinyl amine)
PVAc	-	Poly(vinyl acetate)
SEM	-	Scanning Electron Microscope
VAc	-	Vinyl acetate
VFS	-	Vaginal fluid stimulant
UV-VIS	-	Ultraviolet/visible spectroscopy
XRD	-	X-ray Diffraction

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Hydrogels are polymeric networks capable of absorbing large amount of water while remaining insoluble in water with regards to chemical or physical cross-linking of individual polymer chains (Lin and Metters, 2006). Hydrogels are of special interest in controlled release applications due to their soft tissue biocompatibility, easy dispersion of drugs within their network and the high degree of control by selecting suitable physical and chemical properties of the hydrogel (Chen *et al.*, 2004; Risbud *et al.*, 2000). The capability of them to prepare good dispersion of therapeutic agents along with sustained delivery of drug make them as excellent candidate for biomedical applications (Risbud, *et al.*, 2000).

Among different medical shape devices, vaginal ring have been attracted lots of interests. Vaginal rings are pliable, circle-shaped, devices that prepare long time, controlled release of materials to the vagina for native or corporal efficacy. Controlled release returns to steady distribution of drug in a extended time. They are patterned as self-inserted and deleted, that placed in the over third of the vagina, generally close to the cervix (Barnhart *et al.*, 2005). Vaginal ring device are gained a great deal of attention for birth control and estrogens substitution treatment along with their ability to prepare

controlled release of drugs. Recently, a significant concern has been devoted in producing equivalent rings for the management of microbicidal combination to pull up vaginal HIV transfer (Malcolm *et al.*, 2010).

Several polymers have been utilized in the synthesize of vaginal rings including thermoplastics, silicon rubbers and hydrogel rings. Elastomeric compounds and thermoplastics are considered as the most common types of vaginal rings. Among them, polydimethylsiloxane (PDMS) as a class of elastomeric materials have been widely used in biomedical applications due to their excellent biocompatibility. Silicon rubbers are cured by condensation and addition-cure that eliminate their application in biomedical and pharmaceutical studies. The poor drug release from silicon elastomer is known as a drawback of the systems (Mashak and Rahimi, 2009).

Another important types of vaginal rings are thermoplastic materials. Thermoplastics have been used in pharmacuetical device areas and are significant material class from which Food and Drug Administration (FDA) approved intervaginal devices (Foran, 2003; Novak *et al*., 2003; Thyssen *et al*., 2001). Polyurethanes (PU) are a class of highly flexible thermoplastic that are being used for construction of vaginal devices. The reaction between polyethylene oxide (PEO) or polytetramethylene oxide (PTMO) a diol and aliphatic asocyanate are responsible for formation of PU. Among PU materials, aromatic isocyanates have used extensively due to reasonable cost and excellent physical characteristics (Ali *et al.*, 1993b). However, under unsuitable storing and processing conditions they can hydrolytically decompose into aniline derivatives, dangerous compounds that are known as chemotype of toxic carcinogens, mutagens, and teratogens (Ali, *et al.*, 1993b).

1.2 Problem Statement

The delivery of drug from vaginal comprise a wide diversity of medical shapes containing vaginal films, vaginal rings, semi-solids, foams, pessaries, liquid preparations, tablets, capsules and tampons (Vermani and Garg, 2000). Vaginal drug delivery (VDD) have several disadvantages that eliminate their applications such as short time for retention of vaginal, leakage, poor users satisfactory and coital dependence (in the case of HIV microbicides and spermicides) (Barentsen *et al.*, 1997). In addition, fast elimination from demand place is referred as conventional vagina drawback delivery (Garg *et al.*, 2003).

All the drawbacks associated with vaginal route of delivery can be solved by vaginal ring (Morrow *et al.*, 2011). To improve the efficiency of applying vaginal rings several factors should be taken in account specially for microbicide rings that are used for a long periods in a body such as user satisfaction, time of product service. In recent years, using biopolymers in vaginal drug delivery have attracted many attentions due to their excellent compatibility with body parts that lead to decrease side effects (Malcolm, *et al.*, 2010).

A few numbers of hydrogel vaginal rings have been manufactured to outreach barriers related to more formal designs and fabrication substances, particularly the limits placed on the permeation of high molecular weight and/or relatively hydrophilic HIV microbicide candidates through conventional vaginal rings manufactured from silicone and thermoplastic. By using the ring body as a holder for insertion and retention of alternative solid dosage forms, these permeation obstacles might be defeated. PAAm/NaCMC hydrogel rings are introduced to release drugs in the vagina environment since they are non-toxic and easy to synthesized.

In polyacrylamide (PAAm) based hydrogels, lots of applications have been found. Cross-linked polymers which can imbibe large amount of water can be used in broad various fields such as biotechnology, biomedical engineering, food industry and separation process. Due to specific properties like considerable amount of swelling in water, biocompatibility, absorbing water easily or hydrophilicity and non-toxicity this hydrogel can be utilized in various fields of biologic, medical, pharmaceutics and environment (Karadağ and Saraydın, 2002).

Sodium carboxymethylcellulose (NaCMC) is an anionic derivative of cellulose which is regarded as a non-toxic and non-irritant material. In addition, it has been used for drug delivery release and mucoadhesive properties. Also, it has been employed to reduce the rate of mucociliary and improve release and comprehension of gene treatment (Griesenbach *et al.*, 2010; Ludwig, 2005; Rokhade *et al.*, 2006). NaCMC is physiologically safe, inexpensive and possesses good compatibility with mucous membrane as well as high capacity of water bonding (Liu *et al.*, 2007; Ludwig, 2005; Sudhakar *et al.*, 2006).

Recently, the medical characteristics of montmorillonite (MMT) have gained many attentions. MMT has large surface area, shows great adsorb ability which make it as a potent detoxifier and able to adsorb dietary toxins, bacterial toxin related to gastrointestinal disturbance, metabolic toxins like steroidal metabolites attached to pregnancy (Dong and Feng, 2005). The layered structure of MMT is responsible for intercalation of therapeutic agents between layers and providing controllable release of drugs (Joshi *et al.*, 2009a, 2009b).

1.3 Research Objectives

The overall objective of this research is to synthesize PAAm/NaCMC/MMT hydrogel and to characterize the property of drug delivery system :

i. To prepare and characterize PAAm/NaCMC hydrogel nanocomposite vaginal ring for drug delivery.
ii. To study the effect of MMT concentration on the drug release of PAAm/NaCMC hydrogel
iii. To investigate the effect of MBA (crosslinkinking agent) concentration on PAAm/NaCMC hydrogel.

1.4 Research Scopes

In this research nanocomposite hydrogels composed of PAAm/NaCMC loaded with MMT nanoparticles will be prepared. Then, methylene blue as a model drug will be encapsulated within hydrogel network. The hydrogel will be characterized by using various characterization tests. In addition, its chemical and physical properties will be studied. Finally, the release behavior of methylene blue will be tested.

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