

# Evaluation of Irinotecan Drug-Eluting Beads: A New Drug-Device Combination Product for the Chemoembolization of Hepatic Metastases

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## ABSTRACT

Irinotecan drug eluting beads (DEB) were characterized *in vitro* with regard to their properties as a chemoembolization agent. Drug plasma levels and histopathology were performed in a porcine model of hepatic arterial embolization and compared to intra-arterial bolus injection of drug, resulting in a reduction in peak plasma levels with DEB. A good correlation between *in vitro* and *in vivo* drug release was obtained. These data support the use of irinotecan DEB for the chemoembolization of hepatic metastases.

## INTRODUCTION

Colorectal carcinoma (CRC) is the third leading cause of death from cancer in both males and females in the western world. 5-Fluorouracil-based chemotherapy has been the cornerstone of treatment of metastatic CRC for more than 40 years, and new drugs such as irinotecan and oxaliplatin with a definite activity have recently broadened the options for treatment. In addition, there is renewed interest in local delivery of chemotherapy to the liver in an attempt to increase the effectiveness of these drugs against liver metastases [1,2]. One approach to local therapy is the use of transarterial chemoembolization (TACE), which involves administration of chemotherapeutic agents directly within the feeding artery of hypervascular tumors, followed by a subsequent step to occlude the vessel with an embolic device [3,4]. As such, the tumor is starved of its oxygen and nutrient supply and the washout of the drug is minimized. Irinotecan drug eluting beads (DEB) combine the drug with the embolization device and can be administered intra-arterially in the same manner as TACE. This drug-device combination may offer the possibility of precisely controlling the release and dose of the drug into the tumor bed. This study presents both *in vitro* and *in vivo* characterization with respect to how the drug influences the physical properties and handling of the device, and how the device matrix is able to modulate release of the drug over a therapeutically-meaningful timeframe.

## EXPERIMENTAL METHODS

The DEB were prepared by combining embolization beads (DC Bead™, Biocompatibles UK Ltd) with irinotecan hydrochloride solution (Campto®, Pfizer). The resulting irinotecan DEB were characterized *in vitro* with respect to size, compressibility, suspension, microcatheter deliverability and drug elution by T-apparatus. Porcine hepatic arterial embolization was performed in 4 groups of animals (n=5/group): 100-300µm control beads, 100-300µm irinotecan DEB, 700-900µm irinotecan DEB and intraarterial injection of drug alone. Plasma samples were taken over 90d and histopathology performed at 30d and 90d.

## RESULTS AND DISCUSSION

### *In vitro* Characterization:

The rate of drug uptake was seen to be bead size dependent, the smaller beads loading more quickly due to increased surface area to volume ratio. The maximum loading of bound drug was shown to be around 50-60 mg irinotecan/ mL beads for all sizes (Fig 1(a)). Drug loading was accompanied by a corresponding decrease in the average diameter of the beads and a concomitant increase in the force required to compress the beads as water is displaced from the matrix by the drug. Drug elution did not occur in pure water but did when the beads were placed in phosphate-buffered saline due to the presence of ions that could displace the drug from the matrix. A T-apparatus was used to better emulate *in vivo* release by a diffusion/convection based mechanism rather than elution into an infinite sink [5]. This demonstrated that the smaller beads eluted more quickly, particularly with respect to a larger burst effect attributed to an increased surface area (Fig 1(b)).

Drug interaction with the bead was shown to be by an ion-exchange process whereby the positively-charged drug associates with the negatively-charged polymer-bound sulfonate groups within the poly(vinyl alcohol)-based hydrogel structure of the beads, by a predominantly electrostatic mechanism [6] (Fig 2).

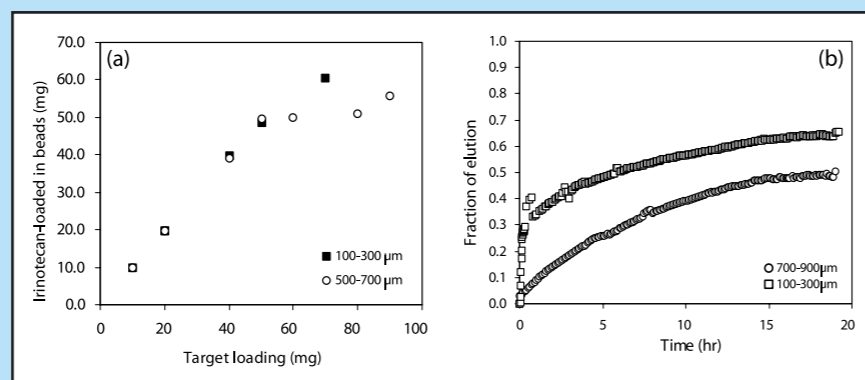


Figure 1: (a) Actual vs target drug loading of beads; (b) Drug elution profiles using a T-apparatus

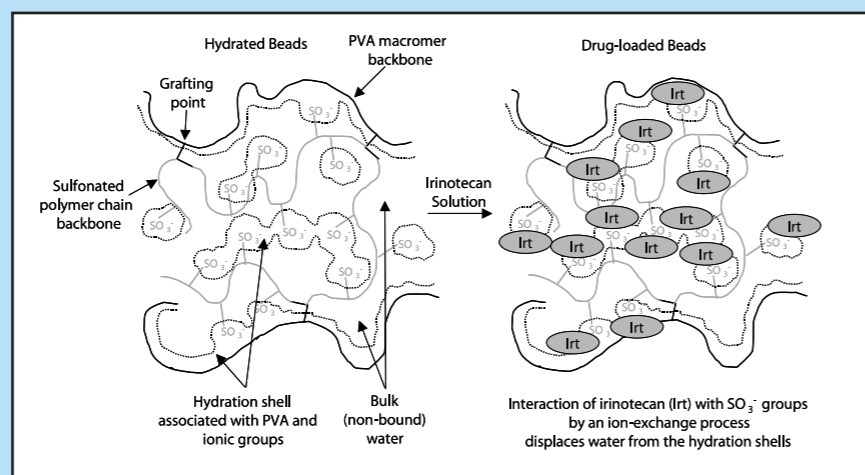


Figure 2: Mechanism of irinotecan (Irt) loading within the sulfonated hydrogel beads

The time required to reach suspension in contrast agent: saline mixture was both bead size and drug dose dependent and ranging between 1-12 minutes. All beads were deliverable through a 2.4 or 2.7Fr microcatheter at maximum dose and thus suitable for use in embolization.

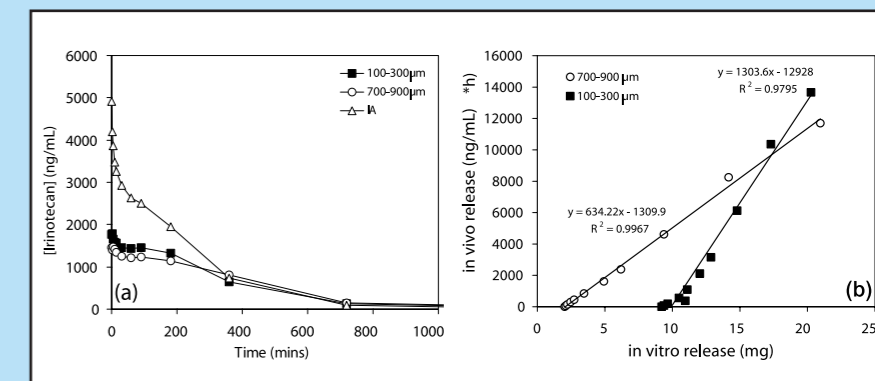


Figure 3: (a) Irinotecan plasma levels *in vivo* (n=5/group); (b) IVIVC.

### *In vivo* Characterization:

Maximum systemic irinotecan and SN38 concentrations were observed at T=0 minutes after intra-arterial (IA) administration of irinotecan. Following embolization of the hepatic artery, maximum plasma levels were 70-75% lower for both irinotecan and SN38 compared to IA administration, with peak levels observed at 2 and 5 minutes after completion of the embolization procedure (Fig 3 (a)). In all groups, drug plasma levels were below the limit of quantification by 24 hours. Upon histopathological examination of the liver, necrotising vasculopathy in the arteries/arterioles containing beads was observed and subsequently a granulomatous inflammatory reaction around the beads, as typical of embolization. This did not result in any significant liver damage as indicated by the normal levels of liver enzymes.

### *In vivo:in vitro* Correlation (IVIVC):

Figure 3(b) shows the IVIVC data of irinotecan release from DEB with the size range of 100-300µm and 700-900µm. A good linear IVIVC with the area under the curve after irinotecan release in plasma was observed ( $R^2 = 0.98$  and  $0.99$  respectively). The results indicate that the T-apparatus test can be used to model and predict the *in vivo* irinotecan release from DEB.

## CONCLUSION:

The data from these studies support the further evaluation of irinotecan DEB in clinical studies for the treatment of CRC hepatic metastases.

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