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The proper use of extractables data - aspects beyond extractables-measurment

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The proper use of extractables data – Aspects beyond extractables measurement: 
estimates in complex single use systems by the use of equilibrium calculation

Armin Hauk, Ina Pahl, Roberto Menzel, Samuel Dorey, Thomas Loewe, Victor Rauch, Simon Souin * – Sartorius Stedim Biotech

The single-use systems used in the biopharmaceutical industry can release extractables. The extractable concentrations can be determined using different extraction matrices, which can mean different solvents. The purpose of this study was to show the possibility to calculate the extractable concentration in different solvent systems, in combination of systems of different sizes and assembled with different components.

Theoretical background

When single-use systems are in contact with a fluid, extractables can distributed between the two phases. At long contact times an equilibrium can be reached, which is described by the partition constant \( K_{p/l} \) which is the ratio of extractables concentration in the polymer versus the liquid phase:

\[
K_{p/l} = \frac{c_p}{c_l}
\]

The initial quantity \( m_0 \) of a chemical in the polymer is the sum of the quantity extracted by the solvent and the remaining quantity in the polymer (condition of conservation of mass).

Based on that one can calculate the quantity of any extractables in any solvent, \( n \), as it only depends on \( K_{p/l,n} \) and \( m_0 \) \([1]\):

\[
C_{l,n} = \frac{m_0}{V_l + K_{p/l,n} \cdot V_p}
\]

Experimental determination of \( K_{p/l} \)

When not taken from literature, \( K_{p/l} \) values can be estimated experimentally, using different methods:
- direct measurement of \( C_i \) and \( C_p \)
- doping (or fortifying) of the extraction solution, and measurement of \( C_l \) after equilibrium is reached
- correlation methods (e.g. based on HPLC retention times \([2]\))

This graph shows the \( K_{l/p} \) of ten compounds which were experimentally determined by doping in pure ethanol and in a 50% ethanol/50% water mixture, for several films.

Multi-component assembly

In real conditions, a product is made of several parts (bag, tubing, connectors...) which will have product contact. It is possible to determine the extractables concentrations of the entire device:

\[
C_l = f(m_{tot}; K_{p/l}; V_p/V_l)
\]

Application

We calculated the extractable concentration \( C_{l,exp} \) in 50% ethanol/50% water mixture from values experimentally measured \( C_{l,exp} \) in pure ethanol from the S80 film (PE/EVOH/PE).

The initial concentrations in the film \( C_{p,0} \) were calculated. Then the quantity of these compounds that would be extracted by a 50% ethanol/50% water mixture* was calculated \( C_{l,exp} \) and compared to the experimental values \( C_{l,exp} \):

<table>
<thead>
<tr>
<th>Compound</th>
<th>( C_{p,0} ) (µg/g)</th>
<th>( C_{l,th} ) (µg/mL)</th>
<th>( C_{l,exp} ) (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caprolactam</td>
<td>21.8</td>
<td>3.4</td>
<td>2.9</td>
</tr>
<tr>
<td>2,4-Di-tert-butylphenol ([1])</td>
<td>24.1</td>
<td>4.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Irganox® 1010 ([2])</td>
<td>0.7</td>
<td>0.06</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

* Extraction conditions: 70 days, 40°C, S/V = 6 cm²/ml.

\([1]\) Prodox 146
\([2]\) Irganox is a registered trademark of BASF Group: Pentaerythritol tetrakis(3,5-Di-tert-butyl-4-hydroxyhydrocinname)


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