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ABSTRACT SUMMARY
Megestrol acetate (MGA) is chemotherapy treatment for breast cancer, ovarian carcinoma and prostate carcinoma. Megestrol acetate nanoparticles (MGA NPs) were successfully prepared using nano spray dry technique for improving the relative oral bioavailability. When compared to MGA, the spray dried MGA NPs demonstrated reduced size, favorable reduction in PXRD signal improved bioavailability. The relative oral bioavailability of Sucrose Palmitate NP was also increased by up to 2.4 fold as calculated in AUC in the fasting state as compared to the original. The data presented here support sucrose palmitate containing MGA nanoparticles as a promising formulation approach for oral delivery of megestrol acetate.

INTRODUCTION
Megestrol acetate is primarily used as treatment for breast cancer, prescribed to treat ovarian carcinoma and metastatic prostate carcinoma. According to the biopharmaceutical classification system (BCS), MGA is a biopharmaceutic class II drug, which has low water solubility and high permeability. Previous studies with low water-soluble drugs have shown that particle size reduction leads to an increase in dissolution rate and a higher oral bioavailability.

In this study, the solid dispersion of MGA NPs were prepared using a nano spray dryer. The influence of process parameters on the size and physicochemical properties of the spray dried MGA NPs were investigated by scanning electronic microscopy (SEM) and powder X-ray diffraction analysis (PXRD). The oral bioavailability of MGA NPs were evaluated in mice.

EXPERIMENTAL METHODS
MGA NPs were fabricated with different polymers, excipients and solvent. MGA and polymer mixtures were dissolved in solvent and fed to a BUCHI, B-90, Nano spray dryer: inlet temperature, 100° C; outlet temperature, 50–55° C, gas flow rate, 133 L/min.(Table 1).

The morphology of MGA NPs were observed using field emission scanning electron microscopy (FESEM; S-4800, Hitachi High-Technologies Co., Japan). MGA NPs were coated with gold and palladium using a vacuum evaporator and examined using an SEM at 20 kV accelerating voltage.

The X-ray diffraction patterns of MGA NPs were obtained on a PANalytical X’pert PRO. The samples were run over the most informative range from 5° to 40° of 20.

The relative oral bioavailability of MGA NPs were compared with the commercial product, Megace© oral suspension (Bristol-Myers Squibb Co.) in mice. Studies used 23-26g male Balb/c. Blood samples were collected immediately at 20min, 40min, 1h, 2h, 4h, 6h, 12h and 24h. Plasma was separated by centrifugation at 4 °C, 13,000 rpm for 10min, analyzed by LC-MS/MS (AB SCIEX, 3200 Q TRAP).

The relative bioavailability—i.e., maximum plasma drug concentration (Cmax) and area under curve (AUC)—of the test formulations was assessed and compared with that of Megace® oral suspension.

RESULTS AND DISCUSSION

<table>
<thead>
<tr>
<th>Components</th>
<th>Weight (mg)</th>
<th>Contain (%)</th>
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<tbody>
<tr>
<td>Active pharmaceutical ingredients (API)</td>
<td>Megestrol acetate</td>
<td>500</td>
</tr>
<tr>
<td>*Exipient</td>
<td>Sucrose palmitate</td>
<td>500</td>
</tr>
<tr>
<td>Slip Modifier</td>
<td>Magnesium stearate</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Silicon dioxide</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>1030</td>
<td>100</td>
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</table>

*Exipient: Sucrose Palmitate, PVP25, Eudragit S100, Captisol, HP-β-CD, Eudragit RS100

Table 1. Components of the spray dried MGA NPs.
In this study, we evaluated MGA NPs prepared by using nano spray drying. (Table 1) Formulations were prepared using a 1:1 drug to polymer ratio with excipients: e.g. Sucrose Palmitate, PVP 25, Eudragit S 100, Captisol, HP-β-CD, Eudragit RS 100. SEM images of the spray dried MGA NPs are shown in Figure 1. Most of the produced MGA nanoparticles demonstrated particle sizes ranged between 0.1 μm and 1 μm (Figure 1).

The PXRD patterns of the parent MGA and the MGA NPs are displayed that the peak corresponding to MGA crystals disappeared completed which is favorable for rapid dissolution (Figure 2).

Figure 3. Plasma concentration profiles of MGA after oral administration of Megace® oral suspension and the spray dried MGA NPs.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Megace Suspension</th>
<th>Sucrose Palmitate-NP</th>
<th>PVP25-NP</th>
<th>Eudragit S100-NP</th>
<th>Captisol-NP</th>
<th>HP-β-CD-NP</th>
<th>Eudragit RS100-NP</th>
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</thead>
<tbody>
<tr>
<td>AUC (mg/hr/mL)</td>
<td>9926.49</td>
<td>24020</td>
<td>15547</td>
<td>15698</td>
<td>16476</td>
<td>13142</td>
<td>5118</td>
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<tr>
<td>Cmax (ng/mL)</td>
<td>1053.8</td>
<td>2687.2</td>
<td>1792.33</td>
<td>2716.3</td>
<td>1694.33</td>
<td>1932.5</td>
<td>535.16</td>
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<tr>
<td>Tmax (h)</td>
<td>1.4</td>
<td>1.22</td>
<td>0.86</td>
<td>0.5</td>
<td>1.15</td>
<td>0.67</td>
<td>1.53</td>
</tr>
<tr>
<td>Relative Bioavailability</td>
<td>1</td>
<td>2.4</td>
<td>1.54</td>
<td>1.58</td>
<td>1.63</td>
<td>1.32</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Table 2. Pharmacokinetic parameters and relative bioavailability

The relative oral bioavailability of the spray dried MGA NPs were increased when compared to Megace® oral suspension, with exception, Eudragit RS100_NP. Sucrose palmitate containing nanoparticle had an increase in AUC (area under the curve) by 2.4 fold and Cmax, Tmax were 2687 ng/ml, 1.22 hour, respectively (Table 2). The data presented here support oral bioavailability was affected by the type of polymer.

CONCLUSION

MGA NPs with diameters of 0.1 μm ~ 1 μm, were prepared using nano spray dry technique. MGA NPs with sucrose palmitate can provide higher oral bioavailability than Megace® oral suspension. Based on the results presented here, significant reduction in particle size and crystallinity resulted in increased oral bioavailability. Also, MGA nanoparticles with various excipients gave distinct oral bioavailability profiles.

REFERENCES

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