MALEIMIDE-FUNCTIONALISED LIPOSOMES AS MUCOADHESIVE VEHICLES FOR DRUG DELIVERY TO URINARY BLADDER

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Bladder cancer has the 9th highest incidence rate worldwide, with a greater prevalence among men than women.

In the UK:
- 10,100 new cases of bladder cancer in 2014, that’s 28 cases diagnosed every day.
- BC is the 10th most common cancer (2014).
- In males, BC is the eight most common cancer and 14th in females.
Urinary bladder: intravesical delivery

- Normal capacity: 400–600 mL;
- 150–300 mL triggers the urge to urinate;
- Urinary bladder wall is highly impermeable
Intravesical therapy is used only for non-invasive (stage 0) or minimally invasive (stage I) bladder cancers.

**Intravesical immunotherapy:** Bacillus Calmette-Guerin (BCG)

**Intravesical chemotherapy:** Mitomycin, valrubicin, doxorubicin, and gemcitabine
Non-toxicity, biocompatible, and completely biodegradable

Increasing drug efficacy

Site avoidance effect

Increasing stability via encapsulation process

Reducing the toxicity of encapsulated drugs
THE COMPOSITION OF LIPOSOMAL FORMULATIONS

<table>
<thead>
<tr>
<th>Liposome formulations</th>
<th>PC (%)</th>
<th>Chol (%)</th>
<th>PEG&lt;sub&gt;2000&lt;/sub&gt;-DSPE (%)</th>
<th>PEG&lt;sub&gt;2000&lt;/sub&gt;-DSPE-Mal (%)</th>
<th>NaFlu (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>0.773</td>
<td>0.077</td>
<td>-</td>
<td>-</td>
<td>0.2</td>
</tr>
<tr>
<td>PEGylated</td>
<td>0.773</td>
<td>0.077</td>
<td>0.075</td>
<td>-</td>
<td>0.2</td>
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<tr>
<td>PEG-Mal</td>
<td>0.773</td>
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<td>0.2</td>
</tr>
</tbody>
</table>

![Liposome structures](image)
<table>
<thead>
<tr>
<th>Liposome formulations</th>
<th>Mean diameter (nm)</th>
<th>PDI</th>
<th>Zeta potential (mV)</th>
<th>%EE</th>
<th>%LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>97 ± 1</td>
<td>0.145</td>
<td>-53 ± 1</td>
<td>53 ± 6</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>PEGylated</td>
<td>85 ± 1</td>
<td>0.217</td>
<td>-32 ± 2</td>
<td>27 ± 2</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>PEG-Mal</td>
<td>86 ± 1</td>
<td>0.224</td>
<td>-37 ± 1</td>
<td>25 ± 2</td>
<td>5 ± 1</td>
</tr>
</tbody>
</table>

**PHYSICOCHEMICAL CHARACTERISTICS**

![Intense image of liposome formulations](image-url)
Application of mucoadhesive onto a bladder mucosa

Exemplary fluorescent images of the retention of formulations on urinary bladder mucosa

- FITC-chitosan
- PEG-Mal liposomes
- PEGylated liposomes
- Conventional liposomes
- FITC-dextran

0  10  20  40  60  80  100 mL
Retention (%)

Volume of artificial urine (mL)

- FITC-chitosan
- PEG-Mal liposomes
- PEGylated liposomes
- Conventional liposomes
- FITC-dextran

ns

*
Wash Out\textsubscript{50} (WO\textsubscript{50}) values are defined as the volume of liquid necessary to remove 50% of a mucoadhesive material from a substrate.

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Penetration into bladder mucosa

Exemplary fluorescence microscopy images:

Conventional liposomes

PEGylated liposomes

PEG-Mal liposomes

15 minutes  30 minutes  45 minutes  60 minutes
Penetration (mm) vs. Time (min) for different types of liposomes:

- Conventional liposomes
- PEGylated liposomes
- PEG-Mal liposomes

PEGylated liposomes show significantly higher penetration compared to conventional liposomes and PEG-Mal liposomes at all time points (15, 30, 45, 60 minutes).

Maleimide-terminated PEG liposomes also show increased penetration compared to conventional liposomes, but not as significantly as PEGylated liposomes.
Cumulative release (%) vs. Time (h) for Conventional liposomes, PEGylated liposomes, and PEG-Mal liposomes.
Toxicity – Slug mucosal irritation test

METHOD:

1. Slugs sourced from Harris Garden, UoR

2. Kept in desiccators lined with paper towels soaked with 20 mL of PBS at RT for 48 h

3. Weighed before the experiment
   Filter paper moistened with test materials
   Left to contact for 1 h
   Rinse and wiped
   Re-weighed

Mucus production:

\[ MP = \left( \frac{m_b - m_a}{m_b} \right) \times 100\% \]
Positive control

Negative control

Poly(ethylene glycol) methyl ether

pH 7.76  7.66  7.65  7.73

Methoxypolyethylene glycol maleimide

pH 7.29  7.20  7.13  6.92

6-Maleimidohexanoic acid

pH 7.78  7.56  6.93  4.34

Results published in

Acknowledgements

Sponsor:

THANK YOU!