pH - Responsive Polymeric Nanoparticles Fabricated By Dispersion Polymerization As A Platform For The Delivery Of Anticancer Drugs

Reema Puri*, Solomon Berhe* and Emmanuel Akala*

*Department of Pharmaceutical Sciences, Howard University, Washington, D.C. U.S.A

Room # 308, 2300 4th Street, NW, Washington, D.C. 20059, eakala@howard.edu

ABSTRACT

In the present study, pH- resposive nanoparticles were prepared with acetal crosslinkers. Three different acetal crosslinkers were synthesized by reacting a methacrylate monomer with three different benzaldehydes.The formation of acetal crosslinkers was confirmed by nuclear magnetic resonance (NMR) spectroscopy and high resolution mass spectroscopy (HR-MS). The hydrolysis studies of the crosslinkers showed that the rate of hydrolysis of the crosslinkers was faster in the acidic pH 5 compared to physiological pH 7.4. These results confirm acid sensitivity of the acetal crosslinkers. Blank nanoparticles were synthesized with acetal crosslinker and characterized in terms of morphology, particle size and zeta potential. Results suggest that these nanoparticles can be used in the fabrication of systems for treatment of cancer.

Keywords: Acetal, pH sensitive, dispersion polymerization, nanoparticles, hydrolysis

1 INTRODUCTION

In diseased conditions such as tumors, pH is slightly more acidic than in the blood and normal tissues. The endocytic pathway of cells begin near the physiological pH of 7.4, but it drops to a lower pH of 5.5 – 6.0 in endosomes and approaches pH 4.5 – 5 in lysosomes [1]. Therefore, pH responsive systems can potentially be exploited for targeted delivery of drugs to tumors. In the present study, we have used acetal linkages to form pH sensitive nanoparticles. Acetals are promising candidates for the development of acid sensitive linkages because their hydrolysis is generally first order relative to the hydronium ion, making the expected rate of hydrolysis several times faster with each unit of pH decrease [1, 2].

2 EXPERIMENTAL METHODS

2.1 Synthesis of Acid Labile Crosslinkers:

Three different acid labile acetal crosslinkers were synthesized by reacting methacrylate monomer with corresponding benzaldehyde (4-methoxybenzaldehyde, 2,4-dimethoxy benzaldehyde or 2,4,6-trimethoxybenzaldehyde). The crude mixtures were purified by flash chromatography, and characterized by nuclear resonance spectroscopy and high resolution mass spectroscopy.

2.2 Hydrolysis Studies of the Crosslinkers:

Rate of hydrolysis of the crosslinkers was studied at pH **7**.4 and pH 5 after incubation of the solutions at 37° C using a UV-VIS spectrophotometer at wavelength of 283 nm for crosslinker 1, 275 nm for crosslinker 2 and 291nm for crosslinker 3, which are λ_{max} for respective benzaldehydes generated on hydrolysis of the crosslinkers.

2.3 Synthesis of Nanoparticles:

Nanoparticles have been synthesized with acetal crosslinkers using dispersion polymerization technique [3].

3 RESULTS/DISCUSSION

The formation of crosslinkers was confirmed by nuclear magnetic resonance and high resolution mass spectroscopy. The hydrolysis studies showed that the rate of hydrolysis of the crosslinkers was faster at the acidic pH 5 as compared to physiological pH 7.4. These results confirm acid sensitivity of the acetal crosslinkers. The nanoparticles were characterized by scanning electron microscopy for morphology, and by dynamic light scattering for size and zeta potential.

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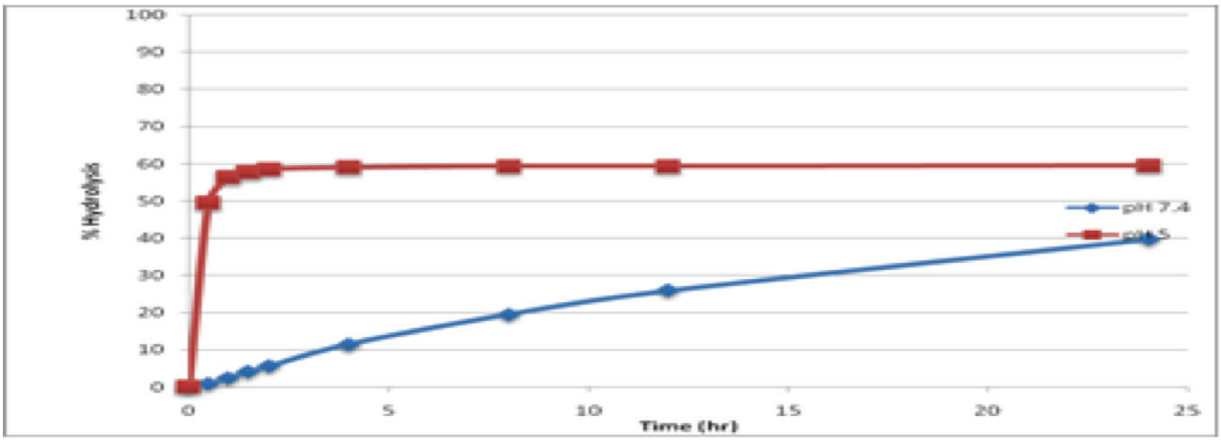

Fig 1: Hydrolysis study of crosslinker at pH 5 and pH 7.4

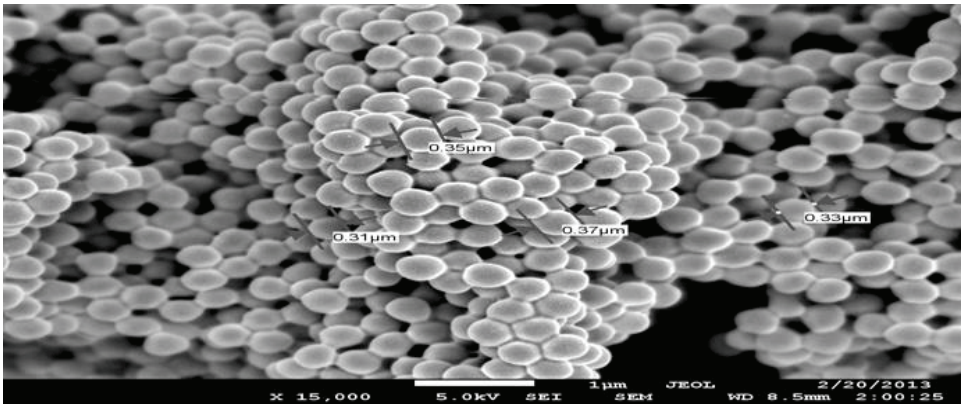

Figure 2: SEM image of nanoparticles with acetal crosslinker

4 CONCLUSION

We have synthesized three acetal crosslinkers. pH sensitivity of the crosslinkers was confirmed by hydrolysis studies. Nanoparticles were synthesized with the acetal crosslinkers and characterized. Studies on *in vitro* availability of drug (docetaxel) from the nanoparticles are ongoing

REFERENCES

[1]. Chan Y, Bulmus V, Zareie MH, Byrne FL, Barner L and Kavallaris M. Acid-cleavable polymeric core-shell particles for delivery of hydrophobic drugs. J Control Release. 2006;115(2):197-207

[2]. Volga Bulmus, Yannie Chan, Quyen Nguyen and Hong L. Tran. Synthesis and Characterization of Degradable p(HEMA) Microgels: Use of Acid-Labile Crosslinker . Macromolecular Bioscience . 2007; 7(4): 446 -455.

[3]. Akala, E., Okunola, A. O, Stealth Polymeric particles for delivery of bioactive or diagnostic agents. United States patent application publication number US 2012/0129798 A1.