Original Research Article

Formulation and evaluation of finasteride sustained-release matrix tablets using different rate-controlling polymers

ABSTRACT

The aim of the present investigation was to developoral controlled release matrix tablet formulations of Finasteride with different polymer ratios. Finasteride is chemically considered a synthetic 4-azasteroid drug. The granules were evaluated for angle of repose, bulk density and Compressibility index before being punched as tablets. The tablets were subjected to weight variation test, drug content, hardness, friability, and in vitro release studies. Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopoeias and/or standard references. Different models for kinetic study were applied like zero order, first order, Higuchi, HixsonCrowell and Korsmeyer to study the release pattern and mechanism.

Key words: Sustained release, matrix tablets,wet granulation

INTRODUCTION

Sustained release systems drug delivery system achieves slow release of drug over an extended period of time. It provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintainthe therapeutic response for a specific extended period of time[1]. Sustained release of drugs in gastrointestinal tract followed by oral administration is not affected by the absorption process and, it provides blood levels that are devoid of the peak and valley effect which are characteristics of the conventional intermittent dosage regimen[2].

Matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. In matrix system of sustained release drug is dispersed homogenously throughout a polymeric matrix[3]. It includes coating and pelletization during manufacturing and rate of drug release from the dosage form is controlled mainly by the typeand proportion of polymer used in the preparations.

Advantages of matrix tablets are[4, 5, 6, 7]:

1. Easy to fabricate in different shape and size. High level of reproducibility
2. Suitable for both non degradable and degradable system.
3. No dose dumping.
4. Effective, stable and economical.
5. Suitable for drugs having high molecular weight.

Finasteride is chemically considered a synthetic 4-azasteroid drug[8]. It is an enzyme inhibiting agent. It is used in the treatment of anti-hyperplasia and also used as anti-baldness agent.

The mechanism of action of Finasteride is based on its preferential inhibition of Type II 5a-reductase by formation of a stable complex with the enzyme. This enzyme converts testosterone to dihydrotestosterone (DHT), which is a more potent androgenic hormone. Inhibition of Type II 5a-reductase blocks the peripheral conversion of testosterone to DHT[9]. Significant decrease in serum and tissue DHT concentrations, increase in serum testosterone concentrations, and substantial increases in prostatic testosterone concentrations. Thedrug is an effective therapeutic

agent in the treatment of benign prostatic hyperplasia. Inhibition of the enzyme 5 alpha-reductase is believed to be the mechanism of action of this drug[10]. An increase in the level of DHT in the prostate results in prostate hyperplasia and urinary tract obstruction. The drug is practically insoluble in water, with a mean bioavailability of 63%[11].

In present study matrix type tablets of Finasteride were prepared to improve the bioavailability of it.

MATERIAL AND METHOD:

Finasteride was a gift sample from Fidson healthcare. Eudragit RS-100 was obtained from Neimeth, and HPMC from Zolon healthcare. All other chemicals used were of analytical grade.

Preparation of tablets

The granules prepared by wet granulation of drug, filler and hydrophilic polymers were compressed into flat faced tablets using by using KBr press. The diameter of the die was 12mm and the batch size prepared for each formulation was of 20 tablets.

Table 1: Composition of matrix type tablets of Finasteride

Ingredients (mg)	Formulation Code				
	MT1	MT2	MT3	MT4	MT5
Finasteride	80	80	80	80	80
HPMC	100	100	100	100	100
EC	-	100	100	-	-
Eudragit RS 100	-	-	100	100	100
Ethanol	qs	qs	qs	qs	qs
Magnesium stearate	4	4	4	4	4
Dicalcium phosphate	90	90	90	90	90
Talc	5	5	5	5	5

Evaluation of Granules

1. Angle of repose[12]

The angle of repose of prepared granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The granuleswere allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$\tan \theta = h/r$

Where, h and r are the height and radius of the powder cone.

2. Bulk and tapped density[13]

A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its ownweight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

Bulk density= (Mass of the powder)/(Volume of the bulk powder)

Tapped density= (Mass of the powder)/(Tapped volume of the powder)

3. Carr's compressibility index[14]

The Carr's compressibility Index was calculated from Bulk density and tapped density of the granules. A quantity of 2g of granules from each formulation, filled into a 10 ml of measuring cylinder. Initial bulk volume was measured, and cylinder wasallowed to tap from the height of

2.5 cm. The tapped frequency was 25± 2 per min to measure the tapped volume of the granules. The bulk density and tapped density were calculated by using the bulk volume and tapped volume.

Carr's index (%)=(Tapped density-Bulk density)/(Tapped density) X100

4. Hausner's ratio[15]

Hausner ratio (Hr) is an indirect index of ease of powder flow. It is calculated by the following formula:

Hausner^' s ratio= (Tapped density)/(TaBulk density)

5. Drug content[16]

An accurately weighed amount of powdered Finasteride granules (100 mg) was extracted with water and the solution was filtered through 0.45µ membrane.The absorbance was measured at 254 nm after suitable dilution.

Table 2: Evaluation parameters of granules

Formulation code	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose (θ)
MT1	0.304	0.358	12.5		39° 6'
MT2	0.392	0.384	13.41		38° 4'
MT3	0.341	0.427	14.52		37° 9'
MT4	0.322	0.403	15.6		37° 6'
MT5	0.298	0.358	16.5		35° 2'

Evaluation of tablets

1. Thickness and diameter[17]

Thickness and diameter of tablets was determined using Vernier caliper. Five tablets from each batch were used, and average values were calculated.

2. Weight variation test[18]

Twenty tablets were selected randomly from each batch were weighed individually and together using an electronic balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

% Deviation=(Average weight-Individual weight)/(Individual weight) X 100

3. Drug content[19]

Five tablets were weighed individually and triturated. Powder equivalent to the average weight of the tablet was weighed and drug was extracted in water for 6 hours. The solution was filtered through 0.45µ membrane. The absorbance was measured at 254 nm after suitable dilution.

4. Hardness[20]

For each formulation, the hardness of 6 tablets were determined using the Monsanto hardness tester. The tablet was held along its oblong axis in betweenthe two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2. Generally, a minimum of 4 kg/cm^2 hardness is considered acceptable for uncoated tablets.

5. Friability[21]

For each formulation, the friability of 6 tablets was determined using the Roche friabilator. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre weighed 6 tablets was placed in Rochefriabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight in generally considered acceptable**.**

% Friability=(Initial weight-Final weight)/(Final weight) X100

6. In vitro release studies[22]

In vitro drug release study for the prepared matrix tablets were conducted for period of 8 hours using a six station USP XXVI type II (paddle) apparatus at 37 ± 0.5^0C and 50 rpm speed. The dissolution studies were carried out in triplicate for 10 hours in phosphate buffer of pH 6.8 under sink condition. At first half an hour and then every 1- hour interval samples of 5 ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutionwas analyzed at 254 nm for Finasteride by a UV- spectrophotometer. The amounts of drug present in the samples were calculated with the help of appropriate calibration curve constructed from reference standard.

Table 3- Evaluation parameters of Finasteride tablets

Formulation code	Hardness	Thickness	% Friability	% Weight variation	% Drug content
MT1	4.4± 0.21	2.25± 0.04	0.73± 0.05	2.63± 0.05	96.32± 0.08
MT2	4.5± 0.14	2.37± 0.11	0.71± 0.08	2.84± 0.06	97.53± 0.15
MT3	4.1± 0.09	2.18± 0.06	0.78± 0.09	3.22± 0.11	98.43± 0.16
MT4	4.6± 0.15	2.43± 0.15	0.70± 0.04	3.12± 0.09	99.11± 0.05
MT5	4.8± 0.22	2.32± 0.07	0.81± 0.03	2.93± 0.08	99.65± 0.06

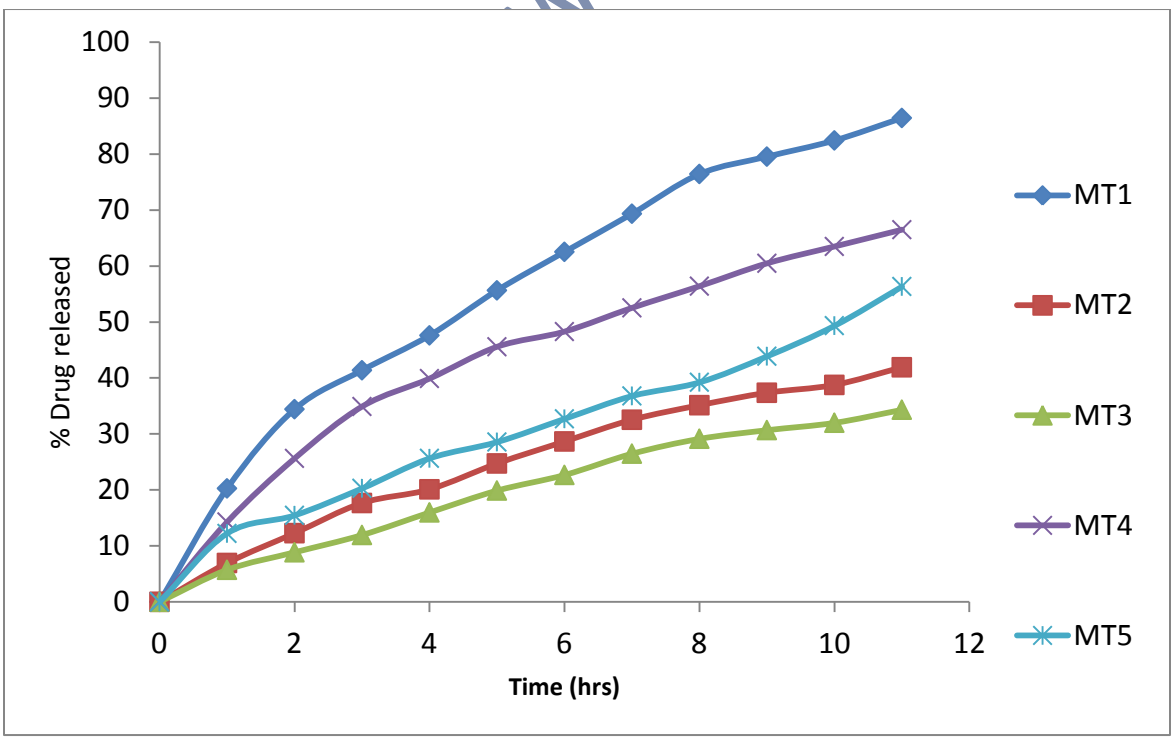

Fig-1: *In-vitro* drug release profile of Finasteride tablets.

Table 4- Dissolution profile of Finasteride tablets.

Formulation code	Zero order	First order	Higuchi	Korsemeyer-peppas	Hixon crowell
MT1	0.8350	0.9215	0.9562	0.9892 n=0.3942	0.9452
MT2	0.9108	0.9558	0.9845	0.9926 n= 0.5214	0.9832
MT3	0.9217	0.9315	0.9915	0.9946 n=0.6011	0.9915
MT4	0.8864	0.9011	0.9965	0.9921 n=0.5246	0.9924
MT5	0.8075	0.9295	0.9872	0.988847 n=0.5642	0.9835

RESULTS AND DISCUSSION

The current investigation deals with the optimization of sustained release matrix tablets of Finasteride using different polymers. Polymers used were HPMC, Ethyl cellulose and Eudragit RS100.

All the formulations showed uniform thickness. In a weightvariation test, the pharmacopoeial limit for percentage deviation for the tablets of more than 250 mg is ± 5%.The average percentage deviation of all the tablet formulations was found to be within the above limit, and hence all the formulations passed the test for uniformity of weight as per the official requirements.

Satisfactory uniformity in drug content was found among different batches of tablets, and percentage of drug content was more than 96 %. The formulation MT5 showed a comparatively high hardness value of 4.8±0.22 kg/cm^2.

This could be due to the presence of more ethylcellulose which is generally responsible for more hardness of the tablet.

In the present study the percentage friability for all theformulations was below 1% indicating that the friability is within the prescribed limits.

All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness and friability.

The release of drug mainly depend upon the polymer concentration. Matrix tablets of batch MT1 shows maximum release 86.42% in 10 hrs. The quick release was observed in tablets containing ethylcellulose, it may be due to high solubility of EC at pH 6.8. This polymer characteristic gives to the matrix a quick gel erosion rate and a high erosion degree of the overall system.

The in vitro release data was applied to various kinetic models to predict the drug release kinetic mechanism. Nanoparticles were fitted with various kinetic equations like zero order, first order and Higuchi'smodel, Korsemeyer-peppas and Hixon crowell.

CONCLUSION

The ultimate aim of the present study was to prepare sustainedrelease matrix tablet of Finasteride using hydrophilic polymers like HPMC, EC and Eudragit by wet granulation technique. The present research work was successful in improving the efficacy of Finasteride oral therapy as the

drug release was extended for ten hours thus reducing dosing frequency thereby improving patient compliance.

The hydrophilic matrix tablet prepared were containing a blend of gel forming polymers. Based on different evaluation parameters formulation of batch MT1 is concluded as an optimum formulation.

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