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Review article

Intraperitoneal drug delivery systems for peritoneal carcinomatosis: Bridging the gap between research and clinical implementation

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ABSTRACT

Several abdominal-located cancers develop metastasis within the peritoneum, what is called peritoneal carcinomatosis (PC), constituting a clinical challenge in their therapeutical management, often leading to poor prognoses. Current multidisciplinary strategies, including cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC), and pressurized intraperitoneal aerosol chemotherapy (PIPAC), demonstrate efficacy but have limitations. In response, alternative strategies are explored in the drug delivery field for intraperitoneal chemotherapy. Controlled drug delivery offers a promising avenue, maintaining localized drug concentrations for optimal PC management. Drug delivery systems (DDS), including hydrogels, implants, nanoparticles, and hybrid systems, show potential for sustained and region-specific drug release. The present review aims to offer an overview of the advances and current designs of DDS for PC chemotherapy administration, focusing on their composition, main characteristics, and principal experimental outcomes, highlighting the importance of biomaterial rationale design and *in vitro/vivo* models for their testing. Moreover, since clinical data for human subjects are scarce, we offer a critical discussion of the gap between bench and bedside in DDS translation, emphasizing the need for further research.

1. Introduction

Peritoneal carcinomatosis (PC) constitutes a clinical challenge for managing many gastrointestinal and gynecological malignancies. The spread of cancer cells across the peritoneum and intraperitoneal cavity (IPC) is a common outcome of most abdominal cancers, such as ovarian, gastric, and colorectal cancers, pseudomyxoma peritonei, and peritoneal mesothelioma. This unfavorable evolution of the malignancy is often related to a poor prognosis, notably decreasing overall survival, thus making the locoregional spread of the tumor the principal cause of death

Abbreviations: 5-FU, 5-fluorouracil; AuNPs, Gold nanoparticles; CA4P, A4 disodium phosphate; CDDP, Cisplatin (cis-diaminodichloroplatinum); CPC, Cooperative Patent Classification; CPT-11, Camptothecin-11; CRS, Cytoreductive surgery; DDS, Drug delivery systems; DOX, Doxorubicin; DTX, Docetaxel; HA, Hyaluronic acid; HIPEC, Hyperthermic intraperitoneal chemotherapy; IC_{50}, Maximal inhibitory concentration; IPC, Intraperitoneal cavity; IPEC, Intraperitoneal chemotherapy; MMC, Mitomycin; MNPs, Magnetic nanoparticles; MPC, Mitomycin-PEG24-cholesterol; MVLs, Multivesicular liposomes; NPs, Nanoparticles; OXA, oxaliplatin; PAA, Poly (acrylic acid); PACA, Poly(alkyl cyanoacrylate); PC, Peritoneal carcinomatosis; PCL, Poly(Ɛ-Caprolactone); PDLLA, Poly-D,L-lactide; PIPAC, Pressurized intraperitoneal aerosol chemotherapy; PEG, Polyethylene glycol; PELG, Poly(y-ethyl-l-glutamate); PEO, Poly(ethylene oxide); PLA, Polylactic acid; PLGA, Polylactic-*co*-glycolic acid; PNC, Paclitaxel nanocrystals; PNIPAM, Poly(N-isopropylacrylamide); PPO, Poly(propylene oxide); PPT, Paclitaxel precipitates; PTX, Paclitaxel; ULVs, Unilamellar vesicles; UPy, Ureido-pyriminone..

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[1–3].

Although multidisciplinary strategies have been developed in recent years, which have allowed for increased survival or even the cure of highly selected cases, the prognosis remains grim. Regarding the disease's characteristics and counterpart with other cancerous manifestations, systemic chemotherapy has an evident lack of effectiveness, partly due to the physiology of the peritoneum [3,4]. The histological disposition of this serous membrane (Fig. 1), composed of a monolayer of mesothelial cells attached to a basement membrane overlying the submesothelial stroma (connective tissue), implies the main difficulty for some circulating chemotherapeutic agents since diffusion across the membrane reduces their concentration and effectiveness [1–3,5]. The so-called peritoneum-plasma barrier functions like a filter for molecules and substances, allowing the transport of water and small solutes but restricting the access of certain circulating molecules, depending on their size, charge, or hydrophobicity [3]. In fact, the peritoneal membrane is often described following a working model derived from its study as a dialysis membrane [6]. Strikingly, it has been suggested that the blood capillary wall and the surrounding interstitial matrix make a major contribution to this barrier function, with a minor role given to the mesothelial lining [6–8]. Additionally, many peritoneal tumor nodules are nearly avascular, thus being hardly treatable by intravenous chemotherapy as there is a lack of vascular drug source within the tumor [9]. Consequently, systemic chemotherapy is better distributed to the patient's extraperitoneal vascularized tissues and poorly distributed to peritoneal tumor nodules, resulting in limited effects and undesired

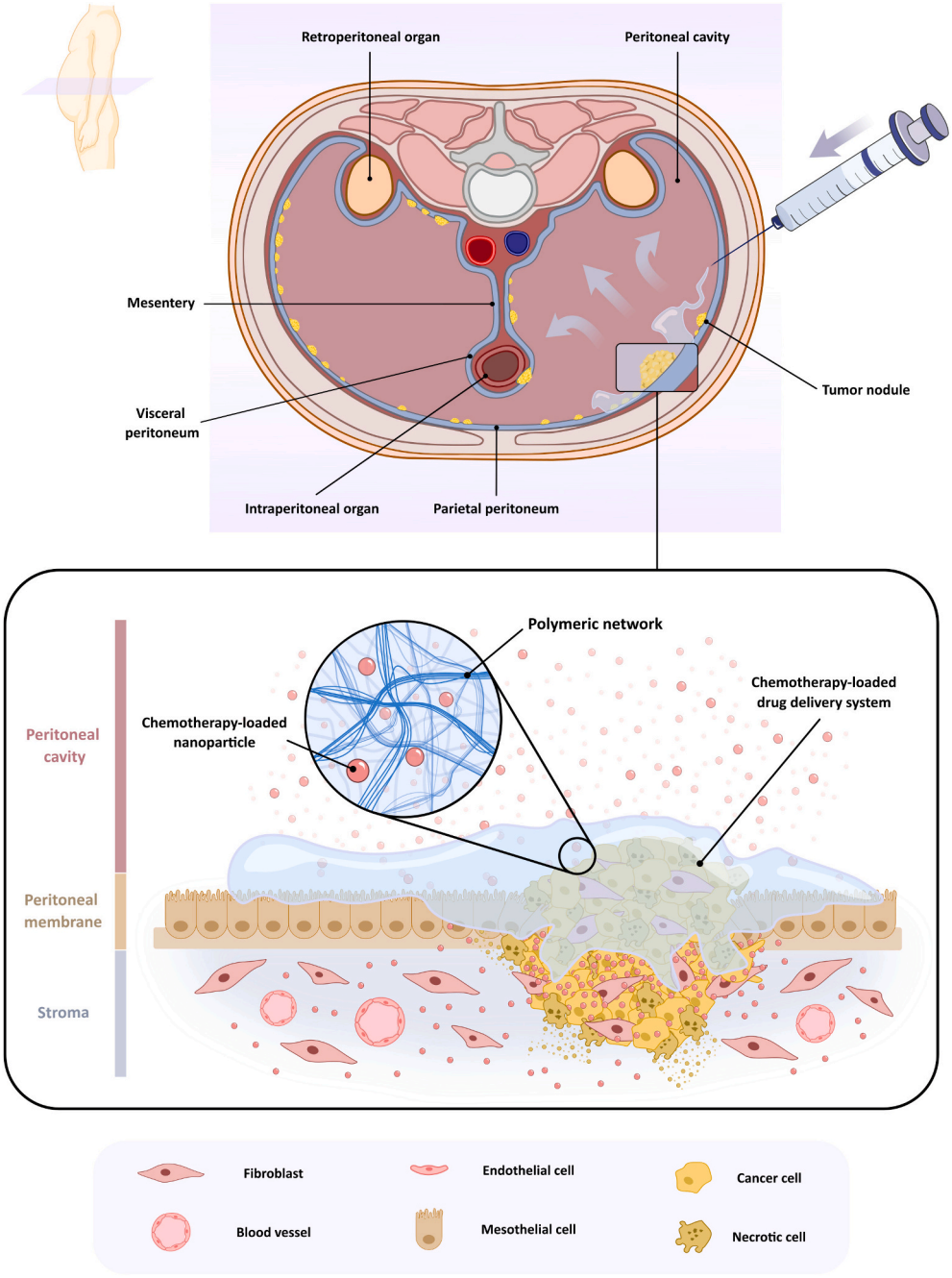

Fig. 1. Example of DDS for IPEC applications. Representation of the mechanism of action of an ideal hybrid DDS composed of chemotherapy-loaded NPs embedded in a hydrogel. As soon as the hydrogel degrades, the NPs are released to the peritoneal cavity and surrounding submesothelial stroma, acting on the tumor nodules responsible for the PC. Some icons were taken and modified from Servier Medical Art, licensed under CC BY 4.0..

toxicity.

Surgical and therapeutical advances in peritoneal metastasis are shedding some light on improving the oncologic outcomes of PC. In general terms, two strategies are currently in the spotlight: cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPEC). Both strategies have proven effective in PC management and are implemented in clinical guidelines [2,10,11]. CRS is the principal component of PC treatment, consisting of resectioning visible cancer nodules in the peritoneum and within the IPC. The resection of the peritoneum or peritonectomy and other visceral resections are performed to eliminate adhered tumor nodules [2,12]. In fact, the completeness of cytoreduction is the primary prognostic factor influencing survival in these patients [13]. For its part, IPEC has gained increasing attention among practitioners for the management of PC, although controversies remain. In any case, IPEC is not a new thing. The earliest intraperitoneal "drug therapy" was first reported by Christopher Warrick, who in 1744 injected a mixture of "Bristol water" and Bordeaux wine in the IPC of a woman with intractable ascites [5,14]. Thereafter, IPEC reports to the late 1950s and early 1960s [14]. However, it was not until the work of Dedrick et al. in 1978 [15] that interest in IPEC was encouraged. Dedrick proposed the pharmacokinetic advantages of the direct instillation of chemotherapy into the IPC, obtaining a high drug concentration in the IPC and low systemic exposure due to the characteristics mentioned above of the peritoneum-plasma barrier. The pharmacokinetic rationale of IPEC is, thus, based on the dose intensification given by the direct instillation of chemotherapeutic agents into the IPC and on the delayed clearance due to the peritoneal plasma barrier. As proposed by Dedrick and collaborators, the peritoneal permeability of many hydrophilic anticancer drugs is considerably less than the plasma clearance of the same, being the peritoneal clearance inversely proportional to the square root of their molecular weight, resulting finally in a higher concentration in the IPC than in the plasma after intraperitoneally administered. In addition to these advantages, IPEC procedures allow a higher exposure of avascular tumor nodules to chemotherapeutic agents, and their clearance through the portal vein favors their hepatic metabolism, resulting in reduced systemic side effects [6].

Current intraperitoneal administration approaches involve two main procedures: hyperthermic intraperitoneal chemotherapy (HIPEC) and pressurized intraperitoneal aerosol chemotherapy (PIPAC). HIPEC is the most common practice used in PC, in combination with CRS. The heating and localization of chemotherapeutical agents such as platin agents or taxanes allow a more significant cytotoxic effect, maintaining a high locoregional chemotherapeutic concentration and limiting their systemic diffusion and derived toxicity, killing residual microscopic disease that remains after CRS [1,2,5,10–12]. HIPEC, as well as normal IPEC, has proven its effectiveness in several cancers with PC manifestations, like ovarian cancer [16]. Studies such as the one carried out by Di Giorgio et al. [17] or the pivotal study OVHIPEC-1 RCT led by van Driel et al. [18] reported the feasibility of HIPEC and how HIPEC in combination with interval CRS significantly improves both progression-free survival and overall survival in the treatment of stage III ovarian cancer, respectively. Despite its main advantages, HIPEC presents drawbacks that limit its use in clinics. High temperatures (41–43 °C) promote systemic and abdominal cavity alterations and inactivate thermosensitive chemotherapeutic agents. Patients undergo major hemodynamic, metabolic, and respiratory alterations, especially stressing the cardiovascular system, resulting in an increase in the heart rate, cardiac index, and oxygen consumption, which require constant attention and timely assistance from the anesthesiologist [19,20]. A recent study performed by Hendrix and collaborators [21] reported how developing systemic hyperthermia (defined as an increase of core body temperature -CBT- over $\geq$39.5 °C) at any time during HIPEC is associated with a higher risk of presenting both 30-day postoperative complications (perianastomotic abscess, ileus, pleural effusion, urinary tract infection, *etc.*) and severe Claiven-Dindo grade III or higher complications. Moreover, its clinical execution implies a medical procedure that impossibilities the repetition of the cycle (due to the surgery procedure for intraperitoneal perfusion), which in turn supposes a limitation in managing carcinomatosis [3,5,10,11]. PIPAC is a recent development for patients with unresectable peritoneal metastases. Combining a diagnostic laparoscopy and local administration of chemotherapeutic agents in an aerosol formula presents several advantages, like a better spatial distribution of the drug and improved tissue penetration. Moreover, contrary to HIPEC, the PIPAC procedure can be repeated in different interventions [5,11]. However, the use of IPEC has been met with limitations and partial acceptance by oncologists. Some reasons for its failure can be attributed to poor penetration into the tumor nodules, reduced only to the outer layers and attributed to the high interstitial fluid pressure and the dynamic nature of the peritoneal cavity [22,23], a non-uniform drug distribution due to the adhesion formations after CRS [6], or even the premature clearance of small molecular weight drugs from IPC due to vascular and lymphatic drainage [24].

To overcome the limitations of currently available treatments for PC, such as conventional IPEC procedures, new approaches are emerging in the field of biomaterials and drug delivery systems (DDS). Controlled drug delivery is a technique that increases drug concentration in a specific body part by delivering therapeutical molecules while maintaining a constant level of drug release [25]. In this way, a localized and controlled chemotherapy release offers the optimal features for PC management [3,5]. The rapid clearance of some chemotherapeutics from IPC suggests that a sustained release of the antitumoral agents could provide a more accurate and effective drug administration [2]. Moreover, the release kinetics of DDS are also crucial in designing new therapeutic tools for IPEC since maintaining the drug concentration between the minimum effective concentration and toxic concentration constitutes a clinically critical aspect [5,25].

In general terms, DDS can be classified according to their chemical composition and formulation in different manners: particulate and non-particulate, natural or synthetic, organic or inorganic, stimuli-responsive or constitutive, *etc.* However, each system offers specific and distinctive characteristics and traits that must be considered before choosing the most suitable one for each application [1,25,26]. Referring to IPEC, a vast diversity of chemotherapy-loaded DDS have been developed. Among the most common ones used in systemic chemotherapy and IPEC, special mention should be made to hydrogels, implants, nanoparticles (NPs), and hybrid DDS [1,5,26]. Fig. 1 shows an ideal hybrid DDS for IPEC, as an example. All these chemotherapy delivery systems offer the possibility of administering the chemotherapeutic agents in a locoregional manner, performing a time-sustained release that benefits from the physiology of the peritoneum and IPC, concentrating the drug in the affected zone [5].

Despite the numerous and promising animal studies implementing DDS for IPEC, clinical data referring to human subjects are lacking [2]. Altogether, the main objective of this literature review is to offer an overview of the existing DDS for their application in IPEC to manage PC, focusing on their characteristics, mechanisms of action, and prospective application into clinical practice. Furthermore, and in contrast to other published literature about DDS for IPEC [24,27], a critical and updated analysis of the gap between bench and bedside has been conducted to check for the main limitations of DDS in their human application and the preferable qualities they should have. First, we discuss the main formulations of DDS designed for IPEC, emphasizing their chemical composition and structural disposition, release capacity, functionalization, and other specific properties. Next, we summarize the most significant results that have been derived from testing these formulations on *in vitro* and *in vivo* models, to finally delve into a thorough analysis of the patent panorama and clinical studies, deciphering the main restraining factors for the development of novel DDS for IPEC and arguing why there is an urgent need to bridge the gap between bench and bedside.

2. Search strategy

2.1. Publications

A general research strategy was designed to review all the available literature on DDS for IPEC (Fig. 2). First, in May 2023 and again in January 2024 (to select new publications during this period) using the database PubMed®, a general literature search was conducted using the search terms "DDS" OR "drug delivery" AND "intraperitoneal chemotherapy" as these terms represent the broadest definition of DDS for their application in intraperitoneal locoregional chemotherapy. A total of 2919 articles resulted from this search, as seen in Fig. 3A. The publication date was not limited, aiming for a comprehensive exploration of all available literature. To further narrow the search, the following filters and critical terms were added or modified sequentially to the previous search:

- ("DDS" OR "drug delivery") [All fields] AND "intraperitoneal chemotherapy" [Title/Abstract]
- ("DDS" OR "drug delivery") [All fields] AND "intraperitoneal chemotherapy" [Title/Abstract] and English Filter
- ("DDS" OR "drug delivery") [All fields] AND "intraperitoneal chemotherapy" [Title/Abstract] and English Filter and NOT "review" [Publication Type] NOT "systematic review" [Publication Type] NOT "clinical trial" [Publication Type]

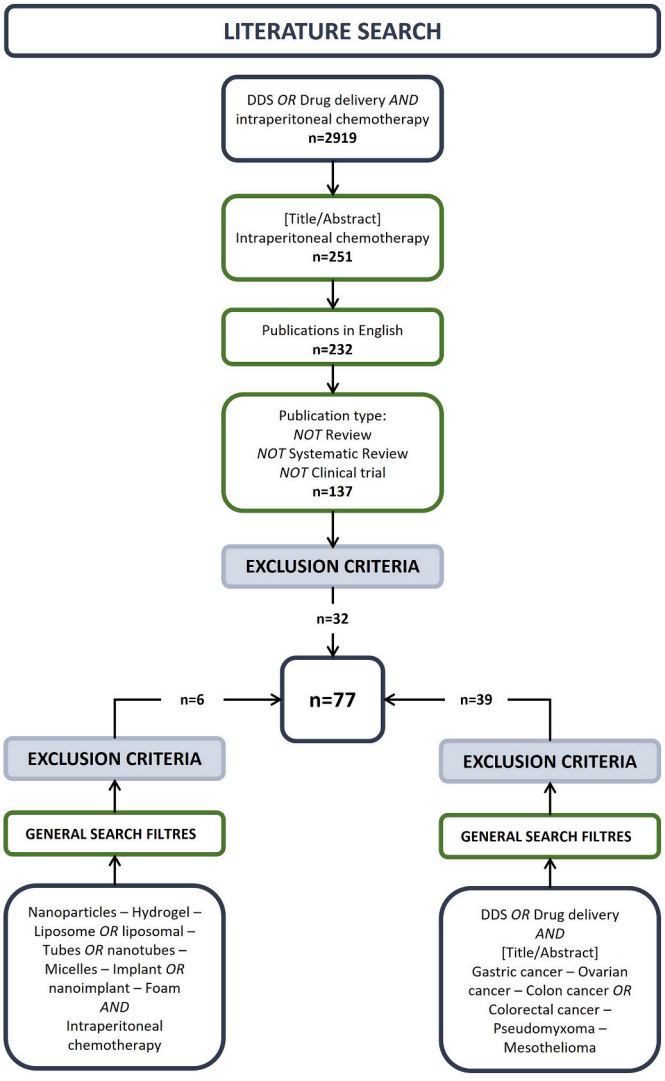

Fig. 2. Followed literature search strategy. Three different searches were performed using the PubMed® database. All results were narrowed and filtered according to the procedure detailed in the text, obtaining 77 articles for the literature review.

After applying the mentioned filters, 128 publications were eligible for title, abstract, and text screening. Since the main objective of this literature review was to check for the advances and new approaches in DDS for IPEC, publications about HIPEC and PIPAC systems were excluded as they have been used in clinics for years and are currently being implemented in randomized clinical trials for assessing their effectiveness and safety. The National Institute of Biomedical Imaging and Bioengineering (https://www.nibib.nih.gov/) defines DDS as *"[…]* technologies that carry drugs into or throughout the body. These technologies include the delivery method, such as a pill you swallow or a vaccine that is injected. DDS can also describe how drugs are 'packaged'-like a micelle or a NPs-that protects the drug from degradation and allows it to travel wherever it needs to go in the body". As this definition is extensive and does not allow for the screening of delivery devices, we have considered DDS to be those specifically designed to be loaded with the desired active substance to facilitate delivery to the affected site and protect it from degradation. This consideration, therefore, excludes administrations such as vaccines, tablets, or crystallizations of the active compound. Moreover, publications referred to gene therapy DDS were excluded. In addition, all DDS not designed for locoregional administration were removed from the search. The resting publications of DDS loaded with chemotherapy agents for locoregional intraperitoneal administration were included in the literature review. Finally, 32 publications were selected for review after screening and using inclusion and exclusion criteria.

To enrich the previous general search, two additional specific searches in PubMed® were subsequently performed:

- On the one hand, a specific search was performed according to the different types of DDS. In this case, the searched terms were "nanoparticles", "hydrogel", "liposome OR liposomal", "tubes OR nanotubes", "micelles", "implant OR implants", and "foam", each one followed by AND "intraperitoneal chemotherapy" [All fields].
- On the other hand, a specific search according to the different types of cancer was performed. In this way, the searched terms were "DDS" OR "drug delivery" followed by AND "gastric cancer", "ovarian cancer", "colon cancer" OR "colorectal cancer", "pseudomyxoma" and "mesothelioma", each one in [Title/Abstract] fields.

The same filters applied to the general search were used to narrow both specific searches. After the screening, involving the inclusion criteria, and eliminating the repeated publications, 45 articles were added to the previous 32 to perform the review. Fig. 3B illustrates the distribution of DDS types utilized in IPEC studies, with particles as the most frequently used DDS, followed by hydrogels. Furthermore, Fig. 3C offers insights into the landscape of targeted cancer types in the design of DDS for IPEC, with ovarian and colorectal cancer as the most recurrent targeted cancer types investigated.

2.2. Patents

Another way to assess the activity level in translating DDS for IPEC basic science is to look at the number of patents issued in the area. Thus, a patent search was conducted in September 2023 using The Lens's open-source patent database (https://www.lens.org/) to explore the latest technological advancements and innovations on DDS for IPEC. The search was saved as a Dynamic Collection to allow an automatic update. The search term used was "(DDS OR drug delivery) AND intraperitoneal chemotherapy", giving 275 patent records grouped into 118 simple patent families that stemmed from the same initial document (priority document). We did not use patent classification systems, such

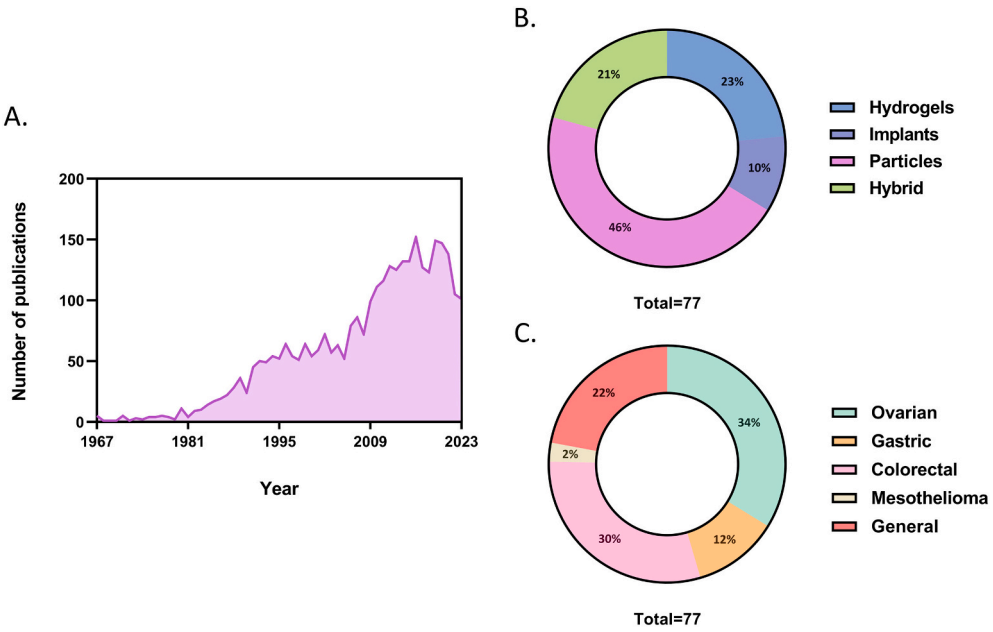

Fig. 3. Data analysis of DDS for IPEC research literature. (A) PubMed® publications with ("DDS" OR "drug delivery") AND "intraperitoneal chemotherapy" per year. (B) Absolute frequency diagram of DDS types used in IPEC research. The percentage of articles corresponding to each DDS type is also given. (C) Absolute frequency diagram of the targeted cancer types in the design of DDS for IPEC. The percentage of articles corresponding to each targeted cancer type is also given.

as Cooperative Patent Classification (CPC) and International Patent Classification, since narrowing our search further to specific technology areas was unnecessary. We carefully analyzed the retrieved patent families for relevance, assessing their titles, abstracts, claims, and full descriptions. After screening and applying the aforementioned inclusion criteria, 58 patent records, grouped into 28 simple patent families, were selected for review. After manually curating, the collection was saved as Static Collection to allow its consultation with the following link: https://www.lens.org/lens/search/patent/list?collectionId=212682. The resulting patents served as valuable resources to support our review, enabling us to identify gaps in the existing literature and gain insights into the latest advancements and emerging trends in DDS for IPEC. From the analysis using The Lens, the top CPC classification codes for the patents found were A61P35/00 (Human Necessities Antineoplasic agents), A61K31/337 (Human Necessities having four-membered-rings, *e.g.* taxol), and A61K9/0019 (Human Necessities Injectable compositions), as seen in Fig. 4A. Fig. 4B illustrates patent documents (granted patents or patent applications) over time.

2.3. Clinical trials

Finally, a comprehensive research strategy was devised to systematically evaluate the clinical trials related to DDS for IPEC. The search was performed in May 2023 and again rechecked in January 2024 and encompassed the following databases: ClinicalTrials.gov, EudraCT, and NIPH clinical trials. The search term used was "intraperitoneal chemotherapy". All clinical trials in Phase 1 or Phase 2 were included. A total of 50 clinical trials were identified through ClinicalTrials.gov, while an additional 44 were found in the EudraCT database. Furthermore, the NIPH Clinical Trials portal yielded six further trials, bringing the total number of trials obtained from all sources to 100. Only three clinical trials were eligible for review after excluding the clinical trials related to HIPEC and PIPAC. Therefore, the search yielded almost no trials that met the criteria of investigating alternative DDS beyond HIPEC and PIPAC. This indicates a gap in current research regarding novel approaches to drug delivery for IPEC, highlighting the need for further exploration in this area.

3. Types of DDS for IPEC

A wide range of DDS has been described and characterized in the literature to develop an ideal carrier that improves cancer treatment efficacy. These systems can offer several advantages, such as better drug solubility and permeability, protection from degradation, improved drug stability, prolonged release, and increased half-life in the peritoneal cavity (Fig. 5). Furthermore, successfully accessing diseased sites is essential for the drug's effectiveness. DDS can be targeted to decrease the exposure of healthy cells to cytostatic drugs, overcoming drug resistance and reducing toxic side effects.

Within Fig. 6, different characteristics are depicted and associated with prevalent DDS. Each system accounts for specific properties that may confer either an advantage or a disadvantage relative to other devices. For instance, synthetic inorganic NPs commonly exhibit biocompatibility issues compared to alternative DDS, such as hydrogels made of biopolymers like hyaluronic acid (HA). However, they concurrently offer the advantage of facile functionalization for specific cell targeting, a capability that most hydrogels lack. Analyzing and comprehending the attributes of each DDS and biomaterial is a crucial preliminary step before developing a novel device for a specific therapeutic application. Furthermore, considering the clinical implementation of the DDS and aligning it with the desired characteristics ensures an improved outcome of the resultant application and design. For this reason, DDS tailoring must be performed according to the characteristics of intraperitoneal administration, assessing their suitability by taking into account the pharmacokinetics and physiology of the IPC discussed earlier. Table 1 offers an overview of the advantages and disadvantages of each type of DDS for their use in IPEC.

Next, this review delves into the most relevant advancements in DDS for treating PC and IPEC applications according to the aforementioned characteristics and features.

3.1. Non-particulate DDS

3.1.1. Hydrogels

Hydrogels are three-dimensional (3D) hydrophilic polymer networks widely used as a matrix for drug encapsulation. Some key features and

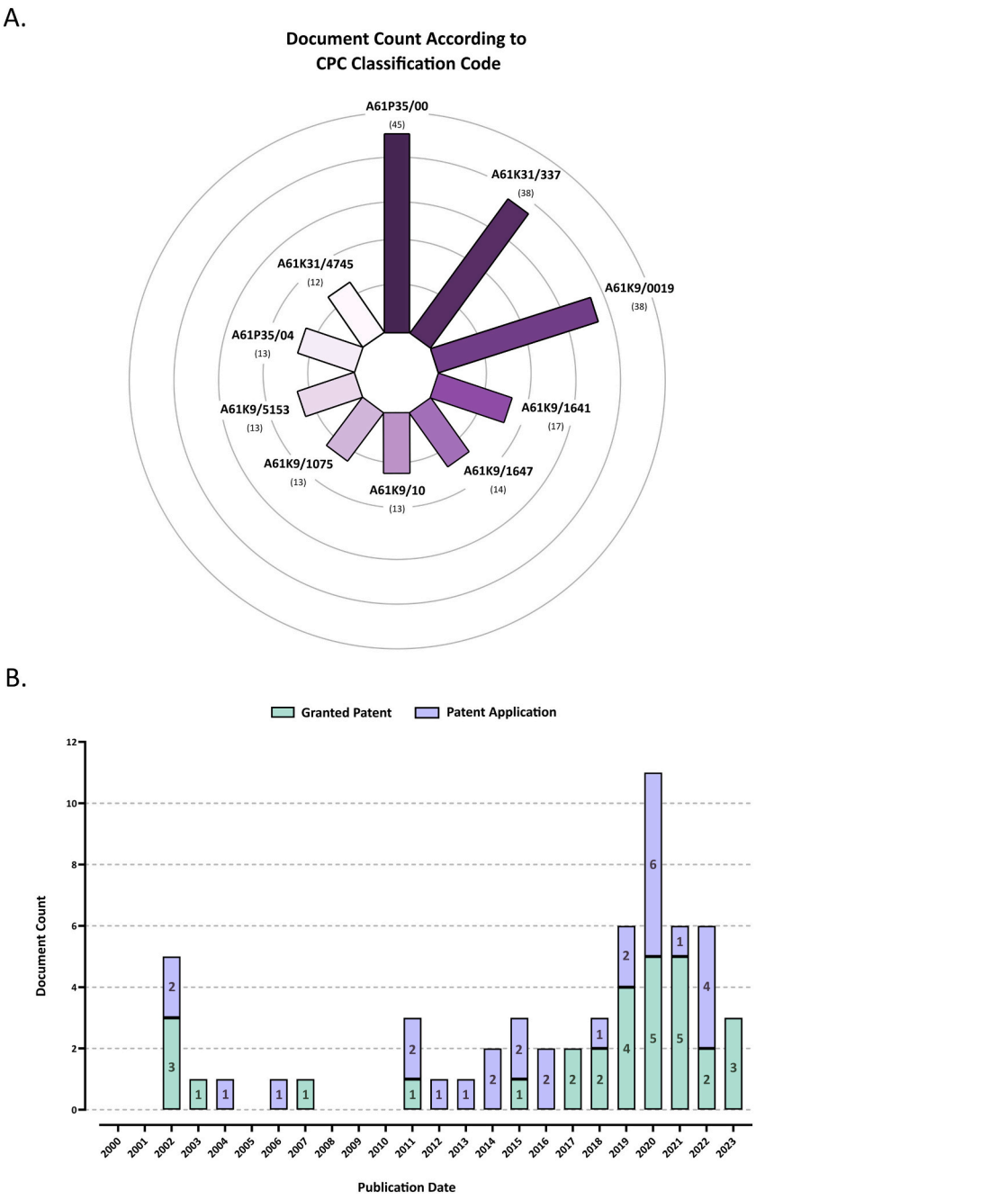

Fig. 4. Data analysis of DDS for IPEC patents research. (A) Top CPC classification codes for the patents found in The Lens patent analysis. (B) Patent documents timeline. Granted DDS for IPEC patents are shown in green, whereas the patent application count is represented in purple. The left axis represents the total document count per year. *(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)*

properties for their use in biomedicine, especially in site-specific and controlled DDS *via* intraperitoneal administration, are 1) their high water content; 2) their high affinity for biological fluids; 3) a porosity structure where different types of substances can be retained; 4) high deformability and moldability; 5) and their injectable nature. Thus, traits such as pore size, gelation time, degradability, swelling capacity, and release rate can be controlled during their synthesis. For example, Ailincai et al. designed and synthesized different hydrogels based on chitosan and citral, varying the crosslinking ratios [28]. They demonstrated that these supramolecular 3D structures, in which 5-fluorouracil (5-FU) was homogenously dispersed, had different release profiles depending mainly on the crosslinking degree.

Targeted delivery into tumors is another potential advantage achieved through hydrogels. HA is widely used as a biomaterial for biomedical applications, including drug delivery, due to its biocompatibility, biodegradability, and diversity of chemical modifications. Moreover, HA constitutes a ligand of CD44, which is known to be overexpressed in various cancer cells. Aiming to develop a suitable drug delivery platform for targeted drug release, Emoto et al. encapsulated cisplatin (CDDP) inside an *in situ* cross-linkable HA-based hydrogel. HA was modified to obtain one aldehyde form (HA-CHO) and one adipic dihydrazide (HA-CHO) [29]. When mixed, these polymers can form a gel, thus allowing drug loading. In this example, CDDP was gradually released from the gel over four days as it was degraded by hyaluronidase incubation, with a cumulative release of 80%. For their part, Sun and colleagues also developed an HA-based hydrogel depot [30]. To improve

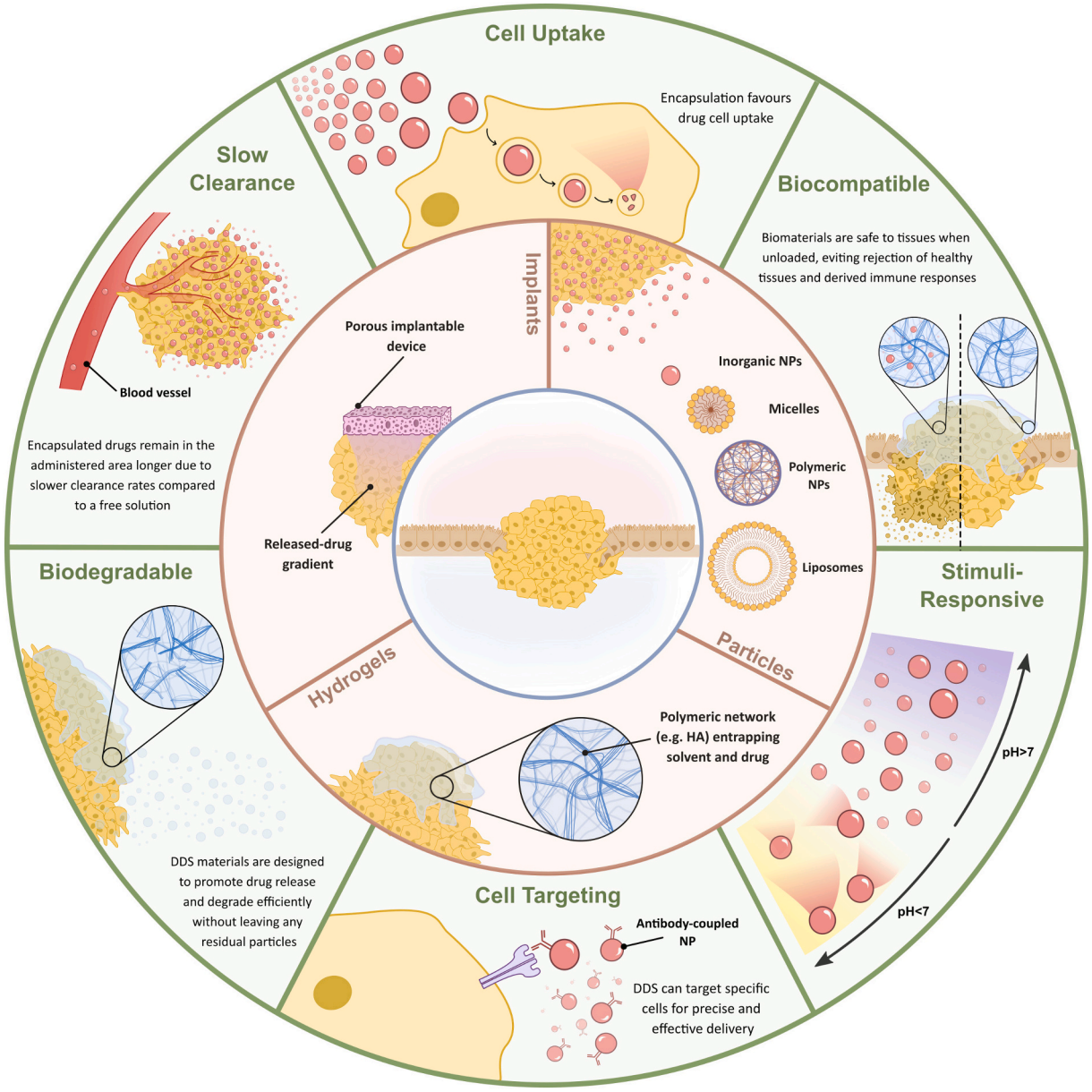

Fig. 5. DDS overview: types and leading advantages. A vast diversity of DDS is currently being studied in cancer treatment. Biomaterials can adopt different formulations to constitute suitable drug carriers, such as hydrogels, NPs, or implantable solid devices. These formulations can, in turn, be combined to form hybrid DDS, which count with the advantages of both origin formulations. All these DDS present different properties that enhance and facilitate the administration of chemotherapeutic agents, such as stimuli-responsive capacity, easy functionalization for specific cell targeting, slow tissue clearance, or even improved cell uptake capacity.

the solubility of paclitaxel (PTX) in the hydrogel, they produced and loaded PTX nanocrystals (PNC) into the gel and compared it with PTX precipitates (PPT), obtaining a 30.6% and 32.6% of PTX release from PNC-gel and PPT-gel, respectively, in 19 days. Although both studies used practically the same hydrogel, differences in the drug release profile may be mainly due to the larger molecular size of PTX *versus* CDDP and the solubilizing effect of nanocrystals [29,30].

It is essential to control the mechanical properties of the hydrogel to achieve a proper viscosity. If the hydrogel is too low-viscous, it can diffuse too fast in the peritoneal cavity, while if it is too high, it can be difficult to inject intraperitoneally. These viscosity-related challenges can be targeted by "smart" hydrogels, such as stimuli-response hydrogels sensitive to pH or temperature. These hydrogels can respond with chemical or physical modifications to the surrounding environment conditions or external stimuli. Bakker et al. developed a pH-responsive supramolecular hydrogel based on ureido-pyriminone (UPy) and polyethylene glycol (PEG) with hydrophobic compartments where drugs can be trapped [31]. This UPy-PEG hydrogel is injectable at pH 9.0 and performs a sol-gel transition when in contact with physiological pH. Moreover, mitomycin (MMC) was modified with cholesterol (MPC) to achieve a sustained release profile and increase chemical stability. This conjugation enhanced the affinity between the modified drug and the hydrophobic compartments in the UPy-PEG gel. As a result, MMC and MPC exhibited different release profiles, with MMC being totally released in 24 h through a typical diffusion profile. In contrast, MPC was released according to the erosion of the hydrogel, achieving only 7% release on the first day and then a sustained release of 1% per day. Also, Wintjens and colleagues modified this UPy-PEG hydrogel formulation to attain the required viscous properties for minimally invasive intraperitoneal administration [32].

For its part, thermosensitive hydrogels exhibit a sol-gel transition in response to temperature, being liquid at room temperature that allows

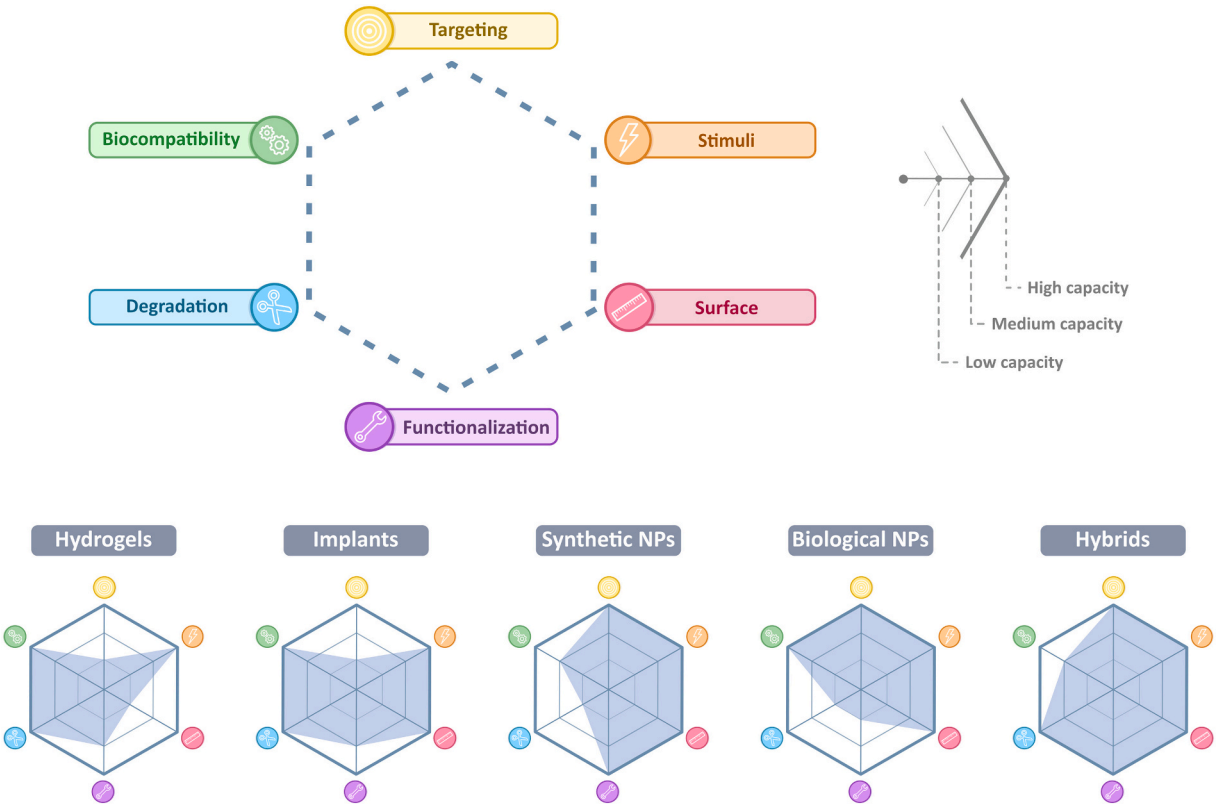

Fig. 6. DDS characteristics and properties. This figure comprehensively depicts diverse characteristics associated with prevalent DDS. Each system possesses distinct properties that confer advantages or drawbacks on other devices. Radar charts represent the degree of capacity of each DDS to present (or not present) the selected characteristics. Characteristics ordered clockwise: cell targeting feasibility (yellow circle), stimuli-responsive capacity (pH, redox reaction, magnetic field, light, *etc.*) (orange circle), high surface area (pink circle), functionalization ease (purple circle), controlled degradation capacity (blue circle), and biocompatibility (green circle). *(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)*

Table 1
Suitability of DDS for their use in IPEC.

Drug delivery system	Advantages	Disadvantages
Hydrogels	Prevention of postsurgical peritoneal adhesions Easy injectable	Heterogeneous drug distribution within the peritoneum Viscosity issues (low viscous hydrogels may fail in providing delayed drug release, while high viscous hydrogels may present difficulties in administration)
Implants	Can be fixed near the tumor side Increased and more localized drug delivery	Invasive Surgical expertise needed for application Increased tissue damage
Particles	High tumor nodule penetration and cell uptake	Rapid peritoneal clearance through lymphatic openings-mediated drainage (depending on particle size)

an easy administration of drugs without invasive surgery, facilitating its manipulation and intraperitoneal injection. After injecting the drug-loaded mixture, it changes spontaneously into a hydrogel by forming physical links in response to body temperature, thus generating a depot system *in situ*. Many amphiphilic block copolymers, specifically di- and triblock copolymers, are commonly used as biomaterials for developing DDS. These materials comprise hydrophobic blocks such as polylactic acid (PLA) or polylactic-*co*-glycolic acid (PLGA) and hydrophilic blocks such as PEG. Temperature-responsive hydrogels can be obtained by combining thermo-sensitive polymers into block copolymers. PEG is one of the most used hydrophilic polymers in block formulations due to its biocompatibility and endowing stability. Yu and collaborators loaded A4 disodium phosphate (CA4P) and CDDP in a thermo-gelling hydrogel based on a diblock copolymer PEG-b- Poly(y-ethyl-l-glutamate) (PELG), showing differences in drug-release behavior due to the different solubilities. Thus, CDDP had a slower drug release rate when compared with CA4P at day 7 (66% *vs.* 90%). However, burst drug release phenomena were observed from both CA4P and CDDP in the first hours, probably due to the open, micrometric porous network of the depot [33].

A broad type of polymers has been used to develop thermosensitive drug-loaded triblock copolymers. Wang et al. developed a 5-FU-loaded PEG- poly(Ɛ-Caprolactone) (PCL)-PEG (PECE) hydrogel system based on PEG-PCL-PEG copolymers [34]. The release profile was studied with two initial drug loadings of 0.5 mg and 1 mg. Both hydrogels showed an initial burst release of 26.2% and 19.8% during the first hour, respectively. Furthermore, the drug was almost wholly released in one day, being 95.3% and 65.8% the cumulative release rates. This shows that with a lower initial drug loading, 5-FU was released more rapidly and achieved a higher cumulative release rate, demonstrating that the initial drug loading has an impact on the release profile. Shin and colleagues loaded epothilone B, 17-AAG, and rapamycin in another type of triblock copolymer (PLGA-b-PEG-PLGA), resulting in a temperature-dependent hydrogel [35]. In another study, a temperature-dependent hydrogel based on poly-D,L-lactide (PDLLA) and PEG (PDLLA-PEG-PDLLA triblock copolymer) showed a burst release of 5-FU and CDDP on day 1. However, a sustained release was observed over the following days, with 92.42% of 5-FU and 47.42% of CDDP released after 28 days [36]. Poly (ethylene oxide) (PEO)- poly(propylene oxide) (PPO) -PEO triblock copolymers with different proportions of PPO and PEO were marketed under the trade name Pluronic® (or Poloxamer). Chang et al. used Pluronic® lecithin organogel with thermosensitive properties to locally co-deliver docetaxel (DTX) and CDDP [37]. This DDS was formed with

an organic solvent, phospholipids such as lecithin, and a polar solvent containing Pluronic® F127, which was able to retain the anticancer drugs at the tumor's local injection site, leading to an improved therapeutic outcome while reducing side effects. Al Sabbag et al. selected alginate and chitosan, two natural bioadhesive polymers, and added them to Poloxamer P407 and P188 to provide thermosensitive properties and locally deliver 5-FU [38]. The bioadhesive polymers decreased syringability by increasing viscosity, which reduced the diffusivity coefficient of 5-FU loaded in the hydrogel. Therefore, it is crucial to maintain the balance between adhesiveness, injectability, and release.

Poly(N-isopropylacrylamide) (PNIPAM) is another popular thermosensitive polymer that has attracted researchers' interest in drug delivery thanks to its ability to enhance drug solubility, allow a sustained release, and reduce side effects [39]. Carreño et al. loaded doxorubicin (DOX) into two thermo-responsive hydrogel formulations formed through the cross-linking of PNIPAM with other monomers (maleic acid and 4-penten-1-ol) using specific crosslinker agents and termed PNIMaTH and PNIPenpH [40]. Both release profiles were characterized by a burst effect and rapid DOX release at 12 h, followed by a slower and continuous release. However, PNIPenpH demonstrated a lower swelling and a more sustained release of DOX due to maleic acid in the hydrogel matrix. In another study, to enhance the intraperitoneal chemotherapeutic efficacy and prevent postsurgical adhesions, Chen et al. combined chitosan and HA with PNIPAM hydrogel and loaded it with DOX, too [41].

Although drug release profiles can be controlled by changing the type of polymer, the crosslinking degree, or even the intermolecular interactions between the chemotherapeutic agent and the hydrogel network, the initial burst effect is still challenging. Generally, drug release profiles from hydrogels follow a bi-phasic pattern: 1) drug diffusion during the initial release profile and 2) drug release by erosion or degradation of the hydrogel during the downstream phase. This first phase results in a relatively fast drug release due to high water content and large pore size. Consequently, there is no sustained and prolonged drug release over time.

3.1.2. Implants

Implantable DDS allow targeted and localized drug delivery within IPC, potentially achieving therapeutic effects with lower concentrations and reducing the systemic toxicity that conventional chemotherapy produces. Their main advantage is their ability to be implanted at the tumor site for local drug delivery. Moreover, implants offer other relevant benefits for their use as DDS in IPEC. For example, to avoid the burst release effect characteristic of triblock copolymers hydrogels such as PEO-PPO-PEO, Cho et al. (2019) dehydrated gels to form thin solid discs carrying PTX and rapamycin, achieving a better handling and storage temperature of the system [42]. This procedure allowed only 14% of PTX and 20% of rapamycin to be released in the first 30 min, compared to 33% and 39% released from the gel, respectively. After 12 h, the drug released from both DDS became almost identical. Thus, this formulation overcomes one of the main drawbacks of Poloxamer 407 gels, which is associated with the initial burst release of the drug and the rapid erosion of the gel.

In addition to using PLGA to form di- or tri-block copolymers, as discussed in the previous section, this biodegradable copolymer has also been widely used to develop drug-delivery implants. In fact, PLGA is the best-known and most preferred polymer in controlled delivery systems to date. Yanqin Wang and collaborators fashioned PLGA into a stent and loaded it with CDDP to be surgically implanted near the tumor site in the peritoneal cavity [43]. The manufacturing parameters of the drug-loaded PLGA stents can be adjusted according to the required degradation time and drug release rate, thus enabling a sustained therapeutic range over a long period [44]. The authors described one more phase in the drug release profile resulting in a total of 3 stages: 1) a burst release was observed during the first eight days; 2) the gentle release phase occurred during days 8 to 20; 3) and finally, a rapid release phase happened. In two other studies, PLGA implants were loaded with Talazoparib or 5-FU, respectively [45,46]. Both studies highlighted the relationship between implant biodegradability and drug release profile. Faster drug release was observed in an acidic environment due to enhanced degradation of PLGA, resulting in lactic acid and glycolic acid. This change in release rate may be advantageous for targeted release, as the tumor microenvironment is slightly more acidic than the physiological environment [47,48].

Electrospinning is used for fabricating drug-loaded nanofibers, which are employed as implants in several applications, including cancer therapy. Many polymers are used in fiber production, both natural (*i.e.*, gelatin and chitosan) and synthetic (*i.e.*, PCL and PLA) [49,50]. Electrospun PCL and PLA were chosen by Yohe et al. [51] and Zhang et al. [52], respectively, to develop fibers that act as drug carriers, providing a large surface area for high drug loading and encapsulation efficacy. In the first study, PCL was doped with 10% poly(glycerolmonostearate-*co*-ε-caprolactone) to increase hydrophobicity and achieve slower release of camptothecin-11 (CPT-11) and 7- ethyl-10-hydroxycamptothecin. In the second study, PLA nanofibers were used to deliver oxaliplatin (OXA) and 5-FU, resulting in an initial burst release of both drugs. Although initial burst release is still a challenge in drug delivery for most studies, some authors argue that a biphasic delivery pattern is necessary to achieve enough initial dosage to kill tumors and a continued release to prevent the proliferation and migration of those surviving cells.

Although implantable drug delivery devices have numerous advantages, such as providing a sustained release for weeks or even months, their therapeutic impact still requires improvement. Nevertheless, implants also come with their fair share of challenges, such as peritoneal tissue damage, adhesion-associated complications, and the requirement that a healthcare professional perform invasive insertion.

3.2. Particulate DDS

3.2.1. Nanoparticles

NPs are a type of biomaterial widely used as a controlled release system. Nanocarriers allow the protection and release of the drug selectively in the therapeutic target. Among the requirements sought in this type of DDS, we can find 1) biocompatibility, 2) biodegradability, 3) high loading of the therapeutic agent, 4) stability in the bloodstream, 5) selective vectorization, and 6) stimuli-responsive release. One key parameter in the case of particles intended for IPEC is their size, which determines their release, residence time in the IPC, and systemic passage. Small particles avoid the induction of immune responses and exhibit a high tumor penetration, but they are readily cleared from the peritoneal cavity and end up in the systemic circulation after passing through lymph nodes and ducts [1,32,53] As for the types of vectorizations, there are two types to consider: passive vectorization, which involves targeting through passive diffusion with the help of the enhanced permeability and retention (EPR) effect, and active vectorization, which involves modifying the surface with specific ligands that are overexpressed at the target site (such as monoclonal antibodies, peptides, *etc.*). The EPR effect occurs in solid tumors due to imperfect angiogenesis [54], meaning it is not relevant in the intraperitoneal administration of NPs, as it involves systemic circulation and intravenous administration of the DDS. Therefore, active vectorization is a more useful tool for functionalizing NPs for intraperitoneal administration.

According to their structure and chemical composition, they can be grouped into inorganic, polymeric, micelles, and liposomes.

3.2.1.1. Inorganic nanoparticles. Inorganic NPs can be synthesized from different chemical compositions, such as silica, gold, and iron oxides [55]. Moreover, this type of device presents many characteristics for their application in drug delivery, the most outstanding being the

capacity to get their surface easily functionalized or generate heat against different stimuli. For example, gold NPs (AuNPs) count with a layer of free electrons on their surface, allowing heat production when irradiated near-infrared. Following the same concept as in HIPEC, the heat-generating ability of AuNPs can be exploited to increase the antitumor activity of chemotherapeutic agents, such as in 5-FU-conjugated AuNPs [56]. In addition, other chemical properties of inorganic NPs can be further used in drug delivery, like pH-dependent conjugations, which allow a double release kinetic: a more effective release when the medium is acidified (pH close to 5) and a slower release when the pH turns neutral [57].

Furthermore, complex particulate devices have been designed for IPEC applications, combining different inorganic NPs with other NPs formulations. In this case, niosomes (polymeric amphipathic liposomes) loaded with DOX and magnetic NPs (MNPs) were developed by Behnam et al., achieving a loading efficiency of 60–65% for both cargos [58]. The presence of MNPs allowed a temperature rise that mimics the temperatures reached in HIPEC. In fact, magnetization constitutes one of the most widely used approaches to inorganic NPs for cancer treatment. Despite hyperthermia, this targeting method permits the localization of the NPs at the tumor site by applying a magnetic field [59]. Another example of such complex devices is the one proposed by Thirunavukkarasu et al., producing polymeric NPs composed of PLGA loaded with DOX and MNPs [60].

3.2.1.2. Polymeric nanoparticles. In general terms, polymeric NPs comprise all those particles whose composition is constituted by one or more polymers. These devices can effectively encapsulate chemotherapeutic drugs through different and variable encapsulation strategies. Drugs can be either attached to the polymeric network, encapsulated within the polymeric network, or even joined to the surface of the NPs [61]. Sabatelle et al. developed polymeric NPs composed of glycerol, CO_2, succinic acid and PTX building blocks, in which 58% of the loaded PTX was conjugated to the polymer. The remaining 25% was encapsulated inside the NPs [62]. This allowed the achievement of a high loading concentration and a controlled release of PTX. Furthermore, using different polymeric structures makes particles dependent on stimuli such as pH or heat [63,64]. Colson and collaborators designed expandable NPs in acidic environments exhibiting stimulus-dependent release, obtaining significant PTX release at 24 h for particles incubated at pH 4, contrary to the ones subjected to physiological pH (7.4) [65].

Another advantage of polymeric NPs is their ability to enhance and establish better retention in the peritoneal cavity due to their increased size (compared with drugs) decreasing capillarity, and delaying their passage into the bloodstream [66,67]. This fact has been reported in multiple publications, such as in Hyldbakk and colleagues' work, where they designed poly(alkyl cyanoacrylate) (PACA) NPs that reduced the mean elimination time of cabazitaxel up to 10-fold [68]. However, if NPs exceed specific dimensions, their retention is limited due to different factors, such as their recognition and elimination by the immune system or even their inability to access tissues. Thus, Lu et al. observed that particles with a size of 4 μm allowed better diffusion and retention throughout the peritoneal cavity compared to particles of 30 μm [69].

As well as in hydrogels, different NPs designed for their usage in IPEC count with cellular targeting strategies to enhance their antitumor effect [70,71]. Kim et al. synthesized a cathepsin B-specific DOX prodrug assembled with Pluronic® F58 [72]. This formulation produced a higher affinity of the drug for cells overexpressing this protein and, thus, a higher affinity, such as for cancer cells. Werner et al. demonstrated increased internalization of folate-labeled NPs into cancer cells with overexpression of the folate receptor, a common feature of several cancers [73].

Another essential characteristic to consider in the production of NPs for IPEC is the degradation rate of the material since if it is too fast, it can accelerate the release of the drug. Numerous enzymes usually increase this degradation when the polymers are of natural origin (biopolymers). This is mainly observed in compounds such as HA or collagen. There are different strategies to increase the half-life of these NPs [74]; among them, PEGylation [75,76] stands out. PEGylation is based on anchoring PEG molecules on the particle's surface to avoid aggregation, opsonization, and consequent phagocytosis, thus increasing the bioavailability of the drug until it reaches the target cell. Another strategy that can be followed to reduce the degradation rate is modulating the concentration of the polymers. For example, Yamashita et al. showed that the degradation rate increased with decreasing gelatin concentration [77].

Finally, one of the most critical points of NPs, in general, that must be kept in mind when using them as DDS is the release time that can be achieved depending on the formulation and chemical structure. Although most designs allow a relatively short release time, different studies have developed devices with which the release time can be extended for more than a week. Cymbaluk-Płoska et al. achieved a release profile for 20 days [66]. Besides release time, studying and discussing which drug concentration must be loaded to reach the maximum therapeutic effect with the most negligible cytotoxicity to healthy tissue is crucial. In this case, polymeric NPs make it possible to reduce the toxicity and solubility of the drugs administered so that higher doses can be administered [78,79].

3.2.2. Liposomes and micelles

Lipid-based nanocarriers are gaining attention in drug delivery due to their biocompatibility and biodegradability. Liposomes, a type of lipid-based system, are composed of amphipathic phospholipids and can be classified into four types based on their structure: unilamellar vesicles (ULVs), oligolamellar vesicles, multilamellar vesicles and multivesicular liposomes (MVLs). Moreover, based on the particle size, ULVs can be divided into small, large, and giant [80]. Yamamoto and colleagues used monoclonal antibody-conjugated small ULVs as carriers for DTX [81]. In another study, the combination of phospholipids, cholesterol, and triolein was used to develop MVLs depots in which DOX was efficiently encapsulated [82].

Anionic liposomes, which are formed by lipids with a negative charge, have been found to exhibit a solid binding affinity for certain drugs [83]. Chang and colleagues selected and used this property and described that cardiolipin liposomes showed the strongest binding affinity for mitoxantrone, a well-known chemotherapeutic agent [84]. Additionally, liposomes can be designed to respond to the tumor microenvironment, triggering drug release only at acidic pH. In this way, Leite et al. achieved specific release in an acidic medium using pH-sensitive liposomes as CDDP carriers, allowing them to localize the DDS closer to the tumor site and increasing the drug retention in the IPC [85].

Other lipidic formulations have also been considered for developing DDS for IPEC. While lipid NPs have been studied widely, solid lipid microparticles have been used as drug carrier systems due to their sustained release properties and high loading efficiency [86]. For its part, micelles composed of amphiphilic block copolymers constitute promising vehicles for the loading and delivery of hydrophobic drugs such as DTX. The aqueous environment of liposomes limits their loading with chemotherapeutic agents, restricting it to hydrophilic molecules. Zhang and colleagues developed mPEG-PDLLA as a micellar carrier with high encapsulation (99.24 ± 0.62%) efficiency and slower drug release due to the physical entrapment [87].

3.3. Hybrid DDS

Since "there is strength in numbers," hybrid DDS emerge as potential devices combining the main advantages of simple DDS such as hydrogels or NPs, achieving new characteristics and traits favoring their application in sustained loco-regional IPEC. Thus, hybrid DDS are based on two or more DDS, overcoming their principal limitations per separate. As

previously commented, one example of this limitation is the initial burst release of drug-loaded hydrogels. A double formulation combining NPs embedded in hydrogels allows a slower drug release, avoiding the direct liberation of the chemotherapeutic *via* simple diffusion or even retaining the NPs in the IPC, eviting their rapid clearance, which is, in turn, another potential drawback of this system. In fact, this is the most studied hybrid DDS system in IPEC for PC. Different authors have contributed to the development of such devices, which combine particulate nanodevices such as NPs [88–94], nanocomplexes [95], nanocolloids [96], or even micelles [97–99], incorporated in injectable hydrogels. Moreover, combining different DDS strategies favors managing and resolving other technical difficulties in their synthesis, such as loading a hydrophobic drug (*i.e.*, PTX) into a hydrophilic depot (*i.e.*, a hydrogel). An example of this approach was used by Qian et al., who generated red blood cells-based NPs loaded with PTX combined with a PEG-modified bovine serum albumin injectable hydrogel [93]. Thanks to this formulation, PTX could be encapsulated in the hydrogel. In contrast, a free-drug condition could not be conceived since PTX cannot disperse homogeneously in the PEG-modified bovine serum albumin hydrogel.

Most hybrid DDS are based on the same combination of copolymers but in different formulations. [89,92,99–101] In this case, the device's synthesis is initiated with the same chemicals, but their differential processing allows the obtention of both particulate and hydrogel formulations. Yamaguchi et al. designed an alginate-based CCDP-loaded nanogel in an alginate-based hydrogel. [100] In this case, the device consisted of two different gel formulations encapsulated together and composed of the same copolymer. For its part, Wang and collaborators developed gelatinase-responsive PEG-PCL NPs with salinomycin and DTX, which were introduced in a PEG-PCL-PEG nanohydrogel [89]. This device included, in turn, a targeting for gastric cancer cells since they produce high amounts of gelatinase, favoring the release of the chemotherapy in a more specific manner.

Among different hydrogels, thermosensitive hydrogels are the most preferred for developing hybrid DDS. The various consistencies of these hydrogels offer the feasibility of loading the NPs inside the hydrogel when liquid and their posterior localization and gelation at a specific spot when injected, avoiding their dispersion and clearance. Fan et al. synthesized a PLA-Pluronic® L64-PLA thermosensitive hydrogel with DTX and LL37 (an antimicrobial peptide)-loaded PLA-Pluronic® L35-PLA NPs. This formulation achieved a slower DTX release when compared to the NPs alone, with approximately a 55% cumulative release in 24 days, compared with 75% in the same period [88]. Xu and collaborators characterized a PTX-loaded PCL-PEG-PCL gel, loaded with PTX-incorporated particles, achieving a sol-gel transition at 37 °C [92]. For its part, Jhan et al. described an injectable thermosensitive hydrogel based on PF127 and HA-DOX nanocomplexes [95]. Although most of these depots are designed to solidify at body temperature, Zhang and colleagues developed tetrandrine and PTX-loaded PEG-b-PCL NPs encapsulated into a physically cross-linked gelatin hydrogel with a phase-shift from solid to liquid as the temperature increases, contrary to the sol-gel transition of the other hybrid systems [94]. This property allowed the continuous release of the encapsulated NPs as long as the gel liquified (starting at 35 °C). However, other strategies have been explored and bet on a non-thermosensitive device since covalently cross-linked hydrogels are less susceptible to dilution once injected intraperitoneally. Teja Surikutchi et al. generated a chemically cross-linked PEG-based hydrogel containing DTX-loaded HA nanocapsules, resulting in good *in vitro* release results, where the increasing percentage of PEG attenuated the release of the nanocapsules, achieving a 45% of release after five days [90].

Although most hybrid DDS consist of nanodevices embedded in hydrogels, other approaches have been considered for treating PC. For example, Long et al. patched DOX-loaded NPs on the surface of orange-derived extracellular vesicles [102]. Vakili and collaborators developed cellulose nanocrystals with CDDP grafted with poly(acrylic acid) (PAA) to form a so-called hard-core bottle-brush polymer [103]. The PAA grafting enhanced the mucoadhesive and mechanical properties of the nanocrystals so that the final materials withstood the washing effect of biological fluids on the mucosal membrane where they were applied.

Despite the remaining limitations of these kinds of DDS, hybrid depots count with several benefits and characteristics that turn them into suitable controlled and sustained drug delivery devices for the treatment of PC and the application of IPEC. Combining different simple DDS allows a vast range of biomaterial and formulation possibilities that grant researchers the choice between the most desirable properties for each specific application, turning them into tunable therapeutic strategies with excellent prospects and advantages on currently available treatments.

4. Translating DDS to *in vitro* and *in vivo* models of PC

DDS can be either simple or highly complex, utilizing the unique properties of biomaterials to achieve optimal drug loading, encapsulation efficacy, drug release rate, and other chemical and pharmacokinetic considerations. As discussed earlier, various formulations are explored and studied to create the perfect DDS for IPEC, focusing on sustained release, high loading efficiency, scalability, and even specific cell targeting or stimuli-dependent response to improve precision in managing PC. Moreover, their safety and efficacy must be explored in relevant *in vitro* and *in vivo* preclinical models to help with their clinical translation. In this evaluation, assessing the materials' biocompatibility, the depot's efficacy and cytotoxicity, and their implementation in cancer and PC animal models as a bridge between preclinical and clinical evidence is crucial. Achieving this needs a multidisciplinary approach, with a joint effort in different fields involving biology, material science, chemistry, engineering, medicine, and tissue engineering. Moreover, it is crucial to visualize the final objective of DDS during their design and testing to bridge the gap between laboratory research and clinical practice. Thus, PC is commonly associated with ovarian, gastric, and colorectal cancers. However, most specific DDS formulations are not tailored to treat a particular cancer type. Instead, a general formulation is used to load generic chemotherapeutics for IPEC in PC. Table 2–6 show *in vitro* and *in vivo* studies analyzed using DDS for PC, organized by targeted cancer types (ovarian, colorectal, gastric, mesothelioma, non-specific).

4.1. Biocompatibility and cytotoxicity of DDS: Are they safe and effective enough?

Using biopolymers in DDS synthesis and design, such as HA, ensures their biocompatibility and null cytotoxicity when applied to cells and animal models. However, if these polymers are modified to achieve desired properties like a higher crosslink ability or an enhanced union to the drug, they must be further tested in cells to ensure that the cytotoxic effects that they exhibit are only due to the presence of therapeutic drugs. This case is also given in synthetic polymers. In this way, biocompatibility and biosafety assays must be performed *in vitro* before concluding the effectiveness of the depot loaded with the therapeutic drugs. In general terms, all DDS are tested with no cargo or blank depots to assess their biocompatibility. The results indicate that the devices alone are non-toxic in cancer cell lines, thus making them good clinical administration candidates.

A joint event is usually noted when DDS are tested *in vitro* on different cancer cell lines. There is an apparent reduction in half maximal inhibitory concentration (IC_{50}) of formulated drugs compared to free drug administration. So, the chemotherapeutics in different DDS, especially hybrid, achieve a more significant cytotoxic effect on cancer cells than if they are administrated freely in solution [92–94,97,99,102]. Various authors have reported and described this effect as a crucial advantage of DDS in treating PC because a lower drug concentration can be administered in the depot. Drug encapsulation favors cell uptake, thus achieving a higher effect with the same dosage. Moreover, the

Table 2
In vitro and *in vivo* evaluation of DDS designed for ovarian cancer.

Ovarian Cancer								
DDS			*In vitro* model		*In vivo* model			*Ref.*
Type	Biomaterial	Loaded drug	Cell lines	Main Results [a]	Animal strain	Injected cells	Main Results [b]	
Hydrogel	Pluronic® F127, lecithin and organic solvent	DTX and CDDP	SKOV-3	↑ Cytotoxicity	BALB/c Nude mice	SKOV-3	↓ Systemic drug concentration ↓ Tumor progression	[37]
	PLGA-b-PEG-b-PLGA	Epothilone B, 17-AAG and rapamycin	n.d.	n.d.	Athymic Nude mice	ES-2-Luc	↓ Tumor progression ↑ Overall survival ↓ Ascites fluid volume	[35]
	Chitosan and phospholipids	DTX	n.d.	n.d.	SCID mice and C57BL/6 mice	SKOV-3 or ID8	↑ Peritoneal cavity drug concentration ↓ Systemic drug concentration ↓ Ascites fluid volume	[104]
	HA	PNC	SKOV-3	↑ Uptake	Athymic Nude mice	SKOV-3	↓ Tumor progression ↑ Overall survival	[30]
	PLCA with hydrazone-type spacer arms	DOX	n.d.	n.d.	BALB/c Nude mice	SKOV-3-Luc	↑ Peritoneal cavity drug concentration ↓ Systemic drug concentration ↓ Tumor progression ↓ Nr., size and weight of tumor nodules ↑ Overall survival	[105]
	Electrospun polydioxanone	PTX	ID8-VEGF	↓ Cytotoxicity	C57BL/6 mice	ID8-VEGF	↓ Tumor progression	[106]
	PLGA	Talazoparib	mFT3666	Biocompatible	NCr Nude nu/nu	mFT3666	↓ Side effects ↑ Overall survival	[46]
	PLGA	CDDP	SKOV-3 and A2780	Biocompatible	BALB/c Nude mice	SKOV-3	↓ Tumor growth ↓ Side effects	[43]
Implant	Poloxamer P407	PTX and rapamycin	n.d.	n.d.	Athymic NCr-nu/nu mice	ES-2-Luc	↑ Residence time in the peritoneal cavity ↓ Peritoneal adhesions ↑ Overall survival	[42]
	Chitosan and phosphatidylcholine	PTX	n.d.	n.d.	CD-1 Nude mice	SKOV-3	Biocompatible ↑ Tumor tissue drug concentration ↓ Tumor growth	[50]
	mPEG-PDLLA	DTX	SKOV-3	↑ Uptake	BALB/c Nude mice	SKOV-3	↓ Systemic drug concentration ↑ Overall survival	[87]
	Lipids	PTX	SKOV-3	↑ Cytotoxicity	Wistar rats	n.d.	↑ Residence time in the peritoneal cavity ↓ Systemic drug concentration	[86]
	Pluronic® F68	DOX	SKOV-3, HeyA8, MC38 and CT26	↑ Uptake = Cytotoxicity	BALB/c Nude mice	HeyA8	↑ Tumor tissue drug concentration ↑ Residence time in the peritoneal cavity ↓ Tumor progression ↑ Overall survival	[72]
Particles	Glucosa-mine/L-lactide and poly-lactide/PEG copolymers	CDDP	SKOV-3	Cytotoxicity: ↓ 24 h; ↑ 72 h.	Athymic nude-Fox1nu mice	SKOV-3-Luc	↑ Drug bioavailability ↑ Residence time in the peritoneal cavity	[75]
	Poly(D,L-lactide-*co*-glycolide)	PTX	n.d.	n.d.	BALB/c Nu/Nu mice	SKOV-3	↓ Tumor progression ↑ Residence time in the peritoneal cavity	[69]
	PLGA and PEG	PTX	BR5FVB1-Akt, SKOV-3 and Calu6	= Cytotoxicity	FVB mice	BR5FVB1-Akt	↑ Peritoneal cavity drug concentration ↓ Systemic drug concentration ↑ Overall survival	[76]
	PLGA, PEG and folate	PTX	SKOV-3, OVCAR-3 and SW626	↑ Uptake SKOV-3 *vs* SW626	Nu/nu mice	SKOV-3	↑ Overall survival	[73]
	PLGA	CDDP	n.d.	n.d.	Wistar rats	n.d.	↑ Toxicity ↑ Overall survival	[78]

(*continued on next page*)

Table 2 (*continued*)

Ovarian Cancer								
DDS			*In vitro* model		*In vivo* model			*Ref.*
Type	Biomaterial	Loaded drug	Cell lines	Main Results [a]	Animal strain	Injected cells	Main Results [b]	
Hybrid	Poly(ethylene terephthalate-ethylene dilinoleate)	Carboplatin	SKOV-3	↑ Cytotoxicity	BALB/c Nude mice	n.d.	↑ Peritoneal cavity drug concentration Biocompatible	[66]
	Lipids	Olaparib	4306 and 4412	= Cytotoxicity	NOD/SCID mice	404	= Overall survival	[107]
	Genipin and gelatin	PTX	SKOV-3 and OVCAR-3	Cytotoxicity: ↓ 72 h; = 168 h and 336 h	BALB/c Nude mice	SKOV-3-Luc	= Overall survival	[108]
	Gelatin and PLGA	PTX	n.d.	n.d.	BALB/c Nude mice	Hs766T	↑ Residence time in the peritoneal cavity ↓ Systemic drug concentration	[67]
	Acrylate derivates	PTX	OVCAR-3	Biocompatible ↑ Cytotoxicity	Nude mice	OVCAR-3 or OVCAR-3-Luc	↑ Overall survival ↑ Tumor tissue drug concentration ↓ Tumor progression	[63]
	Alginate	CDDP	ID8-KRAS	↓ Cytotoxicity	C57BL/6	ID8-KRAS	↑ Overall survival	[100]
	HA-ADH and HA-CHO	CDDP	SKOV-3	Cytotoxicity: ↓ short term; = at 3 days	BALB/c wild-type mice	SKOV-3 or SKOV-3-Luc	= Tumor growth	[101]
	Orange-derived extracellular vesicles and arginylglycylaspartic acid	DOX	SKOV-3	↑ Uptake ↑ Cytotoxicity	BALB/c Nude mice	SKOV-3-Luc	↑ Tumor tissue drug concentration ↓ Tumor growth	[102]

The table summarizes the characteristics and main results derived from the testing, both *in vitro* and *in vivo*, of DDS designed for ovarian cancer treatment. n.d., non-determined.

[a] Table shows significant results obtained and described in each scientific work referred to the DDS formulation compared to the free-drug solution. For example, if the formulation exhibits a higher cytotoxic effect *in vitro* than the free-drug solution under the same conditions, it is noted as ↑ *Cytotoxicity*.

[b] Following the same concept as *a)*, the table shows the main results observed *in vivo* for each reference, according to the DDS and the loaded drug. Significant noted results can refer either to the comparison with the free-drug solution (*e.g.*, higher residence in the peritoneal cavity) or simply to the observed effects of the DDS devices (*e.g.*, tumor progression).

increasing solubility of hydrophobic drugs also leads to an enhanced cytotoxic effect. Yang and collaborators reported that a hybrid mixed micelle gel system encapsulating DTX had a more significant cytotoxic effect on MCF7 breast cancer and SKOV-3 ovarian cancer cell lines, lowering the IC_{50} compared to free drug administration [97,99]. In addition, Yun et al. described the enhanced therapeutic effect of 5-FU-loaded PCL-PEG-PCL micelles and CDDP entrapped in a CS hydrogel on the CT26 colon cancer cell line [97].

Nonetheless, this phenomenon is not always seen when testing DDS on cancer cell lines. In fact, an excessive slow release of drugs can be a drawback in cytotoxic terms, thus decreasing the therapeutic effect of chemotherapy, at least at the initial stages. Therefore, different authors have reported that encapsulated drugs exhibited reduced cytotoxicity on cancer cells compared to free chemotherapeutics at equal concentrations [40,62,65,100,103,106]. This evidence is consistent with the definition of DDS since, to produce a sustained and controlled release, the bioavailability of the drug at the initial stages is significantly lower than that of free drug formulations. In any way, several studies report how the cytotoxicity of the depot increases over time, matching the values of free drugs [84,89,101,108] or even surpassing them [36,52,75] when the released drug is accumulated and permits significant exposure to cells. Finding a suitable drug concentration to load into a DDS and achieving the desired amount of release at the desired timing is hard work and implies the fine-tuning of the biomaterial and the evaluation of each depot *in vitro* with specific cancer cell lines and other models, such as spheroids or organoids. In this way, assessing the designed DDS and evaluating their effects before moving to animals is a critical step that should be remembered, regardless of the physical and chemical characterization of the depot.

4.2. Testing DDS in vivo: can animal models unveil IPEC success?

Animal models can bring basic research closer to clinical reality. As previously described by Wintjens et al. [114], experiments using *in vivo* models are crucial in developing new therapeutic approaches such as intraperitoneal DDS. Animal models offer valuable data to evaluate and study the hypothesized effects of the designed devices in a realistic environment to treat PC. Thus, parameters such as drug biodistribution, antitumor efficacy, systemic side effects, or even more feasible biocompatibility testing cannot be examined *in vitro*.

One of the main exploited advantages of DDS is their ability to release the loaded drug in a loco-regional way, thus eviting high systemic concentrations and favoring their action and effectiveness. This characteristic is fundamental in IPEC, where habitual approaches imply a rapid clearance of the administered treatment and low IPC concentrations. Several depots have released and maintained high chemotherapy concentrations intraperitoneally, directly localizing and enhancing the antitumor effect on tumor nodules [45,102,104,105,107,113]. Zahedi et al. developed a chitosan and phospholipids-based hydrogel for DTX delivery in ovarian cancer IPEC. Using SCID and C57BL/6 mice, they achieved high drug concentrations in tumor masses and ascites fluid, with a DTX concentration of several folds more significant in the IPC than plasma [104]. Furthermore, this high concentration of chemotherapeutic agents is often combined with an increased residence time in IPC, exhibiting greater and more prolonged effects, regardless of multiple clinical interventions [42,67–69,72,74,84,86,93,97]. Abuzar and colleagues loaded phospholipids, cholesterol, and triolein liposomes with OXA to treat colorectal cancer PC [82]. Implementing these devices in male Sprague-Dawley rats improved bioavailability, and the continuous erosion of the MVLs yielded a sustained OXA release, significantly increasing peritoneal absorption.

Related to the commented advantages, localizing the therapeutic device at the tumor site reduces, in turn, systemic concentration and generic distribution of administered drugs. Animal models allow the evaluation and analysis of drug biodistribution, thus knowing if the depot releases chemotherapy in a spatial and controlled way, serving as an alternative to systemic administration. Different studies have corroborated that intraperitoneal administration of DDS effectively reduces systemic drug concentration compared to free drug formulations

Table 3
In vitro and *in vivo* evaluation of DDS designed for colorectal cancer.

Colorectal Cancer								
DDS			*In vitro* model		*In vivo* model			*Ref.*
Type	Biomaterial	Loaded drug	Cell lines	Main Results[a]	Animal strain	Injected cells	Main Results[b]	
Hydrogel	UPy and PEG	MPC	CC531	↑ Uptake ↑ Cytotoxicity	n.d.	n.d.	n.d.	[31]
	PEG-PLC-PEG	5-FU	n.d.	n.d.	BALB/c mice	CT26	↓ Nr. and size tumor nodules ↓ Side effects ↑ Overall survival	[34]
	PEG-b-PELG	CA4P and CDDP	C26 and MCF-7	Biocompatible ↓ Cytotoxicity	BALB/c mice	C26	↓ Tumor growth	[33]
	Poloxamers P407 and P188, alginate and chitosan	5-FU	n.d.	n.d.	BALB/c JRJ mice	CT26.WT	↓ Tumor growth	[38]
	UPy and PEG	MMC	n.d.	n.d.	WAG/Rij rats	CC531-Luc	Biocompatible ↓ Tumor progression ↑ Overall survival	[109]
	PNIPAM, maleic acid, 4-penten-1-ol and crosslinker agents	DOX	HCT116	Biocompatible ↓ Cytotoxicity	n.d.	n.d.	n.d.	[40]
Implant	PLGA	5-FU	n.d.	n.d.	Sprague-Dawley rats and nude mice	DLD-1-Luc	↑ Peritoneal cavity drug concentration ↓ Systemic drug concentration ↓ Side effects	[45]
	PLA	5-FU and OXA	HCT-8	Cytotoxicity: ↓ 3-36 h; ↑ long term	BALB/c mice	CT26	↓ Tumor growth ↑ Overall survival	[52]
Particles	Gold	Methotrexate	HCT-116	↑ Cytotoxicity	n.d.	n.d.	n.d.	[57]
	Iron	OXA	CCD-18, T-84, HT-29, SW480, HCT-15, RAW 264.7 and MC-38	↑ Cytotoxicity	n.d.	n.d.	n.d.	[55]
	Pectin-chitosan PEC and thiolated pectin-based composites	5-FU	HT29 and HEK293	↑ Cytotoxicity	n.d.	n.d.	n.d.	[70]
	Iron and PLGA	DOX	NIH-3 T3	↑ Cytotoxicity (with hyperthermy) ↓ Cytotoxicity (without hyperthermy)	BALB/c mice	CT26	↓ Tumor growth	[60]
	Phospholipids, cholesterol, and triolein	OXA	n.d.	n.d.	Sprague-Dawley rats	n.d.	↑ Residence time in the peritoneal cavity ↑ Tumor tissue drug concentration	[82]
	Gold and citrate	5-FU	CT26	Biocompatible	BALB/c mice	CT26	↓ Systemic drug concentration ↓ Side effects	[56]
	PLA-PEO-PPO-PEO-PLA	DTX	n.d.	n.d.	BALB/c mice	CT26	↓ Tumor progression ↓ Nr. and size tumor nodules ↑ Overall survival	[110]
Hybrid	PECT and HA	5-FU, CDDP and PTX	CT26	Biocompatible ↑ Cytotoxicity	BALB/c Nude mice	CT26	↓ Tumor growth and progression ↓ Ascites fluid volume	[91]
	PLA-Pluronic-L35-PLA, PLA-Pluronic and L64-PLA	DTX and LL37	n.d.	n.d.	BALB/c Nude mice	HCT116	↓ Nr. and size tumor nodules ↑ Overall survival	[88]
	PCL-PEG-PCL and CS	5-FU	CT26	Biocompatible	BALB/c mice	CT26	↓ Tumor progression ↓ Nr., size and weight of tumor nodules ↑ Overall survival	[97]
	PCL-PEG-PCL	PTX	CT26	Biocompatible ↑ Cytotoxicity	BALB/c mice	CT26	↑ Residence time in the peritoneal cavity = Tumor growth	[92]
	Cellulose and PAA	CDDP	HCT116	↓ Cytotoxicity	n.d.	n.d.	n.d.	[103]

The table summarizes the characteristics and main results derived from the testing, both *in vitro* and *in vivo*, of DDS designed for colorectal cancer treatment. n.d., non-determined.

[a] Table shows significant results obtained and described in each scientific work referred to the DDS formulation compared to the free-drug solution. For example, if the formulation exhibits a higher cytotoxic effect *in vitro* than the free-drug solution under the same conditions, it is noted as ↑ *Cytotoxicity*.

[b] Following the same concept as *a)*, the table shows the main results observed *in vivo* for each reference, according to the DDS and the loaded drug. Significant noted results can refer either to the comparison with the free-drug solution (*e.g.*, higher residence in the peritoneal cavity) or simply to the observed effects of the DDS devices (*e.g.*, tumor progression).

Table 4
In vitro and *in vivo* evaluation of DDS designed for gastric cancer.

Gastric Cancer								
DDS			*In vitro* model		*In vivo* model			*Ref.*
Type	Biomaterial	Loaded drug	Cell lines	Main Results[a]	Animal strain	Injected cells	Main Results[b]	
Hydrogel	Poly(organophosphazenes) polymers[c]	PTX	n.d.	n.d.	BALB/c Nude mice	HSC44-Luc	↓ Side effects	[111]
	PDLLA-PEG-PDLLA	5-FU and CDDP	MKN45-Luc	Biocompatible Cytotoxicity: ↓ short term; ↑ at 48 h	BALB/c Nude mice	MKN45-Luc	↓ Relapse ↓ Tumor progression ↓ Tumor growth ↓ Ascites fluid volume ↓ Side effects ↑ Overall survival	[36]
Particles	Bacterial cellulose nanofibers	DOX	n.d.	n.d.	BALB/c mice	NCI-N87-Luc	↓ Tumor growth ↓ Side effects	[112]
	HA	CDDP	MKN45P	Biocompatible	BALB/c Nude mice	MKN45P	↓ Weight tumor nodules	[29]
	PEG and hydrophobic polyaspartate	PTX	MKN45P	= Cytotoxicity	BALB/c nude mice	MKN45P	↑ Tumor tissue drug concentration ↓ Tumor growth	[113]
	Monoclonal antibody-liposome	DOX and Trastuzumab	n.d.	n.d.	BALB/c nu/ nu mice	NCI-N-87	↑ Tumor tissue drug concentration ↓ Tumor growth	[81]
	Red blood cells, PEG and bovine serum albumin	PTX	MKN-45	Biocompatible ↑ Cytotoxicity	BALB/c nude mice	MKN-45	↑ Resident time in the peritoneal cavity ↓ Tumor growth	[93]
Hybrid	PEG-b-PCL and gelatin	PTX and Tetrandrine	BGC-823 and SGC-7901	↑ Cytotoxicity	BALB/c athymic Nude mice	BGC-823	↓ Tumor growth	[94]
	PEG-PCL and PEG-PCL-PEG	DTX and Salinomycin	MGC803	Cytotoxicity: ↓ short term; = at 48 h	BALB/c nude mice	MGC803-Luc	↓ Tumor growth ↓ Side effects	[89]

The table summarizes the characteristics and main results derived from the testing, both *in vitro* and *in vivo*, of DDS designed for gastric cancer treatment. n.d., non-determined.

[a] Table shows significant results obtained and described in each scientific work referred to the DDS formulation compared to the free-drug solution. For example, if the formulation exhibits a higher cytotoxic effect *in vitro* than the free-drug solution under the same conditions, it is noted as ↑ *Cytotoxicity*.

[b] Following the same concept as *a)*, the table shows the main results observed *in vivo* for each reference, according to the DDS and the loaded drug. Significant noted results can refer either to the comparison with the free-drug solution (*e.g.*, higher residence in the peritoneal cavity) or simply to the observed effects of the DDS devices (*e.g.*, tumor progression).

[c] Synthesis and characterization of the depot are described in previous works.

Table 5
In vitro and *in vivo* evaluation of DDS designed for mesothelioma.

Mesothelioma								
DDS			*In vitro* model		*In vivo* model			*Ref.*
Type	Biomaterial	Loaded drug	Cell lines	Main Results[a]	Animal strain	Injected cells	Main Results[b]	
Particles	Glycerol, CO_2 and succinic acid	PTX	MSTO-211H, H28, H226 and H2452	Biocompatible ↓ Cytotoxicity	Athymic Nude mice	MSTO-211H	↑ Tumor tissue drug concentration ↓ Systemic drug concentration ↑ Overall survival	[62]
	Acrylate and 2,4,6-trimethoxybenzaldehyd	PTX	MSTO-211H	↓ Cytotoxicity	Athymic Nude mice	MSTO-211H-Luc	↓ Relapse ↓ Tumor growth ↑ Overall survival	[65]

The table summarizes the characteristics and main results derived from the *in vitro* and *in vivo* testing of DDS designed for mesothelioma treatment.

[a] Table shows significant results obtained and described in each scientific work referred to the DDS formulation compared to the free-drug solution. For example, if the formulation exhibits a higher cytotoxic effect *in vitro* than the free-drug solution under the same conditions, it is noted as ↑*Cytotoxicity*.

[b] Following the same concept as *a)*, the table shows the main results observed *in vivo* for each reference, according to the DDS and the loaded drug. Significant noted results can refer either to the comparison with the free-drug solution (*e.g.*, higher residence in the peritoneal cavity) or simply to the observed effects of the DDS devices (*e.g.*, tumor progression).

[37,45,56,66,67,76,86,87,104,105]. Moreover, their local administration or implantation results in a decreased drug level in surrounding healthy organs and tissues, focusing the main cytotoxicity on the malignancy and avoiding chemotherapy-derived undesired side effects [34,36,45,46,56,61,84,85,115]. Thus, minimizing chemotherapy's adverse effects is crucial for PC patients already struggling with a highly aggressive disease. Wang et al. evidenced this reduction of side effects in an animal model of gastric cancer (MGC803-Luc intraperitoneally injected BALB/c nude female mice) [89]. The administration of a hybrid depot loaded with salinomycin and DTX evited the shortening and distortion of small intestinal villi compared to free salinomycin-DTX groups, which exhibited chronic injuries after treatment. Similar

Table 6
In vitro and *in vivo* evaluation of DDS designed for non-specific peritoneal malignancies.

Non-specific								
DDS			*In vitro* model		*In vivo* model			*Ref.*
Type	Biomaterial	Loaded drug	Cell lines	Main Results[a]	Animal strain	Injected cells	Main Results[b]	
Hydrogel	Chitosan and citral	5-FU	n.d.	n.d.	Swiss mice	n.d.	= Side effects	[28]
	PNIPAM, HA and chitosan	DOX	CT-26	Biocompatible	BALB/c mice	CT-26	↓ Tumor growth ↑ Overall survival	[41]
	Anionic lipids and PEG	Mitoxantrone	L1210	Biocompatible Cytotoxicity: ↓12 h; = 48 h	BDF1 mice	L1210	↑ Residence time in the peritoneal cavity ↓ Side effects ↑ Overall survival	[84]
	DOPE, CHEMS and DSPE-PEG2000	CDDP	n.d.	n.d.	Swiss mice	n.d.	↓ Side effects	[85]
Particles	PACA	Cabazitaxel	B76	Biocompatible = Cytotoxicity	Sprague Dawley rats and Athymic foxn 1nu mice	B76-GFP/ Luc	↑ Tumor tissue drug concentration ↑ Residence time in the peritoneal cavity ↑ Overall survival	[68]
	POEGMA and PDPA	PTX	MKN-45P, CT26 and SKOV3	↑ Cytotoxicity ↑ Uptake	Athymic Nude mice	MKN-45P-luc or CT26	↑ Tumor tissue drug concentration ↓ Nr. tumor nodules = Tumor growth	[64]
	Gelatin	CDDP	n.d.	n.d.	BALB/c Nude mice	C26	↓ Side effects ↑ Overall survival	[61]
	Gelatin	CDDP	MKN45-Luc	↓ Cytotoxicity	MKN45-Luc	Balb/c mice	↑ Residence time in the peritoneal cavity ↓ Tumor growth ↓ Side effects ↑ Overall survival	[77]
	Lithocholic acid and disulfide-linked polythyleneimine	PTX	CT-26	Biocompatible ↑ Cytotoxicity	CT-26 or HTC-116	Balb/c mice	↑ Tumor tissue drug concentration ↑ Residence time in the peritoneal cavity	[74]
	Magnetite and non-ionic surfactant	DOX	A549 PC-12	Biocompatible ↑ Cytotoxicity Biocompatible = Cytotoxicity	n.d.	n.d.	n.d.	[58]
	Pluronic® PF127 and HA	DOX	C26 and HT29	Biocompatible ↑ Cytotoxicity	BALB/c mice	C26	↑ Tumor tissue drug concentration ↓ Tumor growth	[95]
Hybrid	Pluronic® PF127 and Tween 80	DTX	MCF7 and SKOV-3	↑ Cytotoxicity	BALB/c Nude mice	SKOV-3	↑ Tumor tissue drug concentration ↓ Tumor growth	[99]
	Chitosan and inorganic phosphate	CPT	SKOV-3	n.d.	BALB/c mice	n.d.	Biodegradable	[96]
	PNIPAM, cellulose and Pluronic® F127	DOX and Niclosamide	HCT116 and OVCAR-3	= Cytotoxicity	Wistar rats	n.d.	Biocompatible	[98]

The table summarizes the characteristics and main results derived from the *in vitro* and *in vivo* testing of DDS designed for general peritoneal cancer treatment. n.d., non-determined.

[a] Table shows significant results obtained and described in each scientific work referred to the DDS formulation compared to the free-drug solution. For example, if the formulation exhibits a higher cytotoxic effect *in vitro* than the free-drug solution under the same conditions, it is noted as ↑*Cytotoxicity*.

[b] Following the same concept as *a)*, the table shows the main results observed *in vivo* for each reference, according to the DDS and the loaded drug. Significant noted results can refer either to the comparison with the free-drug solution (*e.g.*, higher residence in the peritoneal cavity) or simply to the observed effects of the DDS devices (*e.g.*, tumor progression).

results were obtained by Yu and collaborators, who found that HSC44-Luc xenografts treated with a PTX-loaded hydrogel did not show therapy-derived side effects when compared to the PTX solution group, which had dilated edematous changes in the intestine [111].

All these advantages of DDS are added to an enhanced antitumor effect compared to systemic or intraperitoneal administration of the chemotherapeutic drugs, which is translated in a reduction of tumor nodules, an inhibition of tumor progression, an increased cytotoxic effect *in vivo*, a marked rise in overall survival of treated animals [35,73,78,109,110], a reduction of ascites volume [36,91,104] and even a reduction and inhibition of relapse [36,65]. In this way, animal models have been and still are crucial to assess new DDS for IPEC, providing insight into a clinical response before translation to patients and bridging, in turn, the gap between bench and bedside.

5. Translation of DDS into patients: is there a gap between bench and bedside?

Discovery and development of DDS are complex and arduous processes that demand substantial time and investment to gain approval for a novel DDS. Drug development involves years of research, development, and rigorous testing before a DDS can progress to clinical trials. The high costs associated with this process further highlight the need for careful consideration and efficient decision-making throughout the DDS discovery and development journey.

Preclinical studies play a vital role in assessing the safety and efficacy of potential DDS. Researchers must select animal models closely resembling the clinical condition when conducting preclinical studies. Species, strain, age, sex, and health should be carefully considered. Validating these models is essential to ensure their reliability and

relevance to the targeted disease. In many cases, a combination of animal models is more suitable than a single model, as it provides a more comprehensive understanding of the DDS's effects [116]. When referring to PC, it's important to consider the differences in how the disease manifests in human patients and animal models when discussing the gap between research and clinical implementation. PC is the result of molecular interaction between tumor cells and host elements, involving various stages such as primary tumor detachment, transcoelomic spread, attachment, invasion, and angiogenesis. These stages collectively make up the "peritoneal metastatic cascade". Factors such as interstitial fluid pressure and iatrogenic dissemination during surgery (including accidental tumor rupture or cutting of lymphatics and blood vessels) can worsen the spontaneous shedding of tumor cells from the primary tumor [117,118]. Virtually all animal models used to test DDS for IPEC are generated through intraperitoneal administration of cancer cells, bypassing some of the stages discussed above. Addressing such a complex pathological condition with simplified animal models may have a significant impact on the accuracy of the results. The human peritoneal environment is highly dynamic and challenging to replicate in animals like rodents accurately [119]. This dynamism is important to consider when evaluating the effectiveness of DDS, as it is crucial to determine the pharmacokinetics of the administered devices. Advancing in the development of animal models, including advanced strategies such as patient-derived xenografts is a critical step to bridge the gap between bench and bedside.

Furthermore, despite their potential, preclinical studies often yield inconclusive data due to various factors. Experimental design issues, lack of model validation, inadequate reporting, and subjective interventions can all contribute to the limited translational relevance of preclinical research. To enhance the translatability of preclinical findings, it is essential to use validated animal models and reliable biomarkers. These elements can provide valuable information on *in vivo* situations and mechanisms after interventions, increasing the likelihood of successful translation into clinical settings.

As it has been reviewed, there are numerous studies where DDS are highlighted, designed, and studied as promising alternatives to systemic chemotherapy. However, translating these findings to the clinics seems to be hindered. Looking at the patent panorama in DDS for IPEC can provide significant information to understand the gap between bench and bedside, allowing a better comprehension of the commercial situation. Table 7 contains the selected patent entries obtained in The Lens search. This included 28 simple patent families, 3 already expired (typically after 20 years from the filing date), 3 inactive (patents that are no longer active and which cannot be enforced or monetized anymore), 1 discontinued (indicating either the patent holder's decision not to maintain the patent, leading to abandonment due to unpaid fees, or the discontinuation of a covered product or process.), 12 pending (when the patent has not been granted yet and application is in either filing, examination, pre-grant stage) and 9 active (valid and enforceable patents, which have not expired and can be utilized, licensed, or enforced by the patent holder).

After analyzing both active and pending patents, we have identified the same pattern as for the literature search discussed in earlier sections. Particles are the most patented DDS, whereas hydrogels [120,121], implants [122,123], and hybrid [124–126] DDS are less common. Different types of particulate DDS, such as polymeric NPs [127–130], liposomes [131], and micelles [132], have been patented for intraperitoneal use to treat PC. In some cases, the controlled and sustained release of different drugs is achieved and documented [133,134]. For instance, Zeineldin patented a DDS that releases the chemotherapeutic agent directly at the tumor site within the peritoneal cavity, triggered by reactive oxygen species generated in this environment [135]. In other applications, the description refers to drugs encapsulated into particles to enhance solubility and protect them from degradation but not to achieve a sustained and prolonged drug release. CritiTech INC has several patents in which a particulate crystalline formulation of taxanes is used [136–139]. This type of formulation allows for slower drug delivery and higher bioavailability due to better solubility of the active ingredient. In the present revision, these types of formulations have not been considered as DDS because they are not stand-alone devices loaded with an active ingredient, in which the amount of active compound could be changed, or even the drug used could be modified. In this case, the active ingredient has been included within a crystalline lattice by chemical crystallization techniques. Therefore, such inclusions have been considered as pharmaceutical formulations rather than an encapsulation method for controlled release.

Obtaining a granted patent is crucial to securing intellectual property rights, attracting collaborators and investors, and ensuring exclusivity for the patent through the development pipeline during the transition from preclinical research to clinical trials.

While preclinical studies may demonstrate impressive efficacy, the benefits of drug carriers can diminish when applied to human tumors, raising questions about their performance in clinical trials [148]. The IPC represents a challenge when considering its pharmacokinetics and pharmacodynamics. For this reason, the clinical application of DDS intraperitoneally may significantly alter the results observed in preclinical models. Significant pharmacokinetic and pharmacodynamic variables in IPEC must be considered in the rationale design of DDS for IPEC, such as the drug's molecular weight, drug dose, hepatic metabolism, renal clearance, open or closed abdominal lavage, intra-abdominal pressure, tumor nodule size, *etc.* [149] Like the low success rate for drugs reaching clinical trials, with approximately nine out of ten drug candidates failing in phase I, II, and III clinical trials, the same can be applied to DDS for IPEC. Only three clinical trials implementing DDS for IPEC in PC have been found in our case. All of them are related to novel formulations for the intraperitoneal administration of PTX. On the one hand, the first trial (NCT00005046) aimed to assess the safety and pharmacokinetics of an intraperitoneal administration of Paclimer® microspheres (polilactofate/PTX 10% *w*/w) in patients with ovarian cancer. This Phase I study highlighted that intraperitoneal administration of PTX microspheres was well tolerated up to 1200 mg Paclimer®/m^2 without further evidence of dose-limiting toxicities [150]. In any case, the study was discontinued due to the Paclimer® manufacturer's decision (Guilford Pharmaceuticals, Inc) before achieving significant findings such as the maximum tolerated dose of the formulation. Still, the reasons for this decision were not made public. On the other hand, Chan and collaborators are carrying out another Phase I study (NCT05159050) that aims to determine the pharmacokinetics and antitumor effects of PTX-loaded tumor penetrating microparticles in PC patients who are not eligible for standard-of-care therapeutic interventions. This trial is currently still recruiting patients and is estimated to finish in November 2024. The company CritiTech INC also conducted a clinical trial (NCT00666991) in which crystalline NPs of PTX (NanoTax) were administered intraperitoneally as a chemotherapeutic. The study aimed to determine the tolerated doses of this new chemotherapeutic formulation, as well as the pharmacokinetics and preliminary efficacy of the drug. However, more studies in this field are still lacking, hindering the translation of preclinical knowledge to the clinics. To address this issue, preclinical stages should adopt stringent criteria to reduce failure rates. In any case, clinical trials face challenges, including differences in attitudes, goals, training, protocols, and sample population characteristics. These variations can contribute to heterogeneity in trial results and further complicate the translation of research findings into clinical practice.

Translational research serves as a critical bridge between basic science and clinical research. Its primary objective is to ensure that innovations progress to clinical trials with a higher probability of success regarding safety and efficacy. To achieve this, a comprehensive understanding of the *in vivo/in vitro* models used, their limitations, and their applicability to specific diseases is crucial. Strategies such as personalized medicine, theranostics, and tumor environment modifications can help bridge the gap between research and clinical practice, ultimately

Table 7
The Lens patent entries of DDS designed for IPEC.

Patent Search							
Lens ID	Earliest Priority Date	Title	Applicants	Document Type	Legal Status	DDS[a]	*Ref.*
071–396–176-371-008	16/05/1994	Sustained release hydrophobic bioactive PLGA microspheres	US Army	Granted Patent	Expired	P	[140]
192–999–120-040-648	11/01/1999	Methods for treating ovarian cancer, poly (phosphoester) compositions, and biodegradable articles for same	Guilford Pharm INC	Granted Patent	Expired	n.s.	[141]
128–664–534-201-40×	09/04/1999	Methods and compositions for enhancing delivery of therapeutic agents to tissues	Au Jessie L; Wientjes MG	Granted Patent	Expired	P	[142]
100–675–756-005-831	16/11/2000	Compositions for treatment of malignant effusions, and methods of making and using the same	Dang Wenbin	Patent Application	Discontinued	P	[143]
159–302–178-184-282	03/04/2003	Tumor-targeting drug-loaded particles	Au Jessie L; Wientjes M G	Patent Application	Pending	P	[127]
146–042–753-542-18×	02/04/2004	Tumor targeting drug-loaded particles	Au Jessie L; Wientjes M G	Patent Application	Inactive	P	[144]
036–551–518-195-947	21/10/2009	Block copolymer for intraperitoneal administration containing anti-cancer agent, micelle preparation, and cancer therapeutic agent comprising the micelle preparation as active ingredient	Nippon Kayaku KK; Akatsu Yuichi; Mashiba Hiroko	Patent Application	Pending	P	[131]
011–116–307-766-486	15/12/2009	Polymer-based compositions and methods for treatment of peritoneal disorders	Univ Johns Hopkins; Fu Jie; Hanes Justin; Yang Ming	Patent Application	Pending	P	[145]
186–774–751-402-487	26/11/2010	Pharmaceutical composition	Chirwa Nthato; Pillay Viness, Choonara Yahya Essop; Kumar Pradeep, Du Toit Lisa Claire; Univ Witwatersrand JHB	Granted Patent	Inactive	P, HYB	[124]
189–344–730-832-874	27/06/2011	Controlled release system	Cristal Delivery B.V.	Patent Application	Active	P	[146]
004–300–958-612-508	19/07/2011	Intraperitoneally-administered nanocarriers that release their therapeutic load based on the inflammatory environment of cancers	Zeineldin Reema; STC UNM	Granted Patent	Active	P	[135]
115–306–741-271-265	09/05/2012	Medicament, method, and drug delivery device for treatment of ovarian cancer	Massachusetts Institute of Technology; Gen Hospital Corp	Patent Application	Pending	I	[123]
056–162–863-255-548	22/07/2013	Thermogel formulation for combination drug delivery	Wisconsin Alumni Research Foundation	Granted Patent	Active	HG	[120]
079–524–037-627-346	25/09/2013	Compositions and methods for treating ovarian cancer including preventing the recurrence thereof	Markland Francis S JR; Swenson Stephen D; Minea Radu O	Patent Application	Pending	HG	[121]
145–106–773-334-234	09/05/2014	Hyperbranched polyglycerol-coated particles and methods of making and using thereof	Univ Yale	Granted Patent	Active	P	[128]
106–442–136-258-281	01/06/2014	Use of paclitaxel particles	CritiTech INC	Patent Application	Pending	P	[136]
024–753–828-731-127	13/02/2015	Compositions and methods of tumor treatment utilizing nanoparticles	Op Nano Co Ltd.; Trendmed Co Ltd	Patent Application	Inactive	P	[147]
190–505–888-605-647	04/06/2015	Taxane particles and their use	CritiTech INC	Granted Patent	Active	P	[137]
163–965–871-224-539	04/04/2016	Methods for solid tumor treatment	CritiTech INC	Granted Patent	Active	P	[138]
170–043–364-608-32×	03/05/2017	Intraoperative topically-applied non-implantable rapid release patch	Privo Techn INC	Granted Patent	Active	HYB	[125]
152–463–115-205-210	03/10/2017	Local delivery of antineoplastic particles in combination with systemic delivery of immunotherapeutic agents for the treatment of cancer	CritiTech INC	Granted Patent	Active	P	[139]
167–958–205-928-817	23/02/2018	Formulations containing mucin-affecting proteases	Mucpharm Pty Ltd	Patent Application	Pending	P	[134]
003–072–200-605-736	27/03/2018	PACA and cabaxitaxel for anti-cancer treatment	Sintef Tto AS, Univ Oslo HF	Granted patent	Active	P	[129]
183–315–067-215-27×	02/11/2018	Liposomal enhanced intra-peritoneal chemotherapy	TesoRx Pharma LLC	Patent Application	Pending	P	[132]
136–803–276-086-812	11/02/2019	Gold nanoparticle-containing hydrogel films and chemotherapeutic methods for using same	Methodist Hospital	Patent Application	Pending	HYB	[126]
146–894–172-231-877	26/02/2019	Delayed delivery of anticancer drugs	CapnoMed GmbH	Patent Application	Pending	P	[133]
123–068–228-769-520	27/03/2019	Drug delivery system for treatment of cancer	Sintef Tto AS	Patent Application	Pending	P	[130]
190–653–894-912-146	14/10/2020	Implantable depots for localized, sustained, controlled release of therapeutic agents to treat cancer and related conditions	Foundry Therapeutics INC	Patent Application	Pending	I	[122]

The table summarizes patent entries in The Lens database for DDS designed to administer IPEC. Patents are listed in order of Earliest Priority Date, from earliest to latest.

[a] The DDS formulation is listed in the patent description. HG, hydrogel; HYB, hybrid; I, implant; P, particle; n.s., non-specified.

improving patient outcomes.

To enhance research-to-clinical translation, it is essential to establish consistent protocols, promote transparent reporting of results (including negative findings), and create platforms for publicly available clinical trial results. These measures can contribute to more efficient and informed decision-making in clinical practice by facilitating collaboration and knowledge sharing. However, translational research faces numerous challenges, including limited resources, high dropout rates, lengthy DDS development, a lack of proper targets, and the heterogeneity of sample populations. Addressing these challenges is crucial for advancing translational research and successfully navigating the "Valley of Death" between bench and bedside research.

Several suggestions have been proposed to improve translational research [151]. Refining hypotheses before experiments, integrating extensive data from *in vitro/vivo* and clinical studies, and screening compound libraries are among the approaches that can enhance the efficiency and effectiveness of translational research. Additionally, repurposing existing DDS, fostering collaborative efforts between research organizations and pharmaceutical industries, and harnessing the potential of machine learning and artificial intelligence can also contribute to overcoming the challenges in translational research.

Bioresources, such as human tissues, play a crucial role in biomarker discovery and precision medicine. These resources offer valuable insights into disease pathophysiology and aid in identifying targets and biomarkers for specific disease subtypes. Human tissues can sometimes replace animal models for preclinical studies, providing more accurate and relevant data. Furthermore, human tissues allow researchers to gain insight into safety profiles and off-target effects, ultimately contributing to developing safer and more effective DDS.

6. Conclusion

Nowadays, DDS development and implementation are pivotal in advancing the therapeutic landscape for peritoneal malignancies such as PC in advanced cancers like gastric, colorectal, or ovarian. Throughout this literature revision, we have delved into the complexity and diversity of different drug delivery devices, remarking on their unique attributes and characteristics and addressing the challenges associated with their design and application. To conceive the most suitable DDS for each application, many variables must be considered. Preclinical studies are essential to ensure that the materials used in DDS are biocompatible and do not cause toxicity. Therefore, the body's response to the delivery system and potential side effects must be thoroughly studied and addressed. Moreover, it is crucial to maintain drugs' stability within the delivery system. Drug instability or degradation before reaching the target site can reduce therapeutic efficacy and excessive release or burst effects due to diffusion events.

The peritoneal cavity is a complex microenvironment, and delivering drugs effectively to the tumor site while avoiding healthy tissues is challenging. Factors such as ascites and variable blood supply are added to this complexity. In general terms, addressing these challenges through continuous research, technological advancements, and collaborative efforts is essential for developing and implementing novel DDS in intraperitoneal cancer therapy. Interdisciplinary collaboration between scientific disciplines, including medicine, pharmacology, materials science, and engineering, ensuring effective communication and cooperation between experts, constitutes a crucial element that cannot be overlooked.

Developing novel DDS for IPEC also faces other important restraining factors, such as regulatory challenges to meet all regulatory requirements for novel DDS that can be time-consuming and expensive since ensuring compliance with safety and efficacy standards is essential for market approval. While the knowledge gained from the approval and use of intravenous DDS can be beneficial, the specific application to the IPC introduces unique challenges that need to be addressed. Thus, successful implementation of novel DDS for IPEC will require a comprehensive understanding of how they affect specifically the peritoneal ecosystem (local tissue reaction, drug retention, distribution and penetration, drug metabolism and clearance, effect on the peritoneal microenvironment, systemic exposure and potential toxicity, *etc.*), and their clinical evidence base through randomized trials. Moreover, research and development of novel DDS require high development costs, which can be a significant barrier, particularly for academics and smaller pharmaceutical companies. All this has been translated into the limited clinical data for the long-term safety and efficacy of novel DDS for IPEC that hinders their clinical implementation. Addressing all these challenges through continuous research, technological advancements, and collaborative efforts between academics, clinics, and the private sector is essential for developing and implementing novel DDS in intraperitoneal cancer therapy.

CRediT authorship contribution statement

M. Teresa Perelló-Trias: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation. **Antonio Jose Serrano-Muñoz:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Ana Rodríguez-Fernándéz:** Writing – original draft, Methodology, Investigation. **Juan José Segura-Sampedro:** Writing – review & editing, Writing – original draft, Conceptualization. **Joana Maria Ramis:** Writing – review & editing, Supervision. **Marta Monjo:** Writing – review & editing, Writing – original draft, Validation, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

None

Data availability

No data was used for the research described in the article.

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References

[1] P. Roy, N. Mignet, M. Pocard, V. Boudy, Drug delivery systems to prevent peritoneal metastasis after surgery of digestives or ovarian carcinoma: a review, Int. J. Pharm. 592 (2021) 120041, https://doi.org/10.1016/j.ijpharm.2020.120041.

[2] D. Cortés-Guiral, M. Hübner, M. Alyami, A. Bhatt, W. Ceelen, O. Glehen, F. Lordick, R. Ramsay, O. Sgarbura, K. Van Der Speeten, K.K. Turaga, M. Chand, Primary and metastatic peritoneal surface malignancies, Nat. Rev. Dis. Primers 7 (2021) 91, https://doi.org/10.1038/s41572-021-00326-6.

[3] K. Ren, X. Xie, T. Min, T. Sun, H. Wang, Y. Zhang, C. Dang, H. Zhang, Development of the peritoneal metastasis: a review of Back-grounds, mechanisms, treatments and prospects, J. Clin. Med. 12 (2022), https://doi.org/10.3390/jcm12010103.

[4] J. Franko, Q. Shi, J.P. Meyers, T.S. Maughan, R.A. Adams, M.T. Seymour, L. Saltz, C.J.A. Punt, M. Koopman, C. Tournigand, N.C. Tebbutt, E. Diaz-Rubio, J. Souglakos, A. Falcone, B. Chibaudel, V. Heinemann, J. Moen, A. De Gramont, D.J. Sargent, A. Grothey, Analysis and research in cancers of the digestive system (ARCAD) group, prognosis of patients with peritoneal metastatic colorectal

cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the analysis and research in cancers of the digestive system (ARCAD) database, Lancet Oncol. 17 (2016) 1709–1719, https://doi.org/10.1016/S1470-2045(16)30500-9.
[5] W. Ceelen, H. Braet, G. Van Ramshorst, W. Willaert, W. Ceelen, Intraperitoneal chemotherapy for peritoneal metastases : an expert opinion, Expert Opin. Drug Deliv. 17 (2020) 511–522, https://doi.org/10.1080/17425247.2020.1736551.
[6] N. Bakrin, M. Deraco, O. Glehen, D.L. Morris, K. van der Speeten, Cytoreductive Surgery & Perioperative Chemotherapy for Peritoneal Surface Malignancy: Textbook and Video Atlas, Second Edition, Canada, 2017.
[7] M.F. Flessner, The transport barrier in intraperitoneal therapy, Am. J. Physiol. Ren. Physiol. 288 (2005) F433–F442, https://doi.org/10.1152/ajprenal.00313.2004.
[8] K. Van der Speeten, O.A. Stuart, P.H. Sugarbaker, Pharmacokinetics and pharmacodynamics of perioperative cancer chemotherapy in peritoneal surface malignancy, Cancer J. 15 (2009) 216–224, https://doi.org/10.1097/PPO.0b013e3181a58d95.
[9] M. Steuperaert, C. Debbaut, P. Segers, W. Ceelen, Modelling drug transport during intraperitoneal chemotherapy, Pleura Peritoneum 2 (2017) 73–83, https://doi.org/10.1515/pp-2017-0004.
[10] F. Coccolini, F. Gheza, M. Lotti, S. Virzì, D. Iusco, C. Ghermandi, R. Melotti, G. Baiocchi, S.M. Giulini, L. Ansaloni, F. Catena, Peritoneal carcinomatosis, World J. Gastroenterol. 19 (2013) 6979–6994, https://doi.org/10.3748/wjg.v19.i41.6979.
[11] M. Alyami, M. Hübner, F. Grass, N. Bakrin, L. Villeneuve, N. Laplace, G. Passot, O. Glehen, V. Kepenekian, Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications, Lancet Oncol. 20 (2019) e368–e377, https://doi.org/10.1016/S1470-2045(19)30318-3.
[12] H. Abdel Mageed, K. Van Der Speeten, P. Sugarbaker, The many faces of intraperitoneal chemotherapy, Surg. Oncol. 40 (2022) 101676, https://doi.org/10.1016/j.suronc.2021.101676.
[13] P.H. Sugarbaker, Management of peritoneal-surface malignancy: the surgeon's role, Langenbeck's Arch. Surg. 384 (1999) 576–587, https://doi.org/10.1007/s004230050246.
[14] R. Shegokar (Ed.), Exploring Drug Delivery to the Peritoneum, Springer International Publishing, Berlin, 2023, https://doi.org/10.1007/978-3-031-31694-4.
[15] R.L. Dedrick, C.E. Myers, P.M. Bungay, V.T. DeVita, Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer, Cancer Treat. Rep. 62 (1978) 1–11. http://www.ncbi.nlm.nih.gov/pubmed/626987.
[16] J.Y. Wang, M. Gross, R.R. Urban, S. Jorge, Intraperitoneal and Hyperthermic intraperitoneal chemotherapy for the treatment of ovarian Cancer, Curr. Treat. Options in Oncol. 25 (2024) 313–329, https://doi.org/10.1007/s11864-023-01171-3.
[17] A. Di Giorgio, E. Naticchioni, D. Biacchi, S. Sibio, F. Accarpio, M. Rocco, S. Tarquini, M. Di Seri, A. Ciardi, D. Montruccoli, P. Sammartino, Cytoreductive surgery (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of diffuse peritoneal carcinomatosis from ovarian cancer, Cancer 113 (2008) 315–325, https://doi.org/10.1002/cncr.23553.
[18] W.J. van Driel, S.N. Koole, K. Sikorska, J.H. Schagen van Leeuwen, H.W. R. Schreuder, R.H.M. Hermans, I.H.J.T. de Hingh, J. van der Velden, H.J. Arts, L. F.A.G. Massuger, A.G.J. Aalbers, V.J. Verwaal, J.M. Kieffer, K.K. Van de Vijver, H. van Tinteren, N.K. Aaronson, G.S. Sonke, Hyperthermic intraperitoneal chemotherapy in ovarian Cancer, N. Engl. J. Med. 378 (2018) 230–240, https://doi.org/10.1056/NEJMoa1708618.
[19] D.B. Sheshadri, M.R. Chakravarthy, Anaesthetic considerations in the perioperative Management of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy., Indian, J. Surg. Oncol. 7 (2016) 236–243, https://doi.org/10.1007/s13193-016-0508-2.
[20] M.H. Kim, Y.C. Yoo, S.J. Bai, K.-Y. Lee, N. Kim, K.Y. Lee, Physiologic and hemodynamic changes in patients undergoing open abdominal cytoreductive surgery with hyperthermic intraperitoneal chemotherapy, J. Int. Med. Res. 49 (2021), https://doi.org/10.1177/0300060520983263, 300060520983263.
[21] R.J. Hendrix, J.P. Kassira, L.A. Lambert, Elevated maximum Core body temperature during Hyperthermic intraperitoneal Chemoperfusion (HIPEC) is associated with increased postoperative complications, Ann. Surg. Oncol. 27 (2020) 232–239, https://doi.org/10.1245/s10434-019-07495-5.
[22] D. Fukumura, R.K. Jain, Tumor microvasculature and microenvironment: targets for anti-angiogenesis and normalization, Microvasc. Res. 74 (2007) 72–84, https://doi.org/10.1016/j.mvr.2007.05.003.
[23] R.K. Jain, Delivery of molecular and cellular medicine to solid tumors, Adv. Drug Deliv. Rev. 46 (2001) 149–168, https://doi.org/10.1016/s0169-409x(00)00131-9.
[24] G. Bajaj, Y. Yeo, Drug delivery systems for intraperitoneal therapy, Pharm. Res. 27 (2010) 735–738, https://doi.org/10.1007/s11095-009-0031-z.
[25] S. Adepu, S. Ramakrishna, Controlled drug delivery systems: current status and future directions, Molecules 26 (2021) 5905, https://doi.org/10.3390/molecules26195905.
[26] N. Desai, U. Hasan, J.K.R. Mani, M. Chauhan, S.M. Basu, J. Giri, Biomaterial-based platforms for modulating immune components against cancer and cancer stem cells, Acta Biomater. 161 (2023) 1–36, https://doi.org/10.1016/j.actbio.2023.03.004.
[27] L. De Smet, W. Ceelen, J.P. Remon, C. Vervaet, Optimization of drug delivery systems for intraperitoneal therapy to extend the residence time of the chemotherapeutic agent, ScientificWorldJournal 2013 (2013) 720858, https://doi.org/10.1155/2013/720858.
[28] D. Ailincai, L. Tartau Mititelu, L. Marin, Drug delivery systems based on biocompatible imino-chitosan hydrogels for local anticancer therapy, Drug Deliv. 25 (2018) 1080–1090, https://doi.org/10.1080/10717544.2018.1466937.
[29] S. Emoto, H. Yamaguchi, T. Kamei, H. Ishigami, T. Suhara, Y. Suzuki, T. Ito, J. Kitayama, T. Watanabe, Intraperitoneal administration of cisplatin via an in situ cross-linkable hyaluronic acid-based hydrogel for peritoneal dissemination of gastric cancer, Surg. Today 44 (2014) 919–926, https://doi.org/10.1007/s00595-013-0674-6.
[30] B. Sun, M.S. Taha, B. Ramsey, S. Torregrosa-Allen, B.D. Elzey, Y. Yeo, Intraperitoneal chemotherapy of ovarian cancer by hydrogel depot of paclitaxel nanocrystals, J. Control. Release 235 (2016) 91–98, https://doi.org/10.1016/j.jconrel.2016.05.056.
[31] M.H. Bakker, M. Grillaud, D.J. Wu, P.K.H. Fransen, I.H. de Hingh, P.Y. W. Dankers, Cholesterol modification of an anticancer drug for efficient incorporation into a supramolecular hydrogel system, Macromol. Rapid Commun. 39 (2018) e1800007, https://doi.org/10.1002/marc.201800007.
[32] A.G.W.E. Wintjens, P.-P.K.H. Fransen, K. Lenaerts, H. Liu, G.C. van Almen, S. van Steensel, M.J. Gijbels, I.H.J.T. de Hingh, P.Y.W. Dankers, N.D. Bouvy, Development of a supramolecular hydrogel for intraperitoneal injections, Macromol. Biosci. 24 (2024) e2300005, https://doi.org/10.1002/mabi.202300005.
[33] S. Yu, S. Wei, L. Liu, D. Qi, J. Wang, G. Chen, W. He, C. He, X. Chen, Z. Gu, Enhanced local cancer therapy using a CA4P and CDDP co-loaded polypeptide gel depot, Biomater. Sci. 7 (2019) 860–866, https://doi.org/10.1039/c8bm01442f.
[34] Y. Wang, C. Gong, L. Yang, Q. Wu, S. Shi, H. Shi, Z. Qian, Y. Wei, 5-FU-hydrogel inhibits colorectal peritoneal carcinomatosis and tumor growth in mice, BMC Cancer 10 (2010) 402, https://doi.org/10.1186/1471-2407-10-402.
[35] D.H. Shin, G.S. Kwon, Pre-clinical evaluation of a themosensitive gel containing epothilone B and mTOR/Hsp90 targeted agents in an ovarian tumor model, J. Control. Release 268 (2017) 176–183, https://doi.org/10.1016/j.jconrel.2017.10.022.
[36] W. Chen, K. Shi, J. Liu, P. Yang, R. Han, M. Pan, L. Yuan, C. Fang, Y. Yu, Z. Qian, Sustained co-delivery of 5-fluorouracil and cis-platinum via biodegradable thermo-sensitive hydrogel for intraoperative synergistic combination chemotherapy of gastric cancer, Bioact. Mater. 23 (2023) 1–15, https://doi.org/10.1016/j.bioactmat.2022.10.004.
[37] C.-E. Chang, C.-M. Hsieh, L.-C. Chen, C.-Y. Su, D.-Z. Liu, H.-J. Jhan, H.-O. Ho, M.-T. Sheu, Novel application of pluronic lecithin organogels (PLOs) for local delivery of synergistic combination of docetaxel and cisplatin to improve therapeutic efficacy against ovarian cancer, Drug Deliv. 25 (2018) 632–643, https://doi.org/10.1080/10717544.2018.1440444.
[38] C. Al Sabbagh, J. Seguin, E. Agapova, D. Kramerich, V. Boudy, N. Mignet, Thermosensitive hydrogels for local delivery of 5-fluorouracil as neoadjuvant or adjuvant therapy in colorectal cancer, Eur. J. Pharm. Biopharm. 157 (2020) 154–164, https://doi.org/10.1016/j.ejpb.2020.10.011.
[39] X. Xu, Y. Liu, W. Fu, M. Yao, Z. Ding, J. Xuan, D. Li, S. Wang, Y. Xia, M. Cao, Poly (N-isopropylacrylamide)-based Thermoresponsive composite hydrogels for biomedical applications, Polymers (Basel) 12 (2020) 1–22, https://doi.org/10.3390/polym12030580.
[40] G. Carreño, A. Pereira, F. Ávila-Salas, A. Marican, F. Andrade, M.M. Roca-Melendres, O. Valdés, S. Vijayakumar, S. Schwartz, I. Abasolo, D. Rafael, E. F. Durán-Lara, Development of "on-demand" thermo-responsive hydrogels for anti-cancer drugs sustained release: rational design, in silico prediction and in vitro validation in colon cancer models, Mater. Sci. Eng. C Mater. Biol. Appl. 131 (2021) 112483, https://doi.org/10.1016/j.msec.2021.112483.
[41] C.-H. Chen, C.-Y. Kuo, S.-H. Chen, S.-H. Mao, C.-Y. Chang, K. Shalumon, J.-P. Chen, Thermosensitive injectable hydrogel for simultaneous intraperitoneal delivery of doxorubicin and prevention of peritoneal adhesion, Int. J. Mol. Sci. 19 (2018) 1373, https://doi.org/10.3390/ijms19051373.
[42] H. Cho, U. Jammalamadaka, K. Tappa, C. Egbulefu, J. Prior, R. Tang, S. Achilefu, 3D printing of Poloxamer 407 Nanogel discs and their applications in adjuvant ovarian Cancer therapy, Mol. Pharm. 16 (2019) 552–560, https://doi.org/10.1021/acs.molpharmaceut.8b00836.
[43] Y. Wang, X. Qiao, X. Yang, M. Yuan, S. Xian, L. Zhang, D. Yang, S. Liu, F. Dai, Z. Tan, Y. Cheng, The role of a drug-loaded poly (lactic co-glycolic acid) (PLGA) copolymer stent in the treatment of ovarian cancer, Cancer Biol. Med. 17 (2020) 237–250, https://doi.org/10.20892/j.issn.2095-3941.2019.0169.
[44] D.J. Hines, D.L. Kaplan, Poly(lactic-co-glycolic) acid-controlled-release systems: experimental and modeling insights, Crit. Rev. Ther. Drug Carrier Syst. 30 (2013) 257–276, https://doi.org/10.1615/CritRevTherDrugCarrierSyst.2013006475.
[45] L. Li, C. Li, J. Zhou, Effective sustained release of 5-FU-loaded PLGA implant for improving therapeutic index of 5-FU in colon tumor, Int. J. Pharm. 550 (2018) 380–387, https://doi.org/10.1016/j.ijpharm.2018.07.045.
[46] S. Yang, A. Green, N. Brown, A. Robinson, M. Senat, B. Testino, D.M. Dinulescu, S. Sridhar, Sustained delivery of PARP inhibitor Talazoparib for the treatment of BRCA-deficient ovarian cancer, Front. Oncol. 13 (2023) 1175617, https://doi.org/10.3389/fonc.2023.1175617.
[47] S. Mei, X. Chen, K. Wang, Y. Chen, Tumor microenvironment in ovarian cancer peritoneal metastasis, Cancer Cell Int. 23 (2023) 11, https://doi.org/10.1186/s12935-023-02854-5.
[48] E. Boedtkjer, S.F. Pedersen, The acidic tumor microenvironment as a driver of Cancer, Annu. Rev. Physiol. 82 (2020) 103–126, https://doi.org/10.1146/annurev-physiol-021119-034627.

[49] N.E. Elsadek, A. Nagah, T.M. Ibrahim, H. Chopra, G.A. Ghonaim, S.E. Emam, S. Cavalu, M.S. Attia, Electrospun nanofibers revisited: an update on the emerging applications in nanomedicine, Materials 15 (2022) 1–30, https://doi.org/10.3390/ma15051934.
[50] V. Vassileva, J. Grant, R. De Souza, C. Allen, M. Piquette-Miller, Novel biocompatible intraperitoneal drug delivery system increases tolerability and therapeutic efficacy of paclitaxel in a human ovarian cancer xenograft model, Cancer Chemother. Pharmacol. 60 (2007) 907–914, https://doi.org/10.1007/s00280-007-0449-0.
[51] S.T. Yohe, V.L.M. Herrera, Y.L. Colson, M.W. Grinstaff, 3D superhydrophobic electrospun meshes as reinforcement materials for sustained local drug delivery against colorectal cancer cells, J. Control. Release 162 (2012) 92–101, https://doi.org/10.1016/j.jconrel.2012.05.047.
[52] J. Zhang, X. Wang, T. Liu, S. Liu, X. Jing, Antitumor activity of electrospun polylactide nanofibers loaded with 5-fluorouracil and oxaliplatin against colorectal cancer, Drug Deliv. 23 (2016) 794–800, https://doi.org/10.3109/10717544.2014.916768.
[53] S. Alavi, A. Haeri, I. Mahlooji, S. Dadashzadeh, Tuning the physicochemical characteristics of particle-based carriers for intraperitoneal local chemotherapy, Pharm. Res. 37 (2020) 119, https://doi.org/10.1007/s11095-020-02818-8.
[54] M. Ikeda-Imafuku, L.L.-W. Wang, D. Rodrigues, S. Shaha, Z. Zhao, S. Mitragotri, Strategies to improve the EPR effect: a mechanistic perspective and clinical translation, J. Control. Release 345 (2022) 512–536, https://doi.org/10.1016/j.jconrel.2022.03.043.
[55] Y. Jabalera, B. Garcia-Pinel, R. Ortiz, G. Iglesias, L. Cabeza, J. Prados, C. Jimenez-Lopez, C. Melguizo, Oxaliplatin-biomimetic magnetic nanoparticle assemblies for Colon Cancer-targeted chemotherapy: an in vitro study, Pharmaceutics 11 (2019) 4–6, https://doi.org/10.3390/pharmaceutics11080395.
[56] V. Mulens-Arias, A. Nicolás-Boluda, A. Pinto, A. Balfourier, F. Carn, A.K.A. Silva, M. Pocard, F. Gazeau, Tumor-selective immune-active mild hyperthermia associated with chemotherapy in Colon peritoneal metastasis by Photoactivation of fluorouracil-gold nanoparticle complexes, ACS Nano 15 (2021) 3330–3348, https://doi.org/10.1021/acsnano.0c10276.
[57] B. Álvarez-González, M. Rozalen, M. Fernández-Perales, M.A. Álvarez, M. Sánchez-Polo, Methotrexate gold Nanocarriers: loading and release study: its activity in Colon and Lung Cancer cells, Molecules 25 (2020), https://doi.org/10.3390/molecules25246049.
[58] B. Behnam, M. Rezazadehkermani, S. Ahmadzadeh, A. Mokhtarzadeh, S. N. Nematollahi-Mahani, A. Pardakhty, Microniosomes for concurrent doxorubicin and iron oxide nanoparticles loading; preparation, characterization and cytotoxicity studies, Artif. Cells Nanomed. Biotechnol. 46 (2018) 118–125, https://doi.org/10.1080/21691401.2017.1296850.
[59] G.A. Marcelo, J. Galhano, T.T. Robalo, M.M. Cruz, M.D. Marcos, R. Martínez-Máñez, M.P. Duarte, J.L. Capelo-Martínez, C. Lodeiro, E. Oliveira, Magneto-fluorescent mesoporous Nanocarriers for the dual-delivery of Ofloxacin and doxorubicin to tackle opportunistic bacterial infections in colorectal Cancer, Int. J. Mol. Sci. 23 (2022) 4–7, https://doi.org/10.3390/ijms232012287.
[60] G.K. Thirunavukkarasu, K. Cherukula, H. Lee, Y.Y. Jeong, I.-K. Park, J.Y. Lee, Magnetic field-inducible drug-eluting nanoparticles for image-guided thermo-chemotherapy, Biomaterials 180 (2018) 240–252, https://doi.org/10.1016/j.biomaterials.2018.07.028.
[61] S. Gunji, K. Obama, M. Matsui, Y. Tabata, Y. Sakai, A novel drug delivery system of intraperitoneal chemotherapy for peritoneal carcinomatosis using gelatin microspheres incorporating cisplatin, Surgery 154 (2013) 991–999, https://doi.org/10.1016/j.surg.2013.04.054.
[62] R.C. Sabatelle, R. Liu, Y.P. Hung, E. Bressler, E.J. Neal, A. Martin, I. Ekladious, M. W. Grinstaff, Y.L. Colson, Ultra-high drug loading improves nanoparticle efficacy against peritoneal mesothelioma, Biomaterials 285 (2022) 121534, https://doi.org/10.1016/j.biomaterials.2022.121534.
[63] D. Gilmore, M. Schulz, R. Liu, K.A.V. Zubris, R.F. Padera, P.J. Catalano, M. W. Grinstaff, Y.L. Colson, Cytoreductive surgery and intraoperative administration of paclitaxel-loaded expansile nanoparticles delay tumor recurrence in ovarian carcinoma, Ann. Surg. Oncol. 20 (2013) 1684–1693, https://doi.org/10.1245/s10434-012-2696-5.
[64] L. Simón-Gracia, H. Hunt, P.D. Scodeller, J. Gaitzsch, G.B. Braun, A.-M. A. Willmore, E. Ruoslahti, G. Battaglia, T. Teesalu, Paclitaxel-loaded Polymersomes for enhanced intraperitoneal chemotherapy, Mol. Cancer Ther. 15 (2016) 670–679, https://doi.org/10.1158/1535-7163.MCT-15-0713-T.
[65] Y.L. Colson, R. Liu, E.B. Southard, M.D. Schulz, J.E. Wade, A.P. Griset, K.A. V. Zubris, R.F. Padera, M.W. Grinstaff, The performance of expansile nanoparticles in a murine model of peritoneal carcinomatosis, Biomaterials 32 (2011) 832–840, https://doi.org/10.1016/j.biomaterials.2010.09.059.
[66] A. Cymbaluk-Płoska, P. Sobolewski, A. Chudecka-Głaz, E. Wiśniewska, J. Łapczuk, M. Frankowski, M. Droździk, M. El Fray, Double-emulsion Copolyester microcapsules for sustained intraperitoneal release of carboplatin, J. Funct. Biomater. 10 (2019), https://doi.org/10.3390/jfb10040055.
[67] M. Tsai, Z. Lu, J. Wang, T.-K. Yeh, M.G. Wientjes, J.L.S. Au, Effects of carrier on disposition and antitumor activity of intraperitoneal paclitaxel, Pharm. Res. 24 (2007) 1691–1701, https://doi.org/10.1007/s11095-007-9298-0.
[68] A. Hyldbakk, K.G. Fleten, S. Snipstad, A.K.O. Åslund, C.L. de Davies, K. Flatmark, Y. Mørch, Intraperitoneal administration of cabazitaxel-loaded nanoparticles in peritoneal metastasis models, Nanomedicine 48 (2023) 102656, https://doi.org/10.1016/j.nano.2023.102656.
[69] Z. Lu, M. Tsai, D. Lu, J. Wang, M.G. Wientjes, J.L.-S. Au, Tumor-penetrating microparticles for intraperitoneal therapy of ovarian cancer, J. Pharmacol. Exp. Ther. 327 (2008) 673–682, https://doi.org/10.1124/jpet.108.140095.
[70] T.E. Leonard, A.F. Liko, M. Gustiananda, A.B.N. Putra, A.B. Juanssilfero, P. Hartrianti, Thiolated pectin-chitosan composites: potential mucoadhesive drug delivery system with selective cytotoxicity towards colorectal cancer, Int. J. Biol. Macromol. 225 (2023) 1–12, https://doi.org/10.1016/j.ijbiomac.2022.12.012.
[71] C. Feng, J. Li, M. Kong, Y. Liu, X.J. Cheng, Y. Li, H.J. Park, X.G. Chen, Surface charge effect on mucoadhesion of chitosan based nanogels for local anti-colorectal cancer drug delivery, Colloids Surf. B: Biointerfaces 128 (2015) 439–447, https://doi.org/10.1016/j.colsurfb.2015.02.042.
[72] J. Kim, M.K. Shim, Y.-J. Cho, S. Jeon, Y. Moon, J. Choi, J. Kim, J. Lee, J.-W. Lee, K. Kim, The safe and effective intraperitoneal chemotherapy with cathepsin B-specific doxorubicin prodrug nanoparticles in ovarian cancer with peritoneal carcinomatosis, Biomaterials 279 (2021) 121189, https://doi.org/10.1016/j.biomaterials.2021.121189.
[73] M.E. Werner, S. Karve, R. Sukumar, N.D. Cummings, J.A. Copp, R.C. Chen, T. Zhang, A.Z. Wang, Folate-targeted nanoparticle delivery of chemo- and radiotherapeutics for the treatment of ovarian cancer peritoneal metastasis, Biomaterials 32 (2011) 8548–8554, https://doi.org/10.1016/j.biomaterials.2011.07.067.
[74] K. Cherukula, W.K. Bae, J.H. Lee, I.-K. Park, Programmed "triple-mode" anti-tumor therapy: improving peritoneal retention, tumor penetration and activatable drug release properties for effective inhibition of peritoneal carcinomatosis, Biomaterials 169 (2018) 45–60, https://doi.org/10.1016/j.biomaterials.2018.03.051.
[75] B. Bortot, M. Mongiat, E. Valencic, S. Dal Monego, D. Licastro, M. Crosera, G. Adami, E. Rampazzo, G. Ricci, F. Romano, G.M. Severini, S. Biffi, Nanotechnology-based cisplatin intracellular delivery to enhance chemo-sensitivity of ovarian Cancer, Int. J. Nanomedicine 15 (2020) 4793–4810, https://doi.org/10.2147/IJN.S247114.
[76] Z. Amoozgar, L. Wang, T. Brandstoetter, S.S. Wallis, E.M. Wilson, M.S. Goldberg, Dual-layer surface coating of PLGA-based nanoparticles provides slow-release drug delivery to achieve metronomic therapy in a paclitaxel-resistant murine ovarian cancer model, Biomacromolecules 15 (2014) 4187–4194, https://doi.org/10.1021/bm5011933.
[77] K. Yamashita, S. Tsunoda, S. Gunji, T. Murakami, T. Suzuki, Y. Tabata, Y. Sakai, Intraperitoneal chemotherapy for peritoneal metastases using sustained release formula of cisplatin-incorporated gelatin hydrogel granules, Surg. Today 49 (2019) 785–794, https://doi.org/10.1007/s00595-019-01792-y.
[78] S. Kumagai, T. Sugiyama, T. Nishida, K. Ushijima, M. Yakushiji, Improvement of intraperitoneal chemotherapy for rat ovarian cancer using cisplatin-containing microspheres, Jpn. J. Cancer Res. 87 (1996) 412–417, https://doi.org/10.1111/j.1349-7006.1996.tb00238.x.
[79] H.-J. Cho, J.-H. Park, D.-D. Kim, I.-S. Yoon, Poly(lactic-co-glycolic) acid/Solutol HS15-based nanoparticles for docetaxel delivery, J. Nanosci. Nanotechnol. 16 (2016) 1433–1436, https://doi.org/10.1166/jnn.2016.11918.
[80] S. Bhattacharya, D. Saindane, B.G. Prajapati, Liposomal drug delivery and its potential impact on Cancer research, Anti Cancer Agents Med. Chem. 22 (2022) 2671–2683, https://doi.org/10.2174/1871520622666220418141640.
[81] Y. Yamamoto, M. Yoshida, M. Sato, K. Sato, S. Kikuchi, H. Sugishita, J. Kuwabara, Y. Matsuno, Y. Kojima, M. Morimoto, A. Horiuchi, Y. Watanabe, Feasibility of tailored, selective and effective anticancer chemotherapy by direct injection of docetaxel-loaded immunoliposomes into Her2/neu positive gastric tumor xenografts, Int. J. Oncol. 38 (2011) 33–39. http://www.ncbi.nlm.nih.gov/pubmed/21109923.
[82] S.M. Abuzar, E.J. Park, Y. Seo, J. Lee, S.H. Baik, S. Hwang, Preparation and evaluation of intraperitoneal Long-acting Oxaliplatin-loaded multi-vesicular liposomal depot for colorectal Cancer treatment, Pharmaceutics 12 (2020) 1–17, https://doi.org/10.3390/pharmaceutics12080736.
[83] G.Y.W. Tseu, K.A. Kamaruzaman, A review of different types of liposomes and their advancements as a form of gene therapy treatment for breast Cancer, Molecules 28 (2023), https://doi.org/10.3390/molecules28031498.
[84] R.S. Chang, J. Kim, H.Y. Lee, S.-E. Han, J. Na, K. Kim, I.C. Kwon, Y.B. Kim, Y.-K. Oh, Reduced dose-limiting toxicity of intraperitoneal mitoxantrone chemotherapy using cardiolipin-based anionic liposomes, Nanomedicine 6 (2010) 769–776, https://doi.org/10.1016/j.nano.2010.05.003.
[85] E.A. Leite, S.C. dos Giuberti, A.J.A. Wainstein, A.P.D.L. Wainstein, L.G.V. Coelho, A.M.Q. Lana, P.R. Savassi-Rocha, M.C. De Oliveira, Acute toxicity of long-circulating and pH-sensitive liposomes containing cisplatin in mice after intraperitoneal administration, Life Sci. 84 (2009) 641–649, https://doi.org/10.1016/j.lfs.2009.02.002.
[86] S. Han, P. Dwivedi, F.A. Mangrio, M. Dwivedi, R. Khatik, D.E. Cohn, T. Si, R. X. Xu, Sustained release paclitaxel-loaded core-shell-structured solid lipid microparticles for intraperitoneal chemotherapy of ovarian cancer, Artif. Cells Nanomed. Biotechnol. 47 (2019) 957–967, https://doi.org/10.1080/21691401.2019.1576705.
[87] Y. Zhang, S. Wang, X. Duan, X. Xu, Y. Gao, J. Zhou, X. Xu, J. Li, mPEG-PDLLA micelles potentiate docetaxel for intraperitoneal chemotherapy in ovarian Cancer peritoneal metastasis, Front. Pharmacol. 13 (2022) 861938, https://doi.org/10.3389/fphar.2022.861938.
[88] R. Fan, A. Tong, X. Li, X. Gao, L. Mei, L. Zhou, X. Zhang, C. You, G. Guo, Enhanced antitumor effects by docetaxel/LL37-loaded thermosensitive hydrogel nanoparticles in peritoneal carcinomatosis of colorectal cancer, Int. J. Nanomedicine 10 (2015) 7291–7305, https://doi.org/10.2147/IJN.S89066.
[89] X. Wang, J. Gao, C. Li, C. Xu, X. Li, F. Meng, Q. Liu, Q. Wang, L. Yu, B. Liu, R. Li, In situ gelatinase-responsive and thermosensitive nanocomplex for local therapy of gastric cancer with peritoneal metastasis, Mater. Today Bio. 15 (2022) 100305, https://doi.org/10.1016/j.mtbio.2022.100305.

[90] B. Teja Surikutchi, R. Obenza-Otero, E. Russo, M. Zelzer, I. Golán Cancela, J. A. Costoya, J. Crecente Campo, M. José Alonso, M. Marlow, Development of a nanocapsule-loaded hydrogel for drug delivery for intraperitoneal administration, Int. J. Pharm. 622 (2022) 121828, https://doi.org/10.1016/j.ijpharm.2022.121828.
[91] J. Luo, Z. Wu, Y. Lu, K. Xiong, Q. Wen, L. Zhao, B. Wang, Y. Gui, S. Fu, Intraperitoneal administration of biocompatible hyaluronic acid hydrogel containing multi-chemotherapeutic agents for treatment of colorectal peritoneal carcinomatosis, Int. J. Biol. Macromol. 152 (2020) 718–726, https://doi.org/10.1016/j.ijbiomac.2020.02.326.
[92] S. Xu, H. Fan, L. Yin, J. Zhang, A. Dong, L. Deng, H. Tang, Thermosensitive hydrogel system assembled by PTX-loaded copolymer nanoparticles for sustained intraperitoneal chemotherapy of peritoneal carcinomatosis, Eur. J. Pharm. Biopharm. 104 (2016) 251–259, https://doi.org/10.1016/j.ejpb.2016.05.010.
[93] H. Qian, K. Qian, J. Cai, Y. Yang, L. Zhu, B. Liu, Therapy for gastric Cancer with peritoneal metastasis using injectable albumin hydrogel hybridized with paclitaxel-loaded red blood cell membrane nanoparticles, ACS Biomater Sci. Eng. 5 (2019) 1100–1112, https://doi.org/10.1021/acsbiomaterials.8b01557.
[94] H. Zhang, Y. Tian, Z. Zhu, H. Xu, X. Li, D. Zheng, W. Sun, Efficient antitumor effect of co-drug-loaded nanoparticles with gelatin hydrogel by local implantation, Sci. Rep. 6 (2016) 26546, https://doi.org/10.1038/srep26546.
[95] H. Jhan, J. Liu, Y.-C. Chen, D.-Z. Liu, M.-T. Sheu, H.-O. Ho, Novel injectable thermosensitive hydrogels for delivering hyaluronic acid-doxorubicin nanocomplexes to locally treat tumors, Nanomedicine (London) 10 (2015) 1263–1274, https://doi.org/10.2217/nnm.14.211.
[96] X. Li, X. Kong, J. Zhang, Y. Wang, Y. Wang, S. Shi, G. Guo, F. Luo, X. Zhao, Y. Wei, Z. Qian, A novel composite hydrogel based on chitosan and inorganic phosphate for local drug delivery of camptothecin nanocolloids, J. Pharm. Sci. 100 (2011) 232–241, https://doi.org/10.1002/jps.22256.
[97] Q. Yun, S.S. Wang, S. Xu, J.P. Yang, J. Fan, L.L. Yang, Y. Chen, S.Z. Fu, J.B. Wu, Use of 5-fluorouracil loaded micelles and cisplatin in thermosensitive chitosan hydrogel as an efficient therapy against colorectal peritoneal Carcinomatosis, Macromol. Biosci. 17 (2017) 1–12, https://doi.org/10.1002/mabi.201600262.
[98] F. Andrade, M.M. Roca-Melendres, M. Llaguno, D. Hide, I. Raurell, M. Martell, S. Vijayakumar, M. Oliva, S. Schwartz, E.F. Durán-Lara, D. Rafael, I. Abasolo, Smart and eco-friendly N-isopropylacrylamide and cellulose hydrogels as a safe dual-drug local cancer therapy approach, Carbohydr. Polym. 295 (2022) 119859, https://doi.org/10.1016/j.carbpol.2022.119859.
[99] Y. Yang, J. Wang, X. Zhang, W. Lu, Q. Zhang, A novel mixed micelle gel with thermo-sensitive property for the local delivery of docetaxel, J. Control. Release 135 (2009) 175–182, https://doi.org/10.1016/j.jconrel.2009.01.007.
[100] K. Yamaguchi, O. Hiraike, H. Iwaki, K. Matsumiya, N. Nakamura, K. Sone, S. Ohta, Y. Osuga, T. Ito, Intraperitoneal Administration of a Cisplatin-Loaded Nanogel through a hybrid system containing an Alginic acid-based Nanogel and an in situ cross-linkable hydrogel for peritoneal dissemination of ovarian Cancer, Mol. Pharm. 18 (2021) 4090–4098, https://doi.org/10.1021/acs.molpharmaceut.1c00514.
[101] E.J. Cho, B. Sun, K.-O. Doh, E.M. Wilson, S. Torregrosa-Allen, B.D. Elzey, Y. Yeo, Intraperitoneal delivery of platinum with in-situ crosslinkable hyaluronic acid gel for local therapy of ovarian cancer, Biomaterials 37 (2015) 312–319, https://doi.org/10.1016/j.biomaterials.2014.10.039.
[102] F. Long, Y. Pan, J. Li, S. Sha, X. Shi, H. Guo, C. Huang, Q. Xiao, C. Fan, X. Zhang, J.B. Fan, Y. Wang, Orange-derived extracellular vesicles nanodrugs for efficient treatment of ovarian cancer assisted by transcytosis effect, Acta Pharm. Sin. B 13 (2023) 5121–5134, https://doi.org/10.1016/j.apsb.2023.04.006.
[103] M.R. Vakili, W. Mohammed-Saeid, A. Aljasser, J. Hopwood-Raja, B. Ahvazi, Y. Hrynets, M. Betti, A. Lavasanifar, Development of mucoadhesive hydrogels based on polyacrylic acid grafted cellulose nanocrystals for local cisplatin delivery, Carbohydr. Polym. 255 (2021) 117332, https://doi.org/10.1016/j.carbpol.2020.117332.
[104] P. Zahedi, J. Stewart, R. De Souza, M. Piquette-Miller, C. Allen, An injectable depot system for sustained intraperitoneal chemotherapy of ovarian cancer results in favorable drug distribution at the whole body, peritoneal and intratumoral levels, J. Control. Release 158 (2012) 379–385, https://doi.org/10.1016/j.jconrel.2011.11.025.
[105] P.-E. Colombo, M. Boustta, S. Poujol, M. Jarlier, F. Bressolle, I. Teulon, M.-Z. Ladjemi, F. Pinguet, P. Rouanet, M. Vert, Intraperitoneal administration of novel doxorubicin loaded polymeric delivery systems against peritoneal carcinomatosis: experimental study in a murine model of ovarian cancer, Gynecol. Oncol. 122 (2011) 632–640, https://doi.org/10.1016/j.ygyno.2011.05.032.
[106] S. Padmakumar, N.N. Parayath, S.V. Nair, D. Menon, M.M. Amiji, Enhanced anti-tumor efficacy and safety with metronomic intraperitoneal chemotherapy for metastatic ovarian cancer using biodegradable nanotextile implants, J. Control. Release 305 (2019) 29–40, https://doi.org/10.1016/j.jconrel.2019.05.022.
[107] P. Baldwin, A.W. Ohman, S. Tangutoori, D.M. Dinulescu, S. Sridhar, Intraperitoneal delivery of NanoOlaparib for disseminated late-stage cancer treatment, Int. J. Nanomedicine 13 (2018) 8063–8074, https://doi.org/10.2147/IJN.S186881.
[108] K. De Clercq, F. Xie, O. De Wever, B. Descamps, A. Hoorens, A. Vermeulen, W. Ceelen, C. Vervaet, Preclinical evaluation of local prolonged release of paclitaxel from gelatin microspheres for the prevention of recurrence of peritoneal carcinomatosis in advanced ovarian cancer, Sci. Rep. 9 (2019) 14881, https://doi.org/10.1038/s41598-019-51419-y.
[109] A.G.W.E. Wintjens, H. Liu, P.-P.K.H. Fransen, K. Lenaerts, G.C. van Almen, M. J. Gijbels, M. Hadfoune, B.T.C. Boonen, N.G. Lieuwes, R. Biemans, L.J. Dubois, P. Y.W. Dankers, I.H.J.T. de Hingh, N.D. Bouvy, Treating colorectal peritoneal metastases with an injectable cytostatic loaded supramolecular hydrogel in a rodent animal model, Clin. Exp. Metastasis 40 (2023) 243–253, https://doi.org/10.1007/s10585-023-10210-0.
[110] R. Fan, X. Li, J. Deng, X. Gao, L. Zhou, Y. Zheng, A. Tong, X. Zhang, C. You, G. Guo, Dual drug loaded biodegradable Nanofibrous microsphere for improving anti-Colon Cancer activity, Sci. Rep. 6 (2016) 28373, https://doi.org/10.1038/srep28373.
[111] J. Yu, H. Lee, K. Hur, M.K. Kwak, T.S. Han, W.H. Kim, S.-C. Song, K. Yanagihara, H.-K. Yang, The antitumor effect of a thermosensitive polymeric hydrogel containing paclitaxel in a peritoneal carcinomatosis model, Investig. New Drugs 30 (2012) 1–7, https://doi.org/10.1007/s10637-010-9499-y.
[112] H. Ando, T. Mochizuki, A.S.A. Lila, S. Akagi, K. Tajima, K. Fujita, T. Shimizu, Y. Ishima, T. Matsushima, T. Kusano, T. Ishida, Doxorubicin Embedded into Nanofibrillated Bacterial Cellulose (NFBC) Produces a Promising Therapeutic Outcome for Peritoneally Metastatic Gastric Cancer in Mice Models via Intraperitoneal Direct Injection, Nanomaterials (Basel) 11 (2021), https://doi.org/10.3390/nano11071697.
[113] S. Emoto, H. Yamaguchi, J. Kishikawa, H. Yamashita, H. Ishigami, J. Kitayama, Antitumor effect and pharmacokinetics of intraperitoneal NK105, a nanomicellar paclitaxel formulation for peritoneal dissemination, Cancer Sci. 103 (2012) 1304–1310, https://doi.org/10.1111/j.1349-7006.2012.02274.x.
[114] A.G.W.E. Wintjens, G.A. Simkens, P.P.K.H. Fransen, N. Serafras, K. Lenaerts, G.H. L.M. Franssen, I.H.J.T. de Hingh, P.Y.W. Dankers, N.D. Bouvy, A. Peeters, Intraperitoneal drug delivery systems releasing cytostatic agents to target gastro-intestinal peritoneal metastases in laboratory animals: a systematic review, Clin. Exp. Metastasis 39 (2022) 541–579, https://doi.org/10.1007/s10585-022-10173-8.
[115] R. Ando-Matsuoka, H. Ando, A.S. Abu Lila, N. Maeda, T. Shimizu, Y. Ishima, T. Ishida, I.P.-injected cationic liposomes are retained and accumulate in peritoneally disseminated tumors, J. Control. Release 341 (2022) 524–532, https://doi.org/10.1016/j.jconrel.2021.12.004.
[116] V. Mahalmani, S. Sinha, A. Prakash, B. Medhi, Translational research: bridging the gap between preclinical and clinical research, Indian J. Pharm. 54 (2022) 393–396, https://doi.org/10.4103/ijp.ijp_860_22.
[117] L. Lemoine, P. Sugarbaker, K. Van der Speeten, Pathophysiology of colorectal peritoneal carcinomatosis: role of the peritoneum, World J. Gastroenterol. 22 (2016) 7692–7707, https://doi.org/10.3748/wjg.v22.i34.7692.
[118] P.H. Sugarbaker, Update on the prevention of local recurrence and peritoneal metastases in patients with colorectal cancer, World J. Gastroenterol. 20 (2014) 9286–9291, https://doi.org/10.3748/wjg.v20.i28.9286.
[119] Á. Bella, C.A. Di Trani, M. Fernández-Sendin, L. Arrizabalaga, A. Cirella, Á. Teijeira, J. Medina-Echeverz, I. Melero, P. Berraondo, F. Aranda, Mouse models of peritoneal carcinomatosis to develop clinical applications, Cancers (Basel) 13 (2021) 1–11, https://doi.org/10.3390/cancers13050963.
[120] G.S. Kwon, H. Cho, Thermogel Formulation for Combination Drug Delivery, US 10682415 B2, 2013.
[121] F.S.J. Markland, S.D. Swenson, R.O. Minea, Compositions and Methods for Treating Ovarian Cancer Including Preventing the Recurrence Thereof, WO 2015/048354 A1, 2013.
[122] K. Steven, K. Naga, I. Gifford, J. Su, N. Mokarram-Dorri, M. Deem, S. Boyd, K. Teu, W. Lee, D. Chung, E. Gifford, Implantable Depots for Localized, Sustained, Controlled Release of therapeutic Agents to Treat Cancer and Related Conditions, WO 2022/082196 A1, 2020.
[123] M.J. Cima, H. Ye, M. Del Carmen, M. Birrer, Medicament, Method, and Drug Delivery Device for Treatment of Ovarian Cancer, WO 2013/170069 A1, 2012.
[124] N. Chirwa, V. Pillay, Y.E. Choonara, P. Kumar, T.L.C. Du, Pharmaceutical Composition, US 9220773 B2, 2010.
[125] M.N. Golberg, B. Laporte, A. Manzi, A. Jahjaa, Intraoperative Topically-Applied Non-Implantable Rapid Release Patch, US 10478403 B1, 2017.
[126] A. Ziemys, A. Holder, Gold Nanoparticle-Containing Hydrogel Films and Chemotherapeutic Methods for Using Same, WO 2020/167868 A1, 2019.
[127] J.L.-S. Au, M.G. Wientjes, Tumor-Targeting Drug-Loaded Particles, WO 2004/089291 A2, 2003.
[128] Y. Deng, A. Ediriwickrema, W.M. Saltzman, Hyperbranched Polyglycerol-Coated Particles and Methods of Making and Using Thereof, US 10238581 B2, 2014.
[129] Y. Morch, E. Sulheim, K. Flatmark, K.G. Fleten, P. Stenstad, H. Johnsen, R. Schmid, PACA and Cabazitaxel for Anti-Cancer Treatment, US 11806330 B2, 2018.
[130] Y. Morch, R. Schmid, E. Sulheim, P. Stenstad, H. Johnsen, K. Flatmark, K. G. Fleten, Drug Delivery System for Treatment of Cancer, US 2022/0257525 A1, 2019.
[131] Y. Akatsu, H. Mashiba, Block Copolymer for Intraperitoneal Administration Containing Anti-Cancer Agent, Micelle Preparation, and Cancer Therapeutic Agent Comprising the Micelle Preparation as Active Ingredient, WO 2011/049042 A1, 2009.
[132] M.G. Oefelein, N. Venkatesan, N.K. Swarnakar, T.B. Hong, G.V. Betageri, R. Thirucote, L.Z. Hutchinson, Liposomal Enhanced Intra-Peritoneal Chemotherapy, US 2022/0000777 A1, 2018.
[133] R. Sahoo, Delayed Delivery of aNticancer Drugs, EP 3701943 A1, 2019.
[134] D. Morris, S. Valle, J. Akhter, K. Pillai, Formulations Containing Mucin-Affecting Proteases, US 2021/0008180 A1, 2018.
[135] R. Zeineldin, Intraperitoneally-Administered Nanocarriers that Release Their Therapeutic Load Based on the Inflammatory Environment of Cancers, US 9532949 B2, 2011.

[136] S.K. Williamson, C.J. Decedue, S.A. Fontana, M. Baltezor, Use of Paclitaxel Particles, WO 2015/187194 A1, 2014.
[137] M. Baltezor, J. Farthing, J. Sittenaeur, J. Espinosa, S. Campbell, M. Mcclorey, J. K. Fischer, M.D. Williams, G.E. Clapp, Taxane Particles and Their Use, US 9814685 B2, 2015.
[138] M. Baltezor, G. Dizerega, C. Decedue, S. Campbell, M. Mcclorey, Methods for Solid Tumor Treatment, US 10391090 B2, 2016.
[139] G.S. Dizerega, M. Baltezor, S. Campbell, C.J. Decedue, M. Mcclorey, Local Delivery of Antineoplastic Particles in Combination with Systemic Delivery of Immunotherapeutic Agents for the Treatment of Cancer, US 11058639 B2, 2017.
[140] N.C. Vook, E. Jacob, J.A. Setterstrom, H.J. Van, W. Vaughan, H. Duong, Sustained Release Hydrophobic Bioactive PLGA Microspheres, US 6447796 B1, 1994.
[141] W. Dang, Methods for Treating Ovarian Cancer, Poly (Phosphoester) Compositions, and Biodegradable Articles for Same, US 6350464 B1, 1999.
[142] J.L.-S. Au, G. Wientjes, Methods and Compositions for Enhancing Delivery of Therapeutic Agents to Tissues, US 7217735 B1, 1999.
[143] W. Dang, Compositions for Treatment of Malignant Effusions, and Methods of Making and Using the Same, US 2002/0141966 A1, 2000.
[144] J.L. Au, M.G. Wientjes, Tumor Targeting Drug-Loaded Particles, US 2006/0034925 A1, 2004.
[145] J. Fu, J. Hanes, M. Yang, Polymer-Based Compositions and Methods for Treatment of Peritoneal Disorders, WO 2011/084458 A2, 2009.
[146] C.J.F. Rijcken, M. Stigter, Holthuis Josephus Johannes Maria, Controlled Release System, US 2014/0199244 A1, 2011.
[147] C.-M. Chuang, C.-T. Chang, Compositions and Methods of Tumor Treatment Utilizing Nanoparticles, US 2018/0028444 A1, 2015.
[148] D.L. Stirland, J.W. Nichols, S. Miura, Y.H. Bae, Mind the gap: a survey of how cancer drug carriers are susceptible to the gap between research and practice, J. Control. Release 172 (2013) 1045–1064, https://doi.org/10.1016/j.jconrel.2013.09.026.
[149] E. de Bree, D. Michelakis, D. Stamatiou, J. Romanos, O. Zoras, Pharmacological principles of intraperitoneal and bidirectional chemotherapy, Pleura Peritoneum 2 (2017) 47–62, https://doi.org/10.1515/pp-2017-0010.
[150] D.K. Armstrong, G.F. Fleming, M. Markman, H.H. Bailey, A phase I trial of intraperitoneal sustained-release paclitaxel microspheres (Paclimer) in recurrent ovarian cancer: a gynecologic oncology group study, Gynecol. Oncol. 103 (2006) 391–396, https://doi.org/10.1016/j.ygyno.2006.02.029.
[151] R.C. Shah, V. Hoyo, P. Moussatche, B.B. Volkov, Improving quality and efficiency of translational research: environmental scan of adaptive capacity and preparedness of clinical and translational science award program hubs, J. Clin. Transl. Sci. 7 (2023) e42, https://doi.org/10.1017/cts.2022.423.