K.C. Spindeldreier
J. Thiesen
I. Krämer

Apotheke der Universitäts-medizin Mainz

Langenbeckstr.1
55131 Mainz
Germany

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Contact:

Kirsten.Spindeldreier
@unimedizin-mainz.de

Loading, release and stability of epirubicin-loaded drug-eluting beads used for transarterial chemoembolization

Background and Purpose

Determination of loading efficiency, physico-chemical stability, and release of epirubicin-loaded DC Bead™ (Biocompatibles UK Ltd) after either loading with

- epirubicin solution (2 mg/mL) or
- reconstituted powder formulation (25 mg/mL)

and storage at room temperature, protected from light.

Materials and Methods

DC Bead™

- 70–150 µm (= DC Bead*M1*™)
- 100–300 µm

were loaded with 75 mg epirubicin (37,5 mL Epimedac™ (Medac GmbH) or 3 mL Farmorubicin™ (Pfizer) per 2 mL of beads.
Each combination was prepared in triplicate and a sample was taken at predetermined intervals. Each sample was assayed three times by a validated reversed-phase HPLC assay with ultraviolet detection to analyze the concentration and purity of epirubicin (see Sarakbi et al.).

Drug loading efficiency and stability of the beads were determined by measuring the epirubicin concentration in the excess solution at predetermined intervals (5 min to 6 h and 0 to 28 d, respectively). Beads were loaded under three different loading conditions, i.e. static, non-standardized agitation, standardized agitation.

Syringes with loaded beads were stored protected from light at room temperature (22 °C) for up to 28 days.

Drug release and stability were analyzed in vitro over a 4-week period on day 0, 7, 14 and 28. The beads were transferred into 200 mL phosphate buffered solution (PBS, pH 7.2) not followed or followed by addition of 200 mL of 20% NaCl (yielding 400 mL 10% NaCl) as elution medium and stirred for 2 h.

Results

Loading Profile

The loading procedure for DC Bead™ with epirubicin drug solutions resulted in maximum loading levels of 95 - 99% depending on the concentration of the epirubicin loading solution. The rate of loading varied according the concentration of epirubicin, the bead size, and the degree of agitation during loading (s. Fig.1, 2).

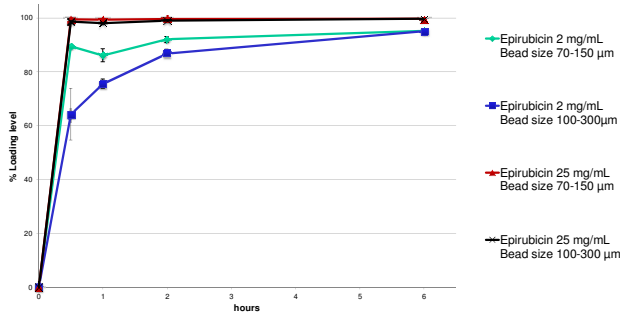

Figure 1: Loading profiles of differently sized DC Bead™ loaded with 75 mg epirubicin per 2 ml beads of different concentrations over 6 h (n=3). Agitation during loading was not standardized . Error bars indicate the relative standard deviation

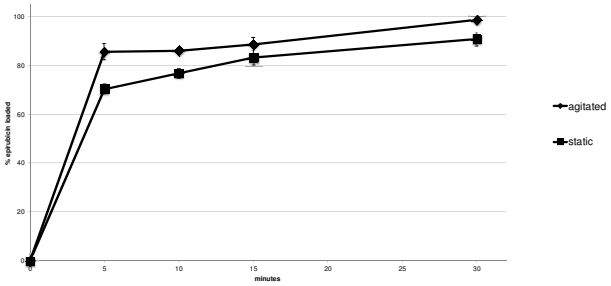

Figure 2: Loading profiles of DC Bead™ 100-300 µm loaded with 75 mg epirubicin (25 mg/mL) over 30 minutes (n=3). Bead slurries were not agitated or agitated in a standardized manner after 0 and 15 minutes. Error bars indicate the relative standard deviation

Stability of the epirubicin-loaded beads

Loading levels remained stable and no epirubicin degradation products were observed over the period of 28 days, while the loaded beads were stored light protected at room temperature.

Table 1: Loading level of DC Bead™ loaded with 75 mg epirubicin expressed as percentage rate [%] of epirubicin loaded after 0,7,14 and 28 days of storage ± RSD (n=3).

	% epirubicin loaded			
	d0	d7	d14	d28
Epirubicin 2 mg/mL Bead size 70-150 µm	95.3± 0.6	98.3± 0.2	98.4± 0.1	99.2± 0.0
Epirubicin 2 mg/mL Bead size 100-300 µm	95.1± 0.3	99.1± 0.0	99.2± 0.1	99.5± 0.0
Epirubicin 25 mg/mL Bead size 70-150 µm	99.7± 0.0	99.7± 0.0	99.7± 0.1	99.8± 0.0
Epirubicin 25 mg/mL Bead size 100-300 µm	99.7± 0.0	99.9± 0.0	99.8± 0.0	99.9± 0.0

in vitro Release

The release of epirubicin amounted to 5% and 20% of the loaded epirubicin after stirring in 200 mL PBS elution medium and consecutive admixture of 200 mL 20% NaCl solution, respectively. Integrity of loaded epirubicin was given over 28 days because no impurities were detected.

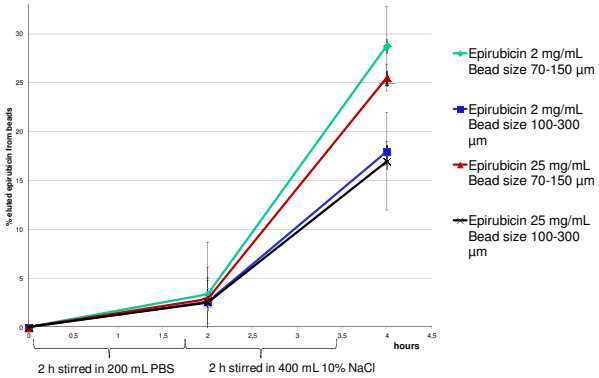

Figure 3: *in vitro* Release of epirubicin from loaded DC Bead™ after 28 d of storage. Epirubicin loaded beads were stirred for 2 hours in 200 mL PBS and the concentration analyzed. Consecutively 200 mL 20% NaCl solution were added resulting in 400 mL 10% NaCl solution and stirred for another 2 h. Error bars indicate the relative standard deviation.

Conclusion

Loading efficiency of epirubicin to DC Bead™ depends on the concentration of epirubicin in the loading solution, the size of the beads loaded, and the rate of agitation during loading. The ten fold higher concentration of epirubicin resulted in a maximum loading level of after 30 min. Smaller bead sizes and agitation accelerate the loading rate.

With regard to the loading level, release rate and purity of epirubicin in the excess solution and elution medium the epirubicin-loaded DC Bead™ can be categorized as stable over a minimum of 4 weeks when stored light protected at room temperature.

In the free-flowing *in vitro* method epirubicin is released from the beads up to 5% and 20% of the loaded dose depending on the volume and the cation exchange capacity of the elution medium. Further differences in the release rates are related to the bead size.

Acknowledgement

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References

Sarakbi et al., Compatibility of epirubicin-loaded DC Bead™ with different contrast media, Poster ECOP 2014 .