DRUG DELIVERY and NANOSTRUCTURING: DIVERGENT EFFECTS

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pSivida Inc.
Evolution of pSivida’s Drug Delivery Systems

1st Generation

2nd Generation

3rd Generation

4th Generation
DME

- Affects 1m in US
- Leading cause of vision loss in people under 65
- Laser therapy (burns to retina) limited efficacy
- No FDA approved drug treatments
- US Market estimated $1.5-4B

Iluvien Status

- Phase III clinical trials in approx. 1,000 patients
- NDA given Priority Review
- Received CRL December 2010
- Positive 36 month data released in Feb, subgroup analysis in May
- Resubmitted May 2011
- Potential approval in Q4 2011
Efficacy in Patients with Chronic DME
ILUVIEN Side Effects

Intraocular Pressure (IOP) > 30mm Hg
3 Years All Patients: 14.1% risk
18.4% Iluvien vs 4.3% control
4.8% required procedure
3 Years Chronic DME: 9.4% risk
14.8% Iluvien vs 5.4% control
5.2% required procedure

Cataract
34% of patients in trial had already undergone cataract surgery
Approx. 85% of low dose patients developed cataract

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New Generation Drug Delivery Technologies

- Fully bio-erodible
- Potential to deliver drugs, peptides and proteins
- Very promising preliminary data
BioSilicon: A highly porous material

1 cm$^3$ of BioSilicon™
i.e. sugar cube

Total surface area equivalent to 2 tennis courts

If the columnar pores were Stacked the length would measure 6 million miles
BioSilicon Technology:
Stabilization of amorphous forms
Enhanced dissolution and Bioavailability of poorly soluble molecules

Tethadur Systems:
Protein Adsorption
Sustained Release Anti-Bodies
Drug Loaded BioSilicon

BioSilicon

Unprocessed API

API and BioSilicon

API in BioSilicon

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Indomethacin in BioSilicon

DSC Analysis

- A. Crystalline Indomethacin
- B. Physical Mixture
- C. BioSilicon™ Co-formulation

XRD Analysis

- A. Crystalline Indomethacin
- B. BioSilicon™
- C. Physical Mixture
- D. BioSilicon™ Co-formulation

FTRI Analysis

- Crystalline Indomethacin
- Amorphous Indomethacin
- BioSilicon™ co-formulation
Stability of Amorphous Indomethacin

Time 0

Weeks at 40°C/75% RH
Indomethacin in BioSilicon

Time 0

6 month at 40°C/ 75% RH
Stabilization of Amorophous Form

- **a-polymorph**
  - 20% (w/w) drug loading
  - Drug molecule = 4.8Å at longest dimension
  - Drug layer = 22Å
  - Drug layer is 4 molecules thick
  - Insufficient volume to allow recrystallisation

- **γ-polymorph**
  - a=9.3Å
  - b=11.0Å
  - c=9.7Å

Formulations:
- Indomethacin
- BioSilicon™

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Indomethacin Dissolution

Supersaturation

Indomethacin (μg/mL)

Time (minutes)

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Indomethacin Oral Bioavailability

![Graph showing Indomethacin levels over time for different formulations]

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Indomethacin I.V.</th>
<th>BioSilicon Co-formulation</th>
<th>Indocid®</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>n/a</td>
<td>2.75 ± 0.65</td>
<td>0.56 ± 0.31</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (µg/ml)</td>
<td>n/a</td>
<td>2.48 ± 0.38</td>
<td>6.46 ± 0.52</td>
</tr>
<tr>
<td>$AUC_{0-24h}$ (h*µg/ml/mg)</td>
<td>66.92 ± 6.73</td>
<td>35.83 ± 1.95</td>
<td>66.98 ± 2.62</td>
</tr>
<tr>
<td>$F$ (%)</td>
<td>n/a</td>
<td>53.54 ± 2.91</td>
<td>100.1 ± 3.9</td>
</tr>
</tbody>
</table>

Sprague-Dawley rates (n=3)
Tethadur System

- Fully bioerodible
- Microparticulate (< 10 µm)
- Nanostructured
- Can be tailored to adsorb and release proteins
Protein Adsorption

1. Pore Size (Å) | Adsorption (µg/mg) | K (µM)
--- | --- | ---
60 | 299.2 | 0.238
150 | 257.1 | 0.107
250 | 251.1 | 0.069
500 | 105.8 | 0.030

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Effect of Pore Size on Protein Release Rate

![Graph showing the effect of pore size on protein release rate over time.](attachment:graph.png)
In-Vitro Release Rate of “real” Protein

Avastin Release Profile

- Formulation 1
- Formulation 2

Avastin Cumulated Amount (µg)

Time (days)

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Nano-structuring can maintain target molecules in amorphous form

Effect on release a function of elimination of lattice energy versus creation of agent/wall interaction

Agent/wall interaction adjustable allowing release rate to be controlled