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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

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]. A well-designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug [3]. 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. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. The process of targeting and site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposome, bioerodible polymer, implants, monoclonal antibodies and various particulate. One such approach is using microspheres as carriers for drugs [4]. Microsphere can be used for the controlled release of drugs, vaccines, antibiotics, and hormones .For example, by taking advantage of the characteristics of microspheres, beyond the basic benefits, the microspheres could provide a larger surface area and possess an easier estimation of diffusion and mass transfer behavior [5]. 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. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm) [6]. Microspheres are sometimes referred to as microparticles. Biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin, the synthetic polymer include poly lactic acid and polyglycolic acid. The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubility and stabilities, process safety and economic considerations [7].

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. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided [8]. The aim of this study is to development and characterization of Finasteride using using Ionotropic gelation technique. Finasteride is used to is used to shrink an enlarged prostate (benign prostatic hyperplasia or BPH) [9] in adult men. It may be used alone or taken in combination with other medications to reduce symptoms of BPH and may also reduce the need for surgery. Microspheres are multiparticulate drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the drug to specific site at a predetermined rate. A well-designed controlled drug delivery system can overcome the problems of convention drug therapy and gives better therapeutic efficacy of a drug. The present study is planned with the following objectives. To prepare Finasteride Microspheres To improve patient compliance by reducing frequency of dosing. Toprepare microspheres by Ionotropic gelation technique In-vitro characterization of the developed microspheres. To determine the In-vitro drug release studies.

2. Materials and Method

2.1. Materials

Finasteride was collected as a gift sample from Aurobindo Laboratories Ltd, Hyderabad and all other excipients were purchased from Vijaya chemicals Pvt. Ltd, HYD.

2.2 Methododology

Compatibility studies Fourier transform infrared (FTIR) analysis

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 [10].

SEM Analysis

Study of surface morphology by scanning electron microscope (SEM) The prepared formulations were dispersed in deionized water and sonicated for 30 minutes. A circular metal plate is taken onto which carbon double tape (1 mm×1 mm) is stickered; a drop of the resultant dispersion is placed onto the tape and allowed to dry for a while. Then, it is scanned under SEM for morphology [11].

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 [12].

Evaluation of sustained microspheres [13, 14, 15]

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.

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:

% Yield = Actual weight of microspheres / Total weight of drug and polymer x 100.

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:

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:

% 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 [16].

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 [17].

3. Results and Discussion

FT-IR Spectrum of Finasteride

FT-IR Spectra of Finasteride and F2 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Finasteride and polymer. It also confirmed that the stability of drug during microencapsulation process.

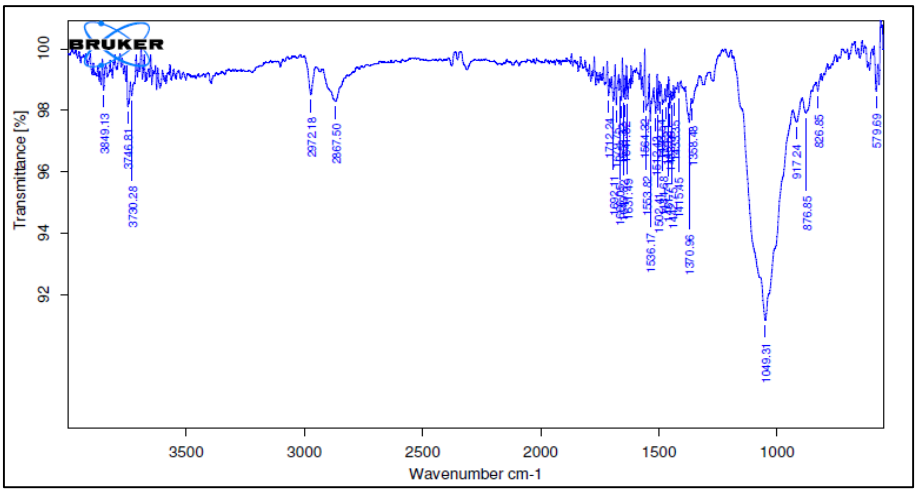

Fig 1: FTIR Studies of Finasteride

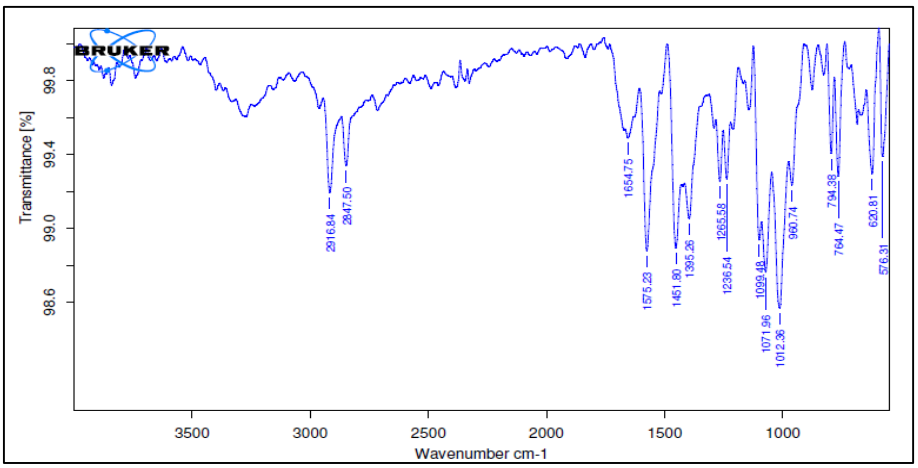

Fig 2: FTIR Studies of optimized formulation

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 microspheres were also studied.

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

Table 3: 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 4: Drug release studies all formulations in P^H 7.4 buffer

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

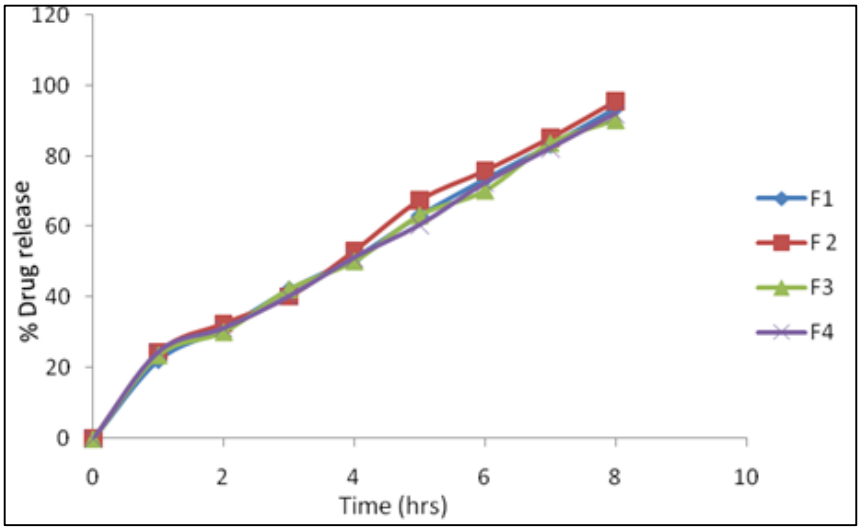

Fig 3: In vitro drug release studies of all formulation

Here, keeping drug ratio constant and varied polymer ratio as the polymer concentration increases viscosity; this influences the interaction between disperse phase and dispersion medium that affects the size distribution of particle. And F2 formulation shows good results when compared to other formulations.

Conclusion

Above graph indicates that %Drug release of F2 formulation shows better drug release when compared with other formulations

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.

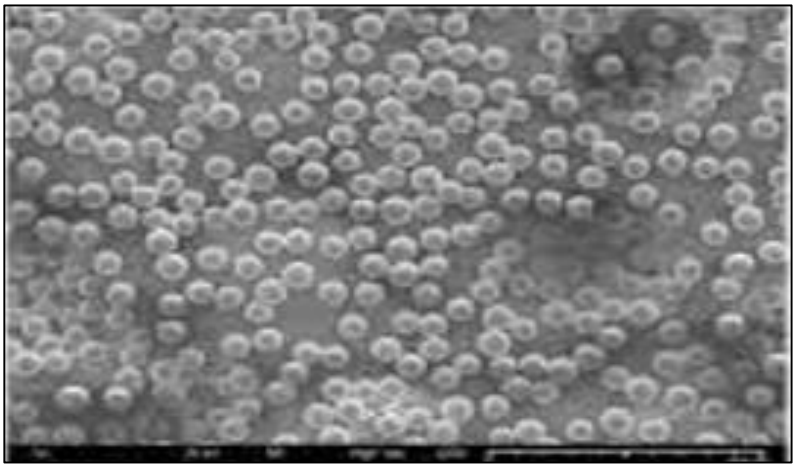

Fig 5: SEM photograph of Finasteride microspheres at 100x and 1000x magnification

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 5: Results of stability studies of optimized formulation

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

4. Conclusion

The present study was to prevent extensive metabolism of the drug and consequently to increase the bioavailability of the drug improve patient compliance, decreases toxicity, and increase efficacy in the form of controlled release microspheres. Microsphere drug delivery systems have used to Attempt has been made to prepare controlled release microspheres of Finasteride, It is used to is used to shrink an enlarged prostate (benign prostatic hyperplasia or BPH) in adult men. The microspheres were prepared by Ionotropic gelation technique method using natural polymers as retarding polymers and evaluated for parameters like percentage yield, particle size, entrapment efficiency and the effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on evaluated parameters. Microsphere's morphology was evaluated by SEM. The yield and entrapment efficiency were high for Sodium alginate polymers microspheres were Particle size, entrapment efficiency and production yield were influenced by the type of polymer, polymer concentration, stirring speed and combination of polymers. *In vitro* dissolution of optimized formulations of various Polymer in pH 7.4 formulations are releasing the drug up to 8 hrs.

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