FORMULATION AND EVALUATION OF FINASTERIDE MICROSPHERES

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ABSTRACT :

The main aim of any drug therapy is to achieve a desire concentration of the drug in blood or tissue, which is therapeutically effective and non-toxic for an extended period of time. This can be achieved by proper design of sustained release dosage regimen .Various approaches have been developed for sustained release, Microspheres are the potential candidate for oral sustained release of drug. Finasteride microspheres were prepared by ionotropic gelation technique and different evaluation parameters were assessed, with a view to obtain oral control release of Finasteride. Optimized formulation shows that more sustained release was observed with the increase in percentage of sodium alginate. The best formulation was observed as F-2, by the observation of all results of the four formulations Finasteride microspheres.

Keywords: Finasteride, ionotropic gelation technique, Ethyl cellulose, sodium alginate, FTIR studies, in vitro drug release studies.

I.INTRODUCTION

To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects[1]. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. The development of new delivery systems for the controlled release of drugs is one of the most interesting fields of research in pharmaceutical sciences.[2] Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level.[3] Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as microparticles. Microspheres for oral use have been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multi particulate delivery systems spread out more uniformly in the gastrointestinal tract.[4] The aim of this study is to development and characterization of Finasteride using Ionotropic gelation technique. Finasteride (Propecia) is used to treat male pattern hair loss in men. Finasteride (Proscar) is used to treat symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged prostate. Finasteride acts as a competitive and specific inhibitor of Type II 5α-reductase, a nuclear-bound steroid intracellular enzyme primarily located in the prostatic stromal cell that converts the androgen testosterone into the more active metabolite, 5α-dihydrotestosterone (DHT). DHT is considered to be the primary androgen playing a role in the development and enlargement of the prostate gland.[6] It serves as the hormonal mediator for the hyperplasia upon accumulation within the prostate gland. DHT displays a higher affinity towards androgen receptors in the prostate gland compared to testosterone10 and by acting on the androgen receptors, DHT modulates genes that are responsible for cell proliferation.[6]

II. MATERIALS AND METHOD

2.1 MATERIALS

Finasteride was collected as a gift sample from Hetro drugs ltd, Hyd ,polymers and other excipients were purchased from Vijaya Chemicals, Hyd

2.2 METHODODOLOGY

Compatibility studies Fourier transform infrared (FTIR) analysis [7]

The FTIR analysis of the Finasteride was carried out for qualitative compound identification. To check the compatibility of the drug with various polymers, IR spectra of drug, polymers, and combination of the drug and polymers were taken on an FTIR spectrophotometer in the wave number region of 4000-400/cm.

Formulation development

Table-: 1 Preparation of Finasteride microspheres

Ingredients	F1	F2	F3	F4
Drug	20	20	20	20
Sodium alginate	100	200	-	-
Ethyl cellulose	-	-	100	200
Methanol	5 ml	5 ml	5 ml	5 ml
Cacl $_2$	5 %	5 %	5 %	5 %

Method:

Alginate particulate system for Finasteride SR microspheres was prepared using sodium alginate and Ethyl cellulose. In order to get the complete solution stirring is continued and after that it was added drop by drop into a solution containing calcium chloride. Microspheres, which were formed, were kept in original solution for 24hr for internal jellification followed by filtration for separation. The complete release was observed at pH 6.4-7.4 but the drug release was not observed in acidic formed during this phase.[8]

Evaluation of sustained microspheres

Particle size

All the microspheres were evaluated with respect to their size and shape using optical microscope fitted with an ocular micrometer and a stage micrometer. The particle diameters of more than 100 microspheres were measured randomly by optical microscope[9]

Yield of microspheres:

Product yield The yield of the prepared formulations was calculated as the percentage of the weight of the dried product at room temperature compared to the theoretical amount. Production yield is calculated using the following equation[9]

Drug content:

The various batches of the formulations were subjected for drug content analysis. Accurately weighed microsphere samples were mechanically powdered. The powdered microspheres were dissolved in adequate quantity of pH 6.8 phosphate buffer in two-necked round bottomed flask. With the help of mechanical stirrer, it was allowed to stir for 3 hrs then filter. The ultraviolet (UV) absorbance of the filtrate was measured using a UV spectrometer at 212 nm. The drug content for the formulations was determined by calculating[10]

Drug content = Practical drug content × Entrapment efficiency/ Theoretical drug content *100

Entrapment efficiency

The various batches of the formulations were subjected for entrapment efficiency. Accurately weighed microsphere samples were added in adequate quantity of pH 7.4 phosphate buffer and were centrifuged in ultracentrifuge at 17,240 rpm at −4°C for 40 minutes. The free drug concentration was determined spectrophotometrically at 212 nm. The entrapment efficiency for all the formulations was calculated by[11]

% Drug Entrapment = Practical drug loading/ Theoretical drug loading X 100

In Vitro drug release

To carry out In Vitro drug release, accurately weighed 50 mg of loaded microspheres were dispersed in dissolution fluid in a beaker and maintained at 37±2° C under continuous stirring at 100 rpm. At selected time intervals 5 ml samples were withdrawn through a hypodermic syringe fitted with a 0.4 µm Millipore filter and replaced with the same volume of pre-warmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples were analyzed spectrophotometrically. The released drug content was determined from the standard calibration curve of given drug.[12]

Stability studies

The stability protocol was designed based on the ICH guidelines. The microspheres formulations chosen were

stored at 30 ± 2 0 C and 65 ± 5% RH for a period of 3 months and at 40 ± 20 C and 75 ± 5% RH for a period of 3 months. The stored samples were tested for their drug release and for any physical change[13]

III.RESULTS AND DISCUSSION

Drug and Excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected polymers and other excipient was evaluated using FTIR peak matching method.

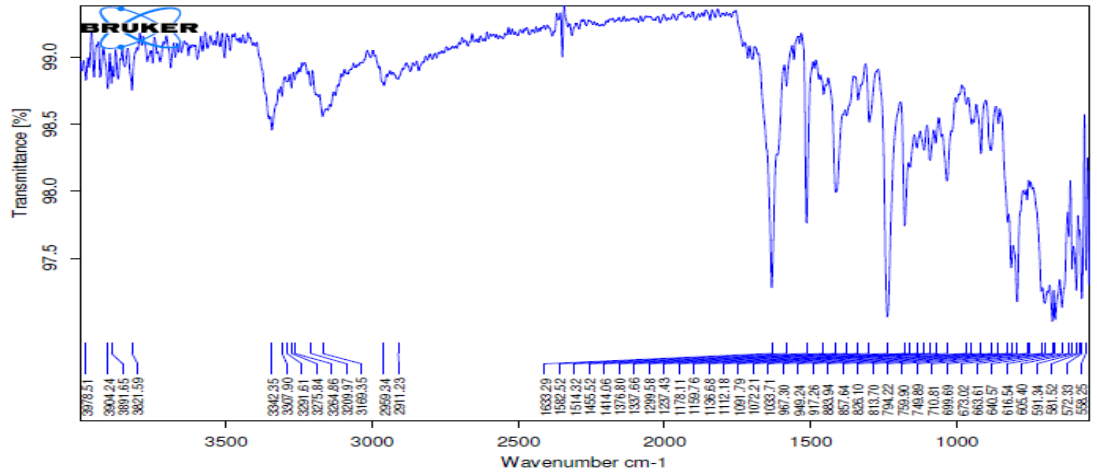

Fig-: 1 FTIR spectra data for finestaride

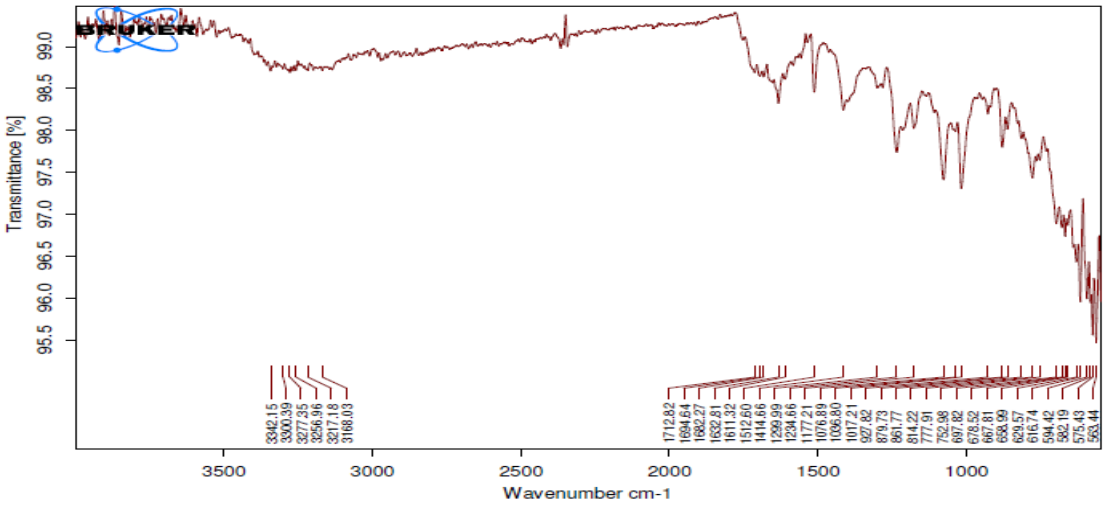

Fig-: 2 FTIR spectra data for optimized formulation

Formulation and Evaluation of Microspheres of Finasteride

Optimization of formulation variables

Therefore, the optimized conditions for the formulation of sustained release microspheres were:

Results of the evaluation parameters of formulated sustained release microspheres

The prepared sustained release microspheres were evaluated for various parameters such as yield, drug entrapment efficiency, particle size, and in vitro drug release. And effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on particle size, yield, entrapment efficiency, and *in-vitro* release of Finasteride from sustained microspheres were also studied.

Effect of formulation and process variables on Yield of sustained release microspheres, Particle size, Drug entrapment efficiency

Table-: 2 Effect of drug polymer ratio on Yield of microspheres, Particle size, Drug entrapment efficiency

Formulation code	%yield	Particle size	Drug Entrapment Efficiency
F1	83.46	267.30	86.29
F2	90.25	256.12	90.24
F3	75.26	288.39	83.69
F4	68.28	293.64	79.36

Drug release studies

Table-: 3 Drug release studies all formulations

TIME (hours)	F1	F 2	F3	F4
0	0	0	0	0
1	22.28	24.58	23.68	24.58
2	31.15	32.65	30.28	31.29
3	42.25	40.25	42.35	40.28
4	51.25	53.26	50.26	51.28
5	63.25	67.59	63.28	60.46
6	73.56	75.96	70.25	72.35
7	83.25	85.26	83.69	82.15
8	93.65	95.63	90.23	92.01

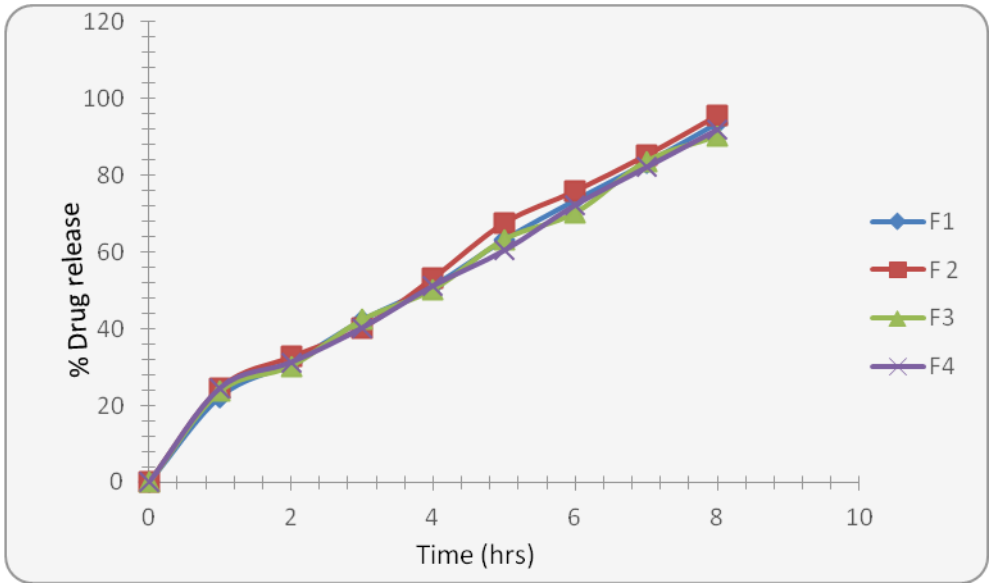

Fig-:3 In vitro drug release studies of all formulation

Characterization of microspheres

A. Surface topography by scanning electron microscopy (SEM)

Figure 4.13 A shows SEM photograph of optimized microspheres at 100× magnification, at 1000× magnification. SEM photographs showed discrete, spherical microspheres. SEM photographs also showed the presence of drug crystal on the surface of microspheres revealing that the microspheres were having some rough surface**.** The drug crystals on microspheres were may be due to the presence of un entrapped drug in dispersion medium.

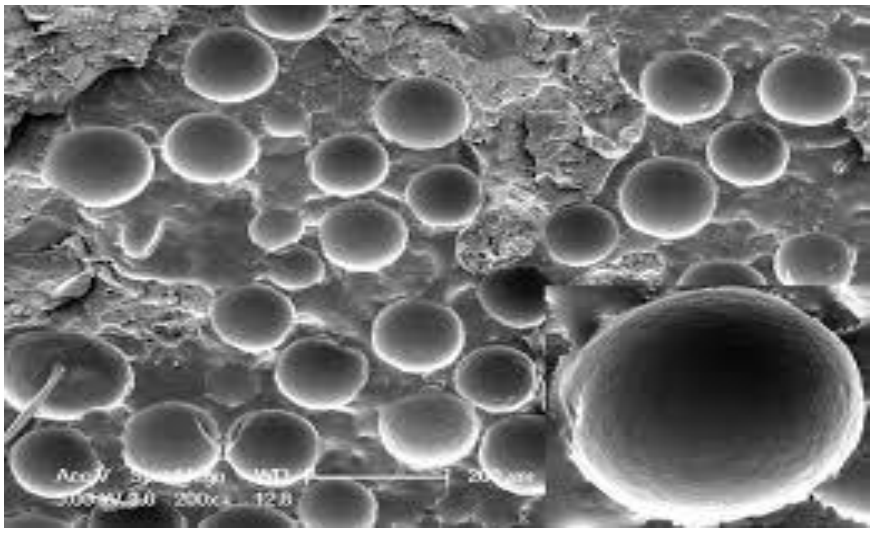

Fig-: 4 SEM analysis of Microsphere

Stability studies

There was no significant change in physical and chemical properties of the Microspheres optimized formulation after 90 days. Parameters quantified at various time intervals were shown;

Table-: 4 Results of stability studies of optimized formulation

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-2	**25^{0}C/60%RH % Release**	95.63	95.59	95.41	95.37	**Not less than 85 %**
F-2	**30^{0}C/75% RH % Release**	95.63	95.52	95.49	95.31	**Not less than 85 %**
F-2	**40^{0}C/75% RH % Release**	95.63	95.49	95.41	95.38	**Not less than 85 %**

IV. SUMMARY AND CONCLUSION

In the present study, the microspheres were formulated in such a way that it could control the drug release based on disease conditions or by using external stimuli. The Finasteride loaded gelatin microspheres were formulated for intraarticular injection, thereby localizing the drug in the arthritic knee. The microspheres were formulated by using ionotropic gelation technique. The formulated microspheres were characterized by drug loading, percentage of entrapment/encapsulation and by various analytical techniques such as optical microscopy, scanning electron microscopy, particle size analysis, FT-IR spectroscopy. All formulated 4 microspheres with different percentage of loading and magnetite content showed good entrapment (above 81%) and encapsulation efficiency (above 75%). The average particle size of magnetic microspheres meant for intravenous administration was 2.4 µm. The particle sizes of microspheres were well within the injectable range through desired routes with 20-27 gauge needle. The optical microscopy and SEM analysis revealed the spherical geometry of the microspheres. The SEM photographs showed the presence of magnetite particles on the surface of magnetic microspheres. The microspheres were compact, discrete and free flowing in nature. The FT-IR spectrum of microspheres loaded with drug showed many characteristics peaks of Finasteride and revealed the absence of drug carrier interaction. The SEM photographs of microsphere surfaces, which showed no crystalline drug particles, further supported the

amorphous nature of Finasteride present in the microspheres.

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