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ENHANCEMENT OF FINASTERIDE AQUEOUS SOLUBILITY BY NANOSUSPENSION OPTIMIZATION DESIGN

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Abstract:

In this study, an attempt was conducted to enhance finasteride aqueous solubility by preparing drug nanosuspension. The formulation of this drug delivery system was developed by bottom-up technology using the optimization technique. We explored the effect of four formulation and processing variables that affect the particle size of the prepared formulation. Solubility study of the optimized finasteride nanoparticles was evaluated. The results revealed that solvent ratio (X2), homogenization speed (X3), and stabilizer concentration (X1) had a significant effect on the particle size. The interaction effect of X1X4, X2X4, X3X4, and X22 also significantly affects the particle size. The prepared nanoparticles enhanced the aqueous drug solubility by more than 2.5 folds compared to the drug alone. Finally, it could be concluded that nanosuspension is a successful technique in enhancing the solubility of poorly water-soluble drugs with a possible impact on the drug bioavailability.

Key wards: *Nanosuspension, aqueous solubility, finasteride, optimization*

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INTRODUCTION:

Drug solubility and permeability are considered to be the two major factors affecting the development of successful therapeutic dosage forms as both influences the extent of drug bioavailability[1]. Of the newly chemical compounds developed by the medicinal drug design program, more than 40% are of limited water solubility[2]. Aqueous drug solubility affects the process of drug dissolution and so the rate and extent to which the drug reaches the systemic circulation[3,4].

Nanosuspension is the colloidal dispersion of nano-sized drug particles stabilized by surfactants. They can also be defined as a biphasic system of pure drug particles dispersed in an aqueous vehicle. The diameter of the suspended particle is less than one µm in size. Nanosuspension can be used to enhance the solubility of poorly soluble drugs in aqueous and lipid media. The principal techniques used in recent years for preparing nanosuspension are classified into four basic methods: (a) wet milling, (b) homogenization, (c) emulsification-solvent evaporation, and (d) supercritical fluid method[5].

Finasteride is considered a synthetic 4-azasteroid drug (Figure 1) chemically. The drug is an effective therapeutic agent in the treatment of BPH[6]. Inhibition of the enzyme 5 alpha-reductase is believed to be the mechanism of action of finasteride. This enzyme converts testosterone to di-hydro testosterone (DHT), which is a more potent androgenic hormone[7,8,9]. An increase in the level of DHT in the prostate results in prostate hyperplasia and urinary tract obstruction[8,10]. The drug is practically insoluble in water, with a mean bioavailability of 63%.

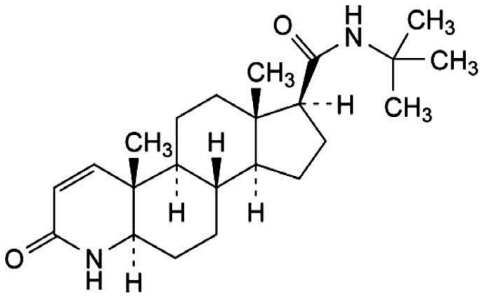

Figure (1): Chemical structure of finasteride

Design of Experiments (DoE) or experimental design is an application used to develop optimized drug formulation suitable for drug delivery. This design has found several pharmaceutical applications in developing controlled release dosage forms, semisolids, transdermal, microparticulate, macroparticulate, bioadhesive systems, floating systems, vesicular systems, and inhalations[11].

In this study, nanosuspension of finasteride by the bottom-up technique was prepared. Development of the nano-sized particles was conducted utilizing the response surface optimization technique to study the effect of the independent variables on the process. A transmission electron microscope characterized the optimized formulation to study the morphological characteristics of the prepared nanosuspension.

MATERIALS AND METHODS:

Materials

Finasteride was a kind gift from SAJA Pharmaceuticals (Jeddah, Saudi Arabia). Poly vinyl alcohol (PVA) was procured from Spectrum chemicals& laboratory products (NJ, USA). Methanol from Sigma-Aldrich (St. Louis, USA).

Method

Draper-Lin small composite design

Statgraphics® plus software, version 4 (Manugistics Inc., Rockville, MD) was utilized to design the formulation. A 43 Draper-lin small composite design was applied in which the variables, their level, and the studied responses are illustrated in table 1. The stabilizer concentration (X1), miscible solvent ratio (X2), Homogenization speed (X3), and homogenization time (X4) were selected as independent variables, while the particle size was studied as dependent responses. A total of 18 runs were obtained, as illustrated in table 2.

Preparation of the formulation

The solvent evaporation-high speed homogenization technique prepared the finasteride nanosuspension formulations depicted in table 2. Briefly, the known weight of the drug was dissolved in methanol, selected as a water-miscible solvent, to obtain a 100 mg/ml drug concentration. The drug solution was then added dropwise into 50 ml water containing a known concentration of PVA, selected as a stabilizer, and the mixture was kept stirring overnight at 1000 rpm on a magnetic stirrer until complete evaporation of the organic solvent and precipitation of the drug solid particles. The obtained suspension was homogenized at the specified speed for the specified time using UltraTurax, IKA® T18 basic Homogenizer (Campinas, Brazil).

Characterization of the formulation

Dynamic light scattering was the technique utilized to measure the particle size and zeta potential of the obtained nanosuspension in which Zetatrac of

Microtrac Inc., (PA, USA) was used. Characterization of both properties was done in triplicate.

Draper-Lin small composite design statistical analysis

The results obtained for the particle size were analyzed, and statistical analysis of the obtained data was considered to be significant at a p-value < 0.05.

Preparation and characterization of the optimum formulation

An optimized formulation was suggested after identifying the optimum level for each independent variable that achieves our goal. This formulation was prepared, characterized for the particle size and zeta potential as previously mentioned, and results compared to the predicted response for the particle size.

Solubility study

Solubility study for the freeze-dried optimum formulation, as compared to that of the pure drug by placing an excess amount of each sample in a screw cap vial containing 3 ml of distilled water, the vials were kept shaking for 72 h at room temperature in a thermostatically controlled shaking water bath (Model 1031; GFL Corporation, Burgwedel, Germany). Aliquots of each vial were taken every day, filtered using acrodisc® syringe filter of 0.45 µm, and analyzed by HPLC until reaching equilibrium solubility.

RESULTS AND DISCUSSION:

Draper-Lin small experimental design has been utilized to investigate the influence of four variables on the particle size of the prepared nanosuspension formulations, as illustrated in the table (1). The software has proposed Eighteen formulations. Each formulation has been prepared, characterized for the particle size, and the results are depicted in the table (2). Zeta potential, which reflects the surface charges on the prepared particles, was in the range 0.94-2.40 mv. The charge on the particles is an important character that affects the stability of the prepared particles[12]. Formulations F15 and F17 showed the higher zeta potential values among the studied formulation, which could be attributed to the low percentage of PVA in these formulations. It has been previously stated that adsorption of PVA on the surface of the particles leads to decreased zeta potential values as in silica macromolecules[13]. They attributed this effect to the presence of acetate group in the PVA polymer chain and shift of the slipping plane.

Table (1): Draper-Lin small design studied variables, response and their levels

Studied variables	**Variables level**		
	High	Medium	Low
X1(%)	1	0.65	0.3
X2 (%)	35	22.5	10
X3 (rpm)	20000	15000	10000
X4 (minutes)	15	10	5
Responses		**Aim**	
Y (nm)		Minimize	

X1: Stabilizer concentration, X2: Miscible solvent ratio, X3: Homogenization speed, X4: Homogenization time, Y: Particle size

Table (2): Composition of finasteride nanosuspension formulation suggested by the optimization design along with the observed particle size values

Run	Stabilizer %	Solvent ratio	Speed (rpm)	Time (min)	Y (nm)
1	0.65	22.5	15000	1.59	2280
2	0.3	10	10000	5	1977
3	1	10	10000	15	2735
4	1	35	10000	5	3955
5	0.65	43.52	15000	10	3767
6	0.061	22.5	15000	10	2356
7	0.3	35	20000	15	2076
8	0.65	22.5	23409	10	1688
9	0.65	22.5	15000	18.41	2508
10	1	35	20000	5	2827
11	0.65	1.478	15000	10	745
12	0.3	10	20000	5	934
13	0.3	35	10000	15	2310
14	1	10	20000	15	2357
15	1.24	22.5	15000	10	2841
16	0.65	22.5	6591	10	2902
17	0.65	22.5	15000	10	2601
18	0.65	22.5	15000	10	2612

Effect of the studied parameters on the particle size of the prepared nanosuspension

The solvent ratio (X2), homogenization speed (X3), and stabilizer concentration (X1) had a significant effect on the particle size of the prepared nanosuspension, as illustrated in the standardized Pareto chart, figure (2). The interaction effect of X1X4, X2X4, X3X4, and X22 also significantly affected the particle size. The main effect plot for the studied variables on the particle size indicated the significance of X2, X3, and X1. To illustrate the effect of X1 and X2 on the particle size when X3 and X4 were kept at their intermediate levels, an estimated response surface was constructed figure (2). The equation of the fitted model is:

$$Y = 2179.97 - 2991.76*X1 + 151.543* X2 - 0.0443091* X3 - 100.019* X4 + 222.312*X1^2 + 21.6366*X1X2 - 0.0163571* X1X3 + 287.326* X1X4 - 0.600694* X2^2 + 0.000118* X2X3 - 6.84695* X2X4 - 0.00000320984* X3^2 + 0.007795* X3X4 - 1.80272* X4^2$$

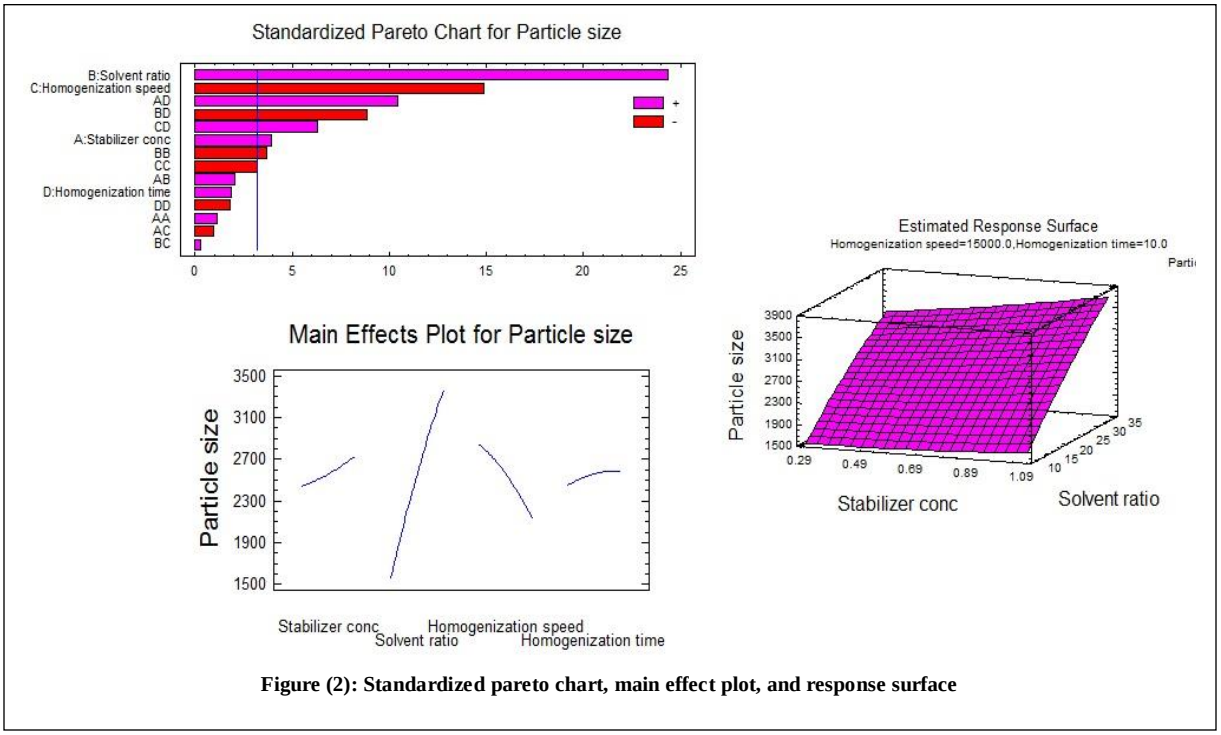

Figure (2): Standardized pareto chart, main effect plot, and response surface

The optimized desirability was identified, and the composition of the optimized formulation is illustrated in table 3. This formulation's preparation and characterization for the particle size were achieved, and the values for the predicted and observed responses are illustrated in the table (3).

Table (3): Optimum formulation composition, predicted and observed responses

X1	X2	X3	X4
0.575	2.578	14655	6.83
Particle size			
Expected		Observed	Residual
500 nm		593	+93

Solubility study revealed enhancement in the aqueous solubility of finasteride in the form of nanoparticles by more than 125% compared to the pure drug.

CONCLUSION:

It could be concluded that the experimental design has been successfully implemented to develop finasteride nanosuspension with uniform particle size. The prepared particles enhanced the aqueous drug solubility and the oral bioavailability of finasteride.

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