

## REVIEW OPEN



# Solid lipid nanoparticles in pancreatic cancer treatment

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Pancreatic cancer comes with one of the poorest prognoses of all cancers and as such it is crucial that new therapies are developed to improve on the current statistics. Currently, chemotherapy is the cornerstone of pancreatic cancer treatment with several drugs, and combinations of drugs being utilised for their anti-cancer effect. However, pancreatic cancer has a dense stroma around the tumour and intratumoral bacteria which result in drugs having difficulty penetrating the tumour or being metabolised by bacteria rendering them inactive. The utilisation of nanotechnology in chemotherapy for pancreatic cancer has been a huge area of focus for researchers worldwide with most of the focus being on lipid-based, inorganic and polymer-based nanoparticles. Solid lipid nanoparticles which have been studied since being first published in the 1990s, have been poorly researched for pancreatic cancer applications. Being composed of physiological lipids, solid lipid nanoparticles offer a greatly reduced risk of acute or chronic toxicities arising compared to inorganic or polymeric nanoparticles. They also possess the ability to improve on circulation time, permeability, and bioavailability of many first-line chemotherapeutics.

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## INTRODUCTION

Globally, pancreatic cancer (PC) is the third leading cause of death from cancer [1]. Across the 2013–2019 period, PC was shown to have a relative 5-year survival rate of only 12.5% [2], a predictive study of PC from 2022 to 2050 indicated that the ratio of mortality to incidence will continue to increase [3]. In addition to this, a study investigating the potential to achieve a 50% reduction in mortality caused by cancer by 2047 suggested that with current technologies the prospect of significantly reducing PC mortality rates was poor [4]. PC can be subdivided into two main categories: exocrine and endocrine, of these the exocrine cancer pancreatic ductal adenocarcinoma (PDAC) accounts for almost 90% of all cases [5, 6]. A huge factor in the low survival rate of PC arises from PDAC displaying early metastatic growth and minimal response to treatment by chemotherapy or radiotherapy [7]. Whilst there are many chemotherapeutic agents available which can be used as a single or in combination therapy for the treatment of PC, the low survival rate shows a severe need to continue efforts to develop novel drugs or delivery platforms for treatment of PC [7, 8].

## STATE OF THE ART

In the search for increasingly more effective cancer treatments, nanotechnologies are a huge area of focus. Nanoparticle formulations are utilised due to the possession of several characteristics such as the exhibiting their own inherent cytotoxicity or ability to inhibit cell proliferation [9–11] or in the entrapment and delivery of drugs [12–15]. Additionally, nanoparticles possess a large surface area to volume ratio which offers scope for a wide range of ligands and targeting moieties to be attached onto their surface, providing a site-specific delivery mechanism [16–19].

Due to their versatility, lipid-based nanoparticles saw a huge rise during the COVID-19 pandemic with liposomes being at the

forefront [20]. Liposomes are primarily composed of phospholipids and can form either a single bilayer or multiple concentric bilayers wherein hydrophilic drugs can be entrapped within the aqueous core and hydrophobic drugs reside within the bilayer structure [21]. Physical stability is a common issue in liposomal formulations, utilisation of solid lipid nanoparticles (SLNs) in their place offers the ability of overcome these issues. These nanoparticles are comprised of a solid lipid core surrounded by a layer of surfactant molecules which offer greater stability in suspension [22]. SLNs are a versatile platform for the delivery of both hydrophobic and hydrophilic drugs and being primarily comprised of biocompatible lipids, there is a lower risk of cytotoxicity compared to other nanoparticle technologies [23]. Water solubility remains an ongoing issue with many chemotherapeutics thus resulting in poor bioavailability or complete inability to administer effectively and safely. SLNs offer a shield from the ‘hostile’ aqueous environment and entrap the lipophilic drugs within their lipid core. This entrapment acts as a sheath protecting the drug from premature degradation and aiding their permeation across biological barriers. These factors open the possibility of other administrative routes being utilised which can also have a positive impact on patient compliance compared to that of intravenous administration [23, 24].

## Challenges in pancreatic cancer treatment

Unfortunately, due to the vague symptoms of PC, it is often not diagnosed until very late stages, which renders it very difficult to treat, hence the poor patient prognosis. Whilst there are many treatments available, there remains a significant need to develop more effective treatments which can overcome the barriers posed by PC such as penetrating the dense stroma surrounding the tumour, ability to survive the harsh tumour microenvironment, retard the rapid rate of cell proliferation and ability to overcome

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drug resistance [25, 26]. The poor prognosis of PC is also partly due to the high recurrence rate, in patients who underwent surgical resection over 80% had recurrences within 5-years and over 60% within 2-years [27]. Effective adjuvant therapy for PC hopes to reduce the rates of tumour recurrence, and increase overall survival for patients, however chemotherapeutic resistance makes this very challenging. The tumour microenvironment in PC poses significant issues for drug delivery and effective treatments, intratumoral bacteria found in PC tumours has been shown to metabolise gemcitabine to its inactive metabolite 2',2'-difluoro-odeoxyuridine [28]. Significant fibrosis is displayed in PC tumours with the main source of extracellular matrix components being myofibroblasts, leading to a large presence of collagen which results in poor delivery of drugs into the tumour [29]. Elevated expression of programmed cell death ligand-1 also contributes to resistance to chemotherapy by reducing the density of cytotoxic T-cells (CD8<sup>+</sup>) within the tumour [30, 31]. Within PC tumours, the desmoplastic stroma leads to a dense, hypoxic environment which also significantly inhibits the ability of CD8<sup>+</sup> cells to penetrate within the tumour [31]. The glycoprotein, MUC-1 is overexpressed in over 80% of PDAC cases, leading to the upregulation of ATP-binding cassette transporters which contributes to multidrug resistance (MDR) in PC by facilitating the efflux of any chemotherapeutic agents from the cell, thus by targeting MUC-1 there is a potential to mitigate the upregulation of the ATP-binding cassette transporters and decrease the overall efflux of drugs from within the cell [25, 26].

### Current chemotherapy for pancreatic cancer

Therapies for PC vary depending on the progression and stage of the cancer. In cases where tumours are classified as resectable or borderline resectable, surgery may be possible to remove the tumour. However, in many cases such as those non-resectable or metastatic, there is a requirement for chemotherapeutics either pre-operatively in neoadjuvant therapy, or post-operatively in adjuvant therapies [32].

Until the late 1990s, 5-fluorouracil (5-FU) was the most prevalent chemotherapeutic used in PC treatment however patient survival rates remained exceptionally low. In 1997, an early investigation into the use of gemcitabine as a first line therapeutic for PC treatment, was published [33]. This study found that gemcitabine offered an increased survival time of 5.56 months and 1-year survival probability of 18% compared to 5-FU with 5.51 months and 2% respectively [33].

To reduce PC recurrence, disease-free survival and overall survival in post-operative PC patients, adjuvant gemcitabine has been extensively studied. The German Study Group for PC, in the CONKO-001 study [34], saw an overall survival of 22.8 months versus 20.2 months, and an increased disease-free survival of 13.4 months versus 6.7 months without adjuvant gemcitabine. Recurrence of the disease, whilst decreased slightly, remained high at 81% with therapy compared to 87% without [34]. A similar study by the Japanese Study Group for PC, JSAP-02 [35], saw an increase in disease-free survival of 11.2 months from 5.0 months and a decrease in recurrence rate to 77% from 88% [35].

A study by the European Study Group for PC, ESPAC-1 [36], using 5-FU as an adjuvant chemotherapeutic found an increase in overall survival from 14.0 months to 19.7 months. The same study also showed no statistically significant impact on survival rate when chemoradiotherapy was utilised [36]. A later study by the same group, ESPAC-3 [37], compared gemcitabine to 5-FU as adjuvant therapeutics and saw no significant increase in survival rate, with a 63% recurrence rate in both groups used in the study [37].

In cases where surgery is not immediately possible or to improve the outcomes of tumour resection, the application of chemotherapeutics as a neoadjuvant therapy has also been extensively investigated. A 2017 study by Mokdad et al. showed an increased overall survival in patients with early-stage PC

treated initially with neoadjuvant therapies before surgical resection of 26 months compared to 21 months in those with surgical resection only [38]. The 1-, 3- and 5-year survival rate of patients undergoing neoadjuvant therapy increased to 83, 35 and 21% versus 71, 29 and 18% in upfront resection patients, respectively. This study also investigated the use of adjuvant therapy in those who underwent upfront resection compared to those who were treated with neoadjuvant therapy. The overall survival was 23 months, and 1-year, 3-year and 5- year survival rates in this case were 78, 31 and 18% which remained to show comparatively better results in the use of neoadjuvant therapy [38].

A retrospective study by the California Cancer Surveillance Program for Los Angeles County compared the overall survival of PC patients treated with neoadjuvant therapy to those treated with adjuvant therapy. They found that patients treated with neoadjuvant therapy survived considerably longer with average overall survival rates of 33.8 months versus 19.0 months. This was also observed for cancers originating outside of the pancreas, with overall survival rates of 31.1 months for neoadjuvant therapy compared to 19.0 months for adjuvant therapy [39].

A common drug used in combination with gemcitabine is capecitabine, this combination was evaluated in a cohort of 319 patients. The study showed an increase in overall survival of 8.4 months from 7.2 months, and an increase in 1-year survival from 30 to 32% when compared with gemcitabine alone. These figures prompted a follow up study made up of a larger cohort of 533 patients where the overall survival and 1-year survival rate was shown to increase by 0.9 months and 2.3% respectively [40].

In addition to the delivery of single drugs, many combinations of drugs have been investigated for their efficacy as first-line therapies, and for the ability to treat cases where gemcitabine resistance has developed [28, 41, 42]. Another promising combination drug is FOLFIRINOX<sup>®</sup>, comprised of a combination of leucovorin, 5-FU, irinotecan, and oxaliplatin. FOLFIRINOX<sup>®</sup> has been investigated as a neoadjuvant therapeutic, with an increase achieved in overall survival and 1-year survival rates [43]. The use of neoadjuvant FOLFIRINOX<sup>®</sup> has also been coupled with chemoradiotherapy in a patient cohort of 48 who were deemed borderline resectable. 32 patients in this cohort underwent surgical resection, with 96% seeing full microscopic scale, R0 resection of the tumour [44].

Traditional chemotherapeutics do not possess the ability to selectively target cancer cells and owing to their level of cytotoxicity result in the death of both healthy and unhealthy cells. The lack of specificity results in a requirement of increased dosages to reach a therapeutic level within the tumour site [45].

### Nanotechnology in pancreatic cancer treatment

Nanoparticles (NPs) offer the ability to overcome specificity issues by incorporation of chemotherapeutics within proteins such as in nab-paclitaxel wherein paclitaxel is bound to albumin [46], or by anchoring targeting moieties onto the NP surface. Such targeting moieties include ssDNA aptamers such as XQ-2d which has been shown to bind to the CD71 protein [17] or cytokines such as the tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) [47].

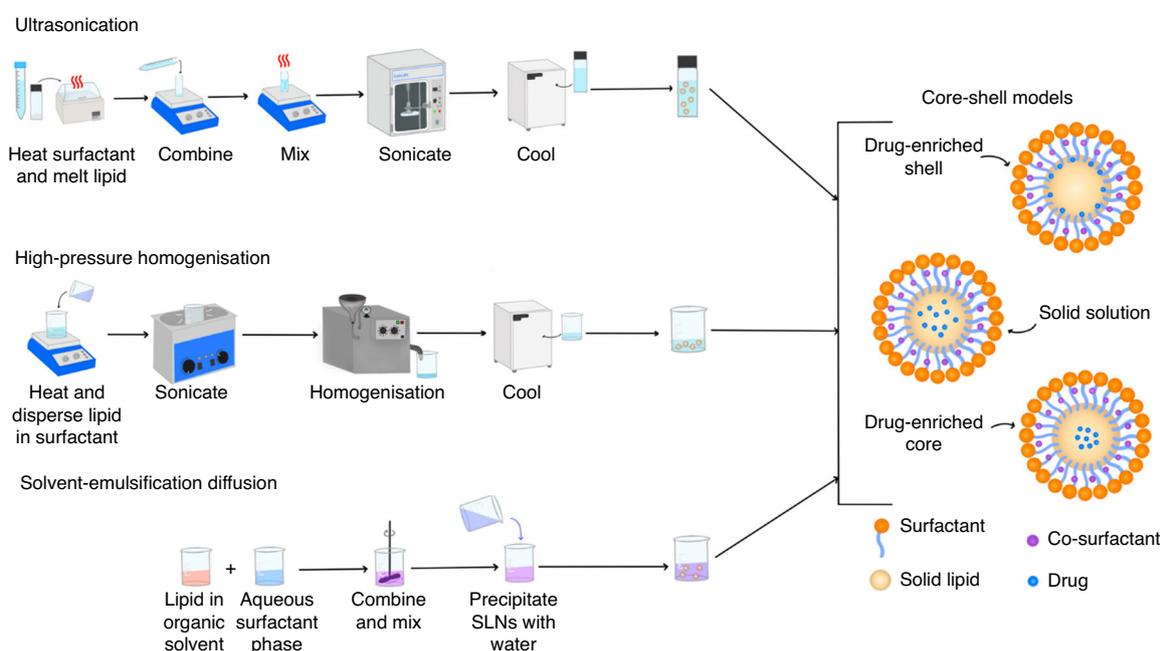
NP formulations of chemotherapeutics cover a broad range of platforms with various treatment strategies being employed. NP platforms aiming towards better pancreatic cancer treatments span across the entire field, from inorganic NPs to polymer or lipid based, some examples of these are outlined in Table 1.

### SOLID LIPID NANOPARTICLES

Since being discovered in 1991 [48], solid lipid nanoparticles (SLNs) have been utilised in a wide variety of applications including cancer therapeutics. These spherical nanoscale particles are comprised of a crystalline lipid core surrounded by surfactant

**Table 1.** A summary of the nanoparticle platforms investigated for pancreatic cancer treatment by utilisation of various treatment strategies.

Treatment strategy	Nanoparticle platform	Therapeutic agent	Ref
Chemotherapy	Liposome	Irinotecan	[88]
	Superparamagnetic iron oxide	Curcumin and gemcitabine	[89]
	Lipid nanocapsules	Lauric acid derivative 5-fluorouracil	[90]
Immunotherapy	Polymeric micelles	Volasertib	[91]
	Mesoporous silica	Volasertib	[92]
	Lipid-based	Monophosphoryl lipid A and cyclic diguanosine monophosphate	[93]
Photothermal	Silver	Immunoglobulin G	[94]
	Gold nanorod	Gold nanorods	[95]
	Semiconducting polymer	<sup>177</sup> Lu and glucose-dependant insulinotropic polypeptide	[96]
Theranostic	NaLuF <sub>4</sub> :Nd@NaLuF <sub>4</sub>	Gemcitabine monophosphate	[97]
	Gadolinium	Gd-NPs	[98]
	Titanium dioxide	TiO <sub>2</sub> -NPs	[99]

**Fig. 1** Schematic representation of common SLN fabrication methods and a simple representation of the core-shell models of drug entrapment within an SLN. Ultrasonication and high-pressure homogenisation are commonly utilised due to being free of organic solvents, ultrasonication is readily available at laboratory scale and high-pressure homogenisation is a common scale-up formulation methodology. Solvent-emulsification diffusion has little requirement for specialised equipment making it more easily accessible as a formulation method.

molecules which provide colloidal stability [49] and can exhibit varying physicochemical properties depending on their chemical composition and formulation method. Formulation methods include ultrasonication, high pressure homogenisation or solvent emulsification diffusion (Fig. 1). SLNs are capable of entrapping lipophilic and hydrophilic drugs in either their lipid core or their surfactant layer (respectively) which offers the potential to overcome issues with solubility, permeability, or both in drugs categorised by the Biopharmaceutics Classification System as class II, III, or IV [24].

SLNs are a drug delivery platform with several distinct advantages over other lipid-based and polymer-based NPs. SLNs allow for protection from degradation to entrapped drugs, possess excellent colloidal stability, and allow for a controlled release of drug to be achieved [13, 50]. In addition to this, their composition from physiological lipids makes them readily biodegradable [51]. Also, they are primarily composed of biocompatible lipids which are “generally regarded as safe” by the FDA, this reduces the risk

of acute and chronic toxicities arising, such as those in inorganic and some of the synthetic polymeric nanoparticles [51–53].

As SLNs can either be suspended in aqueous media or lyophilised for storage as a dry powder, they have a wide scope for delivery via multiple routes. Most commonly, intravenous administration is utilised as this removes significant biological barriers that must be overcome in other routes [54]. However, due to the versatility in their composition SLNs have been studied for their use in delivery by oral, topical, ocular, rectal, and nasal routes [50, 55–58].

#### SLN formulation

At their core is a lipid matrix which remains solid at physiological temperature, alongside a coating layer of surfactant and in some cases also with a co-surfactant [23, 59, 60]. The surfactants used offer stability to the SLNs by exhibiting electrostatic or steric repulsive forces which counteract the tendency towards aggregation [59].

**Table 2.** Some key advantages and disadvantages of the most common methods of SLN formulation.

Formulation method	Advantages	Disadvantages	Ref
Ultrasonication	- Simple and accessible at lab scale - Free from organic solvents	- Potential metal contamination - Wide size distribution	[63–65]
Solvent-based methods	- Low cost with no expensive apparatus - No risk of thermal degradation	- Residual solvents may cause toxicities - Low energetic cost	[64, 76, 79]
Hot/Cold-high pressure homogenisation	- Expensive and energy intensive - Easily scalable	- High polydispersity - May cause thermal degradation	[13, 72, 73]

Depending on the formulation method and the raw material concentrations, SLNs can be formulated in three different forms. The first of these is the homogenous matrix model which forms when SLNs are made from solution of lipid and drug using a cold homogenisation process in the absence of surfactant. The remaining two forms are core-shell models, formation of a drug-enriched core occurs when the drug concentration is sufficiently high leading to the drug becoming supersaturated. This causes the drug to precipitate first upon cooling allowing the lipid to recrystallise around the drug as it cools. The other core-shell model is the drug-enriched shell which forms under hot homogenisation processes in which the lipid recrystallises first, and the active ingredient then concentrates around the surface as the solution cools [61, 62].

There are many methods available for producing SLNs which offer individual advantages depending on the composition of the desired SLNs or the scale of production. One of the key advantages of many production methods for SLNs is the absence of organic solvents at all stages. Solvent-free formulation methods not only remove potential toxicities that may arise from residual solvents but also remove some of the environmental risks by maintaining a more sustainable aqueous-based process. Some advantages and disadvantages of some common formulation methods are detailed in Table 2.

Ultrasonication is a commonly employed method of SLN production as it is simple and readily available at lab-scale. Here, a molten lipid is dispersed in an aqueous phase containing surfactant wherein sound waves produce sufficient cavitation forces to facilitate a reduction in particle size towards a nanometre range [63]. Depending on the scale of production, either an ultrasonic bath or a probe sonicator can be employed. Whilst the probe sonicator is preferred for smaller scale productions, there is a potential for metal contamination from the tip. In the use of ultrasonication, the resulting SLNs have a wider distribution of sizes which can stretch as far as the micrometre scale [64, 65].

An alternative method is high pressure homogenisation (HPH) which can be used at elevated, or cold temperatures (hot-HPH or cold-HPH). In the use of hot-HPH, the formulation method is carried out as with ultrasonication before the resulting dispersion is passed into a homogeniser where it is forced multiple times through an opening of only a few micrometres at pressures upwards of 500 bar [13, 48, 66]. In the formulation of SLNs with heat sensitive drugs, cold-HPH can be employed. This is carried out by forming a suspension of drug in a molten lipid which is then rapidly cooled with dry ice and liquid nitrogen. The resulting solid is milled to a fine powder and dispersed in a cold aqueous phase containing surfactant. Finally, the homogenisation is carried out in the same fashion as in hot-HPH [13].

In the encapsulation of hydrophilic drugs within SLNs, it is typically required to use a method that employs an organic solvent. The organic solvent used is partially soluble in water and is saturated with water before use to ensure thermodynamic equilibrium across the solvent systems [67]. A technique used in this instance is solvent-emulsification diffusion, here a water-saturated organic solvent is used to dissolve the lipid, this solution is then added to a surfactant solution containing the same water-saturated solvent. The resulting solution is emulsified by high

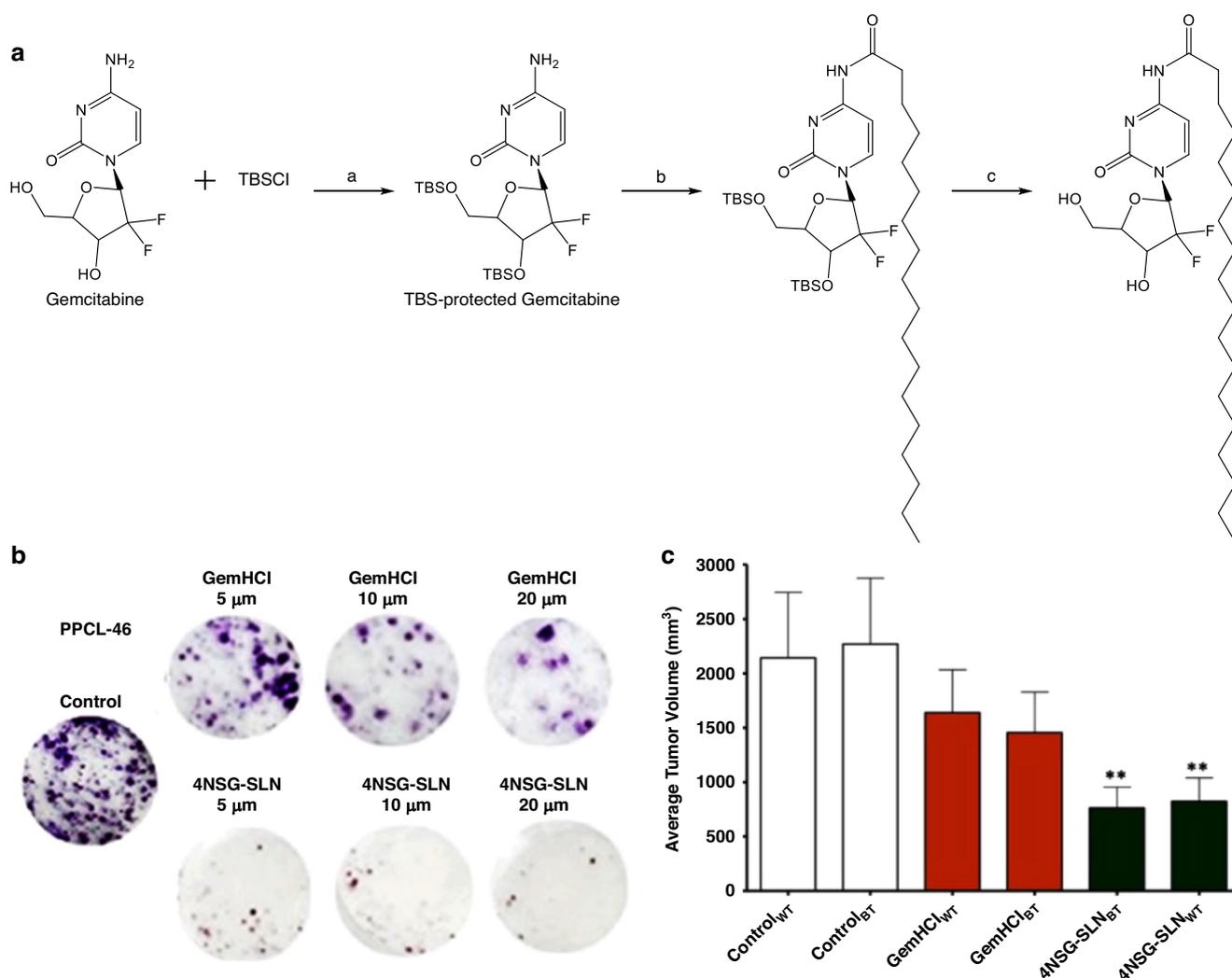
shear mixing before the addition of a large volume of water to cause the precipitation of the SLNs as the organic solvent moves into the large aqueous phase [68].

### Application of solid lipid nanoparticles in pancreatic cancer treatment

Current first-line therapeutics for PC have been shown to exhibit several huge drawbacks such as their toxicity, short half-lives and wide array of side effects which can be mitigated by entrapment within SLNs as a drug carrier [13]. Incorporation of drugs within SLNs offers scope to increase their anti-cancer activity [13] and overcome multidrug resistance due to the uptake their uptake occurring primarily by endocytosis-associated routes, rather than active transport such as in P-glycoprotein efflux [15, 69]. Surface modification and coatings of SLNs can also be employed to offer advantageous characteristics. The use of P-glycoprotein inhibitors such as hyaluronic acid or Pluronic® F-127 can decrease the effect of MDR [70]. SLNs coated with chitosan and various derivatives of chitosan have been shown to protect against burst release allowing for a controlled release of drugs upon administration thus allowing for drugs to be delivered over a prolonged period [71]. Many surface proteins are overexpressed in cancerous cells when compared with healthy cells. By conjugation of peptides or other bioactive compounds that bind with these surface proteins onto the surface of SLNs there is potential to offer a more selective, targeted therapy [72].

*Chemotherapeutic delivery with solid lipid nanoparticles.* A study published in 2020 [13] examined the cytotoxicity of SLNs loaded with 15 mg (0.05%w/v) gemcitabine hydrochloride against MIA PaCa-2 and PPCL-46 cell lines. SLNs were formed by cold homogenisation with a glyceryl monostearate core stabilised by either Poloxamer 188 or Tween® 80. Formulations comprising Poloxamer resulted in particles with sizes ranging from 264 to 684 nm, and entrapment efficiency from 16.5% to 56.6%. The formulations stabilised by Tween® 80 resulted in particle sizes ranging from 387 to 603 nm, and entrapment efficiency from 0% to 68.3%. Of those formulations entrapping more than 50%, a drug release study determined that an initial burst release occurred within 12 h and a sustained release over the following 60 h. Over the total 72 h the total amount of drug release ranges from <50 to 73%. The highest total drug release was from a formulation stabilised by Tween® 80, which was tested in vitro with gemcitabine hydrochloride as a control and displayed significantly lower IC<sub>50</sub> values. This study showed the clear potential of nanocarriers to increase the anticancer activity of first line chemotherapeutics against delivery of the drugs alone [13].

In efforts to improve the therapeutic efficacy of gemcitabine hydrochloride several studies have shown that SLNs comprised of a stearic acid derivative of gemcitabine can increase cell uptake and overcome drug resistance pathways [14, 15, 73]. To determine the increased therapeutic efficacy of gemcitabine in its derivatised form, a biological evaluation has been conducted [73]. SLNs comprised primarily of 30 mg the derivative 4-(N)-stearoyl-gemcitabine, with a mixture of labrosol®, Tween® 80, and lecithin were formulated by cold high-pressure homogenisation. The final entrapment of the gemcitabine derivative was 98.7 ± 4.5%. In a cytotoxicity study of



**Fig. 2** Synthesis and biological evaluation of a stearic acid gemcitabine derivative used in the formation of an SLN. **a** Three step synthesis of stearic acid gemcitabine derivative. **a**) TBS protection of hydroxyl groups **b**) formation of gemcitabine – stearic acid amide bond **c**) removal of the TBS protecting groups. **b** Colony formation assay showing significant reduction in cell survival in those treated with SLNs. **c** Average tumour volume in mice with patient derived xenografts of pancreatic cancer showing significant reduction in tumour growth in mice treated with SLNs over a 3-week study period. Adapted from ref. [73].

gemcitabine compared against the SLNs in four patient-derived pancreatic cancer cell lines the  $IC_{50}$  values were significantly lower for the SLNs in all cases. The pharmacokinetic profile was determined in mice, with  $20 \text{ mg kg}^{-1}$  of SLN formulation and an equivalent dosage of gemcitabine hydrochloride being administered intravenously. The study showed the half-life of the SLNs to be  $1.93 \pm 0.06 \text{ h}$  approximately three times higher than gemcitabine hydrochloride with a half-life of  $0.70 \pm 0.01 \text{ h}$ . There was also an approximately three-fold increase in bioavailability as shown by the area under curve, the SLNs resulted in a value of  $86.2 \pm 5.43 \mu\text{g}(\text{mL}\cdot\text{h})^{-1}$  and gemcitabine hydrochloride only  $21.3 \pm 3.2 \mu\text{g}(\text{mL}\cdot\text{h})^{-1}$ . In vivo testing also determined that the SLN formulation resulted in a significantly smaller tumour volume of around  $500 \text{ mm}^3$  compared to those treated with gemcitabine hydrochloride where the final tumour volume was in the region of  $1200 \text{ mm}^3$  (Fig. 2) [73].

*Phytochemical delivery with solid lipid nanoparticles.* Phytochemicals are a large area of focus in chemotherapeutics research, of these, coumarins are a well-known class of chemical which have been studied due to their low toxicity and effective anti-cancer properties. Herniarin, a derivative of the coumarins possesses both

poor water solubility and cell permeability, however, by entrapment within SLNs issues of solubility can be negated and the pharmacokinetic parameters of the drug may be improved. A study published in 2023 [74] formulated herniarin SLNs comprised of stearic acid, lecithin, and Tween® 80 which were tested in vitro against AGS, HT-29, HFF, and Panc-1 cells. The final characterised SLNs achieved a 91% entrapment efficiency from 10 mg of herniarin added as well average particle size of 198 nm and polydispersity index of 0.301. In vitro testing showed the SLNs had no effect on HFF cells but caused a significant reduction in cell viability in Panc-1, HT-29, and AGS cell lines. The cytotoxic effect of these SLNs was most pronounced when tested against the Panc-1 cell line which shows promise in the treatment of PC [74].

Chrysin, a flavone derivative has been studied for its anti-cancer potential within an SLN platform against cell lines pancreatic, liver, breast, and ovarian cancer [75]. The SLNs composed of lecithin and stearic acid were loaded with chrysin before being coated with chitosan modified with folic acid. This coating results in a positive surface potential on the nanoparticle which offers increased interaction with the cells and a decreased clearance by the immune system. The cell lines tested in this study were folic acid receptor positive cells, namely, PANC, MCF-7, A2780, and

HepG2. HFF cells were used as a normal cell comparison for preclinical toxicity. The formulated SLNs had an average size of 125 nm and a zeta potential of +34.9 mV. Cell viability studies resulted in IC<sub>50</sub> values of 53.43 and 55.73 µg mL<sup>-1</sup> for PANC and MCF-7 respectively, whereas A2780 had an IC<sub>50</sub> of almost 250 µg mL<sup>-1</sup> and HepG2 showed very little decrease in viability up to 250 µg mL<sup>-1</sup>. The IC<sub>50</sub> results show the formulation to be most effective against cancers of the pancreas and breast, with liver and ovarian cancer cells showing little to no response. The normal cell line, HFF, displayed no reduction in cell viability up to 250 µg mL<sup>-1</sup> which was a strong indication of preclinical safety when compared to the cancer cells tested [75].

*Immunotherapeutic delivery with solid lipid nanoparticles.* In efforts to overcome the global issues with PC, different strategies are constantly being developed. Of these, immunotherapy is a promising field of study for treatment of PC [76, 77]. Combination therapies of CB-5083, an inhibitor of the VCP/p97 protein, alongside an inhibitor of PD-L1, miR-142, and agonist of the Toll-like receptor 7/8, resiquimod have been studied in the hopes to induce immunogenic cell death in PC cells. SLNs containing these have been formulated with average sizes around 180 nm, PDI around 0.15, and zeta potential upwards of -30 mV. These formulations have been evaluated in mouse PDAC cells, Panc-02 [76], and in vivo in Panc-02 tumour-bearing C57BL/6 mice [77]. This combination therapy within an SLN platform has been shown in vitro to result in immunogenic cell death through CB-5083 suppressing the epithelial-mesenchymal transition, as well as causing endoplasmic reticulum stress resulting in apoptosis. In addition to this, the incorporation of miR-142 blocking PD-1 from interacting with PD-L1, and resiquimod which improves the effect of immune antitumour responses [76]. A biodistribution study in vivo showed the ligands on the SLN surface were effective in targeting the tumour site as there was significantly higher accumulation of CB-5083 in the tumour than in the liver, spleen, kidney or heart. This is a promising result in that the use of SLNs may mitigate off target effects which have been seen in the administration of CB-5083 such as impaired retinal function, and toxicities associated with its use. In studies assessing the antitumour effect the final formulation showed a significant reduction in tumour volume following 14 days of treatment with twice weekly injections into the tail vein. Following the 14 days of treatment, the primary tumours were surgically excised before being reinoculated after 7 days, herein the growth of the secondary tumour was observed with the combination SLN formulation showing enhanced suppression of tumour growth as well as elevated effector memory T cells (CD62L<sup>-</sup>CD44<sup>+</sup>) [77]. These results show immunotherapeutics to be in not only resulting in immunogenic cell death in PDAC, but also in preventing recurrence of the cancer by increasing the populations of memory T cells [76, 77].

### **Solid lipid nanoparticles in cancer therapeutics and theranostics**

Whilst there is limited research utilising SLNs in the treatment of PC, there is a breadth of evidence that shows them to have high potential in the treatment of other cancers. In the treatment of colorectal cancer, SLNs loaded with topotecan and incorporated into a thermoresponsive hydrogel have been shown to exhibit a significantly larger antitumour effect compared to the native drug. In addition to this, an in vivo study showed a reduction in the toxicity of the drug as the final formulation had no significant weight loss whereas IV delivery of topotecan in solution resulted in a significant loss in the average weight in the study group [58]. Entrapment of 5-FU within SLNs has also been shown to exhibit heightened anticancer ability in the treatment of colorectal cancer, causing a significant reduction in cell viability in HCT-116 cells as well as reducing tumour growth in vivo compared with the same dose of 5-FU [78].

Treatment of breast cancer has been another huge area of focus for SLN research. A 2014 study showed the delivery of docetaxel entrapped in SLNs achieve a lower IC<sub>50</sub> than docetaxel alone in MDA-MB-231 cells [64]. In 2018 a study [79] compared the delivery of paclitaxel by SLNs, DMSO, or Cremophor<sup>®</sup> EL and ethanol. The SLN formulation was tested in vitro against MCF-7 cells and the multidrug resistant variant of the same cells, MCF-7/ADR both with and without the cotreatment of a P-glycoprotein inhibitor, verapamil. In MCF-7 cells, the resulting IC<sub>50</sub> values were higher than the other delivery methods in both treatment with and without verapamil, however in the resistant variant the IC<sub>50</sub> was lower for the SLN formulation than delivery by either of the other two methods [79].

Many of these studies show hugely positive results for the delivery of chemotherapeutics where in many cases the entrapped drugs vastly outperform any delivered free drug. In efforts to further improve on previously shown results, the surface chemistry of SLNs has become a focal point for research. Conjugation of antibodies [69], peptides and proteins [72] have been explored with many promising outcomes. The glycoprotein transferrin has been covalently conjugated onto the surface of solid lipid nanoparticles containing tamoxifen citrate for the treatment of breast cancer. It was shown that the uptake of the SLNs containing transferrin is higher than SLNs without surface modification into MCF-7 cells due to the occurrence of receptor-mediated endocytosis. Also, an MTT assay showed the IC<sub>50</sub> values of unmodified-SLNs to be less than half of the tamoxifen in solution with the modified-SLNs offering a further reduction in IC<sub>50</sub> [72].

In many cancers, multidrug resistance is a significant issue [15, 25, 69]. In some cases, this is due to overexpression of P-glycoprotein which acts as an efflux transporter. A 2017 study [69] investigated the impact of conjugating an antibody, anti-CD44v6 onto the surface of SLNs loaded with paclitaxel for the treatment of breast cancer. When tested against MDA-MB-436 cells, the resulting IC<sub>50</sub> values showed that the formulation containing the antibody was similar to that of free paclitaxel however the other SLN formulations either with or without poly(ethylene glycol) showed a significant decrease. Whilst the surface functionalisation did not yield an improved IC<sub>50</sub>, it was shown that the overall P-glycoprotein expression was reduced which is a positive result in cases where multidrug resistance is a significant concern [69].

A 2018 study [80] investigated the potential of paclitaxel-loaded SLNs that had been surface functionalised with Tyr-3-octreotide for the treatment of melanoma with overexpression of somatostatin receptors. When compared with dacarbazine, an approved chemotherapeutic in melanoma therapy, the modified SLNs caused a higher percentage of apoptosis in B16F10 cells. The SLN formulation was radiolabelled with <sup>99m</sup>Tc and tested in vivo using C57BL/6 mice. Intratumoral injection showed the formulation had spread to the entire tumour after 5 min and remained visible up to 24 h which shows the potential of sustained paclitaxel release at the tumour site. The study showed elevated numbers of CD8<sup>+</sup> T cells which shows promise for increased overall survival rates [80].

Some studies have shown SLNs to have some theranostic capability when loaded with fluorescent dyes [54] or in some cases, other nanoparticle platforms [81]. A study published in 2023 [54] investigated maslinic acid SLNs coated with either Poloxamer 407 or dicarboxylic acid Poloxamer 407 loaded with Nile Red or IR780 fluorescent dye. The SLNs were tested against BxPC3, MCF7 and fibroblasts to determine the therapeutic index based on the IC<sub>50</sub> values, in all cases the therapeutic index value was >1. In cellular uptake studies, Nile Red loaded SLNs were demonstrated to be taken up within a timeframe as short as 1–5 min. In vivo studies in male CD1 mice for biodistribution after oral and intravenous administration of formulations comprised of 0.05 or

0.5%w/w of the IR780 dye showed an even fluorescence across the entire mouse after 48 h when administered intravenously for the higher concentration of dye but no signal was detected at any time point for the lower concentration. In the oral administration the dye was only visible in the gastrointestinal tract with no evidence of systemic delivery. The lower concentration was visible up to 6 h and the higher concentration maintained some fluorescence up to 24 h post administration [54].

A different theranostic strategy in SLNs is the co-entrapment of a drug and superparamagnetic iron oxide nanoparticles which act as a contrast agent for magnetic resonance imaging. Preparation of these particles has been displayed in a study showing the potential to magnetically guide sorafenib to the liver with a significant difference in  $IC_{50}$  values after 72 h when tested against HepG-2 cells [81].

## NANOTECHNOLOGY THERAPIES APPROVED FOR CLINICAL USE IN CHEMOTHERAPY

Whilst many of the currently available drugs for PC treatment have been investigated within NP formulations, only two, Abraxane<sup>®</sup> and Onivyde<sup>™</sup> have been approved for clinical use [82]. Abraxane<sup>®</sup> is a formulation of paclitaxel bound to albumin that has been shown to improve penetration and uptake, as well as antitumour efficacy of the drug [46]. Onivyde<sup>™</sup> is a liposomal formulation of irinotecan that has demonstrated an increase in overall survival when used in conjunction with 5-FU compared to the same combination with non-liposomal irinotecan [83, 84]. Recently, the FDA approved the use of NALIRIFOX as a combination therapeutic in which Onivyde<sup>™</sup>, oxaliplatin, leucovorin, and 5-FU are administered in sequence intravenously [85]. The approval of NALIRIFOX came after the efficacy was evaluated in an international multi-centre clinical trial (NAPOLI 3), this trial showed a significant increase in overall survival rates compared to a regime of gemcitabine and nab-paclitaxel [85, 86].

## CONCLUSION AND FUTURE OUTLOOK

Whilst there is a vast array of published works investigating the use of nanotechnology in PC treatment and two formulations that have been approved for clinical use, it remains a devastating disease with a poor prognosis. As such, it is critical that novel therapies are found to offer more effective and efficient treatments. Most of the currently published works focus on liposomes, inorganics, or polymer-based nanoparticles. In overcoming the challenges posed by PC, SLNs offer distinct advantages in their long circulation time, high biodegradability and sustained release potential. There are limited studies investigating SLN formulations for PC but of those published works there are promising results in chemoprevention, targeting PC specific cell lines, and overcoming resistance to gemcitabine and other first-line therapeutics. SLNs see large drawbacks with stability due to polymorphism of the lipid crystal structures. Upon formation, the solid lipid core is in the least stable  $\alpha$ -form, which is then thermodynamically driven either in dispersion or as a solid to rearrange into the metastable  $\beta'$ -form or the most stable  $\beta$ -form. In this process, lipophilic drugs lying within imperfections in the  $\alpha$ -form lipid crystal will be expelled, which may occur during storage before the formulation is administered [49]. In addition to expulsion of the drug, the transition to more stable crystal forms causes an increase in surface area to volume ratio which could encourage interactions between SLN particles driving aggregation or agglomeration [49, 87]. Moving forward in the development of SLNs for the treatment of PC, there are many currently accepted models that have been utilised in studies. One model which is not well utilised in this context is the KPC murine model, this is a promising in vivo model for those investigating chemotherapy resistance and immunotherapeutics for PC

treatment. Unfortunately, given the promising results with SLNs in the treatment of PC, and in many other fields, there has been little clinical success with SLNs. This is due in part to the limited knowledge of safety with administration of SLNs, as although the excipients used are “generally regarded as safe”, it remains true that the acute and chronic effects of intravenous administration of SLNs have not been thoroughly studied. However, the cutting edge of SLN research continues to display hugely positive results. The ability of SLNs to entrap large quantities of drugs or indeed other nanocarriers such as gold nanoparticles offer significant promise in the treatment of PC. They are capable of increasing the anticancer effect of drugs, targeting specific receptors through surface functionalisation, or harnessing the photothermal or sonodynamic abilities of nanocarriers entrapped within them for applications in combination therapies or theranostics.

## DATA AVAILABILITY

No datasets were generated or analysed during the current study.

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## AUTHOR CONTRIBUTIONS

MD and LD contributed to reviewing the literature and preparing the draft manuscript. CH conceptualised and supervised the work and approved draft manuscripts. All authors contributed to and agreed upon the final manuscript.

## COMPETING INTERESTS

CH is an Associate Editor for this journal.

## ADDITIONAL INFORMATION

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