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DESIGN AND CHARACTERIZATION OF DUTASTERIDE NANOPARTCILES

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ABSTRACT

It has recently become possible to treat alopecia with the 5-reductase inhibitor Dutasteride, a 4-aza-3-oxosteroid that was initially used to treat benign prostatic hyperplasia. The goal of the research was to develop a novel dosage form, gel-loaded nanoparticles using PLGA, which uses slight modification of the nanoprecipitation method, in order to increase drug bioavailability and improve drug penetration at the target location.

Preformulation studies, which concentrate on the physicochemical characteristics of the drugs and excipients that could influence drug performance and the development of an effective dosage form, are the main stage of a product's development.

Drug excipient investigations, and solid state characterization, including solubility, pH, partition coefficient, and flow properties of the drug, were evaluated duringpreformulation studies. Particle size, entrapment efficiency, and in vitro drug release profile were all evaluated for the formulations.

The findings demonstrated the compatibility of all the chosen excipients, which were used in the prepared nanoformulation, which produced the highest degree of entrapment efficiency and the smallest possible particle size of 245.4nm, 90.45 % EE and drug release of
% 85.87. This nanoformulation may offer a potential means of administering drugs to treat alopecia at the hair follicle.

KEYWORDS: *alopecia, nanoparticles, pre-formulation, Dutasteride*

I: INTRODUCTION

The 5 alpha-reductase inhibitor Dutasteride prevents testosterone from being converted to dihydrotestosterone (DHT). The endogenous androgen testosterone, which regulates libido,is made in the adrenal glands[1, 2].Body hair is produced by the conversion of testosterone to DHT by the enzyme 5 alpha reductase in the skin, liver, and prostate. Type I and type II ofthe 5 alpha reductase enzymes are present in human tissues[3, 4].The hair follicle's outer sheath contains type I, and the prostate and seminal vesicles contain type II enzymes[5,6].

The 5-reductase inhibitor Dutasteride is a 4-aza-3-oxosteroid molecule. It was first made available for the treatment of benign prostatic hyperplasia (5 mg/day), and it was also given orally once a day in a dose of 1 mg for androgenic alopecia[7]. Following oral administration of 1 mg, the bioavailability varies from 26% to 70%, with a mean of 65%[8].

Other treatments for alopecia, such as topical viprostol, and anti-androgens like oestrogen, and cioteronel, have had varying degrees of success. The first drug chosen to treatAGA is dutasteride, a more strong medication that works by blocking 5 alpha type II enzymes. Alopecia is a prevalent cause of hair loss, affecting 5 percent of guys under the age of 20 and >50 percent of men over the age of 40. And in women over 30 years old, roughly30 percent is shown[9, 10].

The biopharmaceutical classification system (BCS) class II drug Dutasteride is a lipophilic molecule with limited permeability and high solubility. Adverse effects from oral medication administration include sexual dysfunction, mental impairment, gynecomastia, lowering of temperature, weight gain, etc. Because the stratum corneum (SC), a lipid barrier that makes up the skin, is poorly permeable to DS, these innate characteristics prevent DS from permeating the skin[11,12].

A nanoparticle is a particle of materials with a dimension between one and one hundred nanometers (nm). In large part because of

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their tiny size and enormous surface area, nanoparticles frequently display unusual size-dependent characteristics[13, 14].
Compared to other drug delivery techniques generally, nanoparticles have a numberof advantages[15,16]. They are utilized to (i) make highly hydrophobic pharmaceuticals more soluble (by chemical or physical techniques); (ii) enable continuous and regulated release of encapsulated drugs; and (iii) boost the stability of therapeutic substances. (iii) Used an enhanced permeation and retention (EPR) effect to deliver greater drug concentrations to the targeted locations[17].

Before developing a pharmaceutical formulation, research was doneon each drug's inherent chemical and physical qualities. This characteristic offers a framework for combining drugs with pharmaceutical components to create dosage forms[18].

The goal of the pre-formulation study is to create a dosage form that is elegant, stable,safe, and effective by determining the interaction with other ingredients, and physicochemical parameters of new therapeutic compounds[19]. Drug solubility, partition coefficient, dissolving rate, and stability are among these characteristics and play a significant role in pre-formulation investigation[20].

The current work aims to increase drug permeability by creating a novel carrier system, i.e.nanoparticles dispersed in mucoadhesive gel via topical application[21], which results in a decrease in adverse effects and an increase in drug pharmacokinetic parameters like drug absorption, bioavailability, and drug retention for a longer period of time[22].

II: MATERIALS AND METHODS

Dutasteridewas procuredfrom Sun Pharma Pvt. Ltd., Hyderabad, India. Dimethylsulfoxide, methanol, ethanol, chloroform, n-octanol obtained from S.D. Fine Chemicals Ltd., India. PLGA was procured from Nomisma Healthcare. Carbopol 940 was procured from S.D. fine chemicals.Polaxomer 407 was purchased from Sigma Aldrich (Mangalore, India).

III: EXPERIMENTAL STUDIES A: SOLUBILITY DETERMINATION

Drug solubility was evaluated by dissolving extra amounts of the drug in the chosen solvents. The absorbance was calculated using UV-visible spectrophotometry at 215 nm after the supersaturated drug was added to 2 ml of solvent, the sample was vortexed for 5–10 min, and 100µL of supernatant was collected and properly diluted with methanol[23, 24]. To calculate solubility, three measurements in each solution were made.

B: pH

A digital pH meter was used to determine the drug sample's pH. The pH of the sampledrug dispersion at 1% by weight was determined[25]. Data was in triplets.

C: True density

The true density of DS was determined using the liquid displacement method. It is calculated using the amount of incursion fluid (toluene) that a specific quantity of powder displaces in the pycnometer[26].

$$D = \frac{M}{Vp - Vi}$$

Vp = total volume of the pycnometer, Vi is the volume of intrusion fluid in the pycnometerM= mass of the powder

D: Determination of bulk density and compressibility index

The three tap method was used to determine the bulk density of DS. The graduated cylinder holding 100 ml of DS powder was slowly filled with 5g of the powder. For two minutes, the cylinder was dropped from a height of one inch onto a wooden surface [27]. By dividing the sample's weight by its volume inside the cylinder, the bulk density was calculated. The bulkiness was caused by the reciprocal of bulk density or the particular bulk volume.The formula below was used to calculate the percent compressibility index

$$\text{Compressibility Index} = \frac{Vo - VF}{Vo}$$

Vo = Unsettled apparent VolumeVF = Final Tapped Volume

E: Angle of repose

The highest angle of descent or dip in relation to the horizontal plane at which granular material can be poured without collapsing is known as the angle of repose or critical angle of repose. The measurement procedure employed a fixed funnel method[28].Graph paper was laid on a flat, horizontal surface and a funnel was secured with its tip 2 cm above the paper. Until the peak of the cone that was thus produced just touched the funnel tip, the powders were gently poured down the funnel. The following equation was used to compute the tangent of the angle of repose andthe average diameters (D) of the powder cone bases:

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$$\theta = \tan - 1\frac{h}{r}$$

Where h = height of pileD = Diameter of pile
The data presented here is obtained from triplicate determinations.

F: Determination of Partition Coefficient:
In a separating funnel, 10 mg of the drug was added to a solvent made up of 50 mL of n-octanol and a 7.4 pH phosphate buffer. Using a mechanical shaker, the mixture was shaken for 24 hours. As a result, two phases are separated[29]. Three millilitres of each phase were thencollected, and the absorbance was determined using a UV-visible spectrophotometer.

$$\text{Log P} = \frac{Concentration\ of\ drug\ in\ n-octanol}{concentration\ of\ drug\ in\ pH\ 7.4\ buffer}$$

G: Percentage of moisture loss
The nanoparticles moisture loss percentage was assessed. The initial weight of the produced nanoparticles was measured, and they were stored for 24 hours at 37 °C in calcium chloride-based desiccators. The following equation was used to determine the percentage lossof moisture by dividing the final weight of the sample by its initial weight[30].

$$\%\ \text{moisture Content} = \frac{Initial\ \text{weight} - final\ \text{weight}}{Initial\ \text{weight}}\ \text{X}\,100$$

IV: SOLID STATE CHARACTERIZATION

A: Infrared spectroscopy
FTIR spectroscopy (ATR-FTIR; Bruker Alpha; Germany) was used to do study of the interactions between drugs and polymers. The spectrum deviation of the formulations was contrasted with that of the pure drug sample, including PLGA, Polaxomer 407, DS-NPs, and Carbopol 94031. The frequency range used in the study was 4000 to 400 cm-1

B: Differential Scanning Calorimetry
Differential scanning calorimetry (DSC) was used to study the thermal characteristics of drug, PLGA, polaxomer 407, and DSnanoparticles (Netzsch, Selb, Germany). A 5 mg sample was placed in an aluminium pan and sealed with a perforated lid32. Dry nitrogen carrier gas was used to heat the sample at a rate of 10 oC/min from 30 to 250 oC and 30 K/min.

V: PREPARATION OF NANOPARTICLES LOADED GEL

The nanoprecipitation process with modest modifications was used to develop DS nanoparticles33. The needed amount of drug and polymer are dissolved in acetone in the aqueous phase, and polaxomer 407 is used in water for the organic phase. The drug and polymer mixture is gradually put into the aqueous phase while being stirred with a homogenizer at 3000 rpm for 10 min34.
A magnetic stirrer was used to heat the resulting dispersion until the solvent had evaporated. The filtrate was centrifuged two times in a cooling centrifuge (made by Remi Equipment, India) for 15 minutes at 10,000 rpm. In a 1 percent Carbopol 940 solution, nanoparticles were further mixed with contact stirring at 300 rpm for one hour using a magnetic stirrer. Two percentage of benzylkonium, which serves as preservatives, was added to the gel after it had been freed from air bubbles for 24 hrs, and the pH was adjusted with triethanolamine35,36.

VI: CHARACTERIZATION OF NANOPARTICLES

A: Particle size distribution
The diameter of nanoparticles and their particle size distribution were measured by laser diffractometry with the mastersizer 2000 (Malvern Instruments, Malvern, UK). In order to produce the sample, 10 mg of nanoparticles were added to a nonidet P40 solution that contained 0.1% distilled water. The nanoparticle suspension was added to the compact recirculation device and circulated at a speed of 3500 rpm. Values are presented as mean standard deviation37.

B: Entrapment Efficiency
5 mg of DS-equivalent nanoparticles were dissolved in 2 ml of ethanol. A UV-visible spectrophotometer set to 285 nm was used to measure the sample's absorbance after centrifuging the aliquot at 5000 rpm for 10 minutes.

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$$EE = \text{total drug} - \frac{\text{unentraped drug}}{total\ drug} \ x\ 100$$

C: Percentage of drug release

5mg equivalent drug was placed in a dialysis bag consisting of 10 ml 6.8 pH phosphate buffer maintained at constant temperature of 37 0C and 50 rpm. At predetermined time intervals sample was withdrawn by marinating sink condition. The collected sample was filtered, diluted and absorbance was determined using UV-visible spectrophotometer38.

VII: RESULTS AND DISCUSSION

The results of solubility, true density, bulk density, compressibility index, Angle of repose, moisture content, pH, partition coefficient, and melting point determination are given in Table 1.

Table1: Physicochemical Properties of Drug

SI. No	Parameters	Results
1	Description	Off–white crystalline powder, odorless powder
2	Solubility	Freely soluble in chloroform, ethanol, DMSO, slightly soluble in water
3	pH	7.2+0.34
4	True density	1.21 + 0.15
5	Bulk density (g/cc)	0.305 + 0.18
6	Compressibility Index (%)	13.41
7	Angle of repose (^{0})	37 + 0.61
8	Moisture content	7.31 + 0.55
9	LogP	3.01
10	Melting point	253 °C
11	pKa	4.85
12	Biological half-life	5hrs

A: Particle size distribution

The size distribution of drugs has influence on bulk properties such as bulk density,true density, cars index, flow properties, etc. The size distribution is given in table 2.

Table:2 Particle size distribution of drug

S .No	Size range (µm)	No. of particles
1	0-30	40
2	30-60	100
3	60-90	150
4	90-120	250
5	>120	45

Table: 3 Physical Characteristics of Individual Components

S.No	Name of the sample	Initial colour	Final colour
1	DS	Off –white powder	No changes
2	PLGA	White crystalline powder	
3	DS-PLGA	White powder	
4	Polaxomer 407	Fine white powder	
5	Carbopol 940	Fine white powder	

Table: 4 Chemical characteristics of drug-excipients

S.No	Name of the sample	Percentage purity at initial time	Final time
1	DS	99.87	99.60
2	PLGA	99.47	99.15
3	Polaxomer 407	99.77	99.65

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B: Drug excipient compatibility studies by FTIR

The results of ftir studies of the drug and mixture of drug and mixtures showed no deviation in the position of functional groups, which confirm that there are no compabailtiy problem with the selected chemicals. The results are shown in fig 1,2,3.

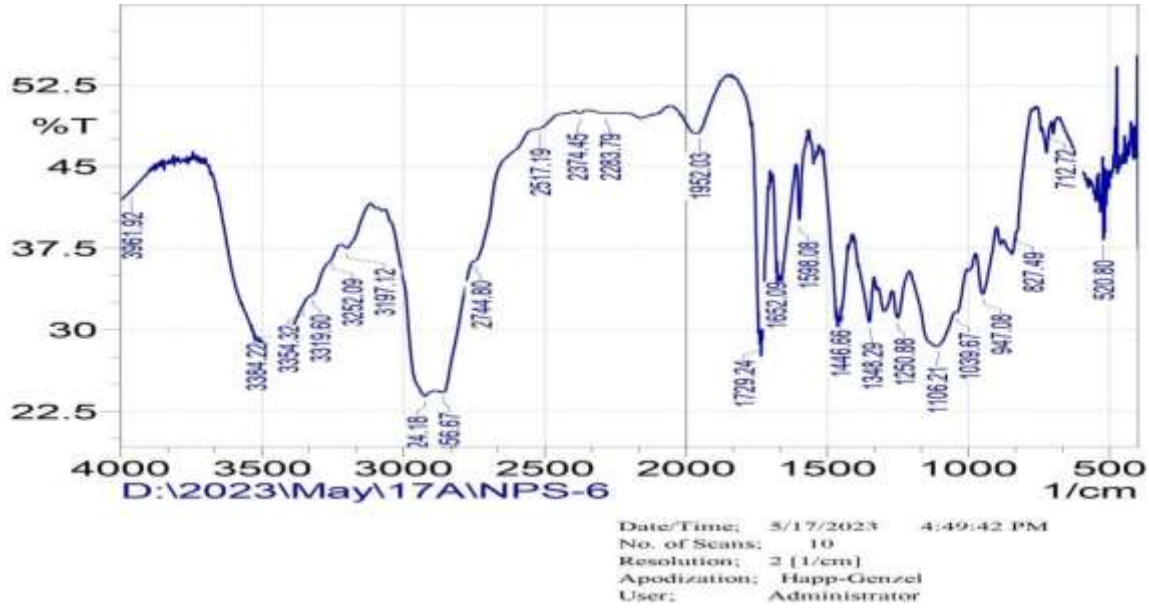

Fig: 1 FTIR spectrum of poloxamer 407

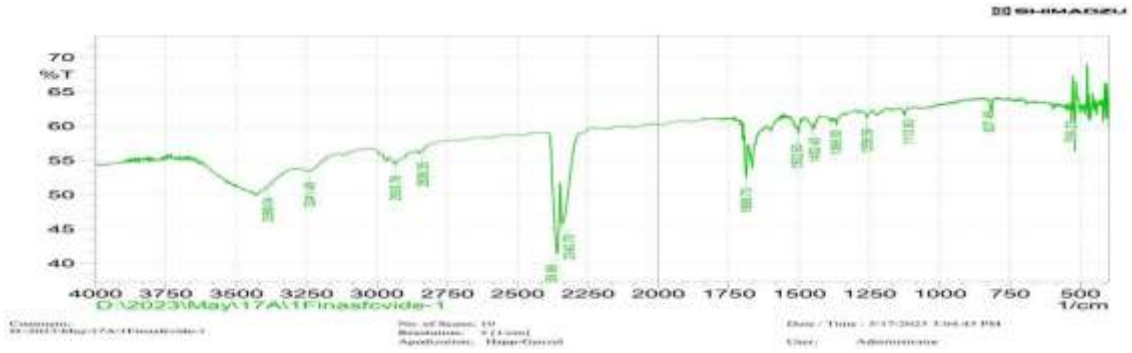

Fig: 2 FTIR spectrum of Dutasteride

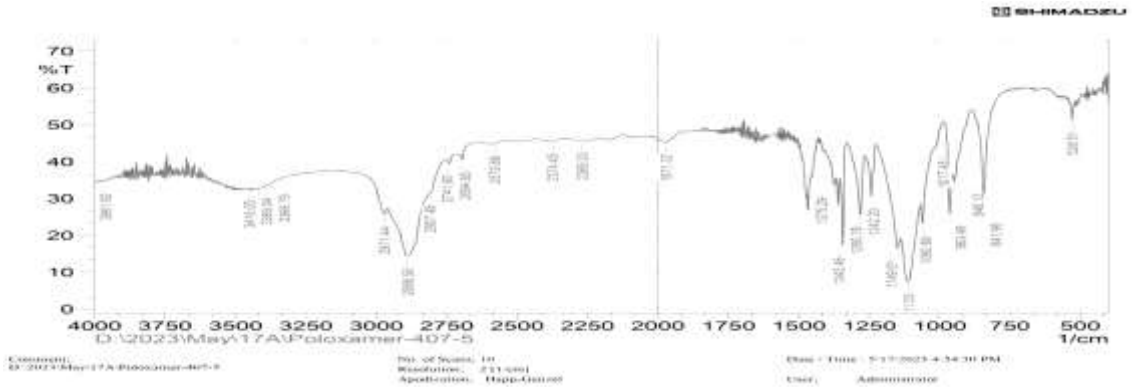

Fig: 3 FTIR of the nano formulation

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C: Differential scanning calorimetry (DSC)

DS displayed a strong FIN displayed a strong endothermic peak at 258.64°Cdemonstrating its distinctive crystalline form. The peak of the drug in nanoparticles is disappreated because the drug molecule was completely dissolved in the polymer matrixshown in fig 4.

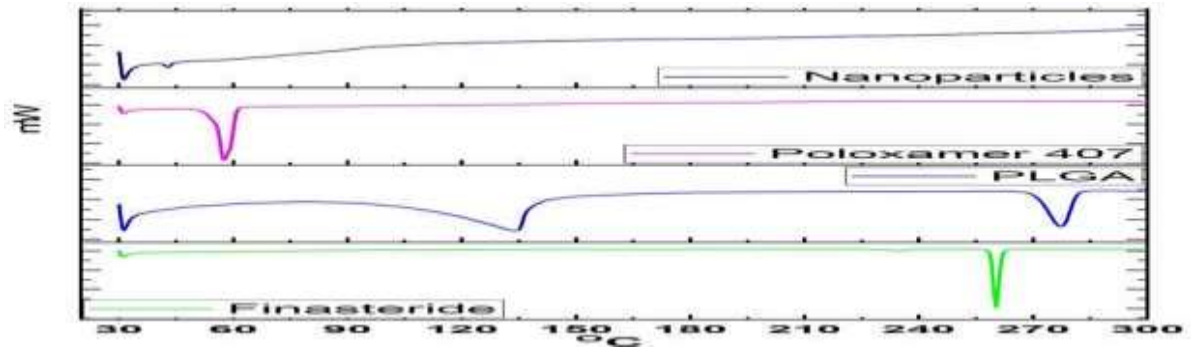

Fig: 4 DSC thermograph of drug, polaxmoer 407 and nanoformulation

D. Evaluation of nanoparticles

The prepared nanoparticles were evaluated for the following parameters. Particle size,entrapment efficiency, percentage drug release and percantage yield.

Table: 5Evaluation of PLGA- DS nanoparticles

Formulation	(PS) nm	%(EE)	% (drug release)	%(Practical yield)s
DS-PLGA NP	245.4	90.45	85.87	90.45

CONCLUSION

Preformulation studies strengthen the scientific basis in the drug development and evaluation process, enhance product quality, raise public safety standards, and make it easier to use new technologies. The results of this study's data collection could help this specific drug delivery system's future development. In this work, we finished characterizing drug physicochemical properties, including determining its particle size, solubility, flow property, solid state characterization, drug excipient interaction studies ,and drug release.This information can be helpful in developing targeted drug delivery formulations, particularly for Dutasteride nanoparticle formulation. PLGA is used act as an ideal carrier for predation of nanoparticles and poloxamer 407 which acts as a surfactant shows an effect the dependent variables like particle size, drug release, and entrapment efficiency. The results showed that this data can be used further for optimization.

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