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Review on Targeted Drug Delivery in Pancreatic Cancer

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Targeted delivery systems are the advanced systems where the active pharmaceutical ingredient is delivered accurately to the specific site for the necessary pharmacological action and better therapeutic Index. The main motto of these transport systems is to increase the drug activity at specific target sites with a low amount of drug as compared to high doses of conventional dosage forms. This helps to reduce the side effects of medication, as the drug acts directly at the specific tissues or cells and shows its intended action at the given concentration without getting dissipated in the other areas of the body or the surrounding environment. The evolution of these new approaches plays a vital role in the treatment of chronic diseases like diabetes, tumors, and cancer, etc. This context mainly talks about the delivery agents for the treatment of pancreatic cancer, delivery agents, and the recent advancements made in this area.

Keywords: Target delivery systems; liposomes; nanoparticles; carbon nanotubes; dendrimers; layered double hydroxides; micelles; SMART DDS; etc.

1. INTRODUCTION

Cancer, a typical disease that involves rapid multiplication of cell growth at the tumor site and has a chance to spread to other parts of the body if early effective chemotherapy is not started. Now a day this has become a common disease all over the world and reports say that most cases were found in developed countries. The probable symptoms of the disease include loss of

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body weight, continuous cough, blood loss, defecation problems, and symptoms vary from person to person depending on the type of cancer. The reason for the cause of this typical disease is due to several factors such as consumption of tobacco, excessive body weight above the BMR level, Irregular food habits with more junk foods, no physical exercises, excessive consumption of alcohol, Environmental Pollution, and other infections caused by micro-organisms. Among all the above several factors, cancer occurring due to excessive alcohol consumption occupies the first position in many countries [1,2].

Pancreatic cancer is having common symptoms, like impaired glucose metabolism resulting in higher blood glucose levels, excessive loss of body weight, back pain, yellow skin, etc; that are not generally observed during the early stage but only at the advanced stage of this cancer which makes it critical for treatment. Different types of pancreatic cancers have been identified in which pancreatic adenocarcinoma takes a major position. A lot of research work is being carried out on this cancer chemotherapy especially focussing on target delivery systems for the effective delivery to the tumour site because the conventional delivery system faces the biggest challenge of involving normal cells. For this approach, few targets have been identified, like Growth Factor Receptor, Urokinase plasminogen activator receptor, Transferrin, Stem cell markers, etc for effective targeting of any given drug [1-4].

2. TARGETED DELIVERY SYSTEMS

Targeted delivery systems are of choice because of the major advantage that it eliminates the major challenge of accumulation of potent drugs at other nontarget tissues which further reduces the toxicity. These delivery systems used for cancer chemotherapy are non-toxic and biocompatible to the human body environment. At present Targeted delivery systems like Liposomes, Nanoparticles, Carbon nanotubes, Dendrimers, Micelles, SMART DDS, etc. play an organized role in delivering the medications to the site of action on time. Among the above-mentioned delivery systems Liposomes, Nanoparticles, Carbon nanotubes are widely used for Pancreatic Chemotherapy. 2,3 These delivery systems control the rate of drug movement into the target site with high safety and efficacy for prolonged periods along with the other benefits illustrated in Fig. 1.

Fig. 1. Image showing advantages of targeted drug delivery system

3. LIPOSOMES

The liposome is a tiny, concentric sphere in which an aqueous layer is surrounded by a phospholipid bilayer. Normally the size of liposomes ranges from a few nanometres to micrometers. They are amphiphilic in nature with an external hydrophobic phospholipid layer and an internal aqueous compartment. The amphiphilicity nature enhances the solubility of poorly water-soluble drugs thereby acting as carrier systems for many active pharmaceutical ingredients. These are self-assembled lipid bilayers made up of ether phospholipids, cholesterol, or any other synthetic amphiphilic component.

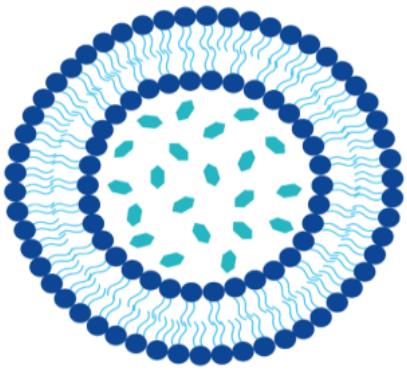

Fig. 2. Structure of a liposome

The variable composition of liposomes made them suitable carriers for anticancer drugs. The external hydrophobic layer of phospholipids acts as a binding agent to the tumor cells or tissues and rapidly transports the active ingredient [4].

Table 1. Examples of some liposomal formulations

Name of the Drug	Liposomal Formulation
Gemcitabine	Combination with PEG-treated liposomes for pancreatic cancer treatment has shown a rapid reduction in the cancer cells in comparison to gemcitabine alone [3].
Doxorubicin	Combination with Hydrogenated soya phosphatidylcholine (HSPC), DSPE, and Cholesterol in different ratios for the colorectal cancer treatment (under in-vitro trials) [4]. Combination with Cholesterol, Distearoyl phosphatidylcholine (DSPC), DSPE, and DSPE-PEG2000 for colorectal cancer treatment (under in-vitro and in-vivo trials) [5]. Association with Hydrogenated soya phosphatidylcholine (HSPC), Cholesterol, DSPE-PEG2000at different molar ratios for colorectal cancer treatment (under in-vitro trials) [4]. Combination with 1-Palmitoyl-2-oleoylphosphatidylcholine and Cholesterol at the different ratios for Metastatic Cancer treatment (under clinical trials) [2].
Daunorubicin	Formulation of Daunorubicin in combination with DSPC and Cholesterol at the different ratios for the treatment of Kaposi's sarcoma [6].
All-trans retinoic acid	Combination with DSPC, Cholesterol, DSPE -Methoxy PEG2000 and at the different ratio for the treatment of Human Thyroid carcinoma (under in-vitro trials) [2].
Mitoxanthrone	Combination with Hydrogenated soya phosphatidylcholine (HSPC), DSPE-PEG2000, Cholesterol, Anacardic acid at the different ratios for the treatment of Melanoma cancer (under *in-vitro* trials) [7].
Paclitaxol	Combination with Egg phosphatidylcholine, Cholesterol, TPGS1000-TPP at the different ratios for Lung cancer treatment (under in-vivo and in-vitro trials) [2]. Combination with Egg phosphatidylcholine, Cholesterol, TPGS1000-TPP at the different ratios for Lung cancer treatment (under in-vivo and *in-vitro* trials) [2]
Irinotecan	Formulation of Irinotecan for pancreatic ductal adenocarcinoma treatment [8].
Cytarabin and Daunorubicin	Formulation with Distearoyl phosphatidylcholine, Distearoyl phosphatidylglycerol, and Cholesterol for the treatment of tumors [9].
Cisplatin	Combination with 6-amino nicotinamide for ovarian cancer treatment [10].

4. NANOPARTICLES

Nanoparticles are carrier systems developed for target-specific action and prolonged release of medicament. In general, optimum-sized nanocarriers are used in the formulation design, as smaller surface area of these nanocarriers makes them better delivery systems for interacting with the target tissue. The target-specific action of the nanocarriers helps in reducing the dose of the drug which in turn reduces the cost of the formulation [11]. These nanoparticles may be comprised of single or more than one polymer having a size range of 10-1000 nm known as polymeric nanoparticles or it may be a simple lipid nanoparticle, which is nothing but an advanced nanoparticle which is comprised of a central core of solid lipid phase in place of liquid lipid component. Another well-known of nanoparticles is metallic nanoparticles like gold nanoparticles, iron nanoparticles, zinc nanoparticles etc. [4].

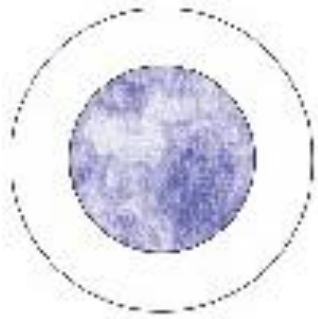

Fig. 3. Structure of nanoparticles

Table 2. Examples of nanoparticle formulations

Name of the Drug/System	Nanoparticle Formulation
Irinotecan	Formulation of polymer-drug conjugates by combining with polymers like methoxy Poly(ethylene glycol) and methoxy (polyethylene glycol)-Polylactide (under preclinical studies) [12].
Gemcitabine	Formulation of polymer-drug conjugate (monomer) by combining with polymers like Methacrylate (under preclinical studies) [13]. Formulation of the polymer-drug conjugate by combining with polymers like PEG-b-poly(2-methyl-2-carboxyl-propylene carbonate)-graft-dodecanol (under preclinical studies) [14]. Formulation of polymer-drug conjugates by combining with conjugated polymers of Epidermal Growth Factor Receptor peptide on the gelatin surface via PEG linkage (under preclinical studies) [15].
Nanoparticulate System	Formulation of CDF with block copolymer Styrene+maleic acid which enhances systemic half-life (under preclinical studies) [16].
Oxaliplatin	Formulation with block co-polymerPEG-b-poly (glutamic acid) (under preclinical studies) [17].
Gemcitabine, Doxorubicin and its hydrochloride salt, 5-Fluorouracil, Paclitaxol	Formulation with Mixed micelles like PVP-b-PCL and PVP-b-P(DX-co-MeDX) with increase efficiency in pancreatic chemotherapy (under preclinical studies) [18].
Bisnaphthalimido propyldiamino octane (BNIPDAOct)	Formulation with grafted polymer Poly- allylamine – g-cholesterol (Under studies) [19].
Candesartan	Formulation with the Grafted polymer of Chitosan with Poly (ethyleneimine) (preclinical studies) [20].
Sqalenoyl gemcitabine and Paclitaxel	Combined Formulation with Thermo-responsive polymer Poly (diEGMA-co-OEGMA300)-b-PEHMA (under preclinical studies) [21].
Curcumin	Formulation with PH-responsive polymer Poly (styrene-alt-maleic anhydrate) for enhanced cellular uptake (under Preclinical studies). [22].
Paclitaxel	Formulation of Paclitaxel as Ultrasound-responsive nano-emulsion with PEG-PLLA (under preclinical studies) [23]. Formulation with protein Albumin as Abraxane mainly for Breast cancer (Approved by FDA in 2013) [24].
	Combined Formulation of Paclitaxel and Gemcitabine with protein Albumin as Abraxane / Gemcitabine (Under phase III clinical trials). [25].
Doxorubicin	Formulation of Doxorubicin with dextran (a branched poly-α-d-glucoside) coated with iron oxide as inorganic nanoparticles (under preclinical studies) [26].
Gemcitabine	Formulation with Iron oxide and antiCD47 antibodies as inorganic nanoparticle formulation for pancreatic cancer chemotherapy (under preclinical studies) [27].
BNIPDSpm (Bisnaphtalimide spermine)	Formulation of BNIPDSpm (Bisnaphtalimide spermine) with Iron oxide and gold as inorganic nanoparticles (under preclinical studies) [28].
Gemcitabine	Formulation with Iron oxide and gold as inorganic nanoparticle formulation for pancreatic cancer chemotherapy (under preclinical studies) [29].
Irinotecan	Formulation of a nanosystem by combining with Folfirinox for pancreatic cancer chemotherapy (FDA approved 2015) [30].
Nanoparticle systems	Formulation of Modified nanoparticles, sequentially triggered nanoparticles, Fucose bound Nanoparticles for pancreatic cancer Treatment (preclinical studies) [31,32,33].

Name of the Drug/System	Nanoparticle Formulation
Iron-oxide nanoparticles	Formulation of Iron-oxide nanoparticles using phospholipids and PEG-coated paramagnetic iron oxide for solid cancer treatment [34].
Doxorubicin	A formulation as Mesoporous silica nanoparticles system by coating with silica and converting nanoparticles into Mesoporous by Azobenzene for Near IR-laser triggered anticancer drug transport [35]. Formulation of as Mesoporous silica nanoparticles system as controlled drug transport in cancer chemotherapy by controlling PH [35].
Camptothecin	Formulation of Camptothecin as Polymeric Nanoparticles system (CRLX101) by conjugating covalently with Cyclodextrin and Polyethylene glycol for Lung and Ovarian cancer treatment [36].
Docetaxel	A formulation as Polymeric Nanoparticles system (BIND-014) using PEG and PLGA for cancer chemotherapy [37].
Paclitaxel	Formulation of Paclitaxel as Protein Nanoparticles system using Human serum albumin for Metastatic Breast cancer [38].
	Formulating as Protein Nanoparticles system using Bovine serum albumin conjugated with Folate for Prostate cancer treatment [39].

5. CARBON NANOTUBES

Carbon Nanotubes is among the class of advanced nanocarrier systems used for delivering active Pharmaceutical Ingredients [40]. These are versatile tube-like structures with large surface areas, altering the functional groups attached to the surface, which in turn makes them a better carrier for anti-cancer drugs [41]. The safety and efficacy make them better delivery systems for many medicines to the target sites, comprising of graphene as a hydrophobic moiety [42]. These structures are typically used in the photo-thermal treatment of cancer because of their capability to absorb heat energy.

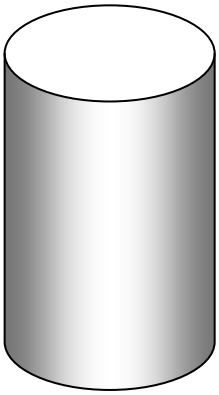

Fig. 4. Structure of carbon nanotube

Table 3. Examples of carbon nanotube based delivery systems

Name of the Drug	Carbon Nanotube Formulation
Doxorubicin	Water-soluble single-wall carbon nanotubes (SWCN) with anti-P-glycoprotein for encountering leukaemia cells [43]. Multi-walled carbon nanotubes for cancer treatment [44].
Paclitaxel	SWCN covalently bonded with Chitosan; used in the treatment of lung cancer [45]. SWCN is linked using Epidermal Growth Factor (EGF) for targeting cancer cells [46].
Arg/Gly/Asp (RGD) peptides	SWCN for treating cancer cells [47].
Gadolinium	MWCN with better efficacy than the other drug formulations [48].
Gemcitabine	Magnetic multi-walled nanotubes for treatment of Lymph node metastasis [49].
Cisplatin	SWCN complexed with folic acid derivative for Cancer treatment [50].

6. DENDRIMERS

Dendrimers are three-dimensional, multibranched, synthetic molecules having a size lesser than 15 nm. The recent development made dendrimers a better system of drug delivery for cancer chemotherapy. These are smart systems that deliver more than one API to the cancer cells selectively, maintaining good plasma concentration for a suitable period under cytotoxic conditions. The first dendrimer was designed using poly-amidoamine in the year 1980, providing the three distinct sites for attachment namely core, branching zone, and the branch edges. The dendrimers can carry the drugs either via encapsulation or by conjugation. These nano-formulations can provide drug targeting via both passive and active targeting [51-54].

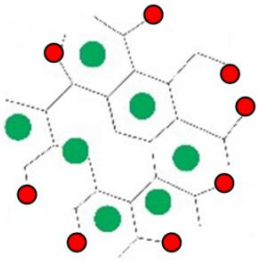

Fig. 5. Structure of dendrimer

7. MICELLES

Micelles are polymeric structures having a size ranging from 10-100 nm [55]. These Polymeric structures are amphiphilic in nature with an inner hydrophobic core and outer hydrophilic core. They are capable of enhancing the solubility of poorly soluble molecules that in turn increase the blood plasma concentration at the specific site. Apart from increasing the solubility, these polymeric micelles liberate the drug in a controlled state at the targeted site which mainly contributes to effective cancer chemotherapy [56]. These micellar products involve different types of mechanisms for binding drug molecules namely, conjugation, complexation and entrapment [57]

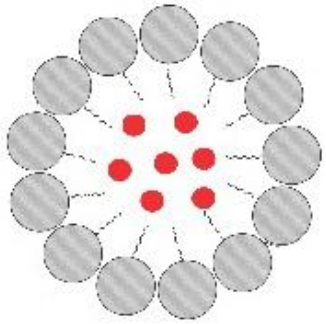

Fig. 6. Structure of micelle

8. SMART DDS

These most advanced nanotechnological drug delivery systems are also known as stimulus-responsive drug delivery systems or intelligent drug delivery systems. These systems are the most advantageous drug delivery systems due to their capability to provide controlled release at the target site, lesser dose frequency, maintaining the steady concentration of the drug at the site, lesser toxicity, and better therapeutic efficacy [66]. The drug targeting and release from these systems depend on different types of stimuli like the climate at the site of action, pH, availability of reactive oxygen species (ROS), Enzymes, or any other endogenous or exogenous cellular conditions like ultrasonic waves [4].

Table 4. Examples of polymeric micelles for cancer treatment

Name of the Drug	Micellar Formulation
Doxorubicin	Conjugating via amide bonding with Poly (aspartic acid) chain of PEO-b-poly-aspartic acid to form polymeric micelles [57]
Paclitaxel	Polymeric micelles by solubilizing paclitaxel in amphipathic co-polymer containing PEG and Poly-vinylbenzyloxy-N,N-Diethylnicotinamide [58].
Taxol	Polymeric micelles with PEG and Polylactide [59]. Polymeric micelles with PEG and Poly-aspartate (under Phase III clinical trials) [60]. Polymeric micelles with PEG-b-Polycaprolactone [61].
Doxorubicin	Polymeric micelles with Dextran and Poly (DL-Lactide-co-glicolide) [62]. Polymeric micelles of PEG, n-butyl methacrylate and Methacrylic acid [63]. Polymeric micelles of Poly-histidine-co-phenylalanine [64]. Polymeric micelles comprising of m-PEG-PCL-PDMA and m-PEG-PCL-PVBA [65].

9. CONCLUSION

The severity of pancreatic cancer is one of the major reasons for the higher mortality rate in almost every of the globe. A lot of research work has been carried out to date and is in progress to explore the possibilities of designing efficient chemotherapy for pancreatic cancer. Many treatments like radiation therapy, tumor surgery, and conventional chemotherapy are available, still, the percentage of recovery is on the lower side because of the complexity of the disease and limitations of treatment. Now a day the practice of advanced delivery systems has improved a lot due to the need for site-specific drug action without affecting surrounding normal organs or tissues. These approaches have led to the use of lower concentrations and the frequency of drugs due to site-specific action and controlled release of drugs for a prolonged period. Therefore, further research must be performed on these advanced drug delivery systems focusing on their target specificity of action.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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