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Nanoparticular Drug Delivery System of Anticancer Drug – Flutamide

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ABSTRACT: The present study deals with the formulation of flutamide nanoparticles. Flutamide is an oral antiandrogen drug primarily used to treat prostate cancer. The purpose of this research is to minimize the frequency of doses and toxicity and to improve the therapeutic efficacy by formulating flutamide nanoparticle. Flutamide nanoparticles were formulating by solvent evaporation method using Methacrylic acid copolymer (RL100) with three different ratios. Nanparticles were characterized by determining its particle size, drug entrapment efficiency, drug release and stability studies. The partical size ranged between 335nm to 620nm. Drug content was found of be supportive to the drug release pattern. The invitro release of flutamide nanoparticles were carried out which exhibited a sustained release of flutamide from nanoparticles upto 16 hrs. The results showed that nanoparticles were more beneficial in providing drug delivery system.
KEY WORDS: Flutamide, Nanoparticles, Methacrylic Acid Copolymer(RL100), Solvent Evaporation.

INTRODUCTION

In recent decades there been increased interest in the use of Nanoparticles for drug delivery applications. Nanoparticles are colloidal - sized particles, possessing diameters ranging between 1 and 1000 nm, and drugs may be encapsulated, adsorbed or dispersed in them. A wide varity of nanoparticles composed of a range of materials including lipids, polymers and inorganic materials have been developed, resulting in delivery systems that vary in their physicochemical properties and thus their applications[1].

Prostate cancer is the most common cancer in men in Western countries and it is the second leading cause of cancer death. Flutamide is a potent nonsteroidal pure androgen receptor antagonist used clinically (250 mg 3 times daily) for the management of metastatic carcinoma of the prostate[2] .Flutamide undergoes extensive first – pass metabolism[3]. Frequent administration of flutamide is required to reduce the level of testosterone and this may cause hepatotoxicity.

The purpose of this study is to reduce the frequency of doses and toxicity and to improve the therapeutic efficacy by formulating fluatamide nonparticles and to evaluate their particle size, entrapment efficiency, drug release and stability studies.

The drug (flutamide) was gift sample obtained from CIPLA Ltd. Bangalore and polymer Methacrylic acid copolymer (RL100) is from ROHM CHEMICALS. Remaining all other chemicals and solvents were used in this formulation were of analytical grade.

Preparation of Flutamide Nanoparticles by solvent Evaporation Method[4]

The polymer was dissolved in chloroform and the drug flutamide is dissolved in the above solution, and this mixture is emulsified by sonication for 45 min. at 15^{o}C in an aqueous 0.5% w/v gelatin solution. After the formation of a stable emulsion, the organic solvent is evaporated by increasing the temperature at 40^{o}C under continuing sonication. The Nanoparticles were separated by fractional centrifugation using a cooling centrifuge at 1×10^{4}rpm for 15 mins, same method used for the 3 different formulation with

various proportion of polymer concentration (Table No-I)

Characterization of Flutamide Nanoparticles

Particle Size Analysis.

The particle size of the Flutamide Nanoparticles were evaluated by Scanning Electron Microscope were ranging from 335 nm to 620 nm, particle size varies depending on the polymer load (Table No-II)

Determination of percentage of drug entrapment efficiency.[5,6]

The Flutamide Nanoparticles were suspended in phosphate buffer saline to make a 1% solution and this solution was used for further studies. Flutamide nanoparticle suspension was added with equal part of acetonitrile to precipitate the polymer. To this added aqueous potassium dihydrogen phosphate (30 mM) solution. This mixture is subjected to centrifuge at 16000 rpm in cooling centrifuge at 15°C for 30 min. The clear supernatant fluid was analysed spectrophotometrically at 306 nm.(Table No-II).

$$\text{Drug Entrapment (\%)} = \frac{\text{The Amount of Drug in the Nanoparticles}}{\text{The Amount of Drug fed in to system}} \times 100$$

***In vitro* release of Flutamide from Nanoparticles**

The *in vitro* release of Flutamide from nanoparticles was studied by using simple diffusion cell apparatus which is opened at both ends, One end tied with sigma dialysis membrane which serves as a donor compartment. The dissolution medium used was freshly prepared 2% w/v Sodium Laryl Sulphate solution. Sigma membrane was soaked overnight in the dissolution medium. The medium was stirred by using the magnetic stirrer and the temperature was maintained at 37°C ± 0.5°C. Periodically 5 ml of sample was withdrawn and analysed spectrophotometrically at 306 nm. (Table No-III).

Stability Studies[7]

The Nanoparticles were kept in small air tight glass containers and stored at different temperature such as 4°C, room temperature and 45°C. The Drug content was observed in different time interval of Ist week,IInd,IIIrd and IVth week. There was no appreciable changes in drug content was observed in room temperature and 4°C. So suitable storage condition was room temperature and 4°C Table (IV) showed the stability of flutamide nanoparticles.

RESULTS AND DISCUSSION

[8]The Nanoparticles were prepared by solvent evaporation method by using polymer Methacrylic acid copolymer (RL100) .The particle size were evaluatd by SEM were manging from 335nm to 620nm.. The entrapment efficiency of the drug was enhanced by increasing the load of polymer. Batch no FN-III 1:3 ratio of drug and polymer has highest percentage of entrapment efficiency.The percentage of drug release were observed in three different formulations[9]. The cumulative percentage of drug release from flutamide nanoparticles after 16th hour was 88.06, 82.12, 74.61 respectively for FN-I, FN-II, FN-III. Sustained release was observed in 1:3 drug polymer ratio when compared with other two formulations. In stability studies there were no Changes in the drug content in room temperature and 4°C which was suitable for the storage condition. From all the above results the flutamide nanoparticles with 1:3 ratio of drug polymer showed significant sustained release with efficient drug delivery.

Table No-I: Formulation of Flutamide Nanoparticles

Sr.No	Batch Code	Drug (mg)	Polymer (mg)	Drug:Polymer Ratio
1	FN-I	50	50	1:1
2	FN-II	50	100	1:2
3	FN-III	50	150	1:3

Table No-II: Particle Size and Percentage of Entrpement Efficiency

Sr.No	Batch Code	Drug:Polymer Ratios	Particle Size(nm)	Entrapment Efficiency (%)
1	FN-I	1:1	335	61.62 ± 0.3
2	FN-II	1:2	450	68.56 ± 0.2
3	FN-III	1:3	620	73.18 ± 0.7

Table No-III: Invitro Release of Flutamide from Flutamide Nanoparticles

Sr.No	Time in Hours	FN-I (%)	FN-II(%)	FN-III (%)
1	0	0	0	0
2	0.5	11.2	8.37	7.32
3	1	23.68	16.33	13.99
4	1.5	28.12	22.6	21.98
5	2	34.04	29.74	25.31
6	3	39.96	34.32	29.74
7	4	44.4	41.43	34.31
8	5	51.07	43.56	40.64
9	6	57.72	47.29	42.63
10	8	69.57	52.36	46.3
11	10	76.97	59.06	50.3
12	12	80.66	64.09	55.63
13	14	85.1	75.42	67.29
14	16	88.06	82.12	74.61

Fig.No-I:

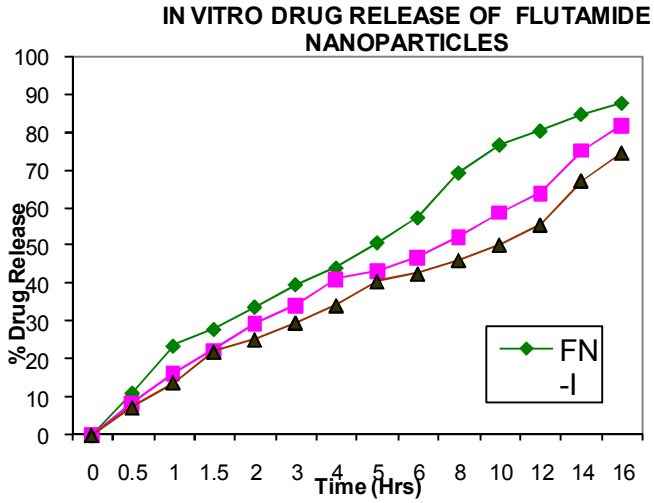


Table No-IV: Stability Studies

% of Drug Remaining									
Batch	**FN-I**			**FN-II**			**FN-III**		
Time	$4^{O}C$	Room Temp	$45^{O}C$	$4^{O}C$	Room Temp	$45^{O}C$	$4^{O}C$	Room Temp	$45^{O}C$
Initial	100	100	100	100	100	100	100	100	100
I^{st} Week	97.2	97.54	95.31	98.3	98.8	96.7	98.6	99.1	97.8
II^{nd} Week	94.6	95.68	91.21	96.4	96.9	92.8	96.3	97.26	94.5
III^{rd} Week	90.8	92.33	87.12	93.5	95.46	89.7	94.0	95.65	90.4
IV^{th} Week	89.8	91.96	84.14	90.9	93.79	85.4	92.8	93.32	86.8

Fig.No-II

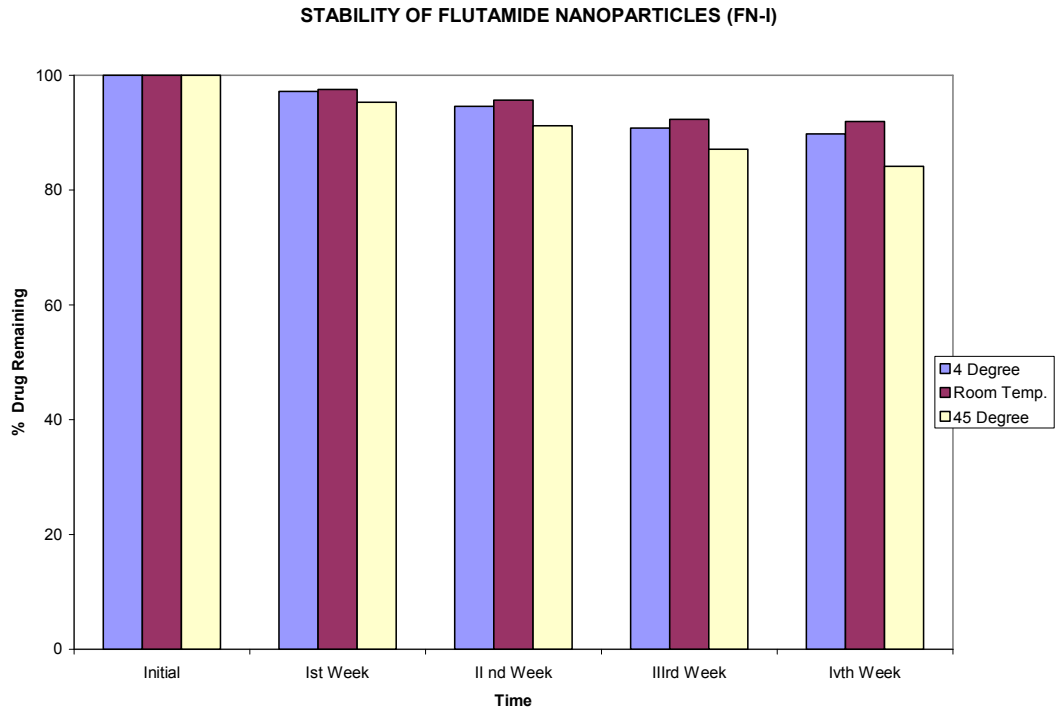


Fig.No-III

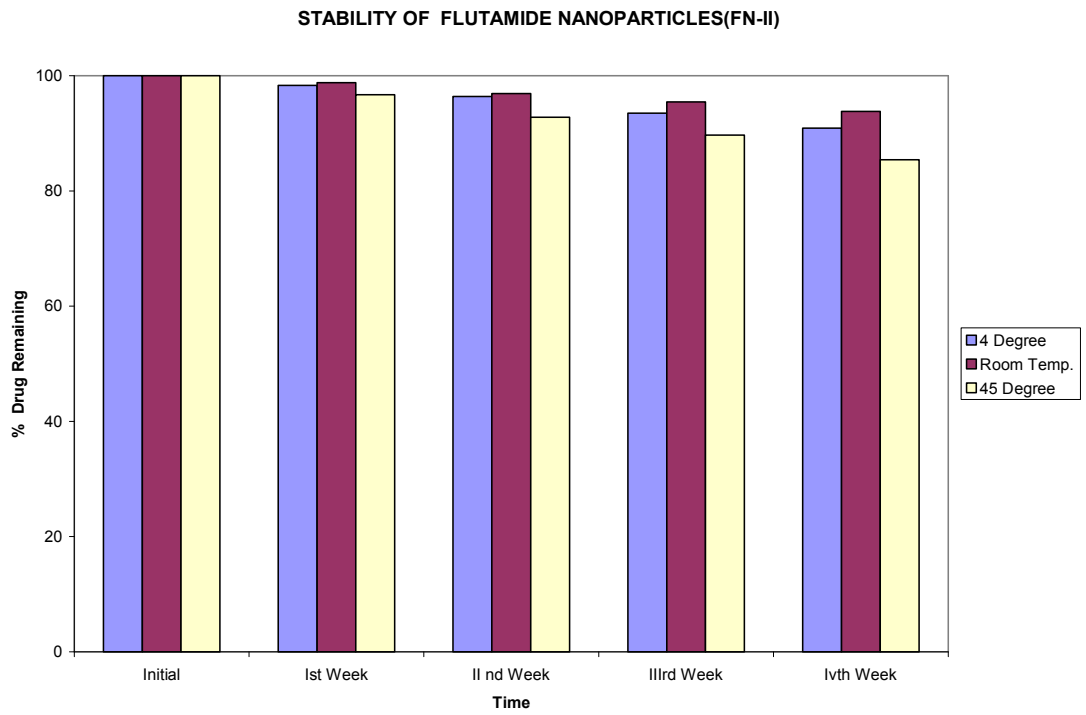
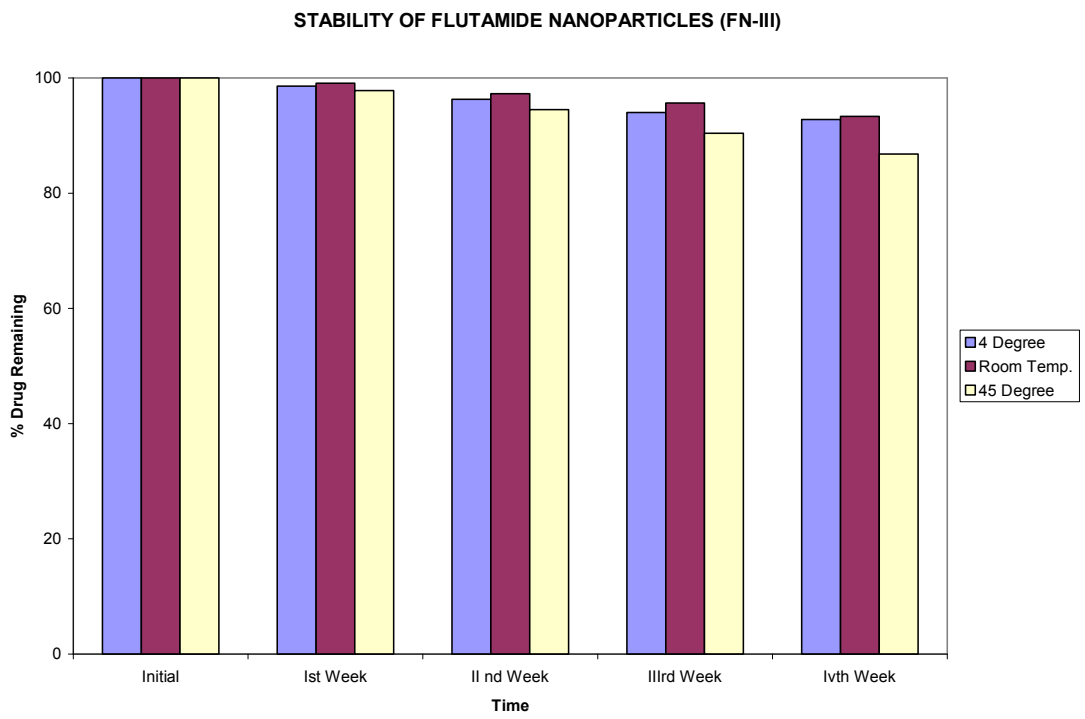


Fig.No-IV



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