Application of Proniosomal Powder Technology to Prepare Fast Water Dissolving Tablets for Dutasteride

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Abstract

Objective: The aim of the study is to prepare fast water dissolving dutasteride tablets containing a pronisomal powder that yield niosomal dispersion of dutasteride upon dissolving in hot water. The niosomes derived from dissolved tablets may improve the dissolution and permeability of dutasteride since it is loaded in the niosomal vesicles and avoid the high cost and other disadvantages of the soft gelatin capsules commercially available. Method: Ten formulas of dutasteride proniosomal gels were prepared by coaservation method and niosomes derived from them were evaluated for their loading capacity, particle size, particle size distribution, zeta-potential and in-vitro drug release in order to determine the optimum type and quantity of proniosomal contents that will be used to prepare maltodextrin based proniosomal powder formulas which were evaluated and the optimum proniosomal powder formula was used to prepare dutasteride tablet. Results: Thickness, hardness, disintegration time and in-vitro drug release for the optimum dutasteride tablet T5 were 5.57±0.08 mm, 3.1±0.11 Kg/cm², 2.9±0.03 and reaches 100% release after 30 min. Particle size, polydispersity index (PDI), and zeta potential of niosomes derived from dissolving dutasteride tablet (T5) were ~263±3.8 nm, 0.225, and -5.43±0.436 mV Conclusion: This results indicating the contribution niosomes derived from proniosomal powder in improving the dutasteride solubility and gave higher dissolution rate compared to the conventional soft gelatin capsule of the same drug. Therefore presenting an oral dosage form that is more convenient and having all the advantage of tablets.

Keywords: Cholesterol, Dutasteride, Niosomes, Proniosomes, Span 60, and Tween 20.

Introduction

Dutasteride is a competitive inhibitor of isoenzymes 1 and 2 of 5 alpha-reductase which are intracellular enzymes responsible for the conversion of testosterone to 5-alpha-dihydrotestosterone (DHT). The main indication of dutasteride is for the treatment of benign prostate hypertrophy (BPH) in men with enlarged prostate and can be used in combination with tamsulosine (alpha blocker) to treat moderate to severe symptomatic BPH in men [1].

Dutasteride is practically insoluble in water (0.9 µg/ml) and marketed as a soft gelatin capsule in which dutasteride is dissolved in an organic solvent [2]. However, soft gelatin capsules having some problems like its high cost, limited margin of excipients used and needs specialized equipments [3]. Therefore, many techniques have been developed to improve solubility and dissolution of dutasteride that may improve the bioavailability of this drug. A solid dispersion of dutasteride was prepared by solvent evaporation method using hydrophilic carriers (Eudragit E) [4]. However, this method has two with drawals, first, the choice of the suitable solvent is difficult because of the high difference in polarity between the hydrophobic drug and the hydrophilic carrier. Second, there is a chance of phase separation during solvent evaporation that will prevent the formation of solid dispersion [5]. A powder dosage form of dutasterid was prepared by incubating it in hydroxypropyl-β-cyclodextrin nanostructures using supercritical antisolvent process [6].

For appropriate incubation of the drug inside the hydroxypropyl- β-cyclodextrin nanostructures, it should has a molecular weight less 250 gm/mole which could be unsuitable for dutasteride [7]. In addition, supercritical process is difficult to scale up because it needs a highly pressurized and
sophisticated equipment to get the final formulation. One of the most important techniques to improve the water solubility of some drugs is by incorporating them into liposomal vesicles. Liposomes are spherical particles consisted from phospholipids and relies on the fact that phospholipids interact with water to form spherical particles with a bilayer membrane [8] that can entrapped the hydrophobic drugs in this bilayer system [9].

Liposomes have some disadvantage including leakage of drug during storage, oxidation and hydrolysis of the phospholipids and difficulty in sterilization that limit their wide applications as a modern drug delivery system [10]. These issues making an urgent need to manipulate liposomes into more advanced drug delivery system like niosomes.

Niosomes are vesicles similar to liposomes in structure and physical properties prepared using surfactant. Niosomes preparation overcomes many technical problems associated with liposomes preparation like high cost, difficulties in sterilization [11]. Also it has a simple preparation method and more suitable for large scale production.

Niosomes drug delivery system may have some problems like aggregation or fusion of the vesicles, and leakage of the drug that limit its long term stability [12]. In addition, niosomes are available in liquid form only that make it inconvenient during transportation and storage. Proniosomes are dry formulations of water soluble carriers coated with a thin film of surfactants. Proniosomal powder yields aqueous niosomal dispersion upon simple agitation with hot water [12].

Proniosomes offer several advantages over simple niosomal formulation making them superior for oral drug delivery system, these advantages include that proniosomes are in a dry, free flow powder which is more convenient for further processing into unit dosage form like tablets, pellets, or capsules.

In addition, hydration of proniosomal powder yielding niosomal dispersion in much easier way and shorter time than niosomes obtained by thin film method [12]. The objective of work is to apply proniosomal powder technology to prepare fast water dissolving tablets for dutasteride that can yield niosomes upon dispersion in hot water that is swallowed by patient to improve its solubility, permeability, and drug dissolution that may improve its absorption.

Materials and Methods

Materials

Dutasteride powder [Hyperchem, Co., China], Cholesterol [BDH Co., UK], Span 60 [Sinopharm Co, China], Chloroform [BDH Co., UK], Tween 20 [Himedia, India], Maltodextrin [Segmaaldrich, Germany] for all the experiments, deionized Distilled water (DDW) was used.

Methodology

Preparation of Proniosomal Gel of Dutasteride

Proniosomal gel was prepared by using simple coacervation phase separation method. In this method, 0.5 mg of dutasteride, different types and molar ratio of surfactants and membrane stabilizer (cholesterol) were added into a glass tube (Table 1) and small quantity of ethanol (0.5 ml) was added and the opened-end of the tube was covered with a para film.

Then, the tube was placed in a water bath at 60-70 °C for 5 min until all the ingredients were dissolved and sonicated for 2 min. Then, 0.5 ml of phosphate buffer at pH 7.4 was added and the mixture further heated until a clear solution was formed, then upon cooling a proniosomal gel was obtained [13]. The niosomal vesicles were formed when the prepared proniosomal gel was hydrated with 10 ml of preheated phosphate buffer (80 °C) with simple agitation just prior to characterization.

Table 1: Composition of different dutasteride proniosomal gel formulas

<table>
<thead>
<tr>
<th>Formula number</th>
<th>Dutasteride (mg)</th>
<th>CH (mg)</th>
<th>T (mg)</th>
<th>S (mg)</th>
<th>CH:T:S molar ratio</th>
<th>Total CH: surfactant ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.5</td>
<td>24.2</td>
<td>150.4</td>
<td>-</td>
<td>0.5:1</td>
<td>0.5:1</td>
</tr>
<tr>
<td>F2</td>
<td>0.5</td>
<td>48.3</td>
<td>150.4</td>
<td>-</td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>F3</td>
<td>0.5</td>
<td>96.6</td>
<td>150.4</td>
<td>-</td>
<td>2:1</td>
<td>2:1</td>
</tr>
<tr>
<td>F4</td>
<td>0.5</td>
<td>144.9</td>
<td>150.4</td>
<td>-</td>
<td>3:1</td>
<td>3:1</td>
</tr>
<tr>
<td>F5</td>
<td>0.5</td>
<td>24.2</td>
<td>75.2</td>
<td>-</td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>F6</td>
<td>0.5</td>
<td>48.3</td>
<td>75.2</td>
<td>27.4</td>
<td>1:1:1</td>
<td>1:2</td>
</tr>
<tr>
<td>F7</td>
<td>0.5</td>
<td>72.5</td>
<td>75.2</td>
<td>27.4</td>
<td>2:1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>F8</td>
<td>0.5</td>
<td>32.1</td>
<td>51.1</td>
<td>18.3</td>
<td>2:1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>F9</td>
<td>0.5</td>
<td>32.1</td>
<td>51.1</td>
<td>18.3</td>
<td>2:1:1</td>
<td>1:1</td>
</tr>
</tbody>
</table>

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Preparation of Proniosomal Powder

The proniosomal powder is prepared by simple slurry method. A specific quantity of dutasteride, cholesterol, Tween 20 and span 60 (which is used in F10 proniosomal gel) is dissolved in 20 ml organic solvent mixture of chloroform and methanol in (2:1) ratio. The proniosomal solution is poured into a round bottom flask containing a specific quantity of maltodextrin. The organic solvents evaporated by rotating the round bottom flask under vacuum for 15-20 min at 42 °C until a free-flow powder is formed. The proniosomal powder is reserved in the disecator overnight to insure a complete evaporation of the organic solvent. The composition of different proniosomal powders (Table 2). The proniosomal powder is converted into niosomal suspension by adding 10 ml of preheated (80 °C) phosphate buffer (pH 7.4) prior to characterization [14].

Table 2: Composition of different proniosomal powders

<table>
<thead>
<tr>
<th>Formula NO.</th>
<th>Dutasteride (mg)</th>
<th>Cholesterol (mg)</th>
<th>Tween 20 (mg)</th>
<th>Span 60 (mg)</th>
<th>maltodextrin (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>0.5</td>
<td>24.2</td>
<td>37.6</td>
<td>13.7</td>
<td>76.5</td>
</tr>
<tr>
<td>P2</td>
<td>0.5</td>
<td>24.2</td>
<td>37.6</td>
<td>13.7</td>
<td>114</td>
</tr>
<tr>
<td>P3</td>
<td>0.5</td>
<td>24.2</td>
<td>37.6</td>
<td>13.7</td>
<td>152</td>
</tr>
<tr>
<td>P4</td>
<td>0.5</td>
<td>24.2</td>
<td>37.6</td>
<td>13.7</td>
<td>190</td>
</tr>
<tr>
<td>P5</td>
<td>0.5</td>
<td>24.2</td>
<td>37.6</td>
<td>13.7</td>
<td>209</td>
</tr>
<tr>
<td>P6</td>
<td>0.5</td>
<td>24.2</td>
<td>37.6</td>
<td>13.7</td>
<td>228</td>
</tr>
</tbody>
</table>

Preparation of Dutasteride Tablet from Dutasteride Proniosomal Powder

Dutasteride tablets were prepared using direct compression method. All the materials used to prepare the tablet (including P5 of dutasteride proniosomal powder which is equivalent to 0.5 mg dutasteride) were passed through sieve and then blended together for 15 min to insure a complete homogenization of the powder mixture. The quantity of Mg-stearate (lubricant) necessary to prepare dutasteride tablet is calculated according to the real number of tablet and mixed with the blended powder for 5 min [15]. The final powder is compressed into a tablet using tablet machine with 11 mm punch. The composition of different dutasteride tablets is shown in Table 3.

Table 3: Composition of different dutasteride tablets

<table>
<thead>
<tr>
<th>Formula NO.</th>
<th>Proniosomal powder</th>
<th>Microcrystalline cellulose</th>
<th>Crosspovidone</th>
<th>Crosscarmellose</th>
<th>Mg stearate</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>285</td>
<td>203.8</td>
<td>10</td>
<td>-</td>
<td>1.2</td>
</tr>
<tr>
<td>T2</td>
<td>285</td>
<td>188.8</td>
<td>25</td>
<td>-</td>
<td>1.2</td>
</tr>
<tr>
<td>T3</td>
<td>285</td>
<td>163.8</td>
<td>50</td>
<td>-</td>
<td>1.2</td>
</tr>
<tr>
<td>T4</td>
<td>285</td>
<td>203.8</td>
<td>-</td>
<td>10</td>
<td>1.2</td>
</tr>
<tr>
<td>T5</td>
<td>285</td>
<td>188.8</td>
<td>-</td>
<td>25</td>
<td>1.2</td>
</tr>
<tr>
<td>T6</td>
<td>285</td>
<td>163.8</td>
<td>-</td>
<td>50</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Characterization of Proniosomal Gel Derived Niosomes

Loading Capacity

The loading capacity of dutasteride loaded niosomes is estimated using centrifugation method. The niosomal dispersion is placed in a centrifuge and run at 14000 rpm. The niosomal vesicles precipitated and unloaded dutasteride is found in the supernatant layer. The concentration of dutasteride in the supernatant layer estimated by HPLC [16]. The loading capacity calculated using the following equation:

\[
\text{Loading capacity} (\%) = \left[ \frac{(C_t - C_f)}{C_t} \right] \times 100
\]
Where, $C_t$ is the total concentration of dutasteride and $C_f$ is the concentration of free dutasteride.

**Particle Size, Polydispersity Index (PDI), and Zeta Potential**

The concentrated niosomal suspension is opaque and milky-white. The sample is diluted with phosphate buffer at pH 7.4 by adding few drops of the suspension into 20 ml phosphate buffer and agitated gently. Then, the particle size and PDI is measured using dynamic light scattering (DLS) instrument [17]. The same device is used to measure the zeta potential using a unique cell provided with two electrodes.

**In-vitro Dissolution Test of Dutasteride Loaded Niosomes Prepared from Proniosomal Gel**

The in-vitro dissolution test of dutasteride is performed using rotary dissolution apparatus type II (the paddle type). The dissolution medium is 900 ml of 0.1 N HCl with pH 1.2 (simulated gastric fluid) that contains 2% w/v sodium dodecyl phosphate [18]. The paddle rotates at 50 rpm. The accurately weighted proniosomal gel, that contain 0.5 mg dutasteride, is converted into niosomes (by the same procedure explained previously) and added into the dissolution vessel, 3 ml sample is withdrawn from the dissolution medium at different time intervals (5, 10, 15, 30, 45, 60 min) and filtered using 0.11 μm filter syringe. The concentration of dutasteride in different samples are measured using HPLC with a mobile phase of acetonitrile: water in a ratio of (50: 50) and the flow rate is 1.5 mL per minute. The wave length used to detect dutasteride is 210 nm.

**Characterization of Proniosomal Powder**

The characterization of proniosomal powder involves the characterization of the features of proniosomal powder itself and the niosomes derived from proniosomal powder.

**Angle of Repose of Proniosomal Powder**

The angle of repose of the proniosomal powder was performed using the traditional funnel method. In this method, the funnel nozzle is centered above a horizontally placed circular paper, usually 2 cm above this paper. The proniosomal powder is poured into the funnel at a rate similar to that leaving the funnel nozzle [19].

The diameter and height of proniosomal powder cone is measured and the angle of is calculated using the following equation:

$$\tan \theta = \frac{H}{r}$$

Where, $\theta$ is the angle of repose, $H$ is the height of power cone, and, $r$ is the radius of the power cone

The angle of repose is correlated with the flow property according to USP parameters.

**Morphology of Proniosomal Powder**

For scanning electron microscopy (using electron dispersive spectroscopy SEM-EDS, the samples were loaded on sample stub using double side carbon tape and sprinkle the powder on it then tight all stubs on specimens holder after blowing to remove non-adhesive particles. The prepared samples were loaded on field emission scanning electron microscopy FE-SEM from zeiss supra 55 VP via air lock door depended on low voltage to exceed the coating technique and avoid charging using secondary electron detector SE2 [20].

**Morphology of Niosomes Derived from Proniosomal Powder**

For TEM, a copper grid hexagonal mesh were adhered to carbon tape on clean petri and liquid sample spread on grid and left for few min and loaded on TEM holder to image it with STEM detector [21].

**Loading Capacity, Particle Size, PDI, Zeta Potential and In-vitro Drug Release of Niosomes Derived from Proniosomal Powder**

Characterization of niosomes derived from proniosomal powder by these tests follow the same procedures used in characterization of niosomes derived from proniosomal gel.

**Characterization of Duasteridde Tablet**

The following tests were applied for the prepared tablets (T1-T6) as follow:

**Thickness Test**

Tablet thickness test is performed using Vernier caliper. In this test, the concaved end
of dutasteride tablet is placed between the arms of the device and tablet thickness is recorded. This procedure is performed for three tablets and the average thickness ± SD is calculated [22].

Hardness Test
The hardness test is performed using Monsanto hardness tester device. Dutasteride tablet is placed in a longitudinal aspect and the force required to break the tablet is recorded. The procedure is performed for three tablets and the average hardness ± SD is recorded in kg/cm² [22].

Friability Test
The friability test gives an indication about the tablet resistance to abrasion and chipping during packaging and shipping. The friability test is performed by weighing 20 tablets and placing them in the friabilator. The friabilator has acrylic drums with curves baffles. The friabilator rotates at 25 rpm for 4 min. After that, the dust is removed and the tablets are weighed. The highest acceptable weight loss not more than 1% from the original tablet weight [22].

Disintegration Test
The disintegration test is performed by placing one tablet in each transparent tube with 77.5 mm long of the disintegrator basket and placed in water at 80 °C (the media needed to prepare niosomes from proniosomal tablets). The time needed for disintegration of all tablet is recorded [22].

In-vitro Dissolution Test of Dutasteride Loaded Niosomes Derived from Dutasteride Proniosomal Tablet (T5) to the Commercially Available Soft Gelatin Capsule
In-vitro dissolution of dutasteride loaded niosomes derived from the proniosomal tablet is performed using the same US food and drug administration dissolution procedure described previously and compared with the dissolution of the drug from the marketed dutasteride soft gelatin capsule (Avodart®).

Drug-excipient Compatibility Studies of Dutasteride Tablet
The drug-excipient compatibility was performed using gas chromatography (GC-mass, Shimadzu GCMS QP 2010 Ultra). A standard solution of pure dutasteride in chloroform (50 µg/ml) is prepared and 1 ml of the standard solution is injected in the column (semi-polar 5MS with length 30 meter capillary tube and internal diameter of 0.25 mm with diffraction pore size of 0.25 µm, stationary phase inert CAP 5 and mobile phase is Helium 99.999%). The prepared tablet (T5) is dissolved in chloroform and filtered then injected in the column of the GC-mass and the mass spectra of the two samples were compared.

Results and Discussion
Characterization of Niosomes Derived from Proniosomal Gel
Different formulations of proniosomal gels were prepared (F1-F10) and evaluated to choose the optimum proniosomal content, the following parameters were evaluated:

Loading Capacity
Formulas F1-F5 were designed to study the effect of cholesterol on drug loading capacity of proniosomal gel-derived niosomes prepared from Tween 20 and cholesterol (Table 4). Drug loading capacity increases with increasing the quantity of cholesterol and reaches its maximum capacity when the quantity of cholesterol is equimolar to that of Tween 20 (F2), since, Tween 20 forms a stable bilayer system by hydrogen bonds with OH-terminal of cholesterol and cholesterol increases the stability and hydrophobicity of the bilayer system that increases the entrapment of dutasteride [23,24]. Further increase in cholesterol level above the equimolar quantity (F3 and F4) decreases drug loading capacity. This decrease in the drug loading capacity can be explained by the fact that cholesterol competes with dutasteride for the entrapment site in the hydrophobic domain of the bilayer system during surfactant assembling [25].

Decreasing the quantities of both cholesterol and Tween 20 (F5 contains half the quantity of F2 with reserving equal molar ratio) has no effect on drug loading capacity. Using cholesterol, Tween 20, and span 60 in equimolar ratio (1:1:1) results in the formation of new niosomes in which the bilayer system is a combination of the two surfactants stabilized by cholesterol where the hydrophilic head of span 60 forms hydrogen-bonds with the hydrophilic head of tween 20 as well as the hydrophobic tail of span 60 is bonded to the hydrophobic portion of the Tween 20 [26]. It was found that the
addition of span 60 in F5 (to give F6) had no effect on drug loading capacity. The best drug loading capacity was obtained when the quantity of cholesterol (in cholesterol, Tween 20, and span 60 combination) is equimolar to the total amount of surfactant (2:1:1) which is represented by F7. The increase in the quantity of cholesterol will accommodate the increased quantity of surfactants. This proves the fact that highest loading capacity is found when the quantity of cholesterol is equimolar to that of surfactant and this agreed with the reported data [27]. Further increase in the quantity of cholesterol above the equimolar ratio (as in F8) causes decrease in drug loading capacity similar to that observed in F3 and F4 (in comparison to F2). Formula F9 and F10 showed that decreasing the total quantity of cholesterol, Tween 20 and span 60 keeping the amounts in the same molar ratio for that of F7 had no significant effect on drug loading capacity (in comparison to F7). Therefore, F10 is the most feasible formula to be used for further study.

<table>
<thead>
<tr>
<th>Formula code</th>
<th>CH:T:S molar ratio</th>
<th>Total CH: surfactant ratio</th>
<th>% loading capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.5:1</td>
<td>0.5:1</td>
<td>46.6</td>
</tr>
<tr>
<td>F2</td>
<td>1:1</td>
<td>1:1</td>
<td>72.1</td>
</tr>
<tr>
<td>F3</td>
<td>2:1</td>
<td>2:1</td>
<td>35.4</td>
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<td>F4</td>
<td>3:1</td>
<td>3:1</td>
<td>31.5</td>
</tr>
<tr>
<td>F5</td>
<td>1:1</td>
<td>1:1</td>
<td>71.5</td>
</tr>
<tr>
<td>F6</td>
<td>1:1:1</td>
<td>1:2</td>
<td>71.7</td>
</tr>
<tr>
<td>F7</td>
<td>2:1:1</td>
<td>1:1</td>
<td>98.5</td>
</tr>
<tr>
<td>F8</td>
<td>3:1:1</td>
<td>1.5:1</td>
<td>58.3</td>
</tr>
<tr>
<td>F9</td>
<td>2:1:1</td>
<td>1:1</td>
<td>96.4</td>
</tr>
<tr>
<td>F10</td>
<td>2:1:1</td>
<td>1:1</td>
<td>97.4</td>
</tr>
</tbody>
</table>

Particle Size, Polydispersity Index (PDI), and Zeta Potential

The principle of particle size measurement by DLS is based on measuring the quantity of scattered light caused by the suspending particle moving by Brownian motion [28]. DLS of different formulations (F1-F10) showed a uniform bell-shaped peak which indicates a normal size distribution and reliable results (Fig. 1). The results (tablet 5) showed that formulas (F1-F4) have approximately similar mean particle size indicating that increasing the molar ratio of cholesterol (0.5, 1, 2, 3) has no significant effect on the mean particle size of the niosomes derived from proniosomal gel. Formula F5 and F2 also showed approximately similar mean particle size. The results also showed that incorporation of span 60 into the formulation (in combination with Tween 20 as a surfactants) caused an increment in the mean particle size of niosomal vesicles derived from proniosomal gel (F6-F10), since, span 60 has a large tail (18 aliphatic carbon chain compared with 12 aliphatic carbon chain in Tween 20) that will increase the width of the niosomal bilayer system [28].

![Fig. 1: Particle size distribution of niosomes prepared from proniosomal gel of F10](image)
All niosomes derived from proniosomal gel (F1-F10) have polydispersity index (PDI) less than 0.3 which is within the acceptable level [30]. The zeta potential of all formulas are comparably low, ranging between 0.852 to 5.86 mV, that could be attributed to absence of charge in all proniosomal gel ingredients, mainly due to the use of non-ionic surfactants. Proniosomes to be constituted (by adding them to a hot water) to produce niosomes just before use and there is no time to aggregate or coalescence and eliminate the need to add charged molecules such as dicetyl phosphate which is usually used in the direct preparation of niosomes in order to eliminate coalescence during storage that lead to dose variation.

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Mean particle size (nm)</th>
<th>PDI</th>
<th>Zeta-potential mV</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>136.2 ±1.4</td>
<td>0.208</td>
<td>0.852±0.104</td>
</tr>
<tr>
<td>F2</td>
<td>132.8 ±1.4</td>
<td>0.144</td>
<td>0.414±0.222</td>
</tr>
<tr>
<td>F3</td>
<td>130.8 ±2.07</td>
<td>0.165</td>
<td>0.627±0.098</td>
</tr>
<tr>
<td>F4</td>
<td>129.6 ±4.06</td>
<td>0.121</td>
<td>0.567±0.963</td>
</tr>
<tr>
<td>F5</td>
<td>131.6 ±3.7</td>
<td>0.132</td>
<td>0.546±0.238</td>
</tr>
<tr>
<td>F6</td>
<td>290.9 ±4.2</td>
<td>0.101</td>
<td>-1.51±0.924</td>
</tr>
<tr>
<td>F7</td>
<td>234.0 ±3.8</td>
<td>0.220</td>
<td>-4.43±0.657</td>
</tr>
<tr>
<td>F8</td>
<td>230.8 ±5.6</td>
<td>0.197</td>
<td>-3.43±0.738</td>
</tr>
<tr>
<td>F9</td>
<td>239.7 ±3.2</td>
<td>0.232</td>
<td>-4.83±0.783</td>
</tr>
<tr>
<td>F10</td>
<td>234.3 ±5.8</td>
<td>0.225</td>
<td>-5.86±0.164</td>
</tr>
</tbody>
</table>

In-vitro Dissolution Test of Dutasteride Loaded Proniosomal Gel

In-vitro dissolution test is performed using a dissolution medium consist of 0.1 N HCl containing 2% SDS.

The presences of SDS in the dissolution medium insure complete dissolution of the dutasteride released from proniosomal gel-derived niosomes.

The results showed that the dissolution of dutasteride from niosomes derived from proniosomal gel (F1-F5) gave a rapid release (~90% in 15 min). This is attributed to the presence of large head of Tween 20 that permits rapid penetration of the dissolution media into the niosomes vesicles [29].

The results also showed that the addition of span 60 (F6-F10) had no significant difference on dutasteride release except a slight decrease in the drug after 15 min (~80%) in comparison to that of formulas F1-F5 since span 60 may increase the hydrophobicity of the niosomes derived from proniosomal gel (F6-F10). Although all the formulas reach 100% release after 30 min.

Characterization of Proniosomal Powder

Angle of Repose of Proniosomal Powder

Angle of repose is regarded as the most common parameter used to reveal the flow property of powder.

Table 6 showed the flow properties of all the prepared proniosomal powder (P1-P6).

Formulas P1 and P2 had a very poor flow property due to the presence of low quantities of the hydrophilic carrier in these formulas which resulted in a very greasy proniosomal powder that increases the frictional and cohesiveness forces that prevent the slipping of the powder particle on each other resulting in a high angle of repose [31].

While formula P4-P6 showed a good flow property due to the presence of a high quantity of maltodextrin which improved the flow property of proniosomal powder since it offers more hydrophilic carrier available to adsorb niosomal components through its surface area [32].

<table>
<thead>
<tr>
<th>Formula NO.</th>
<th>Niosomes: maltodextrine ratio</th>
<th>Flow property</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>1:1</td>
<td>Very poor</td>
</tr>
<tr>
<td>P2</td>
<td>1:1.5</td>
<td>Very poor</td>
</tr>
<tr>
<td>P3</td>
<td>1:2</td>
<td>Passable</td>
</tr>
<tr>
<td>P4</td>
<td>1:2.5</td>
<td>Good</td>
</tr>
<tr>
<td>P5</td>
<td>1:2.75</td>
<td>Good</td>
</tr>
<tr>
<td>P6</td>
<td>1:3</td>
<td>Good</td>
</tr>
</tbody>
</table>

Table 5: The mean particle size, PDI, and zeta-potential of different proniosomal gel formulations

Table 6: Flow properties of different proniosomal powder formulation
Morphology of Proniosomal Powder

Fig. 2 showed the morphological changes in maltodextrin surface before and after loading with the proniosomal components. Pure maltodextrin had a high porous structure making it capable to adsorb more components on its surface (high loading capacity) [32] and can be used even with high surfactant to carrier ratio that cover the surface of maltodextrin indicating a successful coating.

Fig. 2: Maltodextrin powder, A: Before loading B: After loading with proniosomal components (P5)

Morphology of Niosomes Prepared from Proniosomal Powder

The shape of niosomes derived from proniosomal powder is demonstrated using transmission electron microscopy (TEM). The proniosomal powder derived niosomes appears as a uniform spherical particles as shown in Fig. 3, indicating mainly unilaminar niosomal vesicles which may give a higher surface area leading to higher drug dissolution.

Fig. 3: TEM spectrum for a niosomal vesicle derived from proniosomal powder (P5)

Drug Loading Capacity, Particle Size, PDI, Zeta Potential and in-vitro Drug Release of Niosomes Derived from Proniosomal Powder

Table 7 showed the loading capacity of dutasteride in the proniosomal powder-derived niosomes, where, formulas P1-P3 showed lower loading capacity since they contain less quantity of maltodextrin (the lowest quantity in formula P1) causing the presence of insufficient surface area available for complete adsorption. Increasing the quantity of maltodextrin (P4-P6) causes a significant increase in the drug loading capacity due to a complete absorption of niosomal components on maltodextrin surface.
Table 7: % loading capacity of different proniosomal powders

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Niosomes: carrier ratio</th>
<th>% loading capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>1:1</td>
<td>43</td>
</tr>
<tr>
<td>P2</td>
<td>1:1.5</td>
<td>62.1</td>
</tr>
<tr>
<td>P3</td>
<td>1:2</td>
<td>76.1</td>
</tr>
<tr>
<td>P4</td>
<td>1:2.5</td>
<td>95.2</td>
</tr>
<tr>
<td>P5</td>
<td>1:2.75</td>
<td>95.3</td>
</tr>
<tr>
<td>P6</td>
<td>1:3</td>
<td>96.1</td>
</tr>
</tbody>
</table>

The mean particle size of niosomes derived from proniosomal powder of formula P4-P6 is found to be ~263±3.8 nm which is non-significantly different from that of niosomes derived from proniosomal gel formula (F10) which contain the same quantity of Tween 20, span 60 and cholesterol. The slight difference could be attributed to the high stress conditions (heat and sonication) used to prepare proniosomal gel [33].

The zeta potential of formulas P4-P6 is found to be -4.43±0.638 to -5.43±0.436 mV indicating the stability of the prepared formulas. In-vitro dissolution of proniosomal powder-derived niosomes of P5 and P6 had no significant difference from that obtained from proniosomal gel-derived niosomes (F10) due to their similar niosomal components. In addition, the presence of hydrophilic additives could increase the supersaturation of dutasteride after its release from proniosomes powder-derived niosomes and prevent aggregation after release.

From all the results obtained formula P5 is selected for preparation of tablet dosage form of dutasteride.

Characterization of Dutasteride Tablets

Thickness Test

The thickness of different dutasteride tablets is shown in Table 8 and no significant difference is observed. All the prepared tablets have acceptable thickness that makes it easily packed.

Hardness Test

The results of hardness tests for the entire prepared dutasteride tablet (T1-T6) is shown in Table 8 and proved that as the quantity of microcrystalline cellulose (MCC) is increased the hardness of tablets increased (where T1 showed hardness more than T2 and T3).

The same results observed with T4-T6 (where T4 containing higher MCC). Therefore, formulas T1, T4 and T5 showed acceptable hardness within the acceptable range (3-5 kg/cm²) [34].

Friability Test

Friability test gives an idea about the ability of tablets to withstand transportation and handling stresses. The results of friability test of different dutasteride tablets is shown in Table 8 and showed that formula T1, T2, T4 and T5 had passed the friability test.

Disintegration Test

The disintegration time for water dispersable tablets should be within 3 min [34]. The disintegration medium used is hot water at 80 °C at which the dutasteride proniosomal tablet dissolved and converted into niosomal suspension. Table 8 revealed that formulas T5 and T6 had disintegration time within the acceptable range (< 3 min) indicating that using cross carmellose (as a super disintegrant) is more effective than crosspovidone on the disintegration of tablets. Since, T5 contains the maximum allowable quantity of super disintegrant (5%) of tablet formulation in addition it gave acceptable thickness, hardness and friability, therefore, it is selected for further studies.

Table 8: Tablet thickness, hardness, and friability and disintegration time of the prepared dutasteride

<table>
<thead>
<tr>
<th>Tablet code</th>
<th>Tablet thickness</th>
<th>Tablet hardness kg/cm²</th>
<th>Friability test</th>
<th>Disintegration time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>5.64±0.04</td>
<td>3.6±0.12</td>
<td>Passed</td>
<td>7.5±0.11</td>
</tr>
<tr>
<td>T2</td>
<td>5.55±0.07</td>
<td>2.8±0.13</td>
<td>Passed</td>
<td>5.3±0.06</td>
</tr>
<tr>
<td>T3</td>
<td>5.47±0.11</td>
<td>1.9±0.15</td>
<td>Not passed</td>
<td>3.5±0.04</td>
</tr>
<tr>
<td>T4</td>
<td>5.69±0.05</td>
<td>4.1±0.21</td>
<td>Passed</td>
<td>5.3±0.06</td>
</tr>
<tr>
<td>T5</td>
<td>5.57±0.08</td>
<td>3.1±0.11</td>
<td>Passed</td>
<td>2.9±0.03</td>
</tr>
<tr>
<td>T6</td>
<td>5.51±0.09</td>
<td>2.3±0.16</td>
<td>Not passed</td>
<td>2.3±0.03</td>
</tr>
</tbody>
</table>
Drug-excipient Compatibility Study of Dutasteride Tablet

The drug-excipient compatibility was performed using gas chromatography (GC-mass). Same peak was observed in both chromatograms (standard dutasteride solution & the prepared dutasteride tablet) at 21min as well as same mass spectra were recorded for both (Fig. 5) indicating that no changes observed for dutasteride in the prepared tablets revealing its compatibility with the added materials in its formula.

Fig. 5: Mass spectrum of dutasteride (A): Mass spectrum of dutasteride standard solution (B): Mass spectrum of dutasteride tablet

Comparison of the Selected Formula (T5) with the Marketed Dutasteride Soft Gelatin Capsule (Avodart®)

The in-vitro release of dutasteride from niosomes derived from dutasteride tablet (T5) and the marketed soft gelatin capsule of dutasteride (Avodart®) is shown in Fig. 6 which revealed that the dissolution from formula (T5) is higher than the commercially available Avodart® indicating the contribution of niosomes in improving the solubility and dissolution of the poorly soluble drug.

Fig. 6: The in-vitro release of niosomes derived from dutasteride tablet (T5) and the marketed soft gelatin capsule of dutasteride (Avodart®)

Conclusion

The results prove the possibility of improving the solubility and the dissolution rate of dutasteride by incorporating it in niosomes derived from proniosomal powder from which a fast dissolving tablets for dutasteride is prepared.

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References


