MODIFIED ACRYLAMIDE HYDROGEL NANOCOMPOSITES FOR VAGINAL DRUG DELIVERY SYSTEM

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To my lovely father and mother

For their love, support, sacrifices and blessings

And to all other beloved ones

God bless them all!

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ABSTRACT

This study conducted on the structure of modified acrylamide-based hydrogel by synthesizing the nano composites. The hydrogels employed in this study were provided through a combination of acrylamide monomers, montmorillonite clay, Sodium carboxymethylcellulose (NaCMC) and magnesium oxide (MgO) nanoparticles by crosslinking polymerization. *N, N, N', N'*-tetramethyl ethylenediamine and ammonium persulfate as the initiator were applied in the structure of the polymer. In addition, the total of the polymerization and characterization were utilized based on three types of hydrogels which are acrylamide (Aam), Aam/NaCMC and Aam/NaCMC/MgO hydrogels. The properties of surface morphology of the hydrogels were characterized by swelling ratio, field emission scanning electron microscope (FESEM), texture analysis, x-ray diffraction and Fourier transform infrared spectroscopy (FTIR). Findings of the study considered the nano composites consisting of MgO have the highest swelling ratio and gel strength compared to Aam and Aam/NaCMC hydrogels. Thus, MgO is an appropriate nanoparticle to be used in the nano composites. The role of NaCMC was also studied in the swelling and consequently in drug release. The systems were characterized regarding rheological behavior of hydrogel, FTIR, and FESEM. The dispersion of the nanoparticles MgO and drug (acyclovir) inside the hydrogel was shown by transmission electron microscopy. Acyclovir, one of the famous drugs to treat the vaginal infections, was used as the drug for delivery and release in the vagina conditions. It was loaded into the polymer through the soaking method in an aqueous solution contained acyclovir. The drug release was studied in two different mediums, phosphate-buffer saline (PBS) (pH 7.4) and vaginal fluid simulant (SVF) (pH 4.5) aqueous solutions were utilized. The amount of released drug from the hydrogels was determined using high performance liquid chromatography. The best amount of NaCMC and MgO used in this study was 0.2 g and 0.01 g at pH 6, respectively. The aggregate percentage of released acyclovir diversed between 89.7% and 35.1% in SVF and 76.41% and 22.24% in PBS. In this study, the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay test showed that the acrylamide-based hydrogel demonstrated a cytotoxicity effect at 12.5, 25,50, 100 and 200 mg/ml concentrations.

ABSTRAK

Kajian ini dijalankan ke atas struktur hidrogel berasaskan akrilamida yang diubahsuai untuk mensintesis komposit nano. Hidrogel yang digunakan dalam kajian ini telah disediakan melalui gabungan monomer akrilamida, tanah liat montmorilonit, natrium karboksilmetilselulosa (NaCMC) dan partikel nano magnesium oksida (MgO) menerusi pempolimeran silang. *N, N, N ′, N′*-tetrametiletilenadiamina dan ammonium persulfat sebagai pemula telah digunakan di dalam struktur polimer. Di samping itu, jumlah pempolimeran dan pencirian telah digunakan berdasarkan kepada tiga jenis hidrogel iaitu akrilamida (Aam), Aam/NaCMC dan hidrogel Aam/NaCMC/MgO. Sifat-sifat morfologi permukaan hidrogel telah dicirikan oleh nisbah pengembangan, mikroskop elektron pengimbas pancaran medan (FESEM), analisis tekstur, pembelauan sinar-x dan analisis inframerah transformasi Fourier (FTIR). Hasil kajian ini menunjukkan komposit nano terdiri daripada MgO mempunyai nisbah pengembangan dan kekuatan gel yang paling tinggi berbanding dengan lain-lain jenis komposit. Oleh itu, MgO merupakan partikel nano yang sesuai untuk digunakan dalam komposit nano. Sistem tersebut dicirikan berdasarkan kelakuan reologi hidrogel, FTIR dan FESEM. Penyebaran partikel nano MgO dan drug (*acyclovir*) di dalam hidrogel telah ditunjukkan oleh mikroskop elektron penghantaran. *Acyclovir*, iaitu salah satu drug yang terkenal untuk merawat jangkitan faraj telah digunakan sebagai drug dalam sistem penghantaran dan dilepaskan ke dalam faraj. Ia telah dimuatkan dalam polimer melalui kaedah rendaman dalam larutan akueus yang mengandungi *acyclovir*. Pelepasan drug telah dikaji dalam dua medium yang berbeza, larutan akueus salinus penimbal-fosfat (PBS) (pH 7.4) dan penyelaku cecair faraj (SVF) (pH 4.5) telah digunakan. Untuk menentukan jumlah drug yang dibebaskan daripada hidrogel kromatografi cecair prestasi tinggi telah digunakan. Jumlah terbaik bagi NaCMC dan MgO yang digunakan dalam kajian ini adalah masing-masing 0.2 g dan 0.01 g pada pH 6. Peratusan agregat bagi *acyclovir* yang dibebaskan berbeza antara 89.7% dan 35.1% untuk SVF dan 76.41% dan 22.24% untuk PBS. Dalam kajian ini, ujian assai 3-(4,5-dimetiltiazol-2-yl)-2,5-difeniltetrazolium bromida mendapati bahawa hidrogel berasaskan akrilamida telah menunjukkan kesan sitotoksik pada kepekatan 12.5, 25,50, 100 dan 200 mg/ml.

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LIST OF ABBREVIATIONS

PDMS	-	polydimethylsiloxane
FDA	-	Food and Drug Administration
VDD	-	Vaginal Drug Delivery
HIV	-	Human immunodeficiency virus
Aam	-	Acrylamide
MMT	-	Montmorillonite
MgO	-	Magnesium oxide
NaCMC	-	sodium carboxymethyl cellulose
SVF	-	Simulated Vaginal Fluid
TP	-	Topological
SR	-	Slide-Ring
NC	-	Nanocomposite
DN	-	Doublenetwork
MMC	-	Macromolecular microsphere composite
HEMA	-	2-hydroxyethylmethacrylate
IPN	-	Interpenetrating networks
FTIR	-	Fourier Transform Infrared Spectroscopy
FESEM	-	Field emission Scanning Electron Microscopy
TEM	-	Transmission Electron Microscope
DSC	-	Differential scanning calorimetry
NMR	-	Nuclear magnetic resonance
HCl	-	Hydrochloric Acid
PMMA	-	Polymethyl methacrylate
PAA	-	poly-acrylic acid
RSM	-	Response Surface Methodology
polydimethylamino ethylmethacrylate	-	PDEAEMA

HSV	-	Herpes Simplex Virus
VZV	-	Varicella Zoster Virus
SR	-	Swelling Ratio
MW	-	Molecular Weight
EPR	-	Enhanced permeability and retention
HUVECs	-	human umbilical vein endothelial cells
MPA	-	Medroxyprogesterone acetate
SA	-	Polyacrylamide sodium acrylate
BDMA	-	1,4-butanediol dimetacrylate
EGDMA	-	Ethylene glycol dimethaacrylate
TMPTA	-	Trimethylolpropane triacrylate
HA	-	hydroxy- apatite
TEMED	-	*N,N,N*-tetramethylethylenediamine
APS	-	Amunium persulphate
MBA	-	*N, N'*-methylenebisacrylamide
TGA	-	Thermogravimetric analysis
DTA	-	Differential thermal analysis
DSC	-	Differential Scanning Calorimetry
XRD	-	X-ray diffraction
PBS	-	Phosphate Buffered Saline
MTT	-	3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide
DMSO	-	Dimethyl sulfoxide
STD	-	Standard

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

Hydrogels are polymeric networks that are able to absorb large amount of water without solubility in the 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 functions due to their soft tissue biocompatibility, easy dispersion of drugs within their network and the high degree of control by selecting appropriate chemical and physical properties of the hydrogel (Chen et al., 2004; Risbud et al., 2000). The competency of them to organize good dispersion of therapeutic agents beside with sustained delivery of drug make them an excellent candidate for biomedical applications (Risbud et al., 2000).

Amongst different medical shape devices, vaginal ring has been attracted lots of interests. Vaginal rings have round-shape and are flexible devices that formulate prolonged, controlled release of materials to the vagina for native or corporal efficacy. Controlled release proceeds to steady distribution of drug in an extended time. They are marbled as self-inserted and removed, that placed in the over third part of the vagina, usually near to the cervix area (Barnhart et al., 2005). Vaginal ring devices are extended a great deal of attention for birth control and estrogens substitution treatment along with their aptitude to prepare controlled release of drugs. Recently, an exceptional concern has been devoted to producing corresponding rings for the control of microbicidal combination to pull up vaginal Human immunodeficiency virus (HIV) transfer (Malcolm et al., 2010).

Numerous polymers have been applied in the manufacture of vaginal rings containing thermoplastics, silicon rubbers and hydrogel rings. Elastomeric mixtures and thermoplastics are deliberated as the most common types of vaginal rings. Amongst them, polydimethylsiloxane (PDMS) as a class of elastomeric materials have been extensively used in biomedical applications because of their excellent biocompatibility. Silicon rubbers are preserved by condensation and addition-cure that exclude their application in biomedical and pharmaceutical studies. The deprived drug release from silicon elastomer is recognized as a problem of the systems (Mashak and Rahimi, 2009).

Another significant varieties of vaginal rings are thermoplastic materials. Thermoplastics have been used in pharmaceutical device areas and are significant material class from which Food and Drug Administration (FDA) approved for intervaginal devices (Malcom et al., 2010).

1.2 Statement of Problem

The delivery of drug from vaginal consists of an inclusive diversity of medical shapes comprising vaginal films, foams, semi-solids, vaginal rings, tablets, capsules, liquid preparations, pessaries and tampons (Vermani and Garg, 2000; Barentsen et al., 1997). The main advantages of vaginal drug delivery is prolonged release, minimal systemic side effects, an increase in bioavailability, use of less total drug than an oral dose, self-medication is possible, contact with digestive fluid is avoided and degradation of drug is minimized, nausea, vomiting, emesis induced through oral administration is avoided (Garg et al., 2003).

E Entirely the disadvantages related with vaginal route of delivery can be solved by vaginal ring (Barnabas et al., 1999). To expand the competence of applying vaginal rings, numerous factors should be taken into account particularly for microbicide rings that are used for a long period in a body - for instance customer satisfaction and period of product service. In current years, expending biopolymers in vaginal drug delivery have involved lots of considerations because of their

excellent compatibility with body portions that lead to reduction of side effects (Malcolm et al., 2010).

A rare amounts of hydrogel vaginal rings have been manufactured to outreach barriers related to more formal designs and fabrication ingredients, predominantly the limits located on the relatively hydrophilic HIV microbicide candidates and/or pervasion of high molecular weight over usual vaginal rings manufactured from thermoplastics and silicone. By consuming the ring body as a holder for enclosure and holding of alternative solid dosage systems, these penetration obstacles could be overwhelmed. Instead, the problems in the fabrication of these novel components may eradicate their presentations for a short period of time in biomedical and pharmaceutical uses (Malcolm et al., 2010). To overwhelm this problem, Aam/NaCMC/MgO hydrogel ring is introduced to release drugs in the vaginal environment meanwhile they are non-toxic and easy to synthesize.

In general, the swelling ratio of the acrylamide-based hydrogels would change with the pH and ionic strength of the media. It is well known that the pH of the solution in which an ionic polymer is swollen affects the extent of swelling. The ionization of the acidic groups can cause the dissociation of hydrogen bonds. The increase in pH causes ionization of the carboxylic acid groups, the polymer chains extend more in the higher pH as the ionic groups repel each other. The drug loading by a swelling method can be performed based on the hydrogel swelling data in the selected solution. The drug loading content is controlled by the polymer composition and can be estimated from the swelling level in the loading solution. Hydrogel swelling influences the release kinetics via a swelling controlled mechanism. By reaching to higher swelling of the hydrogels then the higher drug loading will be achieved. Therefore, better drug loading can cause for better drug release. To reach the better release condition, optimization of the materials and conditions can be done to improve the result.

In polyacrylamide (Aam) based hydrogels, plenty of applications have been found. Cross-linked polymers which can imbibe large amount of water can be used in broad 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. It is highly water-absorbent and forming a soft gel when hydrated (Karadağ and Saraydın, 2002).

Sodium carboxymethylcellulose (NaCMC) is an anionic derivative of cellulose which is regarded as a non-toxic and non-irritant material. Furthermore, it has been used for drug delivery release and mucoadhesive properties. Likewise, it has been engaged to decrease the amount of mucociliary and improve release and comprehension of gene treatment (Griesenbach et al., 2010; Ludwig, 2005; Rokhade et al., 2006). NaCMC is physiologically safe, reasonable and keeps decent compatibility with mucous membrane as well as extraordinary capacity of water bonding. Carboxymethylcellulose (CMC) is an anionic polyelectrolyte that is available as the free acid or, more commonly as the sodium salt; due to the polar nature of the carboxyl groups, NaCMC is soluble in both hot and cold water. CMC is used in a wide range of pharmaceutical and related applications where thickening, suspending, stabilizing, binding, and film forming properties are important, e.g., in the formulation of gels, suspensions and wound dressings (Liu et al., 2007; Ludwig, 2005; Sudhakar et al., 2006).

Lately, the medical characteristics of montmorillonite (MMT) have gained many considerations. MMT has enormous surface area, displays abundant adsorb ability which make it as a potent detoxifier and able to adsorb dietary toxins, bacterial toxin related to gastrointestinal disruption, metabolic toxins conforming steroidal metabolites attached to pregnancy (Dong and Feng, 2005). The layered structure of MMT is liable for intercalation of therapeutic agents between layers and providing controllable release of drugs (Joshi et al., 2009a, 2009b).

In the current study, to control the initial burst release by modification of matrix structure, the magnesium oxide (MgO) nanoparticles are used, thus can effect on the release mechanism. As the metal oxides such as MgO are essential minerals for human health, it is preferred to apply in the matrix of hydrogel. The application

of MgO micro- and nano-sized particles has become interesting owing to its biomedical applications (Hezaveh et al., 2013).

Based on research about different crosslinkers and different initiators, it is concluded that the best gel-forming cross linkers are N, N'-methylenebisacrylamide (BIS) and poly(ethylene glycol) PEG (1000), dimethacrylate (DMA) which were similar in their performance. The three initiators ammonium persulphate (APS), azobis (2-Mi propane) hydrochloride (AZAP and AZIP) were judged to be similar in their general performance, as far as the neat gels were concerned (Janney et al., 1998).

1.3 Objectives of Study

The objectives of the study are:

(i) To design acrylamide-based hydrogel as the vaginal ring for vaginal drug delivery (pH 4.5, 37ºC)

(ii) To study the effect of nanoparticles (MgO), on drug release in the vaginal condition (SVF, pH 4.5, 37ºC)

(iii) To determine the main factors of optimum drug release efficiency in SVF

1.4 Scope of Study

This study is divided into three major scopes:

(i) Design and synthesis of Aam/NaCMC/MgO hydrogel vaginal ring that to be loaded with a drug (Acyclovir) in a suitable condition for vaginal fluid (pH 4.5, 37ºC). The designing of the Aam/NaCMC/MgO will be run by formulation of the hydrogel

using Design Expert software. The NaCMC and MgO as variables will be studied. After the designing and synthesis step, the best formulation of the Aam/NaCMC/MgO hydrogel to be determined. To study the drug release, the hydrogels will be drug-loaded in the simulated vaginal fluid (SVF) medium at 37ºC.

(ii) Study on the effect of MgO on drug release in the vaginal condition. To study the effect of MgO on drug release, a range of (0.01-0.02 mg) MgO content will be chosen to apply in the polymer matrix to find out the best amount of the nanoparticle to reach to the best drug release from Aam/NaCMC/MgO hydrogel.

(iii) Release of the acyclovir in the SVF (pH 4.5, 37ºC) and determination of optimum efficiency of release. The release in the PBS (pH 7, 37ºC) is selected as the control. To study the drug release from Aam/NaCMC/MgO hydrogels in two different mediums, the HPLC method will be applied because of its high accuracy and qualification. The results of the drug release will be shown in the graph plots to find out the best condition of drug release.

1.5 Significance of Study

The vaginal administration of different pharmacologically active molecules is a current medical practice, with particular interest in the management of the conditions of the local genital, such as infection, neoplastic lesions or atrophic vaginitis, or with contraceptive and labor prevention/inducing purposes (Alexander et al., 2004; Srikrishna & Cardozo, 2013). The most important beneficial features of this drug delivery route is because of possibility of reduced systemic drug exposure and the easiness of administration. Semi-solid dosage forms, namely gels, have been traditionally regarded as preferable for vaginal drug administration but others such as inserts, vaginal suppositories, solutions, tablets and foams have also been frequently used (Khutoryanskiy, 2014; Das Neves et al. 2014). In the drug delivery system based on hydrogel, the swelling ratio is a very significant parameter because of its

determination by the pore size or mesh that has an important effect on the drug carrying. The swelling ratio is known to be controlled by cross-linking ratio, network structure and hydrophilicity (Kim et al. 2009).

Controlled-release technologies allow for effective use of existing drugs and successful development of new drug candidates. Therefore, developing new drug delivery technologies and utilizing them in product development is crucial for pharmaceutical companies to compete and survive (Omidian & Park 2008).

The strategy to improve the structure of hydrogel and efficiency of drug loading and drug release of the hydrogels is to applying the NaCMC and MgO in the formulation of the matrix. Using NaCMC in the acrylamide hydrogels will cause the high hydrophilic and pH sensitive effect on the polymer. Composite hydrogels from cellulose and other polymers have been prepared by different technology to combine the different properties of cellulose and other polymers. With the development of nanotechnology, this strategy is suitable for fabricating novel cellulose-based hydrogels with multifunctional properties. NaCMC in the hydrogels structures have many favorable properties such as hydrophilicity, biodegradability, biocompatibility, transparency, low cost, and non-toxicity. Therefore, using NaCMC in the hydrogels creates wide applications in tissue engineering (Vinatier *et al.,* 2009) and controllable delivery system (Chang *et al.,* 2010).

Among inorganic materials, metal oxides such as MgO are of particular interest as they are stable under harsh process conditions and are known to be essential minerals for human health. Recently, the application of MgO nano- and micro-sized particles has attracted attention due to its biomedical applications.

The novelty of this research is using acrylamide copolymers as hydrogel base in combination with MgO and NaCMC. The purpose of using NaCMC is to increase the swelling ratio of the hydrogels hence increasing the drug loading respectively. Moreover, use of MgO in the nanocomposite helps in controlling the drug release and increasing the strength of the hydrogel.

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