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# Drug delivery systems to prevent peritoneal metastasis after surgery of digestives or ovarian carcinoma: A review.

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## Abbreviation list

5-FU: 5-fluorouracil  
AUC: Area under the curve  
BMA: n-butyl methacrylate  
CLA: Linoleic acid  
CRS: Cytoreductive surgery  
DDS: Drug delivery system  
DMPC: L- $\alpha$ -dimyristoylphosphatidylcholine  
DSPC: L- $\alpha$ -distearoylphosphatidylcholine  
DTX: Docetaxel  
EMA: European medicines agency  
EPIC: Early post-operative intraperitoneal chemotherapy  
FDA: Food and drug administration  
HA: Hyaluronic acid  
HA-CHO: aldehyde form of HA  
HA-ADH: adipic dihydrazide modified HA  
HIPEC: Hyperthermic intra peritoneal chemotherapy  
IDA: Iminodiacetic acid  
IP: Intraperitoneal  
MA: Malonic acid  
MP: Microparticle  
MPC: 2-methacryloxyethyl phosphorylcholine  
MS: Microsphere  
NP: Nanoparticle  
OX: Oxaliplatin  
PCI: Peritoneal cancer index  
PDPA: Poly(2-(diisopropylamino) ethyl methacrylate)  
PECE: Poly(ethylene glycol)-poly( $\epsilon$ -caprolactone)-poly(ethylene glycol)  
PEG: Poly ethylene glycol  
PEO: Polyethylenoxide

42 PLA: Polylactic acid  
43 PLGA: Polylactic co-glycolic acid  
44 PM: Peritoneal metastasis  
45 PNIPAM: Poly(N-isopropylacrylamide)  
46 POEGMA: Poly(oligoethylene glycol) methacrylate  
47 PPO: Polypropylenoxide  
48 PTX: Paclitaxel  
49 RES: Reticuloendoplasmic system  
50 TA: Tannic acid  
51 Tf: Transferrin  
52

## 53 Abstract

54  
55 Peritoneum represents a frequent site of metastasis especially for digestive and ovarian primary  
56 cancers. The conventional approach to treat peritoneal metastasis consists in systemic  
57 chemotherapy, but the median survival associated is only a few months. Recent therapeutic  
58 developments result in an aggressive strategy associating cytoreductive surgery (CRS) and  
59 hyperthermic intra peritoneal chemotherapy (HIPEC). However, a recent study failed to show an  
60 improvement in the overall survival and relapse free survival of this combo in comparison to CRS  
61 alone. Confronted to a lack of guidelines, several drug delivery systems (DDS) had been developed  
62 and tested in animal models to offer an effective easy-to-use solution for surgeons to prevent  
63 peritoneal metastasis. In this work, we reviewed most of the strategies used to treat peritoneal  
64 metastasis (PM) from digestive or ovarian origin and concentrated on 3 different DDS strategies:  
65 particulates DDS, non particulates DDS (including implants, films and gels) and combination of both  
66 (in particular hydrogels loaded with particles).

67  
68 *Keyword: Drug delivery system; peritoneal metastasis; microparticle; nanoparticle; hydrogel;*  
69 *thermogel.*

## 70 1. Introduction

71  
72 The peritoneum is a single layer of squamous mesothelial cells closely connected together. The sub-  
73 mesothelial layer supports the vascular network of blood vessels as well as lymphatics. This  
74 connective tissue is also composed of collagen, adipose tissue, lymphocytes, fibroblasts and  
75 macrophages (Albertine et al., 1982). Together, it constitutes a continuous serous membrane  
76 composed of two layers, the parietal one covering the abdominal wall and pelvic cavities, and the  
77 visceral one covering the outer side of the organs (Figure 1). Both layers delimit the peritoneal cavity  
78 with a volume of fluids near 50 mL in healthy human (Sherwood, 2015). The peritoneal fluid is  
79 composed of water, cells, electrolytes, antibodies, leukocytes exhibiting a physiological pH (Howard

and Singh, 1963). The peritoneum main function is to facilitate organs and viscera free movement by preventing frictions and adherences.

## Figure 1

It represents a frequent site of metastasis especially for digestive and ovarian primary cancers (Desai and Moustarah, 2020). Peritoneal metastasis (PM) is often characterized by small nodules spread all over the peritoneal surface, which can occur via natural metastasis process with cell dissemination, invasion, adhesion, proliferation; or via iatrogenically by stalling cancer cells during surgical resection of primary cancer, or other tumor perforations. The disease represented by carcinomatosis apparition is associated with a limited survival of only a few months if untreated (Lambert and Hendrix, 2018), (Sadeghi et al., 2000). The conventional approach to treat PM consists on systemic chemotherapy, but the median survival associated is low and varies from 5.2 to 12.6 months for colorectal origin (Koppe et al., 2006).

Two decades ago, a novel dual strategy treatment was introduced associating cytoreductive surgery (CRS) with immediate hyperthermic intra peritoneal chemotherapy (HIPEC). Protocol consists in the heating of one or several drugs such as mitomycin C, oxaliplatin, cisplatin or doxorubicin until 41-43°C followed by administration in peritoneal cavity during 30 to 90 min depending on groups (Turaga et al., 2014)(Sugarbaker, 2019) The rational of this combination treatment is based on surgical removal of macroscopic tumors, strengthen by local intraperitoneal (IP) chemotherapy targeting the residual microscopic disease. Macroscopically complete CRS is a major prognostic factor, with 5-year survival rates as high as 45% compared to less than 10% when CRS is incomplete (Verwaal et al., 2008). The advantage of IP route results in the encirclement by peritoneum/plasma barrier of peritoneal cavity, slowing clearance of drug which prolonged its contact in peritoneum, with limitation of blood passage and systemic toxicity, allowing higher dose of drug administration (Jacquet and Sugarbaker, 1996)(Van der Speeten et al., 2010). Verwaal et al proved the efficacy of CRS + mitomycin HIPEC treatment in a randomized clinical trial with systemic chemotherapy alone as comparison. The median survival was significantly prolonged in CRS + HIPEC arm (22.3 *versus* 12.6 months), making this aggressive strategy the current standard care for colon peritoneal metastasis (Verwaal et al., 2003).

However, two pharmacokinetic problems appear to limit the effectiveness of IP therapy: poor tumor penetration and no uniform IP distribution(Mohamed and Sugarbaker, 2003). Since recent publication of PRODIGE-7 trial results on colorectal cancer, benefits of CRS + HIPEC gold standard of care is questioned. 265 patients were randomized to CRS + HIPEC with oxaliplatin arm or CRS alone arm. No significant difference in overall survival was found, with a median of 41.7 months in the HIPEC arm vs 41.2 months in the non-HIPEC arm and no significant difference in relapse-free survival (13.1 vs 11.1 months) (Quenet et al., 2019). Moreover, a recent study felled to prove the peritoneal metastasis-free survival improvement at 18 months in patients with T4 or perforated colon cancer after prophylaxis administration of oxaliplatin based HIPEC (Klaver et al., 2019).

IP route of drug administration is studied since many years. The absorption in blood circulation can occurs by two different ways: through capillaries or lymphatics depending on the molecule size. Macromolecules are mainly taken up by lymphatic vessels then drained into lymph nodes and finally

join the venous circulation through thoracic and right lymphatic duct (Figure 2) (Miller, 1981), whereas small molecule and solutes are absorbed by capillaries and drained to the portal vein (Williams and White, 1986). The rate of peritoneal-plasma barrier passage depends on the physicochemical properties of the drug, dissolution rate of the particle suspension in the peritoneal cavity and particle size. Indeed, molecules have to cross several obstacle like mesothelium, basal membrane, interstitium with bundle of collagen fibrils and blood vessel with glycocalyx, before reaching systemic circulation (Flessner, 2008; Jacquet and Sugarbaker, 1996).

The efficacy of the IP chemotherapy still investigated in many clinical trials, and at the moment, there is no consensus or guidelines on the treatment strategy of PM of colorectal origin, only expert opinion (Abboud et al., 2019)

As a result, the need of alternative development strategies to prevent and treat PM is important to resolve recurrence problems with successful outcomes. This real clinical need led to many investigations since more than thirty years. Several drug delivery systems (DDS) had been developed and tested in animal models to offer an efficient and easy solution to use for surgeons to prevent PM. We propose to review them in the following of the article.

## 2. Particulate drug delivery systems used in IP route

Administration of cytotoxic drugs intraperitoneally represent a multiple challenge reflected by a lack of formulations approval for this administration route. The molecular structure of the cytotoxic influences its behavior in the peritoneal cavity: small and hydrophilic drugs are rapidly absorbed in the blood circulation leading to hematologic or systemic side effects (cisplatin (István Rusznyák et al., 1967), 5-fluorouracil (Speyer et al., 1980)), while high molecular weight or hydrophobic ones induce local toxicity and dose-limiting effect (Taxol® (Markman et al., 1992; Morgan et al., 2003), docetaxel (Morgan et al., 2003)).

While there is not only one delivery system for these drugs with various physical properties, one can still draw the ideal properties of a DDS dedicated to IP carcinoma: i) remain stable in the peritoneal cavity, ii) release high concentration of chemotherapeutic locally in the peritoneal cavity to have a therapeutic effect and tumor penetration, iii) avoid the formation of adherences, inflammation or local toxicity, iv) prolong the release of the drug over at least one week to avoid tumor implantation, v) limit systemic passage to avoid side effects.

### 2.1 Microparticles

This is the most studied drug delivery system (Table 1). One key parameter is their size ( $> 1 \mu\text{m}$ ) which determines their release, their residence time in the peritoneal cavity and their systemic passage. Comparing various DDS, Tsai et al. showed that after IP injection, paclitaxel release from microparticles (MP) (about  $4 \mu\text{m}$ ) was about 70% in 24 h while it was 90% in 2 h for gelatin nanoparticles of 660 nm (Tsai et al., 2007). The authors proposed a schematic explanation of two major elimination pathways from the peritoneal cavity: absorption through the peritoneum of the free drug or lymphatic drainage for corpuscular DDS with lymph node blockage as a function of the size (Figure 3). Basically, bigger was the DDS longer was the residence in the peritoneal cavity.

As regard to the size, a more homogeneous distribution was obtained with small MP made of poly(D,L-lactide-co-glycolide) ( $4 \mu\text{m}$ ) as compared to bigger ones ( $30 \mu\text{m}$ ) which stayed near the injection site (Lu et al., 2008).  $4 \mu\text{m}$  is the smallest size which can be envisioned to avoid rapid

clearance of MP through subdiaphragmatic pores (3  $\mu\text{m}$ ) (Lu et al., 2008). This value remains unprecise because other median and mean values are trackable in the literature (5-6  $\mu\text{m}$ (Simer, 1948) or 2.8-3.5  $\mu\text{m}$  (Tsai et al., 2007)). Their MP formulation called “tumor priming technology” was designed to have two release phases: a first rapid one to enable cancer cells apoptosis with a 70% release of paclitaxel at day 1 (polymer ratio 50:50 Lactide:Glycolide), then a slower release phase corresponding to 1% paclitaxel release each day (polymer ratio 75:25 Lactide:Glycolide). This technology enabled with a single drug administration, a better MP tumor uptake, lower host toxicity and a better therapeutic efficacy feed through prolonged survival (Lu et al., 2008).

Liggins et al. also analyzed two size range 10-40  $\mu\text{m}$  and 30-120  $\mu\text{m}$  of poly (L-lactic acid) MP and highlighted the presence of small MP (10  $\mu\text{m}$ ) in the mediastinal lymph nodes after intraperitoneal administration. They chose to carry their study with bigger MP in order to maintain them in the peritoneal cavity. The cumulative release of Liggins’s formulation was considerably slower compared to Lu and Tsai studies, with a total amount of paclitaxel reaching 25% 30 days after IP administration. The efficacy of this DDS was proved by the absence of tumor nodules neither ascites in the MP treated group 6 weeks after administration, in contrast with the no treated control group (Liggins et al., 2000).

Another critical component in the management of MP release is the polymer choice. It must be biodegradable, biocompatible and nontoxic. The principal polymer used is poly lactic acid (PLA) combined or not with acid glycolic (PLGA). PLA and PLGA are approved by the U.S. Food and Drug Administration (FDA) and used in many medical devices as surgical sutures, implants, prostheses (Athanasίου et al., 1996)... Hagiwara et al. designed 5-fluorouracil (5-FU) PLGA MP of 24  $\mu\text{m}$  diameter and analyzed 5-FU concentration in omentum and mesentery during 16 days. For both, 5-FU was significantly higher with a 39 to 1153 folds ratio compared to 5-FU solution. Moreover, a small amount of 5-FU was found in plasma for the MP treated group causing a systemic toxicity reduction about 41.5% as regard to the solution group (Hagiwara et al., 1996). Kumagai et al. also demonstrated a decrease in systemic toxicity with cisplatin encapsulated in PLGA MP. Cisplatin concentration in kidney, liver and plasma were lower with MP formulation than cisplatin solution. This was in correlation with an improvement of mean survival around 74 days for rats treated with cisplatin MP compared with 48 and 9 days for cisplatin and saline solutions respectively (Kumagai et al., 1996).

Some authors chose to combine various polymers in order to improve the MP formulation properties. Fan et al. used Pluronic®, consisting of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) blocks with a PEO–PPO–PEO arrangement, and PLA. Pluronic® brings strong affinity toward small intestines and high permeation to the cell membrane. The MP obtained measured around 45  $\mu\text{m}$  and were spherical and porous allowing a cumulative release of 60%, 14 days after treatment. Results indicated that DTX MP could induce more tumor cell apoptosis, and better suppressed tumor cell proliferation as compared to DTX solution (Fan et al., 2014).

Gelatin MP were considered to enable a release mediated with gelatinases secreted in the tumor microenvironment. Cisplatin (Gunji et al., 2013) and paclitaxel (De Clercq et al., 2019) prolonged the effect of the chemotherapy while reducing their toxic effects. The optimal dose of paclitaxel to achieve a good survival without drug related toxicity was evaluated by authors between 7.5 to 15 mg/kg (De Clercq et al., 2019). Taken together, those promising results compel authors to continue with pharmacology and toxicology studies prior to begin a first-in-human phase I trial.

Finally, in a phase I trial, Armstrong et al studied the sustained release of paclitaxel MS (Paclimer®) in peritoneal cavity of 13 patients suffering from ovarian cancer. MS of Paclimer® were made by the incorporation of paclitaxel in a biodegradable polyphosphoester polymer matrix. Approximately 800 cm<sup>3</sup> of warmed normal saline (30°C) was administered with the paclitaxel MS. The starting dose of paclitaxel MS was 60 mg/m<sup>2</sup>. Thanks to a prolonged release, the treatment was administered every 8 weeks for two cycles. Unfortunately, the pharmaceutical development of Paclimer® MS was stopped, thus only 1 patient received 2 cycles of treatment and the maximum tolerated dose was not reached. To note, one patient developed extensive, diffuse adhesions completely obliterating the peritoneal space in the lower abdomen and pelvis moreover, foreign body giant cell reaction with residual polymer filaments was found (Armstrong et al., 2006).

As a result, MP DDS seems to be effective in PM treatment on animals' models, depending on disease stage and MP formulation. However, the main challenge still remains the safety management. Indeed, it was well established that MP can induce inflammation and risk of adhesion. Kohane et al. demonstrated the implication of the size and polymer molecular weight in this process. They showed residues of closely apposed MP surrounded by a capsule of granulation tissue and early fibrosis attesting inflammatory reactions (Kohane et al., 2006). Tabata et al. demonstrated also that small MP (5µm) could be phagocytosed and induced a vigorous chemotactic response from cytokine release and subsequent inflammatory reaction to the adjacent tissues (Tabata and Ikada, 1990). Authors added that MP made with lower molecular weight polymers and nanoparticles appeared considerably safer in terms of reduction of the adhesion risk.

## 2.2 Nanoparticles

Paclitaxel is a hydrophobic cytostatic drug solubilized by Cremophor EL® in its commercial formulation (Taxol®). As Cremophor EL® is well known to induce toxicity (Gelderblom et al., 2001; Weiss et al., 1990), De Smet et al. proposed a nanocrystalline suspensions of paclitaxel solubilized in Pluronic F127®, forming nanoparticles (NP) of 400 nm diameter. No significant differences on tumor growth were measured at day 7 & 14 after 45 min HIPEC between Taxol® and NP suspension (De Smet et al., 2012). This is consistent with the limited drug penetration in tumor described by Fujiwara et al. involving a treatment efficiency of IP chemotherapy only if micro metastases or tumor < 5mm are considered (Fujiwara et al., 2007). Another formulation of paclitaxel formed by copolymerization of 2-methacryloxyethyl phosphorylcholine (MPC) and n-butyl methacrylate (BMA) was proposed (Soma et al. 2009). These co-polymers, forming NP around 50 nm, led to a significant decreased of tumor growth and prolonged survival compared with paclitaxel dissolved in Cremophor EL® solution *in vivo* (Soma et al., 2009). Evaluating the route of administration, they assessed a higher accumulation of the nanoparticles after i.p. injection as regard to i.v.. Kamei et al. observed that after i.v. injection, NPs were restricted to peripheral area, while i.p. administration allowed deeper paclitaxel infiltration within the tumor and in the tumor nodule (Kamei et al., 2010).

Kamei et al. worked on peritoneal tumor measuring 2-3 mm. This team developed paclitaxel NP formed by copolymerization of 2-methacryloxyethyl phosphorylcholine (MPC) and n-butyl methacrylate (BMA). Authors demonstrated the ability of NP to infiltrate until 1 mm inside the tumor nodule after 48 h contact compared to paclitaxel Cremophor EL® solution only found at 200 µm from the tumor surface. However, Kohane et al. reported a strong localization of NP in the spleen suggesting they were not suitable for drug release in peritoneal cavity (Kohane et al., 2006). This

limitation could explain the limited amount of cytotoxic reaching the tumor with traditional NP needing further development.

In 2008, FDA approval was delivered to another formulation of paclitaxel consisting in albumin NP (Abraxane® i.e. nab-paclitaxel) measuring 130 nm in diameter. Albumin is well tolerated, crosses natural physiological barriers thanks to receptor mediated transcytosis and enhanced permeability and retention effect (Yu and Jin, 2016). Moreover, it is devoid of surfactant such as Cremophor EL®, therefore, leading to increased tissue distribution and decreased side effects (Yardley, 2013). The penetration of paclitaxel in peritoneal cavity tissues was studied after a 60 min HIPEC procedure. Using mass spectrometry, paclitaxel was only detected when using Abraxane® whereas no paclitaxel was observed with Taxol®. This was confirmed by the pharmacokinetics results. The paclitaxel concentration found in the peritoneal cavity of rabbits was  $13.22 \pm 0.97 \mu\text{g/g}$  for Abraxane® compared to  $3.55 \pm 1.75 \mu\text{g/g}$  for Taxol® (Coccolini et al., 2017). Those results were consistent with the one obtained by Kinoshita et al. who demonstrated a better antitumor activity of Abraxane® compared to Taxol® on PM of gastric cancer after IP injection of equitoxic doses of paclitaxel in a murine model ( $p < 0.05$ ) (Kinoshita et al., 2014). The interest of Abraxane® encouraged Van de Sande et al. to use it as PM treatment in a phase I first-in-human study for patients with upper gastrointestinal, breast, or ovarian cancer, using pressurized intraperitoneal aerosol chemotherapy (Van De Sande et al., 2018).

Innovative NP were also proposed, such as NP with expansile properties allowing NP size to swell from 100 nm to 1000 nm reducing their clearance. These NP made with acrylate-based polymer and a trimethoxybenzaldehyde derivative, allowed polymer expansion and paclitaxel release at acidic pH only ( $\text{pH} \leq 5$ ). After IP injection, NP showed a minimal release of paclitaxel at physiologic pH and began to swell after exposition to acidic pH found intracellularly. The release was slow and prolonged with 4% delivered to the peritoneal cavity per hour over 24 h and persisted several days after injection. Another advantage of these NP was their ability to target tumor sites with a preferential localization in endosomes, where pH is acidic. Those qualities resulted in upper antitumoral efficiency compared to Taxol® and non-expansile NP, showing both total tumor mass and cumulative disease severity score decrease, and mice survival improvement ( $p < 0.005$ ) (Colson et al., 2011). Authors did not find any toxicity neither adhesion nor obstruction relative to their NP. In 2013, Gilmore et al. tested those promising expansile NP in a mice model undergoing debulking surgery. No significant recurrence was observed in expansile NP group whereas more than 40% ( $n=7$ ) were found in the Taxol® solution group (Gilmore et al., 2013).

Targeted nanoparticles were also proposed in particular to target the folate receptor or HER2. PLGA NP loaded with paclitaxel targeting the folate receptor showed improved mice survival as compared to mice receiving untargeted NP ( $p = 0.01$ ) (Werner et al., 2011). Polymeric poly (DL-lactic acid) NPs targeting HER2 with the antibody Herceptin® (Trastuzumab) showed a better response with NP-Herceptin® compared to free paclitaxel solution at the end of the IV/IP alternated protocol treatment but unfortunately no complete recovery was observed in any treated mice. The biodistribution experiment demonstrated that a majority of NP was found in the spleen, independently of the NP administration mode (Cirstoiu-Hapca et al., 2010). This is consistent with Kohane et al. findings, which could explain the relapse following the treatment sequence (Kohane et al., 2006).



NP seems to be an interesting DDS allowing deep infiltration in tumor with an antitumor efficacy which can be enhanced by the functionalization of the NP surface with targeting ligands (Table 2). However, the main challenge is to avoid the rapid localization in the spleen attenuating the cytotoxic effect of drug contained inside.

## 2.3 Micelles

Micelles have been less studied in the context of IP. Nevertheless, few examples are reported below. Core-shell-type polymeric formulation was obtained by the association of PEG as hydrophilic component and hydrophobic polyaspartate. These micelles of 85 nm with paclitaxel enclosed in the core, exhibited a significantly higher peritoneal nodules number and weight reduction as compared to paclitaxel-Cremophor EL<sup>®</sup> solution, with no difference in toxic side effects. A high concentration of paclitaxel was found in peritoneal nodules early after IP administration due to rapid enhanced penetration of nanomicelles. However, paclitaxel was cleared from peritoneal cavity more rapidly with nanomicellar solution as compared to paclitaxel-Cremophor EL<sup>®</sup> solution, leading in increased its concentration in plasma. The superiority of  $C_{max}$  and  $AUC_{0-48h}$  in plasma of paclitaxel nanomicelles could also explain their significant better efficiency in reducing weight and volume of subcutaneous tumors thanks to a systemic effect (Emoto et al., 2012).

Gong et al. developed as well nano micelles for peritoneal use. They encapsulated doxorubicin in a biodegradable and biocompatible poly (ethylene glycol)–poly(ε-caprolactone)–poly (ethylene glycol) (PECE) copolymer leading to 30 nm spherical micelles. PECE copolymer had a temperature-sensitive behavior, when temperature increased (>25°C), micelles size increased turning in a flexible and during gel at body temperature in 20s. This property was supposed to offer a promising dual antitumor and anti-adhesion effect in peritoneal cavity. *In vitro* release study revealed a cumulative release about 52% at day 14 reaching a plateau at day 7. The therapeutic effect of doxorubicin-micelles on colorectal peritoneal metastasis mouse model was significantly higher considering the number and weight of tumor nodes compared to the doxorubicin solution group ( $p < 0.001$ ). Additionally, doxorubicin-micelles proved an integral neo-mesothelial cell layer formation of the injured parietal and visceral peritoneum in 5-7 days without concerns of further adhesion formation (Gong et al., 2012b).

Taken together, those results proved a real interest of this DDS, which might improve simultaneously intraperitoneal chemotherapeutic effect and preventing peritoneal adhesions post-surgery.

## 2.4 Polymersomes

Polymersomes are a class of artificial vesicles formed by the self-assembly of amphiphilic block copolymers. It can encapsulate water-soluble components in its hydrophilic core and water-insoluble components in its hydrophobic surface. This nano-supramolecular structure can be made of biodegradable polymers making them potentially interesting DDS. Simòn-Gracia et al. chose poly (oligoethylene glycol methacrylate) (POEGMA) as hydrophilic polymer, and poly(2-(diisopropylamino) ethyl methacrylate) (PDPA) as hydrophobic polymer yielding a pH-sensitive structure encapsulating paclitaxel. At physiological pH 7.4, no paclitaxel was found in the cell culture medium, whereas at pH 6 polymersomes disassembled leading to the drug release (Simon-Gracia et al., 2016). After

peritoneal administration of paclitaxel-polymersomes, the authors showed selective accumulation and penetration of paclitaxel in peritoneal lesions simultaneously in periphery or deeper in tumor's parenchyma. This suggests that polymersomes reached tumor using both direct penetration and systemic routes enhancing drug delivery capacity compared to IV route. Additionally, paclitaxel polymersomes demonstrated a better efficiency in the treatment of mice bearing peritoneal MKN-45P gastric tumors compared to Abraxane® and paclitaxel-Cremophor EL® solution with a shrank tendency observed after the first day of treatment (Simon-Gracia et al., 2016).

## 2.5 Liposomes

Liposomes are another kind of nanovehicles with a size ranging from 100 to 1000 nm employed as DDS in the peritoneal cavity. The main advantage of those DDS is an absence of toxicity and antigenicity thanks to their formulation, containing endogenous lipid such as cholesterol or lecithins. As early as 1996, Sharma et al. encapsulated paclitaxel in liposomes made of phosphatidylcholine and phosphatidylethanolamine to avoid Cremophore EL® utilization. Liposomes reached a higher maximum tolerated dose of paclitaxel compare to Cremophore EL® formulation (Taxol®), but in practice the best efficient dose was the same for both formulations. Authors did not show significant difference in survival between liposomes and Taxol® after IP injection, maybe due to the cell line chosen (P388 murine leukemia model) showing an intermediary sensibility to paclitaxel. However, liposomes demonstrated a lower cumulative toxicity and the elimination of vehicle-mediated toxicity as expected (Sharma et al., 1996).

At the beginning of 80's, Hirano et al. observed liposome in the lymphatic system. This process was shown to be related to liposome size, in which small ones (50 nm) could easily reach the blood circulation by thoracic lymph duct, whereas bigger ones (720 nm) were entrapped in lymph node possibly aided by adhesion. Liposomes found into blood or lymph nodes were intact suggesting a non-impaired drug release potential (Hirano and Hunt, 1985). Mirahamdi et al. also showed a better retention in the peritoneal cavity for larger liposomes with a concentration 3 times higher for 1000 nm ones as compared to 100 nm, however liposomes measuring more than 1000 nm were less stable and precipitated around abdominal organs. Liposome charge, lipid formulation, and PEG coating also impacted the retention of liposomes in the peritoneal cavity. The negative charge of mesothelium can indeed induce interactions with positively charged liposomes resulting in a prolonged residence time in the peritoneal cavity. Moreover, PEG coating or lipid transition can impact the elimination of liposomes, and therefore the residence of liposomes in the peritoneal cavity (Dadashzadeh et al., 2010). Sadzuka et al. investigated the impact of lipid composition on the dissemination in peritoneal cavity of doxorubicin encapsulated in liposomes. They did not show any relation between lipid composition and clearance of doxorubicin from the peritoneal cavity, but once in the blood circulation, doxorubicin plasma concentration from liposomes made of L- $\alpha$ -distearoylphosphatidylcholine (DSPC) was superior to liposomes made of L- $\alpha$ -dimyristoylphosphatidylcholine (DMPC). DSPC also allows a higher tumor penetration of liposomes with a higher intratumoral doxorubicin concentration than DMPC after IP injection ( $p < 0.001$ ) probably due to a better stability of liposomes made with DSPC (Sadzuka et al., 2000). As mentioned above, the particle size also affects the peritoneal cavity residence time. Bigger DSPC liposomes around 4  $\mu\text{m}$  remained in the peritoneal cavity after IP injection and disrupted to release doxorubicin slowly. PEG addition in liposome formulation did not affect doxorubicin clearance from peritoneal cavity neither liposomes absorption to the lymph and did not decrease large liposomes accumulation in heart and liver. However, pegylation of small liposomes avoid accumulation in peripheral tissues (p

< 0,001) decreasing heart and liver toxicity and allowed a higher tumor penetration compared to non-pegylated liposomes (Sadzuka et al., 1997). Authors also demonstrated that pegylation of positively charged liposomes decreased doxorubicin concentration in peritoneal cavity while some authors showed that PEG addition into neutral liposomes augmented their cavity retention (Dadashzadeh et al., 2010).

Targeting was also proposed for liposomes. Liposomes encapsulating cisplatin, grafted with transferrin (Tf) at the extremity of the were proposed (Yuda et al., 1996). Tf-PEG liposomes showed higher survival rates ( $p < 0.01$ ) and higher cisplatin levels in the peritoneal cavity as compared to PEG liposomes without Tf and cisplatin in solution ( $p > 0.01$ ), in a peritoneal dissemination model of gastric cancer. The authors also confirmed by electronic microscopy the internalization of Tf-PEG liposomes by a receptor mediated endocytosis process (Iinuma et al., 2002).

A new promising concept was developed consisting in thermosensitive liposomes. The goal of this formulation was to inject liposomes IP and then induce a localized hyperthermia using high intensity focused ultrasound reaching a maximum of 40°C allowing drug release from liposomes. This exciting prospect still requires some improvements regarding the clinical application of hyperthermia (Rezaeian et al., 2019).

For now, there are two doxorubicin liposomal formulations approved by FDA and EMA: Myocet® which is a standard liposomal formulation and Doxil®/Caelyx®/Evacet®/Doxilen®/Lipodox® pegylated formulations. To our knowledge no studies of Myocet® use in IP routes are available (clinical trial consulted 24/10/2019). In contrast, Sugarbaker et al. just published an evaluation of Doxil® administration by IP route for the treatment of PM after CRS. The first patient received 50 mg/m<sup>2</sup> of Doxil® during 90 min in 2.55 L of 1.5 % dextrose heated at 41.5-43°C. At the end of the HIPEC, only 27% of drug penetrated the tissue surface of peritoneal cavity. The authors tried to prolong the HIPEC duration to 180 min, increase Doxil® dose at 100 mg/m<sup>2</sup> and reduce the volume administered to 2 L but drug uptake in tissues was not reproducible with a range of 22% to 60%. This HIPEC optimization failure led authors to focus on early post-operative IP chemotherapy (EPIC). The protocol consisted in mixture of 50 mg/m<sup>2</sup> Doxil® in 2 L of dextrose 1.5% instilled during 24 h. The mean Doxil® absorption over 24 h was 85 ± 11% (Sugarbaker and Stuart, 2019). This result proved the requirement of prolonged exposition of drug in peritoneal cavity to improve drug absorption into peritoneum tissues. Further studies are needed to solidify the efficiency of Doxil® use in PM treatment.

### 3. Non particulate Drug Delivery Systems

#### 3.1 Implants

Thanks to their advantages allowing long term sustained release, reducing overall doses frequency of administration and systemic side effects, facilitating patient compliance and enhancing their quality of life, implants were considered by a few research teams to be transposable to PM. Li et al. developed a 5-FU-loaded PLGA implant with a 1:1 ratio between the polymer and drug and various molecular weight of PLGA to avoid an initial burst release In mice, middle (15 mg/kg) and high (22.5

mg/kg) dosages of 5-FU in implant of 1 mm diameter and 1 cm length showed significant tumor inhibition compared to 5-FU solution ( $p < 0.01$ ). Interestingly, 5-FU was mainly distributed in rectum, small intestine, stomach and abdominal muscle with a lower amount in plasma (more than 50 times less) (Li et al., 2018). Implant utilization was demonstrated to be safe with minimal off-target toxicities recorded and with a better animal's tolerability compared to 5-FU solution.

However, several studies brought to light that PLGA-based implant developed a fibrous encapsulation around the implant as a result of host inflammatory response (Athanasίου et al., 1996; Ho et al., 2005). Ho et al., showed *in vitro* that increasing the size of implant associated with a higher paclitaxel dose resulted in strongest inhibition of cell proliferation. No inflammation, infection or distress neither encapsulation was observed *in vivo* 2 weeks after administration of chitosan and egg-phosphatidylcholine implant (Ho et al., 2005). In contrast, implants made with other polymers as polycaprolactone or poly(D,L-lactide) acid displayed fibrous encapsulation surrounding the implant area. Drug release mechanism proposed by the authors was biphasic (Lim Soo et al., 2008). Indeed, implant rapidly start to swell leading to the mobility of paclitaxel, followed by hydrolysis of chitosan. Has a result, paclitaxel release was accelerated. *In vivo* studies highlighted several advantages of implant use as compared to Taxol® solution: superior maximum tolerated dose, penetration in tumor, antitumoral effect improved (Vassileva et al., 2007).

Despite these promising results, no clinical trial was performed and no clinical trial using implants have been tested for peritoneal carcinoma. (clinicaltrials.gov)

## 3.2 Smarts Hydrogels

### 3.2.1 Self-sustaining hydrogels

Basically, hydrogels are mainly made of gelatin, pluronics, HA, chitosan, poly (organophosphazene), caprolactone derivatives and are interesting for their rheological properties. Gelatin hydrogel granules incorporating cisplatin was made by cross-linking an aqueous gelatin solution with glutaraldehyde. Gel degradation accelerated when the amount of glutaraldehyde decreased. Granules obtained presented irregular shapes with a size around 80-120  $\mu\text{m}$ . *In vivo*, the proportion of collagenase present in peritoneal cavity allowed a slow gel hydrolysis with 27 % degradation after 7 days and a complete degradation within 3 weeks. Cisplatin granules hydrogel (10 mg/kg) induced less toxicity than free cisplatin in solution (5 mg/kg), probably tanks to a lower passage of cisplatin in the blood when administered in the hydrogel form. Antitumor efficacy was then assessed by the total photon counts significant decreased in hydrogel-cisplatin group compared to the control group ( $p < 0.05$ ) which was in accordance with the survival rate that was prolonged in gel-cisplatin group compared to control ( $p < 0.05$ ) (Yamashita et al., 2019).

Smart hydrogels made with poly (organophosphazene) were also proposed to treat peritoneal metastasis with gastric origin. Poly (organophosphazene) are inorganic polymers with a backbone made of nitrogen and phosphorous atoms alternatively linked by single or double bonds. These polymers are interesting thanks to their high variability in their functionalization. In that study, hydrophilic and hydrophobic components such as isoleucine ethyl esters and  $\alpha$ -amino- $\omega$ -methoxy-PEG were grafted to prevent water/drug contact, and ensure water miscibility of the complex (Kang et al., 2006). IP injection of hydrogel implemented with 15 mg/kg of PTX or one IP injection of PTX solution at 30 mg/kg in mice intraperitoneally injected with HSC44 luc cells did not show significant difference between hydrogel-PTX group and PTX solution group, but side effects like intestinal

dilatation and liver swelling were decreased in hydrogel-PTX group (Yu et al., 2012). Five years later, the same team challenged approximatively the same poly (organophosphazene) based thermosensitive hydrogel mixed with 2 or 8 mg/kg of docetaxel (DTX). They compared the anti-cancer drug effect of one injection of DTX-hydrogel at both DTX concentration and DTX solution administrated IP or IV 2 times a week for 2 weeks at 2 mg/kg. They showed that a single injection of 8 mg/kg DTX-hydrogel reduced 4 times the tumor bioluminescence compared to IP DTX solution ( $p = 0.0001$ ) after 28 days. The prolonged survival time observed in high dose DTX-hydrogel group compared to IP DTX solution group ( $p = 0.0068$ ) confirmed hydrogel capacity to suppress PM growth. Another team chose to incorporate DTX in NP made of linoleic acid (CLA) and Pluronic F-127® to enhance DTX solubility and control its release. At body temperature, the authors assumed that NP turned into a hydrogel after IP injection, thanks to the thermoresponsive property of Pluronic® and CLA. *In vitro*, DTX (10 mg/kg)-hydrogel enhanced cell apoptosis compared to DTX-solution (10 mg/kg) alone with an apoptosis signaling overexpressed. In a PM model of mice injected IP with human gastric cells, intra-abdominal uptake of  $^{18}\text{F}$ -FDG was lower in the DTX-hydrogel group compared to PBS and DTX-solution administrated IP ( $p < 0.05$ ), which was consistent with the lower total number of peritoneal nodules in DTX-hydrogel group ( $p < 0.05$ ) associated with a prolonged survival (Bae et al., 2013).

Polymers association is very common in thermosensitive hydrogel formulation. Wang's team studied a triblock copolymer as follow: PEG methyl ether- $\epsilon$ -caprolactone-PEG methyl ether (PECE) 25 wt %. Release study of 5-FU was done with 2 initial drug loading 0.5 mg and 1 mg. Both showed a burst release during the first hour and reached a plateau after 3 days with respectively 95.3 % and 84.6 % cumulative release. Moreover, a delayed release and increased uptake of methylene blue as a marker of hydrogel was observed during 48h as compared to the methylene blue solution which was discharged after 8h. PECE-5FU-hydrogel showed a smaller and decreased number of nodes compared to 5-FU solution and control normal saline solution ( $p < 0.05$ ), associated with an increased tumor free rate and survival rate ( $p < 0.01$  and  $p < 0.05$  respectively) (Wang et al., 2010).

Our team also showed that the combination of poloxamer and alginate is efficient in PM treatment. Association of P407, P188 and alginate (20/2/1 wt%) formed a non-toxic biocompatible thermogel with a gelation temperature around 25°C. *In vitro*, the thermogel proved its ability to decrease cell adhesion, a promising result to avoid post-surgical adhesions. *In vivo*, in a murine model of PM, the thermogel loaded with both 5-FU and Oxaliplatin permitted to decrease significantly PCI score, number of areas involved and mean ascites volume as compared to control group (respectively  $p < 0.005$ ;  $p < 0.05$  and  $p < 0.001$ ). Further studies to evaluate thermogel distribution and adhesion in a peritoneal cavity in an abrasion model of pig which is closer to the human peritoneal cavity volume (Seguin et al., n.d.).

McKenzie et al. compared the efficacy of 3 drugs mixtures entrapped in PLGA-b-PEG-b-PLGA block hydrogel (TheranoGel) or in PEG-b-PLA micelles measuring 190 nm (TheranoMic). They associated paclitaxel with rapamycin, an mTor inhibitor known to potentiate sensitivity of certain cancer cells to paclitaxel, and a near infrared optical imaging agent LS301. Slow Theranogel degradation kinetic allowed a sustained simultaneous release of the 3 drugs *in vitro* as compared to TheranoMic ( $p < 0.0001$ ). TheranoGel also showed debulking effect with a tumor burden decreased of 93 % within 3 days, whereas TheranoMic increased tumor burden (McKenzie et al., 2016).

Depani et al. developed a thermosensitive hydrogel based on a mixture of chitosan, glycerophosphate as a cross-linker and 5-FU. The release of 5-FU out of the gel was quite fast with 40% after 1h and 75% after 12h. The anti-tumoral efficacy was evaluated after a five injections series within 17 days. No difference was found in tumor volume between 5-FU solution group and 5-FU-hydrogel group, but lower systemic toxicity was observed with less morbidity and mortality in 5-FU-hydrogel group demonstrating interest of such formulations compared to drug in solution with systemic exposure (Depani et al., 2013).

Chen et al. combined chitosan and HA to an intelligent biopolymer system, poly(N-isopropylacrylamide) (PNIPAM) able to exhibit reversible solution-to-gel phase transition behavior. Drug release was biphasic with a burst of 40% in 8h due to fast diffusion of Doxorubicin through pores due to its low molecular weight, and a prolonged phase due to gel degradation reaching 80% after 12 days. *In vivo* studies revealed a lower number of tumors with smaller weight and volume in Dox-hydrogel group compared to Dox-solution group indicating a better suppressing tumor growth effect ( $p < 0.05$ ). Anti-adhesion effect was also assessed on a sidewall defect cecum abrasion animal model. Histology showed a better adhesion score in Dox-hydrogel group compared to Doxorubicin solution and control group ( $p < 0.001$ ). Authors concluded that hydrogel improved Doxorubicin effect by sustained release and extend lifespan of mice with an anti-adhesion effect thanks to its barrier effect until healing to prevent peritoneal adhesion (Chen et al., 2018).

Emoto et al. choose to design a thermosensitive hydrogel based on HA derivatives loaded with cisplatin to treat peritoneal dissemination of gastric cancer. HA was modified to obtain one aldehyde form (HA-CHO) solution and one adipic dihydrazide (HA-ADH) solution separately. Solutions merged together in a single needle at the time of administration in peritoneal cavity and gelation occurred *in situ* in 40 sec. Cisplatin release was prolonged over 4 days with a cumulative release around 80 %. After mice IP treatment once a week for 3 weeks with 1 mg/kg cisplatin for all groups, the antitumor activity was better achieved in gel-cisplatin group compared with cisplatin solution group ( $p = 0.032$ ) which results were not different from PBS control group (Emoto et al., 2014).

### 3.2.2 Hydrogels with DDS incorporated inside

In this last part, we referenced studies associating drug delivery systems into thermosensitive hydrogels to improve sustained release and containment of drug in peritoneal cavity. The solution state of hydrogel prior to use allowed incorporation of DDS as a suspension. *In situ* gelation led to cover the peritoneal cavity keeping particles of drugs in place to have a cytotoxic local effect.

Several teams chose to work with HA-ADH and HA-CHO network.

Ohta's team used the combination of HA-ADH and HA-CHO as a hydrogel matrix in which they inserted a nanogel of HA loaded with cisplatin to treat a mouse model of gastric cancer with peritoneal dissemination. They compared iminodiacetic acid (IDA) or malonic acid (MA) as chelating ligand conjugated to the HA backbone to attach cisplatin, and the load method of cisplatin-nanogel in HA matrix with a physical encapsulation or a chemical conjugation. The release of cisplatin out of HA matrix and HA nanogel polymer was quite inferior in chemical conjugation formulation and MA group after 1 week. The total number of peritoneal nodules was significantly lower in group treated with IDA-nanogel physically encapsulated in HA matrix compared to cisplatin in solution ( $p = 0.032$ ).

Authors also brought to light the enhance therapeutic effect on nodules < 1 mm, results explained by a limited tumor penetration of nanogels in bigger nodules (Ohta et al., 2017).

Bajaj *et al.* compared the anti-tumoral activity of two DDS in HA based hydrogel, the first one was nanoparticles of Taxol® in its commercial form *ie.* in Cremophor EL® micelles around 14 nm (NP-PTX), the other was a suspension of microparticulate PTX precipitates (MP-PTX) around 100 µm. Both solutions contained 0.69 mg/mL of paclitaxel and rapidly formed a gel upon administration stayinc in peritoneal cavity until 2 weeks. The NP-PTX-gel showed a cumulative release of 15.6% in the first 24h followed by no further release, whereas the MP-PTX-gel reached progressively 38.5% after 10 days. This observation matched with the amount of PTX found in peritoneal fluids which was superior with MP than NP at day 14, with respectively 0.9-5.1 µg/mL and 0.02-0.94 µg/mL, confirming the interest of larger particles size to remain in peritoneal cavity. However, the anti-tumor efficacy assessment did not show a statistical difference between gel groups and Taxol® solution group (Bajaj et al., 2012).

To overcome the size particles problem, authors tried to replace PTX aggregates by PTX nanocrystals produced by breaking down large particles or crystallizing drug solution measuring around 258 nm. The *in vitro* paclitaxel retention in SKOV3 was enhanced with PTX nanocrystals compared to PTX aggregates. The *in vivo* anti-tumor activity was evaluated in mice after one single administration of treatment IP with an equivalent of 30 mg/kg of PTX. The survival of mice receiving PTX nanocrystals-gel was significantly prolonged as compared to Taxol® solution group and MP-PTX-gel ( $p < 0.005$ ). However, bioluminescence observation of SKOV3-luc cells showed a minimal tumor burden growth in PTX nanocrystals-gel group up to 7 weeks after treatment. This study point to the beneficial effect of particle size reduction, which lead to a greater dissolution rate and cellular uptake of PTX (Sun et al., 2016).

In a subsequent work, the same team encapsulated cisplatin in NP of HA measuring 270 nm. The entrapment of cisplatin-NP in gel did not impact kinetic of cisplatin release irrespectively of the gel concentration (20 or 40 mg/mL of HA). The hyaluronic gel was still present after 2 and 4 weeks of treatment in peritoneal cavity but no cisplatin was collected in lavages indicating a full release of the drug out of the gel in less than 2 weeks. The authors observed by confocal microscopy a decrease in cellular uptake of cisplatin in SKOV3 cells in presence of HA in excess in the medium culture. This competition between HA-NP based and free HA suggests that NP entered cells via HA receptors as CD44, which are known to be overexpressed on the surface of ovarian cancer cells providing a selective cytotoxic effect (Li and Howell, 2010, p. 44; Zagorianakou et al., 2004, p. 44). Unfortunately, the antitumor effect study did not show any superiority of the cisplatin-NP gel compared to the cisplatin solution even with a total dose of cisplatin in NP superior to the maximum tolerated dose. A later increase in tumor burden suggests potential involvement of empty carriers and degradation products in the growth of residual tumors which can alert on HA use (Cho et al., 2015).

Fan *et al.* associated PLA and Pluronics® to build NPs co-loaded with DTX and LL37, an endogenous tumor-suppressing peptide, to benefit from synergistic effect on cell viability and apoptogenic effects. PLA-(Pluronic L35)-PLA block copolymers-based NPs measured around 129 nm and were monodisperse. Hydrogel made with PLA-(Pluronic L64)-PLA triblock copolymer showed a porous tridimensional structure with homogenous micropores size permitting diffusion of NPs. Hydrogel allowed a slower release of DTX as compared to NPs ( $p < 0.005$ ). *In vivo* antitumor activity of DTX-



LL37-NPs hydrogel attested an important decrease of number and weight of tumor nodules in peritoneal cavity at day 30 after a single IP injection ( $p < 0.01$ ) with a smaller size of nodes compared to other groups. This finding was in accordance with a median survival time increased significantly in DTX-LL37-NPs hydrogel group compared to control ( $p < 0.01$ ) (Zhou et al., 2015).

Another team worked on Pluronic® based hydrogel loaded with a combination of drugs enclosed in NPs. PLA added with Pluronic® 10R5 formed NPs in which oxaliplatin (OX) and tannic acid (TA) were loaded, measuring between 143 and 163 nm depending on drug/polymer ratios. The hydrogel was composed by  $\epsilon$ -caprolactone and Pluronic® 10R5 as block copolymer resulting in a porous three-dimensional structure remaining detectable in peritoneal cavity up to 10 days. The release of OX was considerably increased when NPs were not embedded within the gel with a cumulative rate around 65 %, which is in favor of a delaying effect of the gel. The *in vivo* antitumor activity assay revealed a significant decreased in number, size and weight of tumor nodules with OX/TA NPs hydrogel group compared to control, free OX and OX NPs groups ( $p < 0.05$ ), in accordance with the prolonged median survival time in OX/TA NPs hydrogel group ( $p < 0.05$ ). Tissue sections also showed an increased number of apoptotic cells, a tumor cell proliferation suppression and a lower micro vessels density in OX/TA NPs hydrogel group compared to other groups which is in favor of a better antitumoral activity (Ren et al., 2019).

Yun *et al.* designed a bicompartamental system to deliver two cytotoxic components. Firstly, they encapsulated 5-FU in biodegradable poly- ( $\epsilon$ - caprolactone)-poly (ethylene glycol)-poly( $\epsilon$ -caprolactone) (PCL-PEG-PCL, (PCEC)) copolymers micelles. Then, they mixed the micelles with a chitosan solution crosslinked with  $\beta$ -glycerophosphate and loaded with cisplatin to obtain a thermosensitive hydrogel. The authors also compared the release profiles of 5-FU and cisplatin drugs out of the gel and highlighted an important difference between both drugs with 85 % and 40 % cumulative release respectively in 144h. *In vivo*, the number of tumor and their weight were significantly lower in 5-FU micelles-cisplatin gel group compared to free 5-FU/cisplatin ( $p < 0.05$ ) and control group ( $p < 0.001$ ) in accordance with a prolonged survival time. The absence of liver and lung metastasis in 5-FU micelles-cisplatin gel group was in accordance with the high decrease of proliferation level evidenced by the Ki 67 positive cells number (Yun et al., 2017).

PCEC block copolymers was also chosen by Gong et al. to form 21 nm PTX-micelles and 5-FU hydrogel depending on the molecular weight of PCEC. Release of 5-FU and PTX was assessed through the whole micelle-gel system. Authors highlighted a difference in release kinetic between 5-FU and PTX at day 10, respectively 90% and 30%, explained by hydrophobicity of PTX which had strong interaction with PCEC inducing a lower drug release rate whereas high solubility of 5-FU allowed its diffusion through hydrogel pores more rapidly. *In vivo* pharmacokinetic investigation showed  $AUC_{0-24}$  and  $t_{1/2}$  superior in PTX-micelles-5-FU-gel group compared to free Taxol® and 5-FU in solution group leading to a much higher 5-FU and PTX concentration in the abdominal cavity ( $p < 0.001$ ). A minimal increase of tumor weight and number was observed in mice receiving PTX-micelles-5-FU-gel after one IP injection compared to control and Taxol® + 5-FU solution. These finding was in accordance with increase in the life span observed in PTX-micelles-5-FU-gel group (Gong et al., 2012a).

Another team formulated a “two in one” drug delivery system made of NPs formulated with biodegradable copolymer associating polyester and polyethylene glycol, forming gel after



reconstitution in water. In a previous study, the amphiphilic triblock copolymer poly(e-caprolactone-co-1,4,8-trioxane [4.6]spiro-9-undecanone)-poly(ethyleneglycol)-poly(e-caprolactone-co-1,4,8-trioxane [4.6] spiro-9-undecanone) (PECT) demonstrated a safety of use in mice and formed spherical NPs around 209 nm entrapping PTX after redispersion in water. The cumulative release of NPs-PTX based PECT hydrogel was around 53 % at day 46 with a 2.5 mg/mL concentration of PTX (Wang et al., 2013). In the present study, authors studied the NPs-PTX-PECT hydrogel behavior after IP injection. They identified a modest histological inflammation during the first 3 days disappearing on day 5 which was linked to the concomitant hydrogel degradation. Fluorescence signal demonstrated a major localization of the gel in intestines until day 8, which is in accordance with the absence of toxicity in other organs. The *in vivo* anti-tumor efficacy was assessed after single IP injection treatment of NPs-PTX-PECT hydrogel with 30 mg/kg of PTX. On day 11, weight of tumor nodules was significantly lower as compared to Taxol® in solution group which administration schedule was 3 injections in a week each dosed with 10mg/kg of PTX ( $p < 0.05$ ). However, decreased in tumor burden still important compared to control group at the end point ( $p < 0.01$ ) despite of a tumor cells regrow in all groups. In the first 96h, pharmacokinetic study revealed higher AUC and  $t_{1/2}$  in NPs-PTX-PECT hydrogel compared to Taxol® group ( $p < 0.001$ ) which can explain the enhance therapeutic effect in peritoneal cavity maintaining high PTX concentration near tumor nodules for a prolonged period (Xu et al., 2016).

#### 4. Conclusive prospects

Patients with peritoneal metastasis have a poor prognosis and a median survival reduced compared to other sites of metastasis (Franko et al., 2012; Guimbaud et al., 2014). The conventional approach consisted of a 5-FU based systemic chemotherapy but was associated with poor survival outcome of approximatively 6 months (Klaver et al., 2012). Since 2003, the standard of care of peritoneal metastasis combined cytoreductive surgery with HIPEC but an important relapse rate still observed (Bijelic et al., 2007; Verwaal et al., 2004). There is an important challenge to develop efficient therapeutic innovations to prevent peritoneal metastasis implantation and to treat it if already present.

This area of research attracted many teams since several years and various chemotherapies and carrier were tested to offer surgeons an easy to use solution to treat suspicious carcinomatosis. The ideal DDS for IP therapy might regroup several characteristics such as biocompatibility, high drug concentration in peritoneal cavity maintained for a prolonged period of several days, tumor specificity, low local and systemic toxicity and efficient tumor penetration. We reviewed here most of strategies used to treat peritoneal metastasis from digestive or ovarian origin. We delimited 3 different DDS strategies.

The first one consisted of particulates DDS, we identified five kinds of particles: microparticles, nanoparticles, micelles, polymersomes and liposomes. Basically, quite a few messages came out like drug release depends on particles size, smaller are the particles better is the distribution inside the peritoneal cavity but higher is the risk to accumulate in lymph nodes or spleen. The task is to consider the benefit/risk balance of each kind of particles to avoid side effects like local inflammation and adhesion observed in some cases with microparticles, or systemic passage with micelles for

example. A meticulous choice of polymers is also essential to ensure its biocompatibility and to resolve certain problematics like adhesion. In addition, DDS formulated with component targeting cancer cells seems to be promising. In our point of view, we believe that microparticles are especially interesting because their size could avoid leakage through subdiaphragmatic pores and lymph nodes allowing a prolonged residence time in peritoneal cavity thus increasing contact of nodules with drug with a limited systemic toxicity.

The second strategy used non particulates drug delivery systems including implants, films and gels. Films were mainly described for their anti-adhesion property by a mechanical action (Uguralp et al., 2008)(Paulo et al., 2009)(Mamoudieh et al., 2011). When loaded with drugs the goal of pharmaceutical action was also to prevent post-surgical adhesions but were rarely used as DDS to treat peritoneal metastasis. Implants represent an interesting approach in metastasis care because it can be fixed near tumor site with an important dose of drugs inserted inside protected by a polymer barrier allowing a controlled release with a zero-order kinetic. But for a peritoneal cavity, it is limited to a specific place. For that, implant had to be considered as DDS more as a solution to decrease a local relapse for no margin resection surgery, than for peritoneal metastasis (Baitukha et al., 2019). In contrast, gel can cover the whole peritoneum surface. The main challenge consists in the obtention of a homogenous repartition of the drug with a limited inserted volume, which could be better obtained thanks to a gel with rheofluidifiant behavior. This aspect was not widely described. In a recent work, our team studied *in vitro* and *in vivo* characteristics of such a gel based with a combination of poloxamer and alginate highlighting its anti-tumor and anti-adhesion effects (Seguin et al., n.d.).

The last strategy combined aspects of the two previous ones meaning gels loaded with particles. This option represents many advantages. Gel allows repartition all over the peritoneum wall and remains in place for a prolonged period, thus particles are localized near to nodules and can operate a local release of cytotoxic agents contained inside. Drug liberation is dependent of gel and particles such as diffusion or degradation often resulting in a sustained release in comparison to particles alone. This strategy appears to be the most promising thanks to combination of two compartmentation advantages.

It is important to mention that storage condition needs to be practical and easy, because part of the surgery could be performed in an emergency situation. The surgeon discovers a situation with a high peritoneal metastatic risk and had to offer a solution, without any pre-operative strategy. A storage solution for the DDS had to be simple, easy access and every time during the day and night. By example, a complex DDS using an instable drug needing a complex storage condition or a DDS drugs complex that had to be built in the pharmaceutic unit one hour before could not be a good solution.

To our knowledge, there is no human clinical trial yet assessing efficacy of drug delivering systems to treat or prevent peritoneal metastasis. Current clinical trials focus on HIPEC or pressurized intra peritoneal aerosol chemotherapy (PIPAC) ameliorationBased on promising results obtained with animal models, drug delivery systems listed above might represent an interesting tool being less time consuming and safer for surgerons than HIPEC and PIPAC, and not requiring any additional machinery.

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**Figure 1:** (A) Two layers of peritoneum cover the abdomen: the parietal layer lines the abdominal wall, while the visceral layer lines the abdominal viscera. The narrow space within these two layers is referred to as the peritoneal cavity. (B) The layer of mesothelial cells is referred to as the peritoneum and, collectively, the connective tissue and peritoneum are referred to as the serosa. The serosa is situated directly beneath the abdominal musculature. Reprinted from Capobianco *et al.* 2017 with permission.

**Figure 2:** Schematic representation of the main lymphatic absorption pathways for macromolecules after IP administration. Reprinted from Al Shoyaib *et al.* 2020 with permission (Tsai *et al.*, 2007).

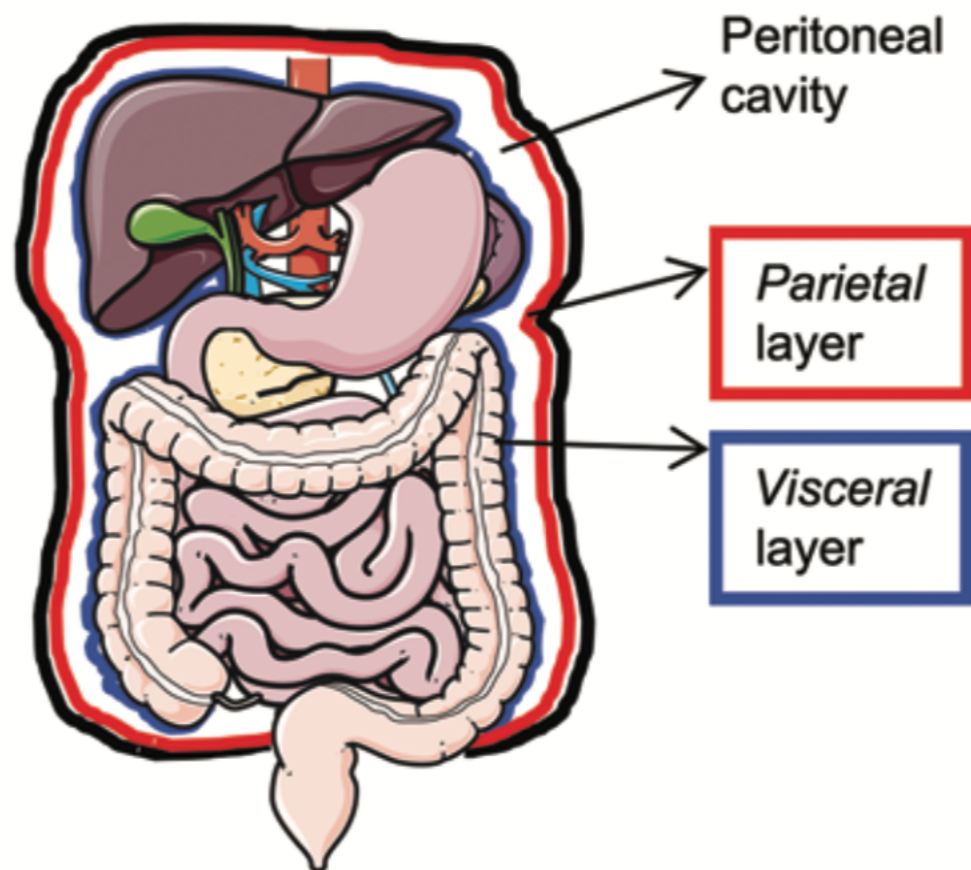
**Figure 3:** Drug distribution in the peritoneal cavity after IP injection of paclitaxel (10mg/kg) depending of formulation: paclitaxel solubilized in Cremophor EL/ethanol (*empty square*), paclitaxel-loaded gelatin nanoparticles (*filled triangle*) and paclitaxel-loaded polymeric microparticle (*filled circle*). A control group of mice received paclitaxel solubilized in Cremophor EL/ethanol intravenously (*filled diamond*) (a). Paclitaxel concentration-time profiles in peritoneal cavity (b) and in plasma (c). \* $p < 0.001$ . Reprinted from Tsai *et al.* 2007 with permission (Tsai *et al.*, 2007).

**Table 1:** Microparticle data summarized.

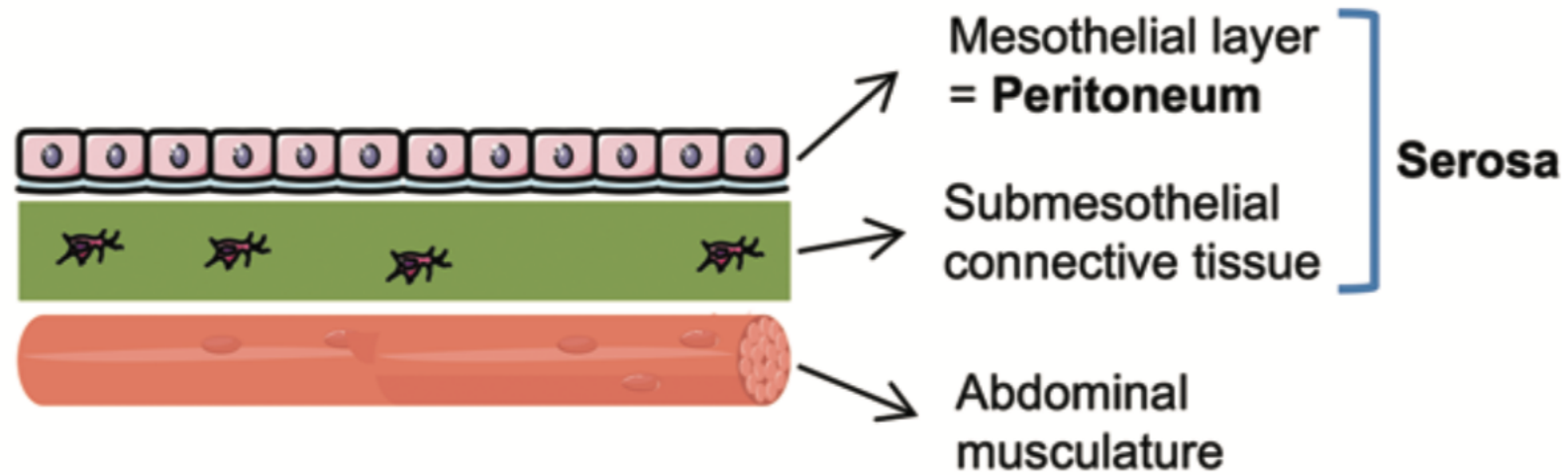
**Table 2:** Nanoparticle data summarized.

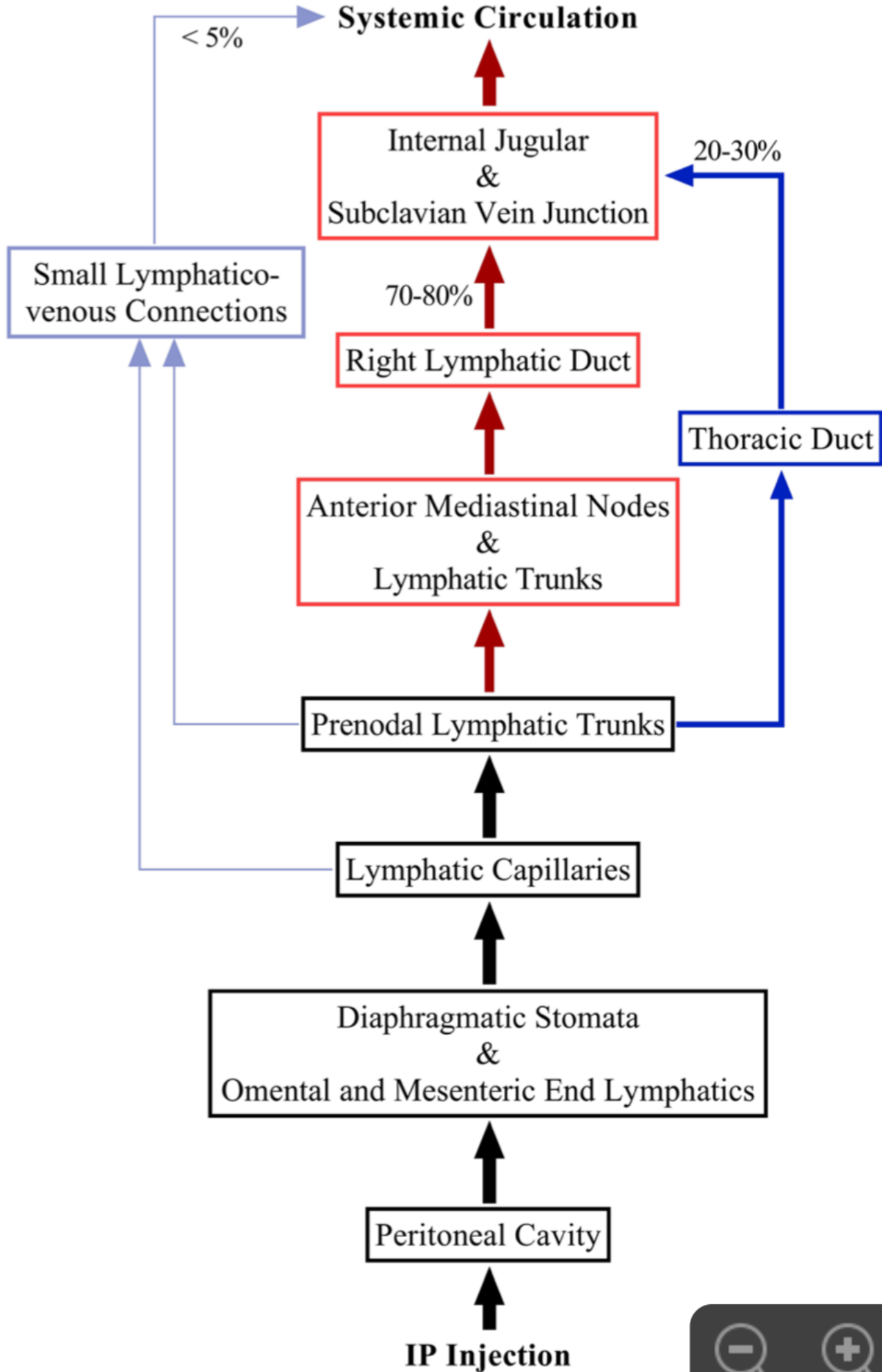
**Table 3:** Advantage and inconvenient of each drug delivery system

A

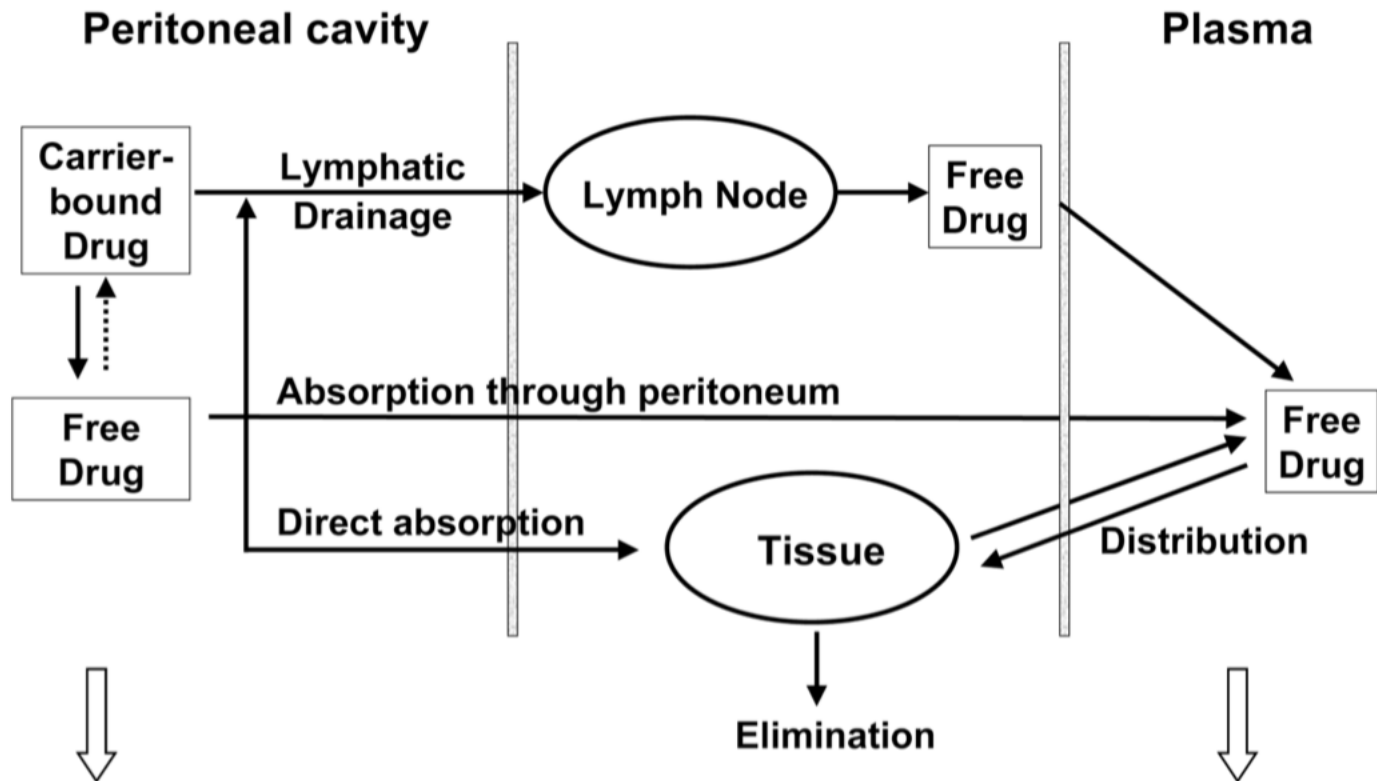


B

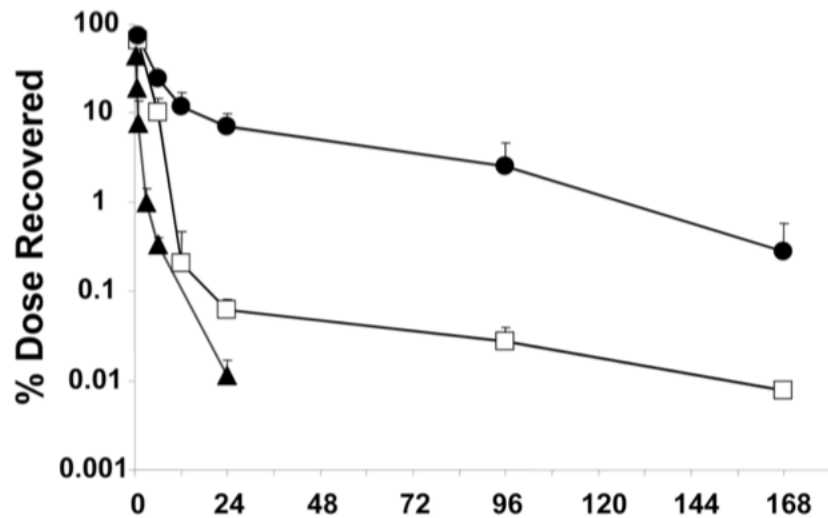




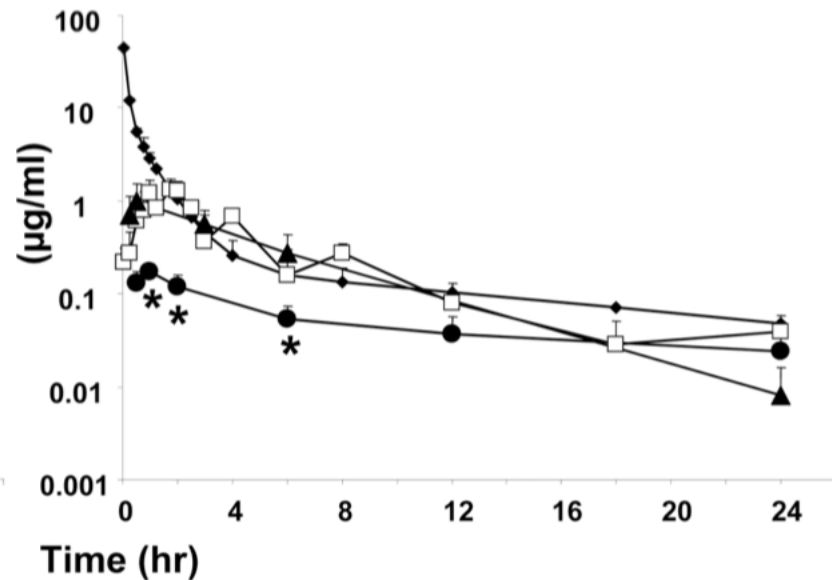
## A. Disposition of IP Therapy



## B. Profiles in peritoneal cavity



## C. Profiles in plasma



Ref	Drug delivery system	Release	Tumor lines	Animal model / Treatment groups	Results
De Clercq 2019	- Gelatin - Genipin - Paclitaxel	24h : 7% Day 14 : 19 to 60%	SKOV3 2x10 <sup>6</sup>	Femal BALB/C nu mice  - MS of paclitaxel as solution - MS of paclitaxel as nanosuspension of nanocrystals - Abraxane®	PTX-treatment IP significantly improved survival of mice in a microscopic peritoneal carcinomatosis mouse mode. MS of paclitaxel as nanosuspension was the only group showing significantly decreased PCI score and decreased of ascites compared to both control groups. The optimal dose of MS of paclitaxel as nanosuspension was ranged from 7.5 to 15 mg PTX/kg.
Fan 2014	- Poly(L-lactic acid) - Pluronic L121 - Docetaxel  Drug loading : 7% Diameter : 45µm	24h: 17% Day 8: 60%	CT26 2x10 <sup>5</sup>	Male BALB/C mice  - Docetaxel-MS 8mg of docetaxel/kg once a week - Docetaxel solution 4mg/kg 2 times a week	Tumor node numbers and size and the Ki-67 from docetaxel-MS group were significantly less than other groups. The median survival in docetaxel-MS group was significantly longer compared with docetaxel solution (p < 0.05).
Gunji 2013	- Gelatine - Cisplatin		Colon-26 1x10 <sup>6</sup>	Male BALB/C mice  - Cisplatin-MS (10mg cisplatin/kg) - Cisplatin solution (10mg cisplatin/kg)	No difference in the tumor weight was detected between the cisplatin-MS and free cisplatin solution groups. Cisplatin-MS showed a prolonged survival time compared with cisplatin solution (p < 0.05).
Lu 2008	- Poly(DL-lactide-coglycolide) - Paclitaxel  Drug loading : 4.1+-0.5% Diameter : 4µm	24h: 70% and then 1% daily	Human ovarian SKOV3 2x10 <sup>7</sup>	Femal athymic BALB/c Nu/Nu mice  - MP: 40 or 120 mg/kg - Paclitaxel/ Cremophor EL 4x10 mg/kg or 8 x15 mg/kg	MP showed higher concentrations and deeper penetration compared with the group treated with the Cremophor EL carrier.
Tsai 2007	- Poly(D,L-lactide-co-glycolide) - Paclitaxel  Drug loading : 3,77% Diameter: 5,77µm	about 70% in 24 h under sink conditions	Hs766T 20x10 <sup>6</sup>	Female nude Balb/C mice  - Paclitaxel-loaded Cremophor micelles, - Paclitaxel nanoparticles, - Paclitaxel microparticles (paclitaxel-equivalent dose of 40 mg/kg for all three formulations)	Microparticles, which had the slowest drug release, yielded the lowest rate and extent of systemic absorption in the first 24 h. Microparticles increased significantly greater the medium survival rate compared to other treatment group.
Armstrong 2006	- Lactide - Propylene glycol - Ethyl phosphate - Paclitaxel (=Paclimer®)  Drug loading : 10%			Human with recurrent or persistent ovarian or primary peritoneal carcinoma Paclimer® starting was 60 mg/m <sup>2</sup> IP every 8 weeks for two cycles	3 out of 13 patients were progression free for at least 6 months after completing therapy. Marked inflammatory response (adhesions, necrosis and fibrous connective tissue and foreign body giant cell reaction with residual polymer filaments) was observed in 1 patient and was supposed to be due to polymer.
Kohan 2006	- Poly-(lactic-co-glycolic) acid (PLGA)  Diameter : 5-25-60µm			Male SV129 mice  - carrier fluid containing MP	MP made from lower Mw polymers had much lower incidences on adhesion.



Liggins 2000	- Poly(L-lactic acid) - Paclitaxel 30% (w/w)  Drug loading : 97% Diameter : 30- 120µm	24h: 4% Day 30: 25%	9-L glioblast oma 2x10 <sup>6</sup>	Mal Wistar rats  - 100mg MS	No tumors or tumor nodules or ascites were visible in the peritoneal cavities of any rats which received paclitaxel loaded MS after either 2 or 6 weeks. All animals in control group died before 4 weeks.
Tokuda 1998	- Poly-d,l-lactic acid (PLA) - Polyethylene glycol acid 10% - Cisplatin  Diameter : 223µm	24h: 14%, Day 30: 85%	Yoshida sarcoma 6x10 <sup>6</sup>	Male Donryu strain rats  - Cisplatin-MS (8-12- 16mg/kg of cisplatin) - Cisplatin solution (8mg/kg of cisplatin)	In the cisplatin-MS group, the number of peritoneal metastasis was more decreased with the smallest dose of cisplatin. The survival time of rats was significantly better with high doses of cisplatin.
Hagiwara 1996	- Poly (glycolide-co- lactide) - 5-FU  Diameter : 24µm		B-16 melanom a 1x10 <sup>6</sup>	Male BDF1 mice  - 5-FU-MS (100-150- 200-300-400mg/kg) - 5-FU aqueous solution (100-150- 200mg/kg)	Survival time was significantly prolonged with 5-FU-MS compared to 5-FU solution at the same dose with a reduced systemic toxicity.
Kumagai 1996	- L-lactic acid and glycolic acid copolymer (PLGA) - Cisplatin  Drug loading : 5% Diameter : 100µm	Slow during 3 weeks	DMBA induced ovarian cancers 1x10 <sup>7</sup>	Female Wistar rats  - Cisplatin-PLGA (2,4- 4,8-7,2mg/kg) - Cisplatin solution 2,4mg/kg	Cisplatin-PLGA group showed a greater increase in their mean survival time compared with cisplatin solution group. This increase is proportional to cisplatin dosage.
Takahashi 1995	- Activated charcoal - Mitomycin  Diameter : <40µm			Human undergoing gastrectomy for gastric carcinoma with serosal infiltration grade S2 or S3. -Mitomycin-MP IP 50mg	Overall survival was greater in Mitomycin-MP group at 1,5-2-2,5 ad 3 years for patient without macroscopically defined peritoneal carcinomatosis.
Hagiwara 1992	- Poly d,l-lactide - Cisplatin  Diameter : 50- 150µm	24h: 40- 50% Day 20: 20-30%	Mouse ovarian histiocyti c sarcoma (M5076) 1x10 <sup>6</sup>	Male BDF1 mice  -Cisplatin-MsS(1-2,5- 5-10-25mg cisplatin/kg) -Cisplatin solution (1- 2,5-5-10-25mg cisplatin/kg)	At equivalent doses in toxicity a significantly greater number of mice survived with cisplatin-MS treatment compared with with cisplatin-solution treatment (p<0,001).

**Table 1:** Microparticle data summarized.

Ref	Drug delivery system	Tumor lines	Animal model / Treatment groups	Results
Coccolini 2017	- Albumine - Paclitaxel (=Abraxane®)		Female New Zealand White Rabbits  -Abraxane 10.83mg/kg - Paclitaxel Cremophor-EL 10.83mg/kg	Paclitaxel penetration in abdominal wall of the rabbits treated with nab-paclitaxel was significantly higher than paclitaxel in solution (p=0.0002).
Gilmore 2013	- Methacrylate monomer - Paclitaxel	OVCAR-3 10 <sup>6</sup>	Femal (Nu/J) mice  - Paclitaxel expansive NP 10mg/kg - Paclitaxel Cremophor-EL 10mg/kg	Expansile NP swelling appears to delay or prevent their exocytosis from tumor cells. Expansile NP demonstrated their ability to accumulate in areas of tumor. No recurrence was observed in eNP group compared with 43% in paclitaxel cremophor-EL group.
De Smet 2012	- Pluronic F127 - Pluronic F68 -Paclitaxel  Diameter: 400nm	SKOV-3 30x10 <sup>6</sup>	Adult female athymic nude rats  -Nanocrystalline paclitaxel formulation - Taxol®	No significant differences were observed on tumor growth between both PTX formulations at day 7 and 14 after HIPEC tratment
Werner 2011	- Poly (lactic-co-glycolic acid) (PLGA) - Lecithin - Distearoyl phosphoethanolamine-PEG-COOH - Folate - Paclitaxel - Yttrium <sup>90</sup>  Diameter: 75+/- 10nm	SKOV-3 14x10 <sup>6</sup>	Female Nu/Nu mice  - folate-targeted NP 20 µg Paclitaxel and/or 50 µCi of Yttrium-90 - non-targeted NPs 20 µg Paclitaxel and/or 50 µCi of Yttrium-90	Mice receiving folate-targeted nanoparticles had significantly longer survival than mice that received non-targeted nanoparticles (p=0.01). No statistical significance when comparing NPs containing both chemotherapy and radiotherapy to either therapeutic alone.
Colson 2011	- Acrylate based polymer - 2,4,6-trimethoxybenzaldehyde - Paclitaxel  Diameter : 100nm at physiological pH and 1000nm at acidic pH	Human malignant pleural mesothelioma cell lines MSTO-211H 5x10 <sup>6</sup>	Female athymic nude (Nu/J) mice  - Paclitaxel expansive NP - Paclitaxel Non expansive NP - Paclitaxel solution	Paclitaxel expansive NP in vivo was associated with slower drug release kinetics, prolonged intracellular accumulation of paclitaxel and a marked affinity of the NP for sites of local tumor in situ that persists for at least several days after injection. Survival was significantly superior in paclitaxel expansive NP group.
Kamei 2011	- 2-methacryloxyethyl phosphorylcholine - n-butyl methacrylate - Paclitaxel  Diameter: 50nm	MKN45P cells 3x10 <sup>6</sup>	Female specific-pathogen-free conditioned BALB/ c nude mice  - Paclitaxel NP administrated IV - Paclitaxel NP administrated IP 5 µg /g - Paclitaxel solution	Paclitaxel penetration in tumor nodules was deeper with paclitaxel NP administrated IP compared to other groups.  NP administrated IP were also found in hypovascular areas
Cirstoiu-Hapca 2010	- Poly(DL-lactic acid) -Taxol® - Herceptin	SKOV-3 5x10 <sup>6</sup>	Females BALB/cOlaHsd mice  - Taxol-NP-Herceptin -Taxol® solution	Tissue concentrations were higher when Taxol® was administered as nanoparticles due to the presence of antibodies at the particle surface.

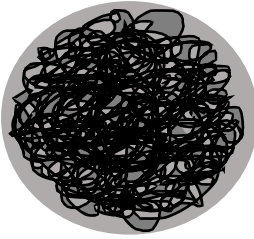
	<p>Diameter: 237±43 nm. About 250 molecules of mAbs were bound per nanoparticle</p> <p>Drug loading : 7.8±0.8% (w/w)</p>	<p>An initial dose of 20 mg/kg administered 10 mg/kg IV via the tail vein and 10 mg/kg IP, followed by five alternative IP and IV injections of 10 mg/kg every 3 days</p>	<p>Survival rate was improved with Taxol-NP-Herceptin.</p> <p>50 days after the end of the treatment, the tumors started to grow again in all treated mice.</p>
Kohane 2006	<p>- Poly-(lactic-co-glycolic) acid (PLGA)</p> <p>Diameter : 265nm</p>	<p>Male SV129 mice</p> <p>- carrier fluid containing MP</p>	<p>NP caused fewer adhesions, because they were cleared rapidly from the peritoneum and subsequently trafficked to the filtering organs (spleen and liver). This may also suggest that they may not be suitable for sustained drug release</p>

**Table 2:** Nanoparticle data summarized.

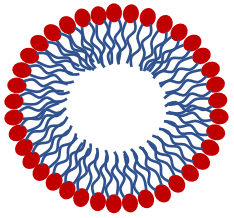
Drug delivery system	Advantages(s)	Inconvenient(s)
Microparticles	Prolonged residence time in peritoneal cavity depending on the particle size	Risk of adhesion Risk of inflammation
Nanoparticles	Small size allows tumor penetration enhancement	Spleen accumulation
Liposomes	Absence of toxicity and antigenicity Prolonged residence time in peritoneal cavity depending on the liposome size	
Micelles	Small size allows tumor penetration enhancement	Systemic passage Rapid elimination
Implants	Long term sustained release	Risk of fibrosis Risk of inflammation
Gel	Residence time prolonged in peritoneal cavity Homogenous repartition of drugs	Storage conditions
Gel + other DDS	Residence time prolonged in peritoneal cavity Drug realase prolonged Dual compartimentation	Storage conditions

# Drug delivery system used to treat peritoneal carcinomatosis

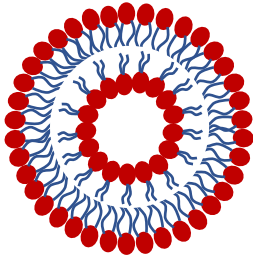
## Particulate drug delivery systems



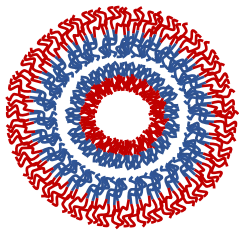
Micro/Nanoparticles



Micelles

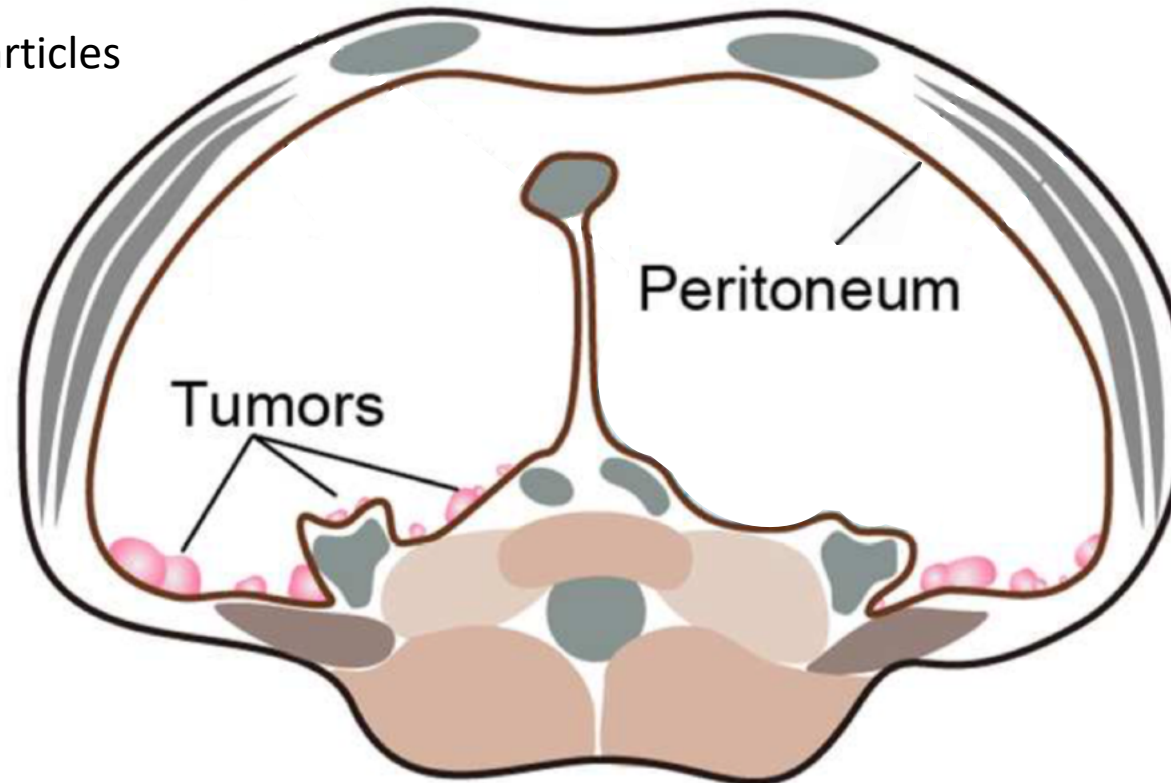
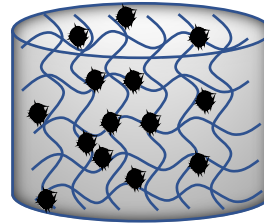


Liposomes



Polymersomes

## Gels loaded with particles



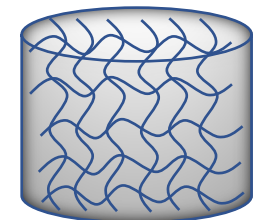
## Non particulate drug delivery systems



Films



Implants



Gels