Flutamide Loaded Polymeric Nanoparticles for prostate Cancer: A Review

S. Venkateswara Rao[1], S. Sathesh Kumar*[2]

[1]Department of Pharmaceutics, Vel's Institute of Science, Technology and Advanced Studies (VISTAS), Vel's University, Chennai – 600117, Tamilnadu, India.

[2]School of Pharmaceutical Sciences, Vel's Institute of Science, Technology and Advanced Studies (VISTAS), Vel's University, Chennai – 600117, Tamilnadu, India.

*Corresponding Author E-mail: **sathesh2000@gmail.com**

ABSTRACT:

Flutamide is a potent nonsteroidal anti androgen used to treat advanced prostate cancer. It blocks the androgen receptors on the cancer cells and inhibits the androgen dependent cell growth. This work was planned to compile the research work available in the scientific publications in the formulation and evaluation of Flutamide loaded polymeric nanoparticles for the treating the prostate cancer including the study of influence of various formulation components such as polymer concentration, organic phase volume, drug content, stabilizer concentrations and the ratio between aqueous to organic phase in the characteristics of nanoparticles. Literature study revealed that, methods like Ionic Gelation Technique, Solvent Evaporation method and Nanoprecipitation have been utilized and polymers like Chitosan, casein, Methacrylic acid, PHEA-IB-p(BMA) graft copolymer, mPEG – PLGA and PVA have been utilized. The drug loaded polymeric nanoparticles were evaluated for their physiocochemical properties along with characterization with FTIR, in vitro release and in vitro and in vivo anticancer potential. From the literature it was understood that, nanoprecipitation method was the most commonly used method in various research perspectives. Based on the findings of the present review, Flutamide loaded polymeric nanoparticles may be used as an treatment adjunctive for prostate cancer.

KEYWORDS: Flutamide, Nanoparticles, Prostate Cancer and Nanoprecipitation.

INTRODUCTION:

Prostate cancer is found to be the sixth leading cause of death among men worldwide and it is expected to grow to 1.7 million new cases and 4,99,000 new deaths by 2030 due to the growth of global population[1]. It is ranked fourth among the typically observed cancers in both sexes and occupies the second place among the cancers found only among men[2]. Globally, among three fourth of the cases registered during the last decades of the 20th century, prostate cancer is identified as the major health problem[3]. Consequently, the incidence rate of prostate cancer is observed to vary by 25 fold in various parts of the world. It is found to be low in Asian and North African countries, and the range varies from 1 to 9/1,00,000 individuals[4]. Demographic and epidemiological transitions in India have confirmed a rise in the growth of various cancer cases inclusive of prostate cancer.

Flutamide is a potent nonsteroidal anti androgen that is used to treat the advanced state of prostate cancer. It blocks the androgen receptors on the cancer cells and inhibits the androgen dependent cell growth. The usual dose of flutamide tablets is 250mg three times a day[5,6]. Its absorption is rapid on oral administration and it attains peak plasma concentration in 1 h after a single dose. The drug has high first pass hepatic metabolism and low elimination half life (5-6h). It is less functional due to its rapid metabolism and less active metabolites (hydroxyl flutamide)[7]. Its bioavailability is less due to its poor wetability and aqueous solubility[8]. Moreover high dose of Flutamide produces hepatotoxicity. Treatment with flutamide may lead to a variety of side-effects which include diarrhea, tiredness, impotence, enlargement of male breast and liver malfunction[9]. In order to decreasing adverse effects and the frequency of drug administration, a sustained release formulation of flutamide is desirable. Hence, the formulation of Flutamide with high plasma half-life, slow and constant release which can deliver to the target tissue is important. The preparation of flutamide nanoparticles makes it possible to increase the bioavailability, reduce the incidence and severity of adverse effects, especially gastrointestinal disorders and hepatic impairment.

Figure 1: Structure of Flutamide

The present work was planned to compile the published research work related to the formulation and evaluation of Flutamide loaded polymeric nanoparticles for the treatment of prostate cancer and study the influence of various formulation components on size, stability and release of nanoparticles. The objective of this article is to understand the various formulation techniques and develop new polymeric nanoparticles for targeting prostate cancer.

Biodegradable Polymers:
Biodegradable polymers are advantageous in many ways over other materials used in nanoparticle drug delivery systems. In the literature, several polymeric nanoparticles have been developed, out of which two researchers used natural polymers like chitosan and casein, where as remaining researchers used synthetic polymers like Meth acrylic acid, PHEA-IB-p (BMA) graft copolymer, mPEG – PLGA and PVA.

Natural Polymers:
Adlin Jino Nesalin J, et.al., 2009[10] developed polymer nanoparticles using chitosan, which the core: coat ratio 1:4 showed better controlled release for about 12hr than compared to other formulations. Ahmed O Elzoghby, et.al., 2013[11] developed polymer nanoparticles using casein, which the drug and casein ratio 1:5 gives small particle size of 70.76nm and better controlled release for about 14hr.

Synthetic Polymers:
K. Umasankar, et.al., 2010[12] formulated flutamide nanoparticle using Methacrylic acid copolymer (RL100) in three different ratios. The partical size ranged between 335nm to 620nm and in vitro release was exhibited upto 16 hrs. Mariano Licciardi, et. al., 2013[13] prepared magnetic nanocarriers (MNCs) using the PHEA-IB-p(BMA) graft copolymer as coating material, the nanocarriers exhibited dimensions of about 300nm with super paramagnetic behavior. Dipsingh SN, 2015[14] investigation suggest the use of methoxy polyethylene glycol (mPEG) functionalized poly(d,l-lactide-co-glycolide) (PLGA) nanocrystals. The optimised formulation exhibited significantly delayed drug release upto 48? hrs. R. S. Surenya, et.al., 2016[15] Poly vinyl alcohol (PVA) coated flutamide nanoparticles exhibited sustained in vitro release upto 120hr.

Techniques for Preparation:
Optimization of the properties of polymer nanoparticles depending on the particular application is necessary. In order to achieve the required properties of nanoparticles the mode of preparation plays a important role. As per literature, different techniques like nanoprecipitation, solvent evaporation and ionic gelation techniques were commonly used.

Figure 2: Techniques for preparation of polymer Nanoparticles

Ionic Gelation Method:
This method involves a mixture of polymer chitosan/casein and polyanion sodium tripolyphosphate (STPP). The positively charged chitosan interacts with negatively charged STPP to form particles with a size in the range of nanometer[16]. The researchers Adlin Jino Nesalin J, et.al., 2009[10] and Ahmed O Elzoghby, et.al., 2013[11] developed nanoparticles of Flutamide by ionic gelation technique.

Solvent evaporation method:
In this method polymer solutions were prepared using volatile solvents to formulate emulsions. On evaporation organic solvent from the polymer, the emulsion gets converted into suspension containing nanoparticles which was allowed to diffuse through the continuous phase of the emulsion[17]. K. Umasankar, et.al., 2010[12] and Mariano Licciardi, et.al., 2013[13] have developed Flutamide nanoparticles by solvent evaporation using dichloromethane and ethyl acetate as organic solvent.

Nanoprecipitation Method:
This method involves the precipitation of preformed polymer following displacement of a semipolar solvent which is miscible with water in the presence or absence of a surfactant[18]. The easiest and reproducible technique for preparing nanospheres was nanoprecipitation method. In the literature Dipsingh SN. 2015[14] and R. S. Surenya, et.al., 2016[15] developed nanoprecipitation method for Flutamide nanoparticles and it shown highest encapsulation efficiency and percent cumulative release with spherical nanoparticles.

Table 1: Reported research work on Flutamide polymeric Nanoparticles

S. No.	Polymers	Technique	Characterization	Reference
1	Chitosan Sodium tripolyphosphate	Ionic Gelation	Total drug content, Loading efficiency, Particle size and in vitro drug release studies	Adlin Jino Nesalin J, *et.al*., 2009
2	Methacrylic acid copolymer (RL100)	Solvent Evaporation	Particle size, Drug entrapment efficiency, Drug release and Stability studies.	K. Umasankar, *et.al*., 2010
3	Casein Sodium tripolyphosphate	Ionic crosslinking	Drug loading, Incorporation efficiency Zeta potential In vitro drug release vivo pharmacokinetics	Ahmed O Elzoghby, *et.al*., 2013
4	PHEA-IB-p(BMA) graft copolymer	Solvent evaporation	Dynamic Light scattering (DLS), Transmission electron microscopy (TEM), Vitro Cytotoxicity (prostate cancer cell line LNCaP) Cell uptake tests Biodistribution studies	Mariano Licciardi, *et.al*., 2013
5	Mpeg -PLGA)	Nanoprecipitation	DSC, FTIR, X-ray diffraction, SEM, Particle size, Zeta potential, Percent entrapment efficiency *In vitro* dissolution, haemolysis, Sterility, bioavailability and stability studies	Dipsingh SN., 2015
6	PVA	Nanoprecipitation	Encapsulation efficiency Loading efficiency In vitro drug release In vitro cytotoxicity, Colony forming ability *In vitro* hemolysis assay and blood aggregation	R. S. Surenya., *et.al*., 2016

Characterization:

The prepared Flutamide polymeric nanoparticles were characterised through, DSC, FTIR, percent entrapment efficiency (%EE), particle size, X-ray powder diffraction, SEM, zeta potential, in vitro dissolution, bioavailability, haemolysis, sterility, and stability studies.

CONCLUSION:

Flutamide is a potent nonsteroidal anti androgen used to treat prostate cancer. The present review concluds that the Flutamide loaded polymeric nanoparticles prepared with nanoprecipitation and synthetic polymers shown versatile characteristics like targeting action, sustained release, biodegradable and biocompatible nature acts as a best nanocarrier for the prostate cancer therapy when compared to nanoparticles prepared with other techniques and natural polymers. Polymeric nanoparticles can achieve tumor targeted drug delivery via passive targeting based on the EPR effect or active targeting by an appropriate ligand, which improves antitumor efficacy and reduces toxicity on healthy tissues. For further advancement, it may be necessary to focus more research attention on the pharmacokinetics, biodistribution, and safety of these novel carrier drug delivery systems.

ACKNOWLEDGMENT:

Authors would like to acknowledge various electronic databases, research/review articles which were the source in compilation of this article.

SSSSS

REFERENCES:

1. J. Ferlay, H.R. Shin and F. Bray. Cancer Incidence and Mortality Worldwide: IARC Cancer Base. International Agency for Research on Cancer. 2010; 45 - 66
2. Beiki O. Cancer and migration: Epidemiological studies on relationship between country of birth, socio-economic position and cancer. 2010; 22 - 35
3. Prakash Galani. Diagnosis and Prognosis of Prostate Cancer. Journal of Advanced Medical and Dental Sciences Research. 2015; Vol. 3: 49 – 53
4. Shalu Jain, Sunita Saxena and Anup Kumar. Epidemiology of prostate cancer in India. Meta Zene. 2014; Vol. 2: 596 – 605
5. Melrose Park, Australian Pharmaceutical Formulary and Handbook. 19th ed. 2004; 105
6. The United Stated Pharmacopeia. 27th ed. Rockville, United States Pharmacopeial Convention, 2004; 2: 837-838
7. Zuo Z, Tam YK, Diakur J, Wiebe LI. Hydroxypropyl-β-cyclodextrin flutamide inclusion complex. II. Oral and intravenous pharmacokinetics of flutamide in rat. J Pharm Pharmaceut Sci. 2002; 5: 292–298.
8. British Pharmacopoeia London, The Stationary Office. 2004; Vol. 1: 864-5.
9. Umrethia M.L, Ghosh P.K, Majithiya R.J. and Murthy R.S.R., Pharmacokinetics and hepatotoxicity of flutamide liposomes after IV administration, Online J. Pharmaco. 2005; Vol. 3: 1-15.
10. Adlin Jino Nesalin J, Gowthamarajan K and Somashekhara C.N. Formulation and evaluation of Nanoparticles containing flutamide. International Journal of Chem Tech Research. 2009; Vol. 1: 1331 – 1334
11. Ahmed O Elzoghby, Maged W Helmy, Wael M Samy, Nazik A Elgindy. Novel ionically crosslinked casein nanoparticles for flutamide delivery: formulation, characterization, and in vivo pharmacokinetics. International Journal of Nanomedicine. 2013; Vol.8: 1721–1732

12. K. Umasankar and c. Umamaheswar Reddy. Nanoparticular Drug Delivery System of Anticancer Drug – Flutamide. International Journal of Pharm Tech Research. 2010; Vol. 4: 1115
13. Mariano Licciardi, Cinzia Scialabba, Calogero Fiorica, Gennara Cavallaro, Giovanni Cassata, and Gaetano Giammona. Polymeric nanocarriers for magnetic targeted drug delivery: preparation, characterization, and in vitro and in vivo evaluation. Mol. Pharmaceutics. 2013: Vol.10: 4397–4407
14. Dipsingh SN. Preparation and *in vitro–in vivo* evaluation of surface-modified poly(lactide-*co*glycolide) nanoparticles as controlled release carriers for flutamide delivery. Journal of Microencapsulation. 2015; Vol. 32: 231 – 239
15. 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; Vol. 2: 312 - 339
16. VJ Mohanraj and Y Chen. Nanoparticles – A Review. Tropical Journal of Pharmaceutical Research, 2006; Vol. 5: 561-573
17. Nagavarma B V N, Hemant K.S. Yadav, Ayaz A, Vasudha L.S and Shivakumar H.G. Different techniques for preparation of polymeric nanoparticles - A review. Asian J Pharm Clin Res, 2012; Vol. 5: 16-23
18. Y. Dastagiri Reddy, D. Dhachinamoorthi and K. B. Chandra Sekhar. A Brief Review on Polymeric Nanoparticles for Drug Delivery and Targeting. Journal of Medical and Pharmaceutical Innovation. 2015; Vol. 2: 19-32

Received on 11.11.2019 Modified on 13.03.2020
Accepted on 17.04.2020
Research J. Pharm. and Tech. 2021; 14(8):4501-4503.
DOI: 10.52711/0974-360X.2021.00782