mPEG-PCL Nanoparticles as New Carriers for Delivery of a Prostae Cancer Drug Fluamide

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ABSTRACT:

The present work was aimed to prepare and evaluate Flutamide loaded methoxy poly (ethylene glycol) poly caprolactone (mPEG–PCL) nanoparticles for targeted delivery to the prostate cancer. The nanoparticles (NPs) were prepared by 2^3 factorial design and nanoprecipitation method. Various trials were evaluated for surface morphology, particle size and zeta potential. The influences of three formulation excipients such as polymer, stabilizer and organic phase volume on the characterization of NPs were investigated. The results of fourier transform infrared (FTIR) studies were indicated no interaction between the drug and polymer. The particle size varied from 79.2 to 89.1 nm and zeta potential value was found to be - 41.5 mv. The surface morphology of NPs was observed using scanning electron microscopy (SEM) and understands the arrangement and orientation of NPs to determine its behavior and stability. Flutamide loaded mPEG–PCL nanoparticle is a potential new carrier system for treatment of prostate cancer, which may overcome the problems associated with conventional formulations such as tablets.

KEYWORDS: Nanoparticles, Targeted delivery, Zeta potential and prostate cancer.

INTRODUCTION:

Polycaprolactone (PCL) is observed to possess good biodegradability and biocompatibility which are essentially made use of in controlled drug delivery and tissue engineering applications in various formulations [1]. It has compatibility with a variety of drugs which ensures uniform drug distribution in the formulation matrix and as it does not degrade for much time, drug release is facilitated up to many days. As a result of its very low Tg (-61^{o}C) and a low Tm (65^{o}C), which retards the biodegradation and sometimes becomes an obstacle in some applications [2].

Synthesis of PCL occurs by ring-opening polymerization of caprolactone (CL) monomers. The high olefin content gives it high degree of hydrophobicity and crystallinity resulting in the slow degradation and as such, becomes less biocompatible with soft tissues, which restricts its further clinical application/s [3]. Therefore, PCL is usually blended or modified as copolymer.

The amphiphilic block copolymers are observed to possess a range of combinations of hydrophobic and hydrophilic block unimers. The variation in unimer ratio alters the surface and also the micelle forming properties of the copolymer. These nanoscopic micelles possess the capacity to encapsulate hydrophobic compounds and function as potential drug carriers. The copolymers are synthesized to enhance the rate of bioabsorption. For instance, copolymers of ϵ caprolactone with methoxy polyethylene glycol are observed to yield more flexible materials with higher degradation rates than that of polycaprolactone [4]. The high permeability of Methoxy poly (ethylene glycol) Poly caprolactone (m-PEG PCL) to various agents has enabled it to be the significant ingredient in the development of drug delivery systems.

MPEG-PCL copolymers are vital synthetic biomedical materials possessing amphiphilicity, controlled biodegradability and good biocompatibility. Their application is seen in the fields of pharmaceutics medicinal chemistry, tissue engineering and nanotechnology and consequently led to other applications in the preparation of

different delivery systems in the form of microspheres, micelles, poly-mersomes, implants, nanospheres, and nanogels [5]. mPEG-PCL encapsulates several varieties of drugs towards targeted drug and controlled drug release. Due to advanced research activities in recent times, m-PEG-PCL copolymers and their end group derived nanoparticles further the drug loading hydrophobic drugs, enhance bioavailability, escape from phagocytes, lower the burst release and increase the circulation time of drugs in systemic circulation [6]. Further, these nanoparticles gather in target places to enhance drug efficiency and diminish toxicity due to their small particle size and modified surface areas. This study aims to develop a new formulation of Flutamide loaded mPEG-PCL nanoparticles as new carriers for targeted delivery to prostate cancer.

MATERIAL AND METHODS:

Flutamide was purchased from Yarrow Chem Products, Mumbai. Methoxy poly (ethylene glycol) poly caprolactone purchased from Sigma-Aldrich, United states. Pluronic F-127 purchased from Coastal chemical Limited, Visakhapatnam and all other ingredients used were of analytical grade obtained from obtained from Qualigens Fine chem, Mumbai.

Preparation of NP'S:

Flutamide loaded mPEG-PCL nanoparticles were prepared by the nanoprecipitation method [8]. Drug and polymer were dissolved in organic and this solution was added to stabilizer in PBS pH 7.4 at 1 ml/min speed using syringe under magnetic stirring conditions. The obtained suspension was stirred at 500 rpm for 2 hr to evaporate acetone. The suspension was centrifuge at 11,000 rpm for 30 minutes to remove precipitants and supernatant was collected, lyophilized and stored at 4°C. The optimization phase was carried out statistically using 2^3 factorial designs in which the polymer concentration, stabilizer and organic solvent volume were kept at two different levels [9]. Total eight formulations were prepared for ease of analysis and comparison.

Drug - polymer compatibility studies:

A stable and effective dosage form was formulated depends on selection of excipients that are promote the drug release and bioavailability and protect it from degradation. If the excipients not were used in formulation containing the active drug, the compatibility study is mandatory. The IR spectra of Flutamide and formulation mixture were recorded on a FT-IR spectrophotometer. About 2mg of the sample was made into pellets using KBr and hydraulic press under a pressure of 6000kg/cm^2. Spectra were scanned between 4000 and 500cm^{-1} at ambient temperature [10].

Physicochemical characterization of NPs:

The obtained formulations of Flutamide loaded mPEG-PCL nanoparticles were characterized for Particle Size Analysis, Surface Morphology and Surface Charge determination. Particle size measurement was carried out by Photon Correlation Spectroscopy (PCS) (Malvern Instruments). Samples were diluted with ultra purified water, and measured at 25° and 90° scattering angles, recorded for 180 sec and the mean diameters for all samples were obtained by cumulative analysis in triplicate [11]. The morphological study of nanoparticles was carried out using scanning electron microscopy (SEM) (Tecnai 20 G2 S TWIN) [12]. SEM was employed to understand the arrangement and orientation of molecules within the nanoparticle to determine its behavior and stability. Nanoparticles were characterized for Zeta potential (ζ) using a Zeta Sizer [13].

RESULTS AND DISCUSSION:

Preparation of NP'S:

Nanoprecipitation method was used for preparation of Flutamide loaded nanoparticles. The formulations were designed by 2^3 factorial design, which contained three variables like polymer concentration, stabilizer and organic solvent volume at two levels. Total eight batches were formulated (F1 - F8) and all the formulations were investigated for various parameters.

Table 1: 2^3 Factorial design of Nanoparticles

Factor	Low level (-1)	High Level (+1)
mPEG-PCL	10 mg	50 mg
Pluronic F-127	1%	1.5%
Acetone	10 ml	30 ml

Drug - Excipient Compatibility Studies:

Fourier Transform Infra Red Spectroscopy (FTIR):

FTIR studies used to determine the interaction between Flutamide, mPEG-PCL and Pluronic F-127 used in nanoparticle preparation. The mixture of drug and excipients were prepared in 1:1 w/w ratio and used for IR analysis. The FTIR spectra of Flutamide (Fig.2) indicates that the characteristic peaks of –NO, NH, C=O and –CH2 are observed at 1344.97 cm^{-1}, 3360.06 cm^{-1}, 1717.71cm^{-1} and 3127.11cm^{-1}respectively.

Table 2: Frequencies of respective functional groups of Flutamide

S. No.	Frequency (cm^{-1})	Functional Group
1	1344.97	–NO
2	1717.71	C=O
3	3127.11	–CH2
4	3360.06	NH

Inference:

The IR spectra of Flutamide was recorded using brooker spectrophotometer with KBr pellet method. IR spectra of formulation had showed absorption peaks which were comparable with absorption peaks of pure drug. The results indicated that, no chemical interaction between drug and excipients.

Physicochemical characterization of NPs:

1. Size Analysis:

Formulation F7 showed minimum particle size of 79.2 nm and the formulation F6 showed maximum particle size of 89.1 nm. The results indicate that the particle size increased with increasing polymer (mPEG-PCL) concentration of 10 and 50 mg, the minimum variation in size may occurred due to capping action of the mPEG [14]. The particle size decreased with increasing organic phase volume of 10 and 30 ml and the particle size decreased with increasing pluronic F-127 from1 – 1.5%. The particle size of NPs is important that influences accumulation in tumour tissue via EPR effect and the targeting ability of NPs after administration.

Figure 4: Mean particle size analysis of nanoparticle formulations F1 – F8

2. Scanning Electron Microscopy (SEM):

Surface morphology of Flutamide loaded copolymeric nanoparticles was evaluated by SEM. As shown in Fig. 7, eight formulations of nanoparticles have regular spherical structure with smooth and uniform surface without signs of collapse.

Figure 5: Scanning electron micrographs of Nanoparticles formulations F1 – F8

3. Surface Charge (Zeta Potential):

The zeta potential of the formulation F7 was found to be -41.5, which implies that it is having good stability. The negative zeta potential values of formulation F7 can be attributed to the presence of uncapped end ionized carboxyl groups of the polymer at the particle surface [15].

Figure 6: Zeta potential of nanoparticles formulation F7

CONCLUSION:

The results of Fourier transform infrared studies were concluded that drug Flutamide, copolymer mPEG-PCL and stabilizer used for the formulation of nanoparticles were found to be compatible and suitable for formulations without any interactions. The various trials with influences of formulation components such as polymer, organic phase volume and surfactant on the physicochemical characteristics of nanoparticles were investigated. The results proved that formulation F7 containing 10mg mPEG–PCL and 30 ml acetone with 1.5% pluronic F127 produced the most ideal nanoparticles with average diameter of 79.2nm. SEM images of formed nanoparticles showed spherical shape with smooth surface. The zeta potential of optimized formulation F7 was found to be - 41.5, which implies that it is having good stability. Flutamide loaded mPEG–PCL nanoparticle is a potential new carrier system for

treatment of prostate cancer, which may overcome the problems associated with conventional formulations such as tablets.

ACKNOWLEDGMENT:

Authors are thankful to Dr. S. Sathesh Kumar, HOD, Department of Pharmaceutics, VISTAS, Vel's University, Chennai for supporting this work.

REFERENCES:

1. Mondrinos M. J, Dembzynski R., Byrapogu V. K, Wootton D. M, Lelkes P and Zhou J. Porogen based solid freeform fabrication of polycaprolactone calcium phosphate scaffolds for tissue engineering. Biomaterials. 2006; 27: 4399–4408.
2. Kim J and Bae Y. Albumin loaded microsphere of amphiphilic poly(ethylene glycol)/ poly(α-ester) multiblock copolymer. Eur J of Pharm Sci. 2004; 23: 245–251.
3. Hossein Danafar. MPEG–PCL copolymeric nanoparticles in drug delivery systems. Cogent Medicine. 2016; 3: 1 – 11
4. Huang M. H, Hutmacher D. W, Schantz J. T, Vacanti C. A, Braud C and Vert M. Degradation and cell culture studies on block copolymers prepared by ring opening polymerization of p-caprolactone in the presence of poly(ethylene glycol). J Biomed Mater Res. 2004; 69: 417–427.
5. Danafar H, Rostamizadeh K, Davaran S, Valizadeh H and Hamidi, M. Biodegradable m- PEG/PCL core- Shell Micelles: Preparation and characterization as a sustained release formulation for curcumin. Adv Pharm Bull. 2014; 4: 501–510.
6. Park E. K, Kim S. Y, Lee S. B and Lee Y. M. Folate conjugated methoxy poly(ethylene glycol)/poly(εcaprolactone) amphiphilic block copolymeric micelles for tumor-targeted drug delivery. J Control Release. 2005; 109: 158–168.
7. Chemical Structure of mPEG-PCL. https://www.google.com/ search?q =Chemical+Structure+of+mPEG-PCL
8. B. V. Nagarjuna yadav, V. Ravichandiran, S. Sathesh kumar. Preparation and characterization of gemcitabine loaded mpeg-pcl polymeric nanoparticles for improved transportation across blood brain barrier. *IJPPS*. 2016; 8: 82 – 90
9. Venkateswara Rao S, Sathesh Kumar S. Design and Evaluation of Flutamide-Loaded Polycaprolactone Nanoparticles by 2^3 Factorial Design and Nanoprecipitation Method. Asian J Pharm Clin Res. 2018; 11: 203-210
10. Dipsingh SN. Preparation and *in vitro–in vivo* evaluation of surface-modified poly(lactide-coglycolide) nanoparticles as controlled release carriers for flutamide delivery. J Microencapsul. 2015; 32: 231 – 239
11. R. S. Surenya, Snima, K. S., V Shantikumar, N., and Lakshmanan, V. Kumar. Assessment of Poly (vinyl alcohol) Coated Flutamide Nanoparticulates and Their Efficacy on Prostate Cancer Cells. Curr Drug Deliv. 2016; 2: 312 - 339
12. Ahmed O Elzoghby, Maged W Helmy, Wael M Samy and Nazik A Elgindy. Novel ionically crosslinked casein nanoparticles for flutamide delivery: formulation, characterization and in vivo pharmacokinetics. Int J Nanomedicine. 2013; 8: 1721–1732
13. Martel CL, Gumerlock PH, Meyers FJ and Lara PN. Current strategies in the management of hormone refractory prostate cancer. Cancer Treat Rev. 2003; 29: 171–187.
14. K. T. Arulmozhi and N. Mythili. Studies on the chemical synthesis and characterization of lead oxide nanoparticles with different organic capping agents. AIP Advances. 2013; 3: 122122 – 122129
15. Cegnar, M., Kos, J., Kristl, J. (2004) Cystatin incorporated in poly (lactide-co-glycolide) nanoparticles: development and fundamental studies on preservation of its activity. Eur J Pharm Sci. 22, pp. 357-364.

Received on 11.11.2019 Modified on 25.03.2020
Accepted on 18.05.2020

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Research J. Pharm. and Tech. 2021; 14(7):3657-3661.
DOI: 10.52711/0974-360X.2021.00632