International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.1, No.4, pp 1331-1334, Oct-Dec 2009

FORMULATION AND EVALUATION OF NANOPARTICLES CONTAINING FLUTAMIDE

ADLIN JINO NESALIN J.*, GOWTHAMARAJAN K and SOMASHEKHARA C.N.

Bharathi College of Pharmacy, Bharathinagara,K. M. Doddi, Maddur Taluk, Mandya District,Karnataka, India – 571 422.

Corres.author:adlinjino@gmail.com
Phone: 09916438666

ABSTRACT :Flutamide, a substituted anilide, is a potent antiandrogenic that has been used in the treatment of prostate carcinoma having short biological half-life of 5-6 hrs; thus it is a good candidate for the formulation of sustained release dosage form. In the present work nanoparticles of Flutamide were formulated using chitosan polymer by ionic gelation technique. Nanoparticles of different core: coat ratio were formulated and analyzed for total drug content, loading efficiency, particle size and *in vitro* drug release studies. From the drug release studies it was observed that nanoparticles prepared with chitosan in the core: coat ratio 1:4 gives better sustained release for about 12 hrs as compared to other formulations.
KEY WORDS :Flutamide, chitosan, ionic gelation technique, nanoparticles.

INTRODUCTION AND EXPERIMENTAL

Colloidal drug delivery systems offer a number of advantages over conventional dosage forms. Due to their small particle size, colloidal preparations lend themselves to parentral preparations and may be useful as sustained release injections for the delivery to a specific organ or target site[1]. The carrier must be biodegradable, non toxic and stable. Chitosan (CS) is a natural biodegradable polymer and the method adopted was ionic gelation. Flutamide is a nonsteroidal antiandrogenic drug used for the treatment of prostate cancer. This drug has quite extensive first pass metabolism, shorter elimination half life and poor bioavailability, which reduces testosterone only when administration on a continuous basis. Moreover high dose of Flutamide produces hepatotoxicity[2]. The present study is to prepare Flutamide nanoparticles to extend the release so as to reduce the adverse effects and to evaluate their particle size, drug loading capacity and drug release. Flutamide USP was obtained from Cipla Ltd, Mumbai. CS was provided as a gift sample from India sea foods, Cochin. All other chemicals and solvents used were of analytical grade. Magnetic stirrer, scanning electron microscopy, visible spectrophotometer systronics 2201 were the equipment used in the study.

Preparation of Flutamide Nanoparticles by Ionic Gelation Technique[3-10]

Flutamide nanoparticles were prepared by ionic cross linking of CS solution with Tri poly phosphate (TPP) anions. CS was dissolved in aqueous solution of acetic acid (6%v/v) at various concentrations such as 1.0, 2.0, 3.0, 4.0, 5.0 mg/ml. Under magnetic stirring at room temperature, 5ml of 0.25% w/v TPP aqueous solution was added drop wise into 10ml CS solution containing 10mg of flutamide dissolved in tween 80. The stirring was continued for about 20 min. The resultant nanoparticles suspensions were centrifuged at 12000x g for 30 min using C24 centrifuge (Table I).

Characterization of prepared nanoparticles[11, 12]

Particle Size Analysis

The Flutamide loaded Nanoparticles were subjected to Scanning Electron Microscope (SEM) for determining its size and shape. The Nanoparticles size and shape were to be characterized and photographed (Fig: 1).

Estimation of Percentage Yield and Drug Loading Capacity of Chitosan Nanoparticles

Percentage Yield

The nanoparticles production yield was calculated by gravimetry. Fixed volumes of nanoparticles

suspensions were centrifuged (16,000×g, 30 min, 15 °C) and sediments were dried.
The process yield (P.Y.) was calculated as follows:

$$\text{P.Y. (\%)} = \frac{\text{Nanoparticles weight}}{\text{Total solids (CS + TPP +Flutamide) weight}} \times 100$$

Loading efficiency

The Nanosuspension with known amount of drug (10mg/20ml) incorporated was centrifuged at 5000 rpm for 15 minutes. The supernatant solution was separated. 5ml of supernatant was distributed with 100 ml of 2% w/v tween 80 solutions and the absorbance was measured using UV spectrophotometer at 306 nm using 2% w/v tween 80 as blank. The amount of drug unentrapped in the supernatant was calculated. The amount of drug entrapped and percentage entrapment was determined from drug unentrapped. Standard deviation was determined for 3 trials.

Loading efficiency

$$= \frac{\text{Total amount of drug - Amount of unbound drug}}{\text{Nanoparticles weight}} \times 100$$

***In vitro* Drug Release studies[13]**

The drug release studies were carried out in 2% tween 80 solutions.

Procedure for the *In vitro* Drug Release

The *invitro* drug diffusion from the formulation was studied by using egg membrane – 110 (cut off: 3500 Da) using modified apparatus. The dissolution medium used was freshly prepared 2% w/v tween 80 solution. Egg membrane – 110, previously soaked overnight in the dissolution medium was tied to one end of a specially designed glass cylinder (open at both ends). 5 ml of formulation was accurately placed into this assembly. The cylinder was attached to a stand and suspended in 50 ml of dissolution medium maintained at 37 ± 5°C so that the membrane just touched the receptor medium surface. The dissolution medium was stirred at low speed using magnetic stirrer. Aliquots, each of 5 ml were withdrawn at hourly intervals and replaced by an equal volume of receptor medium. The aliquots were suitably diluted with receptor medium and analyzed by UV-Vis Spectrophotometer at 306 nm. The quantity of drug equivalent to 10 mg of Flutamide was taken for diffusion study. The cumulative % release of all five formulations were carried out and shown in Table II & Fig: 2

RESULTS AND DISCUSSION

Nanoparticles prepared by ionic gelation technique were found to be discrete and through SEM analysis their size distribution was found to be 400nm. The drug loading capacity of nanoparticles containing drug: polymer in various ratios of 1:1, 1:2, 1:3, 1:4 and 1:5 were found to be 63.3 ±0.43, 66.3 ± 0.5868.1± 0.38, 75.2 ± 0.52, 71.0 ± 0.46. Thus there was a steady increase in the entrapment efficiency on increasing the polymer concentration in the formulation. The formulation F4 registered highest entrapment of 75.2%. Cumulative percentage drug released for F1, F2, and F3 after 12 hours were more than cumulative release of F4 and F5. The cumulative percentage drug release after 12 hours was 77.33%, 73.86%, 64.78%, 52.68% and 58.76% for F1, F2, F3, F4 and F5 respectively. It was apparent that *in vitro* release of Flutamide showed a very rapid initial burst, and then followed by a very slow drug release. An initial, fast release suggests that some drug was localized on the surface of the nanoparticles. F4 was showing sustained release compared to other formulations and it was considered as best formulation.

Based on drug content, drug entrapment efficiency, particle size morphology, zeta potential and *in vitro* release, formulation F4 was selected as an optimum formulation. Thus nanoparticles of Flutamide (F4) with core: coat ratio 1:4 was found to be spherical, discrete and free flowing and able to sustain the drug release effectively.

Table 1: Composition of Flutamide nanoparticles

S.No	Batch code	Amount of drug (mg)	Conc. of Chitosan (mg)	Drug: carrier ratio
1	F1	10	10	1:1
2	F2	10	20	1:2
3	F3	10	30	1:3
4	F4	10	40	1:4
5	F5	10	50	1:5

F1, F2, F3, F4 and F5 represent formulations 1 to 5 respectively.

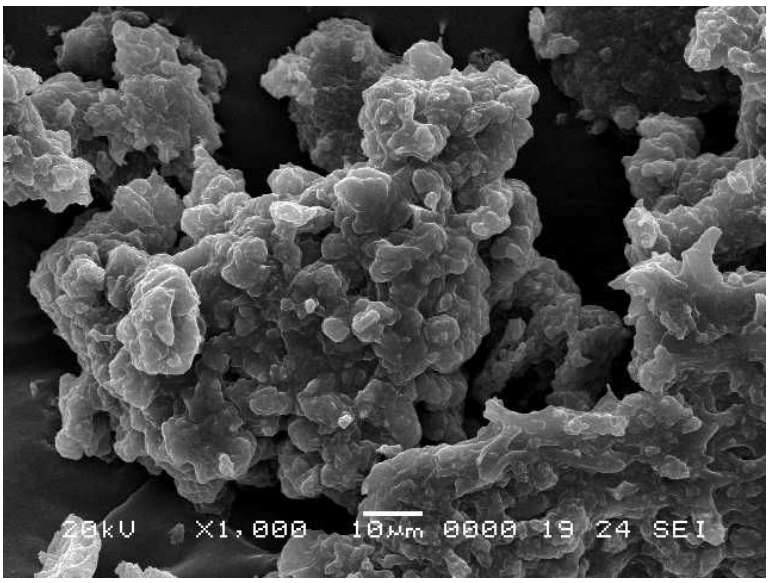

Fig. 1: SEM of formulation F4

Table II: *In vitro* release profiles of various batches of nanoparticles

Time (h)	Percent Cumulative Drug Release for Different Batches of Nanoparticles				
	F1	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
1	28.08	25.92	24.85	22.9	22.65
2	32.46	29.28	27.56	24.87	27.31
3	37.89	34.68	33.06	29.34	34.22
4	43.72	39.72	37.52	32.2	39.73
6	51.02	44.62	40.31	37.7	43.23
8	56.33	51.85	44.78	42.7	49.62
10	62.68	58.72	51.37	47.21	53.71
12	67.45	64.96	59.87	51.63	56.89

F1, F2, F3, F4 and F5 represent formulations 1 to 5 respectively.

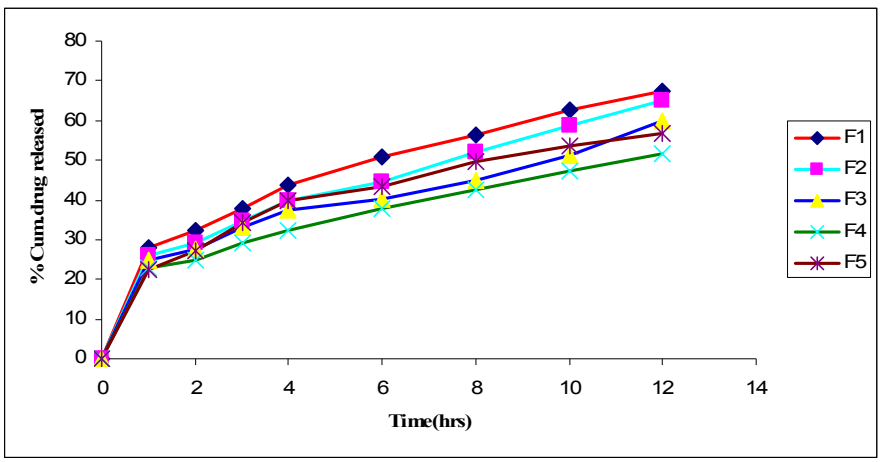

Fig. 2: Cumulative % release of Flutamide nanoparticles

REFERENCES

1. Kreuter J., Nanoparticles-based drug delivery systems, J Control Release, 1991, 16, 169-176.
2. 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, 3, 1-15. Available from URL, http://users. comcen. com.au/~journals /ojpk/full text2005/flutamide-s2005/flutamide-s2005/flutamide2005.html
3. Yan W, Wuli Y, Changchun W, Jianhua H and Shoukuan F., Chitosan nanoparticles as a novel delivery system for ammonium glycyrrhizinate, Int J Pharm, 2005, 295, 235–245.
4. Yesim A., Preparation and in vitro evaluation of chitosan nanoparticles containing a caspase inhibitor, Int J Pharm, 2005, 298, 378–383.
5. Zengshuan M., Tit Meng L. and Lee-Yong L., Pharmacological activity of peroral chitosan insulin nanoparticles in diabetic rats, Int J Pharm, 2005, 293, 271–280.
6. Lopez-Leon T., Physicochemical characterization of chitosan nanoparticles: electrokinetic and stability behavior, J Colloid Interface Sci, 2005, 283, 344–351.
7. Yan P., Bioadhesive polysaccharide in protein delivery system: chitosan nanoparticles improve the intestinal absorption of insulin *in viv,*. Int J Pharm, 2002, 249,139- 147.
8. Ana G., Begona S. and Carmen R., Microencapsulated chitosan nanoparticles for lung protein delivery, Eur J Pharm Sc, 2005, 25, 427–437.
9. Xiong Wei L., Daniel Ken Lem L, Albert Sun Chi C and Oya Alpara H. Sustained expression in mammalian cells with DNA complexed with chitosan nanoparticles, Biochimi Biophys Acta, 2003, 1630, 7 – 18.
10. Tang E.S.K., Huang M. and Lim L.Y., Ultrasonication of chitosan and chitosan nanoparticles, Int J Pharm, 2003, 265, 103–114.
11. Krishna R.S.M, Shivakumar H.G, Gowda D.V, and Banerjee S., Nanoparticles: a novelcolloidal drug delivery system, Indian J Pharm Edu Res, 2006, 40(1), 15-21.
12. Vyas S.P. and Khar R.K., Controlled drug delivery-concepts and advances, Vallabh Prakashan, New Delhi, 2002, 1st ed, p.331-81.
13. Pandey R, Ahmad Z, Sharma S and Khullar G.K., Nanoencapsulation of azole antifungals, Potential applications to improve oral drug delivery, Int J Pharm. 2005, 301, 268-276.

*****