Sunitinib-loaded microspheres for transarterial chemoembolization: *in vitro* drug release and pharmacokinetic profile in rabbits

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BACKGROUND & OBJECTIVE

Transarterial chemoembolization (TACE) in combination with particles loaded with an anti-angiogenic agent is a promising means for the treatment of advanced hepatocellular carcinoma (HCC). Besides depriving the tumor of oxygen and nutrients by embolization of its vessels, the approach provides high drug concentration at the tumor site to prevent hypoxia-induced neoangiogenesis and local recurrence [1,2].

In this context, drug eluting beads (DEBs) were loaded with sunitinib, a multitargeted tyrosine kinase inhibitor. The purpose was to study *in vitro* the loading and release characteristics from differently sized commercially available embolization DC Bead™ microspheres *(Biocompatibles, UK)* as well as to evaluate the pharmacokinetics and tolerance of sunitinib-loaded DEBs in New Zealand white rabbits.

LOADING CHARACTERISTICS

Fig. 1 Drug loading of DC Bead™ particles

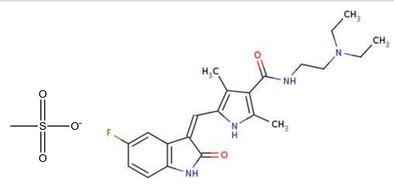


Fig. 2 Ionic interactions between DC Bead™ sulfonate residues and sunitinib

- Incubation of DC Bead™ in a 10 mg/mL sunitinib solution
- Adsorption of sunitinib onto the poly(vinyl alcohol) sulfonate moieties of the beads due to ionic interactions
- Indirect quantification of drug loading by spectrophotometric detection (430 nm)

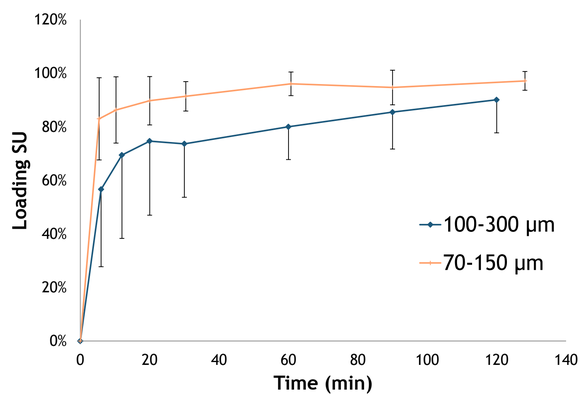
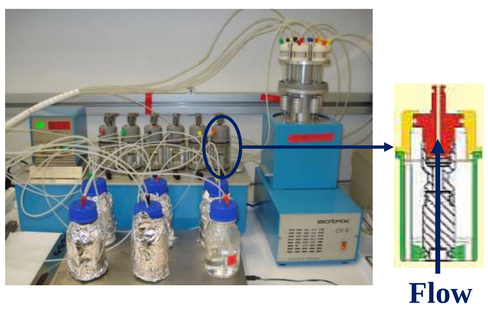


Fig. 3 Loading of differently sized DC Bead™ particles

High, close to complete and homogeneous drug loading was obtained for both microsphere sizes, with a slightly faster loading for the smaller beads ascribed to their higher surface area.

RELEASE CHARACTERISTICS



- USP method 4 (flow-through)
- Sotax CE 6 apparatus (37° C) with 6 cells, constant-flow CY7 pump (NaCl 0.9%, 5 ml/min)
- Spectrophotometric determination at 430 nm

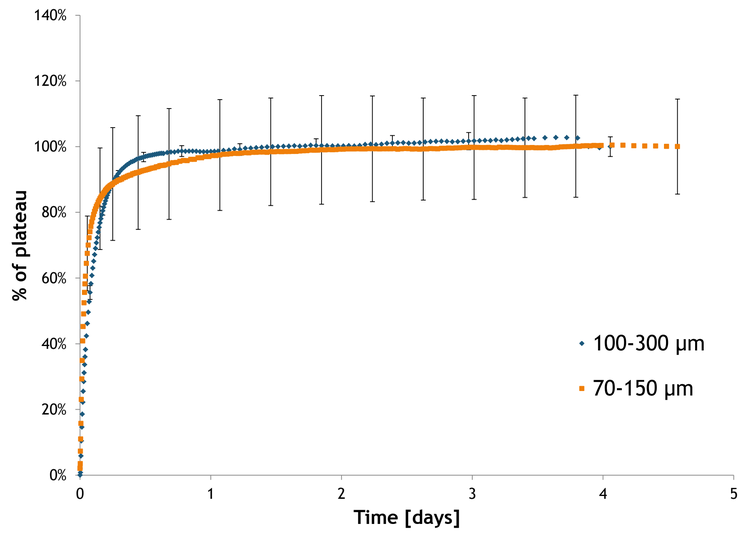


Fig. 4 Release of sunitinib from differently sized beads

Almost complete release was detected under physiological conditions, with very similar and fast release profiles for 70-150 µm ($t_{50\%}$=0.8 h) and 100-300 µm ($t_{50\%}$=1.5 h) DC Bead™ particles.

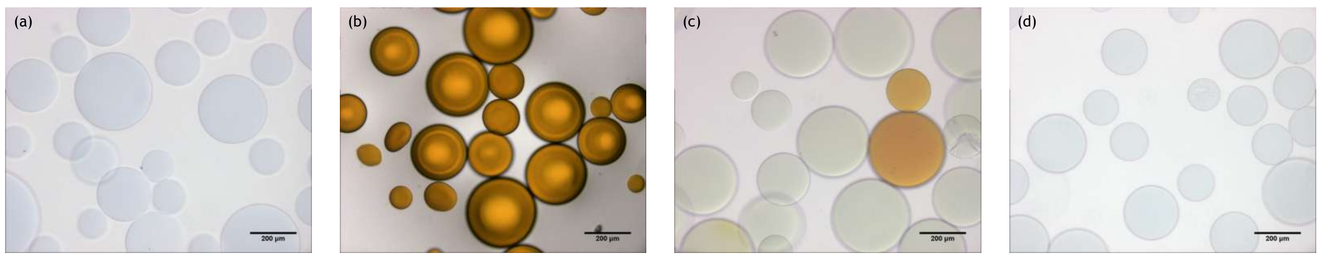


Fig. 5 100-300 µm DC Bead™ before loading (a), after loading (b), after elution in NaCl 0.9% (c) and NaCl 0.9%/EtOH 30% (d)

PHARMACOKINETIC PROFILES

Healthy New Zealand white rabbits received either 0.2 ml of 100-300 micron sized beads loaded with 6 mg of sunitinib in the hepatic artery (n=9) or 6 mg of sunitinib p.o. (n=4). Drug concentrations in plasma and liver tissue were assessed by LC MS/MS spectroscopy.

Administration of sunitinib/DC Bead™ caused a significant elevation of ALT and AST liver enzymes comparable to the cytolysis expected after arterial embolization in the liver. Bilirubin plasmatic levels were not affected by the treatment, staying below the detection threshold in all measurements.
Administration of sunitinib p.o. did not cause any alteration of liver enzymes.

After embolization drug plasma levels remained low (<50 ng/ml) whereas in the liver tissue, very high concentrations at 6 hours (12860 ng/ml) and 24 hours (9500 ng/ml) were found.

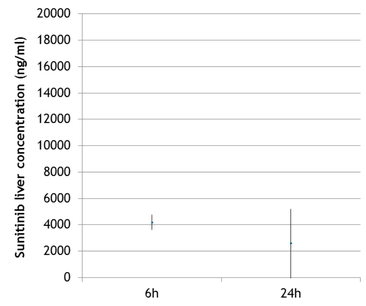


Fig. 6a Measurements of sunitinib levels in the liver 6 hours (n=2) and 24 hours (n=2) after oral administration of 6 mg of sunitinib.

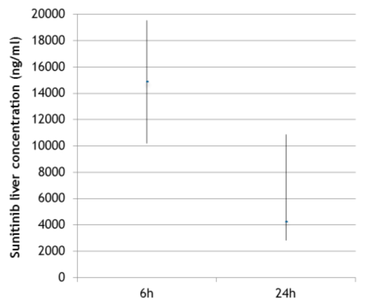


Fig. 6b Measurements of sunitinib levels in the liver 6 hours (n=1) and 24 hours (n=3) after intra-arterial administration of 2 ml DC Beads loaded with 6 mg of sunitinib in the common hepatic artery.

CONCLUSIONS & OUTLOOK

- ✓ DC Bead™ were efficiently and homogeneously loaded with the anticancer agent.
- ✓ Release studies showed an elution of the active ingredient in a controlled manner from DC Bead™ embolization microspheres of different sizes.
- ✓ Sunitinib-eluting beads were well tolerated by rabbits without observation of unexpected effects. High liver drug concentration and low systemic levels indicated the potential of sunitinib beads for hepatocarcinoma treatment.
- ✓ Preliminary animal studies proved antitumoral efficacy of sunitinib-loaded DC Bead™. Investigations are still under way to define the most efficient treatment protocol.

REFERENCES

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