Improved long acting drug delivery: What are the technologies?

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What are the long-acting technologies?

- Gastric residence device
- Vaginal ring
- Microarray / microneedle patch (theoretical)
- Broadly neutralizing monoclonal antibodies
- Implant
- Injectable drug
Broadly neutralising monoclonal antibodies (bNAb)

Passive immunity mediated by disruption of the interaction of the envelope spike (Env) with CD4 receptors.

At least 9 bNAbs in clinical development that target either the CD4 binding site, V3 loop, V1/V2 loop or gp41 membrane-proximal external region (MPER).

Potential application for prevention and therapy.

Resistance to monotherapy has led to investigation of combinations of bNAbs targeting non-overlapping sites.

Changing specific bNAb amino acids increases binding to the neonatal Fc receptor (FcRn), promoting endosomal recycling and extending serum half-life.

Accordingly, bNAbs have been developed for once every 2-month administration.
**bNAbs:** endosomal recycling to extend half-life

Specific amino acid changes within the Fc region increase FcRn binding affinity: Thr250, Met252, Ser254, Thr256, Thr307, Glu380, Met428, His433, and Asn434.
Subcutaneous implant: systemic delivery examples

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Material</th>
<th>Size (D, L)</th>
<th>Dose</th>
<th>Duration</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norplant®</td>
<td>Levonorgestrel</td>
<td>Silicone</td>
<td>2.4, 34 mm</td>
<td>6 x 36 mg</td>
<td>&lt; 5 years</td>
<td>Contraception</td>
</tr>
<tr>
<td>Jadelle®</td>
<td>Levonorgestrel</td>
<td>Silicone</td>
<td>2.5, 43 mm</td>
<td>2 x 75 mg</td>
<td>&lt; 5 years</td>
<td>Contraception</td>
</tr>
<tr>
<td>Implanon® / Nexplanon®</td>
<td>Etonogestrel</td>
<td>Polyethylene vinyl acetate (PEVA)</td>
<td>2, 40 mm</td>
<td>68 mg</td>
<td>&lt; 3 years</td>
<td>Contraception</td>
</tr>
</tbody>
</table>

- Requires highly potent drug because most of the format consists of the implant itself.
- The only reversible approach to systemic long-acting delivery (but biodegradable implants also exist).
- Other examples for localised drug delivery (e.g. intratumour or intraocular).
- Much recent interest in development of antiretroviral implants (mainly TAF and EFdA).
- Other investigators focusing on implantable drug delivery devices.
Long-acting injectables / parenterals: brief history

Using Pubmed search term: "long acting injectable" OR "long acting parenteral" OR "long acting depot"
Long acting injectables / parenterals (LAI/LAP)

- **Intramuscular**
  - Oil depot
  - Polymer microsphere
  - Aqueous particle suspension

- **Subcutaneous**
  - Polymer microsphere
  - Aqueous particle suspension
  - In situ-forming gel

- **Transdermal (theoretical for LA)**
  - Microarray / microneedle patch

Layers:
- Epidermis
- Dermis
- Subcutaneous
- Muscle
- Bone
### Long-acting injectables: examples

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration (weeks)</th>
<th>Dose (mg)</th>
<th>Drug loading (mg /ml)</th>
<th>Formulation</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>2</td>
<td>120</td>
<td>12.5</td>
<td>Microspheres</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Respiridone*</td>
<td>4</td>
<td>120</td>
<td>150</td>
<td>In situ forming gel</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>4</td>
<td>380</td>
<td>95</td>
<td>Microspheres</td>
<td>Opioid addiction</td>
</tr>
<tr>
<td>Olanzapine pamoate</td>
<td>4</td>
<td>405</td>
<td>150</td>
<td>Dispersion</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>4</td>
<td>300</td>
<td>100</td>
<td>Oil depot</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>4</td>
<td>100</td>
<td>25</td>
<td>Oil depot</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Benzathine penicillin</td>
<td>4</td>
<td>1800</td>
<td>450</td>
<td>Dispersion</td>
<td>Rheumatic Fever</td>
</tr>
<tr>
<td>Leuprolide acetate</td>
<td>24</td>
<td>45</td>
<td>120</td>
<td>In situ forming gel</td>
<td>Androgen ablation</td>
</tr>
<tr>
<td>Leuprolide mesylate*</td>
<td>24</td>
<td>50</td>
<td>?</td>
<td>Dispersion</td>
<td>Androgen ablation</td>
</tr>
<tr>
<td>Aripiprazole lauroxil</td>
<td>8</td>
<td>675</td>
<td>280</td>
<td>Dispersion</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Rilpivirine*</td>
<td>8</td>
<td>1200</td>
<td>300</td>
<td>Dispersion</td>
<td>HIV</td>
</tr>
<tr>
<td>Paliperidone Palmitate</td>
<td>12</td>
<td>525</td>
<td>150</td>
<td>Dispersion</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>13</td>
<td>150</td>
<td>150</td>
<td>Dispersion</td>
<td>Contraception</td>
</tr>
<tr>
<td>Cabotegravir*</td>
<td>12</td>
<td>400</td>
<td>200</td>
<td>Dispersion</td>
<td>HIV</td>
</tr>
<tr>
<td>Testosterone undecanoate</td>
<td>12</td>
<td>1000</td>
<td>250</td>
<td>Oil depot</td>
<td>Hypogonadism</td>
</tr>
</tbody>
</table>
Oil depot formulations

- Existing oil depot formulations involve IM delivery and provide exposure between 4 and 12 weeks after administration.
- High drug loading is usually achieved through formation of a prodrug to increase oil solubility.
- Commonly used oils include sesame, peanut, castor or coconut oil.
- Excipient selection for enhancing solubility, reducing viscosity or providing local anaesthesia.
- Must be administered slowly and commonly associated with injection sight pain that can persist for up to 3 months.
Polymer microspheres

- Usually administered intramuscularly as a microparticle suspension.
- Compatible with water soluble and insoluble drugs.
- Usually low drug-loading as most of the formulation is composed of polymers to control drug release.
- Initial release of drug at surface of the polymer but subsequent hydration results in virtually no drug release over first 3 weeks.
- Release then occurs through gradual polymer erosion. Finally, bulk erosion occurs with virtually no remaining drug.

Surface desorption → Surface erosion → Bulk erosion
In situ-forming gel

- An organic solution of polymer is combined with a solution or suspension of drug particles.
- Directly compatible with water soluble or insoluble drugs,
- Following administration, organic solvent dissipates and endogenous water infiltrates the injection site.
- Depot formation is triggered by polymer precipitation due to aqueous insolubility.
- Cross-linking of polymer traps the drug (or drug particles) within the depot site.
- Subsequent erosion of the polymer controls drug release from the depot.
Aqueous suspension

- Examples for intramuscular and subcutaneous administration, and the most successful injectable approach so far.
- Numerous examples for schizophrenia and contraception, as well as rilpivirine and cabotegravir.
- Achieves the highest drug loading of all existing technologies, and better tolerated than oil depot formulations.
- Constitutes a suspension of drug (or prodrug) particles (nano or low micron).
- Excipients require careful selection.
- Wet bead milling most successful to date.
Summary of long-acting therapies

Caveat: Some literature defines polymer microspheres and in situ-forming gels as implants
Conclusions

• Long acting drug delivery surprisingly dates back to the early 1950s.
• There are now multiple technologies being explored for long-acting medicine delivery across indications.
• Ultimate technology selection depends upon drug physical and pharmacological properties.
• Opportunities for reversibility are only currently afforded by certain implant technologies, but these require higher potency than available for most antiretroviral drugs (only near-term opportunities are in PreP).
• Aqueous suspensions have proven most successful to date
  • Highest drug loading of all technologies
  • Better tolerated than oil depot formulations
  • wide near-term opportunities expected
  • Restricted to water-insoluble drugs (prodrug derivatisation may be an option for NRTIs)