UNIVERSITI PUTRA MALAYSIA

PREPARATION AND CHARACTERIZATION OF HYDROGELS FROM CARBOXYMETHYL SAGO STARCH AND METHACRYLIC ACID BY ELECTRON BEAM IRRADIATION FOR CONTROLLED-RELEASE APPLICATION

ZAKIAH BINTI JAMINGAN

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By

ZAKIAH BINTI JAMINGAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Master of Science

August 2014

DEDICATION

To my beloved parents,

Husband and Aisyah Yumna,

Thank you for everything

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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ZAKIAH BINTI JAMINGAN

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Chairman: Professor Mansor Bin Ahmad, PhD

Faculty : Science

Carboxymethyl sago starch (CMSS) is one of the natural polymers that have high value as polymeric devices for medical application due to its potential as a biocompatible material. The aims of this project were to prepare and characterize hydrogels for controlled release application, targeted for gastrointestinal route, using CMSS, with the degree of substitution (DS) 0.75, and methacrylic acid (MAA) via electron beam irradiation technique. The hydrogels were prepared by irradiating the CMSS/MAA mixture with electron beam at 5, 10, 15, 20, and 25 kGy doses. Besides, the effect of preparation conditions, such as the amounts of CMSS and MAA added,the irradiation doses on the gel fraction, and the swelling behavior of the hydrogels, were investigated. The hydrogels were then characterized by infrared analysis, thermal properties, surface morphology, and drug release behavior. The study showed that 40% (w/v) of CMSS hydrogels were sufficient for further formulation as controlled release devices. Furthermore, from the study, it had been proven that the optimum amount of 5.0 g or 12.5% of MAA addition gave the highest gel fraction, which was 66.12% and a swelling degree of 94.23 (g/g). The gel fraction also increased with the increase in dose of irradiation. As a matter of fact, the swelling behavior suggested that the hydrogels are pH responsive, whereby minimal swell occurred at pH 2, and optimal swell took place at pH 7. Then, the Fourier Transform Infrared (FTIR) analysis revealed that MAA took part in the formation of CMSS/MAA hydrogels due to the appearance of a new peak at low intensity at 1698 cm^{-1}, which indicated that the MAA was successfully grafted onto the CMSS hydrogel. Furthermore, the thermal analysis results showed that the thermal stability of the hydrogel increased with the addition of MAA into the CMSS hydrogel by shifting the decomposition temperature to a higher temperature, which was 309.1 °C. In addition, the surface study showed that the morphology of the

CMSS/MAA hydrogel was dependent on the amount of MAA. The study is then, extended for controlled release evaluation by using the Bovine Serum Albumin (BSA) as a model drug. The observation showed that hydrogel irradiated at 15 KGy obtained the optimum loaded drug of 44.0 % (w/w) with 88.5 % (w/w) of drug release within 24 hours. In conclusion, this preliminary study suggested that CMSS/MAA hydrogels could be used as a controlled release device for drug released applications.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENYEDIAAN DAN PENCIRIAN HIDROGEL DARIPADA KARBOKSI METIL KANJI SAGU DAN ASID METAKRILIK MENGGUNAKAN SINARAN ELEKTRON UNTUK APPLIKASI PELEPASAN TERKAWAL

Oleh

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Karboksimetil-kanji sagu (CMSS) adalah salah satu polimer semulajadi yang mempunyai nilai yang tinggi sebagai peranti polimer untuk aplikasi perubatan ini kerana potensinya sebagai bahan yang bersifat bioserasi. Tujuan projek ini adalah untuk menyediakan dan mencirikan hidrogel untuk aplikasi kawalan pelepas untuk laluan gastrousus menggunakan karboksimetil-kanji sago dengan tahap penggantian, (DS) 0.75 dan asid metakrilik (MAA) melalui teknik penyinaran elektron. Campuran hidrogel CMSS/MAA telah disediakan daripada campuran CMSS/MAA melalui teknik penyinaran alur elektron pada dos 5, 10, 15, 20 dan 25 kGy. Kesan komposisi CMSS dan MAA, Kandungan gel yang terhasil dan tingkah laku pembengkakan hidrogel yang disintesis telah disiasat. Hidrogel kemudian dicirikan untuk analisis inframerah, sifat haba, morfologi permukaan dan pelepasan dadah. Kajian menunjukkan bahawa, dengan 40% (w/v) CMSS sudah cukup untuk formulasi seterusnya sebagai bahan pelepasan dadah. Menurut kajian ini lagi, penambahan MAA sebanyak 5.0g atau 12.5% (w/v) akan menghasilkan hidrogel dengan pecahan gel yang tertinggi iaitu 66.12% dan pembengkakan hydrogel sebanyak 94.23 (g/g). Pecahan gel juga dilihat semakin bertambah dengan peningkatan dos penyinaran. Disamping itu, sifat pembengkakan hidrogel pula menunjukkan hidrogel yang terhasil bersifat peka terhadap pH dimana pembengkakan minima berlaku pada pH 2 dan pembengkakan optima pada pH 7. Kemudian, Fourier Transform Infrared (FTIR) pula menunjukkan bahawa, MAA telah terlibat dalam pembentukan hidrogel CMSS/MAA kerana kewujudan puncak baru dengan intensiti rendah pada 1698 cm^{-1} yang menunjukkan MAA berjaya dicantumkan kepada hidrogel CMSS. Tambahan pula, keputusan analisis terma menunjukkan bahawa kestabilan terma hidrogel meningkat dengan tambahan MAA ke dalam hidrogel dengan suhu terkompos

beralih pada 301.9 ºC. Seterusnya, kajian menunjukkan morfologi permukaan hidrogel CMSS/MAA bergantung kepada komposisi MAA. Kajian ini kemudian, dilanjutkan untuk penilaian pelepasan terkawal dengan menggunakan Serum Albumin "Bovine" (BSA) sebagai model dadah. Pemerhatian menunjukkan bahawa, hidrogel dengan dos penyinaran 15 kGy adalah paling optima dengan menunjukkan peratusan pengumpulan dadah sebanyak 44.0% (w/w) dan pelepasan model dadah adalah sebanyak 88.5% (w/w) dalam masa 24 jam. Kesimpulannya, kajian awal ini mencadangkan bahawa, hidrogel CMSS/MAA boleh digunakan untuk aplikasi pelepasan dadah secara terkawal.

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I certify that a Thesis Examination Committee has met on 22 August 2014 to conduct the final examination of ZakiahbintiJaminganon her thesis entitled "**Preparation and characterization of hydrogels from carboxymethyl sago starch and methacrylic acid by electron beam irradiation for controlled-release application"** in accordance with the Universities and University Colleges Act 1971 and the constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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TABLE OF CONTENTS

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LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

AA	Acrylic acid
BC	Bacterial Cellulose
BSA	Bovine Serum Albumin
CMC	Carboxymethyl cellulose
CMS	Carboxymethyl starch
CMSS	Carboxymethyl sago starch
D.S	Degree of substitution
DTG	Differential Thermogravimetry
EB	Electron beam
FTIR	Fourier Transform Infrared Spectroscopy
GI	Gastro Intestine
KGy	Kilogray
MAA	Methacrylic acid
NVP	N-Vinyl Pyrolidone
PMAA	Polymethacylic acid
PVP	Polyvinalpyrolidone
SEM	Scanning Electron Microscopy
SGF	Simulated gastro fluid
SIF	Simulated intestinal fluid
SMCA	Sodium monochloroacetate
TGA	Thermogravimetric Analysis
Wt%	Weight percentage

CHAPTER 1

INTRODUCTION

1.1 Background of the research

Hydrogels are a unique type of polymeric material. Interests on research development in polymeric hydrogels have started around the 1950s (Guenet, 1992). Hydrogels are simply known as materials that swell when placed in a fluid. Hydrogels have a variety of definitions that describe this new polymeric material. Most often, hydrogels can be defined as three dimensional polymer networks that can absorb large amounts of water or biological fluids, and can hold the fluid without dissolution (Peppas and Mikos, 1986). In addition, hydrogels are also known as polymeric material when water-insoluble polymer absorbs a huge amount of water fluid, or else they are simply defined as water-swollen polymer network (Swarbrick, 2006).

Some hydrogels are considered as smart materials due to the uniqueness of their properties. Hydrogels have biocompatible properties, which can be designed to archive desirable properties (e.g. solution-to-gel transitions or swelling/collapse) in response to environmental stimuli, such as pH, temperature, solvent polarity, ionic strength (Mart *et al*., 2006; de las Heras Alarcón *et al*., 2005), and so on. As a result, hydrogels have been applied in various fields, such as food industries, superabsorbent material, and in pharmaceutical area. Among them, the applications of hydrogels in pharmaceutical area and biomedical disciplines are the most vital and promising in their usage. In this area, hydrogels have been used as contact lenses in ophthalmology, as absorbable sutures in surgery, as well as to cure illnesses, such as diabetes mellitus, osteoporosis, asthma, heart diseases, and neoplasm, in other areas of clinical practice (Gibas and Janik, 2010). This polymeric hydrogels can also be used as membranes for biosensors, materials for artificial skin, linings for artificial hearts, and also suitable as drug delivery devices (Peppas, 1997).

Besides, several materials can be used to form hydrogels, either synthetic or natural based copolymer or homopolymer. Among those materials, researches on hydrogels made from natural based (e.g. starch and CMS from various sources, cellulose, CMC, bacterial cellulose, and citosan) have recently increased due to the vast advantages these natural based materials have to offer. Compared to the synthetic materials, the natural based polymer is cheaper and easily obtained due to the abundant growth in the nature.

Carboxymethyl starch (CMS) biopolymer is one of the well known polysaccharide starch derivatives that also can be further developed into hydrogels. CMS has water-soluble biopolymer properties and swells well in water (Yaacob *et al*., 2011). As mentioned earlier, recently, researchers are more interested to fully utilize inexpensive resources that mostly come from the nature to be developed into hydrogels based products. Most commercial CMS are made from corn starch and tapioca. Good news for fellow Malaysians, it has been found that sago starch extracted from sago palms (Metroxylon sago) also has great potential to be synthesized into CMS, and then, further used as hydrogels for various applications.

In Sarawak, Malaysia, sago palms grow well in swampy areas that are inexpensive and are in urgent need of economic development. In a well attended farm, an estimation of 175 kg of sago starch per palm is produced, which contributes to a total yield of 25 tons of sago starch/ha. The starch is produced at the rate of approximately 300 million tons/year, and it is used in many applications, such as processed into monosodium glutamate, fructose syrups, and glucose (Pushpamalar *et al*., 2006).

Hydrogels can be prepared either by using chemical method or irradiation method. Nowadays, with advanced technologies, it is very interesting to prepare hydrogels using the irradiation technique, such as by electron beam irradiation. This radiation based method offers more advantages compared to other conventional method, such as chemical method, especially for medical purposes. The advantages are firstly, radiation solves the problem of sterilization of products and allows the use of advanced and simpler technology than the "conventional" one. Secondly, radiation produces pure products with no contamination in the end products from the residuals of toxic initiators or ballast materials. Lastly, radiation leads to the formation of human friendly products by the application of this ionizing radiation that originates from electron accelerators and also safe for the environment (Rosiak *et al*., 1995b).

In addition, throughout these years, hydrogels have gained increased attention among researchers, especially for drug delivery devices. This is due to the similarities found in the properties between hydrogels and hydrated body tissues, which are highly hydrated in three dimensional networks, and they possess highly biocompatible properties. These unique properties of hydrogels strongly make them possible to be further exposed and to be developed to different biomedical materials, especially for drug delivery devices.

1.2 Problem Statement

The pharmaceutical area, especially the drug delivery application, has gained so much attention due to the high demand and the good prospect of product development. Knowledge on the properties and the behavior of drug delivery devices towards the environmental stimuli of the body is a must, so that, suitable devices can be further improved to make sure optimum delivery using highly safety product is achieved. So, more researches have been continuously conducted in order to offer consumers safe and suitable pharmaceutical products. Besides, many commercial drug delivery devices are made from animal gelatin source and synthetic polymer, while the method for hydrogels preparation that is widely used is copolymerization by chemical initiator.

Nowadays, hydrogels that are made from plant source, especially polysaccharide, using the irradiation method has created great interest among researchers based on increase amount of paper published which covered in this area. Furthermore, irradiation method is a smart way to produce hydrogels compared to chemical method because it does not require any chemical initiators, has short processing time, and the crosslink of the hydrogels is easier controlled through the dose of irradiation. By the hard work from research activities done by various group of researchers such as Yaacob *et al*., (2011), Pushpamalar *et al*., (2013) and many more, hydrogels can be prepared by using the modified starch from sago plant or its derivatives, such as Carboxymethyl Sago Starch. In fact, it has been proven that materials made from sago not only can be used in the food industry, but actually, it can be commercialized as products of medical devices. CMSS has good properties of biocompatibility and blood compatible properties. However, for CMSS to be used as drug delivery devices, it needs to be further modified due to some weaknesses. The main weakness of polysaccharide derivatives is the high solubility properties in aqueous medium, leading to the premature release (Nizam El-Din *et al*., 2010) and the inability to form a stable hydrogel (Sutar *et al*., 2008). Hence, due to this characteristic, polysaccharides cannot be used alone to produce effective gel for certain applications.

Therefore, in order to overcome this problem, cross linking with other polymer, such as from methacrylic acid, is needed. MAA is a water soluble material, which can be found in the form of clear liquid. This monomer has been widely used in the pharmaceutical area due to its smart feature, which is sensitive to pH change. The combination of CMSS and MAA as pH-sensitive monomer improves the thermal stability of the starch derivatives (Saboktokin *et al*., 2009). Furthermore, the addition of MAA into CMSS leads to unique hydrogels with potential applications as a biomaterial that exhibits various properties, depending on the composition of the hydrogels.

Thus, in this study, CMSS from sago starch was synthesized first. The synthesized CMSS was characterized for the determination of the CMSS degree substitution (DS). The synthesized CMSS was characterized by Fourier Transform Infrared Spectroscopy (FT-IR), and morphology analysis. Then, the CMSS/MAA hydrogels were prepared by using the electron beam irradiation technique. Since, the electron beam irradiation itself acted as a crosslink agent, no other chemical crosslink agent was added in this study in order to protect the inherent biodegradable and biocompatible properties of the natural polymers. The properties of gel, such as the gel content and the degree of swelling, were investigated with respect to various compositions and irradiation doses. The thermal study and the morphology of the hydrogels were studied as well. Besides, evaluations of drug load and drug release behaviors of the hydrogels were also looked into. The novelty of this study lied on the capable of producing hydrogels using CMSS and MAA via electron beam irradiation method, which has not been deeply explored previously for drug delivery application.

1.3 Objectives of the study

The main objectives of this study were:

1. To prepare and characterize CMSS from sago starch.
2. To optimize the preparation of hydrogels from CMSS and MAA using electron beam irradiation.
3. To characterize and study the physical properties of the hydrogels, the effects of various irradiation doses, and the composition of gel fraction and swelling behavior.
4. To evaluate the controlled release application of the prepared hydrogels using Bovine Serum Albumin as model drug.

REFERENCES

Abramyan, E. A. (1988). *Industrial electron accelerators and applications* (pp. 302). New York : Hemisphere Publishing Corporation.

Ahmad, F. B., Williams, P. A., Doublier, J.L., Durand, S., and Buleon, A. (1999). Physico-chemical characterisation of sago starch. *Carbohydrate Polymers*, 38(4), 361-370.

Akala, E. O., Kopečková, P., and Kopeček, J. (1998). Novel pH-sensitive hydrogels with adjustable swelling kinetics. *Biomaterials*, 19(11), 1037-1047.

ASTM. (1992). Standard Test Method for Sodium Carboxymethylcellulose. In Annual Book of ASTM Standards, Section 6, Volume 06.02, D1439-83a, 249-256.

Atala, A, and Lanza, R.P. (2006). *Methods of Tissue Engineering* (pp. 99-114). USA : Gulf Professional Publishing.

Bajpai, A. K., Shukla, S. K., Bhanu, S., and Kankane, S. (2008). Responsive polymers in controlled drug delivery. *Progress in Polymer Science*, 33(11), 1088-1118.

Basta, A. H., and El-Saied, H. (2000). Characterization of polymer complexes by thermal and IR spectral analyses. *Polymer-Plastics Technology and Engineering*, 39(5), 887-904.

Bhattacharya, A. (2000). Radiation and industrial polymers. *Progress in Polymer Science*, 25(3), 371-401.

Bhattacharya, A., and Misra, B. (2004). Grafting: a versatile means to modify polymers: techniques, factors and applications. *Progress in Polymer Science*, 29(8), 767-814.

Biswal, D., and Singh, R. (2004). Characterisation of carboxymethyl cellulose and polyacrylamide graft copolymer. *Carbohydrate Polymers*, 57(4), 379-387.

Brazel, C. S., and Peppas, N. A. (1999). Mechanisms of solute and drug transport in relaxing, swellable, hydrophilic glassy polymers. *Polymer*, 40(12), 3383-3398.

Burillo, G., and Ogawa, T. (1985). Effect of pressure on the radiation-induced cross-linking of some vinyl polymers. *Radiation Physics and Chemistry*, 25(1), 383-388.

Charlesby, A. (1992). Radiation effects on polymers. *In Concise Encyclopedia of Polymer Processing and Applications* (pp. 581-588). Oxford: Pergamon Press.

Chauhan, G. S., and Chauhan, S. (2008). Synthesis, characterization, and swelling studies of pH-and thermosensitive hydrogels for specialty applications. *Journal of Applied Polymer Science*, 109(1), 47-55.

Chavda, H., Modhia, I., Mehta, A., Patel, R., and Patel, C. (2013). Development of bioadhesive chitosan superporous hydrogel composite particles based intestinal drug delivery system. *Bio Medical Research International*,1-10.

Chen, Y., Liu, Y.F., Tan, H.M., and Jiang, J.X. (2009). Synthesis and characterization of a novel superabsorbent polymer of carboxymethyl chitosan graft copolymerized with vinyl monomers. *Carbohydrate Polymers, 75*(2), 287-292.

Chmielewski, A.G., Saeid, M.H., and Shamshad, A. (2005). Progress in radiation processing of polymers. *Nuclear Instruments and Methods in Physics Research B* , 236, 44–54.

Choi, J.I., Lee, H.S., Kim, J.H., Lee, K.W., Chung, Y.J., and Byun, M.W. (2008). Effect of electron beam irradiation on the viscosity of carboxymethylcellulose solution. *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms*, *266*(23), 5068-5071.

Chuah, C. T., Sarko, A., Deslandes, Y., and Marchessault, R. H. (1983). Packing analysis of carbohydrates and polysaccharides. Part 14. Triple-helical crystalline structure of curdlan and paramylon hydrates. *Macromolecules*, *16*(8), 1375-1382.

da Silva, R., and Ganzarolli de Oliveira, M. (2007). Effect of the cross-linking degree on the morphology of poly (NIPAAm-co-AAc) hydrogels. *Polymer*, *48*(14), 4114-4122.

Dahlman, O., Jacobs, A., and Sjoberg, J. (2003). Molecular properties of hemicelluloses located in the surface and inner layers of hard wood and softwood pulps. *Cellulose*, 10, 325–334.

Das, N.(2013). Preparation methods and properties of hydrogel: a review. *International Journal of Pharmacy and Pharmaceutical Sciences*, 5(3), 112-117.

de las Heras Alarcón, C., Pennadam, S., and Alexander, C. (2005). Stimuli responsive polymers for biomedical applications. *Chemical Society Reviews*, *34*(3), 276-285.

Dubinsky, S., Grader, G. S., Shter, G. E., and Silverstein, M. S. (2004). Thermal degradation of poly (acrylic acid) containing copper nitrate. *Polymer Degradation and Stability*, *86*(1), 171-178.

Eid, M. (2008). In vitro release studies of vitamin B12 from poly-N-vinyl pyrrolidone/starch hydrogels grafted with acrylic acid synthesized by gamma radiation. *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms*, *266*(23), 5020-5026.

El-Hag Ali, A., and Al Arifi, A. (2009). Characterization and in vitro evaluation of starch based hydrogels as carriers for colon specific drug delivery systems. *Carbohydrate Polymers*, *78*(4), 725-730.

El-Hag Ali, A., Shawky, H., Abd El Rehim, H., and Hegazy, E. (2003). Synthesis and characterization of PVP/AAc copolymer hydrogel and its applications in the removal of heavy metals from aqueous solution. *European Polymer Journal*, *39*(12), 2337-2344.

El-Mohdy, H.L.A (2007). Water sorption behaviour of CMC/PAM hydrogel prepared by c-irradiation and release of potassium nitrate as agrochemical. *Reactive and Functional Polymers*, *67(10)*, 1094-1102.

El-Naggar, A. W. M., Alla, S. G. A., and Said, H. M. (2006). Temperature and pH responsive behaviours of CMC/AAc hydrogels prepared by electron beam irradiation. *Materials Chemistry and Physics*, *95*(1), 158-163.

Fang, M., Fowler, A., Tomkinson, J., and Hill, S. (2002). The preparation and characterization of a series of chemical modified potato starches. *Carbohydrate Polymer, 47, 245-252.*

Fritzsche, J., Teichmann, J., Heuzeroth, F., van den Boogaart, K. G., and Peuker, U. A. (2013). Impact of wetting to the agglomeration of dispersed particles in an aqueous medium. *Advanced Engineering Materials, 15*(12), 1299-1306.

Ghandehari, H., Kopečková, P., and Kopecek, J. (1997). In vitro degradation of pH-sensitive hydrogels containing aromatic azo bonds. *Biomaterials*, *18*(12), 861-872.

Gibas, I., and Janik, H. (2010). Review: synthetic polymer hydrogels for biomedical applications. *Chemistry and Chemical Technology*, 4(4), 297-304

Greminger, G.K. (1978). Cellulose Derivatives, Ethers. In H.F. Mark, M. Grayson, and D. Eckroth (Ed.), *In Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Edition* (pp.143-161). New York: Wiley Interscience.

Guenet, J.M. (1992). *Thermoreversible gelation of polymers and biopolymers* (pp.120-124). London: Academic Press.

Gulrez, S. K., Al-Assaf, S., and Phillips, G. O. (2011). Hydrogels: methods of preparation, characterisation and applications. *Progress in Molecular and Environmental Bioengineering-From Analysis and Modeling to Technology Applications*, 5, 117-150

Gupta, P., Vermani, K., and Garg, S. (2002). Hydrogels: from controlled release to pH-responsive drug delivery. *Drug Discovery Today,* 7(10), 569-579.

Halib, N., Amin, M. C. I. M., and Ahmad, I. (2010). Unique stimuli responsive characteristics of electron beam synthesized bacterial cellulose/acrylic acid composite. *Journal of Applied Polymer Science*, 116(5), 2920-2929.

Hanes, J., Chiba, M., and Langer, R. (1998). Degradation of porous poly (anhydride-co-imide) microspheres and implications for controlled macromolecule delivery. *Biomaterials, 19*(1-3), 163-172.

Hegazy, E. S. A., Abd El-Aal, S., Abou Taleb, M., and Dessouki, A. (2004). Radiation synthesis and characterization of poly (N-vinyl-2-pyrrolidone/acrylic acid) and poly (N-vinyl-2-pyrrolidone/acrylamide) hydrogels for some metal-ion separation. *Journal of Applied Polymer Science, 92*(4), 2642-2652.

Heinze, T., and Koschella, A. (2005). Carboxymethyl ethers of cellulose and starch–a review. *Macromolecular*, 223(1), 13-40.

Heinze, T., Pfeiffer, K., and Lazik, W. (2001). Starch derivatives with high degree of functionalization-Influence of reaction conditions and starting materials on molecular structure of carboxymethyl starch. *Journal of Applied Polymer Science, 81*(8), 2036-2044.

Hennink, W., and Van Nostrum, C. (2012). Novel crosslinking methods to design hydrogels. *Advanced Drug Delivery Reviews, 64,* 223-236.

Hermanson, G. (1996). *Bioconjugate techniques* (pp.235). San Diego, CA: Academic Press, Inc.

Huang, Y., Lu, J., and Xiao, C. (2007). Thermal and mechanical properties of cationic guar gum/poly (acrylic acid) hydrogel membranes. *Polymer Degradation and Stability, 92*(6), 1072-1081.

Ibrahim, S. M., El Salmawi, K. M., and Zahran, A. H. (2007). Synthesis of crosslinked superabsorbent carboxymethyl cellulose/acrylamide hydrogels through electron-beam irradiation. *Journal of Applied Polymer Science, 104*(3), 2003-2008.

Jabbari, E., and Nozari, S. (2000). Swelling behavior of acrylic acid hydrogels prepared by γ-radiation crosslinking of polyacrylic acid in aqueous solution. *European Polymer Journal, 36*(12), 2685-2692.

Johnson, D. (1977). *Distribution of sago making in the old world*. In K. Tan (Ed.), Sago-76: Papers of the first international sago symposium, 5–7 July, 1976, Kuching, Malaysia (pp. 65–75). Kuala Lumpur: Kemajuan Kanji Sdn. Bhd.

Kaparissides, C., Alexandridou, S., Kotti, K., and Chaitidou, S. (2006). Recent advances in novel drug delivery systems. *Journal of Nanotechnology Online, 2,* 1-11.

Karim, A., Nadiha, M., Chen, F., Phuah, Y., Chui, Y., and Fazilah, A. (2008). Pasting and retrogradation properties of alkali-treated sago Metroxylon sagu starch. *Food Hydrocolloids, 22*(6), 1044-1053.

Kim, B., and Lim, S.T. (1999). Removal of heavy metal ions from water by cross-linked carboxymethyl corn starch. *Carbohydrate Polymers, 39*(3), 217-223.

Kwon, K., Auh, J. H., Kim, J. W., Park, K. H., Park, C. H., and Ko, C. J. (1997). Physicochemical properties and functionality of highly carboxymethylated starch. *Starch‐Stärke, 49*(12), 499-505.

Lam, Y. L., Saravanan, M., Hashim, K., Ahmad, M., and Pushpamalar, J. (2014). Radiation cross-linked carboxymethyl sago pulp hydrogels loaded with ciprofloxacin: Influence of irradiation on gel fraction, entrapped drug and in vitro release. *Radiation Physics and Chemistry*,106, 213-222.

Lecamp, L., Youssef, B., Bunel, C., and Lebaudy, P. (1997). Photoinitiated polymerization of a dimethacrylate oligomer: 1. Influence of photoinitiator concentration, temperature and light intensity *Polymer, 38*(25), 6089-6096.

Lee, Y. M., Kim, S. H., and Cho, C. S. (1996). Synthesis and swelling characteristics of pH and thermoresponsive interpenetrating polymer network hydrogel composed of poly (vinyl alcohol) and poly (acrylic acid). *Journal of Applied Polymer Science, 62*(2), 301-311.

Li, X., Yin, M., Zhang, G., and Zhang, F. (2009). Synthesis and Characterization of Novel Temperature and pH Responsive Hydroxylpropyl Cellulose-based Graft Copolymers. *Chinese Journal of Chemical Engineering, 17*(1), 145-149.

Lin, N.J.M., Cheung, P.J., Wilson, D.L., Bellamkonda, R.V. (2005). Sustained in vitro gene delivery from agarose hydrogel prolongs non viral gene expression in skin. *Tissue Engenering*,11, 546-555.

Loh, S., Rajan, A., Wong, S., and Bong, C. (2008). Physiochemical properties of sago starch modified by acid treatment in alcohol. *American Journal of Applied Sciences, 5*(4).

Lopérgolo, L. C., Lugão, A. B., and Catalani, L. H. (2003). Direct UV photocrosslinking of poly (N-vinyl-2-pyrrolidone) (PVP) to produce hydrogels. *Polymer, 44*(20), 6217-6222.

Lu, D., Xiao, C., and Xu, S. (2009). Starch based completely biodegradable polymer materials. *Express Polymer Letters, 3*(6), 366-375.

Mart, R. J., Osborne, R. D., Stevens, M. M., and Ulijn, R. V. (2006). Peptide-based stimuli-responsive biomaterials. *Soft Matter, 2*(10), 822-835.

Mazied, N. A., Ismail, S. A., and Abou Taleb, M. F. (2009). Radiation synthesis of poly (dimethylaminoethyl methacrylate)-co-(ethyleneglycol dimethacrylate) hydrogels and its application as a carrier for anticancer delivery. *Radiation Physics and Chemistry, 78*(11), 899-905.

McGinity J.(1994). Properties of free film prepared from aqueous polymer by aqueous polymeric by spraying technique. *Pharmaceutical Resources*, *11*, 1562-1567.

McNeill, I.C., Ahmed, S., and Memetea, L. (1995). Thermal degradation of vinyl acetatemethacrylic acid copolymer and the homopolymers. II. Thermal analysis studies. *Polymer Degradation and Stability,48,* 89-97.

Mohd Amin, M. C. I., Ahmad, N., Halib, N., and Ahmad, I. (2012). Synthesis and characterization of thermo- and pH-responsive bacterial cellulose/acrylic acid hydrogels for drug delivery. *Carbohydrate Polymers, 88*(2), 465-473

Nadiha, M. N., Fazilah, A., Bhat, R., and Karim, A. A. (2010). Comparative susceptibilities of sago, potato and corn starches to alkali treatment. *Food Chemistry, 121*(4), 1053-1059.

Nagasawa, N., Yagi, T., Kume, T., and Yoshii, F. (2004). Radiation crosslinking of carboxymethyl starch. *Carbohydrate Polymers, 58*(2), 109-113.

Nedkov, E., and Tsvetkova, S. (1994). Effect of gamma irradiation on the crystalline structure of ultra high molecular weight poly (ethylene oxide). *Radiation Physics and Chemistry, 43*(4), 397-401.

Nizam El-Din, H. M., Abd Alla, S. G., and El-Naggar, A. W. M. (2010). Swelling and drug release properties of acrylamide/carboxymethyl cellulose networks formed by gamma irradiation. *Radiation Physics and Chemistry, 79*(6), 725-730.

Pal, K., Banthia, A., and Majumdar, D. (2009). Polymeric hydrogels: characterization and biomedical applications. *Designed monomers and polymers, 12*(3), 197-220.

Panda, A., Manohar, S., Sabharwal, S., Bhardwaj, Y., and Majali, A. (2000). Synthesis and swelling characteristics of poly (N-isopropylacrylamide) temperature sensitive hydrogels crosslinked by electron beam irradiation. *Radiation Physics and Chemistry, 58*(1), 101-110.

Pant, B. R., Jeon, H. J., Park, C. I., Lee, B. C., Park, J. H., and Song, H. H. (2010). Radiation modified carboxymethyl starch derivative as metal scavenger in aqueous solutions. *Starch‐Stärke, 62*(1), 11-17.

Pei-Lang, A., Mohamed, A., and Karim, A. (2006). Sago starch and composition of associated components in palms of different growth stages. *Carbohydrate Polymers, 63*(2), 283-286.

Peppas, N. A. (1997). Hydrogels and drug delivery. *Current Opinion in Colloid & Interface Science, 2*(5), 531-537.

Peppas, N. A., and Mikos, A. G. (1986). Preparation methods and structure of hydrogels. *Hydrogels in Medicine and Pharmacy, 1*, 1-27.

Peppas, N. A., Bures, P., Leobandung, W., and Ichikawa, H. (2000). Hydrogels in pharmaceutical formulations. *European Journal of Pharmaceutics and Biopharmaceutics, 50*(1), 27-46.

Pinardağ, F. E. (2006). *Modified acrylic hydrogels as controlled release systems.* PhD Thesis. Middle East Technical University.88-82p

Prashant, P.K., Vivek, B.R., Deepashree, N.D., Pranav, P.P. (2012).Hydrogels as a drug delivery system and applications: a review. *International Journal of Pharmaceutical Science*,4, 1-7.

Pushpamalar, V., Langford, S. J., Ahmad, M., and Lim, Y. Y. (2006). Optimization of reaction conditions for preparing carboxymethyl cellulose from sago waste. *Carbohydrate Polymers, 64*(2), 312-318.

Pushpamalar, V., Langford, S. J., Ahmad, M., Hashim, K., and Lim, Y. Y. (2013). Absorption characterization of Ca^{2+}, Na^{+}, and K^{+} on irradiation crosslinked carboxymethyl sago pulp hydrogel. *Journal of Applied Polymer Science, 128*(3), 1828-1833.

Rasool, N., Yasin, T., Heng, J. Y., and Akhter, Z. (2010). Synthesis and characterization of novel pH, ionic strength and temperature-sensitive hydrogel for insulin delivery. *Polymer, 51*(8), 1687-1693.

Ražem, D., and Katušin-Ražem, B. (2008). The effects of irradiation on controlled drug delivery/controlled drug release systems. *Radiation Physics and Chemistry, 77*(3), 288-344.

Reinisch, K. M., Chen, L., Verdine, G. L., and Lipscomb, W. N. (1995). The crystal structure of Haelll methyltransferase covalently complexed to DNA: An extrahelical cytosine and rearranged base pairing. *Cell, 82*(1), 143-153.

Rosiak, J. M. (1994). Radiation formation of hydrogels for drug delivery. *Journal of Controlled Release, 31*(1), 9-19.

Rosiak, J., and Ulański, P. (1999). Synthesis of hydrogels by irradiation of polymers in aqueous solution. *Radiation Physics and Chemistry, 55*(2), 139-151.

Rosiak, J., Ulański, P., and Rzeźnicki, A. (1995a). Hydrogels for biomedical purposes. *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms, 105*(1), 335-339.

Rosiak, J., Ulański, P., Pajewski, L., Yoshii, F., and Makuuchi, K. (1995b). Radiation formation of hydrogels for biomedical purposes. Some remarks and comments. *Radiation Physics and Chemistry, 46*(2), 161-168.

Ruddle, K. R. (1977). Sago in the new world. In K. Tan (Ed.), Sago-76: Papers of the first international sago symposium, 5–7 July, 1976, Kuching, Malaysia (pp. 53–64). Kuala Lumpur: Kemajuan Kanji Sdn. Bhd.

Rutenberg, M., and Solarek, D. (1984). Starch derivatives: Production and uses. *Starch Chemistry and Technology, 2,* 311-366.

Sabharwal, S.(2001). *Industrial application of radiation induced crosslink degradation and grafting process*. Regional training course on modification of natural polymers by processing. Quezon City. Philippines.

Saboktakin, M. R., Maharramov, A., and Ramazanov, M. A. (2009). pH-sensitive starch hydrogels via free radical graft copolymerization, synthesis and properties. *Carbohydrate Polymers, 77*(3), 634-638.

Saboktakin, M. R., Tabatabaie, R. M., Maharramov, A., and Ramazanov, M. A. (2010). Synthesis and characterization of chitosan-carboxymethyl starch hydrogels as nano carriers for colonspecific drug delivery. *Journal Pharmaceutical and Education. Resource, 1,* 37-47.

Said, H. M., Abd Alla, S. G., and El-Naggar, A. W. M. (2004). Synthesis and characterization of novel gels based on carboxymethyl cellulose/acrylic acid prepared by electron beam irradiation. *Reactive and Functional Polymers, 61*(3), 397-404.

Schmitz, S. A., Coupland, S. E., Gust, R., Winterhalter, S., Wagner, S., and Kresse, M. (2000). Super paramagnetic iron oxide–enhanced MRI of atherosclerotic plaques in Watanabe hereditable hyperlipidemic rabbits. *Investigative Radiology, 35*(8), 460-471.

Sinha, V., and Kumria, R. (2004). Polysaccharide matrices for microbially triggered drug delivery to the colon. *Drug development and industrial pharmacy, 30*(2), 143-150.

Stojanović, Ž., Jeremić, K., and Jovanović, S. (2000). Synthesis of Carboxymethyl Starch. *Starch - Stärke, 52*(11), 413-419.

Strauss, P., Knolle, W., and Naumov, S. (1998). Radiation-induced radical formation and crosslinking in aqueous solutions of N-isopropylacrylamide. *Macromolecular Chemistry and Physics, 199*(10), 2229-2235.

Sutar, P. B., Mishra, R. K., Pal, K., and Banthia, A. K. (2008). Development of pH sensitive polyacrylamide grafted pectin hydrogel for controlled drug delivery system. *Journal of Materials Science: Materials in Medicine, 19*(6), 2247-2253.

Swarbrick, J. (2006). *Encyclopedia of Pharmaceutical Technology* (pp.501). New York: Informa Healthcare.

Thierry, B., Winnik, F., Mehri, Y., and Tabrizian, M. (2003). A new $Y_3Al_5O_{12}$ phase produced by liquid feed flame spray. *Journal of American Chemical Society, 125*, 7494

Tie, Y. L., and Lim, C. P. (1976). Lowland peat soils for sago-growing in Sarawak. In K. Tan (Ed.), Sago-76: Papers of the first international sago symposium, 5–7 July, 1976, Kuching, Malaysia (pp. 187–189). Kuala Lumpur: Kemajuan Kanji Sdn. Bhd.

Tijsen, C., Kolk, H., Stamhuis, E., and Beenackers, A. (2001). An experimental study on the carboxymethylation of granular potato starch in non-aqueous media. *Carbohydrate Polymers, 45*(3), 219-226.

Tomić, S. L., Mićić, M., Filipović, J., and Suljovrujić, E. (2007). Swelling and drug release behavior of poly (2-hydroxyethyl methacrylate/itaconic acid) copolymeric hydrogels obtained by gamma irradiation. *Radiation Physics and Chemistry, 76*(5), 801-810.

Xu, H., and Li, T. (2005). The analysis of boundary functions of CMS reaction factors. *Journal Nature Science, 3*, 79-81.

Yaacob, B., Amin, M. C. I. M., Hashim, K., and Bakar, B. A. (2011). Optimization of reaction conditions for carboxymethylated sago starch. *Iranian Polymer Journal, 20*(3), 195-204.

Yan, L., Qian, F., and Zhu, Q. (2001). Interpolymer complex polyamphotic hydrogel of chitosan and carboxymethyl cellulose (CMC): Synthesis and ion effect. *Polymer International*,(50),1370-1374.

Yin, L., Fei, L., Cui, F., Tang, C., and Yin, C. (2007). Superporous hydrogels containing poly (acrylic acid-co-acrylamide)/carboxymethyl chitosan interpenetrating polymer networks. *Biomaterials, 28*(6), 1258-1266.

Yoshii, F., Zhao, L., Wach, R. A., Nagasawa, N., Mitomo, H., and Kume, T. (2003). Hydrogels of polysaccharide derivatives crosslinked with irradiation at paste-like condition. *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms, 208*, 320-324.

Yun, J., Im, J. S., Jin, D., Lee, Y.S., and Kim, H.I. (2008). Controlled release behavior of temperature responsive composite hydrogel containing activated carbon. *Carbon Lett, 9*(4), 283-288.

Zarzycki, R., Modrzejewska, Z., and Nawrotek, K. (2010). Drug release from hydrogel matrices. *Eco Chemical Engineering, 17*(2), 117-136.

Zhang, D., Ju, B., Zhang, S., and Yang, J. (2003). *Progress in the synthesis and application of green chemicals, carboxymethyl starch sodium.* Paper presented at the Proceeding 3rd International Conferences Functional Molecules, Dalian, China. September, 2003

Zhao, S. P., Cao, M. J., Li, L. Y., and Xu, W. L. (2010). Synthesis and properties of biodegradable thermo- and pH-sensitive poly[(N-isopropylacrylamide)-co-(methacrylic acid)] hydrogels. *Polymer Degradation and Stability*, *95*(5), 719-724.