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ORIGINAL ARTICLE

Application of multiple regression analysis in optimization of anastrozole-loaded PLGA nanoparticles

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Abstract

The present investigation deals with development of anastrozole-loaded PLGA nanoparticles (NPs) as an alternate to conventional cancer therapy. The NPs were prepared by nano-precipitation method and optimized using multiple regression analysis. Independent variables included drug:polymer ratio (X_1), polymer concentration in organic phase (X_2) and surfactant concentration in aqueous phase (X_3) while dependent variables were percentage drug entrapment (PDE) and particle size (PS). Results of desirability criteria, check point analysis and normalized error were considered for selecting the formulation with highest PDE and lowest PS. Prepared NPs were characterized for zeta potential, transmission electron microscopy (TEM), differential scanning calorimetry (DSC) and *in vitro* drug release studies. DSC and TEM studies indicated absence of any drug–polymer interaction and spherical nature of NPs, respectively. *In vitro* drug release showed biphasic pattern exhibiting Fickian diffusion-based release mechanism. This delivery system of anastrozole is expected to reduce the side effects associated with the conventional cancer therapy by reducing dosing frequency.

Keywords

Anastrozole, multiple regression analysis, nanoparticles, PLGA

History

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Introduction

Treatment of breast cancer has included efforts to decrease estrogen levels by the use of antiestrogen and progestational agents (Chowdhury and Ellis, 2005; Schulz, 2005). Anastrozole (ATZ) is a nonsteroidal aromatase inhibitor. The problems associated with oral delivery of ATZ are low aqueous solubility, short half-life, and uncontrolled release (Sarkar and Yang, 2008). Our main objective was to develop a sustained and targeted delivery system of ATZ that can overcome these problems and increase patient compliance. One of the technological resources to improve the availability of drugs at the site of action is by colloidal carriers like nanoparticles (NPs) prepared using biodegradable polymers like poly(D,L-lactic-*co*-glycolic acid) (PLGA), poly caprolactone, poly alkyl cyanoacrylates, etc. (De Jong and Borm, 2008). PLGA has been studied extensively as a polymeric carrier for NPs. A wide variety of drugs ranging from small molecular weight therapeutic agents to peptide hormones, antibiotics, and chemotherapeutic drugs have been formulated using PLGA (Tuncay et al., 2000). PLGA NPs have proven to be successful targeted drug delivery systems for different classes of drugs, such as anticancer drugs like etoposide (Snehalatha et al., 2008) and rapamycin (Acharya et al., 2009), proteins and peptides like insulin (Shi et al., 2009) and steroidal hormones like estrogen (Kwon et al., 2001). Hence, we aimed at formulating ATZ-loaded PLGA NPs that would be capable of providing targeted delivery for a prolonged duration upon single intravenous administration.

Optimization of any pharmaceutical process begins with the objectives to find out and evaluate independent variables that affect formulation response, determine them and establish their best response values. However, considering the cost of the drugs and polymers, it is desirable to optimize the formulation with minimum batches but with maximum desired characteristics. While developing formulations, various formulations as well as process variables related to effectiveness, safety, and usefulness should be simultaneously optimized. Polynomial non-linear regression analysis is widely used for establishing approximate mathematical models in which the variables are screened by stepwise selection method according to statistical significance (Miller, 1984; Wagner and Shimshak, 2007) and final model would be used to predict the relationship between different variables and their levels. But such predictions are often limited to low levels, resulting in poor estimation of optimum formulation (Shirakura et al., 1991; Levison et al., 1994). Therefore, it is important to understand the complexity of pharmaceutical formulations by using established statistical tools such as multiple regression analysis (MRA), Box Behnken design, etc. The number of formulations required for such studies is dependent on the number of independent variables selected after preliminary experiments. The dependent response is measured for each trial and then either simple linear equation (Equation (1)), or interactive equation (Equation (2)), or quadratic model (Equation (3)) is fitted by carrying out MRA and F-statistic to identify statistically significant terms:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 \quad (1)$$

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ORIGINAL PAPER

Encapsulation of exemestane in polycaprolactone nanoparticles: optimization, characterization, and release kinetics

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Abstract This study was aimed at developing a polymeric drug delivery system for a steroidal aromatase inhibitor, exemestane (exe) intended for sustained targeted delivery of drug through intravenous route. Carboxylated polycaprolactone (cPCL) was synthesized by ring opening polymerization of caprolactone. Exe-loaded cPCL nanoparticles (NPs) were prepared by interfacial deposition of preformed polymer and characterized. A 3-factor, 3-level Box–Behnken design was used to derive a second-order polynomial equation and construct contour and response plots for maximized response of percentage drug entrapment (PDE) with constraints on particle size (PS). The independent variables selected were ratio of exe/cPCL, amount of cPCL, and volume of organic phase. Polymerization of caprolactone to cPCL was confirmed by Fourier transform infrared (FTIR) and gel permeation chromatography. The prepared NPs were evaluated for differential scanning calorimetry (DSC), transmission electron microscopy (TEM), and in vitro release studies. Optimum formulation based on desirability (1.0) exhibited PDE of 83.96 % and PS of 180.5 nm. Check point analysis confirmed the role of the derived polynomial equation and contour plots in predicting the responses. Zeta potential of optimized formulation was −33.8±2.1 mV. DSC studies confirmed the absence of any interaction between drug and polymer. TEM image showed non-aggregated and spherical shaped NPs. Drug release from NPs showed sustained release and followed Korsmeyer–Peppas model, indicating Fickian drug release. Thus, preparation of exe-loaded cPCL NPs with high PDE and desired PS suitable for providing passive targeting could be statistically optimized using Box–Behnken design.

Keywords Exemestane · Polycaprolactone · Nanoparticles · Box–Behnken design

Abbreviations

Exe	Exemestane
PCL	Polycaprolactone
cPCL	Carboxylated polycaprolactone
NPs	Nanoparticles
BBD	Box–Behnken design
DSC	Differential scanning calorimetry
TEM	Transmission electron microscopy
PDE	Percentage drug entrapment
PS	Particle size
FM	Full model
RM	Reduced model

1 Background

Breast cancer is the leading cause of death among women, with one million new cases in the world each year (McPherson et al. 2000), out of which one third are reported to be hormone dependent (Henderson and Canellos 1980; Theobald 2000). Growth of breast cancer cells is often estrogen dependent. Continuous estrogen suppression in patients with hormone-sensitive breast cancer prevents proliferation of tumor. Aromatase is the key enzyme that converts androgens to estrogens both in pre- and postmenopausal women (Lonning 1998; Strassmer-Weippl and Goss 2003). Exemestane (exe) is a third generation, potent irreversible type I steroidal aromatase inhibitor approved by the Food and Drug Administration

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