A Novel Drug Delivery System Based on Raloxifene Nanoparticles Composed of Biodegradable Carboxylated Polyurethane

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ABSTRACT SUMMARY

Biodegradable carboxylated polyurethanes with three molecular weights were synthesized to prepare a nanoparticulate sustained delivery system of raloxifene hydrochloride, the drug with poor bioavailability.

INTRODUCTION

Biodegradable polyurethanes are one of the important classes of polymers which have been investigated as scaffolds for tissue regeneration and as controlled/sustained release drug delivery vehicles. Raloxifene hydrochloride-methanone, [6-hydroxy-2-(4hydroxyphenyl) benzo[b] thien-3-yl]-[4-[2-(1-piperidinyl) ethoxy] phenyl]-hydrochloride (R-HCl) is an estrogen agonist/antagonist, commonly referred to a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds. The drug exhibits high interindividual and intraindividual variability (30 percent) of most pharmacokinetic parameters [2] and this fact makes it attractive for further disposition. Controlled-release formulations of different medicines have been used to reduce the adverse effects of drugs and maintain clinical remission of diseases [3, 4]. Thus, controlled release of raloxifene nanoparticles would probably increase the drugs bioavailability. The purpose of this study was to prepare raloxifene nanoparticles with co-precipitation method and optimization of nanoparticles to result in controlled delivery of raloxifene. The dissolution behavior of the drug from these nanoparticles was evaluated.

EXPERIMENTAL METHODS

Preparation of nanoparticles: Ionomer polyurethanes (IPUs) with three molecular weights were synthesized in glass polymerization tube under nitrogen atmosphere without using a condenser (scheme 1). Raloxifene loaded carboxylated polyurethane nanoparticles (NPs) were prepared using the co-precipitation method which can be applied for poorly water soluble drugs [5].

In this study Box-Behnken design, one of the major RSM techniques, was used for designing of experiments. Box-Behnken is an independent quadratic design with the advantage of investigating three independent factors with fewer numbers of experiments [6]. In this study, one series of experiments is designed for preparation of nanoparticle. For the experiments the independent variables are the concentration of IPU to R-HCl (A), molecular weight of IPUs (B) and speed of stirring (C). Results of the fractional factorial design based on an analysis of variance demonstrated that the model for particle size, zeta potential, PdI and loading efficacy was statistically significant. The loading efficacy (LE) and capacity (LC) of the nanoparticles were determined by HPLC method. Polyurethanes and nanoparticles were characterized by ¹H-NMR, FT-IR, DLS, SEM TGA, DSC and XRD.

In vitro drug release studies: In vitro release of R-HCl from optimum NPs was evaluated by the dialysis bag diffusion [7].

RESULTS AND DISCUSSION

All suggested models for optimization of nanoparticles were acceptable because of R square above 0.8. The obtained model for loading efficacy is shown for instance.
**Loading Efficacy (LE):** Calculated LE% of nanoparticles in the range of 83–91.62 % depended on all three variables (A, B, C). The effects of concentration ratio of IPU/R-HCl and molecular weight of IPU on loading efficacy are shown in Fig. 1.

![3D plot of variables on loading efficacy of nanoparticles.](image)

**Model validation:** The optimum results of trials was obtained with loading efficacy of 89.40±3.32, loading capacity of 11.46±0.40, poly dispersity index of 0.16±0.04, mean diameter of 72.23±2.71 nm and zeta average of -39.70± 3.00 mV, that confirm predicted data by Box-Benkenh design.

**Scanning Electron Microscopy (SEM):** The SEM micrograph of the optimum NPs is shown in Fig. 2 that is in agreement with the dynamic light scattering measurements. It seems the shape of nanoparticles is discrete spherical which assign them suitable features to be used as injectable delivery system.

![SEM micrograph and DLS results of NPs in optimum condition](image)

**Differential Scanning Calorimetry (DSC):** The thermogram of NPs showed R-HCl peak shifted from 270 °C to 220 °C (Fig. 3), suggesting a decrease in its Tg. This negative deviation may be ascribed to physical interaction [8, 9] such as hydrogen bonding [10, 11] between the carbonyl group of IPU and the NH group of R-HCl.

![DSC thermographs of R-HCl, IPU (B2) and NPs](image)

**In vitro release study:** Preliminary studies on the release of the R-HCl from nanoparticles have been made and are shown in Fig. 4. Using these raloxifene nanoparticles will result controlled release system with higher bioavailability.

![Release profile of R-HCl from NPs (Mean±SD)](image)

**CONCLUSION**

All these results indicate that R-HCl loaded biodegradable carboxylated polyurethane are promising sustained drug delivery system and these types of IPUs can be widely used as effective carriers for controlled release injectable drug delivery system.

**REFERENCES**