Embozene TANDEM™ Microspheres Loading Guidance Document - A Step by Step Reference for Clinicians

SUPPLIES

TANDEM™-DOX

Doxorubicin (lyophilized, 50 mg/1 ml microspheres)

TANDEM™-IRI

Irinotecan solution (20 mg/ml solution 50 mg/1 ml beads)

1 × Embozene TANDEM™ syringe (2 ml microspheres)

1 × Embozene TANDEM™ syringe (2 ml microspheres)

2 × 5 µ filter needles

2 × 5 µ filter needles

1 - Waste container (empty 100 ml Solution bag)

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2 × 18-20G needles

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1 × 20-50 ml vial sterile WIFI

GENERAL LOADING INSTRUCTIONS

Embozene TANDEM™ Microspheres can load and deliver drugs that may be useful in the treatment of diseases that embolization also is effective. The platform can load either doxorubicin or irinotecan without modifications.

Doxorubicin - Embozene TANDEM™ Microspheres can load doxorubicin-hydrochloride only. DO NOT USE LIPOSOME FORMULATIONS FOR LOADING Embozene TANDEM™ Microspheres. For best results, use powdered doxorubicin-hydrochloride (generally, for 2 ml Microspheres, 100 mg of powdered doxorubicin-hydrochloride is hydrated with sterile water to give a 20 mg/ml solution of doxorubicin-hydrochloride).

Irinotecan - Embozene TANDEM™ Microspheres can load irinotecan-hydrochloride. For 2 ml Microspheres use 5 ml of irinotecan solution (20 mg/ml irinotecan).

Steps for Loading Embozene TANDEM™ Microspheres

1. Open the Embozene TANDEM™ Microsphere box, remove the syringe package. Inspect for damage. Open the syringe package, gently swirl the contents, then let microspheres settle towards the plunger for 2-5 minutes.

2. Carefully, place a sterile filter needle on the syringe nipple and slowly eject as much saline as possible from the syringe keeping the settled microspheres as undisturbed as possible. Do not compress the microspheres.

3. Remove and discard the filter needle.

4. Aseptically transfer the drug from its vial to the syringe with the Embozene TANDEM™ Microspheres by drawing the drug into the Embozene TANDEM™ syringe with a sterile needle or draw the drug into a separate syringe, then transfer it to the Embozene TANDEM™ syringe via 3-way stopcock.

5. Mix by inverting the syringe every 5 minutes for the first 20 minutes, then continue to mix occasionally thereafter. Let the Embozene TANDEM™ Microspheres settle.

6. The drug loading time is dependant on the drug. Drug and drug loading times are summarized in Table 1A below.

7. At time of use (pharmacy or IR suite), the drug-loaded microspheres settle towards the plunger, and then using a second filter needle, eject the supernatant, may have a reddish tint, but 98 ± 2 % of the doxorubicin is loaded into the microspheres. Do not compress the microspheres.

8. In the IR suite, immediately before use, add contrast agent (8-15 ml, diluted with WFI as necessary:) (new needle or 3-way stopcock), mix by inversion, and use immediately. Deliver to the target vessel via appropriate micro-catheter.

9. Attach the syringe to one port of the luer-lock 3-way stopcock and a 1 ml injection syringe to another port of the stopcock. Attach a delivery catheter to the remaining port on the stopcock.

10. Draw the Embozene TANDEM™ Microsphere mixture slowly and gently into the injection syringe to minimize the potential of introducing air into the system.

11. Under continuous fluoroscopic control, slowly infuse drug-loaded Embozene TANDEM™ Microspheres into the blood stream. Always inject under free flow conditions. To optimize injection through the catheter, it is recommended that the syringe remain in a horizontal position during injection. Avoid reflux of Embozene TANDEM™ Microspheres as this can induce immediate ischemia of the tissue or vessel.

12. Continue infusion until the desired devascularization is obtained or the desired dose is injected.

13. Once the clinical endpoint is reached, wait for 2-3 minutes to observe whether the microspheres redistribute themselves and re-establish flow to the target. If flow is re-established, inject an additional volume of microspheres until the final clinical endpoint is achieved.

14. At the end of the infusion, remove the catheter while maintaining gentle aspiration to avoid dislodging any residual drug-loaded Embozene TANDEM™ Microspheres still inside the catheter.

15. Discard any opened drug-loaded Embozene TANDEM™ Microspheres.

Table 1A: Embozene TANDEM™ Drug-Loading Times:

<table>
<thead>
<tr>
<th>TANDEM™ Microsphere Size</th>
<th>Drug</th>
<th>Loading Time</th>
<th>% Drug Loaded</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANDEM™ 40 µm</td>
<td>Doxorubicin</td>
<td>60 min</td>
<td>98 ± 2 %</td>
</tr>
<tr>
<td>TANDEM™ 75 µm</td>
<td>Doxorubicin</td>
<td>60 min</td>
<td>98 ± 2 %</td>
</tr>
<tr>
<td>TANDEM™ 100 µm</td>
<td>Doxorubicin</td>
<td>60 min</td>
<td>98 ± 2 %</td>
</tr>
<tr>
<td>TANDEM™ 40 µm</td>
<td>Irinotecan</td>
<td>30 min</td>
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<td>Irinotecan</td>
<td>30 min</td>
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</tr>
<tr>
<td>TANDEM™ 100 µm</td>
<td>Irinotecan</td>
<td>30 min</td>
<td>98 ± 2 %</td>
</tr>
</tbody>
</table>

EXAMPLE FOR LOADING 100 MG DOXORUBICIN INTO 2 ML EMBÖZENE TANDEM™ MICROSPHERES

Step 1

- Hydrate 100 mg doxorubicin powder with sterile WFI to a 20 mg/ml solution.
- Let doxorubicin dissolve for approximately 20 minutes.

Step 2

- Open Embozene TANDEM™ syringe (2 ml microsphere) pouch. With plunger facing down, let microspheres settle.
- Place a sterile 5 µ-filter needle on the syringe tip, expel transport solution into an appropriate waste container.

Step 3

- Remove used filter needle. Place a new, sterile 18G-needle onto the syringe and aseptically draw 100 mg of doxorubicin (5 ml of a 20 mg/ml doxorubicin solution) into the Embozene TANDEM™ syringe.
- Remove needle and place syringe cap on syringe and mix by inverting the syringe. Mix every 5 minutes for the first 20 minutes, then occasionally thereafter.

Step 4

- Drug Loading Times:

<table>
<thead>
<tr>
<th>Drug Loading Times</th>
<th>40 µm TANDEM™</th>
<th>75 µm TANDEM™</th>
<th>100 µm TANDEM™</th>
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</thead>
<tbody>
<tr>
<td>98 ± 2 %</td>
<td>60 min</td>
<td>60 min</td>
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<td>60 min</td>
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</table>

- After loading, store the syringe in the dark at 2-8°C until ready for delivery to the IR suite.

Step 5

- After doxorubicin-loading, set the syringe, plunger down, and let the doxorubicin-loaded microspheres settle.
- Place a new filter needle on the syringe and expel the supernatant into a waste container. The supernatant, may have a reddish tint, but 98 ± 2 % of the doxorubicin is loaded into the microspheres.
- Deliver the doxorubicin-loaded microspheres to the IR suite for immediate use.

EXAMPLE FOR LOADING 100 MG IRINOTECAN INTO 2 ML EMBÖZENE TANDEM™ MICROSPHERES

For loading irinotecan, loading of Embozene TANDEM™ Microspheres follow the same general procedure described for doxorubicin, except Step 1 is not necessary since irinotecan is already a solution. Note: Irinotecan has a yellowish tint so beads will be light yellow and discard solution will be clear to very faint yellow.

Drug Loading Times:

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<tr>
<th>Iринотеакan Uptake</th>
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</tr>
</thead>
<tbody>
<tr>
<td>98 ± 2 %</td>
<td>30 min</td>
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After mixing with contrast agent, the irinotecan-loaded Embozene TANDEM™ Microspheres must be used immediately.