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Title: Development, Characterization of Novel Micro/Nano Hydrogels and Study of their Application in Experimental Model for Neurological Disorders

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Abstract

During the past few decades, hydrogels have been in use for biomedical applications such as drug delivery systems, in situ gels tissue scaffolds. Hydrogels have a unique three dimensional cross linked network of natural polymers, which have the ability to imbibe large amount of water. Among the various forms of hydrogel based drug delivery systems, injectable and orally administered forms are gaining interest due to the various benefits associated with these types of hydrogels. Generally, the drugs having low molecular weight of about 150-500 g/mol suffer with a disadvantage of high dosage. Therefore, it becomes imperative to develop drug delivery systems for the sustained release of these drugs. The objective of present thesis is to develop micro/nano hydrogels using natural and synthetic polymers for their applications in delivery of low molecular weight drugs like sodium phenytoin. The characteristic properties of various biopolymers like chitosan, hydroxyl ethyl cellulose, guar gum and sodium alginate have been exploited to synthesize the biodegradable and biocompatible hydrogels. The cross-linking property of polyol derived from linseed oil was used to prepare the interpenetrating networks of polymers for enhancing and distinguishing the useful properties of hydrogels. The efficacy of the drug loaded hydrogels were tested *in vivo* using experimental animal model (rats) for epilepsy. The in vitro drug loading and release studies of antiepileptic drug sodium phenytoin from the hydrogel microspheres have been investigated. The *in vivo* assessment for the sodium phenytoin loaded hydrogel microspheres in Wistar rat model of maximal electroshock (MES) Induced seizures is presented.

Chapter 1: The present chapter discusses the classification, water content in hydrogels and interpenetrating networks (IPN). The various polymers and their characteristic properties important for drug delivery systems have also been highlighted. The various methods employed for drug loading in hydrogels are discussed. Drug release mechanisms are also highlighted. The drug delivery systems used for various parts of human body are given. The detailed literature review on the development of hydrogels and clinical application of hydrogels used as drug delivery system for human body is discussed. Special emphases on neurological disorders as well as hydrogels used for brain disorders are given. An overview of various models for epilepsy is briefed. The various limitation associated with hydrogels are reviewed.
Chapter 2: describes the basic principles and details of various techniques used for the characterization of hydrogels including the spectroscopic characterization techniques viz., FT-IR, UV-Vis spectrometry Optical microscopy, Scanning electron microscopy (SEM), transmission electron microscopy (TEM), X-ray diffraction (XRD), and the thermal characterization by thermo gravimetric analysis (TGA) and

differential scanning calorimetry (DSC) analysis. Procedures for biodegradability and biocompatibility testing have also been elaborated.

Chapter 3: Chapter 3 deals with the preparation of novel pH sensitive hydrogel films of chitosan, HEC and polyol. Their structural characterization by FT-IR, Optical microscopy, SEM and thermal stability behavior by TGA has also been discussed in this chapter. The swelling behaviors of these novel hydrogels and their degradability studies as a function of pH and time are also covered. It was demonstrated that the addition of polyol in chitosan and HEC matrices resulted in the formation of the membrane with improved stability and pH responsive characteristics. The use of these hydrogel membranes may be explored for controlled release of pesticides of agricultural and public health importance with minimum impact on the environment as the matrix material.

Chapter 4: The aim of this chapter is to test the biodegradability and biocompatibility and to investigate the swelling and de-swelling behaviour of the chitosan-MMA/polyol hydrogels in physiological solutions to test their biological performance and applicability as drug delivery systems. The biocompatibility of these hydrogels was assessed in human sera. The swelling studies in various physiological solutions and preliminary biocompatibility studies revealed that these hydrogels have a potential to be used as controlled release drug delivery system and may also find application in tissue engineering.

Chapter 5: embodied the synthesis and characterization of nanocomposite interpenetrating hydrogels networks composed of guar gum and chitosan as matrix material by free radical polymerization reaction. The matrix was hydrophobically modified by linseed oil based polyol and Closite 30B was used as nano-filler. The swelling behaviour of these novel hydrogels and their degradability studies as the function of pH and time were also performed. Swelling behaviour of the synthesized hydrogels was tested in physiological solutions and was further investigated for their biological performance.

Chapter 6: The present chapter explains the designing of proposed hydrogels, used to deliver sodium phenytoin either orally or injected intra-peritonially to the human body. The synthesis and characterization of sodium phenytoin loaded hydrogel microspheres using chitosan and graft copolymer of sodium alginate and acrylamide developed by water-in-oil emulsion polymerization method also reported in this chapter. The drug release behaviour and drug release kinectics in the phosphate buffer of pH 7.2 was also studied in chapter 6. The drug release kinetics was studied in order to understand the release parameters for the drug “sodium phenytoin” present in the microspheres. In the synthesized hydrogel microspheres the linear fit in the Peppas equation, depicted the drug released from these microspheres follow a Fickian diffusion mechanism.

Chapter 7: The *in vivo* efficacy of hydrogel microspheres of chitosan and graft copolymer of sodium alginate and acrylamide-polyol was tested using Wistar rat model Maximal electroshock (MES) model for epilepsy. The protection against MES was seen and the sustained release behavior of the sodium phenytoin loaded microspheres was tested in Wistar rats. The above result suggest that PF-6 hydrogel microspheres carry a potential to be used as an oral drug delivery system for sustained release of phenytoin for treatment of epilepsy.