

Advanced Targeted Drug Delivery of Fluoresceine Isothiocyanate by FOL-PEG-g-PEI-GAL conjugate as the Novel Nanoparticles

Sepideh Ghiamkazemi^{a,b,c,d,*}, Amir Amanzadeh^e, Rasoul Dinarvand^{b,c,f}, Mohsen Amini^d, Morteza Rafiee Tehrani^{b,c}

Authors' Affiliations:

^a Iran Food and Drug Administration, Tehran, Iran

^b Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

^c Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

^d Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

^e National Cell Bank of Iran (NCBI), Pasteur Institute of Iran, Tehran, Iran

^f Drug Design and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran

Abstract Presenter:

Sepideh Ghiamkazemi
Iran Food and Drug Administration, Tehran, Iran

Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

E-mail: s.ghiamkazemi@fda.gov.ir

*Correspondance:

Sepideh Ghiamkazemi
Iran Food and Drug Administration, Tehran, Iran

E-mail s.ghiamkazemi@fda.gov.ir

Abstract

Polyethylenimine (PEI) is a well-known cationic polymer that has gained recent attention as a transfection and transduction agent. However; it is extremely cytotoxic in many cell lines because of its high surface charge (about +40 mV), non-biodegradability and non-biocompatibility. Other drawbacks of this polymer include, low duration of expression, non-specific cell uptake and instability in blood circulation. To enhance Polyethyleneimine biocompatibility, the graft pegylated copolymer was synthesized. To target cancer liver cells, two targeting ligands folic acid and galactose (lactobionic acid) were attached with graft Pegylated copolymer to increase specifically the entrance of this new targeted copolymer to cancer liver cells, because the folic acid and lactobionic acid receptors are over expressed only on human hepatocyte carcinoma. The composition of this new conjugated copolymer was characterized using ¹H-NMR spectra. Its molecular weight and zeta potential were compared to polyethyleneimine. To study the entrance of this targeted carrier to human hepatocyte carcinoma (HepG2), fluoresceine isothiocyanate (FITC) as a model drug was conjugated to this novel carrier and the emission of green fluorescent was determined from three cell lines (HEK293, KB and HepG2) and compared with fluoresceine isothiocyanate alone.

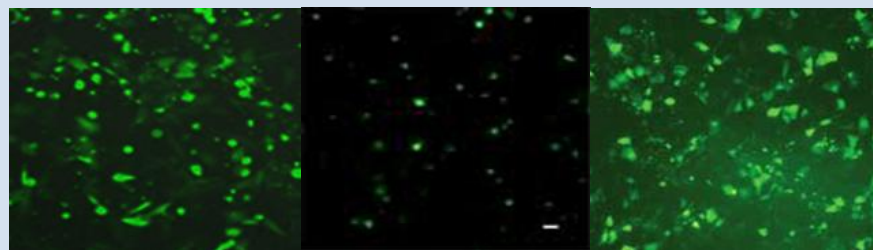
Introduction: In recent years, there has been an enormous interest in the formulation of a targeted carrier for a specific population of cells, either locally or systematically. The targeted drug delivery system can be achieved by either non-polymeric or polymeric carrier methods. Novel drug delivery by non-polymeric carriers has been studied for years; however, the broad use of this system is affected by the limited size of material delivered, cytotoxicity and no targeting interaction to certain cells. Polymeric drug delivery carriers have become a promising alternative since the carriers could be synthesized with higher purity and quality degree and less immunogenic response than the viral and lipidic carriers for drug targeting.

Methods and results: First of all, pegylated polyethylenimine (PEG-g-PEI) was synthesized and then folate-PEG-g-PEI, folate-PEG-g-PEI-galactose was prepared and folate-PEG-g-PEI-galactose conjugated with Fluorescein isothiocyanat as a model drug.

To investigate transduction efficacy of FOL-PEG-g-PEI-GAL conjugated with FITC, as a drug model, the fluorescent activity was measured in transduced HepG2, HEK293 and KB cell lines and the results are monitored.

As shown in **Fig 1**, the emission of green fluorescent had the following order: The intensity of green fluorescent light of HepG2 > the intensity of green fluorescent light of KB > the intensity of green fluorescent light of HEK293.

The Transduction efficacy was further quantified by flow cytometry. The ratios of Fluorescence- positive cells were 79%, 51% and 12% in HepG2, KB and HEK293 respectively (**Fig.1**). The transduction of fluoresceine isothiocyanate alone was not noticeable in any cell lines. This could be due to its high aqueous solubility.



KB

HEK293T

HEPG2

Fig 1. Efficacy of copolymer "FOL-PEG-g-PEI-GAL" conjugated with FITC in HepG2, HEK293T and KB cell lines detected by fluorescent images

Conclusions: In this study, the FOL-PEG-g-PEI-GAL copolymer as a novel biocompatible polymer was synthesized for targeting cancer liver cells and characterized using ¹H-NMR and FTIR. This new copolymer, FOL-PEG-g-PEI-GAL, showed improved degradation in PBS at 37°C compared with PEI.

Key words: Polyethylenimine, FOL-PEG-g-PEI-GAL, targeted drug delivery, fluoresceine isothiocyanate, pegylation, HEK293 and KB and HepG2 cell lines.