Critical attributes for a generic nanosuspension development: physical properties along with *in vitro* release.

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**ABSTRACT SUMMARY**
The abstract summarizes the challenges faced by generic companies in developing a nanosuspension in order to develop a bioequivalent product. The bioequivalence (BE) study recommended for the drugs acting on central nervous system (CNS) are usually to be conducted on patients, since it involves a major risk not only to the health but also to the safety of the patients, it is important to ensure equivalence (physical as well as *in vitro*) before proceeding ahead for BE study. The challenges faced by the generic company, as a consequence of BE failure is an additional dilemma. Thus, it is important to gain sufficient confidence with respect to the comparability in the *in vitro* parameters including dissolution of test product to reference product and/or by using a suitable *in vivo* animal studies prior to BE study.

**INTRODUCTION**
A long acting intramuscular nanosuspension containing drug “A” has been designed to be used for CNS disorder. The suspension consists of drug nanoparticles, surface modifier, buffer, chelating agent, pH modifier, suspending agent and diluent. The study underlines the importance of physical properties of the formulations along with the *in vitro* release profile to maintain the desired long term plasma profile *in vivo*. Different parameters of the formulations like particle size distribution, zeta potential, pH, osmolality, surface modifier content and dissolution release were monitored and the corresponding *in vivo* plasma profile in dogs for all the formulation were evaluated. The study showed that various factors are important for achieving a similar *in vivo* release.

**EXPERIMENTAL METHODS**
Nanosuspension test formulations (DRL 01, DRL 02) comprising drug “A” and suitable excipients were prepared by various processes and their physical properties were noted. Innovator formulations have been procured from an US pharmacy store. Particle size distribution (PSD) and zeta potential were measured by using Malvern Zetasizer. *In vitro* drug release study was performed in an USP apparatus II containing 0.001N HCl with 0.489 (% w/v) Tween 20 in a volume of 900mL as dissolution media at 50 rpm. A single dose, parallel study in Beagle dogs (n= 5), was performed in a three arm study, in comparison to the innovator. Pharmacokinetic analysis was done by non compartmental model using Pheonix 6.3. In addition to this, an *in vitro in vivo* relationship has been established.

**RESULTS AND DISCUSSION**
The physical properties of the prepared nanoparticulate suspensions along with the innovator have been shown in Table 1. Even though similar PSD of the formulations with the innovator was characterized, they gave different dissolution profiles in the release media (Fig 1). The dissolution in the release media has very important relation with the drug release *in vivo*.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ref</th>
<th>DRL 01</th>
<th>DRL 02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>100.7</td>
<td>102.0</td>
<td>101.0</td>
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<tr>
<td>Related Substances</td>
<td>0.24</td>
<td>0.15</td>
<td>0.12</td>
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<tr>
<td>pH</td>
<td>7.16</td>
<td>7.039</td>
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<td>Osmolality (mOsm/kg)</td>
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<td>290</td>
<td>277</td>
</tr>
<tr>
<td>Zeta Potential (mV)</td>
<td>-18.6</td>
<td>-15.6</td>
<td>-8.6</td>
</tr>
</tbody>
</table>

Table 1. Physical attributes of reference (Ref) and the prepared test products (DRL 01, DRL 02).

Percentage released *in vitro* is found to have a proportional relationship with the percentage drug absorbed *in vivo* (Fig. 2) as shown in Levy’s Plot (Fig. 3). Apart from dissolution, role of zeta...
potential, surface modifier content and osmolality also were highlighted in impacting the release of drug in vivo along with the stability of the product.

CONCLUSION
The physical properties of the nanosuspension, in addition to the in vitro dissolution are very important in deciding the bioavailability of the drug in vivo from long acting intramuscular suspension. Along with the in vitro parameters, Beagle dog model can be used for evaluating the in vivo performance of the prepared formulations in comparison to the innovator prior to a BE study.

REFERENCES

ACKNOWLEDGMENTS
The authors would like to acknowledge Dr. Reddy’s Laboratories for providing assistance and support for this study.