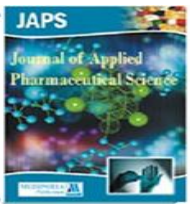
Journal of Applied Pharmaceutical Science 01 (05); 2011: 96-98

Journal of Applied Pharmaceutical Science

Available online at www.japsonline.com



ISSN: 2231-3354
Received: 11-07-2011
Revised on: 13-07-2011
Accepted: 15-07-2011

Formulation and evaluation of Paclitaxel loaded PSA-PEG nanoparticles

Rajat Sharma, Mohd Yasir, Sanjay Bhaskar and Mohd Asif

Rajat Sharma, Mohd Yasir, Mohd Asif
Department of Pharmaceutics, ITS Pharmacy College, Muradnagar, Ghaziabad, India

Sanjay Bhaskar
Department of CPP Wockhardt Pharmaceuticals, Aurangabad, India.

***For Correspondence**:
Mr. Mohd Yasir
Department of Pharmaceutics, ITS Pharmacy College, Muradnagar, Ghaziabad-201206 (UP), India

ABSTRACT

The main objective of this study was to prepare and evaluate PSA-PEG nanoparticles containing paclitaxel as a model drug by nanoprecipitation method. The influence of different experimental parameters on the particles size, entrapment efficiency, percent drug released etc was evaluated. SEM indicated that nanoparticles have discrete spherical structure without aggregation. The average particle size was found to be 123 -405 nm. The particle size of nanoparticles increases gradually with PSA-PEG polymer concentration. The drug content of nanoparticles also increases with increasing polymer concentration up to particular value. The *in-vitro* drug release behavior from all drug loaded batches was found to be zero order and provided sustained release over a period of 24 hours. Nanoparticles were stored at different temperatures and humidity as per ICH guidelines to check the stability.

Key words: Nanoparticles; PSA-PEG; Paclitaxel; Nanoprecipitation.

INTRODUCTION

For many decades treatment of acute and chronic disease has been mostly accomplished by delivery of drugs to patients using various conventional dosage forms such as tablets, capsules etc. During last two decades considerable attention has been given to develop the novel drug delivery system (NDDS) (Aterman et al. 2007). The aim for developing the control drug delivery is to alter the pharmacokinetic and pharmacodynamic of drug substance in order to improve the therapeutic efficacy and safety. Among many NDDS, colloidal drug delivery system has gained more popularity (Moghimi et al. 2007). The major colloidal drug delivery system includes liposomes and polymeric nanaoparticles. These systems have particular advantage for site specific and control drug delivery to enhance the dissolution rate/ bioavailability of poorly water soluble drugs. Colloidal polymer particles are nanoparticles of a size below one micrometer and hold promise as drug delivery for parental, peroral and ocular administration as well as adjuvant for vaccines. Due to greater stability and easier manufacturing, they offer certain advantages over other colloidal carriers such as liposomes like high stability (long shelf life), high carrier capacity, site specific drug delivery, increased bioavailability, feasibility of various route of administration (Thassu et al, 2007). PSA-PEG are biodegradable diblock copolymers of polysebacic acid and polyethylene glycol. Both are routinely used in humans. They have high diffusion capacity and exhibit pH-independent release profile (Subramani et al, 2009).

Paclitaxel is an anticancer drug first isolated from the bark of *Taxus brevifolia* that has an interesting mechanism of action and broad clinical activity. It is used for treatment of various types of cancers e.g. ovarian cancer. Conventional treatment of ovarian cancer has found to have many drawbacks such as adverse side effects due to accumulation of drug in multi-dose therapy which

leads to poor patient compliance (Liebmann et al, 1993). The objective of this study was to prepare and evaluate PSA-PEG nanoparticles containing paclitaxel in different drug to polymer ratio to overcome the problem related to conventional formulation.

MATERIAL AND METHODS

Materials

Paclitaxel (Gift sample from Dabur Pvt. ltd, U P), PSA-PEG (Gift sample from Wockhardt Pharma Pvt. Ltd, Aurangabad), Dichloromethane (Procured from E-.Merck Mumbai) etc. All chemicals used were of analytical grade.

Fabrication of Nanoparticles

Nanoparticles were prepared using nanoprecipitation method. Briefly, drug was formulated in cremophor EL. The polymer and 150 mg of polypropylene glycol were dissolved in sufficient quantity of chloroform. Then this solution was added in drug solution to form dispersion. The dispersion was added to 10ml of aqueous ethanol solution (70%). After 5 minutes of mixing, the organic solvents were removed by evaporation at 35°C under normal pressure. The nanoparticles were separated by centrifugation (10000 rpm for 20 minutes, - 5 ° C). Nanoparticles were washed with water and dried at room temperature in desiccators. (See table 1 for composition of various formulations)

Measurement of Particles Size and zeta potential

Average particle size of optimized formulations of was measured by dynamic light scattering by photon correlation spectroscopy (PCS) using Malvern mastersizer 2000 (UK) at an angle of 90o at 25°C. Samples were diluted appropriately with aqueous phase of formulation for potential measurements. Zeta potential of different formulation of was measured by PCS at 25^{o}C and electrical field strength was around 23.2 V/cm(Lin, 1993).

Scanning Electron Microscopy (SEM)

The sample for the SEM analysis were prepared by applying a monolayer of the nanoparticles dispersion on to one side of double adhesive stub and the stubs were then coated with platinum using the auto fine coater (JFC-1600, JEOL, Japan). The scanning electron microphotographs of SLN were taken using (JSM-6360, JEOL, Japan) scanning microscope (Merdan, 2003)

Drug Content

Drug content was determined by centrifugation method. The redispersed nanoparticles suspension was centrifuged at 15,000 rpm for 40 min at 25°C to separate free drug in the supernatant. Concentration of paclitaxel in the supernatant was determined by UV-visible spectrophotometer at 271 nm after suitable dilution (Feng, 2004).

Drug Entrapment Efficiency

The entrapment efficiency of the drug was determined by UV spectrophotometric method using the formula given below (Mu, 2003).

Drug Entrapment efficiency (%) = (Amount of drug actually present x 100)/ (Theoretical drug load expected)

In-vitro Release Studies

In vitro release studies were carried out by using dialysis tubes with an artificial membrane. The prepared paclitaxel nanoparticles and 10 ml of phosphate buffer pH 7.4 was added to dialysis tubes and subject to dialysis by immersing the dialysis tubes to the receptor compartment containing 250 ml of phosphate buffer pH 7.4 The medium in the receptor was agitated continuously using a magnetic stirrer at a temperature was 37± 0.5 °C. 5 ml sample of receptor compartment were taken at fixed time intervals of time over a period of 12 hrs and each time fresh buffer was replaced. The amount of drug released was determined spectrometrically at 271nm. At fixed time intervals, 1 ml of the aliquot was withdrawn from receptor compartment through the sample port. Fresh phosphate buffer pH 7.4 was replaced to maintain constant volume. Samples were suitably diluted and analyzed UV spectrophotometrically s at 271 nm (Saparia, 2002).

In vitro release kinetics

In order to understand the kinetic and mechanism of drug release, the result of *in-vitro* drug release study of nanoparticles were fitted with various kinetic equation like zero order, first order etc(Chowdary 2004). The value of r^2 and k were calculated for the linear curve obtained by regression analysis of the above plots.

Stability Study

The stability studies were carried using the optimized batch (PN4) as per the ICH guidelines. The stability of drug loaded nanoparticles was evaluated in terms of its drug content**,** entrapment efficiency, % of drug released etc (Aterman, 2007).

RESULTS AND DISCUSSION

Palcitaxel nanoparticles with varying proportions of paclitaxel and PSA-PEG were prepared by nanoprecipitation method. The SEM photographs are shown in fig 1.

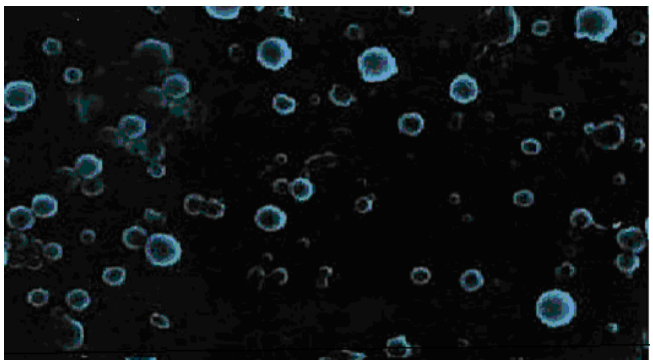


Fig. 1: Scanning electron microphotographs of optimized formulation

The particles shape was found to be fairly spherical structure without aggregation. The particle size of nanoparticles varied between 120±8 - 402±4 among the different formulations. This is due to variation in composition of formulations. Zeta potential of optimized formulation (PN4) was found to be -26.6 mV. Since there was decrease of surface potential it could be concluded that part of drug particle was absorbed on the polymeric

particles. The drug content was determined by centrifugation method and it was highest in formulation PN4. The nanoparticles exhibited an increase in drug content with increase in polymer ratio, up to particular concentration (1:4). A decrease in drug content was observed after that point due to saturation capacity of polymer. The *in-vitro* release profile of all formulation is shown in fig. 2. The release of drug form particles was mainly dependent upon polymer concentration. On increasing the polymer concentration the % drug released from nanoparticles decreased.

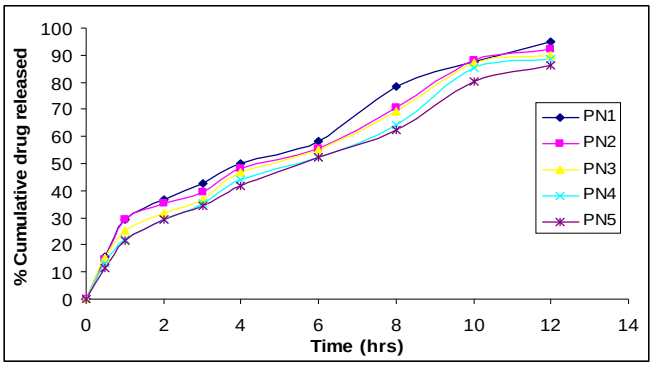


Fig.2: In- vitro release profile of various nanoparticles formulations.

The *in-vitro* release data of optimized formulation was treated with different kinetics models to explain the release kinetics of drug from nanoparticles. Zero order was considered as the best fitted model with the highest value of correlation coefficient (r^2 =0.997, Batch PN4).

The optimized formulation was subjected to stability studies at a room temperature and 40 °C / 75% RH. The optimized formulation was evaluated for their appearance, drug content, particle size, drug content, and percent drug release. Negligible changes were seen in different physicochemical parameters at a room temperature as well as 40°C/ 75 % RH. There was no significance difference in *in-vitro* release and drug content after three-month stability study at both room temperature and accelerated conditions (Table 1).

Table 1: Formulation and Physiochemical Characterization of Paclitaxel Nanoparticles.

FC	D:P	Particle size (nm)	PDI	Zeta potential (mV)	Percent drug content	Percent DEE	Percent CDR after 12 hrs
PN1	1:1	120±8	1.9	- 14.3	57.22±0.02	72.3	95.11
PN2	1:2	263± 5	2.11	- 18.8	63.13 ± 0.08	75.29	92.14
PN3	1:3	285±9	2.16	- 14.6	69.83± 0.03	82.55	89.89
PN4	1:4	231±5	3.14	-26.6	70.52 ± 0.02	83.28	88.56
PN5	1:5	402±4	2.24	-25.9	58.86± 0.04	84.85	8614

FC = formulation code, PDI = Polydispersity index, DEE = drug entrapment efficiency, CDR = cumulative drug released

CONCLUSION

Thus from the whole research work, it can be concluded that the objective of proposed research work has been fulfilled and polymeric nanoparticles of paclitaxel has been prepared using blend of PSA-PEG polymer. Formulation PN4 having the particle size, PDI, Zeta potential, % DC, %DEE, %CDR 231±5, 3.14, -26.6, 70.52 83.28, 88.56 respectively. On the bases of experimental data this formulation was considered as optimized formulation.

ACKNOWLEDGEMENT

We are thankful to Dabar Pvt. Ltd, India (for providing the free gift sample of paclitaxel) and ITS paramedical (pharmacy) Ghaziabad, UP, India (for providing the financial assistance).

REFERENCES

Aterman KC, A Critical Review of Gastro retentive Controlled Drug Delivery. Pharmaceutical Development and Technology. 2007: 12: 1-10.

B Saparia, R.S.R Murthy., A Solanki., Prepration and evaluation of chlroquine phosphate microspheres using cross linked gelatin for long term delievery. Ind J. Pharm Sci, 2002: 64: 48-52.

J. E. Liebmann, J. A. Cook, C. Lipschultz, D. Teague, J. Fisher, and J. B. Mitchell. Cytotoxic studies of paclitaxel (Taxol) in human tumor cell lines. Br. J. Cancer, 1993: 68:1104–1109.

K Subramani, H Hosseinkhani, A Khraisat, M Hosseinkhani, Y Pathak, Targeting Nanoparticles as Drug Delivery Systems for Cancer Treatment. Current Nanoscience, 2009:5: 135-140 .

K.P.R.Chowdary, N.K. RAO, K. Malathi, Ethyl cellulose microspheres of glipizide characterization , in vitro and in vivo evaluation, Ind J Pharm Sci. 2004: 66:412-416.

L. Mu, and S. S. Feng, A novel controlled release formulation for the anticancer drug paclitaxel : PLGA nanoparticles containing vitamin E TPGS. J. Control. Release, 2003: 86:33–48.

R. C. Nagarwa, Shri Kant, P.N. Singh, P. Maiti, and J.K. Pandi, Polymeric nanoparticulate system: A potential approach for ocular drug delivery, Journal of Controlled Release, 2009:136: 2-13.

S. M. Moghimi, A. C. Hunter, and J. C. Murray, Long-circulating and target-specific nanoparticles: theory to practice, Pharmacol. Rev,2010:53:283–318.

S. S. Feng. Nanoparticles of biodegradable polymers for new-concept chemotherapy. Expert Rev. Med. Devices, 2004:1:115–125.

T. Govender, S. Stolnik, M. C. Garnett, L. Illum, and S. S. Davis. PLGA nanoparticles prepared by nanoprecipitation: drug loading and release studies of a water soluble drug, J. Control Release, 1999:57:171–185.

T. Merdan, J. Callahan, H. Petersen, K. Kunath, U. Bakowsky, P. Kopeckova, T. Kissel, and J. Kopecek, Pegylated polyethylenimine-Fab' antibody fragment conjugates for targeted gene delivery to human ovarian carcinoma cells, Bioconjugate Chem,*2003:* 14:989–996.

W. Lin, A. G. A. Coombes, M. C. Davies, S. S. Davis, and L. Illum, Preparation of sub-100 nm human serum albumin nanoparticles using a pH-coacervation method. J. Drug Target. 1993:1: 237-243.