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Stimuli Sensitive Polysaccharide Based Hydrogels as Colon Targeted Drug Delivery Vehicles.

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requirements for the degree of

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ABSTRACT

Stimuli Sensitive Polysaccharide Based Hydrogels as Colon Targeted Drug Delivery Vehicles.

By Iman Kavianinia

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Administering drugs orally is by far the most widely used route of administration that will help eliminate the pain caused by injection, psychological barriers associated with multiple daily injections and possible infection from injection sites. However, it is important for oral drug administration to overcome several different obstacles during the delivery through the gastrointestinal tract. The barriers can be morphological barriers and physiological factors such as a wide range of pH and enzymatic activities. The lower water content and fluid mobility of the colon, which leads to longer retention times and also lower proteolytic activity of colon compared to other areas of the gastrointestinal tract, make the colon an ideal site for both systemic and local delivery of drugs. Therefore aggressive research efforts have recently focused on development of new strategies for delivering drugs to the colon.

As a drug delivery systems, hydrogels have received increasing attention due to their outstanding merits. Among the various hydrogels, including natural, synthetic and natural/synthetic hybrid hydrogels, chitosan has attracted significant attention in a broad

range of pharmaceutical and biomedical applications. Chitosan is a hydrophilic polyelectrolyte heteropolysaccharide composed of randomly (1→4)-linked 2-acetamido-2-deoxy-β-D-glucopyranose and 2-amino-2-deoxy-β-D-glucopyranose linked by (1→4)-β-glycosidic bonds. Unlike most known bioadhesive polymers, chitosan displays unique pharmaceutical and biomedical applications due to the large number of hydroxy and amino groups on the backbone of chitosan. These functional groups can be readily modified. This study was commenced with the aim of engineering a carrier with high enough physicochemical stability to reach the colon and to be able to protect a drug from various obstacles throughout the gastrointestinal tract. In this study, a new generation of chitosan derivatives was developed. Furthermore, their viability was investigated for potential applications as drug carriers to the colon. Chitosan based films with improved physical properties from introducing a cyclic imide moiety into the chitosan matrices was developed and characterised. Mechanical, thermal and chemical analyses of these films show that the heterocyclic imide linkage imparts excellent thermal, mechanical and chemical stability to the chitosan film. Additionally, spray dried chitosan microspheres with improved mechanical stability were examined for the controlled drug release of bovine serum albumin as a model protein drug. Additionally, a novel generation of amphoteric crosslinked chitosan derivatives was designed to be pH sensitive and bacterially degradable. Tabletted carriers were designed to protect the drug from the harsh acidic environment of the stomach and the rigorous enzymic activity of the small intestine and deliver the drug to the colon. Tabletted formulation forms of these novel amphoteric derivatives of chitosan showed the excellent potential formulations as colon specific drug delivery vehicles.

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LIST OF ABBREVIATIONS

AAm	Acrylamide
5-ASA	5-aminosalicylic acid
BSA	Bovine serum albumin
BAPNA	N-α-benzoyl-l-arginine p-nitroanilide
BTEE	N-benzoyl-L-tyrosine ethyl ester solution
BTDA	Benzophenone-3,3′,4,4′-tetracarboxylic dianhydride
CF	Carboxyfluorescein
Cts	Chitosan
CST	Critical solution temperature
CFU	Colony forming unit
CBAA	Amic acid derivative chitosan crosslinked with BTDA
CFAA	Amic acid derivative chitosan crosslinked with FDA
CNAA	Amic acid derivative chitosan crosslinked with NTDA
COAA	Amic acid derivative chitosan crosslinked with ODPA
CPAA	Amic acid derivative chitosan crosslinked with PMDA
CTAA	Amic acid derivative chitosan crosslinked with TMAC
DD	Degree of deacetylation
DMF	Dimethylformamide
DD	Degree of deacetylation
DTG	Differential thermal gravimetric analysis
Da	Dalton
EC	Ethylcellulose
Ea	Electron affinity
EVAC	Ethylenevinyl acetate copolymer
EE	Encapsulation efficiency
ppm	Parts per million
EVAC	Ethylene dimethacrylate
FDA	4,4′-(Hexafluoroisopropylidene) diphthalic anhydride
5-FU	5-Fluorouracil
FTIR	Fourier transform infrared spectroscopy

GIS	Gastrointestinal system
GIT	Gastrointestinal tract
GA	Glutaraldehyde
g	Gram
HCl	Hydrochloric acid
HPLC	High-performance liquid chromatography
HEMA	Hydroxyethylmethacrylate
HPMA	Hydroxypropylmethacrylate
IBD	Inflammatory bowel disease
LCST	Lower critical solution temperature
LC	Loading capacity
LD	Lethal dose
LYZ	Lysozyme
MPEG	Methoxyl poly(ethylene glycol)
Mw	Molecular weight
MAS	Magic angle spinning
MHz	Megahertz
MPa	Megapascal
NTDA	1, 4, 5, 8-Naphthalenetetracarboxylic dianhydride
NaCS	Sodium cellulose sulfate
NMR	Nuclear magnetic resonance spectroscopy
ODPA	4,4′-Oxydiphthalic dianhydride
PBS	Phosphate buffered saline
PAA	Poly (acrylic acid)
PMAAc	Poly (methacrylic acid)
PDMAEMA	Poly (N,N′-dimethylaminoethyl methacrylate)
PL	Poly (lysine)
PHEMA	Poly (2-Hydroxyethyl methacrylate)
PEG	Poly (ethylene glycol)
PNIPAm	Poly (*N*-isopropylacrylamide)
PEO	Polyethylene oxide
PS	Puncture strength
PEGMA	Polyethyleneneglycol methacrylate
PNPAm	Poly (N-n-propylacrylamide)

PDEAM	Poly (N,N-diethylacrylamide)
PVA	Polyvinylalcohol
pH	Measure of acidity and basicity in solution
PPS	Sodium polyphosphate
PMDA	Pyromellitic dianhydride
RDZ	Ronidazole
RPM	Revolutions per minute
SCF	Simulated colonic fluid
SEM	Scanning electron microscopy
S %	Swelling percentage
SGF	Simulated gastric fluids
SIF	Simulate gastric fluids
T. foetus	Tritrichomonas foetus
TGA	Thermal gravimetric analysis
TMAC	Trimellitic anhydride chloride
UC	Ulcerative colitis
UCST	Upper critical solution temperature
XRD	X-ray diffraction

LIST OF PUBLICATIONS

1. **Kavianinia, I.;** Plieger, P. G.; Kandile, N. G.; Harding, D. R., In Vitro Evaluation of Spray-Dried Chitosan Microspheres Crosslinked with Pyromellitic Dianhydride for Oral Colon-Specific Delivery of Protein Drugs. *Article first published online:* 13 Feb **2013**.

2. **Kavianinia, I.;** Plieger, P. G.; Kandile, N. G.; Harding, D. R., Preparation and characterization of crosslinked chitosan based films with excellent physiochemical propertie. *International Journal of Biological Macromolecules*. Manuscript under revision.

3. **Kavianinia, I.;** Plieger, P. G.; Kandile, N. G.; Harding, D. R., Fixed-bed column studies on a modified chitosan hydrogel for detoxification of aqueous solutions from copper (II). *Carbohydrate Polymers*. **2012**, 90 (2), 875–886.

4. **Kavianinia, I.;** Plieger, P. G.; Kandile, N. G.; Harding, D. R., New hydrogels based on symmetrical aromatic anhydrides: Synthesis, characterization and metal ion adsorption evaluation, *Carbohydrate Polymers*. **2012**, 87 (1), 881–893.

Papers to be submitted

1. Development of a pH sensitive carrier system based on a novel water soluble chitosan and alginate for colon targeted drug delivery. *Under preparation*

2. Development and evaluation of a novel colon targeting drug delivery system for the treatment of Tritrichomonas foetus intestinal infection in cats. *Under preparation*

3. Synthesis and characterization of a novel generation of amphoteric pH sensitive hydrogels. *Under preparation*

4. Formulation and evaluation of a novel pH and enzyme controlled colon-specific delivery system of 5-ASA using amphoteric chitosan based matrix tablet. *Under preparation.*

5. Preparation and characterization of an amphoteric chitosan based matrix table chitosan based matrix tablet for oral colon-specific drug delivery of protein therapeutics. *Under preparation.*