Review Article

Recent Advances in the Cancer Drug Delivery: Nanocarrier Approach

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ABSTRACT

The present review work tries to explore the present status of the nano carriers in the delivery of anti cancer drugs. The shortcomings associated with the anticancer drugs like poor solubility, multiple resistance and less bioavailability is been investigating using different nano formulations. The recent advance work on nanoparticles for the delivery of anti tumor drugs is focused along with the different patents available. The different technologies available in the present scenario for the delivery of anti-cancers drugs are being highlightened.

Keywords: Cancer, Nanocarriers, Patents, Advances, Techniques.

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INTRODUCTION

Cancer is a menace which needed to be cured at the earliest. The cancer treatment and management can be done though chemotherapy, radiotherapy, surgery and nutraceuticals. The main predicament with chemotherapy is that it has restricted accessibility of drugs to the cancerous tissues which needs high doses. Moreover, the drugs may produce intolerable toxicity and may even develop multiple drug resistance. The conventional dosing also presents non-specific targeting of the delivered drug. There are the numerous types of the cancer which are being prevailing in the present scenario. Each type of cancer requires specific drug scheduling and delivery methodology. The advancement in nanotechnology has provided the researchers and physicians with the benefits of delivering the drugs to targeted tissues and that too with better retention time and enhanced bioavailability. The nano drug delivery system improves the pharmacokinetics of the loaded poorly soluble drug which is hydrophobic in nature and made it compatible for drug targeting. There are the numerous nanoparticles, including liposomes, niosomes, cubosomes, polyniosomes, polymeric nanoparticles, dendrimers, magnetic and other inorganic nanoparticles which are available as per the requirement of the drug and delivery route.

Drugs For Treatment of Cancer

There are the large numbers of drugs that can be used for the treatment of cancer. This huge number too presents the problem in selecting the appropriate dose and delivery route. Additionally, these drugs are accompanied with large number of formulation problems which needed to be resolved before the commercialization of the drug candidate.

Table 1: Commercially Available Drugs for The Treatment of Cancer [8]

Alphabetical Order	Anti-Cancer Drugs
A.	ABVD, AC, Abemaciclib (Verzenois), Abiraterone (Zytiga), Abraxane, Abstral, Actinomycin D, Actiq, Adriamycin, Afatinib (Giotrif), Afinitor, Aflibercept (Zaltrap), Aldara, Aldesleukin (IL-2, Proleukin or interleukin 2), Alectinib (Alecensa), Alemtuzumab (Campath, MabCampath), Alkeran, Amsacrine (Amsidine, m-AMSA), Amsidine, Anastrozole (Arimidex), Ara C, Aredia, Arimidex, Aromasin, Arsenic trioxide (Trisenox, ATO), Asparaginase (Crisantaspase, Erwinase), Atezolizumab (Tecentriq), Avelumab (Bavencio), Axitinib (Inlyta), Azacitidine (Vidaza)
B.	BEACOPP, BEAM, Bendamustine (Levact), Bevacizumab (Avastin), Bexarotene (Targretin), Bicalutamide (Casodex), Bleomycin, Bleomycin, etoposide and platinum (BEP), Blinatumomab (Blincyto), Bortezomib (Velcade), Bosulif, Bosutinib (Bosulif), Brentuximab (Adcetris), Brufen, Buserelin (Suprefact), Busilvex, Busulfan (Myleran, Busilvex)

C.	CAPE-OX, CAPOX, CAV, CCNU, CHOP, CMF, CMV, CVP, Cabazitaxel (Jevtana), Cabozantinib (Cometriq, Cabometyx), Caelyx, Calpol, Campto, Capecitabine (Xeloda), Caprelsa, CarboTaxol, Carboplatin, Carboplatin and etoposide, Carboplatin and paclitaxel, Carmustine (BCNU), Casodex, Ceritinib (Zykadia), Cerubidin, Cetuximab (Erbitux), ChlVPP, Chlorambucil (Leukeran), Cisplatin, Cisplatin and capecitabine (CX), Cisplatin and fluorouracil (5FU), Cisplatin, etoposide and ifosfamide (VIP), Cisplatin, fluorouracil (5FU) and trastuzumab, Cladribine (Leustat, LITAK), Clasteon, Clofarabine (Evoltra), Co-codamol (Kapake, Solpadol, Tylex), Cometriq, Cosmegen, Crisantaspase, Crizotinib (Xalkori), Cyclophosphamide, Cyclophosphamide, thalidomide and dexamethasone (CTD), Cyprostat, Cyproterone acetate (Cyprostat), Cytarabine (Ara C, cytosine arabinoside), Cytarabine into spinal fluid, Cytosine arabinoside
D.	DHAP, DTIC, Dabrafenib (Tafinlar), Dabrafenib (Tafinlar) and Trametinib (Mekinist), Dacarbazine (DTIC), Dacogen, Dactinomycin (actinomycin D, Cosmegen Lyovac), Dasatinib (Sprycel), Daunorubicin, Decapeptyl SR, Decitabine (Dacogen), Degarelix (Firmagon), Denosumab (Prolia, Xgeva), Depocyte, Dexamethasone, Diamorphine, Disodium pamidronate, Disprol, Docetaxel (Taxotere), Docetaxel, cisplatin and fluorouracil (TPF), Doxifos, Doxil, Doxorubicin, Doxorubicin and ifosfamide (Doxifos), Drogenil, Durogesic, Durvalumab (Imfinzi)
E.	EC, ECF, EOF, EOX, EP, ESHAP, Effentora, Efudix, Eldisine, Eloxatin, Encorafenib (Braftovi) and Binimetinib (Mektovi), Enzalutamide (Xtandi), Epirubicin (Pharmorubicin), Epirubicin, carboplatin and capecitabine (ECarboX), Epirubicin, cisplatin and capecitabine (ECX), Erbitux, Eribulin (Halaven), Erlotinib (Tarceva), Erwinase, Estracyt, Etopophos, Etoposide (Etopophos, Vepesid), Everolimus, Evoltra, Exemestane (Aromasin)
F.	FEC, FMD, FOLFIRINOX, Faslodex, Femara, Fentanyl, Firmagon, Fludara, Fludarabine (Fludara), Fludarabine, cyclophosphamide and rituximab (FCR), Fluorouracil (5FU), Fluorouracil (5FU) and mitomycin C, Fluorouracil, epirubicin, cyclophosphamide and docetaxel (FEC-T), Flutamide, Folinic acid, fluorouracil and irinotecan (FOLFIRI), Folinic acid, fluorouracil and oxaliplatin (FOLFOX), Fulvestrant (Faslodex)
G.	G-CSF, Gefitinib (Iressa), GemCarbo (gemcitabine and carboplatin), GemTaxol, Gemcitabine (Gemzar), Gemcitabine and capecitabine (GemCap), Gemcitabine and cisplatin (GC), Gemcitabine and paclitaxel (GemTaxol), Gemzar, Giotrif, Gliadel (carmustine wafers), Glivec, Gonapeptyl Depot, Goserelin (Zoladex) for breast cancer, Goserelin (Zoladex) for prostate cancer, Granulocyte colony stimulating factor (G-CSF)
H.	Halaven, Herceptin, Hycamtin, Hydrea, Hydroxycarbamide (Hydrea), Hydroxyurea
I.	I-DEX, ICE, IL-2, IPE, Ibandronic acid (Bondronat), Ibrutinib (Imbruvica), Ibuprofen (Brufen, Nurofen), Iclusig, Idarubicin (Zavedos), Idarubicin and dexamethasone, Idelalisib (Zydelig), Ifosfamide (Mitoxana), Imatinib (Glivec), Imiquimod cream (Aldara), Inotuzumab ozogamicin (Besponsa), Instanyl, Interferon alfa (IntronA, Roferon-A), Interleukin, Intron A, Ipilimumab (Yervoy), Ipilimumab and nivolumab, Iressa, Irinotecan (Campto), Irinotecan and capecitabine (XELIRI), Irinotecan de Gramont, Irinotecan modified de Gramont
J.	Javlor, Jevtana
K.	Kadcyla, Kapake, Keytruda
L.	Lanreotide (Somatuline), Lanvis, Lapatinib (Tyverb), Lenalidomide (Revlimid), Lenvatinib (Lenvima, Kisplyx), Letrozole (Femara), Leukeran, Leuprorelin (Prostap, Lutrate), Leustat, Levact, Liposomal doxorubicin, Litak, Lomustine (CCNU), Lynparza, Lysodren
M.	MIC, MMM, MST Continus, MVAC, MVP, MabCampath, Mabthera, Maxtrex, Medroxyprogesterone acetate (Provera), Megace, Megestrol acetate (Megace), Melphalan (Alkeran),, Melphalan, prednisolone and thalidomide (MPT), Mepact, Mercaptopurine (Xaluprine), Methotrexate, Methyl prednisolone, Mifamurtide (Mepact), Mitomycin C, Mitotane, Mitoxana, Mitoxantrone (Mitozantrone), Modified de Gramont, Morphgesic SR, Morphine, Myleran, Myocet, m-AMSA
N.	Nab-paclitaxel, Nab-paclitaxel (Abraxane), Navelbine, Nelarabine (Atriance), Neratinib (Nerlynx), Nexavar, Nilotinib (Tasigna), Nintedanib (Vargatef), Nipent, Niraparib (Zejula), Nivolumab (Opdivo), Novgos, Nurofen
O.	Obinutuzumab (Gazyvaro), Octreotide (Sandostatin), Olaparib (Lynparza), Oncovin, Onkotrone, Opdivo, Oramorph, OxCap, Oxaliplatin (Eloxatin), Oxaliplatin and capecitabine (XELOX)
P.	PC (paclitaxel and carboplatin, CarboTaxol), PCV, PE, PMitCEBO, POMB/ACE, Paclitaxel (Taxol), Paclitaxel and carboplatin, Palbociclib (Ibrance), Pamidronate, Panadol, Panitumumab (Vectibix), Paracetamol, Pazopanib (Votrient), Pembrolizumab (Keytruda), Pemetrexed (Alimta), Pemetrexed and carboplatin, Pemetrexed and cisplatin, Pentostatin (Nipent), Perjeta, Pertuzumab (Perjeta), Pixantrone (Pixuvri), Pixuvri, Pomalidomide

	and dexamethasone, Ponatinib (Iclusig), Potactasol, Prednisolone, Procarbazine, Proleukin, Prolia, Prostap, Provera, Purinethol
Q.	----------
R.	R-CHOP, R-CVP, R-DHAP, R-ESHAP, R-GCVP, RICE, Raloxifene, Raltitrexed (Tomudex), Regorafenib (Stivarga), Revlimid, Ribociclib (Kisqali), Rituximab (Mabthera, Rixathon, Truxima), Rucaparib (Rubraca), Ruxolitinib
S.	Sevredol, Sodium clodronate (Bonefos, Clasteon, Loron), Solpadol, Sorafenib (Nexavar), Steroids (dexamethasone, prednisolone, methylprednisolone and hydrocortisone), Streptozocin (Zanosar), Sunitinib (Sutent), Sutent
T.	TAC, TIP, Tafinlar, Talimogene laherparepvec (T-VEC), Tamoxifen, Tarceva, Targretin, Tasigna, Taxol, Taxotere, Taxotere and cyclophosphamide (TC), Temodal, Temozolomide (Temodal), Temsirolimus (Torisel), Tepadina, Thalidomide, Thiotepa (Tepadina), Tioguanine, Tomudex, Topotecan (Hycamtin, Potactasol), Torisel, Trabectedin (Yondelis), Trastuzumab, Trastuzumab and pertuzumab, Trastuzumab emtansine (Kadcyla), Treosulfan, Tretinoin (Vesanoid, ATRA), Trifluridine and tipiracil (Lonsurf), Triptorelin (Decapeptyl SR, Gonapeptyl Depot), Trisenox, Tylex, Tyverb
U.	----------
V.	VIDE, Vandetanib (Caprelsa), Vargatef, VeIP, Vectibix, Velbe, Velcade, Vemurafenib (Zelboraf), Vepesid, Vesanoid, Vidaza, Vinblastine (Velbe), Vincristine, Vincristine, actinomycin D (dactinomycin) and cyclophosphamide (VAC), Vincristine, actinomycin D and ifosfamide (VAI), Vincristine, doxorubicin and dexamethasone (VAD), Vindesine (Eldisine), Vinorelbine (Navelbine), Votrient
W.	----------
X.	XELOX, Xalkori, Xeloda, Xgeva, Xtandi
Y.	Yervoy, Yondelis
Z.	Z-DEX, Zaltrap, Zanosar, Zavedos, Zelboraf, Zevalin, Zoladex (breast cancer), Zoladex (prostate cancer), Zoledronic acid (Zometa), Zometa, Zomorph, Zydelig, Zytiga

Presently Available Drug Delivery Technologies For Cancer [9]

In the present scenario to overcome the associated problems with the cancer treatment, the numbers of technologies have been utilized. Depending upon the drug candidates the different approaches have been specified though research and commercially employed. By using these technologies the commercial applicability and retention time of the drug candidates can increased and at the same time pharmacokinetics of the drugs can modified as desired.

1. **Lipid Based Systems**
   - ✓ Lipid Based Emulsion
   - ✓ Conventional Liposomes
   - ✓ Long circulating Liposomes
   - ✓ pH-sensitive Liposomes
   - ✓ Immunoliposomes
   - ✓ Solid Lipid Nanoparticle
2. **Specific Strategies**
   - ✓ Antibody based therapy
   - ✓ Carbohydrate based therapy
   - ✓ Delivery of proteins and peptides
   - ✓ RGD based formulations
   - ✓ Albumin based drug carrier
   - ✓ Anti-angiogenesis therapy
   - ✓ Fatty acid as a targeting vector
   - ✓ Tumour active prodrug therapy
   - ✓ Heat activated targeted drug delivery
   - ✓ PEG technologies
   - ✓ Biodegradable polymeric devices
   - ✓ Angiolytic agents
3. **Polymeric Systems**
   - ✓ Nanoparticles
   - ✓ Microspheres
   - ✓ Stealth Nanoparticles
   - ✓ Drug-polymer conjugate
   - ✓ Polymer-DNA complexes
   - ✓ Polymer-protein conjugate
   - ✓ Dendrimers- Dendrons, stealth dendrimer, Diblock & Triblock dendritic copolymers
   - ✓ Micelles-Immuno micelles, thermo-responsive micelles, pH responsive micelles

4. Biological Therapies

- ✓ Genetically Modified Bacteria
- ✓ RNA Interference
- ✓ Antisense Therapy
- ✓ Gene Therapy

Patents in Cancer Therapies [10-24]

The advantages of the patents have boosted many companies and researchers to make new advancements in the field of cancer research therapy. In the lieu of that many companies have filed the patents in the field of cancer research and advancements in the past few years. The patents are further being assigned and are being rented by the patenting companies to earn profits too.

Table 2: Patents Filed for Treatment of Cancer

S. No.	Title of Patent	Patent ID	Inventor	Status	Current Assignee
1.	Cancer treatment method	US4622952A United States (1986)	Robert T. Gordon	Expired	Gordon David Skokie Illinois
2.	Cure for cancer (salicylic acid)	US20040248858A1 United States (2004)	Kaumil Parghi	Abandoned	------
3.	Apparatus for treatment of cancer with photodiode	US4822335A United States (1989)	Yoshio Kawai Kazue Endo Makoto Yoshimura	Expired	Kureha Corp
4.	Method for initiation of tumor cell death by chlorine-e6, ascorbic acid and hf- and shf-energy	RU2739252C2 Russia (2020)	Tsuglenok Nikolay Vasilievich	Application granted	Tsuglenok Nikolay Vasilievich
5.	Method for initiating the death of tumor cells with sodium salts of chlorine-e6, chlorine-p6 and purpurin-5 and hf and microwave radiation with wave radiation energy	RU2724326C2 Russia (2020)	Tsuglenok Nikolay Vasilievich	Application granted	Tsuglenok Nikolay Vasilievich
6.	Method for initiation of tumor cell death by demethylglucamic acid chlorine-e6 and hf and shf wave energy radiation	RU2723882C2 Russia (2020)	Tsuglenok Nikolay Vasilievich	Application granted	Tsuglenok Nikolay Vasilievich
7.	Method of initiating the death of tumor cells with sodium chloride chlorine-e6, succinic acid and hf and shf wave radiation energy	RU2723884C2 Russia (2020)	Tsuglenok Nikolay Vasilievich	Application granted	Tsuglenok Nikolay Vasilievich
8.	Method for initiation of tumor cell death by 5-aminolevuleic acid and hf and uhf radiation wave energy	RU2723680C2 Russia (2020)	Tsuglenok Nikolay Vasilievich	Application granted	Tsuglenok Nikolay Vasilievich
9.	Treating cancer using electromagnetic fields in combination with photodynamic therapy	US8465533B2 United States (2013)	Yoram Palti	Active	Novocure GmbH Bpcr LP

10.	Treating cancer using electromagnetic fields in combination with other treatment regimens	US20070239213A1 United States (2007)	Yoram Palti	Active	Novocure GmbH Bpcr LP
11.	Treatment of cancer with interferon and radiotherapy	US4846782A United States (1989)	Eric Bonnem	Expired	Merck Sharp and Dohme Corp
12.	Method of treating malignant tumors	SU522688A1 USSR - Soviet Union (1977)	A.K. Pankov M.A. Ukolova E.B. Kvakina L.Kh. Harkavi E.I. Brazhnikov R.N. Salads G.R. Solovyova V.A. Eremin	Application granted	----------
13.	Electrochemotherapy	US5468223A United States (1995)	Lluis Mir	Expired	Centre National de la Recherche Scientifique
14.	Apparatus and method for treating a tumor or the like	US20040068296A1 United States (2006)	Yoram Palti	Active	Novocure GmbH Bpcr LP
15.	Breast cancer detection, imaging and screening by electromagnetic millimeter waves	US5807257A United States (1998)	Jack E. Bridges	Expired	Interstitial LLC

Recent Nanoparticles Encapsulated Anticancer Drug Formulations and Advanced Technologies

The review of literature suggested that the numbers of formulations are available in the market with encapsulated drugs for the treatment of malignancies. Even the literature review also suggested that the whole grain products too are very essential for the body and can be used for the treatment of cancer along with the drugs [25-30]. The advancement in the anti-cancer therapy started with development of nano-sciences. The physical properties of most of the drugs used in the treatment of cancer can be altered by using nanotechnological approach.

Fouladi et al., 2017 developed the enzyme- responsive liposomes for the delivery of anticancer drugs. Enzyme-responsive liposomes release their encapsulated drugs upon contact with the enzyme through several destabilization mechanisms[31].

Sapra and Allen 2003 developed the ligand targeted anticancer drugs formulation. The prepared formulation using antibody showed increased therapeutic index of anti cancer drugs[32].

Shim et al., 2011 developed Trilysinoyl oleylamide-based cationic liposomes for systemic co-delivery of siRNA and an anticancer drug. The formulation showed the highest delivery efficiency combined with minimal cytotoxicity[33].

Kim et al., 2008 studied the antitumor efficacy of cisplatin-loaded glycol chitosan nanoparticles in tumor bearing mice. The results indicate that HGC nanoparticles are a promising carrier for the anticancer drug CDDP[34].

Feng et al., 2013 generated the Chitosan/o-carboxymethyl chitosan nanoparticles for efficient and safe oral anticancer drug delivery. Further, the i*n vitro* and *in vivo* evaluation was also carried out to optimize the results[35].

Kim et al., 2016 developed Doxorubicin/gold-loaded core/shell nanoparticles for combination therapy to treat cancer through the enhanced tumor targeting[36].

Xiang et al., 2021 prepared and studied Polyphenol-cisplatin complexation forming core-shell nanoparticles with improved tumor accumulation and dual-responsive drug release for enhanced cancer chemotherapy. PEG-GAx/Pt nanoparticles exhibited improved antitumor efficiency against 4 T1 breast cancer and A549 lung

carcinoma with much-reduced toxicity compared to free CDDP[37].

Kim et al., 2021 developed the combination of cancer-specific prodrug nanoparticle with Bcl-2 inhibitor to overcome acquired drug resistance. Orally administered combination Navitoclax PNPs exhibited more potent therapeutic efficacy in acquired drug resistant models than free DOX plus Navitoclax, whereas PNPs greatly reduced systemic toxic side effects in normal organs[38].

Yao et al., 2020 extensively studied the role of nanotechnology in the treatment of cancer over conventional forms. The mechanisms of cancer drug resistance include over expression of drug efflux transporters, defective apoptotic pathways and hypoxic environment. Nanoparticles targeting these mechanisms can lead to an improvement in the reversal of multidrug resistance[39].

Xu et al., 2021 developed the Zoledronic Acid-Loaded Hybrid Hyaluronic Acid/Polyethylene Glycol/Nano-Hydroxyapatite Nanoparticle for the treatment of osteosarcoma a malignant tumor. Results replicate that the compact and stable structure could achieve high drug loading efficiency, sustained drug release, and great biocompatibility. Further, in vitro and in vivo evaluations revealed the low cytotoxicity and acceptable immune response under low-dose nanoparticles treatment, indicating its potential application[40].

Aguilar et al., 2020 designed green synthesis of nano hydroxyapatite and studied its cytotoxicity effect against fibroblast[41].

Au et al., 2016 synthesized folate-targeted pH-responsive calcium zoledronate nanoscale metal-organic frameworks with an anticancer activity [42].

Dai et al., 2015 synthesized of nanostructure containing methotrexate/hydroxyapatite. Further, the morphology, mechanism of action and bioassay study was carried out to establish its effect[43].

Federman et al., 2012 studied the improved growth inhibition of osteosarcoma by cytotoxic polymerized liposomal nanoparticles targeting the alcam cell surface receptor[44].

Li et al., 2019 synthesized Zoledronic acid containing nanoparticles. This preparation showed minimum premature release with enhanced activity against extra skeletal tumor[45].

Sun et al., 2017 studied the morphological effects of nano-hydroxyapatite as a drug carrier of methotrexate an anti cancer agent. The results concluded that the laminated hybrid exhibits a higher drug loading capacity compared to the other two hybrids. Moreover, the result of in vitro bioassay test confirms that the inhibition efficacy of the three hybrids showed a positive correlation to the drug loading capacity[46].

Yang et al., 2020 reported a novel Rhein- polyethylene glycol (PEG)-nano hydroxyapatite (nHA) conjugate to deliver doxorubicin (DOX) and Phosphorus-32 (^{32}P) simultaneously for enhanced cancer chemo-radiotherapy. DOX/^{32}P@Rhein-PEG-nHA showed the strongest inhibition on the growth of bone metastases of breast cancer[47].

Chun et al., 2021 designed ovarian cancer-targeting drug delivery system based on folic acid-functionalized tea polyphenol. The preparation was evaluated both in vitro and in vivo resulting in enhanced ovarian cancer inhibition efficacy[48].

Fan et al., 2015 studied the enhanced antitumor effects by docetaxel/LL37-loaded thermo-sensitive hydrogel nanoparticles in peritoneal carcinomatosis of colorectal cancer[49].

There are several reported research and review work which suggested the utilization of nano particles like liposomes, niosomes, cubosomes etc in the delivery of anti cancer drugs. Apart from that several herbal formulations and relevant literature is also available which suggested the role of polymeric forms in the delivery of anti malignancy drugs[50-54].

CONCLUSION

Current study evidently signifying the role of nano carriers and nano particles in the delivery for anti cancer drugs. The review of the literature also suggested that the present scenario is focused on the latest techniques of drug delivery. The whole grain products too can be identified as an alternate for the treatment of cancer along with some herbal prospect. In present many magnetic and thermosenstive hydrogels are being formulated for the advanced delivery of anti cancer drugs. The study pointed out the future prospect of nanoformulations and techniques which can be utilized for cancer treatment with better alternate to conventional drug delivery system.

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