Drug-eluting embolic microspheres for local drug delivery - State of the art

Fuchs, Katrin; Duran, Rafael; Denys, Alban; Bize, Pierre E; Borchard, Gerrit; Jordan, Olivier

How to cite

FUCHS, Katrin et al. Drug-eluting embolic microspheres for local drug delivery - State of the art. In: Journal of Controlled Release, 2017, vol. 262, p. 127–138. doi: 10.1016/j.jconrel.2017.07.016

This publication URL: https://archive-ouverte.unige.ch/unige:141548
Publication DOI: 10.1016/j.jconrel.2017.07.016

Drug-Eluting Embolic Microspheres for Local Drug Delivery – State of the Art

Katrin Fuchs[a], R. Duran[b], Alban Denys[b], Pierre E. Bize[b], Gerrit Borchard[a], Olivier Jordan[a,*]
[a] School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Centre Médical Universitaire (CMU), Rue Michel-Servet 1, 1211 Geneva 4, Switzerland
[b] Departments of Radiology and Interventional Radiology, Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 46, 1011 Lausanne, Switzerland

Corresponding author:
Olivier Jordan
Centre Médical Universitaire (CMU)
School of Pharmaceutical Sciences
Rue Michel-Servet 1
1211 Geneva 4
Switzerland
olivier.jordan@unige.ch, Tel.: +41 22 379 65 86

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abbreviations:

HCC: hepatocellular carcinoma, BCLC: Barcelona Clinic Liver Cancer, TACE: transarterial chemoembolization, cTACE: conventional TACE, CT: computed tomography, MRI: magnetic resonance imaging, DEB: drug-eluting bead(s), APTA: (3-acrylamidopropyl) trimethylammonium chloride, HIF-1α: hypoxia-inducible factor-1α, VEGF: vascular endothelial growth factor, DSM: degradable starch microspheres, PLGA: poly(lactide-*co*-glycolide) or poly(lactic-*co*-glycolic acid), PEG: Poly(ethylene glycol), PEGMA: Poly(ethylene glycol) methacrylate, PLA: poly(D,L-lactic acid), PBS: phosphate buffered saline, SDS: sodium dodecyl sulfate, MW: molecular weight

Abstract

Embolic microspheres or beads used in transarterial chemoembolization are an established treatment method for hepatocellular carcinoma patients. The occlusion of the tumor-feeding vessels by intra-arterial injection of the beads results in tumor necrosis and shrinkage. In this short review, we describe the utility of using these beads as devices for local drug delivery. We review the latest advances in the development of non-biodegradable and biodegradable drug-eluting beads for transarterial chemoembolization. Their capability to load different drugs, such as chemotherapeutics and anti-angiogenic compounds with different physicochemical properties, like charge and hydrophilicity/hydrophobicity, are discussed. We specifically address controlled and sustained drug release from the microspheres, and the resulting *in vivo* pharmacokinetics in the plasma vs. drug distribution in the targeted tissue.

Keywords

Drug-eluting beads, microspheres, transarterial chemoembolization, hepatocellular carcinoma, biodegradable, degradable, antiangiogenic, controlled release, local delivery, pharmacokinetics

1. Introduction: Locoregional Drug Delivery in Transarterial Chemoembolization (TACE)

Liver cancer is the second most common cause of death from cancer worldwide, which led to an estimated 746,000 deaths in 2012. The most common primary malignancy of the liver is hepatocellular carcinoma (HCC) [1].

For patients with multinodular hepatocellular carcinoma and preserved liver function (intermediate-stage B according to the Barcelona Clinic Liver Cancer (BCLC) classification), transarterial chemoembolization (TACE) is the standard of care [2-4]. During TACE, the tumor-feeding arteries are selectively catheterized. Conventional TACE (cTACE) is carried out by the infusion of an emulsion composed of a chemotherapeutic agent and iodized oil (Lipiodol®), followed by bland embolization (absorbable gelatin, unloaded beads). For TACE with drug-eluting beads (DEB-TACE), beads are loaded with a chemotherapeutic drug prior to their transarterial delivery. DEB-TACE is considered a more standardized and reproducible methodology in terms of delivered drug dose compared to cTACE, whereas for the latter several regimens exist without a universally accepted protocol [5-8].

Site-specific drug delivery from the beads to the targeted tumor tissue leads to a controlled pharmacokinetic profile [6, 9-11]. Al-Abd et al. [12] recently summarized the unique advantages of embolization to increase local drug levels and concomitantly decrease systemic toxicity by entrapping the drug in the tumor-feeding vessels. As such, local drug delivery is achieved by the synergistic combination of local administration of drug-eluting beads (DEBs) and the prevented wash-out of the drug due to interrupted arterial blood flow [13]. Importantly, drug delivery in the tumor proximity was reported to effectively result in high drug concentration in the targeted tumor tissues [14].

In case embolization with micron-sized beads is not indicated for treatment (patients beyond BCLC stage B), intra-arterially administered nanocarriers are explored to target specifically advanced-stage HCC lesions. Possible biochemical targets and currently developed drug delivery nanosystems were summarized in an excellent recent review by Zhang et al. [15].

The present review aims to highlight the latest advances in the design of embolic drug-eluting beads for DEB-TACE of HCC. With this, it also covers temporary embolizing agents, which show less serious post-embolization side effects [16] and are therefore currently in the research focus [17-27]. Drug loading and release of relevant drugs for HCC treatment from established and novel, among them biodegradable, bead formulations are discussed. Besides chemotherapeutic drugs, anti-angiogenic and immunotherapeutic drugs are beneficial in HCC treatment [12, 28-31], which are not necessarily easy candidates for drug loading on beads by ion exchange such as doxorubicin [32] or irinotecan [33].

Due to different mechanisms of drug loading or due to different affinities to the bead surface, different drugs show different release profiles *in vitro* [34]. This translates in turn into unique pharmacokinetic profiles *in vivo*, and little is known about the local drug distribution in the targeted tissue. We discuss here whether there is an “ideal drug release profile”, and whether sustained drug release is required to achieve long-term exposure of the tumor to the drug.

2. State of the Art of Drug-Eluting Microspheres

Embolic beads have been used since the 1970s [31] and were compared in experimental [32, 34, 35], pre-clinical [36-39] and clinical settings [40]. Massmann et al. [41] provided a complete tabular overview of clinically established and more recent FDA-approved embolic agents. The features of clinically established agents as well as some novel embolic agents were summarized in recent reviews [31, 42]. In this section, we focus on advances in drug-eluting bead development, i.e. beads that are still under preclinical evaluation and were specifically designed to deliver anti-cancer drugs to tumors. Advances in non-biodegradable and biodegradable embolic beads are summarized in Table 1 and Table 2, respectively.

2.1 Non-Biodegradable Beads for Drug Delivery and *In Vitro* Drug Release

Clinically used DC Bead (BTG, London, UK), HepaSphere (Merit Medical, South Jordan, UT, USA), Embozene TANDEM (CeloNova BioSciences, San Antonio, TX, USA), and LifePearl (Terumo, Tokyo, Japan) are non-biodegradable beads, which are capable of drug loading via an ion exchange mechanism [32]. This elegant method does not interfere with drug activity, ensures drug release in contact with physiological fluids [43, 44], and is therefore also mainly employed for bead-drug combinations in development.

Lewis et al. [45-52] and Jordan et al. [53, 54] have recently developed a series of non-biodegradable beads with “special features” for drug delivery (Table 1). Beads for the loading of anionic drugs [45], and X-ray image-able beads with doxorubicin loading capacity [46-49, 52, 55] were presented. DC Bead were also loaded with two drugs at the same time, e.g., doxorubicin was loaded via ion exchange and rapamycin via drug precipitation into the bead [50], or DC Bead were combined with different anti-angiogenic drugs [51, 53, 54].

Table 1. Recently developed non-biodegradable drug-eluting beads.

Bead (brand name if available, matrix)	**Size (µm)**	**Drug**	**Mechanism of loading and/or release**	**Maximal drug loading**	**Release rates (*in vitro*, PBS pH 7.4, 37°C)**	**Reference**
Cationic quaternary (3-acrylamidopropyl)trimethyl ammonium chloride (APTA)	100-300	anionic pyrene model drugs	Ion exchange	Up to 30 mg/mL depending on drug and bead formulation	Monovalent pyrene dye: 80% release, plateau reached at 1 h, for 8.6 µmol/mL loading	[45]
Lipiodol-loaded DC Bead	70-150, 100-300	DOX	Ion exchange	37.5 mg/mL	Radiopaque beads eluted DOX slightly more slowly than non-radiopaque beads	[46]
iBeads (DC Bead modified by iodinated moieties)	100-300, 300-500	DOX	Ion exchange	40-80 mg/mL	Slightly increased released drug dose compared to non-iodinated beads, $t_{50\%}$ = 0.5 h (100-300 µm), $t_{50\%}$ = 0.8 h (300-500 µm)	[47]
DC Bead (Methacryloyl-polyvinyl alcohol (PVA) polymerized with 2-acrylamido-2-methylpropanesulfonate sodium salt (AMPS))	500-700	DOX + rapamycin	Ion exchange (DOX) + (non-solvent-induced) rapamycin precipitation	40 mg/mL DOX + 30 mg/mL rapamycin	Not different from single drug-loaded bead at max. loading: 5% DOX release, 27% rapamycin release	[50]
DC Bead	Not yet published	Vandetanib	Ion exchange	Not yet published	Not yet published	[51]
DC Bead	100-300	Sunitinib	Ion exchange	30 mg/g	PBS: $t_{50\%}$ = 0.8 h, 94% release at plateau; NaCl 0.9%: $t_{50\%}$ = 1.0 h, 100% release at plateau)	[53, 56]
DC Bead	70-150	Bevacizumab	Ion exchange	38 mg/mL	Extended by layer-by-layer technique to 3 days with a 41% release at plateau	[54]

DOX: Doxorubicin

2.1.1 Non-Biodegradable Beads for Anionic Drug Loading

Until today, post-synthesis drug loading on marketed negatively charged beads was limited to cationic drugs. Heaysman et al. [45] have recently prepared beads containing cationic quaternary (3-acrylamidopropyl)trimethylammonium chloride (APTA), which were efficiently loaded with anionic model dyes. Release time *in vitro* was shown to correlate inversely with the number of charged moieties per dye, i.e. multivalence imparted higher affinity between the dye and the bead polymer matrix. These beads display a platform for combination with negatively charged small molecules, which are most likely to penetrate into the bead hydrogel pores. In addition, bigger biologic entities up to 70-250 kDa (pore size of one type of APTA beads) bearing a global negative charge might be loaded, such as miRNA mimetics or antagonists [57, 58], siRNA [15, 59], or antibody fragments [15]. This bead invention might make the delivery of relevant drugs possible, which could not be loaded on anionic drug-eluting beads before.

2.1.2 Image-able Non-Biodegradable Beads for Doxorubicin Delivery

The purpose to visualize beads using fluoroscopy, computed tomography (CT) or magnetic resonance imaging (MRI) during/following DEB-TACE is to judge the endpoint of tumor embolization and consequently, success of the intervention. Image-able and at the same time doxorubicin-loaded beads have been developed: Lipiodol-loaded DC Bead [46, 48] and DC Bead modified by iodinated moieties (iBeads) [47]. Aforementioned radiopaque beads were similar to classic DC Bead in their total doxorubicin loading capacity, with iBeads eluting slightly more drug [47] and Lipidiol-loaded beads releasing more slowly compared to non-iodinated DC Bead [48]. The ability to visualize doxorubicin-loaded radiopaque beads (LC Bead Lumi™) was demonstrated in VX2-tumour bearing rabbits [52]. Safety and long-term X-ray visibility was further shown in a pig hepatic embolization model [60]. A study correlating bead attenuation, and bead distribution in the tissue, with doxorubicin delivery is currently undertaken [61]. This will enable correlating drug delivery to beads per tissue volume. Similarly, doxorubicin and sunitinib fluorescence also allows for evaluation of the drug diffusion in the tissue, which will be discussed in Section 3.2.

2.1.3 Combination of Drug-Eluting Beads with Anti-Angiogenic Drugs

Tumor embolization creates ischemia, which results in tumor necrosis. However, at the same time ischemia equally increases hypoxia-inducible factor 1-alpha (HIF-1α) and vascular endothelial growth factor (VEGF) levels, which leads to neoangiogenesis and eventually tumor recurrence [62-66]. To counteract the formation of new blood vessels induced by the embolization, the combination of TACE with anti-angiogenic agents seems rational [41, 67, 68]. For local delivery of anti-angiogenic drugs, DC Bead were loaded with the multitargeted tyrosine kinase inhibitors sunitinib [53] and vandetanib [51], and an anti-VEGF antibody, bevacizumab [54]. Sunitinib is loaded at high levels of 30 mg/g beads and rapidly released with a release half time of 1 h from 100-300 µm beads [56], comparable to doxorubicin and slightly slower than irinotecan release from 500-700 µm sized DC Bead using the same Pharmacopeia flow-through release set-up [34]. While sunitinib and irinotecan were released to full extent, doxorubicin was only 27% released due to the formation of self-assembled drug aggregates [34]. In a different set-up, bevacizumab (loaded at 38 mg/mL beads) release was deliberately extended to 3 days with a 41% release to match the time span of increased VEGF levels after embolization. This was achieved by applying biocompatible polymer layers on the bead surface by the layer-by-layer (LbL) technique [54]. *In vivo* drug pharmacokinetics, for the time being only available for sunitinib among the anti-angiogenic drugs, is discussed in Section 3.

2.2 Biodegradable Beads for Drug Delivery and *In Vitro* Drug Release

Advantages of temporary embolizing agents have been shown by the clinical use of gelatin sponge and degradable starch microspheres (DSM) for decades [42, 69]. These advantages include potential reduction in the occurrence of post-embolization syndrome [16, 70], tissue inflammation and fibrosis [71], risks arising from non-target embolization [31], and possibility of repeated interventions after vessel recanalization [72, 73]. Transient compared to permanent embolization might also be favorable in terms of avoidance of ischemia-induced neoangiogenesis [41]. While being biodegradable and compressible to pass easily through catheters, commercialized microspheres like DSM

[74] and Occlusin^{TM}500 (collagen-coated poly(lactide-*co*-glycolide) (PLGA), IMBiotechnologies Ltd., Edmonton, AB, Canada) [75], are not drug-loaded particles.

Most recently developed drug-loaded microspheres were also designed to be biodegradable (or resorbable) and compressible (Table 2). To include elastic properties in the spheres, research was inspired by already marketed (bio)polymers, such as compressible hydrogel matrices. While this rational choice should allow for drug loading of hydrosoluble drugs, such as those currently used in DEB-TACE, it however precludes the possibility of loading more hydrophobic drugs, like sorafenib, which cannot be ionized by pH modification of the medium. Sorafenib is an anti-angiogenic multikinase inhibitor targeting Raf, affecting tumor signaling and the tumor vasculature [76]. Sorafenib is considered the standard of care for advanced-stage HCC patients (BCLC stage C), since it is the only drug having demonstrated a survival benefit (compared to placebo) in systemic delivery [77]. Biodegradable microsphere formulations with their loading and release characteristics are summarized in Table 2. Among these microspheres, the ones which are currently at the most advanced stage of development will be further discussed in Sections 2.2.1 through 2.2.3.

Table 2. Recently developed (bio)degradable drug-eluting beads.

Bead matrix (material)	Drug	Mechanism of loading and/or release	Maximal drug loading	Release rates (*in vitro*, PBS pH 7.2-7.4, 37°C)	Degradation time	Reference
Alginate	Lipo-somal DOX	Loading: drug entrapment during alginate bead crosslinking, Release: Heat-triggered	1.5 mg/g MS	HEPES: 37°C: 20% at 3 h, 42°C: 75% in 30 s, 85% at plateau at 1 min; 50% FBS: 37°C: 30% at 3 h, 42°C: 100% in 3 min	n. a.	[25]
Bovine Serum Albumin (crosslinked)	IRI	Loading: into lyophilized MS, Release: swelling-controlled	98 mg/g MS	80.6% at 5 h, 88.4% at plateau	Tyrosine PBS solution (50 µg/mL): almost completely degraded within 4 weeks	[27]
Chitosan-cellulose	DOX	Ion exchange	48-85 mg/g wet MS	$t_{50\%}$ at ca. 4 h, 15-27% at plateau	<10 days (unloaded) *in vivo*	[19, 78-80]
		Loading in lyophilized MS, ion exchange	300-700 mg/g dry MS within 48 h (depending on size)	n. a.	14-88 days (unloaded) *in vitro*, >88 days (drug-loaded) *in vitro*	
Chitosan	DOX	Loading: Drug entrapment during water-in-oil (W/O) emulsion, Release: lysozyme-cleavage	CMs: 115 mg/g, ACMs: 107 mg/g	CMs: 70% at 20 h (plateau), ACMs: 80% at 28 h (plateau)	0.5 mg/mL lysozyme at 45°C, gentle shaking: Mass loss: CMs: 4.2%, ACMs: 6.3% at 1 week, 40.7% of CMs, 58.1% of ACMs degraded at 8 weeks	[22]
Chitosan	DOX	Loading: "Expanding-loading-shrinking" process, Release: presumably enzymatic hydrolysis	100 mg/g MS	22.6% at 7 d	24 weeks *in vivo*	[81, 82]
Gelatin	Cisplatin	Loading: presumably covalent binding, Release: MS degradation	11.145 mg/g MS	12% at 24 h	n. a.	[83]
PEG methacrylate	DOX	Ion exchange	34 mg/mL MS	49% at 1 h, 64% at 6 h (for MS containing 20% methacrylate)	less than 2 days *in vitro*, 1 week *in vivo*	[21, 71, 84, 85]

	IRI	Ion exchange	37 mg/mL MS	75% at 1 h, 87% at 6 h (for MS containing 20% methacrylate)		
	Sunitinib	Ion exchange	40 mg/mL MS	48-62% at 6 h, 100% at 24 h		
	Bevaci-zumab	Ion exchange	20 mg/mL MS	83-92% at 6 h, 100% at 24 h		
Poly(D,L-lactic acid)	Sorafenib	Loading: entrapment during emulsion/solvent evaporation MS preparation, Release: polymer swelling (not yet degradation)	160 mg/g MS	4.2% at 24 h, 9.3% at 14 d	$t_{50\%}$ = 7.2 weeks (modeled, not degraded after 9 months)	[26, 86]
	Cisplatin		120 mg/g MS	4.0% at 24 h, 6.9% at 14 d	$t_{50\%}$ = 7.2 weeks (modeled, not degraded after 9 months)	
	Sorafenib + cisplatin		70 mg sorafenib + 50 mg cisplatin/g MS	23% of sorafenib and 20% of cisplatin at 24 h, 91% of sorafenib and 48% of cisplatin at 14 d	$t_{50\%}$ = 10.4 weeks (modeled, not degraded after 9 months)	
Poly(lactic-*co*-glycolic acid)	Sorafenib	Loading: double emulsion/solvent evaporation	190 mg/g MS	21% at 3 d	n. a.	[23]
Poly(lactic-*co*-glycolic acid)	DOX	Loading: solid-in-oil-in-water emulsion, Release: polymer swelling	25 mg/g MS	35% at 3 d	50% (v/v) FBS in PBS and incubated at 37°C at 50 rpm: visible signs at 2 weeks	[24]

DOX: Doxorubicin, n. a.: not available, MS: microspheres, IRI: Irinotecan, CMs: chitosan microspheres, ACMs: acetylated CMs

2.2.1 Bioresorbable Chitosan-Cellulose Microspheres

Biocompatible microspheres from oxidized carboxymethylchitosan-carboxymethylcellulose are degraded by enzymatic or non-enzymatic hydrolysis over adaptable timeframes [19, 78-80]. The rate of degradation may be modulated by polymer crosslinking density and drug loading, ranging from less than 10 days for unloaded microspheres *in vivo*, to 3 months for doxorubicin-eluting microspheres *in vitro* [78, 80]. Compared to DC Bead standard loading with doxorubicin of 37.5 mg/mL beads, doxorubicin loading on chitosan-cellulose microspheres was similar with maximally 48-85 mg/g wet spheres depending on the degree of crosslinking. Doxorubicin release was claimed to be more sustained than from DC Bead, differences do however not seem of clinical significance [78]. The total release of 27% of the loaded doxorubicin from the least crosslinked microspheres with the largest hydrogel pores and swelling were comparable to doxorubicin total release from DC Bead [34, 79]. Thus, the chitosan-cellulose systems may hold promises in terms of biocompatibility and timeframe of degradation, and compare *in vitro* to doxorubicin delivery from DC Bead. Other chitosan-based microspheres for embolization are summarized in Table 2 [22, 81, 82].

2.2.2 Poly(ethylene glycol) Methacrylate (PEGMA) Microspheres

Several clinically established microspheres are acrylate based hydrogels [31], such as poly(ethylene glycol) methacrylate (PEGMA) microspheres (ResMic, Occlugel, Jouy-en-Josas, France) for the treatment of uterine fibroids. Due to the introduction of a hydrolysable PLGA-PEG-PLGA crosslinker, they are completely resorbed in less than 2 days *in vitro* and within 1 week *in vivo* [21, 71, 72]. For ionic loading of doxorubicin, irinotecan, and sunitinib, carboxylic functions were added to the microspheres by incorporation of up to 20% methacrylate monomer [84]. High loading capacities of 34, 37, and 40 mg/mL of microspheres were achieved for the three drugs, respectively. This was comparable to total loading on DC Bead, which can carry 39 mg doxorubicin per mL of beads [87], 49 mg irinotecan per mL of beads [33], and 30 mg sunitinib per g of beads [53] (~33 mg/mL of beads, all: 100-300 µm). Release in phosphate buffered saline (PBS) showed the most sustained release for sunitinib among the three drugs, with 48-62% of sunitinib released at 6 hours and complete release after 24 hours [84, 85]. Direct

comparison to the release kinetics from DC Bead is not advised due to the use of different release apparatuses, but does not seem to differ strikingly [56]. PEGMA microspheres were also combined with bevacizumab (20 mg/mL microspheres), which was 83-92% released *in vitro* after six hours, and completely after 24 hours [85]. Loading and release of both sunitinib and bevacizumab depend on ion exchange and salt concentration. Concerning the difference in release kinetics for the two anti-angiogenic drugs, bevacizumab was loaded more superficially due to its bigger molecular size, and was thus released more rapidly than sunitinib. Taken together, these results show that PEGMA microspheres and commercial DC Bead microspheres have similar sunitinib and bevacizumab loading capabilities and release profiles. The inclusion of PLGA monomers in the PEGMA spheres assures biocompatibility and degradation, and might enable loading of more hydrophobic drugs mediated by van der Waals interactions.

2.2.3 Poly(D,L-lactic acid) and Poly(lactic-*co*-glycolic acid) Biodegradable Microspheres

Microspheres presented so far are elastic and are loaded with charged molecules post-synthesis via ion exchange. In contrast, different types of biodegradable microspheres containing drugs are prepared from poly(D,L-lactic acid) (PLA) and PLGA [23, 24, 26].

PLA microspheres (from Purasorb PDL 20) with sizes between 200 and 400 µm and catheter deliverability (4-Fr catheter) hold high drug loads up to 16% (w/w) sorafenib, 12% (w/w) cisplatin or both drugs in the same spheres (7% (w/w) sorafenib and 5% (w/w) cisplatin) [26]. Both drugs and the polymer are of hydrophobic nature, allowing for drug incorporation by solvent evaporation, opposed to hydrogels and the more water-soluble, charged drugs. Drug release from the combination microspheres showed an initial burst of superficially bound drug, followed by prolonged drug release over 14 days. At 14 days, 91% of sorafenib and 48% of cisplatin were released at pH 7.4. Compared to the single drug-loaded microspheres, release was faster due to the more porous structure and water swelling of the combination drug-eluting microspheres, precluding subsequent degradation-driven release. The drug combination strategy possibly circumvents tumor drug resistance and in addition, synergic effects were reported both *in vitro* on cell viability and *in vivo* on tumor growth by the simultaneous release of the two drugs [86]. As for

degradability, the three types of microspheres were not degraded after 9 months. The degradation half time was modeled to be 7 weeks for the two single drug-loaded microspheres and around 10 weeks for the combination microspheres. The authors assigned the longer degradation time for the sorafenib+cisplatin microspheres to a more porous structure, outward-diffusion of lactic acid monomers and consequently reduced autocatalytic acidic hydrolysis. PLA microspheres might be modified in the future for faster degradation, although their relatively long degradation time does not necessarily represent a disadvantage.

More hydrophilic PLGA microspheres result in faster degradation. Magnetic resonance (MR) image-able, sorafenib-loaded (19% (w/w)) PLGA microspheres (from 75:25 PLGA Resomer RG 752H) were also proposed for embolization [23]. Inclusion of iron oxide nanoparticles confers the MRI ability. The microspheres were polydisperse with an average diameter of 13 µm, which was adapted for animal embolization, yet is too small for clinical application due to risk of arteriovenous shunting. Sorafenib was released in a sustained manner into PBS + 1% sodium dodecyl sulfate (SDS), with a release of 21% after 3 days. Microsphere degradation was not assessed in this study, but was assumed to be complete during the course of drug release. In a rabbit VX2 model, normalization of VEGF receptor expression and decrease in microvessel density were shown at 24 hours, which were signs of successful sorafenib delivery [23]. Although the size of these microspheres is currently an issue for translation into clinical practice, they combine various features necessary for further development, such as biocompatibility, degradability, combined imaging and efficient entrapment and delivery of sorafenib.

Doxorubicin-loaded microspheres made from a comparable type of PLGA (75:25) led to similar results [24]. The microspheres showed visible signs of partial degradation in serum after 2 weeks, like decrease in size, loss of sphericity, and pore formation. Their diameter was 26 µm before degradation with a doxorubicin load of 25 mg/g PLGA microspheres and a release of 35% after 3 days. For these two similar types of PLGA microspheres, longer degradation and release studies should be carried out to exclude drug dose dumping at later time points.

3. Drug Pharmacokinetics after DEB-TACE

DEB-TACE was adopted in clinical practice after evidence of treatment safety had been assured [88]. Varela et al. [9] and Poon et al. [10] had shown the absence of the initial peak in doxorubicin plasma concentration compared to cTACE right after the procedure. One of the apparent advantages of doxorubicin-eluting beads-TACE is the locally controlled and even sustained drug release. However, drug release profiles of currently developed biodegradable embolic microspheres are not uniformly fast or prolonged (Table 2). For example, the newly developed systems, based on drug loading by ion exchange, were criticized in a recent review for their non-linear, i.e. fast drug release [89]. Fast release kinetics can however always be expected for microspheres with ion exchange triggered drug release, and may even be desired. In a recent study, instantaneous doxorubicin release was aimed for to enhance drug tumor penetration: Rapid release of high doxorubicin doses from liposomes incorporated in embolic microspheres was heat-triggered [25]. Likewise, Lilienberg et al. [90] determined the intracellular doxorubicin concentrations in healthy pig livers to be higher after cTACE than DEB-TACE, i.e. after burst release, however, at the cost of safety.

Given the controversy in literature about fast or sustained release, we will thus approach the question of which drug release profile is actually sought for successful therapy. Since systemic (plasma) concentrations are known to be reduced as a result of the DEB procedure, we will focus on the drug target tissue concentrations and distribution, which currently little is known about.

3.1 Pharmacokinetic Profiles in the Targeted Tissue

The advantage of local administration of DEB as a drug delivery system over systemic delivery is the resulting locally increased and sustained drug concentrations with very low drug concentration in non-targeted tissues [24, 90-93]. Several studies also assess drug pharmacokinetics in the targeted tissue over time (Table 3). For the time being, these were carried out with non-biodegradable beads eluting drugs by ion exchange. Increased drug tissue levels are seen shortly after administration for all drugs in Table 3. For example, Hong et al. [94] observed a clear doxorubicin peak 3 days after the embolization,

after which levels decreased. Rao et al. [92] determined increasing irinotecan tissue levels until 24 hours. Fuchs et al. found sunitinib levels higher at 6 hours than at 24 hours after embolization [53]. Thus, ion exchange microspheres result in fast drug availability in the targeted tissue after fast release from the microspheres. The drug is relatively quickly available first in the tissue compartment and second in the plasma [53]. For the final drug tissue residence time, both physicochemical drug and tissue properties are decisive. Doxorubicin was detected in human liver explants up to 36 days after DEB-TACE [95], whereas irinotecan was present at low concentrations in rabbit livers 7 days after administration [96]. Four days after normal sheep lung embolization, neither irinotecan nor its primary metabolite were detectable [91, 97]. This finding had to be attributed to the specific lung architecture, where blood flow increases and the bronchial arteries enlarge after pulmonary embolization. Taken together, these results demonstrate that drug retention in the tissue is not only governed by the drug release time from the beads, but depends mainly on the physiology of the tissue environment. While Namur et al. did not detect differences in intra- and peritumoral doxorubicin levels at 8 hours, doxorubicin retention was significantly evidenced in necrotic tissue compared to non-necrotic tissue at 32-36 days [95]. For sunitinib, levels were retained in tumor tissue until 14 days after rabbit VX2 liver tumor embolization, more than in normal liver [98]. This was in accordance with a population pharmacokinetic meta-analysis by Houk et al., suggesting that the clearance for both sunitinib and its primary metabolite is reduced in patients compared to healthy adult volunteers [99]. Moreover, anti-angiogenic drugs are known to normalize interstitial pressure and flow in leaky tumor vasculature, eventually leading to enhanced drug tumor penetration and availability [12, 100]. When given orally, low dose regular (metronomic) administration within the therapeutic range is most efficacious [100]. Prolonged release and increased tissue residence time are therefore desired characteristics for anti-angiogenic drug delivery.

These data support that ion exchange microspheres result in fast drug availability in the targeted tissue, whereas both drug and tissue properties are eventually critical for drug tissue residence time.

Table 3. Preclinical and clinical studies investigating drug tissue levels and/or distribution after DEB-TACE.

Drug	DEB	Size (µm)	Dose	Model	Time	Tissue concentration	Samples for quantification	Reference
Doxorubicin (DOX)	DC Bead	100-300	45 mg drug/g wet beads, dose delivered: 11.25 mg	Rabbit VX2 liver tumor	1 h, 12 h, 24 h, 3d, 7 d, 14 d	Tumor: 413.5 at 3 d, 116.7 at 7 d, 41.76 at 14 d (µM), non-tumorous tissue: 2-17 µM (range over 14 d)	Homogenized tumor or liver	[94]
	DC Bead	100-300, 700-900	37.5 mg/mL beads, mean dose delivered: 103 mg	Porcine normal liver	28 d, 90 d	100-300 µm: 3.25 (bead edge)-0.55 (600 µm distance) at 28 d, 1.55-0.60 at 90 d, 700-900 µm: 6.80-0.90 at 28 d, 2.60-0.70 at 90 d (µM)	Microspectrofluorimetry on liver tissue sections	[101]
	DC Bead	100-300	37.5 mg/mL beads, mean dose delivered: 98.3 ± 24.4 mg	HCC patients	8 h, 9-14 d, 32-36 d	8.45 (bead edge)-3.55 (600 µm distance) at 8 h, 4.50-1.40 at 9-14 d, 1.55 to 0.45 at 32-36 d (µM)	Microspectrofluorimetry on liver tissue sections	[95]
	DC Bead	70-150, 100-300	37.5 mg/mL beads, dose delivered: 37.5 mg	Normal swine liver	0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 7 d	Adjacent to bead: 70-150 µm: 30-40 at 0.5 h, 7 at 24 h, 5 at 7 d, 100-300 µm: 30-40 at 0.5 h, 3 at 24 h, close to 0 at 7 d (µM)	Epifluorescent microscopy	[46]
Ibuprofen	Bead Block	500-700	485 mM-loaded beads, 0.5 mL of beads injected	Sheep uterine tissue	1 d, 1 week	8.8 ± 4.8 mM in the vessel wall at 1 d, not detected 100 µm from occluded artery, 1 week: <LLOQ	Fourier transform infrared microspectroscopy on tissue sections	[102]
Irinotecan (IRI)	DC Bead	100-300	10, 20, 50 mg/mL beads, dose delivered: 20, 40, 100 mg	Sheep normal lung	4 d, 4 weeks	IRI and SN38 < LLOQ for all doses	Infrared microspectroscopy on lung tissue sections	[97]

	DC Bead	300-500	0, 10, 25, 50 mg/mL beads, dose delivered: 0, 20, 50, 100 mg	Sheep normal lung	4 d, 4 weeks	IRI and SN38 < LLOQ for all doses	Homogenized lung	[91]
	DC Bead	300-500 for PAE, 100-300 for BAE	50 mg/mL beads, dose delivered: 100 mg single embolization, 200 mg double embolization	Sheep normal lung	4 d	PAE-50+BAE-0: IRI: 1122±237, SN38: 35±21, PAE-50+BAE-50: IRI: 16±1, SN38: 3286±2769 (ng/mL)	Homogenized lung	[103]
	DC Bead	100-300	100 mg/mL beads, no fixed dose administered	Rabbit VX2 liver tumor	1 h, 6 h, 24 h	Tumor: IRI: 101.1 at 1 h, 210.4 at 6 h, 872.2 at 24 h, SN38: 9.7 at 1 h, 23.1 at 6 h, 351.1 at 24 h (ng/g)	Homogenized tumor, normal liver within 2 mm to tumor, contralateral liver	[92]
	QuadraSphere	30-60	20 mg/mL beads, dose delivered: 12 mg	Rabbit VX2 liver tumor	7 d	Tumor: IRI: 32.17, SN38: 463.33 (ng/g)	Homogenized tumor, normal liver adjacent to tumor, normal liver at least 1 cm apart from tumor	[96]
Sunitinib	DC Bead	100-300	30 mg/g beads, dose delivered: 6 mg	Healthy rabbit liver	6 h, 24 h	14.9 µg/g at 6 h, 3.4 µg/g at 24 h	Homogenized liver	[53]
	DC Bead	70-150, 100-300	30 mg/g beads, dose delivered: 1.5 mg	Rabbit VX2 liver tumor	1 d, 14 d	Tumor: 70-150 µm: 40.4 at 1 d, 27.4 at 14 d, 100-300 µm: 17.8 at 1 d, 0.16 at 14 d (µg/g)	Homogenized tumor or contralateral liver	[93]
	DC Bead	70-150			1-2 d, 7 d, 12-14d	Tumor: <LLOQ at 1-2 d, 39 (bead edge)-19 (1.5 mm distance) at 7 d, 54-23 at 12-14 d (µg/g)	Fluorescence microscopy (also: mass spectrometry imaging)	[98]

LLOQ: lower limit of quantification, PAE: pulmonary artery embolization, BAE: bronchial artery embolization, IRI: irinotecan, SN38: primary irinotecan metabolite, PAE-50+BAE-0: PAE with DEB-IRI and BAE with bland DEB, PAE-50+BAE-50: PAE with DEB-IRI and BAE with DEB-IRI

3.2 Drug Tissue Distribution

In order for the drug to yield its pharmacological effect, it has to reach the targeted tissue in effective concentration. Different markers have been employed to estimate drug distribution into the tissue. Since tumor necrosis is an indicator for tumor response and is often increased with concomitant drug delivery in addition to the embolization itself, necrotic tumor regions are also an indicator for the spatial drug distribution [93, 94, 103, 104]. Inflammation factors were also used for indirect determination of drug diffusion [105]. Most conclusive results are, however, obtained by direct determination of drug distribution. For example, doxorubicin and sunitinib have been imaged by means of their inherent fluorescence, and sunitinib and its metabolites were recently also determined by mass spectrometry imaging [46, 95, 98, 101].

Doxorubicin was detected at a distance of up to 600 µm from the bead rim and up to 90 and 32-36 days after embolization in healthy pigs and HCC liver explants, respectively [46, 95, 101]. Compared to non-necrotic tissue, doxorubicin diffusion went farther and was more homogenous in necrotic tissue, where drug distribution profiles appeared “flatter”, possibly due to cellular disorganization [95]. In comparison, sunitinib was detected over at least 1.5 mm away from the beads and still at high drug levels in the tumor 14 days after treatment [93, 98]. This distant diffusion from the delivering beads is desirable to impregnate wide-spread tumor areas. Sunitinib levels were especially high in the necrotic tumor [98]. Moreover, sunitinib metabolism was also evidenced in this study, with four major metabolites present at 7 and 13 days. The available data suggest different tissue distribution for both doxorubicin and sunitinib. Table 4 compares the physicochemical properties of doxorubicin and sunitinib. Sunitinib has a lower molecular weight, higher degree of ionization at physiological pH, higher lipophilicity, higher volume of distribution, and later elimination compared to doxorubicin, favoring farther distribution into the tissue.

Table 4. Physicochemical properties of doxorubicin and sunitinib.

	Doxorubicin [106, 107]	Sunitinib [107, 108]
Molecular weight (g/mol)	543.52	398.47
pKa	7.34, 8.46, 9.46	9.30
Ionized form at pH 7.4	max. 50%	98.30%
log P	pH 7.5: 2.42 ± 0.08	2.47 (XLOGP2), pH 7.4: 5.2 (experimental)
Volume of distribution V_d	809 to 1214 L/m^2	2230 L
Protein binding	74-76%	95%
Half life	20-48 h	40-60 h

4. Conclusions on Controlled Drug Release from Drug-Eluting Beads and Qualitative *In Vitro-In Vivo* Comparison

Initially, we raised the question about the "ideal drug release profile", and whether sustained drug release was required to achieve long-term exposure of the tumor to the drug. Hereby, we differentiated between the release mechanism of the drug from the microspheres and the subsequent interaction of the drug with the tissue. We elucidated that ion exchange microspheres – commercialized ones as well as microspheres under development, biodegradable and non-biodegradable ones – yield fast release, which mainly depends on the kinetics of the ion exchange release mechanism itself rather than the nature of the drug. The extent of release in contrast is more related to the drug and drug-drug interactions as seen for doxorubicin. For biodegradable polymer drug delivery systems, in which a drug is physically entrapped, kinetics is expected to be more prolonged. In the latter case, the drug is released as a result of initial polymer swelling, diffusion and degradation mechanism, certainly with differences for surface or bulk degradation. Complete release will be achieved upon complete degradation of the delivery system.

However, drug diffusion into the targeted tissue and eventual drug residence time depend on the drug's physicochemical properties and tissue characteristics like vascular flow and interstitial pressure, presence of proteins, lipids, and cell metabolism. This step is

independent of the earlier drug release kinetics from the microspheres. Thus, manipulation of a fast-releasing delivery system toward sustained drug release should only be considered if the resulting drug residence time after rapid release is too short to obtain a therapeutic effect. Sustained release is certainly not required for locoregional delivery of small chemotherapeutic molecules such as doxorubicin, which remain in the tissue for several months.

Furthermore, drug residence time in the tissue after locoregional drug delivery might be aimed to resemble drug availability after systemic drug administration. Usual dosing of chemotherapeutics includes a recovery break, which should be taken into account also for local delivery to avoid toxicity or resistance. In contrast to chemotherapeutic drugs, systemic dosing of anti-angiogenic drugs was proven most efficacious with regular low-dose administration. After a single local administration of an anti-angiogenic drug via microspheres, prolonged drug residence time in the tissue might thus be desirable.

Since existing data regarding the PK distribution in the tissue of commonly used agents against HCC is scarce, more quantitative studies are needed. This is of particular importance for new drug delivery systems that are currently under development.

Recently, a mass spectrometry imaging method has been employed for the first time in embolized liver [98]. This method should be an interesting tool in the future to map a drug's spatial diffusion into the tissue and is applicable also to non-fluorescent drugs.

Disclosures

AD is a contracted consultant for BTG, Farnham, UK. Patent WO 2012/073188 A1 was issued and licensed to BTG by AD, PEB, OJ. All other authors do not declare a conflict of interest.

References

[1] N.D. Theise, Liver Cancer, in: B.W. Stewart, Wild, C. P. (Ed.) World Cancer Report 2014, IARC Nonserial Publication, Lyon, 2015.
[2] C.M. Lo, H. Ngan, W.K. Tso, C.L. Liu, C.M. Lam, R.T. Poon, S.T. Fan, J. Wong, Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma, Hepatology, 35 (2002) 1164-1171.
[3] J.M. Llovet, M.I. Real, X. Montana, R. Planas, S. Coll, J. Aponte, C. Ayuso, M. Sala, J. Muchart, R. Sola, J. Rodes, J. Bruix, Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial, Lancet, 359 (2002) 1734-1739.
[4] J.M. Llovet, J. Bruix, Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival, Hepatology, 37 (2003) 429-442.
[5] J.L. Raoul, B. Sangro, A. Forner, V. Mazzaferro, F. Piscaglia, L. Bolondi, R. Lencioni, Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization, Cancer treatment reviews, 37 (2011) 212-220.
[6] A. Forner, M. Gilabert, J. Bruix, J.L. Raoul, Treatment of intermediate-stage hepatocellular carcinoma, Nature reviews. Clinical oncology, 11 (2014) 525-535.
[7] A. Facciorusso, R. Licinio, N. Muscatiello, A. Di Leo, M. Barone, Transarterial chemoembolization: Evidences from the literature and applications in hepatocellular carcinoma patients, World journal of hepatology, 7 (2015) 2009-2019.
[8] R. Lencioni, T. de Baere, M. Burrel, J.G. Caridi, J. Lammer, K. Malagari, R.C. Martin, E. O'Grady, M.I. Real, T.J. Vogl, A. Watkinson, J.F. Geschwind, Transcatheter Treatment of Hepatocellular Carcinoma with Doxorubicin-loaded DC Bead (DEBDOX): Technical Recommendations, Cardiovascular and interventional radiology, 35 (2012) 980-985.
[9] M. Varela, M.I. Real, M. Burrel, A. Forner, M. Sala, M. Brunet, C. Ayuso, L. Castells, X. Montana, J.M. Llovet, J. Bruix, Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics, Journal of hepatology, 46 (2007) 474-481.
[10] R.T. Poon, W.K. Tso, R.W. Pang, K.K. Ng, R. Woo, K.S. Tai, S.T. Fan, A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead, Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association, 5 (2007) 1100-1108.
[11] J. Meza-Junco, A.J. Montano-Loza, D.M. Liu, M.B. Sawyer, V.G. Bain, M. Ma, R. Owen, Locoregional radiological treatment for hepatocellular carcinoma; Which, when and how?, Cancer treatment reviews, 38 (2012) 54-62.
[12] A.M. Al-Abd, Z.K. Aljehani, R.W. Gazzaz, S.H. Fakhri, A.H. Jabbad, A.M. Alahdal, V.P. Torchilin, Pharmacokinetic strategies to improve drug penetration and entrapment within solid tumors, Journal of Controlled Release, 219 (2015) 269-277.
[13] S.W. Shin, The Current Practice of Transarterial Chemoembolization for the Treatment of Hepatocellular Carcinoma, Korean journal of radiology : official journal of the Korean Radiological Society, 10 (2009) 425-434.
[14] K. Hong, H. Kobeiter, C.S. Georgiades, M.S. Torbenson, J.F. Geschwind, Effects of the type of embolization particles on carboplatin concentration in liver tumors after transcatheter arterial chemoembolization in a rabbit model of liver cancer, Journal of vascular and interventional radiology : JVIR, 16 (2005) 1711-1717.

[15] X. Zhang, H.L.H. Ng, A.P. Lu, C.C. Lin, L.M. Zhou, G. Lin, Y.B. Zhang, Z.J. Yang, H.Q. Zhang, Drug delivery system targeting advanced hepatocellular carcinoma: Current and future, Nanomed-Nanotechnol, 12 (2016) 853-869.
[16] T.J. Vogl, S. Zangos, K. Eichler, D. Yakoub, M. Nabil, Colorectal liver metastases: regional chemotherapy via transarterial chemoembolization (TACE) and hepatic chemoperfusion: an update, European radiology, 17 (2007) 1025-1034.
[17] A. Schwarz, H. Zhang, A. Metcalfe, I. Salazkin, J. Raymond, Transcatheter embolization using degradable crosslinked hydrogels, Biomaterials, 25 (2004) 5209-5215.
[18] R.E.J. Forster, F. Thürmer, C. Wallrapp, A.W. Lloyd, W. Macfarlane, G.J. Phillips, J.-P. Boutrand, A.L. Lewis, Characterisation of physico-mechanical properties and degradation potential of calcium alginate beads for use in embolisation, Journal of Materials Science: Materials in Medicine, 21 (2010) 2243-2251.
[19] L. Weng, H.C. Le, R. Talaie, J. Golzarian, Bioresorbable hydrogel microspheres for transcatheter embolization: preparation and in vitro evaluation, Journal of vascular and interventional radiology : JVIR, 22 (2011) 1464-1470 e1462.
[20] T. Toyama, N. Nitta, S. Ohta, T. Tanaka, Y. Nagatani, M. Takahashi, K. Murata, H. Shiomi, S. Naka, Y. Kurumi, T. Tani, Y. Tabata, Clinical trial of cisplatin-conjugated gelatin microspheres for patients with hepatocellular carcinoma, Japanese journal of radiology, 30 (2012) 62-68.
[21] S. Louguet, V. Verret, L. Bedouet, E. Servais, F. Pascale, M. Wassef, D. Labarre, A. Laurent, L. Moine, Poly(ethylene glycol) methacrylate hydrolyzable microspheres for transient vascular embolization, Acta Biomater, 10 (2014) 1194-1205.
[22] X. Zhou, M. Kong, X.J. Cheng, C. Feng, J. Li, J.J. Li, X.G. Chen, In vitro and in vivo evaluation of chitosan microspheres with different deacetylation degree as potential embolic agent, Carbohydrate polymers, 113 (2014) 304-313.
[23] J. Chen, S.B. White, K.R. Harris, W. Li, J.W. Yap, D.H. Kim, R.J. Lewandowski, L.D. Shea, A.C. Larson, Poly(lactide-co-glycolide) microspheres for MRI-monitored delivery of sorafenib in a rabbit VX2 model, Biomaterials, 61 (2015) 299-306.
[24] J.W. Choi, J.-H. Park, S.Y. Baek, D.-D. Kim, H.-C. Kim, H.-J. Cho, Doxorubicin-loaded poly(lactic-co-glycolic acid) microspheres prepared using the solid-in-oil-in-water method for the transarterial chemoembolization of a liver tumor, Colloids and Surfaces B: Biointerfaces, 132 (2015) 305-312.
[25] M. van Elk, B. Ozbakir, A.D. Barten-Rijbroek, G. Storm, F. Nijsen, W.E. Hennink, T. Vermonden, R. Deckers, Alginate Microspheres Containing Temperature Sensitive Liposomes (TSL) for MR-Guided Embolization and Triggered Release of Doxorubicin, PloS one, 10 (2015) e0141626.
[26] Y. Wang, A. Benzina, D.G.M. Molin, N.v.d. Akker, M. Gagliardi, L.H. Koole, Preparation and structure of drug-carrying biodegradable microspheres designed for transarterial chemoembolization therapy, Journal of Biomaterials Science, Polymer Edition, 26 (2015) 77-91.
[27] J. Yan, F. Wang, J. Chen, T. Liu, T. Zhang, Preparation and Characterization of Irinotecan Loaded Cross-Linked Bovine Serum Albumin Beads for Liver Cancer Chemoembolization Therapy, International Journal of Polymer Science, 2016 (2016) 8.
[28] L. Faloppi, M. Scartozzi, E. Maccaroni, M. Di Pietro Paolo, R. Berardi, M. Del Prete, S. Cascinu, Evolving strategies for the treatment of hepatocellular carcinoma: from clinical-guided to molecularly-tailored therapeutic options, Cancer treatment reviews, 37 (2011) 169-177.
[29] A. Villanueva, Rethinking future development of molecular therapies in hepatocellular carcinoma: a bottom-up approach, Journal of hepatology, 59 (2013) 392-395.
[30] Z. Wang, W. Zhou, H. Zhang, L. Qiao, Combination of anti-angiogenesis agents and transarterial embolization: Is it a promising approach for the treatment of liver cancer?, Discovery medicine, 20 (2015) 51-55.
[31] Y.X. Wang, T. De Baere, J.M. Idee, S. Ballet, Transcatheter embolization therapy in liver cancer: an update of clinical evidences, Chin J Cancer Res, 27 (2015) 96-121.

[32] A.L. Lewis, M.V. Gonzalez, A.W. Lloyd, B. Hall, Y. Tang, S.L. Willis, S.W. Leppard, L.C. Wolfenden, R.R. Palmer, P.W. Stratford, DC bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization, Journal of vascular and interventional radiology : JVIR, 17 (2006) 335-342.
[33] R.R. Taylor, Y. Tang, M.V. Gonzalez, P.W. Stratford, A.L. Lewis, Irinotecan drug eluting beads for use in chemoembolization: in vitro and in vivo evaluation of drug release properties, European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, 30 (2007) 7-14.
[34] O. Jordan, A. Denys, T. De Baere, N. Boulens, E. Doelker, Comparative study of chemoembolization loadable beads: in vitro drug release and physical properties of DC bead and hepasphere loaded with doxorubicin and irinotecan, Journal of vascular and interventional radiology : JVIR, 21 (2010) 1084-1090.
[35] A.L. Lewis, C. Adams, W. Busby, S.A. Jones, L.C. Wolfenden, S.W. Leppard, R.R. Palmer, S. Small, Comparative in vitro evaluation of microspherical embolisation agents, Journal of Materials Science: Materials in Medicine, 17 (2006) 1193-1204.
[36] S. Stampfl, N. Bellemann, U. Stampfl, C.M. Sommer, H. Thierjung, R. Lopez-Benitez, B. Radeleff, I. Berger, G.M. Richter, Arterial Distribution Characteristics of Embozene Particles and Comparison with Other Spherical Embolic Agents in the Porcine Acute Embolization Model, Journal of Vascular and Interventional Radiology, 20 (2009) 1597-1607.
[37] V. Verret, S.H. Ghegediban, M. Wassef, J.P. Pelage, J. Golzarian, A. Laurent, The arterial distribution of Embozene and Embosphere microspheres in sheep kidney and uterus embolization models, Journal of vascular and interventional radiology : JVIR, 22 (2011) 220-228.
[38] V. Verret, M. Wassef, J.P. Pelage, S.H. Ghegediban, L. Jouneau, L. Moine, D. Labarre, J. Golzarian, I. Schwartz-Cornil, A. Laurent, Influence of degradation on inflammatory profile of polyphosphazene coated PMMA and trisacryl gelatin microspheres in a sheep uterine artery embolization model, Biomaterials, 32 (2011) 339-351.
[39] J. Namur, F. Pascale, N. Maeda, M. Sterba, S.H. Ghegediban, V. Verret, A. Paci, A. Seck, K. Osuga, M. Wassef, P. Reb, A. Laurent, Safety and Efficacy Compared between Irinotecan-Loaded Microspheres HepaSphere and DC Bead in a Model of VX2 Liver Metastases in the Rabbit, Journal of Vascular and Interventional Radiology, 26 (2015) 1067-1075.e1063.
[40] D.B. Brown, T.K. Pilgram, M.D. Darcy, C.E. Fundakowski, M. Lisker-Melman, W.C. Chapman, J.S. Crippin, Hepatic arterial chemoembolization for hepatocellular carcinoma: comparison of survival rates with different embolic agents, Journal of vascular and interventional radiology : JVIR, 16 (2005) 1661-1666.
[41] A. Massmann, T. Rodt, S. Marquardt, R. Seidel, K. Thomas, F. Wacker, G.M. Richter, H.U. Kauczor, A. Bucker, P.L. Pereira, C.M. Sommer, Transarterial chemoembolization (TACE) for colorectal liver metastases--current status and critical review, Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie, 400 (2015) 641-659.
[42] P. Giunchedi, M. Maestri, E. Gavini, P. Dionigi, G. Rassu, Transarterial chemoembolization of hepatocellular carcinoma--agents and drugs: an overview. Part 2, Expert opinion on drug delivery, 10 (2013) 799-810.
[43] M.J. Abdekhodaie, X.Y. Wu, Drug loading onto ion-exchange microspheres: Modeling study and experimental verification, Biomaterials, 27 (2006) 3652-3662.
[44] M.V. Gonzalez, Y. Tang, G.J. Phillips, A.W. Lloyd, B. Hall, P.W. Stratford, A.L. Lewis, Doxorubicin eluting beads-2: methods for evaluating drug elution and in-vitro:in-vivo correlation, Journal of materials science. Materials in medicine, 19 (2008) 767-775.
[45] C.L. Heaysman, G.J. Phillips, A.W. Lloyd, A.L. Lewis, Synthesis and characterisation of cationic quaternary ammonium-modified polyvinyl alcohol hydrogel beads as a drug delivery embolisation system, Journal of Materials Science: Materials in Medicine, 27 (2016) 1-10.

[46] M.R. Dreher, K.V. Sharma, D.L. Woods, G. Reddy, Y. Tang, W.F. Pritchard, O.A. Chiesa, J.W. Karanian, J.A. Esparza, D. Donahue, E.B. Levy, S.L. Willis, A.L. Lewis, B.J. Wood, Radiopaque drug-eluting beads for transcatheter embolotherapy: experimental study of drug penetration and coverage in swine, Journal of vascular and interventional radiology : JVIR, 23 (2012) 257-264.e254.
[47] A.H. Negussie, M.R. Dreher, C.G. Johnson, Y. Tang, A.L. Lewis, G. Storm, K.V. Sharma, B.J. Wood, Synthesis and characterization of image-able polyvinyl alcohol microspheres for image-guided chemoembolization, Journal of materials science. Materials in medicine, 26 (2015) 198.
[48] C.G. Johnson, Y. Tang, A. Beck, M.R. Dreher, D.L. Woods, A.H. Negussie, D. Donahue, E.B. Levy, S.L. Willis, A.L. Lewis, B.J. Wood, K.V. Sharma, Preparation of Radiopaque Drug-Eluting Beads for Transcatheter Chemoembolization, Journal of vascular and interventional radiology : JVIR, 27 (2016) 117-126.e113.
[49] R. Duran, K. Sharma, M.R. Dreher, K. Ashrafi, S. Mirpour, M. Lin, R.E. Schernthaner, T.R. Schlachter, V. Tacher, A.L. Lewis, S. Willis, M. den Hartog, A. Radaelli, A.H. Negussie, B.J. Wood, J.F. Geschwind, A Novel Inherently Radiopaque Bead for Transarterial Embolization to Treat Liver Cancer - A Pre-clinical Study, Theranostics, 6 (2016) 28-39.
[50] R.E. Forster, Y. Tang, C. Bowyer, A.W. Lloyd, W. Macfarlane, G.J. Phillips, A.L. Lewis, Development of a combination drug-eluting bead: towards enhanced efficacy for locoregional tumour therapies, Anti-cancer drugs, 23 (2012) 355-369.
[51] A. Hagan, W. Macfarlane, A. Lloyd, G. Phillips, R. Holden, Z. Bascal, R. Whomsley, H. Kilpatrick, Y. Tang, A. Lewis, J. Namur, F. Pascale, J. Pelage, In vitro and in vivo characterisation of a multiple tyrosine kinase inhibitor drug eluting bead, Journal of Vascular and Interventional Radiology, 27 (2016) S84.
[52] K. Ashrafi, Y. Tang, H. Britton, O. Domenge, D. Blino, A.J. Bushby, K. Shuturminska, M. den Hartog, A. Radaelli, A.H. Negussie, A.S. Mikhail, D.L. Woods, V. Krishnasamy, E.B. Levy, B.J. Wood, S.L. Willis, M.R. Dreher, A.L. Lewis, Characterization of a novel intrinsically radiopaque Drug-eluting Bead for image-guided therapy: DC Bead LUMI, Journal of controlled release : official journal of the Controlled Release Society, 250 (2017) 36-47.
[53] K. Fuchs, P.E. Bize, O. Dormond, A. Denys, E. Doelker, G. Borchard, O. Jordan, Drug-eluting beads loaded with antiangiogenic agents for chemoembolization: in vitro sunitinib loading and release and in vivo pharmacokinetics in an animal model, Journal of vascular and interventional radiology : JVIR, 25 (2014) 379-387 e372.
[54] O.S. Sakr, S. Berndt, G. Carpentier, M. Cuendet, O. Jordan, G. Borchard, Arming embolic beads with anti-VEGF antibodies and controlling their release using LbL technology, Journal of controlled release : official journal of the Controlled Release Society, 224 (2016) 199-207.
[55] V. Tacher, R. Duran, M. Lin, J.H. Sohn, K.V. Sharma, Z. Wang, J. Chapiro, C. Gacchina Johnson, N. Bhagat, M.R. Dreher, D. Schafer, D.L. Woods, A.L. Lewis, Y. Tang, M. Grass, B.J. Wood, J.F. Geschwind, Multimodality Imaging of Ethiodized Oil-loaded Radiopaque Microspheres during Transarterial Embolization of Rabbits with VX2 Liver Tumors, Radiology, 279 (2016) 741-753.
[56] K. Fuchs, P.E. Bize, A. Denys, G. Borchard, O. Jordan, Sunitinib-eluting beads for chemoembolization: methods for in vitro evaluation of drug release, International journal of pharmaceutics, 482 (2015) 68-74.
[57] M. D'Anzeo, L. Faloppi, M. Scartozzi, R. Giampieri, M. Bianconi, M. Del Prete, N. Silvestris, S. Cascinu, The role of micro-RNAs in hepatocellular carcinoma: from molecular biology to treatment, Molecules, 19 (2014) 6393-6406.
[58] M. Zhang, X. Zhou, B. Wang, B.C. Yung, L.J. Lee, K. Ghoshal, R.J. Lee, Lactosylated gramicidin-based lipid nanoparticles (Lac-GLN) for targeted delivery of anti-miR-155 to hepatocellular carcinoma, Journal of controlled release : official journal of the Controlled Release Society, 168 (2013) 251-261.
[59] J. Varshosaz, M. Farzan, Nanoparticles for targeted delivery of therapeutics and small interfering RNAs in hepatocellular carcinoma, World journal of gastroenterology : WJG, 21 (2015) 12022-12041.

[60] K.V. Sharma, Z. Bascal, H. Kilpatrick, K. Ashrafi, S.L. Willis, M.R. Dreher, A.L. Lewis, Long-term biocompatibility, imaging appearance and tissue effects associated with delivery of a novel radiopaque embolization bead for image-guided therapy, Biomaterials, 103 (2016) 293-304.
[61] A. Mikhail, E. Levy, V. Krishnasamy, F. Banovac, A. Negussie, W. Pritchard, J. Karanian, I. Bakhutashvili, J. Esparza-Trujillo, D. Woods, Y. Tang, C. Macfarlane, S. Willis, A. Lewis, B. Wood, Mapping drug dose distribution with conventional IR imaging following hepatic DEBTACE with drug-eluting radiopaque beads (DEROB), in: Journal of Vascular and Interventional Radiology, Elsevier, 2016, pp. S126-S127.
[62] X. Li, G.S. Feng, C.S. Zheng, C.K. Zhuo, X. Liu, Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effect of transcatheter arterial chemoembolization therapy on plasma vascular endothelial growth factor level, World journal of gastroenterology : WJG, 10 (2004) 2878-2882.
[63] J.H. Shim, J.W. Park, J.H. Kim, M. An, S.Y. Kong, B.H. Nam, J.I. Choi, H.B. Kim, W.J. Lee, C.M. Kim, Association between increment of serum VEGF level and prognosis after transcatheter arterial chemoembolization in hepatocellular carcinoma patients, Cancer science, 99 (2008) 2037-2044.
[64] A. Sergio, C. Cristofori, R. Cardin, G. Pivetta, R. Ragazzi, A. Baldan, L. Girardi, U. Cillo, P. Burra, A. Giacomin, F. Farinati, Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness, The American journal of gastroenterology, 103 (2008) 914-921.
[65] B. Wang, H. Xu, Z.Q. Gao, H.F. Ning, Y.Q. Sun, G.W. Cao, Increased expression of vascular endothelial growth factor in hepatocellular carcinoma after transcatheter arterial chemoembolization, Acta Radiol, 49 (2008) 523-529.
[66] G. Ranieri, M. Ammendola, I. Marech, A. Laterza, I. Abbate, C. Oakley, A. Vacca, R. Sacco, C.D. Gadaleta, Vascular endothelial growth factor and tryptase changes after chemoembolization in hepatocarcinoma patients, World journal of gastroenterology : WJG, 21 (2015) 6018-6025.
[67] G. Ranieri, I. Marech, V. Lorusso, V. Goffredo, A. Paradiso, D. Ribatti, C.D. Gadaleta, Molecular targeting agents associated with transarterial chemoembolization or radiofrequency ablation in hepatocarcinoma treatment, World journal of gastroenterology : WJG, 20 (2014) 486-497.
[68] V. Gogineni, S. White, Inhibition of HIF-1 alpha induced survival under hypoxic conditions in liver cancer cells, in: Journal of Vascular and Interventional Radiology, Elsevier, 2016, pp. S21-S22.
[69] K.Y. Tam, K.C. Leung, Y.X. Wang, Chemoembolization agents for cancer treatment, European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, 44 (2011) 1-10.
[70] K. Wasser, F. Giebel, R. Fischbach, H. Tesch, P. Landwehr, Transcatheter arterial chemoembolization of colorectal liver metastases using degradable starch microspheres (Spherex®), Der Radiologe, 45 (2005) 633-643.
[71] V. Verret, J.P. Pelage, M. Wassef, S. Louguet, E. Servais, L. Bedouet, T. Beaulieu, L. Moine, A. Laurent, A novel resorbable embolization microsphere for transient uterine artery occlusion: a comparative study with trisacryl-gelatin microspheres in the sheep model, Journal of vascular and interventional radiology : JVIR, 25 (2014) 1759-1766.
[72] N. Maeda, V. Verret, L. Moine, L. Bedouet, S. Louguet, E. Servais, K. Osuga, N. Tomiyama, M. Wassef, A. Laurent, Targeting and recanalization after embolization with calibrated resorbable microspheres versus hand-cut gelatin sponge particles in a porcine kidney model, Journal of vascular and interventional radiology : JVIR, 24 (2013) 1391-1398.
[73] J. Golzarian, 701.8 - Resorbable particles: are they the future? (ID: 46), in: GEST 2013 Europe, Prague, Czech Republic, 2013.

[74] C.C. Pieper, C. Meyer, B. Vollmar, K. Hauenstein, H.H. Schild, K.E. Wilhelm, Temporary Arterial Embolization of Liver Parenchyma with Degradable Starch Microspheres (EmboCept®S) in a Swine Model, Cardiovascular and interventional radiology, 38 (2015) 435-441.
[75] R.J. Owen, P.N. Nation, R. Polakowski, J.A. Biliske, P.B. Tiege, I.J. Griffith, A Preclinical Study of the Safety and Efficacy of Occlusin™ 500 Artificial Embolization Device in Sheep, Cardiovascular and interventional radiology, 35 (2012) 636-644.
[76] S. Wilhelm, C. Carter, M. Lynch, T. Lowinger, J. Dumas, R.A. Smith, B. Schwartz, R. Simantov, S. Kelley, Discovery and development of sorafenib: a multikinase inhibitor for treating cancer, Nature reviews. Drug discovery, 5 (2006) 835-844.
[77] J.M. Llovet, S. Ricci, V. Mazzaferro, P. Hilgard, E. Gane, J.F. Blanc, A.C. de Oliveira, A. Santoro, J.L. Raoul, A. Forner, M. Schwartz, C. Porta, S. Zeuzem, L. Bolondi, T.F. Greten, P.R. Galle, J.F. Seitz, I. Borbath, D. Haussinger, T. Giannaris, M. Shan, M. Moscovici, D. Voliotis, J. Bruix, Sorafenib in advanced hepatocellular carcinoma, The New England journal of medicine, 359 (2008) 378-390.
[78] L. Weng, H.C. Le, J. Lin, J. Golzarian, Doxorubicin loading and eluting characteristics of bioresorbable hydrogel microspheres: in vitro study, International journal of pharmaceutics, 409 (2011) 185-193.
[79] L. Weng, P. Rostamzadeh, N. Nooryshokry, H.C. Le, J. Golzarian, In vitro and in vivo evaluation of biodegradable embolic microspheres with tunable anticancer drug release, Acta Biomater, 9 (2013) 6823-6833.
[80] L. Weng, D. Seelig, P. Rostamzadeh, J. Golzarian, Calibrated Bioresorbable Microspheres as an Embolic Agent: An Experimental Study in a Rabbit Renal Model, Journal of vascular and interventional radiology : JVIR, 26 (2015) 1887-1894 e1881.
[81] J.S. Kim, B.K. Kwak, H.J. Shim, Y.C. Lee, H.W. Baik, M.J. Lee, S.M. Han, S.H. Son, Y.B. Kim, S. Tokura, B.M. Lee, Preparation of doxorubicin-containing chitosan microspheres for transcatheter arterial chemoembolization of hepatocellular carcinoma, Journal of microencapsulation, 24 (2007) 408-419.
[82] B.K. Kwak, H.J. Shim, S.M. Han, E.S. Park, Chitin-based embolic materials in the renal artery of rabbits: pathologic evaluation of an absorbable particulate agent, Radiology, 236 (2005) 151-158.
[83] S. Ohta, N. Nitta, A. Sonoda, A. Seko, T. Tanaka, M. Takahashi, Y. Kimura, Y. Tabata, K. Murata, Cisplatin-conjugated degradable gelatin microspheres: fundamental study in vitro, The British journal of radiology, 82 (2009) 380-385.
[84] L. Bedouet, V. Verret, S. Louguet, E. Servais, L. Moine, A. Laurent, Doxorubicin, irinotecan and sunitinib: loading and release with a resorbable embolization microsphere (REM), in: Journal of Vascular and Interventional Radiology, Elsevier, 2013, pp. S48.
[85] L. Bedouet, V. Verret, S. Louguet, E. Servais, F. Pascale, A. Beilvert, M.T. Baylatry, D. Labarre, L. Moine, A. Laurent, Anti-angiogenic drug delivery from hydrophilic resorbable embolization microspheres: an in vitro study with sunitinib and bevacizumab, International journal of pharmaceutics, 484 (2015) 218-227.
[86] Y. Wang, D.G.M. Molin, C. Sevrin, C. Grandfils, N.M.S. van den Akker, M. Gagliardi, M.L. Knetsch, T. Delhaas, L.H. Koole, In vitro and in vivo evaluation of drug-eluting microspheres designed for transarterial chemoembolization therapy, International journal of pharmaceutics, 503 (2016) 150-162.
[87] A.L. Lewis, M.V. Gonzalez, S.W. Leppard, J.E. Brown, P.W. Stratford, G.J. Phillips, A.W. Lloyd, Doxorubicin eluting beads - 1: effects of drug loading on bead characteristics and drug distribution, Journal of materials science. Materials in medicine, 18 (2007) 1691-1699.
[88] J. Lammer, K. Malagari, T. Vogl, F. Pilleul, A. Denys, A. Watkinson, M. Pitton, G. Sergent, T. Pfammatter, S. Terraz, Y. Benhamou, Y. Avajon, T. Gruenberger, M. Pomoni, H. Langenberger, M. Schuchmann, J. Dumortier, C. Mueller, P. Chevallier, R. Lencioni, Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study, Cardiovascular and interventional radiology, 33 (2010) 41-52.

[89] A. Poursaid, M.M. Jensen, E. Huo, H. Ghandehari, Polymeric materials for embolic and chemoembolic applications, Journal of Controlled Release, (2016).
[90] E. Lilienberg, C. Ebeling Barbier, R. Nyman, M. Hedeland, U. Bondesson, N. Axen, H. Lennernas, Investigation of hepatobiliary disposition of doxorubicin following intrahepatic delivery of different dosage forms, Molecular pharmaceutics, 11 (2014) 131-144.
[91] M.T. Baylatry, J.P. Pelage, M. Wassef, H. Ghegediban, A.C. Joly, A. Lewis, P. Lacombe, C. Fernandez, A. Laurent, Pulmonary artery chemoembolization in a sheep model: Evaluation of performance and safety of irinotecan eluting beads (DEB-IRI), Journal of biomedical materials research. Part B, Applied biomaterials, 98B (2011) 351-359.
[92] P.P. Rao, F. Pascale, A. Seck, A. Auperin, L. Drouard-Troalen, F. Deschamps, C. Teriitheau, A. Paci, A. Denys, P. Bize, T. de Baere, Irinotecan Loaded in Eluting Beads: Preclinical Assessment in a Rabbit VX2 Liver Tumor Model, Cardiovascular and interventional radiology, (2012).
[93] P. Bize, R. Duran, K. Fuchs, O. Dormond, J. Namur, L.A. Decosterd, O. Jordan, E. Doelker, A. Denys, Antitumoral Effect of Sunitinib-eluting Beads in the Rabbit VX2 Tumor Model, Radiology, 280 (2016) 425-435.
[94] K. Hong, A. Khwaja, E. Liapi, M.S. Torbenson, C.S. Georgiades, J.F. Geschwind, New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer, Clinical cancer research : an official journal of the American Association for Cancer Research, 12 (2006) 2563-2567.
[95] J. Namur, S.J. Citron, M.T. Sellers, M.H. Dupuis, M. Wassef, M. Manfait, A. Laurent, Embolization of hepatocellular carcinoma with drug-eluting beads: doxorubicin tissue concentration and distribution in patient liver explants, Journal of hepatology, 55 (2011) 1332-1338.
[96] K. Tanaka, N. Maeda, K. Osuga, Y. Higashi, A. Hayashi, Y. Hori, K. Kishimoto, E. Morii, F. Ohashi, N. Tomiyama, In vivo evaluation of irinotecan-loaded QuadraSphere microspheres for use in chemoembolization of VX2 liver tumors, Journal of vascular and interventional radiology : JVIR, 25 (2014) 1727-1735 e1721.
[97] J. Namur, Microsphères d'embolisation pour la vectorisation de principes actifs : étude de la libération in vivo par microspectroscopies optiques, in, Université de Reims Champagne-Ardenne, 2009.
[98] K. Fuchs, A. Kiss, P.E. Bize, R. Duran, A. Denys, G. Hopfgartner, G. Borchard, O. Jordan, Mapping of Antiangiogenic Drug Distribution in a Rabbit Model of Liver Cancer by Fluorescence Microscopy and MALDI-SRM/MS Imaging, in: Controlled Release Society Annual Meeting and Exposition, Seattle, WA, USA. , 2016.
[99] B.E. Houk, C.L. Bello, D.W. Kang, M. Amantea, A Population Pharmacokinetic Meta-analysis of Sunitinib Malate (SU11248) and Its Primary Metabolite (SU12662) in Healthy Volunteers and Oncology Patients, Clinical Cancer Research, 15 (2009) 2497-2506.
[100] J. Folkman, Angiogenesis: an organizing principle for drug discovery?, Nature reviews. Drug discovery, 6 (2007) 273-286.
[101] J. Namur, M. Wassef, J.M. Millot, A.L. Lewis, M. Manfait, A. Laurent, Drug-eluting beads for liver embolization: concentration of doxorubicin in tissue and in beads in a pig model, Journal of vascular and interventional radiology : JVIR, 21 (2010) 259-267.
[102] J. Namur, M. Wassef, J.P. Pelage, A. Lewis, M. Manfait, A. Laurent, Infrared microspectroscopy analysis of ibuprofen release from drug eluting beads in uterine tissue, Journal of controlled release : official journal of the Controlled Release Society, 135 (2009) 198-202.
[103] M.-T. Baylatry, Lung chemoembolization with drug eluting beads : in vivo evaluation of anticancer drug release, in, Université Paris Sud - Paris XI, 2011.
[104] J. Namur, F. Pascale, N. Maeda, M. Sterba, S.H. Ghegediban, V. Verret, A. Paci, A. Seck, K. Osuga, M. Wassef, P. Reb, A. Laurent, Safety and efficacy compared between irinotecan-loaded microspheres

HepaSphere and DC bead in a model of VX2 liver metastases in the rabbit, Journal of vascular and interventional radiology : JVIR, 26 (2015) 1067-1075 e1063.
[105] V. Verret, C. Bevilacqua, I. Schwartz-Cornil, J.P. Pelage, M. Wassef, J. Namur, L. Bedouet, A.L. Lewis, P. Martin, A. Laurent, IL6 and TNF expression in vessels and surrounding tissues after embolization with ibuprofen-loaded beads confirms diffusion of ibuprofen, European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, 42 (2011) 489-495.
[106] I.R. Dubbelboer, E. Lilienberg, E. Ahnfelt, E. Sjögren, N. Axén, Lennernäs, Hans, Treatment of intermediate stage hepatocellular carcinoma: a review of intrahepatic doxorubicin drug-delivery systems, Therapeutic delivery, 5 (2014) 447-466.
[107] D.S. Wishart, C. Knox, A.C. Guo, S. Shrivastava, M. Hassanali, P. Stothard, Z. Chang, J. Woolsey, DrugBank: a comprehensive resource for in silico drug discovery and exploration, Nucleic acids research, 34 (2006) D668-672.
[108] M. Remko, A. Bohac, L. Kovacikova, Molecular structure, pKa, lipophilicity, solubility, absorption, polar surface area, and blood brain barrier penetration of some antiangiogenic agents, Structural Chemistry, 22 (2011) 635-648.