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New developments in injectable Nano-formulations and available marketed products

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ABSTRACT: Nanotechnology was first discussed in 1959 by renowned physicist Richard Feynman in his talk There's Plenty of Room at the bottom, in which he described the possibility of synthesis via direct manipulation of atoms. Nanotechnology is defined as the manipulation of matter on an atomic, molecular and supramolecular scale. The medical application of nanotechnology can therefore be coined as nanomedicine. The use of nanomedicine ranges from the medical applications of nanomaterials and biological devices to nanoelectronic biosensors. The possible future applications of molecular nanotechnology could be biological machines. The desired functional requirements can be added to nanomaterials by interfacing them with biological molecules and their structures. The size of nanomaterials is almost similar to that of most biological molecules and structures. Hence, nanomaterials can be useful for both *in vivo* and *in vitro* biomedical research and applications. Thus far, the integration of nanomaterials with biology has led to the development of diagnostic devices, contrast agents, analytical tools, physical therapy applications, and drug delivery vehicles. During recent times, there has been a remarkable increase in nano based pharmaceutical products approval. These novel Nano based systems are therapeutic agents and act as vehicles to carry different active pharmaceutical agents into specific parts of the body. Different nanostructures include nanocrystals, liposomes, lipid nanoparticles, PEGylated polymeric nanodrugs, nanoducts, protein-based nanoparticles and metal-based nanoparticles.

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INTRODUCTION:

The science of application of nanotechnology for the treatment, diagnosis, monitoring and controlling biological systems is termed as nanomedicine. Nanomedicine combines in a broad sense nanotechnology with pharmaceutical and biomedical concepts with the goal of developing drugs and imaging agents with higher efficacy, improved safety and toxicological profile. Nanomedicines include application areas that are drug delivery, drugs and therapies, *in vivo*

imaging, *in vitro* diagnostics, biomaterials and active implants [1,2].

Nanomedical products appeared in the current market scenario more than a decade ago and some have gone a long way ahead to become the best-sellers in their therapeutic categories. The core areas in which nanomedicines have made an impact are cancer, CNS disease, cardiovascular disease and infections control. Distinct varieties of long-acting injectable nanoparticles are included although liposomal and polymeric nanoparticles are the most commonly used in this category [3,4].

LIPOSOMES:

Liposomes are the Nanopharmaceuticals formed from phospholipids and cholesterol in aqueous medium. Liposomes have a spherical phospholipid liquid crystalline phase. These are produced by the dispersion of phospholipid in water by shaking which results in the formation of multilayer structures consisting of several bi-layers of lipids. These multilayer structures produce unilamellar structures after sonication which is known as vesicles.

Liposomes allow the entrapping of both hydrophilic and hydrophobic drugs thereby giving rise to the possibility of targeting specific sites. The main advantages of liposomal delivery systems are biocompatibility, biodegradability and low toxicity. The reason for the advantage is that the injected liposomes can avoid uptake by the reticulo-endothelial system (RES) which results in the particles remaining in circulation for a prolonged period of time.

The particle sizes of liposomes range from 50 to 200 nm. To let liposomes suitable for therapeutic applications, their size distribution must be controlled which can be known by passing them repeatedly under elevated pressure through membranes with defined pore size [5,6].

Since Alec Bangham first described liposomes in 1961, a massive amount of research has been carried out and their applications are now well-established in various areas such as drugs, bio-molecules and gene delivery. The concept of liposomal drug delivery system has a revolutionary effect on the pharmaceutical field. Due to massive developments in liposome technology, a number of long-acting liposome-based drug formulations are now available for human use and many products are under clinical trials. The most commercial available Liposomes are enlisted in Table 1 [7,8].

LONG-ACTING DRUG DELIVERY IN CONCEPT OF LIPOSOMAL TECHNOLOGIES:

Different widely used liposome technologies are Stealth Liposome Technology (SLT), Non-PEGylated Technology (NPL), DepofoamTM Technology and Lysolipid Thermally Sensitive Technology (LTST) [9,10].

Stealth Liposome Technology (SLT):

In SLT, different strands of the polymer are attached to drug molecules or with the system that can enhance the safety and efficacy of the therapeutic agents.

Non-PEGylated Technology (NPL):

PEGylation is obtained by the incubation of a reactive derivative of PEG with the targeted moiety. Covalent linkage between the liposome and PEG protects the active moiety from the recipient's immune system, which ultimately results in reduced immunogenicity and antigenicity. Thus it produces alterations in the physicochemical properties of the active moiety, with further changes in the hydrodynamic size, which finally reduce its renal clearance and thereby prolongs its respective circulatory time. Similarly, it provides hydrophilicity to hydrophobic drugs and reduces the dosage frequency.

NPL is a unique drug delivery system that came as a breakthrough in cancer therapy which offered the benefits of a PEGylated-liposome and eliminated the side effects associated with PEG, such as hand-foot syndrome. NPL Doxorubicin (NPLD) injection provides a better safety profile over conventional DOX and Doxil®. NPLD not only reduces the cardiac toxicity associated with DOX, but also the dose-limiting toxicity linked with the use of Doxil.

Depofoam TM Technology:

This technology encapsulates drugs in the multivesicular liposomal platform without any changing molecular structure. The multivesicular liposomes release the drug over a required period of time ranging from 1 to 30 days. Upon administration, DepoFoam particles release the drug over a period of hours to weeks following erosion and/or reorganization of the lipid membranes. DepoFoam technology has the improvised properties of both small and large molecules. This technology considerably improves patient care by providing solutions for medications that require frequent multiple injections and has a short period of action or any side effects.

Table 1. Commercially available Liposomal drug formulations [5-11].

Brand name	Description	Mechanism	Approval
Abelcet®	Amphotericin B complex 1:1 with DMPC and DMPG (7:3), ~250nm, ribbon like structures of a bilayered membrane	Mononuclear phagocyte system (MPS) targeting: Selective transfer of drug from lipid complex to fungal cell with minimal uptake into human cells has been postulated	FDA 1995 and 1996 Marketed outside USA as Amphocil® Systemic fungal infections (IV)
Am-Bisome®	Amphotericin B encapsulated in liposomes (60 to 70nm) composed of hydrogenated soy phosphatidylcholine, cholesterol, and distearoylphosphatidyl-glycerol (2/0.8/1 molar)	MPS targeting: Liposomes preferentially accumulate in organs of the MPS. Negative charge contributes to MPS targeting. Selective transfer of the drug from lipid complex to target fungal cell with minimal uptake into human cells has been postulated.	FDA 1997 Systemic fungal infections (IV)
Dauno-Xome®	Daunorubicin citrate encapsulated in liposomes (45nm) composed of distearoyl phosphatidylcholine and cholesterol (2/1 molar)	Passive targeting via EPR effect: Concentration of available liposomal drug in tumors exceeds that of free drug. Liposomal daunorubicin persists at high levels for several days.	FDA 1996 HIV-related KS (IV) HIV-related KS (IV)
Depo-Cyt®	Cytarabine encapsulated in multivesicular liposomes (20 µm; classified as nano pharmaceutical based on its individual drug containing "chambers") made from dioleoyl lecithin, dipalmitoylphosphatidyl glycerol, cholesterol, and triolein	Sustained release: This formulation of cytarabine maintains cytotoxic concentrations of the drug in the cerebrospinal fluid for more than 14 days after a single 50mg injection.	FDA 1999/2007 Lymphomatous malignant meningitis (IV)
Depo-Dur®	Morphine sulfate encapsulated in multivesicular liposomes (17 to 23 µm; per se not a nanopharmaceutical – Made from dioleoyl lecithin cholesterol, dipalmitoyl phosphatidylglycerol, tricaprylin, and triolein	Sustained release: After the administration into the epidural space, morphine sulfate is released from the multivesicular liposomes over an extended period of time	FDA 2004 For treatment of chronic pain in patients requiring a long-term daily around-the-clock opioid analgesic (administered into the epidural space)
Doxil®	Doxorubicin hydrochloride encapsulated in Stealth®liposomes (100nm) composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero3-phosphoethanol aminesodium, fully hydrogenated soy phosphatidylcholine, and cholesterol	Passive targeting via EPR effect: Extravasation of liposomes by passage of the vesicles through endothelial cell gaps present in solid tumors. Enhanced accumulation of doxorubicin in lesions of AIDS-associated KS after administration of PEG-liposomal doxorubicin	FDA 1995 AIDS-related KS, multiple myeloma, ovarian cancer (IV)
Inflexal® V	Influenza virus antigens (hemagglutinin, neuraminidase) on	Mimicking native antigen presentation: Liposomes mimic the native virus	Switzerland 1997 Influenza vaccine

	surface of 150 nm liposomes	structure, thus allowing for cellular entry and membrane fusion.26 Retention of the natural presentation of antigens on liposomal surface provides for high immunogenicity	
Marqibo ®	Vincristine sulfate encapsulated in sphingomyelin/cholesterol (60/40, molar) 100nm liposomes	Passive targeting via EPR effect: Extravasation of liposomes through fenestra in bone marrow endothelium	Passive targeting via EPR effect: Extravasation of liposomes through fenestra in bone marrow endothelium
Mepact ™	Mifamurtide (synthetic muramyltripeptidephosphatidyletha nolamine) incorporated into large multilamellar liposomes composed of 1-palmitoyl-2-oleoyl-sn-glycerol-3- phosphocholine and 1,2-dioleoyl-sn-glycero-3-phospho-L-serine	MPS targeting: The drug, an immune stimulant, is anchored in negatively charged liposomal bilayer membrane	Europe 2009 Nonmetastasizingr esectable osteosarcoma (IV)
Myocet®	Doxorubicin encapsulated 180nm oligolamellar liposomes composed of egg phosphatidylcholine/cholesterol (1/1, molar)	MPS targeting: Forms “MPS depot”, slow release into blood circulation resembles prolonged infusion	Europe 2000 Metastatic breast cancer (IV)
Onivyde ™	Irinotecan encapsulated in to DSPC:MPEG2000:DSPE (3:2:0.015 molar ratio)	The drug contains SN-38, an active metabolite of irinotecan that binds reversibly to the topoisomerase 1-DNA complex and prevents relegation of the single strand breaks.	FDA 2015 Combination therapy with fluorouracil and leucovorin in metastatic adenocarcinoma of the pancreas
Visudyne ®	Verteporfin in liposomes made of dimyristoyl-phosphatidylcholine and egg phosphatidylglycerol (negatively charged); lyophilized cake for reconstitution	Drug solubilization: Rendering drug biocompatible and enhancing ease of IVadministration. No other apparent function of liposomes. Liposomal formulation instable in the presence of serum. Fast transfer of verteporfin from Visudyne®to lipoproteins	FDA 2000 Photodynamic therapy of wet agerelated macular degeneration, pathological myopia, ocular histoplasmosis syndrome (IV)

Lysolipid Thermally Sensitive Technology (LTST):

These thermo sensitive liposomes are developed for drug unleash at sites of elevated temperature. This type of novel liposomes is being developed to exhibit temperature-dependent release of encapsulated drugs. Generally local tissue temperature is generally reached up to 42 °C by radiofrequency ablation, a technique based on the application of radio frequency. The Lipid components which are found in the liposome undergo a gel to liquid transition at elevated temperatures which makes it more permeable, and thus releases the drug.

NANOCRYSTALS:

Nanocrystals have composition of hydrophobic drugs with a small amount of excipient or surfactant and Nano-crystals can be formulated for different types of hydrophobic drugs with high loading and encapsulation efficacy. Micronization is a common formulation procedure for sparingly soluble compounds. Solubility of nanocrystals is highly related to the particle size and increases with particle size decrease due to the increase in surface area mainly when the nanocrystals are below 300 nm. As a result, the concentration gradient between

gut lumen and blood increases resulting in improved absorption by passive diffusion. In such suspension formulations, the rate limiting depends on the dissolution of drug in the formulation or in the *in vivo* fluid surrounding the drug formulation [11,12].

Generally in all formulations, a fatty acid ester of any drug is used to prepare an oil-based parenteral solution and the drug-release rate from the available solution is determined by the drug partitioning between the oil vehicle and the tissue fluid.

Rate of drug release can be influenced by the drug bioconversion rate from the pro-drugs to the parent drugs. So, to increase the half-life of a drug in long-acting formulations, the parent drug should be synthesized into a pro-drug through use of long-chain fatty acids that is esterification. Due to low water solubility, the fatty acid ester of a drug dissolves much slower at the injection site after intramuscular (IM) injection.

All other factors such as injection site, injection volume, the extent of spreading of the drug depot at the injection site and the absorption and distribution of the oil vehicle can also affect the overall pharmacokinetic profile of the drug. Mostly the nanocrystals approved by FDA are used as oral formulations and there are also some approved as a bone substitute. For all long acting injectables, FDA has approved Invega® Sustenna® for schizophrenia and schizoaffective disorder treatment and Ryanodex® for malignant hypothermia treatment. Invega® Sustenna® is a good example of long acting injectable pro-drug formulation (Paliperidone palmitate is the Prodrug of Paliperidonepalmitoyl ester). This long acting injectable formulation is indicated as once-every 28 days injection after an initial titration period. Production of nanocrystals has been applied to both organic and inorganic materials. Synthesis methods available are top-down diminution approaches which are often employed for the organic compounds, and bottom-up precipitation methods that are more commonly used for inorganic materials. Wet milling and high pressure homogenization technologies are widely used for nanocrystal preparation [13-16].

Wet milling technology:

This top-down process is an efficient milling technique for nanocrystal preparation. The process is performed by media milling followed by dispersion of concentrated drug in an aqueous or non-aqueous liquid medium with milling balls. This method has several advantages in its economic value and ease of scaling up. Choosing the right media milling equipment, manufacturers can cost-effectively create uniform fine particles with limited or no contamination. But sometimes, due to the intensive mixing forces in the vessel, erosion of the milling balls is a common problem and has to be monitored closely.

High Pressure homogenization technology:

It is a purely mechanical process which is performed by forcing a fluidic product through a narrow gap (The homogenizing nozzle) at high pressure (150-200MPa or 350 to 400 MPa for ultra-high pressure homogenization, UHPH). High pressure homogenization (Also a top-down process) can also achieve suspensions with narrow particle size distribution. The liquid product available is subjected to very high shear stress causing the formation of very fine particles. Its main advantage is that it can effectively process large volumes of liquid suspension samples thoroughly and reproducibly. As it doesn't use milling balls, contamination of the final product is much less. However, the high pressures applied cause a temperature rise (Due to the heat of compression) and this has to be controlled, especially for a thermally labile drug substance. Alternatively, a combination of bottom-up and top-down processes can be considered, e.g. crystallization via a non-solvent, solvent dissolution of API followed by the homogenization of freshly formed particles.

ANTIBODY-DRUG CONJUGATES (ADCs):

Antibody-drug Conjugates or ADCs are a class of biopharmaceutical drugs designed as a targeted therapy for treating cancer.

ADCs occur in the form of immune-conjugate or bio-conjugate, which are emerging classes of medicines designed for a highly-specific targeting and destruction of cancer cells. The mode of action is targeted delivery of a cytotoxic agent to the cancer cell through monoclonal antibody targeting of a specific cell surface marker. Once after the binding, a biochemical reaction initiates internalization of the ADC into the cell cytoplasm where the drug becomes active thereby killing the cancer cell. The major advantage of ADC therapeutics is that it targets and releases the drug specifically within the cancer cell which ensures healthy cells are not adversely affected and effectively destroys the cancerous cells [17,18].

For all the non-cleavable ADCs, the linker unit remains attached to the drug, which mitigates externalization and the resulting side effect from the drug enters healthy

neighboring cells. On the other hand, with cleavable ADCs, the drug is completely cleaved from the linker unit upon internalization, the antibody is degraded to its amino acid form and the entire complex becomes an active drug. Development in linking technology helps improve cleavage reactions which thereby allow improvements in payload delivery. Almost all of the ADCs payloads are small molecules which act via inducing DNA damage. Till date, there are only four ADCs that have received market approval. However, after approval from the U.S. Food and Drug Administration (FDA), Pfizer/ Wyeth, the developer and marketer of the first ADC to receive marketing approval. The list of ADC products enlisted in Table 2. In the year 2001 for the treatment of patients with acute myelogenous leukemia (Gemtuzumabozogamicin, trade name: Mylotarg®), withdrew the drug from the market in June 2010 (Although it is still marketed in Japan), later again to re-introduce in the US market in 2017. The second and third marketed ADCs are Brentuximabvedotin (Trade name: Adcetris®, marketed by Seattle Genetics and Millennium/Takeda) and Trastuzumabemtansine (Trade name: Kadcyla, marketed by Genentech and Roche). They were approved by the U.S. FDA in 2011 and 2013 respectively. ADC, Inotuzumabozogamicin, was approved by the European Commission as monotherapy for the treatment of adults with relapsed or refractory CD22-positive-B-cell precursor acute lymphoblastic leukemia on June 30, 2017 under the trade name Besponse® (Pfizer/Wyeth) and approved for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia by the U.S. FDA on August 17, 2017. The starting point for ADC manufacturing is basically the parent monoclonal antibody (mAb) [19-22].

POLYMERIC NANOPARTICLES:

Polymeric nanoparticles are defined as sub-microns (1 to 1000 nm) colloidal particles comprising active Drug encapsulated within or adsorbed to macromolecular substances.

Polymeric nanoparticles are stable both in storage and *in vivo* application. For polymeric nanoparticles, the drug is entrapped within the polymer matrix, usually a biodegradable polymeric matrix. Polymer nanomedicines have two categories that are Polymer-drug conjugates for increased drug half-life, bioavailability and Degradable polymer architectures for controlled-release applications [23,24].

Polymeric nanoparticles are recognized as foreign bodies and can be removed from the blood circulation by the phagocyte cells of the RES (Reticulo-endothelial system). Maximum of the nanoparticles are phagocytosed by the macrophages of the liver and spleen shortly following intravenous (IV) injection. The nanoparticles clearance is mediated by the adsorption of blood components to the surface of the particles namely synthetic and pseudo-synthetic. The polymers themselves include those that are those that arise from natural sources. Their application has spanned the full nonmaterial size-scale from single polymer chains up to large aggregates depending on the required therapeutic outcome. To realize long-acting attributes, the polymeric nanoparticles can protect the drug from degradation; thus achieving prolonged drug delivery (and a long shelf-life). For therapeutic purposes, the most commonly used polymers include polyethylene glycol (PEG), poly (lactic acid) (PLA), poly (lacticco-glycolic acid) (PLGA), poly (ε-caprolactone) (PCL), alginate, chitosan, and gelatin base. Polymeric nanoparticles comprise a very heterogeneous group of nanosized therapeutics [25].

The most basic class of polymeric nanomedicines utilizes single polymer chains, either directly as the therapeutic itself, or as a modifying agent for a drug or diagnostic agent. More frequently in terms of polymeric nanomedicines, drugs are attached to a hydrophilic polymer to increase circulation or to improve biocompatibility/solubility. The most well-established polymer is poly (ethylene glycol) (PEG) and PEGylation results in a significant increase in biological half-life in plasma. In addition to PEGylation, other hydrophiles can be utilized to increase circulation half-life. Beyond just extending the circulation time of established drugs, polymeric nanoparticles can be developed based on hydrophobic materials which facilitate the controlled release of the drug. This is achieved by using a slow degradable functionality that subsequently leads to kinetically driven release of the drug. A long-established polymer nanoparticle that has had significant success is based upon incorporation of leuprolide (a testosterone-inhibiting drug) into polylactide-co-glycolic acid (PLGA) nanoparticles. The various commercialized polymeric nanoparticles are presented in Table 3 [26,27].

CONCLUSION:

Pre-existing medicines re-formulation or new formulation developments have been boosted due to the increase in the research of nanomedicines. In the last few

Table 2. The list of approved Antibody Drug Conjugates (ADCs) [17-22].

Drug	Maker	Condition	Trade name
Gemtuzuma-bozogamicin	Pfizer/Wyeth	relapsed acute myelogenous leukemia (AML)	Mylotarg
Brentuxima-bvedotin	Seattle Genetics, Millennium/Takeda	relapsed HL and relapsed sALCL	Adcetris
Trastuzuma-bemtansine	Genentech, Roche	HER2-positive metastatic breast cancer (mBC) following treatment with trastuzumab and a maytansinoid	Kadcyla
Inotuzuma-bozogamicin	Pfizer/Wyeth	relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia	Besponsa
Polatuzuma-bvedotinpiiq	Genentech, Roche	relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)	Polivy
Enfortuma bvedotin	Astellas/ Seattle Genetics	adult patients with locally advanced or metastatic urothelial cancer who have received a PD-1 or PD-L1 inhibitor, and a Pt-containing therapy	Padcev
Trastuzumab - deruxtecan	AstraZeneca/Daiichi Sankyo	adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens	Enhertu

Table 3. The list of approved Antibody Drug Conjugates (ADCs) [17-22].

Name	Description	Mechanism	Approval
Adagen ®	PEGylated adenosine deaminase34 1 enzyme molecule is modified with up to 17 strands of PEG, MW 5000, 114 oxymethylene groups per strand	Increased circulation time and reduced immunogenecity	FDA 1990 adenosine deaminase deficiency Severe combined immune deficiency disease
Copa-xone ®	Polypeptide (average MW6.4kDa) composed of four amino	No mechanism attributable to nanosize, due to its resembla-nce to myelin basic protein	FDA 1996/2014 Multiple
Eligard ®	Leuprolide acetate (synthetic GnRH or LH-RH analog) incorporated in nanoparticles composed of PLGH copolymer (DL-lactide/glycolide; 1/1)	Sustained release	FDA 2002 Advanced prostate
Cimzia ®	PEGylated antibody (Fab'fragment of a humanized anti-TNF-alpha	PEGylation generally increases hydrodynamic radius, prolongs circulation and time, decreases proteolysis and renal excretion, shields antigenic determinants from immune detection	FDA 2008 crohn's disease, rheumatoid arthritis.
Genexol ®	Paclitaxel in 20-50nm miselles39 composed of block copolymer poly(ethylene glycol)-poly(D,L-lactide	Passive targeting via EPR effect	South korea 2001Metastatic breast cancer, pancreatic cancer.
Opaxio ®	Paclitaxel covalently linked to solid nanoparticles composed of polyglutamate	Passive targeting via EPR effect: Drug release inside solid tumor via enzymatic hydrolysis	FDA 2012 Glioblastoma
Zinosta tinstima - lamer®	Conjugate protein or copolymer of styrene maliec acid and an antitumor protein NCS. Synthesized by conjugation of one molecule of NCS and two molecules of poly (styrene-co-maleic acid)	Passive targeting via EPR effect	Japan 1994 primary unresectable hepatocellular carcinoma

decades, namodecines have seen a huge transformation in application in the areas ranging from medical devices to nanopharmaceuticals. However, there are various regulatory hurdles ranging from the creation of harmonized definitions to the characterization protocol development to the process control. A universally acceptable definition of nanomedicines still remains at large. Further, complexities arise from the regulatory aspects which range from the complex structure, full understanding of the pharmacokinetic and pharmacodynamic properties to the chemical composition and physicochemical properties. In the years to come, through all the innovations in science and technology, nanomedicines would definitely see a boom overcoming all the regulatory hurdles.

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