Development of paclitaxel and flurbiprofen co-loaded PLGA nanoparticles: understanding critical formulation and process parameters using Plackett–Burman design

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ABSTRACT

Nano drug co-delivery system is a popular strategy for combined application of two or more anticancer and/or synergistic drugs. Synergistic effects of nonsteroidal anti-inflammatory drugs and anti-cancer drugs in cancer treatment are shown in the literature. This study aimed to screen and understand the critical formulation and process parameters in the preparation of flurbiprofen and paclitaxel co-loaded nanoparticles to develop an anti-cancer nano co-delivery system. With this aim, critical parameters were determined using the Plackett–Burman experimental design (DoE). Flurbiprofen and paclitaxel drug loading amounts were considered as critical quality attributes to control the effective drug loading ratio. Furthermore, average particle size and zeta potential were also defined as critical quality attributes in order to optimize passive drug targeting and colloidal stability. Surfactant type was determined as the most significant factor for the average particle size and zeta potential. For flurbiprofen and paclitaxel drug loading into the nanoparticles, amounts of both flurbiprofen and paclitaxel were determined as critical factors. Consequently, paclitaxel and flurbiprofen were efficiently loaded into nanoparticles, and the impact of the formulation variables was successfully screened by a DoE. By controlling the determined parameters, the therapeutic efficacy of co-loaded drug nanoparticles could be maximized in further studies.

Keywords: Nanoparticles, paclitaxel, flurbiprofen, PLGA, design of experiments, Plackett–Burman

INTRODUCTION

Previous studies showed that nonsteroidal anti-inflammatory drugs (NSAIDs) are promising anticancer drugs, the effects of which were well confirmed in clinical trials (Thun et al. 2002). Anticancer effects of R-flurbiprofen, a NSAID, have been shown in vitro and in vivo models of prostate and colon cancer (Liu et al. 2012). It was demonstrated that R-flurbiprofen increased levels of the tumor suppressor neurotrophin receptor in gastric cancer cells and reversed multidrug resistance (Jin et al. 2010).

Paclitaxel is one of the most important anticancer drugs, approved by the United States Food and Drug Administration (FDA) for clinical use in chemotherapy. It is a Permeability-glycoprotein (P-gp) substrate (Yerlikaya et al. 2013). For increasing pharmaco-
kinetic profiles, reducing toxicity, overcoming multidrug resistance and increasing efficacy of paclitaxel, many nano-delivery systems were developed and evaluated. To date, paclitaxel albumin-bound nanoparticles (Abraxane®) have been approved by the FDA (Ma and Mumper, 2013).

Nanotechnology offers some advantages such as improved drug release, intracellular drug delivery and tumor accumulation by active and passive targeting properties (Hillaireau and Couvreur, 2009; Wicki et al. 2015). Poly (lactic-co-glycolic acid) (PLGA) is the most frequently used polymer to prepare nanoparticles because of its biodegradable and biocompatible nature (Dinarvand et al. 2011; Danhier et al. 2012). Co-delivery of two or more anticancer drugs with PLGA nanoparticles became an attention grabbing strategy to provide a synergistic effect. These nano drug co-delivery systems provide a unique opportunity for targeting and simultaneous drug delivery of drug combinations (Qi et al. 2017; Kozlu et al. 2018). NSAIDs, that could overcome multiple drug resistance by inhibiting P-gp, show synergistic effects while used concurrently with anticancer drugs (Thun et al. 2002; Jin et al. 2010).

To enhance the pharmaceutical development through design efforts, the FDA encourages risk-based approaches and the adoption of Quality-by-design (QbD) principles in drug product development. To identify and control critical source of variability in the process, and understand the impact of formulation components and process parameters on the critical quality attributes are defined in the objectives of the QbD approach. The pharmaceutical characteristics of the nanoparticles could be influenced by many factors in the manufacturing process, including the formulation materials. To evaluate the effects of these factors, many statistical designs of experiment (DoE) are used. The most commonly used (DoE) is Plackett–Burman, which is a very efficient screening design used when only the main effects are of interest to be investigated. (Rahman et al. 2010; Yerlikaya et al. 2013; Yu et al. 2014; Kozlu et al. 2018)

In this study, we aimed to screen and understand the critical formulation and process parameters in the preparation flurbiprofen and paclitaxel co-loaded nanoparticles to develop an anti-cancer nano co-delivery system. With this aim, critical parameters were determined using the Plackett–Burman experimental design. Flurbiprofen and paclitaxel drug loading amounts were considered as critical quality attributes to control effective drug concentration ratios. Average particle size and zeta potential were also defined as critical quality attributes in order to optimize passive drug targeting and colloidal stability.

**MATERIALS AND METHODS**

**Materials**

Paclitaxel was donated by DEVA Pharmaceuticals (Istanbul, Turkey). Flurbiprofen (R/S enantiomer) was donated by ILKO Pharmaceuticals (Istanbul, Turkey). R-Flurbiprofen, PLGA polymers, poly(vinyl alcohol) (PVA), D-α-tocopherol polyethylene glycol 1000 succinate (TPGS), dimethyl sulfoxide (DMSO) and acetone were purchased from Sigma-Aldrich (Saint Louis, USA). All other reagents used were either analytical or reagent grade.

**Methods**

Nanoparticles were prepared using nanoprecipitation technique. Briefly, paclitaxel, R/S-flurbiprofen (or R-flurbiprofen) and PLGA were dissolved in 5 mL of acetone. This organic phase was transferred into the aqueous phase comprising either 10 mL, 1% (w/v) of PVA or 0.2% (w/v) of TPGS by dropping while homogenizing (IKA RET Basic, Germany). Following the acetone’s evaporation overnight on a magnetic stirrer, the obtained suspension was centrifuged at 13,500 rpm for 60 min (2.383 K, Hermle; Germany). The resulting nanoparticles were washed with pure water and collected. For the screening of process parameters and formulation variables, Plackett–Burman DoE was used. Nine factors were tested at 12 runs and statistical evaluation, including the design matrix and randomization, were conducted by using Minitab software (Minitab Ltd., UK). The selected factors and their levels are given in Table 1, and the experimental design matrix is given in Table 2. The selection of the parameters and their levels were based on preliminary studies and on literature data. The average particle size (Y1), zeta potential (Y2), flurbiprofen loading (Y3) and paclitaxel loading (Y4) were determined as response variables. Smaller average particle size was targeted in order to provide enhanced permeability and retention (EPR) effect (Acharya and Sahoo, 2011) and high negative or positive zeta potential was targeted to provide colloidal stability (Malvern; Ostolska and Wiśniewska, 2014). The selection reason for flurbiprofen/paclitaxel loading values is to specify critical parameters that can affect each drug loading because of optimum flurbiprofen/paclitaxel concentration ratio and will be evaluated in further cell culture studies to find to determine maximum synergistic effect. The statistical significance value (p) was set at 0.05. Ethical approval was not required for this study.

**Particle size distribution and surface charge**

To measure particle size distribution and zeta potential of nanoparticles, a particle size analyzer (Malvern Nano ZS, Malvern Instruments, UK) was used. All samples were dispersed in ultrapure water and examined for the mean particle diameter, polydispersity index and surface charge.

**Table 1. The Factors and Their Levels Used in Plackett–Burman Design**

| Factors | Levels |
|---------|--------|
| X1:FLUR Amount (mg) | Low 2 | High 5 |
| X2:PTX Amount (mg) | Low 2 | High 5 |
| X3:FLUR Enantiomers | R | R/S |
| X4:PLGA Amount (mg) | Low 50 | High 100 |
| X5:PLGA Terminal Group | Acid | Ester |
| X6:PLGA Molecular Weight (kDa) | 7-17 | 24-38 |
| X7:Surfactant Type | TPGS | PVA |
| X8:Homogenization Rate (rpm) | 500 | 1100 |
| X9:Dropping Rate [Drop per Second] | 0.5 | 1 |

FLUR: Flurbiprofen; PTX: Paclitaxel
**Determination of drug loading**

Drug loading was determined as paclitaxel or R/S flurbiprofen or R-flurbiprofen amounts in final nanoparticle formulations. For calculation, a certain amount of nanoparticles were dissolved in DMSO, and analyzed using a high-pressure liquid chromatography (HPLC) system equipped (Agilent 1200 Series, USA) with a reversed-phase column (Inertsil® ODS-3, Particle size 5 µm, 4.6x250 mm, GL Sciences, China). For the quantification of paclitaxel, the mobile phase was composed of water:acetonitrile (48:52, v:v). The flow rate of the mobile phase was set to 1 mL/min, and the injection volume was 20 µL. The detector was set to 227 nm. For the quantification of RS or R-flurbiprofen, the mobile phase was composed of acetonitrile:0.1M acetate buffer (40:60). The flow rate of the mobile phase was set to 1 mL/min and the injection volume was 25µL. The detector was set to 247 nm.

Below equations were used to determine the drug loading values: Drug loading (µg/mg) = (Amount of drug in nanoparticles)/(Amount of nanoparticles)

**RESULTS AND DISCUSSION**

The average particle size of the nanoparticle formulations varied between 143.9 nm and 270.5 nm. Formulations showed uniform particle size distributions. The polydispersity indices (PDI) of the nanoparticles were lower than 0.3. The response values are shown in Table 3. The $R^2$ values indicate that a good correlation was obtained between predicted and actual values ($R^2= 0.9798$). However, despite the fact that the p value of main effects obtained from ANOVA was 0.088 and therefore was not statistically significant, the most significant factors and effects of other factors were evaluated. For the average particle size ($Y_1$), the surfactant type (p=0.021) was determined as the most significant factor (Table 4 and Figure 1A). Nanoparticles prepared with 0.2% TPGS showed smaller particle size than the formulations that were prepared with 1% PVA. This could be explained by the stronger emulsification effect of TPGS over PVA (Zhang et al. 2012). It was demonstrated that the emulsification efficiency of TPGS is 66.7 times higher than PVA and TPGS.

**Table 2. Plackett–Burman Randomized Design Matrix**

| Formulation | $X_1$ FLUR Amount (mg) | $X_2$ PTX Amount (mg) | $X_3$ FLUR Enantiomers | $X_4$ PLGA Amount (mg) | $X_5$ PLGA Terminal Group | $X_6$ PLGA Molecular Weight (kDa) | $X_7$ Surfactant Type | $X_8$ Homogenization Rate (rpm) | $X_9$ Dropping Amount (Drop per Second) |
|-------------|------------------------|-----------------------|------------------------|-----------------------|-----------------------------|-----------------------------|------------------------|-----------------------------|-------------------------------|
| A1          | 2                      | 5                     | R                      | 50                    | Acid                        | 24-38                       | PVA                    | 1100                        | 0.5                           |
| A2          | 2                      | 2                     | R                      | 100                   | Ester                       | 24-38                       | TPGS                   | 1100                        | 1                             |
| A3          | 5                      | 5                     | R                      | 100                   | Ester                       | 24-38                       | PVA                    | 500                         | 0.5                           |
| A4          | 5                      | 2                     | R/S                    | 50                    | Acid                        | 24-38                       | TPGS                   | 1100                        | 1                             |
| A5          | 5                      | 5                     | R                      | 100                   | Acid                        | 24-38                       | TPGS                   | 1100                        | 0.5                           |
| A6          | 2                      | 2                     | R/S                    | 100                   | Ester                       | 24-38                       | TPGS                   | 500                         | 1                             |
| A7          | 2                      | 5                     | R/S                    | 50                    | Ester                       | 24-38                       | TPGS                   | 500                         | 1                             |
| A8          | 5                      | 2                     | R/S                    | 100                   | Acid                        | 24-38                       | TPGS                   | 500                         | 0.5                           |
| A9          | 5                      | 5                     | R/S                    | 100                   | Acid                        | 24-38                       | TPGS                   | 1100                        | 0.5                           |
| A10         | 2                      | 2                     | R                      | 50                    | Acid                        | 24-38                       | PVA                    | 500                         | 1                             |
| A11         | 5                      | 2                     | R                      | 50                    | Acid                        | 24-38                       | TPGS                   | 500                         | 1                             |
| A12         | 2                      | 5                     | R/S                    | 100                   | Acid                        | 24-38                       | PVA                    | 500                         | 1                             |

**Table 3. The Results of Dependent Variables Obtained Through Plackett–Burman Design**

| Formulation | $Y_1$ Average Size (nm) | $Y_2$ Zeta Potential (mV) | $Y_3$ Flurbiprofen Loading (µg/mg) | $Y_4$ Paclitaxel Loading (µg/mg) |
|-------------|-------------------------|---------------------------|------------------------------------|----------------------------------|
| A1          | 173.8                   | -3.5                      | 31.4                               | 68.8                             |
| A2          | 154.8                   | -22.8                     | 25.7                               | 22.1                             |
| A3          | 270.5                   | -4.7                      | 49.8                               | 36.2                             |
| A4          | 167.6                   | -4.4                      | 60.4                               | 36.7                             |
| A5          | 153.7                   | -21.4                     | 54.4                               | 32.2                             |
| A6          | 206.1                   | -6.6                      | 16.8                               | 12.4                             |
| A7          | 173.9                   | -19.0                     | 21.7                               | 56.5                             |
| A8          | 165.4                   | -22.5                     | 38.7                               | 19.9                             |
| A9          | 146.6                   | -18.1                     | 53.5                               | 59.6                             |
| A10         | 143.9                   | -23.7                     | 33.1                               | 14.6                             |
| A11         | 203.8                   | -8.0                      | 96.4                               | 28.6                             |
| A12         | 194.1                   | -5.7                      | 13.3                               | 42.4                             |
Emulsified nanoparticles are much more uniform and smaller than the PVA-emulsified nanoparticles (Win and Feng, 2006; Saadati and Dadashzadeh, 2014). Briefly, the results showed that the average particle size was decreased with increasing homogenization rates (Figure 2), since large droplets were mixed more efficiently with higher shear rates (Rahman et al. 2010; Yerlikaya et al. 2013). Also, using higher PLGA amounts and ester-terminated PLGA increased the average particle size (Figure 2). Increasing viscosity of the dispersed phase might enhance the resistance against shear forces and cause agglomeration (Warsi et al. 2014; Sahin et al. 2017). Usage of different enantiomers of flurbiprofen, paclitaxel amount, flurbiprofen amount, dropping rate and PLGA molecular weight slightly affect the average particle size (Figure 1a and Figure 2). These results indicate that the targeted average particle size of nanoparticles could be obtained by controlling the critical parameters.

The zeta potential values of the nanoparticle formulations were found to be negative, and ranged between -3.5 and -23.7 mV. The response values are shown in Table 3. The $R^2$ values indicate that a good correlation was obtained between predicted and actual values ($R^2= 0.9951$). The $p$ value of main effects obtained from ANOVA was 0.022 and was considered as significant. Surfactant type was determined as the most significant factor for zeta potential ($Y_2$) ($p=0.003$) (Table 4 and Figure 1B). It was observed that the zeta potentials of nanoparticles were strongly influenced by the emulsifier used in the preparation process. The nanoparticles that were prepared with TPGS showed more negative surface charges (Figure 3). It is known that increased zeta potential could enhance the colloidal stability. If all the particles in suspension have a high negative or
positive zeta potential, they tend to repel each other, and there will be no tendency for the particles to come together (Malvern 2017; Ostolska and Wśniewska, 2014). Recently, garcinol loaded vitamin E TPGS emulsified PLGA nanoparticles were prepared with nanoprecipitation method by Gaonkar et al., and a similar satisfactory zeta potential (-28.10±2.1) was obtained (Gaonkar et al. 2017). On the other hand, slightly negative zeta potentials were found in previous studies which were used PVA as emulsifier (Sahin et al. 2017a; Sahin et al. 2017b). Additionally, TPGS possess potential to be a preferable surfactant for preparing nanoparticulate systems due to its anticancer activity and P-gp inhibition (Collnot et al. 2010; Yang et al. 2018). Because of these properties, TPGS could be more effective than PVA for the preparation of a P-gp substrate drug containing PLGA nanoparticles.

Figure 4. Main effects plot for flurbiprofen loading.

Nano drug co-delivery system is a feasible and popular strategy for the combined application of two or more anticancer and/or synergistic drugs (Qi et al. 2017). NSAIDs, that could overcome multiple drug resistance by inhibiting P-gp, show synergistic effects while used concurrently with anticancer drugs (Thun et al. 2002; Jin et al. 2010). In this study, critical parameters for flurbiprofen and paclitaxel loading amounts were investigated to provide the targeted optimum drug loading amount and ratio in further studies. Drug loading values ranged between 13.3 and 96.4 µg/mg flurbiprofen nanoparticles and between 12.4 and 68.8 µg/mg paclitaxel nanoparticles. The response values are shown in Table 3. The $R^2$ values indicate that a good correlation was obtained between predicted and actual values ($R^2=0.9705$ and $R^2=0.9409$ for $Y_1$ and $Y_2$, respectively). Although the $p$ values of main effects obtained from ANOVA were 0.126 and 0.240 for $Y_1$ and $Y_2$, respectively, significant factors and effects of other factors were evaluated. The flurbiprofen amount was determined as the most significant factor for flurbiprofen loading ($Y_3$) ($p=0.023$)(Figure 1c and Table 4). Similarly, the paclitaxel amount was determined as the most significant factor for paclitaxel loading ($Y_4$) ($p=0.046$) (Figure 1d and Table 4). Experimental designs showed that an increased flurbiprofen or paclitaxel amount in the organic phase resulted in increased drug loading. Drug amounts in nanoparticles were controlled by drug amounts in used levels (Figures 4 and 5). Additionally, increased PLGA amount decreased flurbiprofen and paclitaxel concentration in nanoparticles, but this factor did not reach a statistically significant level (Table 4, Figures 4 and 5). Additionally, it was observed that drug loading values were not significantly influenced by the emulsifier used in the preparation process. Zu et al. showed that increased encapsulation efficacy was obtained by using TPGS (Zhu et al. 2014). On the other hand, Saadati et al. found that encapsulation efficacy was decreased when TPGS was used as emulsifier in the nanoprecipitation method (Saadati and Dadashzadeh, 2014). These results clearly indicated that targeted drug amounts and ratio of paclitaxel and flurbiprofen for anticancer activity could be loaded together in PLGA nanoparticles.

CONCLUSION

In this study, several process parameters and formulation variables were screened by using a DoE approach to understand the most significant factors influencing the characteristics of the nanoparticles. It was found that the surfactant type was determined as the most significant factor for the average particle size and zeta potential. For flurbiprofen and paclitaxel drug loading into the nanoparticles, the amounts of both flurbiprofen and paclitaxel were determined as critical factors. Consequently, paclitaxel and flurbiprofen were efficiently loaded into nanoparticles and the impact of the formulation variables were successfully screened by a DoE.

Further studies to provide maximum efficacy of co-loaded nanoparticles, firstly the optimum synergistic concentration of flurbiprofen and paclitaxel will be evaluated on cancer cells to achieve superior therapeutic efficacy, and determined formulation parameters will be optimized. By controlling the determined parameters, the therapeutic efficacy of co-loaded drug nanoparticles could be maximized in further studies and prepared formulations could be promising tools for the treatment of various cancer types.
Conflict of Interest: The authors have no conflict of interest to declare.

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