ABSTRACT:
The aim of this study was to investigate the effect of various Prosolv® co-processed excipients in the manufacture of different grades of fast melt tablets (FMTs). Caffeine was chosen as a model drug. Caffeine FMTs were prepared by direct compression using Prosolv® based excipients: Prosolv® SMCC 50, Prosolv® SMCC 90, Prosolv® SMCC HD90, Prosolv® ODT, Prosolv® Easytab Nutra and Prosolv® Easytab SP. Caffeine FMTs were evaluated for weight, thickness, hardness, friability, wetting time (WT), in-vitro disintegration time, and in-vitro dissolution studies. The selected Caffeine FMT was compared with oral commercial tablets (Stay Awake Caffeine Alertness Aid®, Equate, USA) for their antioxidant activities and their impact on reproductive organs of male rats. All Caffeine FMTs were within the pharmacopeial limits for weight, and content. All formulae had acceptable friability percentage (<1%) except Prosolv® SMCC HD based formula. Prosolv® Easytab Nutra based formula showed superiority over Prosolv® Easytab SP and Prosolv® ODT regarding WT and DT. Furthermore, Prosolv® Easytab Nutra based formula gave comparable functionality to its analogous formulae based Prosolv® SMCC 50 and Prosolv® SMCC 90 with superior advantages regarding simplicity of manufacture and the potential minimizing of undesirable issues segregation by reducing the number of steps during production of tablets. The data concluded that the Prosolv® co-processed excipients are promising carriers for Caffeine FMT designed for modulating male reproductive hormone reproductive values and oxidative stress with having greater benefits of dosage form which, in turn, increase compliance.

KEYWORDS: Caffeine, FMTs, silicified microcrystalline cellulose, antioxidant, reproductive.

INTRODUCTION:
Tablets are the most preferred dosage form of pharmaceutical experts because they can offer accurate dosing and provide good patient compliance. However, tablets have some drawbacks, as dysphagia and suffocation risk, especially for geriatric, unconscious and pediatric patients (1). Fast melt tablets (FMTs) help to overcome such obstacles, when become easily swallowed after being disintegrated in the buccal cavity, with no need of water or even chewing. The FMTs are also known as fast dissolving, fast dispersing or orally disintegrating tablets as they rapidly dissolve or melt, and/or quick disintegrating tablet (2). The prompt disintegration provides the main advantage of FMTs as their fast onset of action with better bioavailability and a comparatively high degree of patient compliance and acceptance for cases needing rapid delivery for APIs (3).
The most favorable approach for tablet preparation is by direct compression (DC) as it eliminates other tedious steps represented in dry and wet granulation processes. The majority of the individual excipients that are available failed to fulfill the requirements of functionality, therefore creating the opportunity for the development of new high-functionality excipients to further simplify the straightforward DC process (4).

Co-processing of excipients is a promising method used in the preparation of tablet dosage forms, in which combinations of two or more excipients that possess performance advantages that cannot be attained using a physical mixture of the same combination of excipients (5). Examples include improved flow properties and dissolution stability (6), enhanced tablet strength and compactibility (7), increased resistance to lubricant sensitivity (8) and decreased disintegration time (9). So, co-processed excipients have provided an excellent prospect for developing high functionality excipients by developing new chemical excipients, new grades of existing materials, and new combinations of existing materials (10). This developed class of excipients contains diluents, in addition to, the other excipients such as binders, glidants, disintegrants, and recently, lubricants.

The co-processed silicified microcrystalline cellulose Prosolv® SMCCis the spray-dried product of a combination of 98% microcrystalline cellulose (MCC) as a dry binder, and 2% colloidal silicon dioxide (CSO) as a glidant. It is available in three grades: Prosolv® SMCC 50, Prosolv® SMCC90 and Prosolv® SMCC HD90 which corresponds to a mean particle size of 60 µm, 110 µm, and 110 µm, and a bulk density of ~0.30 g/cm³, 0.30 g/cm³ and 0.44 g/cm³, respectively (11). Prosolv®Easytab Nutra that contains MCC, CSD, croscarmellose as a disintegrant, palm kernel oil saturated as a lubricant, diacetyltartraric and fatty acid esters of glycerol (DATEM) as an emulsifier. Prosolv®Easytab SP contains MCC, CSD, sodium starch glycolate as a disintegrant, and sodium stearyl fumarate as a lubricant. Prosolv® ODT contains MCC, CSD, crospovidone as a disintegrant, mannitol and fructose.

Caffeine is a dietary compound which is widely present in many fruits, vegetables and coffee. Its consumption is large because it is present in most popular coffee and tea worldwide and high caffeine containing energy drinks are widely consumed by adolescents (12). Over the years, accumulating suggestions has indicated a potential antioxidant action for Caffeine based on its ability to scavenge reactive oxygen species (ROS) (13-15). ROS are highly reactive oxidizing agents, with one or more unpaired electrons belongs to the group of free radicals. Most common of those having potential implications in reproductive biology. Although none of ROS should be detected in semen of normal men, they can be detected in the semen of 40% of infertile men (16). ROS did not only include oxygen radicals but also a subclass of nitrogen containing compounds known as reactive nitrogen species (RNS) such as nitric oxide that appear to play a significant role in the reproduction and fertilization. (17, 18).

The aim of this work to formulate Caffeine FMTs using different grades of Prosolv® co-processed excipients by direct compression and comparing their action with the commercial oral Caffeine product (Stay Awake Caffeine Alertness Aid®, Equate, USA) and to study the oxidative stress and reproductive function in male rats.

Materials:
Caffeine was purchased from Titan Biotech Limited, India. Prosolv® SMCC HD90, Prosolv® ODT, Prosolv®Easytab Nutra, and Prosolv®Easytab SP were obtained as a gift from JRS pharma GmbH& Co. KG (Rosenberg, Germany). Other chemicals and solvents were obtained from Sigma-Aldrich (MO, USA). All chemicals used were of the highest analytical grade.

Methods:
Formulation of Caffeine FMTs.
Six formulations of 100 mg Caffeine FMTs were prepared (F1-F10) by direct compression (total tablet weight 200mg) using Prosolv®based co-processed excipients: Prosolv® SMCC 50 (F1), Prosolv® SMCC 90 (F2), Prosolv® SMCC HD90 (F3), Prosolv®Easytab SP (F4), Prosolv®Easytab Nutra (F5), Prosolv® ODT (F6). The mixture of powders was compressed into 8 mm concave tablets of 200 mg by using a single punch tablet machine set (Royal Artist, Mumbai, India).

Evaluation of the prepared Caffeine FMTs:
Weight and thickness variation:
Weight variation was done according to British Pharmacopeia (19). For each formulation, the weights of twenty randomly selected tablets were measured separately then compared with the mean weight, and the standard deviation (SD) was calculated. The thickness of Caffeine FMTs was carried out using a micrometer screw gauge (103-259, Mitutoyo Corp., Japan), and the results were expressed as mean thickness ± SD (Table 1).

Friability test:
Ten tablets of each formulation were weighed and placed in a Friabilator (Mumbai, India) at 25 rpm for 4 min. The tablets were reweighed then the percent friability was calculated according to the following equation (20):

\[
\text{Friability (\%)} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100
\]

Initial Weight -----(1)
Hardness test:
The hardness of five tablets from each formulation was measured using a digital hardness tester (Creve Coeur, MO) and was expressed in Kg (21). Then the mean and SD values were calculated (Table 1).

Drug content:
The test was done on twenty individual formulae. Each formulation was crushed and dissolved in simulated saliva fluid (SSF, pH 6.8) (22). The solution was then filtered, and the absorbance was spectrophotometrically (23) measured at λmax (273 nm) through a pre-constructed standard calibration curve using a UV/VIS spectrophotometer (Model UV-1601 PC, Shimadzu Corp., Kyoto, Japan), (Table 1).

Wetting time test:
A piece of tissue paper folded twice was immersed in a small petri dish containing 6 mL of 2% w/v dye (methylene blue) aqueous solution. A tablet was placed on the surface of the paper and the time required for the dye solution to reach the upper surface of the tablet was accurately measured as the wetting time (WT) (24). The WT was recorded for each formulation as triplicate and the results were expressed as mean ± SD, (Table 1). Any value exceeds 3 min was considered as a slow WT.

In-vitro disintegration time test:
Each formula was dropped into a beaker containing accurate 5 mL of SSF (pH 6.8) at 37±0.5°C. The time (sec) necessary for complete tablet disintegration was observed visually and recorded (25). In-vitro disintegration time (DT) was done in triplicate for each formula and the results were expressed as mean ± SD, (Table 1).

In-vitro dissolution studies:
In-vitro dissolution studies were performed using a USP paddle apparatus type II at 50 rpm (Copley scientific, NE4-COP, Nottingham, NG42JY, UK). The used dissolution medium was 900 mL of SSF (pH 6.8) at 37±0.5°C (26). Aliquots of the dissolution media (5 ml) were withdrawn at accurately measured intervals (2, 4, 6, 10, 15, 20, 25, 30, 45 and 60 min) and compensated immediately with an equal volume of fresh medium at the same temperature. These samples were filtered through 0.22 µm membrane filters, suitability diluted and analyzed at spectrophotometrically at 273 nm. Drug concentration was expressed as cumulative percent drug dissolved. In-vitro dissolution for each formula was carried out in triplicate and the results were expressed as mean±SD. Then drug dissolution of different FMTs was compared with the commercial product (Stay Awake Caffeine Alertness Aid®, Equate, USA). For further characterization and comparison of drug release profiles, the independent parameter, the dissolution efficiency at 1hr (DEt %) was used as a measure of the total amount of drug released during the test period and was calculated using the following equation (27):

\[
DE_t\% = \frac{\int_0^t y \, dt}{100} \times 100
\]

Where \( y \) is the drug percent dissolved at time \( t \).

Pharmacodynamics study of selected Caffeine FMTsin comparison to marketed product in male rats:
Reproductive function study in male rats was used to investigate the effect of selected Caffeine FMT with commercial Caffeine tablets and study the effect of two different dosage forms on the oxidative stress and reproductive organ functions in male rats.

The method adopted by Akomolafe et al. (28) was performed. Thirty male albino Wistar rats weighing between 180 and 200 g were used. The rats were allowed to adapt to the new environment for two weeks before the experiment. They were kept under standard condition (inverted 12-hr light/dark cycles), constant temperature (22±2°C) and humidity (70%±4%) with access to standard feed and water ad libitum. After two weeks of acclimatization, the rats were divided into five groups (n=6) using completely randomized design with six rats in each group. First group (gp I) was used as a control group which was normal rats that received water from gavage throughout the experiment. The second group (gp II) was used to determine the effect of the Stay Awake® with equivalent dose 50 mg/kg body weight (BW) of Caffeine orally. While the last group received sublingually equivalent dose 50 mg/kg body weight (BW) of selected Caffeine FMT (F5). Each tablet was added under the tongue of rats by means of tweezers. The tablet was static and when moved it returned to the tongue. All the animals were treated for seven successive days. Daily feed intake was monitored, and body weight (BW) was taken both at the beginning and at the end of the experiment.

Blood was withdrawn from the retro-orbital sinus of each rat using non-heparinized capillary tubes, allowed to coagulate and then centrifuged at 3000 rpm for 10 min. The separated sera were used for hormonal assays. Afterward, animals were sacrificed by decapitation and reproductive organs were carefully removed and cleared of adhering tissues. The right testis from each rat was weighted in gram (g) after being washed with ice-cold saline for biochemical analysis.

The testicular tissue (50 mg/ml) was homogenized in ice-cold 0.05M potassium phosphate buffer (pH 7.4) to produce homogenate. The resulting homogenate was centrifuged at 5000 rpm and 4°C for 15 min, and the
supernatant was subsequently separated for oxidative stress estimation.

Also, hormonal assay was done where blood samples were collected, and the sera were separated and kept at 20°C till determination of testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) using enzyme-linked immunosorbent assay (ELISA) kits purchased from (Sigma-Aldrich, MO, USA) with catalog numbers SE120089, SE120071, and SE120057, respectively. All procedures were performed according to manufacturers’ instructions.

In addition to, biochemical estimation of testicular oxidative stress where total nitrite and nitrate content as a measure of nitric oxide (NOx) was assessed according to the method of (29). Lipid peroxides formation was determined in rat testis (10% w/v normal saline) by estimating the content of thiobarbituric acid reactive substances (TBARS) using malondialdehyde (MDA) as a standard according to the method described by (30). Superoxide dismutase (SOD) activity was determined according to the method described by (31). Catalase (CAT) activity was estimated using hydrogen peroxide as substrate according to the method of (32).

RESULTS AND DISCUSSION:
Evaluation of Caffeine FMTs:
Weight and thickness variation:
The range of the weights of twenty Caffeine FMTs was found to be from (194.64±1.27 to 198.76±1.96mg). While the average thickness was found to be from (2.967±0.052 to 3.283±0.075 mm). Such reproducibility of the results confirmed the consistency of thickness and weights for all formulae (Table 1).

Friability test:
All Caffeine FMTs did not break or show any capping, cracking or chipping during the friability test. All tablets showed acceptable friability percentage less than 0.92% except F3 had unacceptable friability percentage >1% (19), (Table 1).The F3 contained Prosolv® SMCC HD 90 that had a higher density of SMCC and might decrease die filling volume thus received lower force, as its hardness was additionally low (3.89Kg).

Hardness test:
The compression force used for all formulae was fixed, so the change in hardness of different FMTs observed in Table 1 could be attributed only to the type of tablet composition (33). All Caffeine FMTs showed hardness values ranged from (3.89 ±0.46 to 4.51±0.86 kg). This range is optimum for FMTs (34) as it can provide enough strength and porosity at the same time to ensure rapid wetting and disintegration of the tablets.

Drug content:
Table 1, showed that all formulae complied with the pharmacopeial limits (19), as the average drug content of the sample of tablets ranged from (95.15 to 99.86 % of the label claim).

Wetting time test:
Wetting time (WT) has an important influence that gives an indication of disintegration properties of the tablets (35). Wetting is closely related to the internal structure of tablet and to the hydrophilicity of the excipients (36).

From the results of WT shown in Table 1, it was revealed that all FMTs showed acceptable WT whereas, Prosolv® SMCC 50, Prosolv® SMCC 90, and Prosolv® SMCC HD 90 based formulae had short WT (13.65 ±0.76s, and 14. 42 ±0.44s, 11.81 ±0.33s, respectively). This was attributed to that Silicon Dioxide (SiO2) interacts with cellulose possibly through hydrogen bonding and dipole-dipole interactions and thus, SMCC shows a five-fold bigger surface than microcrystalline cellulose, which provides better disintegration and ensures better flow properties (11, 37).

Prosolv® Easytab Nutra based formula (F5) gave the relatively lower wetting time (12.46 ±0.05s) if compared with WT of Prosolv® Easytab SP based formula,F4 (15.08±0.69s) due to the combination of both diacryltartaric and fatty acid esters of glycerol (DATEM) as emulsifier and croscarmellose sodium as superdisintegrant. Croscarmellose sodium is very hydrophilic (38) and has rapid swelling with minimal gelling and excellent wicking capabilities related to its characteristic porous structure which helps in maintaining capillary flow upon contact with water and thus result in rapid disintegration (39). While Prosolv®Easytab SP contains Sodium starch glycolate whose the disintegration mechanism involves swelling on contact with aqueous medium but accompanied by gelling that can possibly occlude the pores in the tablet preventing further penetration of water into the tablet matrix hence the comparative delay observed in the WT and DT of these tablets (40) if compared with F5.

While Prosolv® ODT based formula (F6) showed relatively longer WT (36.40±0.66s). This was attributed to the complicated matrix of Prosolv® ODT, that containscrospsovidone, in addition to mannitol and fructose that increase the strength of its matrix and thus increased its WT, despite of the presence of crospsovidone(41).Generally, results revealed that formulae with crospsovidone as superdisintegrant had acceptable WT. This was assigned to its rapid water absorbing nature involving both capillary and swelling mechanisms (42, 43).
Disintegration time:
Slow or incomplete disintegration of tablets leads to low bioavailability of the drug (Kucinskaite et al. 2007). The compendial standards (19) state that Disintegration time (DT) for oral disintegrating tablets should be within 3 min. However, many critics find that a maximum disintegration time of 3 min for any tablet is too long and that the presence of a gritty tablet in the patient’s mouth for 3 min would be unpleasant and uncomfortable (Shoukri et al., 2009). Along with the literature, the disintegration time of oral fast dissolving tablets is 1 min or less, preferably about 30 s or less (Kuno et al., 2005). The results of DT of prepared FMTs were shown in Table 1. It was observed that all formulae based on SMCC had short disintegration time, as mentioned before, due to the wettability, hydrophilicity and swelling efficiency of its MCC content as well as the exceptionally increased surface area of SMCC due to its SiO₂ content which provides better disintegration and ensures better flow properties (11, 37).

Prosolv® SMCC HD 90 based formula (F3) had shorter DT (6.84 ±0.69s) than DT of Prosolv® SMCC 50 (F1), and Prosolv® SMCC 90 (F2) based formulae (8.33 ±0.57s, and 7.9 ±0.85s, respectively) that indicated the lesser strength of bonds in Prosolv® SMCC HD 90 (44).
It was revealed that Prosolv® Easytab Nutra based formula (F5) gave shorter DT (7.67 ±0.56s) if compared with DT of Prosolv® Easytab SP formula (F4) which gave DT (16.62 ±0.52s). Croscarmellose sodium can be seen to rapidly disintegrate into more or less uniform fine particles, while tablets formulated with sodium starch glycolate appeared to disintegrate much more slowly into more or less uniform coarse particles (45). As mentioned before, croscarmellose sodium has rapid swelling with minimal gelling and excellent wicking capabilities which helps in maintaining capillary flow upon contact with water and thus result in rapid disintegration (Rowe et al. 2009). While the disintegration mechanism of Sodium starch glycolate involves swelling on contact with an aqueous medium but accompanied by gelling that can possibly occlude the pores in the tablet preventing further penetration of water into the tablet matrix hence the delay observed in the DT of this tablet (Pabari and Ramtoola 2012). Prosolv® ODT based formula (F6) had reasonably slower DT (27.51 ±0.95s). Prosolv® ODT consists of crospovidone, MCC, in addition to mannitol which was probable to be the reason for the delay of the DT of F6.

In-vitro dissolution studies:
Tablet disintegration is required for FMTs, but dissolution is the most essential parameter for drug absorption from tablets (45). Figure 1 represents the in vitro release profile of Caffeine from different FMTs. The amount of Caffeine dissolved after 10 min (Qtₐ) was used as a parameter to compare different FMTs (Table 1).

The data presented that the results of dissolution were in accordance with the obtained results of the WT and DT. All Prosolv® based formulae (F1-F6) exhibited high dissolution rate (more than 90% release of the drug) with dissolution efficiency at 1 hr (DE₁) (more than 90%) and this was relatively better than dissolution rate of the commercial product (Stay Awake Caffeine Alertness Aid®, Equate, USA), especially after 10 min (60.28±3.34%) with (DE₁=79.02%). whereas Prosolv® SMCC 50, Prosolv® SMCC 90, Prosolv® SMCC HD 90 based formula had (Qt₁) (91.67±1.7, 90.37±0.51, and 90.05±6.30, respectively) and their DE₁ were (92.4%, 91.1% and 90.22%, respectively), in addition to, Prosolv® Easytab SP, Prosolv® Easytab Nutra, and Prosolv® ODT based formulae exhibited (Qt₁) (92.42±2.25%, 93.47±3.88%, and 90.25±4.61%, respectively) with DE₁ (92.77%, 91.14 and 91.7, respectively). The fast dissolution rates of formulations with SMCC probably could be referred to the self-disintegration property of microcrystalline cellulose (46).

The above-mentioned findings showed that Prosolv® SMCC HD based formula failed to pass friability test, although, this formula exhibited the superior results in WT and DT. In addition to, Prosolv® Easytab Nutra had advantage over Prosolv® Easytab SP and Prosolv® ODT respective to WT and DT. Prosolv® SMCC50, Prosolv® SMCC 90, and Prosolv® Easytab Nutra showed the acceptable criteria regarding hardness, friability, WT, DT, and dissolution rate; however, Prosolv® Easytab Nutra reduces the number of steps during production of tablets into mixing, compression, and coating. Also, the superdisintegrant and lubricant are already co-processed with the rest of the Prosolv®Easytab components. Thus, only one phase of mixing is involved to prepare final blends of the drug for direct compression. While the Prosolv® SMCC-based formulae will continuously require a second mixing phase to lubricate the final blends. In addition, concerns associated with the number of ingredients and varying particle size of the ingredients are expected to be significantly reduced with Prosolv® Easytab Nutra. These include segregation, mixture homogeneity, and quality attributes of tablet in terms of content uniformity.

Reproductive Function Study:

Body weight and absolute testis weight:
The results showed that following the Caffeine treatment of the rats either by FMTs or by commercial tablet, the body and testes weights of all the groups significantly (p < .05) increased during the period of seven days when
compared with the normal rats (Table 2). This increase may be owed to increase of androgen availability (47). Testicular weight is the most prime assessment of spermatogenesis where increases in testicular weight are frequently relevant to the number of spermatozoa existing in the tissue (48).

Figure 1: In-vitro dissolution profile of different Caffeine FMTs and commercial Caffeine tablets.

Table 1: Evaluation of Caffeine FMTs using Prosolv® based co-processed excipients.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight variation (mg ±SD)</th>
<th>Thickness (mm ±SD)</th>
<th>Friability (%)</th>
<th>Hardness (kg ±SD)</th>
<th>Drug content (%)</th>
<th>wetting time (sec ±SD)</th>
<th>Disintegration time (sec ±SD)</th>
<th>Q10 ± SD</th>
<th>DE1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>195.4±1.61</td>
<td>2.96±0.052</td>
<td>0.77</td>
<td>4.02±0.51</td>
<td>96.68±2.85</td>
<td>13.65±0.76</td>
<td>8.33±0.57</td>
<td>91.67±1.7</td>
<td>92.4</td>
</tr>
<tr>
<td>F2</td>
<td>197.12±2.65</td>
<td>3.11±0.075</td>
<td>0.6</td>
<td>4.25±0.53</td>
<td>97.23±2.241</td>
<td>14.42±0.44</td>
<td>7.94±0.85</td>
<td>90.37±0.51</td>
<td>91.1</td>
</tr>
<tr>
<td>F3</td>
<td>194.64±1.27</td>
<td>3.28±0.075</td>
<td>1.96</td>
<td>3.89±0.46</td>
<td>95.15±3.57</td>
<td>11.81±0.33</td>
<td>6.84±0.69</td>
<td>90.05±0.63</td>
<td>90.22</td>
</tr>
<tr>
<td>F4</td>
<td>196.8±2.46</td>
<td>3.06±0.051</td>
<td>0.65</td>
<td>4.4±0.57</td>
<td>96.65±2.81</td>
<td>15.08±0.69</td>
<td>16.62±0.57</td>
<td>92.42±2.25</td>
<td>92.77</td>
</tr>
<tr>
<td>F5</td>
<td>195.04±2.40</td>
<td>3.21±0.054</td>
<td>0.92</td>
<td>4.51±0.86</td>
<td>95.5±3.69</td>
<td>36.4±0.66</td>
<td>27.51±0.95</td>
<td>90.25±4.61</td>
<td>91.7</td>
</tr>
<tr>
<td>F6</td>
<td>198.76±1.96</td>
<td>3.15±0.054</td>
<td>0.67</td>
<td>4.34±0.12</td>
<td>99.86±2.11</td>
<td>12.46±0.05</td>
<td>7.67±0.56</td>
<td>93.47±3.88</td>
<td>91.14</td>
</tr>
</tbody>
</table>

Q10: The amount of Caffeine dissolved after 10 min. DE1: Dissolution efficiency at 1hr.

Table 2: Effects of selected Caffeine FMT on body and absolute testis weights in male rats.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group number</th>
<th>Gp I</th>
<th>Gp II</th>
<th>Gp III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain (g ±SD)</td>
<td></td>
<td>9.0±1.26</td>
<td>17.83*±1.72</td>
<td>15.83*±1.72</td>
</tr>
<tr>
<td>Weight gain (% ±SD)</td>
<td></td>
<td>5.83*±0.9</td>
<td>11.09*±1.33</td>
<td>9.44*±1.06</td>
</tr>
<tr>
<td>Absolute testis weight (g±SD)</td>
<td></td>
<td>0.81±0.31</td>
<td>1.86*±0.31</td>
<td>1.81*±0.51</td>
</tr>
</tbody>
</table>

Values are the means ± SD of 6 rats in each group; *p<0.05, where * represented a significant difference from the control group (Gp I).

Reproductive hormones:

In males, LH stimulates the Leydig cells of the testis and is responsible for the production of testosterone, a male hormone that has an indispensable effect on spermatogenesis by its both endocrine activity and intratesticular activity (49). While FSH regulates the growth of seminiferous tubules and maintenance of spermatogenesis. It is vital for the function of Sertoli cells, which in turn are essential for sperm cell maturation. Together testosterone and FSH are needed for optimal testicular development and maximal sperm production. Insufficient secretion of LH or FSH can induce a failure of gonadal function (hypogonadism). This case is reported in males as failure in production of normal numbers of spermatozoa (50).

LH and FSH levels were considerably (p <0.05) increased with a concomitant noteworthy increase in testosterone level observed in rats treated with either Caffeine FMTs or commercial tablet (Table 3). This indicates a promising impact of Caffeine on male reproductive function in vivo thereby contributing to the normal testicular functions (51).

Table 3: Effects of selected Caffeine FMT on reproductive hormones of male rats.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group number</th>
<th>Gp I</th>
<th>Gp II</th>
<th>Gp III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum free Testosterone (ng/ml ±SD)</td>
<td></td>
<td>1.41±0.55</td>
<td>3.36±0.79</td>
<td>3.08±0.76</td>
</tr>
<tr>
<td>Serum FSH (mIU/ml ±SD)</td>
<td></td>
<td>0.93±0.44</td>
<td>2.31*±0.71</td>
<td>2.41*±0.54</td>
</tr>
<tr>
<td>Serum LH (mIU/ml ±SD)</td>
<td></td>
<td>0.63±0.36</td>
<td>1.46*±0.41</td>
<td>1.53±0.51</td>
</tr>
</tbody>
</table>

Values are the means ± SD of 6 rats in each group; *p<0.05, where * represented a significant difference from the control group (Gp I).

Testicular antioxidant status:

It was suggested that NO modulates sexual and reproductive functions therefore, the chronic inhibition of NO can affect sperm function (52). Also, NO can act as a free radical scavenger, inactivating and even inhibiting production of superoxide anions which cause lipid peroxidation, a process which causes diminishing...
of spermatozoa functional (53, 54). The result of the current study revealed that Caffeine administration led to a noteworthy increase (p < 0.05) of testis NO levels which in turn may improve male reproductive function in treated rats either by Caffeine FMTs or commercial tablet when compared with normal rats. In the male reproductive system, the balance between antioxidant defense system and production of free radicals (ROS) has been proposed to have an important role to maintain the regulation of normal sperm function/fertility (55). Oxidative damage to spermatozoa in several cases of oligospermia mostly reflects a decline in the antioxidant capacity, which in turns can increase the deleterious effects of the ROS (56). Furthermore, the testicular SOD, and CAT activities levels increased significantly (p < 0.05) in the treated rats either by Caffeine FMTs or commercial tablet with a concomitant decrease in MDA production, a maker of lipid peroxidation (Table 4). These observations could indicate the antioxidant power of Caffeine that is reflected in the sufficient antioxidant status of the testes to efficiently prevent oxidative stress in the treated rats either by Caffeine FMTs or commercial tablet (54).

Table 4: Effects of selected Caffeine FMT on the antioxidant status of the testis in male rats.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group number</th>
<th>Gp I (µmol/mg ±SD)</th>
<th>Gp II (µmol/mg ±SD)</th>
<th>Gp III (µmol/mg ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testis NOs</td>
<td></td>
<td>38.83 ±8.84</td>
<td>98.17* ±14.03</td>
<td>86.67* ±12.1</td>
</tr>
<tr>
<td>Testis MDA</td>
<td></td>
<td>20.17±6.5</td>
<td>9.01±2.01</td>
<td>9.66±4.63</td>
</tr>
<tr>
<td>Testis SOD</td>
<td></td>
<td>38.67 ±6.77</td>
<td>75.02* ±14.06</td>
<td>79.95* ±12.21</td>
</tr>
<tr>
<td>Testis Catalase</td>
<td></td>
<td>102.51 ±10.95</td>
<td>166.21* ±14.74</td>
<td>165.7* ±30.72</td>
</tr>
</tbody>
</table>

Values are the means ± SD of 6 rats in each group; p<0.05, where * represented a significant difference from the control group (gp I).

CONCLUSION:
In the present study, Caffeine FMTs were successfully prepared by using different co-processed excipients by direct compression method. Prosolv® ODT showed relatively prolonged Wt than Prosolv® EasytabSP and Prosolv® Easytab Nutra. Prosolv® Easytab Nutra is a multi-functional co-processed excipient that showed similar functionalities as a direct compression aid to Prosolv® SMCC based formula, with enhancing process-related quality attributes and minimizing undesirable mixing of additional excipients as a lubricant in final blend.

The Caffeine FMT formula improved the reproductive hormone levels and antioxidant status in the testes as the same extent of the commercial drug (Stay Awake®) with an over advantages of our formulations as easy in handling and administration without need of water so it is a useful for people suffering from difficulty in swallowing and for geriatrics.

REFERENCES:


