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RECENT SUCCESS ON CANCER TREATMENT USING NANOMEDICATION

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Abstract : We hypothesized that Nanosuspension may be praomieing for the delievery of the ineffectively water solvent anti-cancer, multi focused on kinase hindrance MTKI-877 Consequently the points of this work were (i) All the nano-formulations displayed a estimate underneath 200 nm (iii) The display ponder points to assessed the anticancer action of puerain nanosuspension in human colon cancer CHT-29 cell line in Vitro and invivo puerarin cancer Proceeds to be one of the most troublesome worldwide Healthrcare issues In spite of the fact that there is a expansive library Of of drugs that can be utilized in cancer treatment, the issue is specifically murdering the cancer cells whereas decreasing collateral toxiciy of solid cells There are a few organic boundary to compelling sedate delievery in cancer such as renal hepatic or Safe clearence. Nanoparticles stacked with drugs can be outlined to overcome these natural obstruction to move forward viability whereas decreasing dreariness Nanomedicine has ashuerred in a unused period for sedate conveyance by progressing the restorative file of the dynamic pharmaceutical fixings, to begin with Greneration of nanomedicines have gotten broad clinical endorsement over the past two decades from Doxi This survey highlight the natural obstructions to compelling sedate delievery in cancer emphasizing the require for nanoparticles for the Making strides restorative results. These hundles needs to be overcomes through multidisciplinary collaborations over the scholarly world, pharmaceutical Industry and administrative agencies.In arrange to achive the objective of the annihilating cancer .The nanomedicine is utilized to focused on cancer cell and for wrecking the cancers cell and treat the cancer.

[Keywords: Nanoparticles,Oncology,Clinical trials,Therapeutics]

INTRODUCTION

Cancer is currently among one of the leading causes of the death worldwilde with 1,688,780 new casses and 600.920 cancer death projected over the next 20 years the number of new case is projected to increases by about 70%[i] current treatments may include chemotherapy radiation and various surgery but the effects of these procedure may damage not only the tumor tissue but also normal tissues. Cancers cells can also migrate to new sites and form new secondary tumors Two emerging hallmarks of cancer include reprogramming

energy metabolism and evading Immune destruelion. The Cancerious cells are the upregulated glucose transpontere expression and then they reprogramming their metabolic pathway" to aerobic glycolysis is due ti this metabollic switch the generation of the nucleosides and amino acide this may pramote the additional growth to and the proliferation Markers that T-lymphocytes used to recongnize and destroy foregin or abnormal cells are not well expressed by cancer cells thus allowing them to avoid the elimination by the imuine system.on by the Immune System [2] fop the charadenization of Cancerous Cells via these hallmanka of the cancer new methods for the treteatment have been the Investiga Nanomedicine can be define as the nanotechnology or the use of the material between the particle ange 1 and 100nm applied to health and medicine [iii] The Nanomedicine is the best and the en emerging method of treating the cancers.

The current problem face In the treatment of the cancer is low specificity, rapid drug clearence and biodegradation. The nanomedicine overcomes the all problem face during the treatment of cancer. due to the properties of the nanomedicines such as nanoscale size, high surface to-volume ratio favourable drug release profiles and targeting modifications can allow them to better reach target tumor tissue and release drug in a stable and the control manner[iii] the nanocarriers can accmulate in leaky vasculature which is the need the permeation and the retension [iv] when the solubility of the of small molecules drug is poor and restrict the delivery to the tumor all that time the drug is encapsulating in the nanocarriers is facillates the blood stream thus prevent the rapid clearence and improving bioavability of the drug the nanomedicine can be future or further extend to early detection of cancer. as well as combinational thearpy that can started treating tumor earlier and more effectievly the nanocarriers use in the cancer treatment including **lipid base ,polymor base,inorganic,viral and the drug cojucated nanoparticles.**

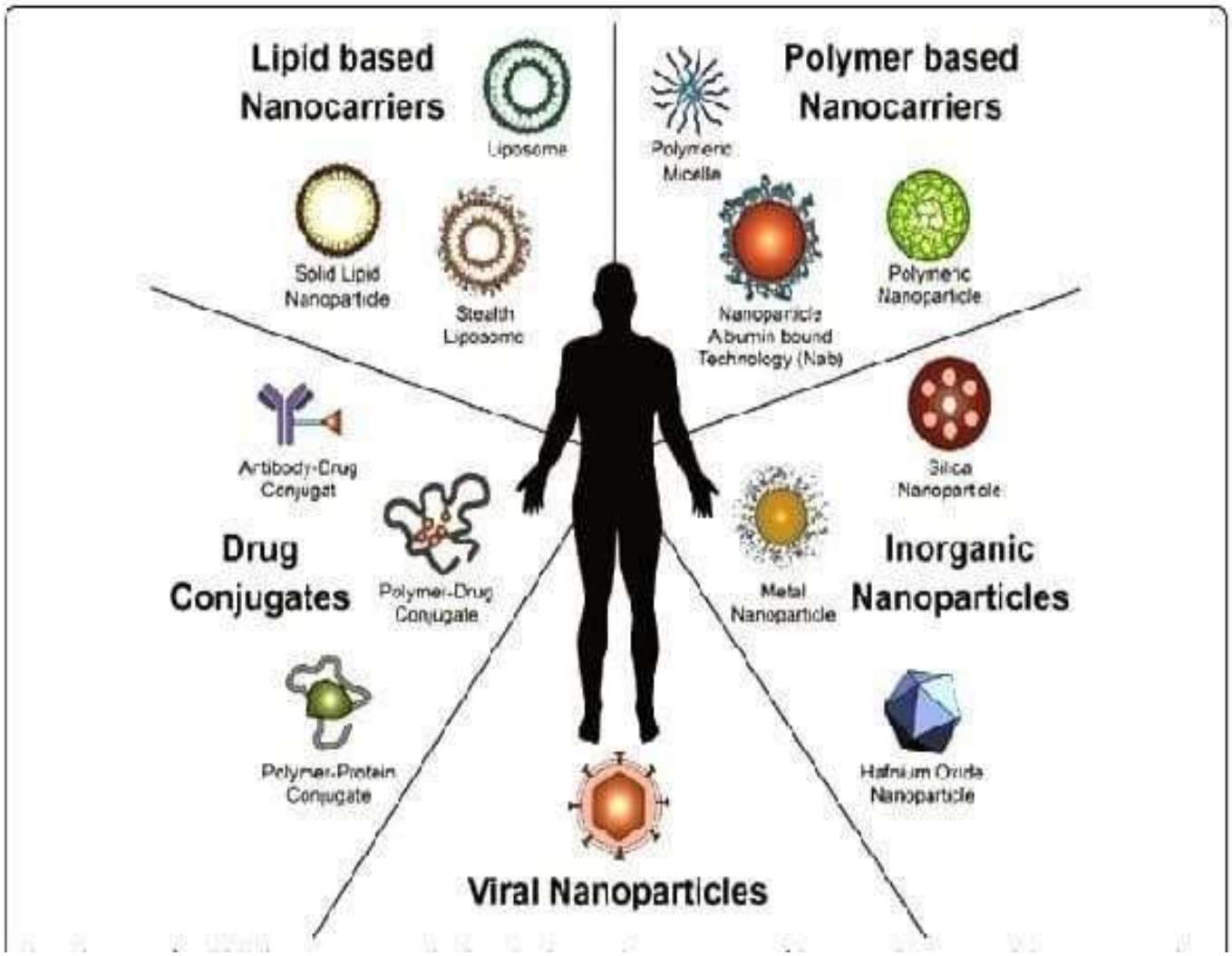

fig 1 : overview of established nanomedicines in the clinic

Table 1 Currently approved nanomedicines in the clinic

Year approved	Name	Type	Active drug	Diameter (references)	Type of cancer
Japan (1994)	Zinostatin stimalamer	Polymer protein conjugate	Styrene maleic anhydride neocarzinostatin (SMANCS)	*	Renal cancer
FDA (1995) EMA (1996)	Doxil/caelyx	liposome (PEGylated)	Doxorubicin	80–90 nm [82]	HIV-associated Kaposi's sarcoma, ovarian cancer, metastatic breast cancer, multiple myeloma
FDA (1996)	DaunoXome	Liposome (non-PEGylated)	Daunorubicin	45 nm [83]	HIV-associated Kaposi's sarcoma
Taiwan (1998)	Lipo-Dox	Liposome	Doxorubicin	180 nm [84]	Kaposi sarcoma, breast and ovarian cancer
FDA (1999)	DepoCyt	Liposome	Cytosine arabinoside (cytarabine)	10–20 μm [84]	Neoplastic meningitis
EMA (2000)	Myocet	Liposome	Doxorubicin	190 nm [84]	Breast cancer
FDA (2005) EMA (2008)	Abraxane	Nanoparticle albumin bound	Paclitaxel	130 nm [27]	Advanced non-small-cell lung cancer, metastatic pancreatic cancer, metastatic breast cancer
FDA (2006)	Oncaspar	PEG protein conjugate	L-Asparaginase	50–200 nm [84]	Leukemia
South Korea (2007)	Genexol-PM	PEG-PLA polymeric micelle	Paclitaxel	20–50 nm [85]	Breast cancer, Lung cancer, Ovarian cancer [126]
EMA (2009)	MEPACT	Liposome (non-PEGylated)	Mifamurtide	*	Osteosarcoma
EMA (2010)	NanoTherm	Iron oxide nanoparticle	-	20 nm [86]	Thermal ablation glioblastoma
FDA (2012)	Marqibo	Liposome (non-PEGylated)	Vincristine	100 nm [87]	Philadelphia chromosome negative acute lymphoblastic leukemia
FDA (2015)	MM-398 (Onivyde)	liposome (PEGylated)	Irinotecan	80–140 nm [88]	Metastatic pancreatic cancer (2nd line)

* Data could not be found

Nonacarrier Properties

Physico-chemical properties The nanomaterials accessible for cancer investigate can be modifed in estimate, shape, and surface characteristics for customization to treat specifc tumors. Estimate is important for travel through the circulation system and ensuing coveyance of the nanocarriers to tumor tissue.Wheareas littler nanoparticles can gather more effortlessly in the defective blood vessels of tumors than those that are bigger, they can more over extravasate into ordinary tissue. On the other hand, bigger nanoparticles cannot extravasate as effectively and hence their disspertion in the circulatory system is exceedingly variable [6]. The optimization of nanoparticle measure may offer assitance improve specifc takeup into tumor tissue. The shape of the nanocarriers may affect liquid dynamics and in this way infuence takeup.Right now, the utilize of sphericalnanocarriers shows up to be more common than that of the nonspherical assortment due to challenges in blend and testing [7].

The surface of the nanocarriers can moreover be modifed with ligands that may draw out blood circulation and advance specifc sorts of endocytosis and cellular take-up into tumor tissue.The charge of nanocarriers may moreover influence their soundness and dispersion in the blood. Positively charged nanoparticles were already appeared to most successfully target tumor vessels, but a switch to a unbiased charge after extravasation permitted faster difusion of the nanoparticles to the tumor tissue.The charge of nanocarriers may too influence their steadiness and distriution in the blood.Positively charged nanoparticles were already appeared to most effectively target tumor vessel,but switch to a unbiased charge after extravasation permitted quickly dissemination of the nanoparticles to the tumor tissue [8].

Solubility, degradation and clearance

Drugs with poor water solubility may be eliminated from the bloodstream before reaching tumor tissue. The use of hydrophilic nanoparticles to encapsulate these drugs may improve their solubility, in turn improving

their bioavailability in vivo and thus allow more effectivedelivery [3]. Coating nanoparticles with polyethylene glycol (PEG), a hydrophilic and nonionic polymer, was shown to increase solubility and stability of nanoparticles [6]. Since PEG is uncharged, it does not disrupt the function of charged molecules, such as DNA [9].

Opsonization of hydrophobic molecules can reduce their ability to reach the tumor tissue and trigger infammation following the secretion of cytokines from the phagocytic cells [10,11]. pegylated nanoparticles mask their hydrophobicity and therefore can prolong theircirculation in the blood to allow adequate time to reach tumor tissue [9]. This reduction in clearance not only increases the half-life of the nanoparticle but also improves its bioavailability [9, 10].

Targeting

Nanocarriers may be modifed to utilize passive and active targeting mechanisms to reach tumor tissue (Fig. 2). Te enhanced permeability and retention (EPR) effect allows nanoparticles to passively accumulate in the leaky blood vasculature exhibited by tumors without any surface modifcations[3,5,6].

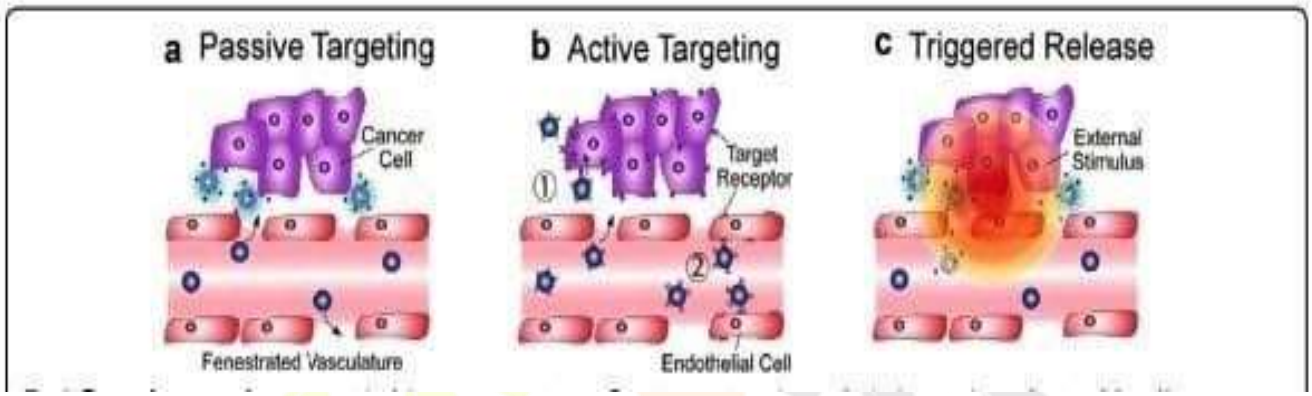

Fig 2: Types of Targeting for Nanoparticles delivery to Tumor Tissue

Combination therapy and theranostics

The ability of nanomedicines to carry multiple therapeutic agents may increase their ability improve treatment. Co-loaded nanoparticles with bortezomib and doxorubicin were found to exhibit an antitumor synergistic effect on ovarian cancer [21]. Loading multiple siRNAs alone or together with other drugs may increase sensitivity of the tumor to the treatment [22,23].

Successful delivery of chemotherapeutic drugs is often dependent on the properties of the biological barriers involved (Fig. 3) in cancer. Next, we will discuss multiple biological barriers in cancer.Next,we will discuss multiple biological barriers to effective drug delivery

Barriers

Biological Barriers

Biological barriers to effective drug delivery Reticulor endothelial system The reticuloendothelial system (RES), also known as the mononuclear phagocyte system (MPS), consists of both cellular and noncellular components. Phagocytic cells may bind nanoparticles and cause a release of cytokines, increasing nanoparticle clearance from the bloodstream and local infammation of tissue [11]. Proteins, lipids, and other macromolecules may also bind to the surface of the nanoparticles and create a Coating the nanoparticles with membranes derived from leukocytes or erythrocytes may enhance their selfrecognition [11]. Use of ligands such as CD47-SIRPα to create signals may inhibit phagocytic clearance [28]. Spherical nanoparticles may congregate in the center of blood vessels and thus be less likely to extravasate via interactions with endothelial

cells [29]. Use of disc-like nanoparticles may increase endothelial cell interactions and thus enhance their ability to extravasate into tumor tissue[30,31].

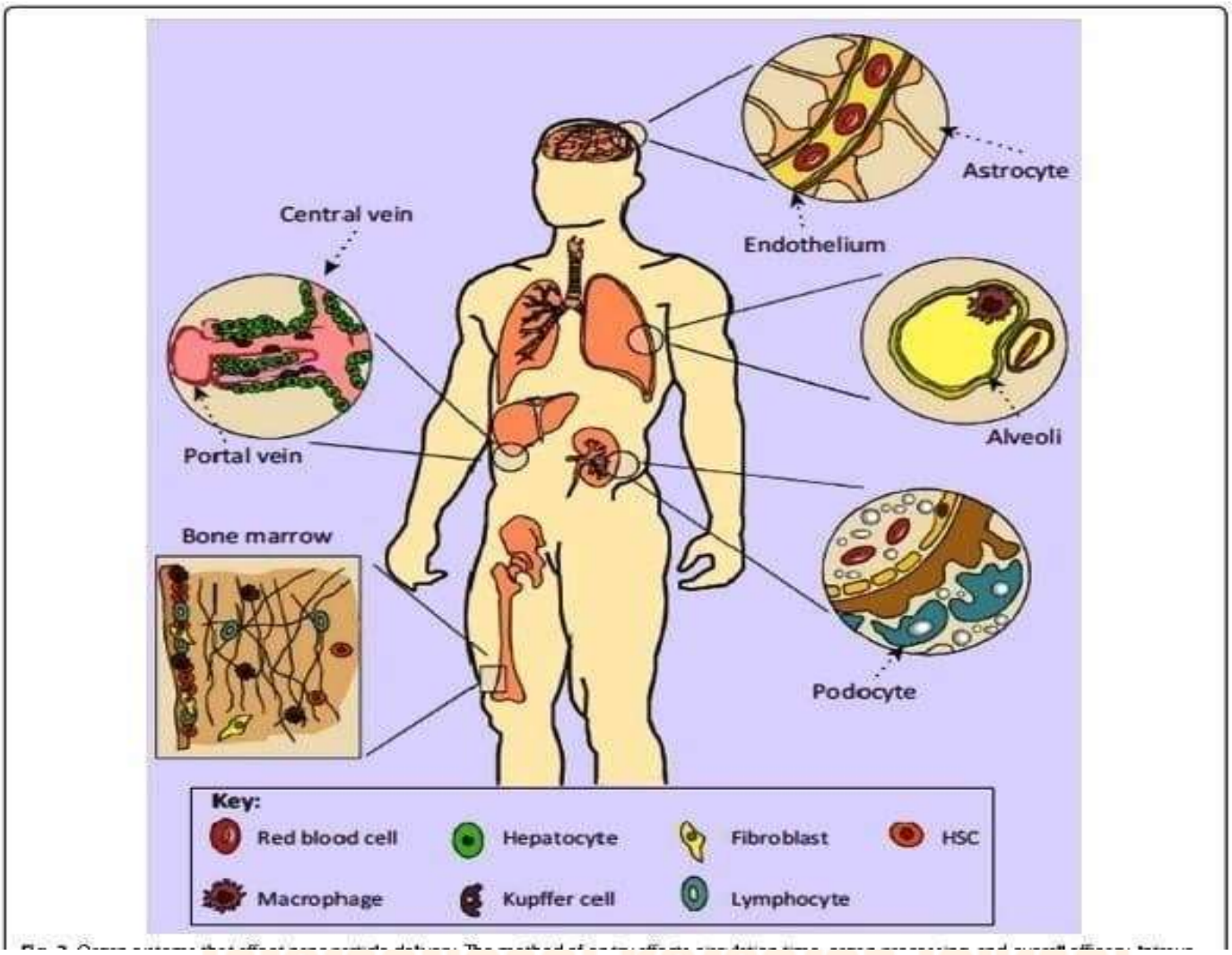

Fig : Organ System that affect Nanoparticle delivery

Renal system

The kidney is mindful for sifting circulating blood, and in this manner the obstructions includedin kidney filtration require to be considered when planning nanoparticles. After passing through the fenestrated endothelium with 70–100 nm pores, nanoparticles must pass through the glomerular storm cellar layer, a thick layer of extracellular lattice that sitsbetween the capillary endothelium and podocytes that allow clearance for 2–8 nmparticles[11]. Openings of opening stomachs that lie between epithelial podocyte expansions areregulated by proteins such as nephrin and CD2-associated protein, which for the most part permit thepassage of water and little particles [32].

Although decreasing nanoparticle measure may improve renal clearance, effcacy may be compromised. Multistage, biodegradable nanoparticles that break up into littler particles that can be cleared by the kidney may be viable [35]. Be that as it may, this impact may too posturea chance of nonspecifc corruption, in which nanoparticles discharge drugs and other operators earlier to arriving at target tumor tissue. Levels of the nanoencapsulated drugs must be sustained in the plasma for a chemotherapeutic impact, as well as killed from the circulatory system safely to constrain potential longterm unfavorable impacts. Personalized contemplations must moreover be made for patients with renal deffciencies [11].

Blood brain barrier

The blood–brain boundary (BBB) postures a challenge for treating brain cancers, since it as it were permits section of less than 2% of particles, counting particles, supplements, specifc peptides and proteins, and leukocytes [36]. Te obstruction comprises of endothelial cells joined by tight intersections and encased by astrocytic cells, basal lamina, pericytes, and microglia. Current strategies for increasing entrance may include coordinate presentations into the brain such as intraventricular or intracerebral infusion, mixture, and implantation and may increment poisonous quality dangers and nonuniform sedate dispersals [11].

Pathophysiological barriers

In cancer Tumor tissue is frequently characterized by defective vasculature wealthy in fenestrations and poor in pericyte scope. This wonder, known as the improved penetrability and retention (EPR) impact, has been utilized for inactive focusing on of nanoparticles to tumor tissue, but more profound entrance into the tumor is regularly confined due to heterogeneity of the tumor microenvironment [46]. Composition and structure of extracellular framework, along with tumor vasculature, is profoundly variable and subordinate on cancer sort, area, and progression state, along with patient-specific characteristics [11].

Multistage nanoparticles break down into their littler components, and their utilize may extend circulatory half-life, whereas permitting upgraded entrance [35]. Nanoparticles with the capacity to react to natural prompts, named "smart," may moreover make strides bioavailability and be an road for personalized treatment [48].

Types of nanoparticles

Protein-drug conjugated nanoparticles

Protein-drug conjugated nanoparticles consist of proteins directly conjugated to drug molecules. The link between the protein and the drug is typically biodegradable upon arrival in the cell. This can lead to untimely discharge of the medicate, as the biodegradable linker isreadily annihilated by proteases and redox-altering specialists found in blood. Later stages,such as protein-drug conjugated frameworks with linkers that remain in put until the nanoparticles reach the target location, have overcome this boundary. This framework permits more exact and controllable conveyance of the cytotoxic medicate particles, reducing the poisonous impacts of the treatment on the body [49].

Liposomal nanoparticles

Liposome-based nanoparticles are round nanoparticles made by means of the utilize of lipid bilayers. These nanoparticles are made quickly when an amphiphilic lipid is included to water or other hydrophilic fluids, yielding circles generally between 50 and 500 nm. This procedure permits for the epitome of hydrophilic medicate atoms by basically dissolving the sedate in the fluid utilized for arrangement of the nanoparticles. Hydrophobic and amphiphilicdrugs can be typified by coordinate expansion to the lipid arrangement some time recently arrangement of thenanoparticles, driving to a layer of medicate particles between the lipid bilayer [49].

Polymeric nanoparticles

Polymeric nanoparticles are comprised of engineered polymers, permitting customization of many key properties, such as atomic weight, biodegradability, and hydrophobicity. The synthesis of polymeric nanoparticles has moreover been well considered. A assortment of strategies have been outlined to effciently typify medicate particles. A few illustrations of these strategies include nanoprecipitation, electrospray, and emulsiffication. Polymeric nanoparticles are typically comprised of thick frameworks with wellknown debasement bends, making the medicate release of these nanoparticles less demanding to control in comparison to numerous other nanoparticle drug conveyance frameworks [49].

Dendrimeric nanoparticles

Dendrimeric nanoparticles are comprised of dendrimers, which are spherical macromolecules with many branches originating from a central point. Tese nanoparticles are created layer by layer. The initial core of the dendrimer is incorporated onto the previous layer before branches are allowed to form. By using specifc initiator cores, the size and degree of branching of the dendrimer can be easily manipulated, allowing for the polydispersity of the nanoparticle to be minimized. By carefully planning the scheme of cores and branching units, the molecular weight, size, branch density, flexibility, water solubility can be specified [49].

Hydrogels

Hydrogels are three-dimensional systems of crosslinked water dissolvable polymers that are able to hold liquid in expansive amounts. Most engineered hydrogels are not biodegradable, but enzymatic, hydrolytic, and stimuliresponsive components can be included into the hydrogel matrix in arrange to make nanoparticles that are degradable beneath certain conditions. The uniqueness of hydrogels is in their fuid retainment—the tall water substance is exceptionally comparative to natural tissues, decreasing pressure when presented to tissue and making thisnanoparticle biocompatible [56].

Other nanoparticle

stages One well-characterized case of inorganic, metallic nanoparticles is gold. Gold has been broadly utilized for both discovery and coordinate cancer treatment with and without medicate loading. The solid optical absorbance of gold permits it to be utilized for location, whereas its photothermal properties make it reasonable as an anticancer treatment. Complex structures with gold may be outlined to increment the effciency of the sedate discharge. For illustration, sedate molecules may be conjugated to the surfaces of the gold nanoparticles, whereas structures with hollow add may moreover be made to increment embodiment effciency. Numerous of these structures can be effectively made and particularly planned, such as to incorporate a wide extend of optical properties. Controlled medicate discharge is conceivable by including a layer of thermoresponsive polymers on the nanoparticle surface. Tese polymers shrivel in warm and extend in cooler temperatures, permitting for the control of the dissemination rate of the stacked sedate particles. This technology can be combined with the photothermal properties of gold for novel medicate conveyance to specifc locales. Sparkling a laser, for case, on the tumors to warm the gold nanoparticles when they are close the tumor location can increment viable medicate stacking whereas minimizing nonspecifc poisonous quality [49].

Case study: MM-398 clinical trials

To begin with endorsed in 1996, irinotecan (once known as CPT-11) is a semisynthetic analog of the cytotoxic alkaloid camptothecin. It is confined from Camptotheca acuminata (family Nyssaceae), a tree innate to China. Camptothecin is known to have solid antitumor properties, and its analog irinotecan is regularly utilized to combat colon and pancreatic cancers. Irinotecan is thought to have cytotoxic impacts on cells in S stage, embeddings itself into the DNA replication fork and viably ending mammalian DNA topoisomerase in its put, as seen in Fig. 4. This impact pieces DNA replication, hindering nucleic corrosive blend and actuating the DNA strands to break separated, eventually causing cell passing in multiplying cells [62, 63]The dynamic metabolite of irinotecan, SN-38, is in steady balance with irinotecan (Fig. 5). Both substances have a pHdependent balance between their dynamic lactone and dormant carboxylate shapes. In spite of the fact that irinotecan and SN-38 both have the same DNA harming ability, SN-38 is known to be generally 100–1000 times more strong than irinotecan. Using unencapsulated irinotecan can in this way lead to issues in poisonous quality and efcacy. Containing the irinotecan sedate particles in liposomes may be a arrangement. Division of the sedate atoms from the interior of the body comes about in a lower plasma concentration (Cmax) and lower circulation time of the medicate, both of these driving to a lower harmfulness. A higher concentration of the medicate is able to collect in the tumor tissues, conceivably due to expansive and defective vasculature in the tumor tissue[64].

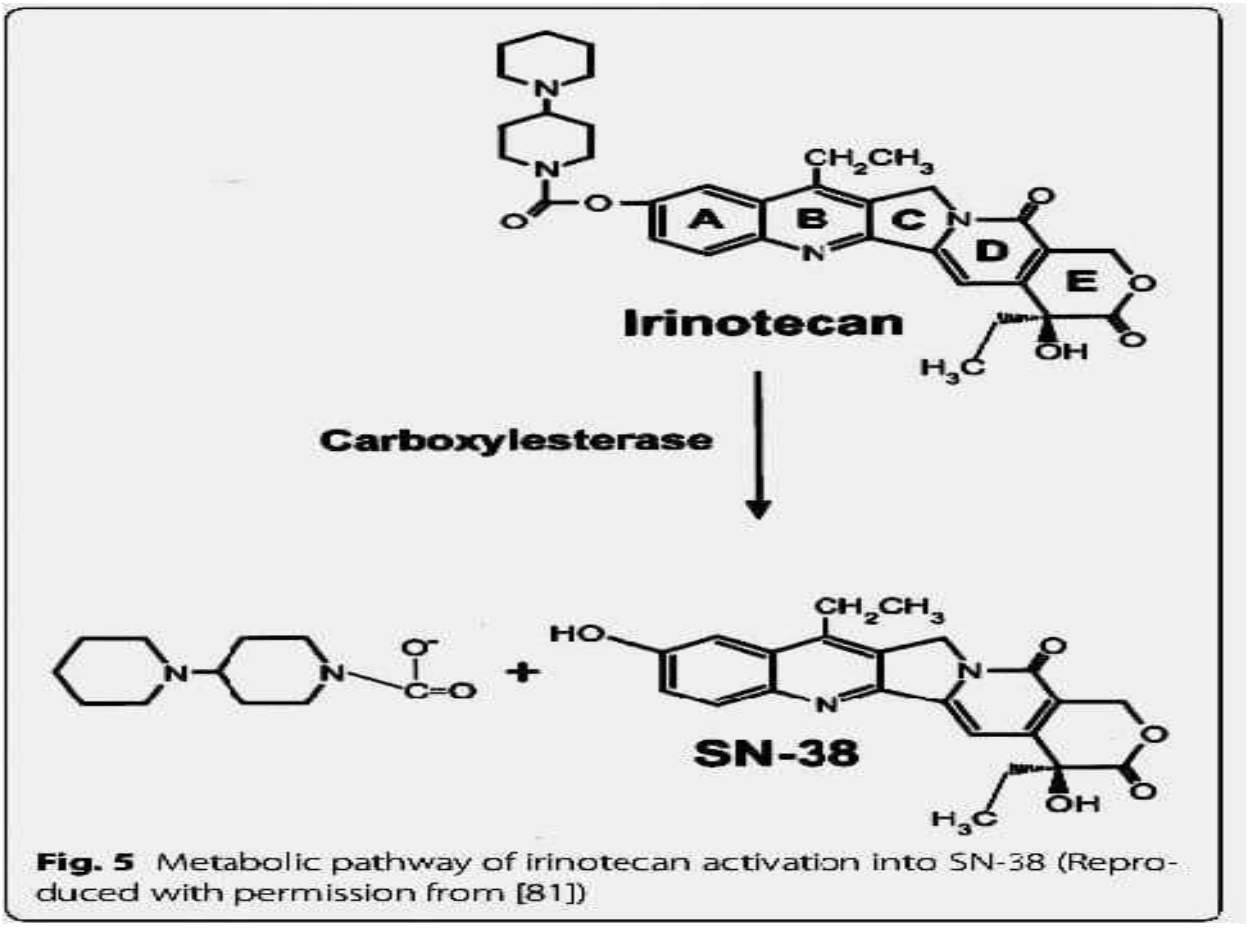

Fig. 5 Metabolic pathway of irinotecan activation into SN-38 (Reproduced with permission from [81])

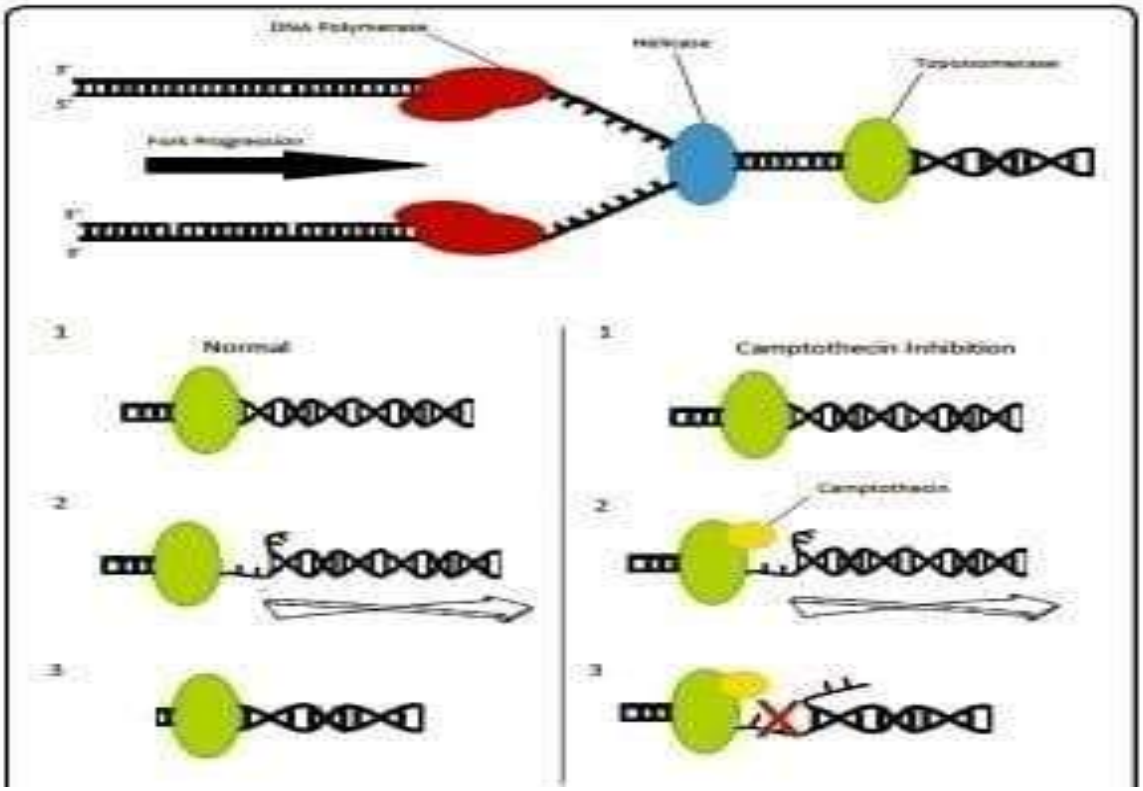

Fig 4: A schematicillustrating replication Fork

Preclinical studies

To progress the actuation of irinotecan and address issues of overaccumulation in the blood,a liposomal epitome of irinotecan (MM-398) was outlined to minimize the harmfulness of the sedate as well as achievea higher efcacy [66]. Drummond et al. utilized profoundly charged amine bunches on a multivalent anionic catching specialist (sucrose octasulfate [SOS] or directpoly(phosphate) [Pn]) to typify irinotecan atoms in liposomes. The irinotecan molecules diffused into the liposomes promptly; a triethylammonium (TEA) salt was utilized in a cation trade instrument to make up for the infux of medicate particles. Once in the liposome, the irinotecan particles shape a steady complex with the SOS or Pn lattice, effectively permitting for an greatly tall drug-to-lipid proportion (109,000 particles per particle) with a sedate discharge half-life in the circulation of 56.8 h in Swiss Webstermouse models; these epitomes will advance be alluded to as TEA-SOS and TEAPn. Union ofthis steady irinotecan-sucrose octasulfate compound is delineated in Fig. 6. In mouse models, the greatest endured measurements (MTD) was found to be much higher for nanoliposomal irinotecan (> 320 mg/kg) compared to free irinotecan (80 mg/kg). The efcacy of nanoliposomal irinotecan was moreover found to be more prominent than that of free irinotecan in cancer models. All mice with human breast (BT474) xenografts were totally cured of their tumors when treated with the typified shape, though “notable restraint of growth” was observed in mice treated with the free shape. Mice with human colon (HT29) xenografts treated with nanoliposomal irinotecan too appeared signifcant advancement in survival compared to the free detailing. Whereas the free irinotecan permitted the tumor volume to reach an normal of generally 2000 mm3 in approximately 35 days posttumor implantation, all regimens including nanoliposomal irinotecan come about in an normal tumor volume of beneath100 mm3 in the same time span. After 66 days post tumor implantation, as it were one of the four nanoliposomal administrations driven to a tumor volume comparative to that of free irinotecan (25 mg/kg of liposomal irinotecan utilizing a TEA-Pn embodiment), coming about in an normal tumor volume of 1750 mm3 . Te most reduced tumor volume found after 66 days was 125 mm3 , which was found in mice with a regimen of 50 mg/kg of liposomal irinotecan with a TEA-SOS epitome. None of the mice with colon cancer were found to be tumor free after experiencing the free irinotecan regimen, whereas 9.1% (n = 1) and 36.4% (n = 4) of mice experiencing the 25 and 50 mg/kg regimens separately were tumor-free at the conclusion of the consider [67].

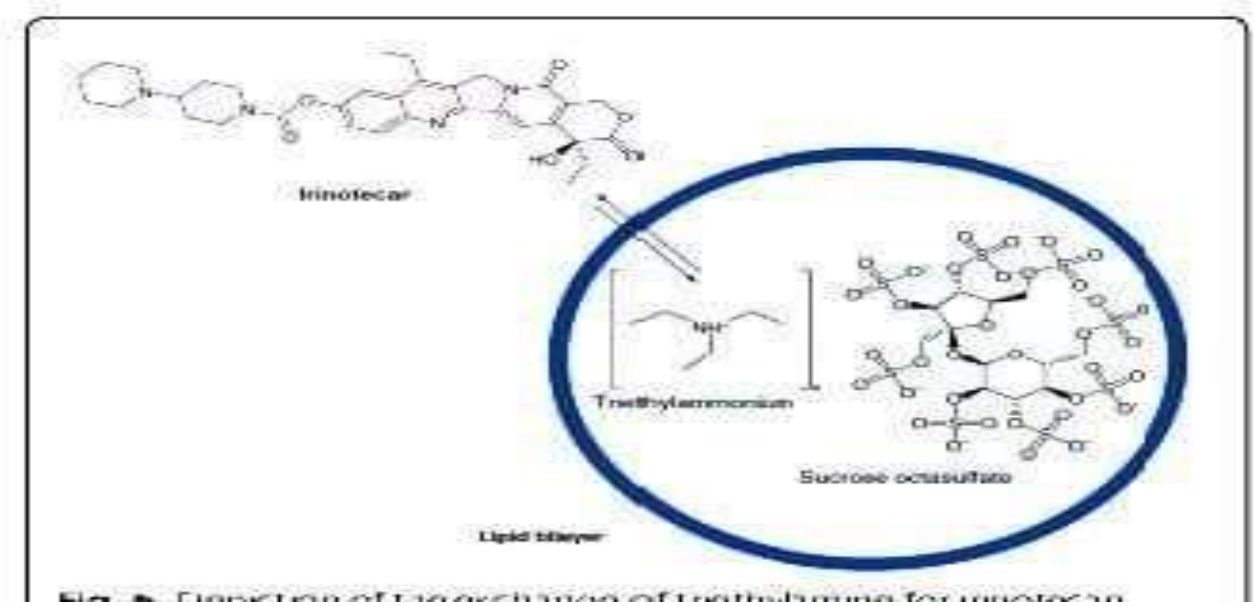

Fig. 6 Depiction of the exchange of triethylamine for irinotecan, which forms a stable complex with sucrose octasulfate inside the liposome (Reproduced with permission from [66])

Advantages and Disadvantages

Advantages

- Nanomedicine has many advantages over traditional cancer treatments, including:
- Targeted drug delivery: Nanomedicine can deliver drugs directly to tumor cells and tissues, minimizing the impact on healthy tissues and reducing side effects.
- Improved therapeutic index: Nanomedicine can increase the therapeutic index of drugs by encapsulating or conjugating them to nanoparticles.
- Novel therapeutic agents: Nanotechnology can create new and effective therapeutic agents.
- Early detection and diagnosis: Nanotechnology can help detect and diagnose cancer early.
- Precise monitoring: Nanotechnology can monitor a patient's response to therapy, which can help optimize treatment.
- Controlled drug release: Nanomedicine can release drugs in a controlled manner.
- Nanomedicine can also:
- Interact with biomolecules inside and on the surface of cells
- Detect molecular changes in a small percentage of cells
- Traverse physiological barriers like the blood-brain barrier
- Improve the specificity of drugs
- Increase the bioavailability of drugs
- Reduce cytotoxicity to normal tissue
- Increase the loading capacity of drugs

Disadvantages

- Toxicity
Nanoparticles can cause toxicities such as anemia, neutropenia, thrombosis, and allergic reactions. They can also be lethal to normal cells, causing neural toxic ity, bone marrow suppression, and cardiomyopathy.
- Drug resistance
Tumor cells can adapt and become resistant to the chemotherapy drugs carried by nanoparticles.
- Biocompatibility
Nanoparticles can interact with biomolecules and disturb their function, making the formulation ineffective.
- Complexity
The complexity and heterogeneity of tumor biology, as well as the incomplete understanding of nano-bio interactions, are obstacles to nanomedicine becoming a standard treatment. Manufacturing
- The chemistry, manufacturing, and controls required for clinical translation and commercialization are challenges.

Applications :

- Nanomedicine has many applications in cancer treatment, including:
- Drug delivery: Nanomedicine can deliver drugs to tumor sites, reducing the side effects of traditional drug therapies. Nanoparticles can be used to encapsulate or conjugate chemotherapeutic drugs to the surface of the nanoparticles.

- Active targeting: Nanoparticles can be designed to target specific cancer cells by attaching ligands to the nanoparticle that bind to the cell surface receptors.

- Imaging: Nanoparticles can be used to improve cancer imaging, which can help with diagnosis.
- Immune cell engagement: Nanomedicine can be designed to help immune cells eliminate cancer cells.
- Gene therapy: Nanomedicine can be used in gene therapy.
- Immunotherapy: Nanomedicine can be used in immunotherapy.

Conclusion and future direction

The advent of nanomedicines represents signifcant advances in the feld of drug delivery. Te options for nanoparticle design and function are extremely varied and the list of potential applications continues to grow, to the point where the drug delivery system can be tailormade to best suit the selected drug. However, it is important to remember that nanoparticle-based treatments are not miracle cures. Tey have both faws and challenges to overcome. Selective targeting, while heralded as an improvement over non-encapsulated drugs, is a challenge unto itself. While many cancers overexpress surface proteins common in normal cells, overabundance of a specifc surface protein is not enough to guarantee selectivity using targeted treatment. Ultimately, some of the drug will end up of-target, afecting non-cancerous cells. Choosing the right surface marker is critical for a targeted treatment to work. For liposomal irinotecan (MM-398), selectivity is achieved through the acidic tumor microenvironment. Irinotecan turns into its more active form, SN-38, in acidic environments. SN-38, then, disrupts the molecular machinery responsible for DNA replication. One could consider this a form of focused targeting: targeting only dividing cells in an acidic environment, such as those found in a tumor.

However, tumor cells are not the only actively dividing cells in an acidic environment the body. Stomach epithelial cells are one such example. Tis may explain why most of the side-efects of MM-398 are digestiverelated. Further, the tumor microenvironment is both heterogeneous and complex. Te tumor is an amalgamation of both cancer and normal cells. Tumor cells invoke wound-repair pathways, recruiting basal laminal cells, blood vessel cells, and tumor-assisting macrophages (TAMs) to assist with growth and survival [2]. Due to cancer cells having a preference towards anaerobic metabolic pathways as well as the partial hypoxia of the tumor environment, pH gradients moving from extracellular to intracellular spaces tend to be reversed in tumor tissue when compared to normal tissue [78]. Differentiation between cancer cells within the same tumor can also occur. Due to genome instability, populations of differentcancer cells can arise within a single tumor. As many as 20 driver mutations, and anywhere between 1000 and 100,000 point mutations can be found within individual cancers. Treatment may further increase the number of these mutations. “For example, gliomas that recure after treatment with the DNA alkylating agent temozolomide have been shown to carry huge numbers of mutations with a signature typical of such agents” [79].

There is also a reproducibility issue with nanoparticle production. Reproducible, large-scale synthesis of nanomedicines is still a challenge for the distribution of a homogeneous batch of nanomedicines, especially when considering that these nanoplatforms often require specifc conditions for production via self-assembly.

Through characterization of these nanomedicines, at every stage of the production process must be enforced to ensure both reproducibility of synthesis and efcacy. Storage of these nanomedicines under appropriate conditions is also critical since colloidal instability can dramatically alter their performance in vivo. Ideal nanomedicines will have a modular design that can be easily scaed u for CGMP manufacturing and stored a long time prior to use in patient.

Table 5 Adverse effects of MM-398. Reproduced with permission from [77]

	Nanoliposomal irinotecan plus fluorouracil and folinic acid combination therapy (n = 117)		Nanoliposomal irinotecan monotherapy (n = 147)		Fluorouracil and folinic acid control (n = 134)	
	Any grade	Grades 3–4	Any grade	Grades 3–4	Any grade	Grades 3–4
Diarrhoea	69 (59%)	15 (13%)	103 (70%)	31 (21%)	35 (26%)	6 (4%)
Vomiting	61 (52%)	13 (11%)	80 (54%)	20 (14%)	35 (26%)	4 (3%)
Nausea	60 (51%)	9 (8%)	89 (61%)	8 (5%)	46 (34%)	4 (3%)
Decreased appetite	52 (44%)	5 (4%)	72 (49%)	13 (19%)	43 (32%)	3 (2%)
Fatigue	47 (40%)	16 (14%)	54 (37%)	9 (6%)	37 (28%)	5 (4%)
Neutropenia*	46 (39%)	32 (27%)	37 (25%)	22 (15%)	7 (5%)	2 (1%)
Anaemia	44 (38%)	11 (9%)	48 (33%)	16 (11%)	31 (23%)	9 (7%)
Hypokalemia	14 (12%)	4 (3%)	32 (22%)	17 (12%)	12 (9%)	3 (2%)

Furthermore, the changes in legislation often occur at a rate different than the development of medicines in the laboratory. One organization, the Nanotechnology Characterization Laboratory, works with the FDA as bridge between scientists and regulatory committees to aid the review of nanomedicines [80] Overcoming these challenges may seem like a herculean efort, but it is not impossible. Tere has been an overall shift in cancer research, from individual-based to a more collaborative approach that has helped achieve success. A complex problem requires a complex solution, and a multidisciplinary approach seems like the best option. Cross collaborations between theoretical and experimental scientists across academia, with the pharmaceutical industry, medical doctors and the regulatory agencies will help translate more findings from the lab to the clinic and user in the next era of clinical cancer nanomedicines.

Abbrivation

EPR: enhanced permeability and retention efect; PEG: polyethylene glycol; RES: reticulo-endothelial system; MPS: mononuclear phagocyte system; BPD: verteporfn; ROS: reactive oxygen species; PLGA: poly(d,llactide-co-glycolide); BBB: blood–brain barrier; PRINT: particle replication in nonwetting templates; SWCNT: single walled carbon nanotube; VEGF: vascular endothelial growth factor; Cmax: plasma concentration; MM-398: liposomal irinotecan; SOS: sucrose octasulfate; Pn: linear poly(phosphate); TEA: triethylammonium; MTD: maximum tolerated dose; DLT: dose-limiting toxicity; PK: pharmacokinet- ics; AE: adverse efects; 5-FU: 5-fuorouracil; LV: leucovorin; ORR: objective response rate; OG: oesophago-gastric cancer; HR: hazard ratio; TAM: tumorassisting macrophages; MDR: multi-drug resistance.

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