Design of a Taguchi statistical experiment for Optimization and in Vitro Evaluation of Nano-Hydrogel prepared by ionotropic gelation method

M. A. Shahbazi[1], *M. Hamidi*[1,2]

1- Department of pharmaceutics, Faculty of pharmacy, Shiraz University of medical sciences, Shiraz, P.O.BOX 71345-1583, Iran
2- Department of pharmaceutics, Faculty of pharmacy, Zanjan University of medical sciences, Zanjan, Iran

Introduction

Preparation of nanoparticle is a well-known method used to modify/control the drug release. In this study, chitosan, the deacetylated derivative of chitin, was used as a natural polymer with approved pharmaceutical applications [1] due to its biodegradability and biocompatibility [2], and low toxicity [3]. The preparation of chitosan-heparin nanoparticles was accomplished using the ionotropic gelation method in order to improvement of heparin efficacy. This technique was selected due to its simplicity and production of nanoparticles with relatively high drug loading. Heparin was selected as a model drug as its short biological half life and side effects makes it a good candidate for sustained release nanoparticulate preparation.

Materials & Method

Sodium Acetate, acetic Acid, heparin, chitosan and other chemicals and solvents used in this study were of analytical grade and were purchased locally. Generally, ionotropic gelation method is used for preparation of hydrogel nanoparticles. Polymer was dissolved in acetate buffer and then the drug was added in this solution while being stirred vigorously. For achievement to desired particle size, a fractional factorial design was used to establish optimum combination of chitosan concentration, heparin concentration, pH of buffer, addition rate of heparin to chitosan solution, temperature and mixer rate. Also effect of these parameters on particle size when one of the parameters is changed and other parameters are fixed was evaluated. The unique qualities and performance of nanoparticles as devices of drug delivery arise directly from their physicochemical properties. Hence, determining such characteristics is essential in achieving a mechanistic understanding of their behavior. Therefore, hydrogel nanoparticles were characterized by evaluation of particle size, morphology, zeta potential, drug encapsulation efficiency, stability, and subsequent release kinetics. Also using chitosan with different molecular weights, the cross-linked nanoparticles was made and evaluated in size, volume, and morphology as well as release kinetics.

Results and Discussion

The ionotropic gelation method was successfully used for production of chitosan-heparin nanoparticles. Morphology of the prepared hydrogels was studied by transition electronic microscope (TEM) technique and results showed spherical and dense shape (Figure 1). Additionally, FTIR spectra of chitosan, heparin, and chitosan-heparin nanoparticles exhibited interactions between carboxyl groups of heparin and amino groups of chitosan. Drug entrapment efficiency was more than 73.44±2.31% which confirmed the suitability of the method for production of nanoparticles with high drug loading. Also, in vitro release behavior of heparin, from hydrogels was studied (Figure 2). Particle size analysis

showed that nanoparticles were in a narrow size distribution with mean particle size of 63±4 nm (Figure 3).

Conclusions

In this study we developed a novel, positively charged and colloidal chitosan nanoparticulate system as a vehicle for delivery of heparin. The finding of this study showed the applicability of this method for delivery of anionic drugs. Further studies such as in vivo toxicity tests and in vivo release should be performed to evaluate the applicability of these nanoparticles as a novel drug delivery system.

References

[1] L. Illum, Pharm Res,15 (1998)1326.
[2] G. Borchard, H.E. Junginger, Adv Drug Del Rev, 52 (2001) 103.
[3] J. Karlsen, O. Skaugrud, Manuf Chem, 62, (1991) 18.

Fig. 1. Transition electron microscopy (TEM) image of Chitosan-Heparin nanoparticles.

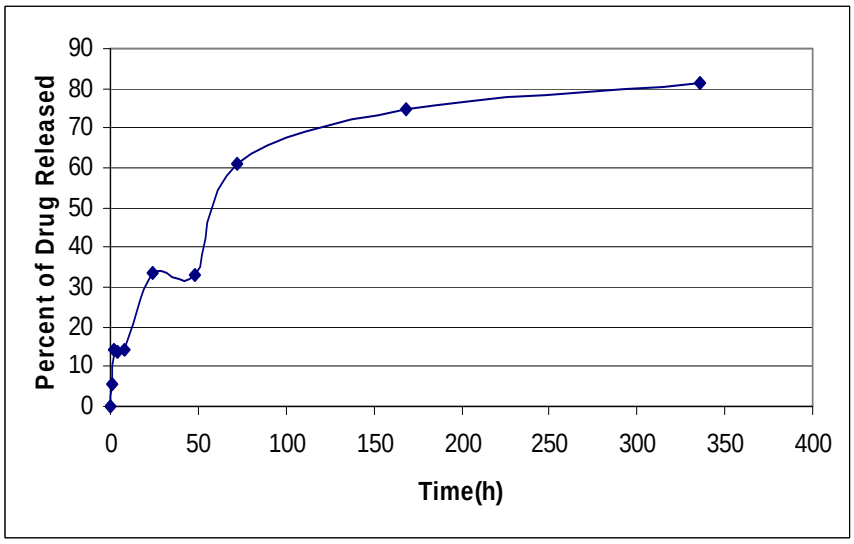

Fig. 2. Release of heparin from chitosan-heparin nanoparticles

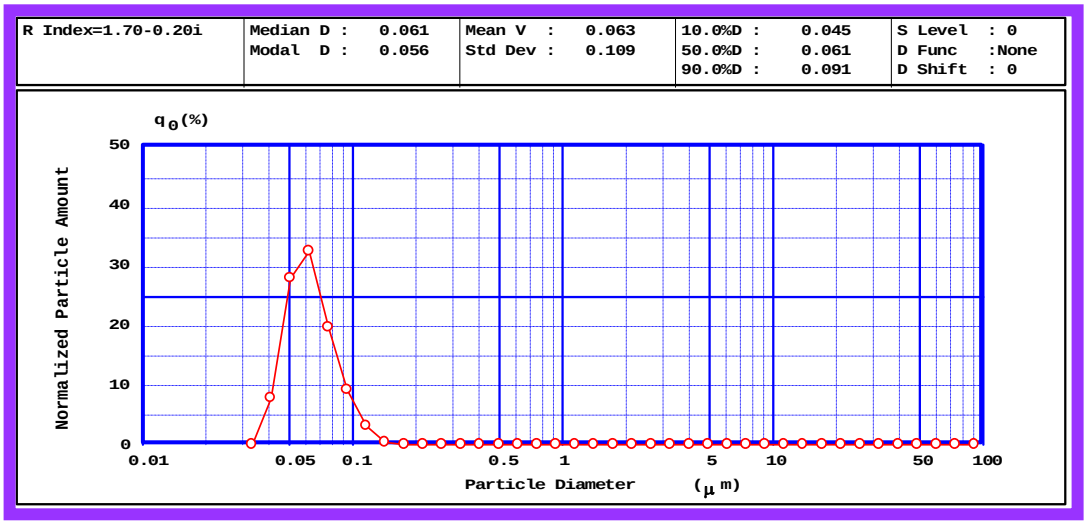

Fig.3. Nanoparticles size distribution