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Process Factors Affecting the Preparation and Characterization of Dutasteride Nanosuspension

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Abstract

Dutasteride, a synthetic compound belonging to the 4-azasteroid class, functions as a selective and competitive inhibitor of both type 1 and type 2 5-alpha-reductase enzymes. It has been approved for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men. Dutasteride has low solubility and high permeability, which classifies it as BCS class II, according to the Biopharmaceutics Classification System, resulting in its exclusive availability in the market as a formulation contained within soft gelatin capsules, and the oral bioavailability of this dosage form is approximately 60%. This study's main objective was to create and characterize dutasteride nanosuspension that would enhance their solubility and release rate. The approach utilized in the study consisted of generating a nanosuspension through the solvent/antisolvent precipitation method using different stabilizers at different concentrations (0.3% w/v, 0.4% w/v, and 0.5% w/v). The research investigated how various process factors affected the particle size and the polydispersity index (PDI) of selected dutasteride nanosuspension formulas. The assessment parameters included particle size, polydispersity index, entrapment efficiency (EE), and in-vitro dissolution patterns. These parameters collectively aided in determining the optimized dutasteride nanosuspension formula. The resulting optimized formula, consisting of 0.5% w/v soluplus as a stabilizer and a solvent/antisolvent (methanol/deionized water) volume ratio of 1:10, yielded a particle size of 73.24 nm, and a polydispersity index of 0.184. The dissolution studies revealed that the optimized formulation enhanced the dissolution rate of dutasteride significantly compared to a pure drug, it displayed complete release of the drug within 15 min. The most favorable formulation underwent compatibility testing using Fourier Transform Infrared Spectroscopy (FTIR), an investigation of surface morphology with a Field Emission Scanning Electron Microscope (FESEM), and an examination of its crystalline structure via X-ray powder Diffraction (XRPD) analysis. The results indicate that using the solvent-antisolvent method proves effective in creating a dutasteride nanosuspension with small particle size and low polydispersity index (PDI), along with high drug content, robust drug entrapment, and enhanced dissolution rate for dutasteride.

Keywords: Dutasteride, FESEM, Nanosuspension, Stabilizers, Soluplus®, Solvent/antisolvent precipitation.

Introduction

Dihydrotestosterone (DHT), a powerful androgen, is synthesized from testosterone through the action of the intracellular enzyme 5 α-reductase [(1)]. Its essential role includes the development of male external genitalia, urethra, and prostate, and the facilitation of male sexual maturation during puberty [(2)]. DHT plays a pathological role in prostatic disorders, notably benign prostatic hyperplasia (BPH) [(3)]. Benign prostatic hyperplasia (BPH) refers to the noncancerous enlargement of the prostate gland caused by the excessive growth of stromal and glandular elements within the prostate, due to elevation levels of the androgen dihydrotestosterone (DHT) [(4)]. It causes a set of symptoms called lower urinary tract symptoms (LUTS). LUTS encompass urinary frequency, urgency, urinary hesitancy, nocturia, weak urine flow, and urinary retention [(5)]. Alpha-adrenergic antagonists (α-blockers) and 5α-reductase inhibitors are the two categories of drugs used to non-surgically treat BPH. α-blockers aid in the relaxation of the bladder neck and prostate, whereas 5α-reductase inhibitors work by decreasing the prostate gland size [(6)]. Two 5α-reductase inhibitors, finasteride, and dutasteride, have been approved for clinical application. Dutasteride, a powerful 4-azasteroid, effectively inhibits both 5α-reductase types 1 and 2. At present, this compound is utilized to treat benign prostatic hyperplasia and androgenic

alopecia [7,8]. Researchers have found that dutasteride can significantly lower DHT levels, reducing them by as much as 99% in both prostate and serum DHT [9-11]. Dutasteride, classified as BCS class II due to its poor water solubility, exhibits a low solubility in water measuring 0.038 ng/mL [12]. It is only available as a soft gelatin capsule that contains monoglycerides and diglycerides of caprylic/capric acid to enhance solubility, the oral bioavailability of this dosage form is 60% [13]. The aim of this study was to create dutasteride nanosuspension to improve its solubility and dissolution characteristics. Nanosuspensions are colloidal dispersions containing drug particles at the nanoscale, stabilized by a stabilizer [14]. They comprise the drug itself, which is poorly soluble in water and lacks any matrix material, suspended in dispersion [15]. Two primary techniques, namely "Bottom-up technology" and "Top-down technology", are predominantly employed for preparing nanosuspensions [16]. Bottom-up technology involves increasing the size of particles from the molecular level to the nanoscale, resulting in the production of nanoscale particles, several methods are involved in this type of NS technique (Solvent-Antisolvent precipitation method, Sonoprecipitation) [17]. Alternatively, the top-down approach entails the fragmentation of bigger particles into nanoparticles through methods like high-pressure homogenization and milling [18,19].

Materials and Experimental Procedures

Materials

Dutasteride (Kathy, China), soluplus (Basf SE, Germany), poloxamer 407 and poloxamer 188 (Eastman chemical company, USA), PVA (Basaf, Germany), PVP K30 (Fluka Chemi AG, Switzerland), methanol (Thomas Baker, India).

Methods

Formulation of dutasteride nanosuspension

Dutasteride nanosuspension was prepared by using the solvent anti-solvent precipitation method [20,21]. This approach involved the preparation of two phases. The organic phase was produced by dissolving 0.5 mg of dutasteride in 1 ml of methanol. The aqueous phase, on the other hand, was formed by dissolving varying concentrations of stabilizers (soluplus, poloxamer 407 (PXM 407), poloxamer 188 (PXM 188), polyvinyl pyrrolidone K30 (PVP K30), and polyvinyl alcohol (PVA)) in 10 ml of deionized water. The organic phase was introduced into the aqueous phase using a syringe at a rate of 1 ml per minute. The resulting mixture was then mechanically stirred at 1500 rpm and 37°C for 30 minutes to allow the volatile solvent to evaporate. After that, the particle size was measured. Table (1) presents extensive information regarding the composition and various preparatory conditions for formulas.

Table 1. The composition and various preparatory conditions for formulas.

F. code	Drug (mg)	Stabilizer type	Stabilizer con. w/v	Temp.	rpm	Organic to aqueous ratio	Inj. speed ml/min
F1	0.5	soluplus	0.3%	37 °C	1500	1:10	1
F2	0.5	soluplus	0.4%	37°C	1500	1:10	1
F3	0.5	soluplus	0.5%	37°C	1500	1:10	1
F4	0.5	Pxm 407	0.3%	37°C	1500	1:10	1
F5	0.5	Pxm 407	0.4%	37°C	1500	1:10	1
F6	0.5	Pxm 407	0.5%	37°C	1500	1:10	1
F7	0.5	Pxm 188	0.3%	37°C	1500	1:10	1
F8	0.5	Pxm 188	0.4%	37°C	1500	1:10	1
F9	0.5	Pxm 188	0.5%	37°C	1500	1:10	1
F10	0.5	Pva cold	0.3%	37°C	1500	1:10	1
F11	0.5	Pva cold	0.4%	37°C	1500	1:10	1
F12	0.5	Pva cold	0.5%	37°C	1500	1:10	1
F13	0.5	Pvp k30	0.3%	37°C	1500	1:10	1
F14	0.5	Pvp k30	0.4%	37°C	1500	1:10	1
F15	0.5	Pvp k30	0.5%	37°C	1500	1:10	1
F16	0.5	soluplus	0.3%	37°C	1500	1:6	1
F17	0.5	soluplus	0.3%	37°C	1500	1:8	1
F18	0.5	soluplus	0.5%	37°C	1500	1:6	1
F19	0.5	soluplus	0.5%	37°C	1500	1:8	1
F20	0.5	soluplus	0.5%	25 °C	1500	1:10	1
F21	0.5	soluplus	0.4%	25 °C	1500	1:10	1

F22	0.5	soluplus	0.5%	50°C	1500	1:10	1
F23	0.5	soluplus	0.4%	50°C	1500	1:10	1
F24	0.5	soluplus	0.5%	37°C	1000	1:10	1
F25	0.5	Soluplus	0.5%	37°C	2000	1:10	1
F26	0.5	soluplus	0.4%	37°C	1000	1:10	1
F27	0.5	soluplus	0.4%	37°C	2000	1:10	1

Evaluation of dutasteride nanosuspension

Measurement of the particle size and polydispersity index of dutasteride nanosuspension:

All formulations of dutasteride nanosuspensions were subjected to analysis using a particle size analyzer (Malvern zeta sizer, Spectris Company, United Kingdom) that operates based on dynamic light scattering theory [22]. The samples are diluted appropriately until we get a suitable solution of the desired viscosity that can detect the Brownian motion of the particles.

Measurement of drug content in selected dutasteride nanosuspension formulas

The investigation focused on determining the drug content of every formulation within the nanoscale. A volumetric flask was utilized to hold 1 ml of nanosuspension formula, which was then diluted with 9 ml of methanol. The resulting mixture underwent sonication for a duration of 1 hour. The collected samples were subjected to analysis via a UV-visible spectrometer, specifically at the wavelength (λ max) where the drug in methanol displayed its highest absorbance, which was measured at 240 nm. The percentage of drug content was determined by applying a designated equation (1).

$$Drug\ content\ \% = \frac{(detected\ drug\ content)}{Theoretical\ drug\ content} \times 100\ \%$$

Eq. (1) [23].

Determination of Entrapment Efficiency

The entrapment efficiency refers to the proportion of a drug or substance that is successfully incorporated within the nanoparticles. It's usually expressed as a percentage and indicates how effectively the nanoparticles entrap and hold the active ingredient [24]. Entrapment efficiency (EE%) of selected dutasteride nanosuspension formulas was evaluated using an Amicon ultra-4 centrifugal filter with Mwt 10 KD. A total of 4 ml of dutasteride nanosuspension was placed in the Amicon tube and centrifuged at 4000 rpm for 30 minutes. Subsequently, the concentration of concentrated dutasteride particles was assessed using UV spectrophotometry. EE% was then measured using the following equation:

$$EE\% = \frac{obtained\ dutasteride\ amount}{theoretical\ dutasteride\ amount} \times 100\ \%$$

Eq. (2) [25].

In vitro dissolution behavior of the pure dutasteride powder and a well-refined dutasteride nanosuspension formula

The release of pure dutasteride powder and the selected formula was evaluated using a USP dissolution test apparatus type II. The nanosuspension of the selected formula was placed inside a dialysis membrane with a molecular weight cutoff of 8000-14000, which was then attached to the paddle and immersed in a dissolution medium consisting of 200 ml of 6.8 buffer with 1% sodium dodecyl sulfate (SDS), the paddle undergoes a rotation speed of 50 revolutions per minute and at 37°C [26]. At specific time intervals (5, 10, 15, 30, 45, and 60 minutes), a 5 ml sample was withdrawn and promptly substituted with 5 ml fresh dissolution medium, the withdrawn sample was then filtered using a 0.11 syringe filter. The absorbance of each sample was measured using a UV-visible spectrophotometer at dutasteride λ max in 6.8 buffer with 1 % SDS (242 nm).

Factors affecting particle size and PDI of selected dutasteride NP formulas

Below, we present a list of factors that can exert an influence on the particle size and PDI of dutasteride nanosuspensions:

1- Stabilizer type effect

To determine their impact on the particle size and PDI of selected dutasteride nanosuspensions, different stabilizer types, namely Soluplus, PXM 407, PXM 188, PVP K 30, and PVA were used at three distinct concentrations.

2- Stabilizer concentration effect

Three different stabilizer concentrations: 0.3% w/v, 0.4% w/v, and 0.5% w/v were used to determine the influence of varying stabilizer concentrations on the particle size and PDI of selected dutasteride nanosuspensions. Additionally, five different types of stabilizers were utilized, resulting in a total of 15 different formulations labeled as F1-F15.

3- Stirring rate effect

Stirring rate influence was studied in formulas F24, F25, F26 and F27. Two distinct stirring rates (1000 rpm, and 2000 rpm) were used to examine the influence of stirring rate on the properties of selected dutasteride nanosuspensions.

4- Temperature effect

Two temperatures (25°C and 50°C) were used in F20, F21, F22, and F23, to study the effect of temperature on particle size and PDI of selected dutasteride nanosuspensions.

5- Solvent / antisolvent ratio effect

Two different solvent /antisolvent ratios (1:6, 1:8) were used to study their effect on particle size and PDI, as shown in F16, F17, F18, and F19.

Lyophilization of the chosen dutasteride nanosuspension formula

The optimized nanosuspension formula underwent freeze-drying with the addition of 1% w/v mannitol as a cryoprotectant. Subsequently, the sample was deep-frozen in a refrigerator for 24 hours before undergoing lyophilization using a vacuum freeze dryer through water sublimation. This process yielded dried powdered nanoparticles. The resulting lyophilized dutasteride nanoparticles were utilized for subsequent compatibility studies.

Compatibility study

Powder X-ray Diffractometric (PXRD) Study

To evaluate the degree of crystallinity and potential alterations in the physical properties of dutasteride resulting from the formulation process, powder x-ray diffraction was utilized [27]. The crystalline structure of pure dutasteride powder and the lyophilized dutasteride nanoparticles were determined by using the X-ray method. The X-ray diffraction experiment was conducted under specific conditions, including an applied voltage of 40 kV and a current of 30 mA [28]. The scan encompassed a 2θ ranging from 5 to 80 degrees, employing a wavelength of 1.5406 Å [29].

Surface morphology determination

Field emission scanning electron microscopy (FE-SEM) is an advanced technology used to capture the microstructure image of the materials. FESEM (Inspect F50, FEI company) was used to examine the surface characteristics of the lyophilized dutasteride nanoparticles. The samples were placed onto double-sided carbon tapes that were affixed to the specimen mount of the FE-SEM. To ensure consistent coverage on the samples, a thin layer of gold was applied using an automated fine coater after sputter-coating. The examination was conducted by employing various levels of magnification [30].

Fourier Transform Infrared Spectroscopy (FTIR)

Fourier Transform Infrared Spectroscopy (FTIR) was used to determine if there are any interactions or complexation between dutasteride and other components used in the formulation of dutasteride nanosuspensions. Pure dutasteride powder and the lyophilized dutasteride NPs, underwent analysis by grinding the substance with potassium bromide (KBr) and subsequently compacting it into a thin film disc using a precise technique. The achieved outcomes were observed within the wave number range of 4000-400 nm [31].

The evaluation of dutasteride nanosuspension

Measurement of the particle size and polydispersity index of dutasteride nanosuspensions:

A particle size analyzer (Malvern zeta sizer, Spectris Company, United Kingdom) was employed to examine all dutasteride nanosuspension samples. The resulting particle size and distribution for all formulations were documented in Table (2). The range of values for the polydispersity index (PDI) typically falls within specific categories: 0-0.05 (monodisperse standard), 0.05-0.08 (nearly monodisperse), 0.08-0.7 (midrange polydispersity), and >0.7 (very polydisperse) [32]. Among all the formulations, most displayed midrange polydispersity (PDI), except for F5, F13, F14, and F15, which exhibited very polydisperse characteristics. (F1-F15) formulas were prepared by using five distinct stabilizers (Soluplus, PXM 407, PXM 188, PVA, and PVP 30) were used at three individual drug-stabilizer concentrations 0.3% w/v, 0.4 % w/v, and 0.5 % w/v. A notable variation in the particle size and PDI ($P<0.05$) was observed among the five types of stabilizers. As shown in Figure 1, using different stabilizers at the same concentration of 0.3% led to different particle sizes and PDI for formulations F1, F4, F7, F10, and F13. This suggests that the affinity of stabilizers for dutasteride particles differs. As demonstrated in Table 2 only F1, F2, and F3 stabilized by soluplus in varying concentrations, exhibit nanosize particles, due to the unique interaction between soluplus and dutasteride.

Soluplus functions as an amphiphilic graft copolymer, comprising a hydrophilic part (polyethylene glycol backbone) and a lipophilic part (vinyl caprolactam/vinyl acetate side chains). When interacting with hydrophobic drugs, the polymer's hydrophobic part attaches to the drug's surface. On the other hand, the hydrophilic portion extends outward into the surrounding water, reducing interfacial tension among the newly formed nanoparticles [33]. This action ensures completed surface coverage and steric stabilization of the nanoparticles, effectively preventing particle growth and agglomeration [33]. The use of various stabilizers, such as PXM 188, PXM 407, PVA, and PVP k30, led to the generation of larger particles, as evident in Table 2 and Figure 1. This phenomenon may be attributed to the absence of an attractive interaction between these stabilizers and the dutasteride molecule. When there is a lack of affinity between the drug particle surface and the stabilizer, electrostatic interactions between the drug particles become more pronounced as the amount of stabilizer between them decreases, giving rise to a depletion

force. Consequently, the variations in particle size observed with different stabilizers are directly related to these stabilizers' ability to bond with the dutasteride molecule [34].

Table 2. The particle size and PDI of dutasteride nanosuspensions.

F. code	Particle size (nm)	PDI	F. code	Particle size (nm)	PDI	F. code	Particle size (nm)	PDI
F1	73.78	0.249	F10	2424	0.582	F19	82.52	0.209
F2	71.24	0.215	F11	2515	0.822	F20	77.1	0.212
F3	73.24	0.184	F12	2577	0.376	F21	76.81	0.279
F4	1396	0.736	F13	2278	1.576	F22	67.65	0.211
F5	1723	0.870	F14	2879	1.148	F23	67.44	0.218
F6	2402	0.380	F15	3489	1.169	F24	71.4	0.214
F7	1525	0.65	F16	94.2	0.299	F25	70.56	0.164
F8	2382	0.435	F17	84.24	0.1004	F26	71.77	0.095
F9	3753	0.309	F18	93.76	0.1649	F27	71.86	0.212

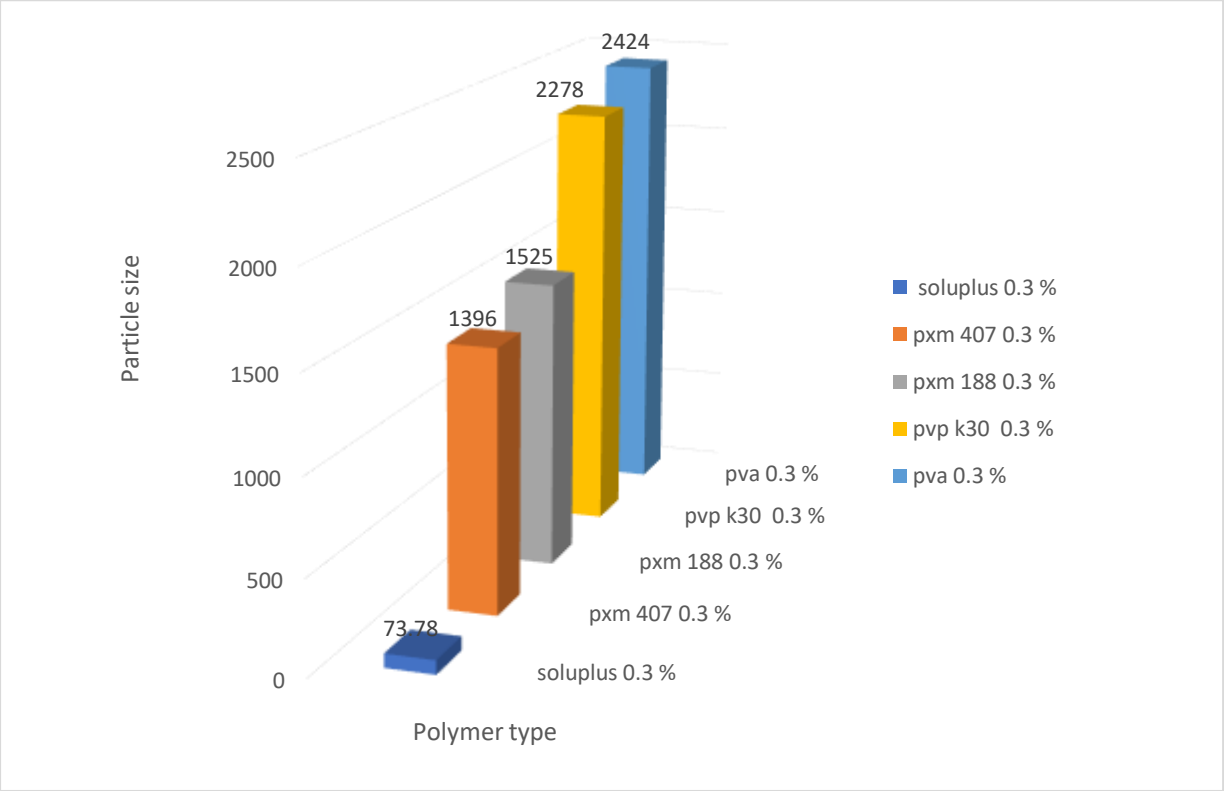

Figure 1. Stabilizer type effect on the particle size of dutasteride nanosuspensions.

To determine the influence of varying stabilizer concentrations on the properties of dutasteride nanoparticles (NPs), F1-F15 were prepared by using three different stabilizer concentrations 0.3%, 0.4%, and 0.5% w/v. as shown in Table 2 and Figure 2, different stabilizers resulted in a significant difference ($P<0.05$) in particle size and PDI with change in stabilizer concentration except for soluplus. An increase in stabilizer concentration resulted in an increase in particle size, this increase in particle size could be attributed to an increase in viscosity, impeding particle mobility within the solution and obstructing effective coverage of the recently developed nanoparticles [35]. Additionally, an elevated concentration of stabilizer might increase the coating thickness encasing the nanoparticles, consequently impeding diffusion between the solvent and antisolvent phases throughout nanoparticle precipitation [35].

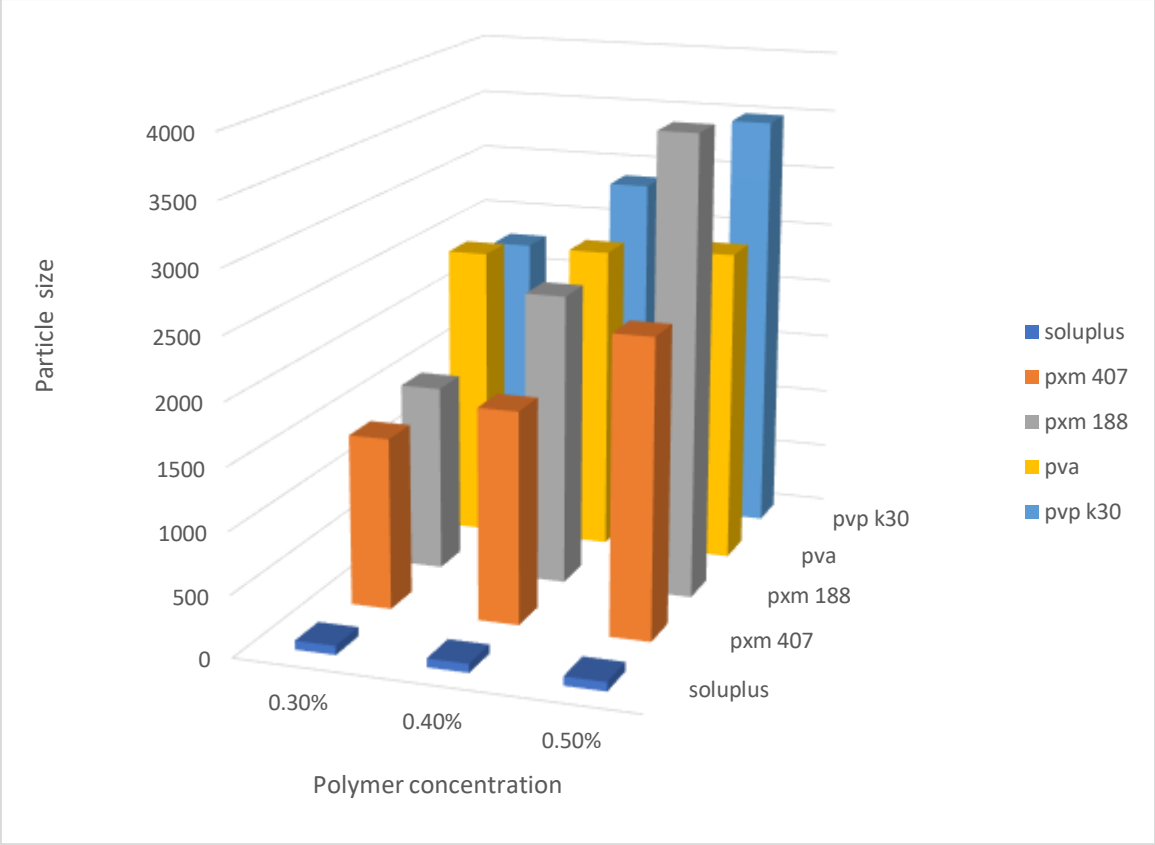

Figure 2. Stabilizer concentrations (0.3%, 0.4%, and 0.5%w/v) effect on the particle size of dutasteride nanosuspensions.

The impact of stirring speed on the particle size of dutasteride nanosuspension was studied. Two distinct speeds, 1000 and 2000 rpm, were used to formulate four different formulations (F24, F25, F26, and F27). The resulting particle sizes of these formulations at 1000 rpm were (71.4, 71.77) while at 2000 rpm, they were (71.86,70.56) for soluplus 0.5% formula and soluplus 0.4% formula respectively. As indicated by the outcomes, there was no significant difference in particle size ($P > 0.05$) with a change in stirring speed during the formulation of the nanosuspension. Additionally, there is a notable variation in PDI with an increase in stirring speed, except for F25.

The impact of different antisolvent-to-solvent ratios on the dutasteride nanosuspension was studied by the preparation of (F16, F17, F18, and F19) formulas, and two different solvent /antisolvent ratios (1:6, 1:8) were used. As indicated by the outcome in Table 2 and Figure 3, there is a significant difference in particle size and PDI ($P<0.05$) with a change in the antisolvent-to-solvent ratio. At low antisolvent-to-solvent ratios, increased solvent content, prompts particle growth, leading to larger particles of F16, F17, F18, and F19 [36], while increasing the antisolvent-to-solvent ratio, as shown in formula (F3), leads to a reduction in particle size [36]. As the ratio of antisolvent to solvent increases, it leads to higher supersaturation. This, in turn, elevates the rate of nucleation and results in a decrease in particle size. However, particle size reduction with an increase in the antisolvent-to-solvent ratio attains a near-constant level following the attainment of a critical solvent/ antisolvent ratio, potentially owing to the balancing of nucleation and growth kinetics [37]. Consequently, optimal antisolvent-to-solvent ratio selection is a pivotal facet of the precipitation process.

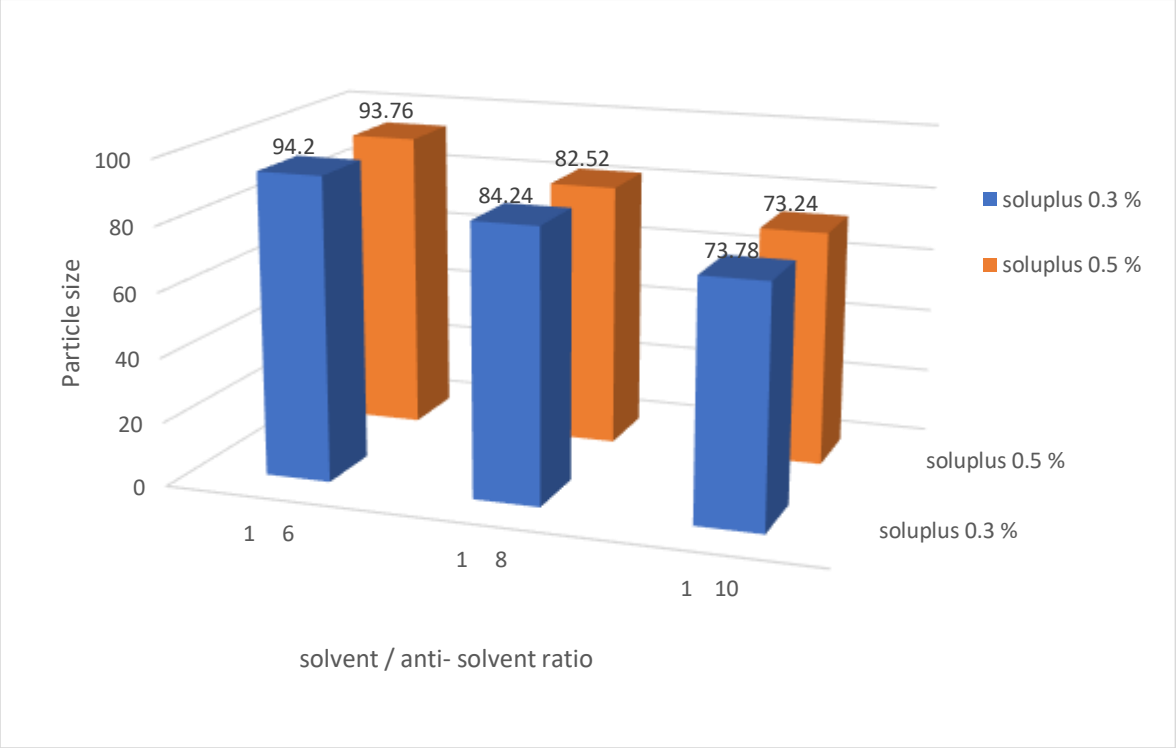

Figure 3. Antisolvent-to-solvent ratio effect on the particle size of dutasteride nanosuspensions.

Temperature effect

To study the effect of temperature on particle size and PDI of dutasteride nanosuspensions, F20 and F21 were prepared by using a temperature of 25°C while F22 and F23 were prepared by using a temperature of 50°C. As shown in Table 2 and Figure 4, there is a significant difference in particle size ($P<0.05$) with a change in temperature. As illustrated, an increase in temperature resulted in a decrease in particle size, this decrease in particle size could be attributed to decreased viscosity, lower viscosity allows for better mixing and reduced resistance to particle movement within the nanosuspension. This enhances the collision and interaction of particles during precipitation, leading to smaller and more uniform particle sizes [38]. Additionally, there is a significant difference ($P<0.05$) in PDI with a change in temperature except for F23.

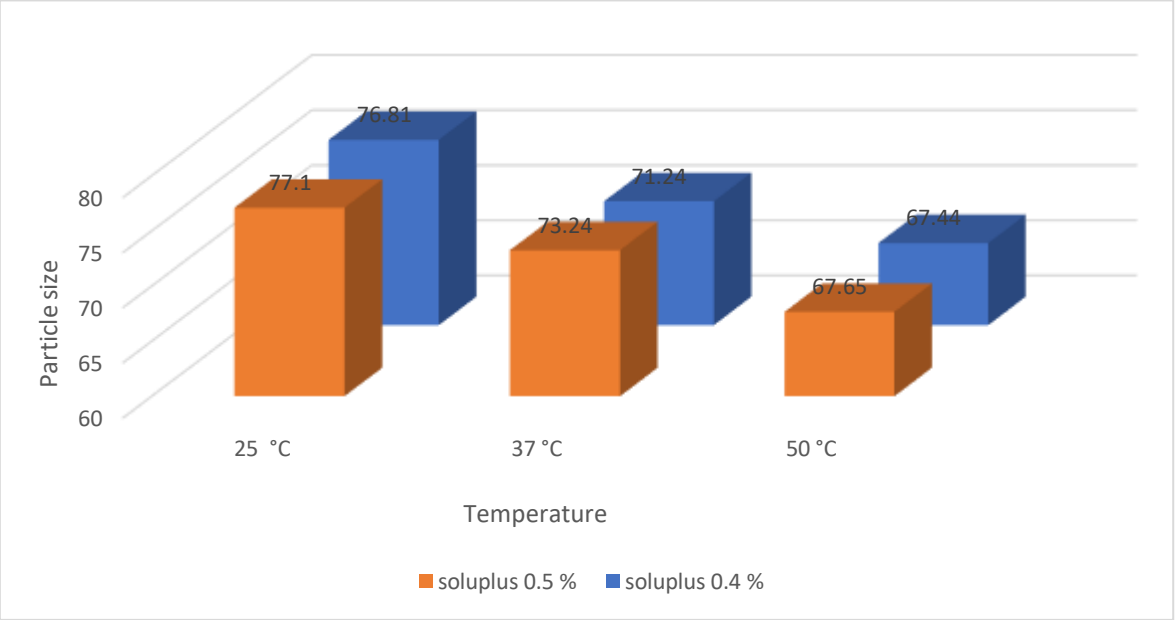

Figure 4. Temperature effect on the particle size of dutasteride nanosuspensions.

Determination of drug content and EE% of the selected dutasteride nanosuspension formulas

The drug content percent of selected dutasteride nanosuspension formulas was investigated, it was determined to be 96% ± 0.0120, 95% ± 0.006, and 99.58% ± 0.0121 for F1, F2, and F3 respectively.

the percentage of dutasteride entrapped into the nanoparticles was determined to be 97.2% ± 3.95, 96.5% ± 4.94, and 99% ± 1.41 for F1, F2, and F3 respectively. stabilizer type and concentration significantly contribute to achieving a considerable level of drug entrapment efficiency [39, 40].

In vitro dissolution behavior of selected dutasteride nanosuspension formulas

The release of dutasteride nanosuspension formulas and dutasteride's pure powder was measured by using USP dissolution test apparatus type II. The dissolution media used was 200 ml of phosphate buffer with a pH of 6.8, and it contained 1% SDS, to maintain the required sink condition. The dissolution test was performed on both pure dutasteride powder and selected formulas, which included formulations F1, F2, and F3, all having sizes smaller than 100 nm. As depicted in Figure 5 and summarized in Table 4, the pure dutasteride exhibited a release rate of 18.38% after 15 minutes. In contrast, the dutasteride nanosuspension formulations (F1, F2, and F3) demonstrated significantly enhanced release profiles, reaching 71.6 %, 90 %, and 100 % release within just 15 minutes, with F3 displaying exceptional in vitro release performance by achieving complete dutasteride release within this short time frame.

A comparison was conducted between the release patterns of dutasteride NS formulations (F1, F2, F3) and the dutasteride's pure powder, which is used as a reference, by using similarity factor f2, which is a parameter used in pharmaceutical sciences to assess the similarity between two dissolution profiles. According to FDA guidelines, the two dissolution profiles are considered similar when the f2 value exceeds 50, ranging from 50 to 100. As shown in Table 5 the resulting similarity factor value is less than 50. This indicates a distinct difference in the dissolution behavior between the prepared dutasteride NS and the pure dutasteride powder [41].

Table 4. Maximum percentage of dutasteride nanosuspension formulation release.

formula	Polymer type	Polymer con.	dutasteride release %	Time for max. release
F1	soluplus	0.3%	71.6 %	15 min
F2	soluplus	0.4%	90 %	15 min
F3	soluplus	0.5%	100 %	15 min

Table 5. Similarity factor test of F1, F2, and F3 compared versus pure dutasteride.

Formula code compared with pure drug	F2 value
F1	13.37
F2	10.14
F3	12.37

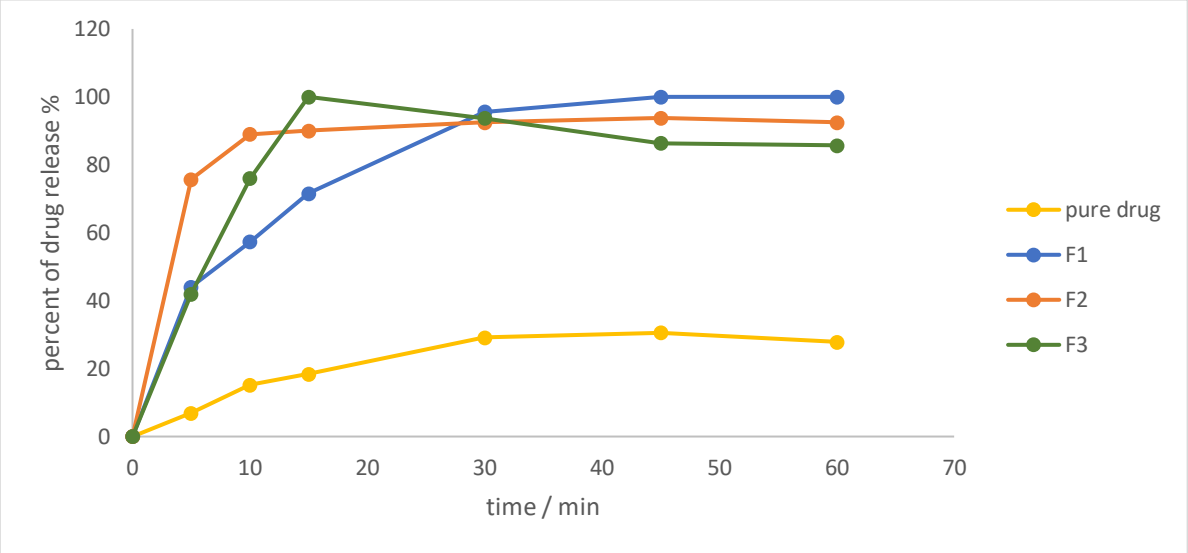

Figure 5. In-vitro release of the pure dutasteride, F1, F2, and F3 in 6.8 buffer with 1% SDS at 50 rpm and 37°C.

Thus, considering the aforementioned outcomes and taking into account the particle size, PDI, entrapment efficiency, drug content, and release, F3 was chosen as the optimal formula and subjected to further examination such as (FTIR, FESEM, XRPD).

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was performed on pure dutasteride powder and the lyophilized dutasteride nanoparticles. The resulting spectra of the dutasteride nanoparticle sample and pure dutasteride showed remarkable similarity owing to the common functional groups they share [42]. There were no changes in the characteristic peaks of the drug and no appearance of new peaks. This indicates that the drug and the polymer used are chemically compatible and there was no detectable interaction. This is illustrated in Figures (6,7) and Table (6).

Table 6. FTIR peaks of pure dutasteride and dutasteride nanoparticles.

Functional group	Reference (cm^{-1})	Pure drug (cm^{-1})	Dutasteride NPs (cm^{-1})
N-H stretch	3192.30	3169.44	3389.28
N-H bend	1592.86	1590.02	1561.09
C=O stretch	1670.95	1670.73	1632.45
The symmetric stretch of CC=C	1670.75	1713.44	1734.66
C-X	1142.68	1111.76	1084.76

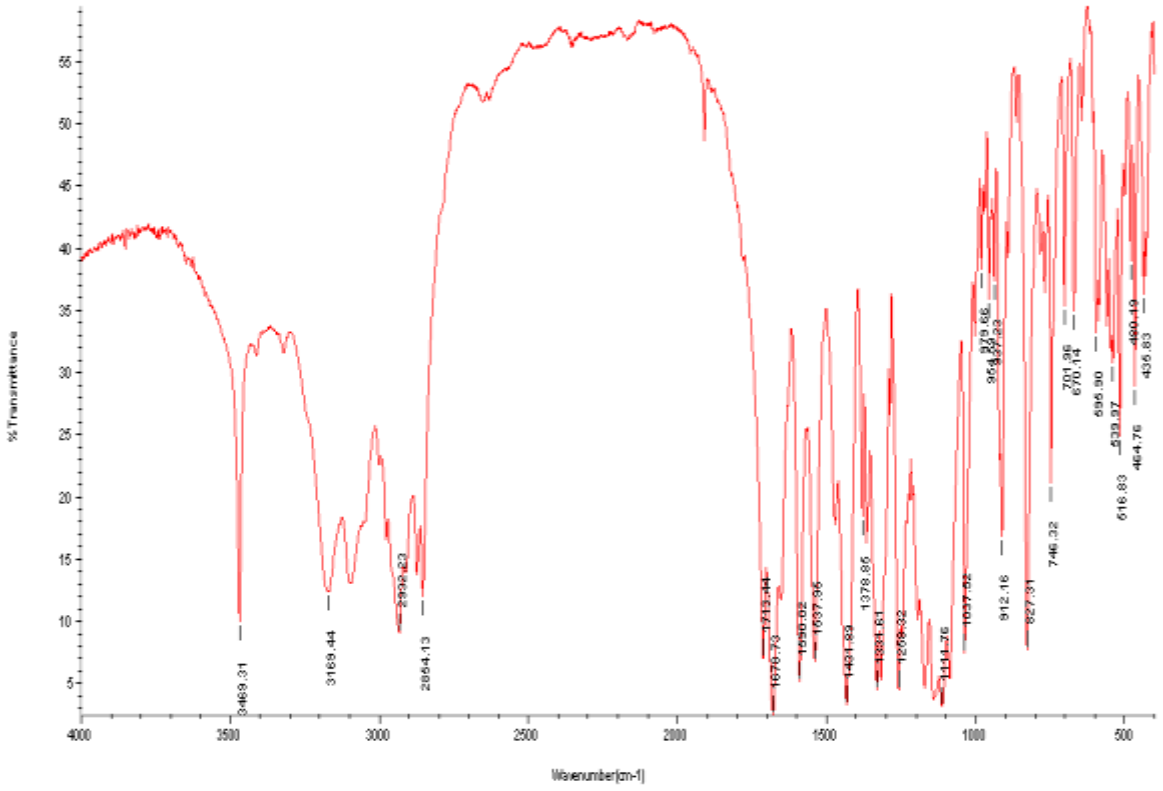

Figure 6. FTIR spectrum of pure Dutasteride.

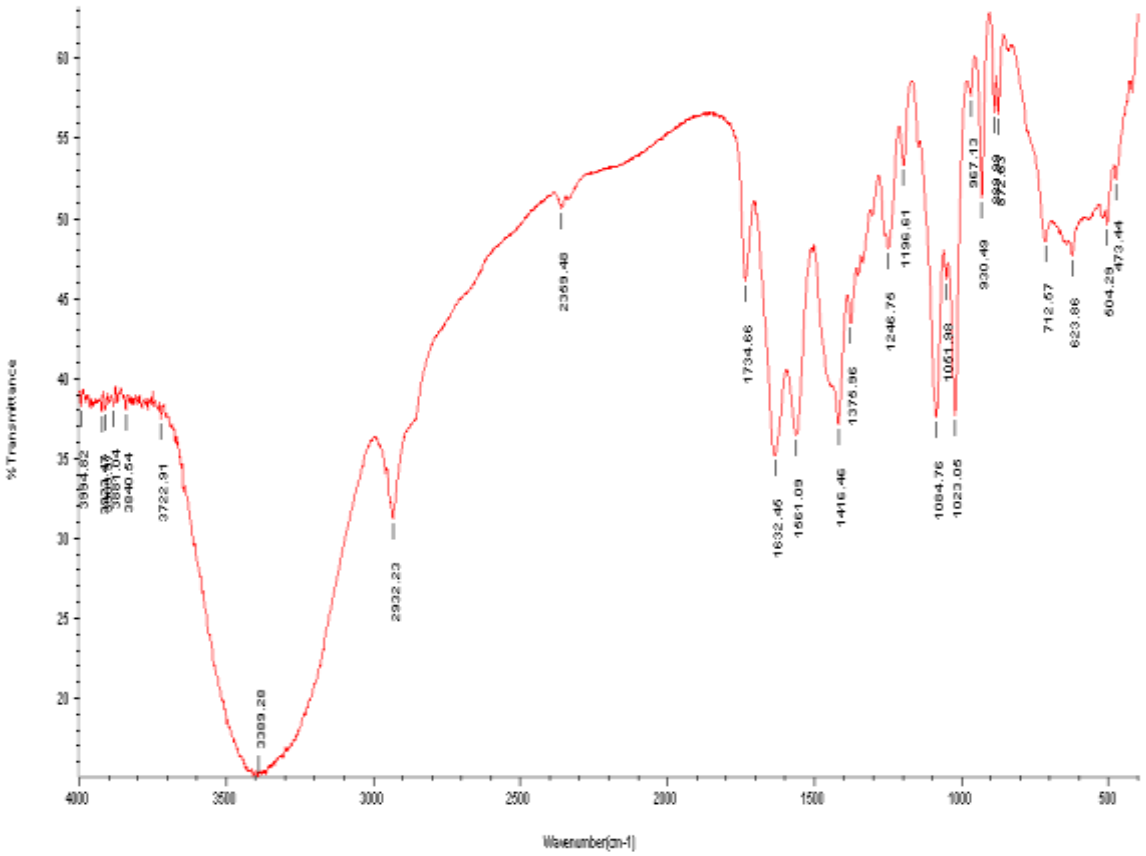

Figure 7. FTIR spectrum of dutasteride nanoparticles (F3).

Field emission scanning electron microscope (FESEM)

The morphology and the size of the lyophilized dutasteride nanoparticles were analyzed utilizing a field emission scanning electron microscope (FESEM) [43]. At different levels of magnification, the images exhibit the nanoparticles of the chosen formula (F3), showcasing a small and uniform particle size distinguished by its smooth and homogeneous surface [44], as shown in Figure (9).

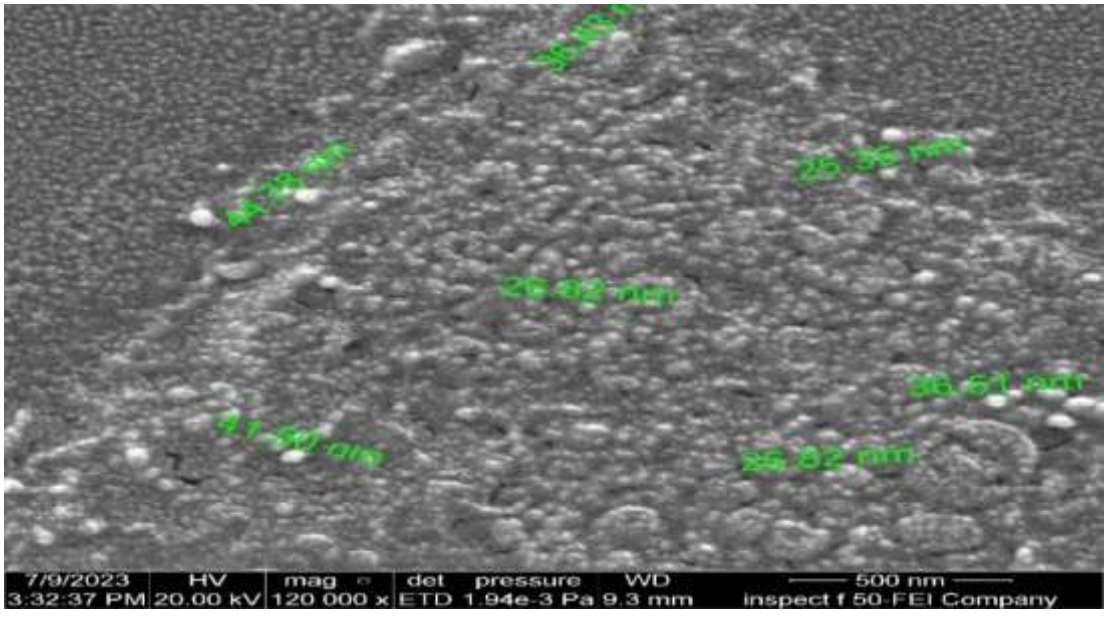

Figure 9. FESEM of the optimized dutasteride nanoparticles formula (F3).

X-ray powder diffraction (XRPD)

An analysis using X-ray diffraction (XRD) was carried out on both pure dutasteride powder and the lyophilized dutasteride nanoparticles, illustrated in Figure (10). Confirmation of a material's crystalline structure can be established through the analysis of X-ray diffraction peaks. This information is utilized to ascertain whether a product possesses a crystalline or amorphous nature [47]. The XRPD pattern of dutasteride NPs confirms a notably lower intensity of X-ray peaks, a reduction in the intensity of dutasteride peaks attributed to the reduced particle size, and a decrease in crystallinity [45,46].

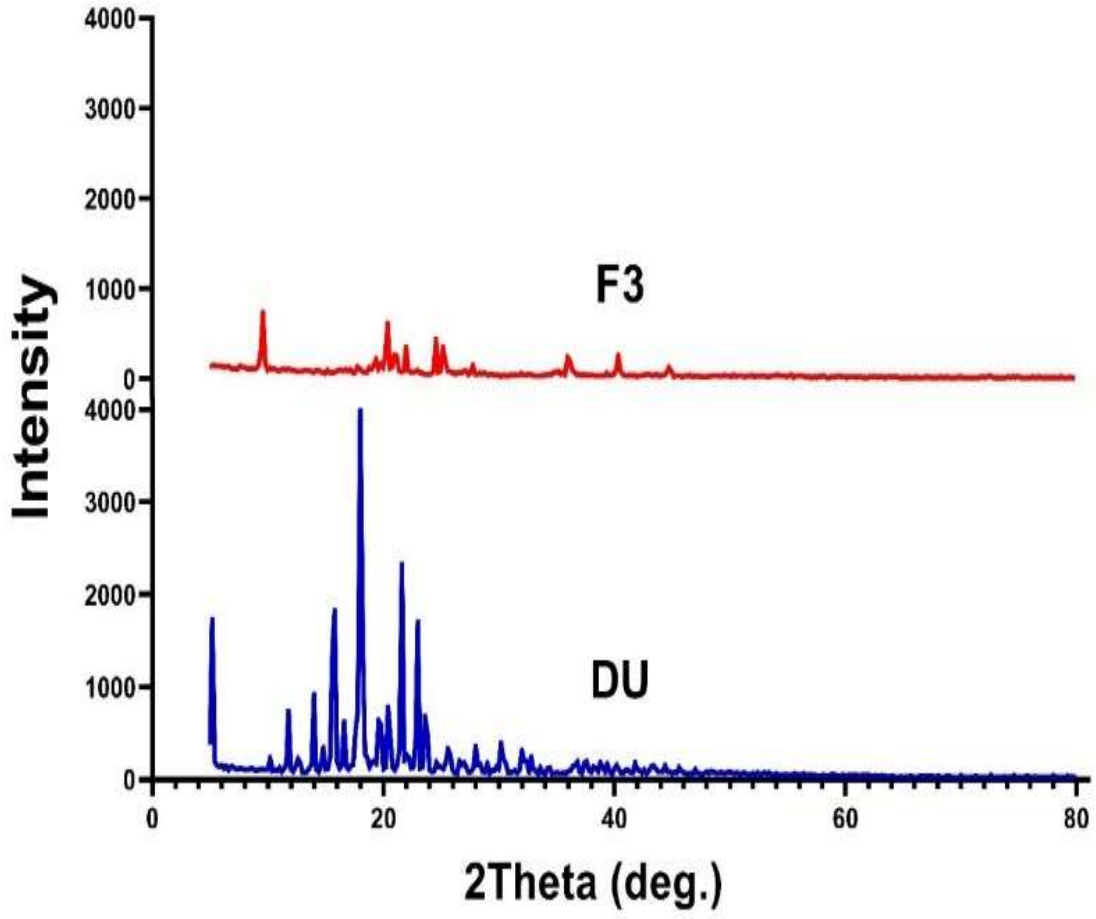

Figure 10. XRPD spectrum of pure dutasteride (DU), and dutasteride nanoparticle (F3).

Conclusion

A successful preparation of dutasteride nanosuspension was achieved by using soluplus as a stabilizer, in different concentrations. The optimized formula that resulted, comprising 0.5% w/v of soluplus and a solvent/antisolvent volume ratio of 1:10, produced nanoparticles with a size of 73.24 nm, and a polydispersity index of 0.184. In vitro dissolution studies revealed that the optimized formulation enhanced the dissolution rate of dutasteride significantly compared to pure drug. Therefore, the preparation of dutasteride nanoparticles by using the solvent anti-solvent method proves to be an effective approach for enhancing the dissolution rate of dutasteride**.**

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Conflicts of Interest

No conflicts.

Funding

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Ethics Statements

In vitro study, no ethical statements are required.

Author Contribution

The authors confirm their contribution to the paper as follows: data collection, analysis and interpretation of results, and draft manuscript

preparation: Rusul Wahhab Kadhum. Shaimaa N Abd-Alhammid reviewed the results and approved the final version of the manuscript.

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العوامل العملية المؤثرة على تحضير وتوصيف جسيمات الدوتاستيرايد النانوية

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الخلاصة

دوتاستيرايد، مركب اصطناعي ينتمي إلى فئة ٤-أزاستيرويد، يعمل كمثبط انتقائي وتنافسي لكل من إنزيمات اختزال ٥-ألفا النوع الاول والنوع الثاني. تمت الموافقة عليه لعلاج أعراض تضخم البروستات الحميد لدى الرجال. يتمتع دوتاستيرايد بقابلية منخفضة للذوبان ونفاذية عالية، مما يصنفه على أنه من الدرجة الثانية، وفقًا لنظام تصنيف المستحضرات الصيدلانية الحيوية، مما ادى إلى توفره حصريًا في السوق كتركيبة موجودة داخل كبسولات جيلاتينية طرية، ويبلغ التوافر الحيوي عن طريق الفم لهذا الشكل الصيدلاني تقريبًا ٦٠٪. الهدف الرئيسي لهذه الدراسة هو إنشاء وتوصيف جسيمات دوتاستيرايد النانوية التي من شأنها تعزيز قابليتها للذوبان ومعدل إطلاقها. يتكون النهج المستخدم في الدراسة من تحضير معلق نانوي من خلال طريقة الترسيب بالمذيبات/مضادات المذيبات باستخدام مثبتات مختلفة بتركيزات مختلفة (٠,٣٪ وزن/حجم، ٠,٤٪ وزن/حجم، و٠,٥٪ وزن/حجم). ناقش البحث كيفية تأثير العوامل المختلفة على حجم الجسيمات ومؤشر تعدد التشتت للعينة المختارة لمعلق الدوتاستيرايد النانوي. شملت عوامل التقييم حجم الجسيمات، مؤشر تعدد التشتت، مؤشر تعدد التشتت، كفاءة الانحباس النانوي، وأنماط الذوبان في المختبر. هذه العوامل مجتمعة ساعدت في تحديد العينة الأمثل لمعلق الدوتاسترايد النانوي. الصيغة المحسنة الناتجة، المكونة من ٠,٥٪ وزن/حجم سولوبلس كمثبت ونسبة حجم مذيب/مضاد مذيب (ميثانول/ماء منزوع الأيونات) تبلغ ١:١٠ أنتجت، حجم جسيم قدره ٧٣,٢٤ نانومتر، ومؤشر تعدد تشتت قدره ٠,١٨٤. كشفت دراسات الذوبان ان التركيبة المحسنة عززت معدل ذوبان دوتاستيرايد بشكل ملحوظ مقارنة بالدواء النقي، فقد أظهرت إطلاقًا كاملاً للدواء خلال ١٥ دقيقة. خضعت التركيبة الأكثر ملائمة لاختبار التوافق باستخدام التحليل الطيفي للأشعة تحت الحمراء ودراسة شكل السطح باستخدام المجهر الإلكتروني لمسح الانبعاثات الميدانية وفحص تركيبها البلوري عبر تحليل حيود مسحوق الأشعة السينية. تشير النتائج إلى ان استخدام طريقة المذيبات المضادة للإذابة أثبت فعاليتها في إنشاء معلق نانوي للدوتاستيرايد مع حجم جسيمات صغيرة ومؤشر تشتت متعدد منخفض إلى جانب محتوى دوائي مرتفع، وانحباس دوائي عالي، ومعدل انحلال معزز للدوتاستيرايد.

الكلمات المفتاحية: دوتاستيارايد، المجهر الالكتروني الماسح الثانوي الانبعاث الحقل، معلق نانوي، مثبتات، سولوبلس، ترسيب الميذيب/ مضاد المذيب.