Development of an oily sustained release depot formulation in a prefilled syringe

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ABSTRACT SUMMARY
In this study, we evaluated the effect of formulation factors on the functional properties of prefilled syringes, for an oil-based sustained release formulation. It was found that the type of oil used, as well as presence of other excipients directly affected the functional properties of the product. A similar impact was also seen on the functional properties of the prefilled syringe employed for drug administration.

INTRODUCTION
Sustained release of poorly soluble drugs can be achieved using a number of approaches such as polymeric systems (either degradable or non-degradable), mechanical systems (implantable pumps) or oil-based depots. Oily depots provide an advantage of being fully biodegradable, while not forming toxic or acidic degradation products at site of injection. Oily depots have been employed in a number of marketed products, including Testosterone depot, Haloperidol decanoate depot etc. Typical release profiles last over 2-4 weeks, depending on the type of oil used\textsuperscript{1}.

Prefilled syringes represent an attractive option for fill-finish of injectable sustained release products. Sustained release formulations are designed to reduce frequency of injections, and improve patient compliance. Prefilled syringes serve to improve patient compliance by easing the administration process.

In this study, we evaluated a prefilled syringe container-closure system for an oil-based injectable formulation. Oil-based formulations create challenges for prefilled syringes, such as, high viscosity, syringeability issues, and potential interactions that can alter the stopper properties. This study serves as a case study for testing of important formulation parameters that can affect the operation of the product in a prefilled syringe format.

EXPERIMENTAL METHODS
Various formulations of the drug were prepared in combination of oil (sustained release agent) and a co-solvent (release modifier). All excipients were of compendial grade, wherever available. Viscosity was measured using a Brookfield viscometer. Syringeability was measured by utilizing the Poiseuille equation for the pressure differential across a needle as the formulation is pushed out.

\[ \Delta P = \frac{8QL\eta}{pr^4} \]

where \(\Delta P\) is the pressure across the needle, \(Q\) is the injection speed, \(\eta\) is the viscosity of the formulation and \(r\) is the radius of the needle\textsuperscript{2}.

Lead formulations were filled in a BD Hypak glass prefilled syringe (Becton Dickenson, Franklin Lakes, NJ). The effect of formulation factors on functional properties of the syringe such as piston breakaway force and glide force were measured using an Instron device.

RESULTS AND DISCUSSION
Various types of oils were tested to formulate the poorly soluble drug, including castor oil and cottonseed oil. Cosolvents tested included ethanol as well as aromatic alcohols.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{syringeability.png}
\caption{Effect of viscosity of the formulation on syringeability}
\end{figure}
The type of oil used as well as the type and quantity of cosolvent directly affected the viscosity of the formulation. As can be seen in Figure 1, this in turn impacted the syringeability of the product.

Table 1. Critical operating parameters for the oily formulations for prefilled syringe functionality.

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Viscosity (cS)</th>
<th>Syringeable</th>
<th>Intron 1 mL</th>
<th>Intron 5 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HyaLgan</td>
<td>284</td>
<td>3.94</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Control 1</td>
<td>90</td>
<td>3.71</td>
<td>3.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Bar-2(b)</td>
<td>211</td>
<td>8.02</td>
<td>6.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Bar-12</td>
<td>283</td>
<td>12.85</td>
<td>6.9</td>
<td>8.4</td>
</tr>
<tr>
<td>Castor Oil</td>
<td>512</td>
<td>25.12</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Control 2</td>
<td>150</td>
<td>3.00</td>
<td>NP</td>
<td>NP</td>
</tr>
</tbody>
</table>

NP = not performed. "Hg. Speed = 25.0 cm/min. Hg. Speed = 129 mm/min. Hg. Speed = 75 mm/min.

Table 1 provides the critical parameters that were measured to understand the effect of formulation on the functionality and operation of the formulation in a prefilled syringe format. Comparison was done against a viscous formulation, HyaLgan, and an oil vehicle, Castor oil. Surprisingly, Syringeability of HyaLgan did not correlate with the high viscosity. This may be due to high shear properties of hyaluronic acid that make the gel flowable despite high viscosity. This demonstrates the importance of syringeability measurement as opposed to only viscosity testing. The presence of higher amounts of cosolvents (Formulation Bax 2B) had improved syringeability properties as compared to those with higher amounts of oils. It was also seen that the force required to syringe a formulation also depends on the volume. All the lead formulations were assessed to be syringeable at or below 3 mL volume.

Finally, piston operating force was measured for various formulations filled in BD Hypak glass prefilled syringes. As can be seen in Figure 2, a direct correlation was observed between the syringeability trend and the piston operating force for the prefilled syringes. Formulations that were less syringeable also required higher amounts of piston operating forces in the actual product configuration. Syringe functional properties would be a part of longer term stability studies to ensure that the piston operating force remains within an acceptable range.

**Figure 2.** Effect of formulation on piston operating forces for the prefilled syringe

**CONCLUSION**

Prefilled syringes are a preferred container closure system for delivery of sustained release formulations, due to ease of administration in an alternate setting (such as home). However, this format adds more complexities, as compared to the conventional vial format. This paper provides a case study of the interplay between formulation development and fill-finish configuration development. It is essential for the two activities to occur simultaneously to develop an effective product. In this specific case, an effective formulation in prefilled syringe was developed by manipulating the oil:cosolvent ratio of the oily depot formulation.

**REFERENCES**