Extended Abstract | Journal of Biopolymers Research | 2019 | Vol.3 Issue.2

Cellular uptake and cytotoxicity studies of pH-responsive polymeric Nano particles fabricated by dispersion polymerization

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Abstract

Puri R, Adesina S, Akala E. Cellular uptake and cytotoxicity studies of pH-responsive polymeric Nano particles fabricated by dispersion polymerization. J Nanosci Nanomed.. April-2018;2(1):3-16.

Objective: A strategy in site-specific drug delivery is the use of pHgradients that exist in diseased conditions such as cancer for the release of loaded drug(s) in the biophase. The objective of this work is to synthesize pH-responsive docetaxel-loaded Nano particles with a bisacrylate acetal crosslinker, which can get internalized into cells, and which will be equivalent to or more cytotoxic than the free drug against cancer cells.

Methods: pH-responsive Nano particles were synthesized by a dispersion polymerization technique. The Nano particles were characterized for physicochemical properties. Cytotoxicity studies of the Nano particles were performed on PC3 and LNCaP prostate cancer cell lines using a cell viability assay. Cellular uptake studies were performed using a confocal laser scanning microscope.

Results: Smooth spherical Nano particles were formed. In-vitro drug release was faster at pH 5.0 than pH 7.4, which confirmed the pHresponsiveness of the Nano particles. Cytotoxicity studies showed that the Nano particles were more effective at the same molar amount than the free drug against cancer cells. Both dose exposure and incubation time affected the cytotoxicity of prostate cancer cells. Furthermore, LNCaP cells appeared to be the more sensitive to docetaxel than PC3 cells. The cellular uptake studies clearly showed the presence of discrete Nano particles within the cells in as little as 2 hours.

Conclusion: pH-sensitive Nano particles were developed; they degraded quickly in the mildly acidic environments similar to those found in endosomes and lysosomes of tumor tissues. These novel pH-sensitive Nano particles would offer several advantages over conventional drug therapies

Keywords

Acetal, crosslinker, pH-responsive, dispersion polymerization, polymeric Nano particles, hydrolysis, cell viability assay, cytotoxicity and cellular uptake

INTRODUCTION

•Administered bioactive agents distribute throughout the body, based on their physicochemical properties, before reaching the bio-phase or site of action resulting in side effects •One way to address this problem is to formulate drug delivery systems such that they are capable of accumulating in desired pathological sites with little or no accumulation in non-target tissues1 •Recent studies on site-specific delivery of therapeutic and diagnostic agents have utilized environmental stimuli to trigger the release of the agents at a particular body compartment1 •Thus the use of stimuli-responsive Nano carriers offers an opportunity to make the delivery system become an active participant, rather than a passive vehicle, in the optimization of therapy •Following cellular uptake via endocytosis, the Nano carrier system faces very well-defined compartments with strongly differential pH status. In cancer cells early endosome has a pH about 5–6 while the late lysosome, which is the most acidic compartment, has a pH around 4–5 . The extra- and intra-cellular pH gradients can be used to design drug delivery systems which selectively release the transported drug(s) at the bio phase (specific site of delivery)

RESULTS AND DISCUSSION

The main aim in the synthesis of acid- labile cross linker is to achieve the desired pH-responsive behaviour, i.e. rapid cleavage in slightly acidic pH such as those present in intracellular vesicles of the cells (pH4.5-6.8), and stability for long time in the blood, i.e. pH 7.4. The acetals synthesized from p-substituted benzaldehydes have been shown by the previous studies [15,30] to be particularly well suited to this purpose as their acidlabile behaviour can be tailored by introducing different substituent's at the para-position of the benzaldehyde. Thus, the use of the cross linkers containing p-substituted benzaldehyde acetals as an intrinsic acidresponsive element provides an easy and versatile way to incorporate and engineer the acid-cleavability to the polymeric colloidal systems for the site-specific drug release

Conclusions

• Three pH-sensitive acetyl cross linkers were synthesized and characterized • Spherical and fairly Monodisperse Nano particles were formed by dispersion polymerization technique • Hydrolysis studies and drug release studies confirmed pH- • The pH-sensitive Nano particles degraded quickly in the mildly acidic environments similar to those found in endosomes and lysosomes of tumour tissues. • In vitro cell viability assay showed that the docetaxel-loaded Nano particles were as effective as free drug in causing cell death in both PC3 and LNCaP cell lines. • These novel pH-sensitive nanoparticles would offer several advantages over conventional drug therapies

References

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This work is partly presented at Joint Event on International Conference on Polymer Waste-Biopolymers & Bioplastics, October23- 25, 2019 at Frankfurt, Germany