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Design and biopharmaceutical evaluation of High molecular weight chitosan based drug carrier for control release of Mebendazole

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Abstract: A major trend in medicine development today is the design of suitable vehicles for controlled release of drug in patients. Delivery vehicles for therapeutics must be biocompatible and benign thin polymer films have also been employed for colonic drug delivery. High molecular weight Chitosan based microspheres were prepared in order to deliver mebendazole as a model drug specifically into the colon. Microspheres were prepared by an emulsion and crosslinking method. The prepared microspheres are characterized by FTIR, SEM, and XRD, swelling studies investigated for controlled release of mebendazole as a model drug. The *in vitro* releases in pH 7.4 are reported. The results of this study suggest that the microspheres could be potentially useful for colon drug delivery of mebendazole over more than 12 hours.
Keywords: Colon drug delivery, mebendazole, High molecular weight chitosan, microspheres.

Introduction

Chitosan is the generic name of a linear random copolymer of β-(1-4) linked –D-glucosamine whose molecular structure comprises a linear backbone linked through glycosidic bonds. The basic amine groups of this polysaccharide are protonated and thus positively charged in most physiological fluids. These characteristics of chitosan have attracted many scientists working in the biomedical field, particularly drug delivery[1-2] Among many methods of modifying the original structures of polymers, graft copolymerization is an easier method[3]. Enteric nematodes are among the most common and widely distributed animal-parasites of humans[4]. The most common intestinal roundworms are those transmitted through contact with the soil (for example Ascaris lumbricoides[4], several polysaccharides are being investigated as carriers for colon specific drug delivery[5-6] Mebendazole (MBZ), methyl-5-benzoyl benzimidazole-2-carbamate, a broad-spectrum antihelmintics drug of the benzimidazole class, The present paper describes the development and evaluation of colon targeted drug delivery systems for mebendazole using high molecular weight chitosan as a carrier.

Material and Experimental:

Mebendazole (98–101% purity), High molecular weight chitosan poly(D-glucosamine) was purchased from Sigma–Aldrich, Belgium; acryl amide was purchased from Qualigens Mumbai, India; while polyethylene glycol 4000, hydrochloric acid, glutaradehyde, acetic acid and sodium hydroxide were purchased from SD Fine Chemicals, India. All other chemicals used in this work were of analytical reagent grade.

Synthesis of polyethylene glycol grafted–acryl amide: Polyethylene glycol 4000 was dissolved in water at 60 -65^{o}C and treated with acryl amide under nitrogen gas atmosphere followed by addition of trace quantity of potassium persulfate under continuous stirring at a temperature of 65 ^{o}C for 5 h have been reported elsewhere[7].

Drug loading: Approximately 2 g of the polymer blend obtained above was dissolved in 2 % acetic acid containing 100mgof Mebendazole and was dispersed with equal quantities of light liquid paraffin stirred at high speed and the resulting water-oil emulsion was stabilized by addition of 1 % Tween 80 solution, have been reported elsewhere[8].

Result:

The FTIR spectra of plain PEG, PEG-grafted copolymer and hydrolyzed PEG-grafted copolymer, The broad band appearing at 3495.09 cm^{-1} corresponds to the associated –OH stretching vibrations of the hydroxyl group of the grafted copolymer, The FTIR spectrum of plain chitosan showed two peaks around 836 and 1020 cm^{-1} corresponding to saccharin structure in the spectra. The spectrum of chitosan blend with acrylamide grafted with PEG hydrolyzed complex was observed at around 1628 cm^{-1} and corresponds to $-NH_3^+$ group (Figure not shown).

Swelling of microgels: The % equilibrium swelling for blend microsphere of chitosan and PEG are higher than plain chitosan microspheres, formulation of C-PEG-50 to C-PEG-100, % equilibrium swelling increased from 245-258% in pH 7.4.

X-ray diffraction: Mebendazole showed characteristic intense peaks at 10 and 30 ^{o} due to its crystalline nature. However, these peaks were not seen in the drug-loaded matrix complex, placebo microgels and drug-loaded microgels which indicates that the encapsulated drug became amorphous as indicated in figure 1.

Differential scanning calorimetry: Thermogram of the pure drug exhibited an endothermic peak at 202 ^{o}C, corresponding to its melting point, but this peak was absent from the thermogram of the drug-loaded microspheres which suggests that most of the drug was well dispersed within the matrix as shown in the figure 2.Drug content and entrapment efficiency of different concentration. Mebendazole formulation are shown in the Table 1.

Scanning electron micrographs (SEM): SEM indicates that the microspheres were fairly spherical in shape and that polymeric material surrounded the microspheres are shown in the figure 4. The type and blend of polymeric used in microsphere formulation did alter surface properties.

Drug release: The release data for the various formulations are shown in Figure 4. In both the pH media release was much faster in plain Chitosan microspheres for instance, only 83% drug was released at 11.5 h for C-grafted copolymer 50 in pH 7.4 media On subjecting the drug release data to Higuchi model (Q = Kt½) in order to ascertain the drug release mechanism, a linear relationship was observed with a regression coefficient close to 1 (r^2 = 0.990).

Discussion:

Chitosan exhibits a pH-sensitive behavior as a weak polybasic due to the large number of amino groups on its chain[8] The ionization of the carboxylic groups results in a repulsive interaction between the PEG chains and acrylic acid molecules at high pH. pH–dependent study suggests that swelling ratio at pH 7.4 was higher than that of micro gels at pH 6. Increase in the amount of glutaraldehyde incorporated in the matrix lowered encapsulation efficiency. XRD and DSC results indicate that there were no interactions between drug, chitosan and other ingredients used in preparing the microspheres. Thus, it suggests that the prepared microsphere would be stable. Sustained drug release over a period of 12 h was achieved by cross linking chitosan with the release data fitting well to the Higuchi model. It suggests that the drug released by diffusion mechanism. The

carboxylic groups of chitosan become gradually ionized at pH 7.4 [9] Thus, the collapsed polymeric matrix played an important role in hindering drug diffusion, effectively contributing to sustained release at pH 7.4.

Table 1: Encapsulation efficiency and equilibrium swelling of Mebendazole formulation.

Formulation code	Drug loading (%)	Encapsulation efficiency (%)*	Particle size (µm)*	(%) Swelling pH 7.4
C-50	50	76.42±0.2	56 ± 0.2	185
C-100	100	79.02±0.8	76.3±0.5	190
C-PEG-50	50	83.96±0.4	89.9±0.4	245
C-PEG-100	100	85.06±0.1	103±0.4	258
C-grafted copolymer 50	50	87.03±0.3	105±0.2	265
C-grafted copolymer 100	100	89.28±0.5	113±0.2	270
C-grafted copolymer 50 (hydrolyzed)	50	91.04±0.2	119±0.5	273
C-grafted copolymer-100 (hydrolyzed)	100	93.01±0.9	124±0.1	283
C-grafted copolymer-100 (hydrolyzed)-(2.5GA)	100	90.4±0.5	122±0.1	294
C-grafted copolymer-100 (hydrolyzed)-(5.0G A)	100	85.9±0.2	114±0.1	292
C-grafted copolymer-100 (hydrolyzed)-(7.5GA)	100	78.9±0.2	104±0.11	289

SD = standard deviation; *mean ± SD (n = 3); GA = glutaraldehyde crosslinked; C = chitosan.
Drug concentration used was 50 mg and 100 mg in each formulation.

Figure1 XRD of (A) pure drug (B) chitosan-drug loaded microspheres, C) Pure drug

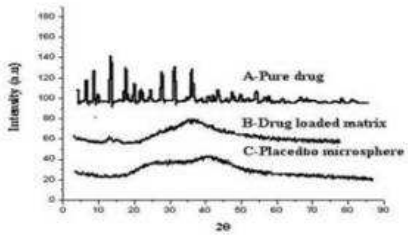
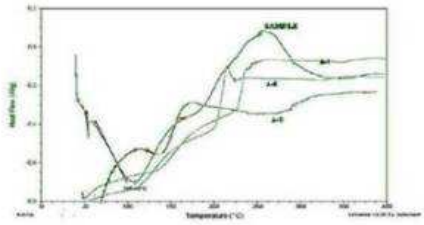


Figure 2: DSC of (A) chitosan, (B) drug-loaded chitosan matrix C) Blank microspheres



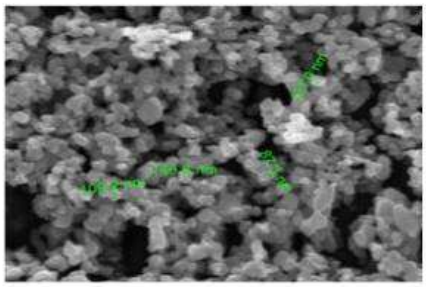


Figure 3 SEM micrograph of micro sphere

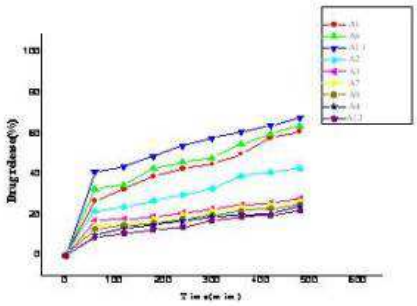


Figure 4: Percentage cumulative release of drug vs. time for chitosan-grafted PEG with different amount of drug in pH 7.4

Conclusion:

The hydrophilic nature of polyacrylamide-modified PEG has been successfully utilized to develop cross linked chitosan microspheres The resulting pH-sensitive interpenetrating network of the microsphere matrix facilitated sustained release of Mebendazole . Further work, including *in vivo* evaluation, is however, required to ascertain the suitability of the procedure used on a large scale.

References:

1. Shivashankar, M., Mandal, BK., Yerappagari, Y., Preveen, V., Chitosan–Based hydro gel for the drug delivery system, Int Res J Pharm., 2011, 2, 1-6.
2. Yao, RD, Peng, T., Goosen, MFA., Min, JM., He, YY., pH-sensitivity of hydro gel based on complex forming chitosan:polyether interpenetrating polymer network. J Appl Polym Sci., 1993, 48,343-354.
3. Elvira, C., Mano, JF., Roman,JS., Reis, RL., Starch-based biodegradable hydro gels with potential biomedical applications as drug delivery system. Biomaterials, 2002, 23, 1955-1966.
4. Cross,JH., Enteric nematodes of humans (chapter 90), Section IV: Parasitology, in: World Book Medical Encyclo-pedia, Concord, MA 01742, USA, 1999.
5. Ashford,M., Fell,J.,Attwood,D.,Sharma,H.,Woodhead,P., Studies on pectin formulations for colonic drug delivery, J. Control. Release,1994, 30,225–232.
7. Krishna, KSV., Naidu, BVK., Subha, MCS., Sairam, M., Aminabhavi, TM., Novelchitosan-based pH-sensitive interpenetrating network microgels for the controlled release of cefadroxil. Carbohyd Polymers, 2006, 66,333-344.
8. Shiva Shankar,, M., Mandal, BK., Design and biopharmaceutical evaluation of chitosan Based novel pH sensitive drug carrier for sustain release of Cefixime, Trop J Pharm Res.,2013,12(2),155-161.
9. Ono, K.,Saito, Y., Yura, H., Ishikawa, K., Kurita, A., Akaike,T., Ishihara, M., Photo-crosslinkable chitosan as a biological adhesive. J Biomed Mat Res., 2000, 49, 289-295.

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