Send Orders for Reprints to reprints@benthamscience.ae

Current Drug Targets, **2018**, *19*, **000-000**

REVIEW ARTICLE

Nanocarrier Based Advances in Drug Delivery to Tumor: An Overview

Ankit Jain[1], Romi Kumari[2], Ankita Tiwari[2], Amit Verma[2], Amita Tripathi[2], Akanksha Shrivastava[2] and Sanjay K. Jain[2,*]

[1]*Institute of Pharmaceutical Research, GLA University, NH-2, Mathura-Delhi Road, Mathura (U.P.) - 281 406, India;* [2]*Pharmaceutics Research Projects Laboratory, Department of Pharmaceutical Sciences, Dr. Hari Singh Gour Central University, Sagar (M.P.) - 470 003, India*

ARTICLE HISTORY

Received: June 09, 2017
Revised: November 28, 2017
Accepted: January 24, 2018

DOI:
10.2174/1389450119666180131105822

Abstract: ***Background*:** Nanotechnology deals with the manufacturing of materials at the atomic and molecular scale. According to the National Nanotechnology Initiative, nanotechnology denotes those structures which are nearly in 1−100 nm size regime in at least one dimension.

***Objective*:** Nanotechnology in drug delivery has been evidenced into nanocarriers that possess distinct properties both *in vitro* and *in vivo*, which may be used in targeting drugs to various diseases especially tumors. In the last few years, there has been a keen concern in the formulation of various new drug delivery systems employing nanotechnology. Different nanodevices or nanocarriers like liposomes, dendrimers, polymersomes, transfersomes, and nanoparticles *etc*. have been employed for the targeted drug delivery.

***Conclusion*:** This review summarizes the advances in nanocarriers in terms of their methods of preparation and potential applications especially in tumors.

Keywords: Nanotechnology, nanocarriers, targeting, dug delivery, tumors.

1. NANOTECHNOLOGY IN DRUG DELIVERY

The word “Nano” implies dwarf in Latin and it counts 10^{-9} divisions or parts. The beginning of nanotechnology is a debatable matter, however, the record of the invention of the scanning tunneling microscope could be found in the year 1980 [1]. The United States launched the National Nanotechnology Initiative in 2000 as one of the world’s first programs of its kind that revolutionized capture quality at nanometric scale like nanorobots killing cancer cells [2]. Nanotechnology deals with the processes and products that exist at molecular and atomic level. Nanotechnology is an emerging field of pharmacy involving changes in physical and chemical properties of materials [3]. It includes control of material shape and size by virtue of design, synthesis and characterization at nano scale. When the particle is reduced to nano size, it results in changes in properties such as increase in the surface area and higher surface area to volume ratio *etc*. So far, there are two basic ways to produce nanoparticles *viz*. (a) the "top-down" technique which refers to reduction of the particles from large size to nanometer size, (b) the "bottom-up" method in which individual atoms and molecules are combined to produce nanodevices in various shapes and sizes such as nanospheres or nanotubes. However, the latter approach is less popular [4]. Many nanoparticle based formulations have been developed and tested to remarkable effect in small animal models, but unfortunately the outcomes thus obtained have depicted a circumscribed clinical success [5]. Various factors like meticulous understanding of the limitations associated with nanoparticles, recognizing the misconceptions which are prevailing in the field *etc*. are necessitated in order to successfully translate the before said results in clinical phases. Various strategies based on nanoparticles can effectively enhance the drug delivery by concentration on the associated problems like increasing their drug loading capacity, targeting affinity, and spatiotemporal control of drug release [6]. (Fig. **1**) represents chronological development of drug delivery systems.

In this view, major attention would be on various aspects of drug-delivery in nanotechnology. Various names like, nanocarriers, nanoconstructs *etc*. have been used to refer to the nanoparticles which have been developed for drug delivery. “Nanoparticle” represents all mentioned various formulations, like liposomes, polymer micelles, and solid particles [7-11]. Nearly all literature including papers on nanoparticles commonly conclude: nanotechnology possess an outstanding potential in drug delivery [12]. There is an urge to define the need in order to attain tangible results.

Numerous reasons fetch the attention of nanoscale sized drug delivery systems by the scientists. Engineering of the drug particles can be done to form nanoscale size materials [13]. Due to the enhanced permeability and retention effect

*Address correspondence to this author at the Department of Pharmaceutical Sciences, Dr. Hari Singh Gour Central University, Sagar (M.P.) - 470 003, India; Tel: +91-9425172184; E-mail: drskjainin@yahoo.com

1389-4501/18 $58.00+.00

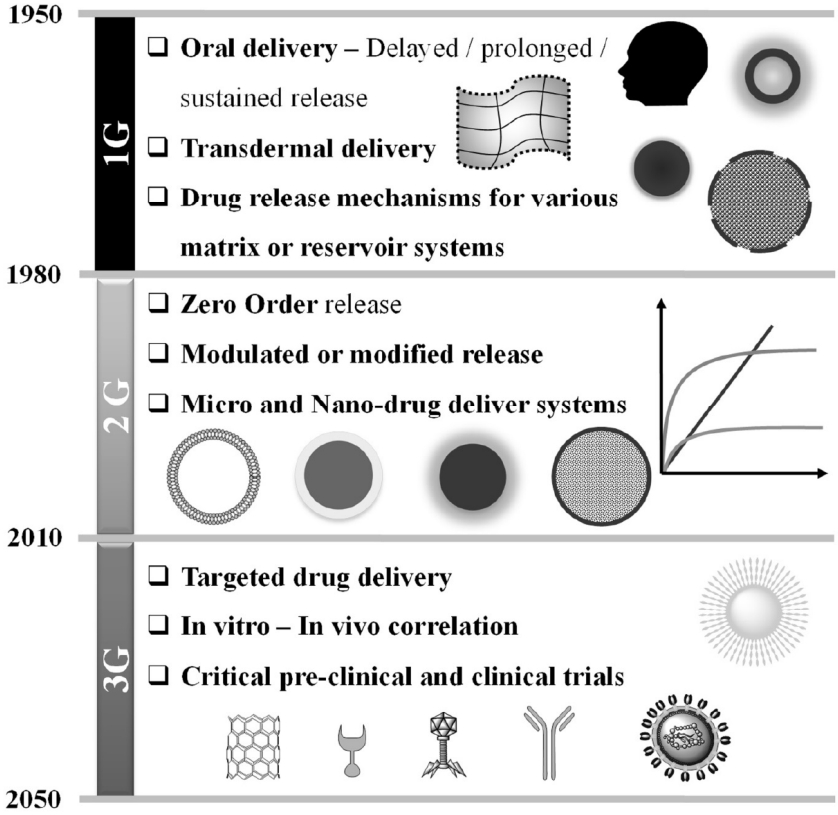

Fig. (1). Chronological development of drug delivery systems.
(1G: First generation, 2G: Second generation and 3G: Third generation).

(*i.e.* EPR), nanosized systems (sizes less than eukaryotic or prokaryotic cells) can ultimately reach the inaccessible areas like tumor cells in high amount and can vitiate the lymphatic drainage therefore, they could be employed for the peroral delivery of proteins and genes [14]. They could be utilized for targeting the reticuloendothelial cells, thereby alleviating passive targeting of drug to the macrophages of liver and spleen and therefore, rendering a natural system for preventing the occurrence of various infections [15]. Safe and biocompatible nanomaterials should be employed for this purpose. They should not impede the blood vessels and need to be less invasive and less toxic in order to safely target the particular tissue [16]. They should protect the drug degradation in the gastrointestinal tract and aid in bypassing the "first-pass" metabolism which occurs in the liver. They usually persist in the blood circulation for a longer period of time, particularly the ones coated with hydrophilic polymers and thus, desirable for increasing the efficacy of drugs with short half-lives and could be employed to monitor the drug as sustained release formulation [17]. The solubility of poor water soluble drugs is increased, onset of therapeutic action is enhanced, and the dose is lowered. The premature loss of drug *via* rapid clearance and metabolism could also be precluded. Retention because of bio-adhesion is also enhanced [18]. (Fig. **2**) represents targeting strategies in drug delivery.

2. NANOCARRIERS

Nanotechnology, applies the principles of engineering, electronics, physical and material science, and manufacturing at a molecular or submicron level [19, 20]. Nanodevices are used in a wide variety of fields, including sensor, targeted drug delivery, therapeutic agents, cellular imaging and diagnostics, and others. Drug delivery systems based on nanomaterials provide important tools to enhance the chemotherapeutics efficacy [21]. Nanotechnology based novel drug delivery systems are being exploited for the treatment of various diseases including cancer and diabetes, and gene therapy *etc*. The major benefits of this mode of treatment are enhanced drug targeting and increased safety. Nanotechnology has also been employed in diagnostic medicine in the form of contrast agents, magnetic nanoparticles *etc*. In conventional systems, safety and efficacy of the drug employed for chemotherapy are the major factors affecting the treatment results in a patient suffering from cancer. These drugs possess poor cell specificity and depict severe toxic effects like bone marrow suppression, gastric erosion, hair loss, cardiomyopathy *etc*. on other systems [22].

2.1. Need of Nanocarriers

Nanotechnology is a novel field of science that renders a new hope, the tools and technology to work at atomic level levels. It displays numerous advantages for an ideal drug delivery as (a) it presents engineering of particles smaller than 100 nm that provide better delivery of drugs to very small parts within the body [23], (b) it promises to bridge the gap between 'the structure' and 'the function' of bio molecules over and above between 'human physiology' and 'pathophysiology', (c) nanocarriers provide efficient drug delivery to ameliorate aqueous solubility of drug [24, 25], that increases the bioavailability [26] for timely release of

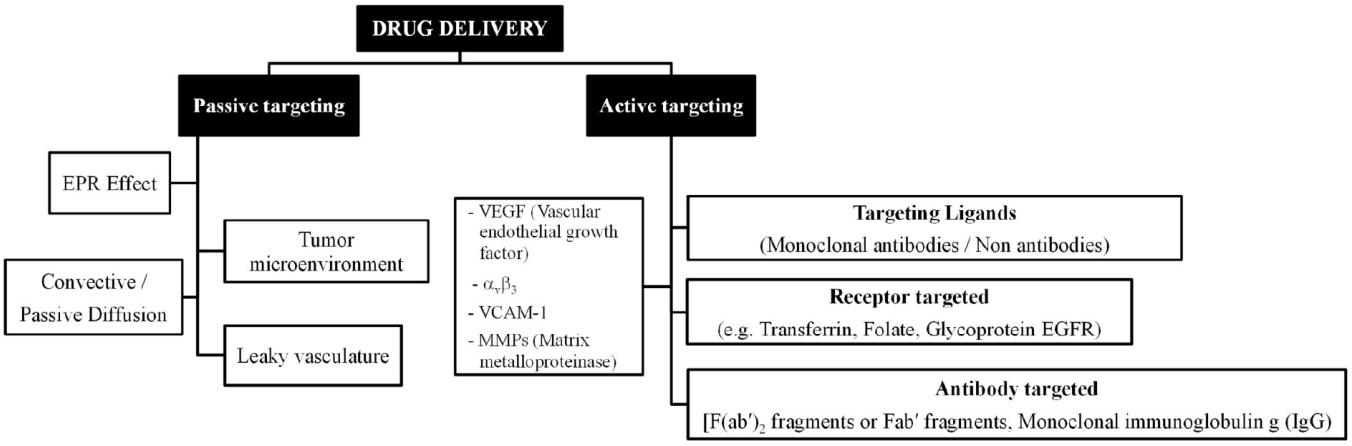

Fig. (2). Targeting strategies in drug delivery.

drug molecules, efficient drug targeting [27], and reducing drug toxicity [28]. (Fig. **3**) represents drug delivery potential of multipronged nanocarrier to tumors.

2.2. Types and General Methods of Preparation

Nanocarriers are devices of nanoscale (below 1 μm) composed of various biodegradable materials like natural or synthetic polymers, lipid or phospholipids and organometallic compounds [29]. Nanocarriers due to their submicron size possess a very high surface to volume ratio resulting in increased dissolution rate. Nanocarriers include various submicron systems like nanoparticles, nanocapsules, lipid complexes, polymeric micelles, liposomes, polymersomes, fullerenes, nanopores, nanoshells, quantum dots, nanocrystals, nanotubes and dendrimers *etc*. (Fig. **4** and Table **1**) [19].

2.2.1. Liposomes

Liposomes are identified for their capability to protect encapsulated agents, prolong their duration of action, rendering effective intracellular delivery. Liposomes allow the enclosed sphere to encapsulate hydrophilic drugs within the central compartment, while the drugs which are insoluble in water can be entrapped in the hydrophobic region of the membrane. The liposome size may vary from very small (0.025μm) to large (2.5μm) vesicles according to their types [30-32]. The method of preparation of liposomes has been represented diagrammatically in (Fig. **5**) [33].

2.2.2. Polymersomes

The core of the vesicles consists of an aqueous phase and the surrounding coating bilayers are of polymer; the resulting particles are called as polymersomes and the size ranges between 5nm-5μm [34]. The vesicles of the polymersomes are analogous to liposomes and useful in the delivery of hydrophilic drugs which can be encapsulated in their aqueous reservoir, but they are different from liposomes in the external bilayer because the external bilayer of polymersomes is composed of amphiphillic copolymers. The diblock copolymers PEG-b-PBD (polybutadiene) and PEG-b-PEE (polyethylethylene) are strong vesicle or polymersome formers [35, 36]. Polymersomes usually own a higher density of PEG on their surface and longer circulation times in comparison to PEGylated liposomes [37]. The complete method of preparation of polymersomes has been represented in (Fig. **6**) [38, 39].

2.2.3. Dendrimers

Dendrimers are systems for targeted drug delivery due to their nanometer size range, functionalization and ease of preparation [62, 63]. Its molecules consist of a small molecule or a linear polymer core using connectors and branching units. Interaction of dendrimer molecules with the molecular environment is mainly controlled by their terminal groups. Loading of drug molecules can occur in the interior of the dendrimers, showing their attachment to surface groups as well. The synthesis of dendrimers starts from the central core and works towards the periphery (Divergent synthesis) since dendrimers are built from ABn – type monomers, and the generation of branching units double or triple the number of peripheral functional groups [63, 64]. (Table **2** and Table **3**) summarize medical application of nanocarriers and marketed products or products in clinical trials with their indications, respectively. (Table **4**) enlists the examples of nanocarriers as drug vehicle for cancer treatment.

2.2.4. Polymeric Micelles

There are various advantages possessed by polymeric micelles above the conventional surfactant micelles due to their better thermodynamic stability in physiological solution, as shown by their low critical micelle concentration (CMC) [100, 101]. Micelles have a reasonably narrow size distribution in the nanometer range (10-100 nm) and these systems are employed for the systemic delivery of water insoluble drugs. The size range of polymeric micelles (less than ~100 nm in diameter) renders them an ideal drug delivery carrier since they evade renal exclusion and the RES, and it also enhances endothelial cell permeability *via* passive diffusion [102, 103]. As for example, a system based on doxorubicin (DOX) is conjugated to poly(ethylene glycol)-poly(α,β-aspartic acid) block copolymer [PEG-PAsp(DOX)] [104]. Various thermosensitive polymers have been employed in the preparation of micelles. For example, thermosensitive amphiphilic block copolymer, and P-(N,N-isopropylacrylamide-co-N-hydroxymethylacrylamide)-b-caprolactone [P-(NIPAAm-co-NHMAAm)-b-PCL] have

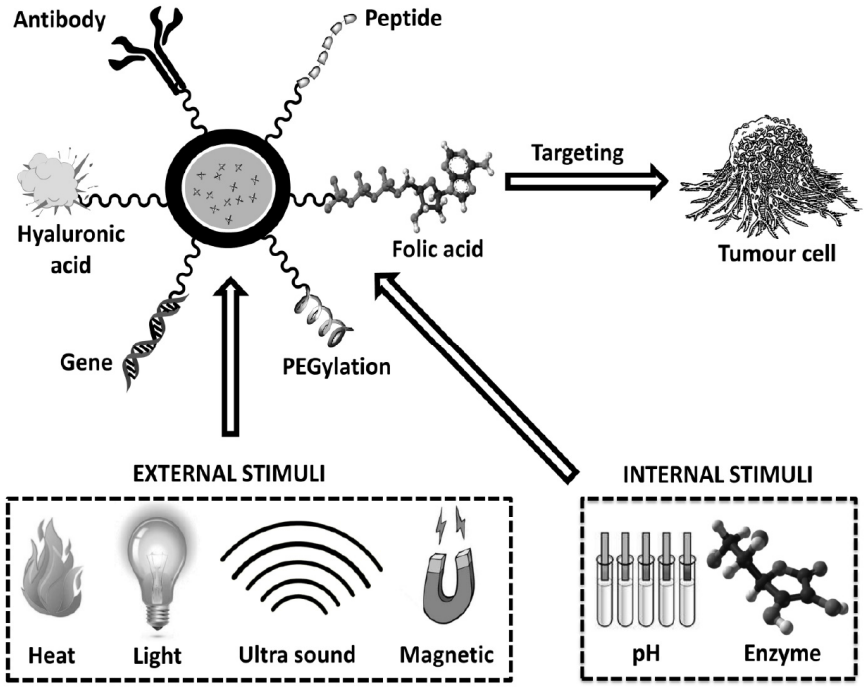

Fig. (3). Drug delivery potential of multipronged nanocarrier to tumors.

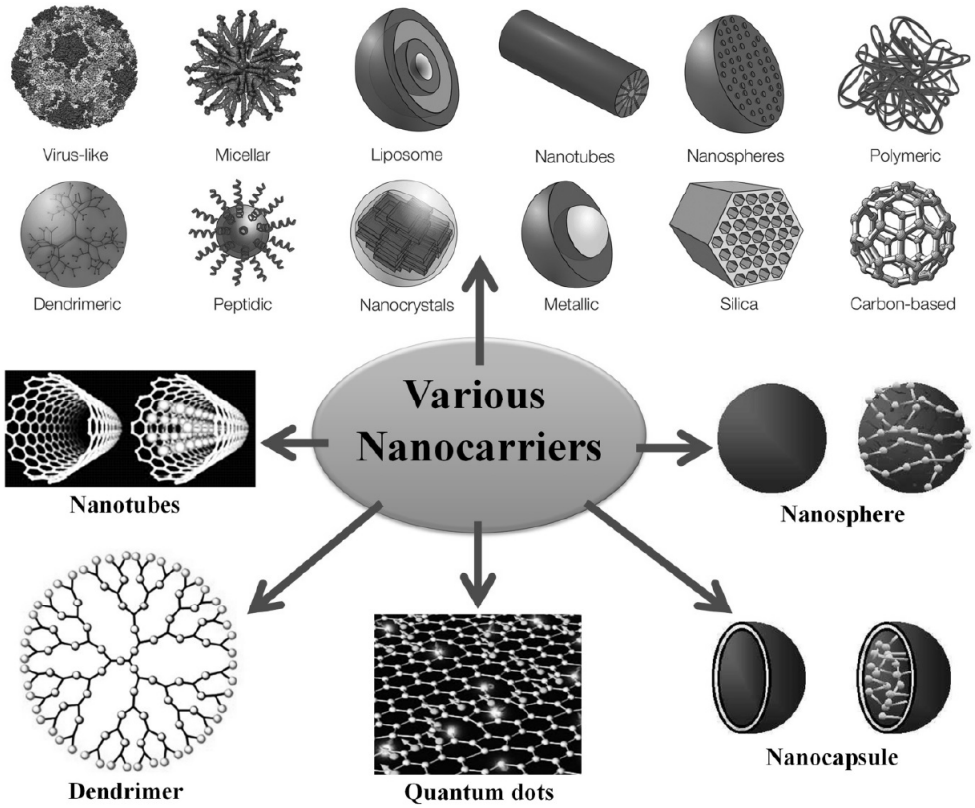

Fig. (4). Different types of nanocarriers.

been used in the preparation of DOX-loaded micelles [105]. The method selected for the preparation of block co-polymer micelles is dependent on the solubility of the co-polymer being used. The methods of preparation of micelles have been represented in (Figs. **7** and **8**) [106-109].

2.2.5. Nanoparticles

The term nanoparticles is used to designate the novel drug delivery systems that are submicron (< 1μm) in size or are colloidal systems, usually made up of polymers. Nanoparticles are constituted of both vesicular (nanocapsules)

Table 1. Different methods of preparation of nanocarriers along with crucial parameters.

	Nanocarrier	Name of Method	Crucial Parameters	Size	Advantages	Disadvantages	Ref.
LIPOSOMES	**Mechanical Dispersion Methods of Passive Loading**						
	➢ Thin film hydration using hand shaking (MLVs) method.		Mechanical energy is needed for the swelling of lipids & dispersion of casted lipid film is lent by manual agitation.	MLVs – 500 nm	Lipid soluble compounds can be encapsulated efficiently (100%). It does not disturb structural composition of the membrane.	Wastage of large amounts of water soluble compounds occurs during swelling (only 25-35%of total volume gets entrapped).	[40]
	➢ Thin film hydration using non-shaking method.		By displaying the film to a stream of water-saturated nitrogen for 15 min accompanied by swelling in aqueous medium without shaking.	ULVs - 20 to >1000 nm	The percent encapsulation efficiency as high as 30% (at 100 mg lipid ml^{-1}) is achieved.	Large amount of water soluble compounds are wasted during swelling.	[40]
	➢ French pressure cell liposome.		Size of FPL (French press liposomal) is variable, depending on lipid composition, temperature and pressure.	Uni- or oligolamellar liposomes of intermediate size (30-80 nm in diameter depending on the applied pressure)	Liposomes show more stability in comparison to sonicated liposomes. Leakage of contents from liposomes is slower & lower than sonicated liposome.	High initial cost of the press that consists of an electric hydraulic press and pressure cell.	[41, 42]
	➢ Sonicated unilamellar vesicles (SUVs)		The size and distribution are affected by composition and concentration, temperature, sonication time and power, volume and sonication tuning.	Approx. 20 to >1000 nm (SUVs)	Bath sonicator is more suitable for large volume of diluted lipids.	It causes leakage of contents from liposomes. It suffers from overheating of the liposomal dispersion causing lipid degradation.	[43]
	➢ Microemulsification liposomes (MEL)		Microfluidiser pumps the fluid at very high pressure (10,000psi, 600-700bar) through 5µm orifices. The nature of hydration medium and the membrane components affect the size distribution of the vesicles.	Small multilamellar vesicles approx. 500 nm	It is able to process sample with a very high proportion of lipids (20% or more by weight) and also efficient for encapsulation of water-soluble materials.	The presence of negative lipids tends to decrease their size.	[44]
	➢ Dried-reconstituted vesicles (DRVs)		It provides organized membrane structure, which on addition of water (one tenth the volume of original SUVs) can rehydrate, fuse and reseal to form vesicles with high capture efficiency.	Uni- or oligolamellar vesicles of the order of 1.0 µm or less in diameter.	High entrapment of water soluble component and suitable only for unilamellar vesicles.	The incorporation rates with multilamellar vesicles are quite low.	[45]
	➢ Freeze thaw sonication (FTS) method		In this process, SUVs rupture and refuse during which the solute equilibrates between inside and outside. And the liposomes fuse amongst themselves & enhance remarkably in size.	ULVs- 20 nm to >1000 nm	It is a simple, rapid and mild for entrapped solutes, and also provides a high proportion of large unilamellar vesicles formation.	Neutral liposomes cannot be subjected to freezing and thawing method. Sucrose, divalent metal ions and high ionic strength salt solution cannot be entrapped efficiently.	[46, 47]

(Table 1) contd….

	Nanocarrier	Name of Method	Crucial Parameters	Size	Advantages	Disadvantages	Ref.
	Solvent dispersion methods for passive loading						
	➢ Ethanol injection method		The rate of injection is high (sufficient) to achieve proper mixing.	100 nm	Low risk of degradation of sensitive lipids.	Difficulty to remove residual ethanol from phospholipid membrane. If the mixing is not enough, it forms lipid aggregates and larger vesicles.	[48]
	➢ Ether injection method		Injecting the immiscible organic solution very slowly into an aqueous phase through a narrow needle at the temperature of vaporizing the organic solvents.	LUVs- 20 nm to >1000 nm	Sensitive lipids are to be treated very gently.	Very low risk of oxidative degradation provided ether is free from peroxides. Encapsulation efficiency is low and it requires long time to produce a batch of liposomes.	[49]
	➢ Reverse phase evaporation method		Removal of solvent from an emulsion by evaporation is essential and bath sonicator is required for the formation of droplets.	ULVs an average diameter of 0.5 μm.	It provides high encapsulation efficiency (nearly 50%).	Removal of free drug is difficult by dialysis, and requires high cost of vortex mixer.	[50]
	➢ Rapid solvent exchange vesicles (RSEVs)		For passing the organic solution of the lipids through the orifice of blue-tripped syringe under the vacuum into a tube containing aqueous buffer is required.	LUVs- 20 nm to >1000 nm	It provides fast and efficient removal of solvents, and does not require a high volatile solvent. It requires not more than a minute for preparation of liposomes.	High initial cost of vortexor is required.	[51]
	Detergent Depletion (Removal) Methods of Passive Loading						
	➢ Dialysis		A higher CMC (critical micelle concentration) depicts that the equilibrium is strongly shifted towards the bulk solution, thus removal from the mixed membrane *via* dialysis turns comparatively easily.	˜100 nm	It provides large unilamellar vesicles, rapid clearance of RES uptake and high entrapped volume.	Its thermodynamic stability is less.	[40]
TRANSFERSOMES	➢ Rotary evaporation method		The organic solvent was evaporated by rotary evaporation under reduced pressure at 40°C, and probe sonicator was employed to prepare small multilamellar from LMVs.	Average diameter of vesicle is 500 nm.	It can deform and pass through narrow constriction (from 5-10 times less than their own diameter) without considerable loss and high deformability gives better penetration of intact vesicles.	It is chemically unstable due to its predisposition to oxidative degradation.	[52, 53]
	➢ Vortexing-sonication method		Vortexing of the blend is performed to obtain a milky suspension and sonicated, accompanied by extrusion *via* a polycarbonate filter.	100nm.	High deformability gives better penetration.	It depicts chemical instability due to its predisposition to oxidative degradation.	[54]

(Table 1) contd….

	Nanocarrier	Name of Method	Crucial Parameters	Size	Advantages	Disadvantages	Ref.
NIOSOMES	➢ Hand shaking method		Mechanical energy is necessitated for the swelling of lipids & dispersion of casted lipid film is imparted by manual agitation.	Approx. 500 nm	It does not disturb structural composition of the membrane.	Wastage of a large amount of water soluble compounds takes place during swelling.	[49, 55]
	➢ Ether injection method		It requires14-gauge needle to slowly inject ether solution into aqueous phase.	LUVs- 20 to >1000 nm	This method is used to treat sensitive lipid very gently.	Little danger of inducing oxidative degradation provided ether is free from peroxides. Encapsulation efficiency is very low.	[49]
	➢ Reverse phase evaporation method		Removal of solvent from an emulsion by evaporation is essential and bath sonicator is required for the formation of droplets.	ULV diameter 0.5 µm.	It provides high encapsulation efficiency (nearly 50%).	Removal of free drug is difficult.	[56]
DENDRIMER	➢ Divergent synthesis		In which the synthesis starts from a polyfunctional core and continues radially outwards by successive stepwise activation and condensation.	1-100 nm	It provides molecular recognition and self-assembling system. Its 3D structure owning besides well-defined surface functionality.	It can cause trailing generations due to impurities. It is very difficult to purify due to the relative size differences between perfect and imperfect dendrimers are quite small.	[57]
	➢ Convergent synthesis		In which the synthesis starts at the periphery of the final macromolecule and proceeds inwards.	Approx. 100 nm	It provides more monodispersed final dendrimers because it is much easier to remove impurities.	Dendrimers made *via* this method are not as large as those made by divergent methods due to the crowding because of steric effects developed along the core	[57]
NANOPARTICLES	**Polymerization of monomers**						
	➢ Radiation polymerization		The molecular weight as well as particle size increases with: increasing monomer concentration, decreasing temperature and decreasing initiator concentration.	Nanospheres <1 µm	Due to their larger surface area, nanoparticles have higher loading capacity.	High surface energy that may lead to high aggregation in biological system.	[58]
	➢ Emulsion polymerization		Precaution should be taken to prevent too quick polymerization that may lead to the formation of unwanted agglomerates.	100 nm diameter of PMMA copolymer and doxorubicin nanoparticles.	This method is used to prepare polycyanoacrylate nanospheres by anionic polymerization.	The molecular weight of the polymers formed cannot be controlled easily and during the polymerization, the monomers may react with the drug, leading to the inactivation.	[58]
	Dispersion of preformed polymers						
	➢ Emulsification/solvent evaporation method		Both these methods need high-speed homogenization or sonication.	Nanoparticle <1 µm	It is commonly used to prepare nanoparticles of water-soluble drugs.	Large amount of emulsifiers, time and energy consuming techniques are required.	[59]

(Table 1) contd….

	Nanocarrier	Name of Method	Crucial Parameters	Size	Advantages	Disadvantages	Ref.
	➢ Controlled precipitation (Desolvation)		In this method, the polymer is precipitated from its solution by the addition of a non-solvent or some salts.	Nanoparticle <1000 nm	There is no need of any additive like surfactants, protective colloids.	Purification step is essential to remove various added materials and also requires continuous monitoring in order to prevent the formation of large agglomerates.	[60]
	➢ Supercritical fluid technology		It is used to process the particles in high purity and without any trace of organic solvents.	Nanoparticles < 100 nm	It consists of the growth of the particles in a well-controlled manner to obtain a desired morphology.	High initial cost of SCF machine.	[61]

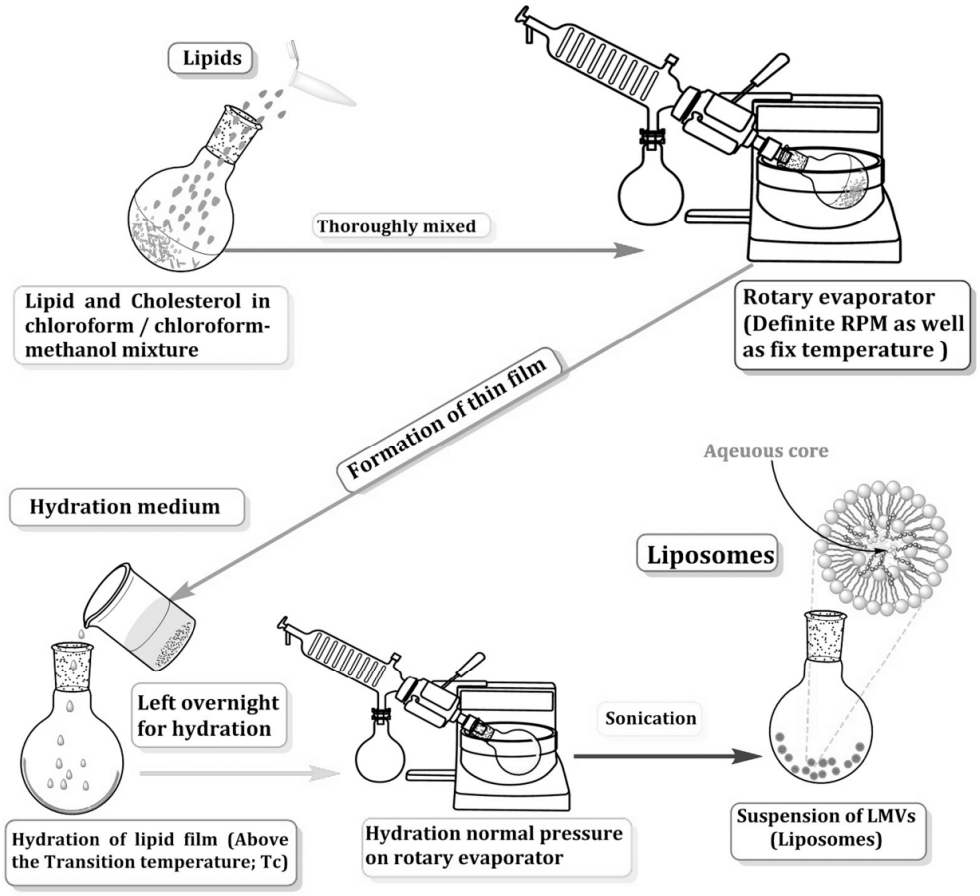

Fig. (5). Method of preparation of Liposomes.

and matrix system (nanospheres). Nanocapsules are systems in which the drug is restricted to a cavity enveloped by a distinct polymeric membrane and size range between 100 – 300 nm, while nanospheres are systems in which the drug is dispersed throughout the polymer matrix with size ranging from 100 – 200 nm [110, 111]. Several thermosensitive polymers have been used in the preparation of nanoparticles. Na *et al.* (2006) prepared biodegradable thermo-sensitive nanoparticles from poly(L-lactic acid)/poly (ethylene glycol) alternating multi-block copolymer as a drug carrier for lung cancer carcinoma [112].

Nanospheres are formulated by two methods depending on the polymers to be utilized. Polymers like biodegradable polyesters in various techniques like solvent evaporation, emulsification and salting out may be employed to prepare the nanospheres. But the most common technique is solvent displacement method which is also known as nanoprecipitation. This has been depicted in (Fig. **9**) [113, 114]. Nanocapsules are commonly prepared by the interfacial deposition of preformed polymers. The method of preparation has been represented in (Fig. **10**) [115].

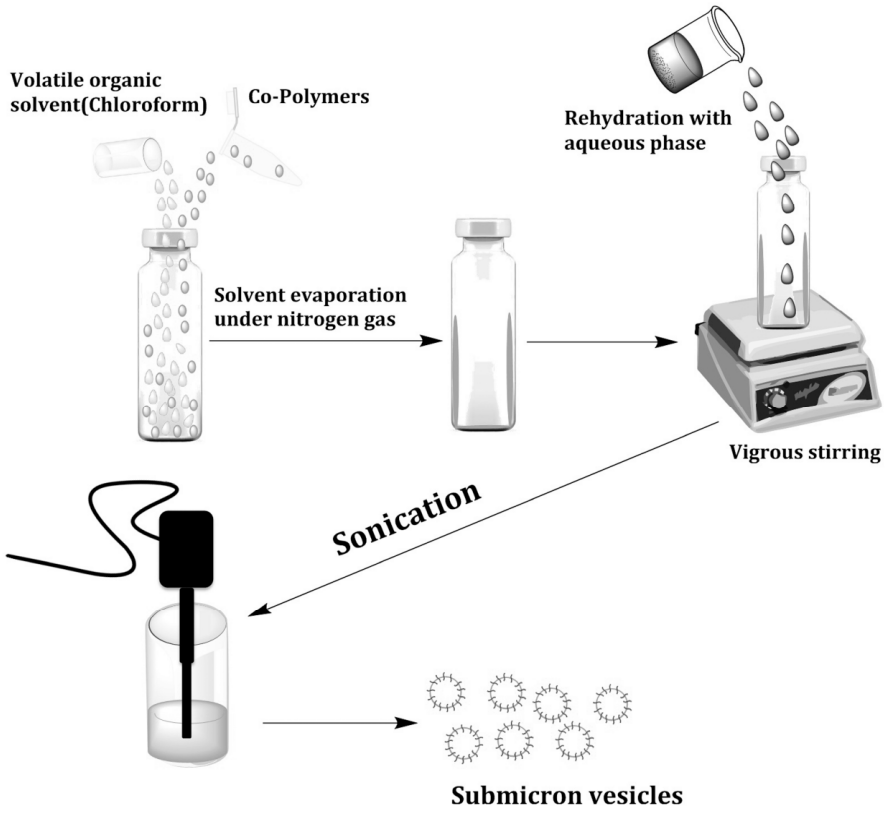

Fig. (6). Method of preparation of Polymersomes.

Table 2. Medical application of nanocarriers.

Systems	Product	Description	Use	Manufacturer
Liposome	Doxil®	Liposomal doxorubicin	Ovarian tumour	Ortho Biotech
Liposome	AmBisome®	Liposomal preparation of amphotericin-B	Fungal infection	Astellas Pharma US
Nanoparticle	Abraxane®	Albumin bound taxane particles	Non-small cell lung cancer	Abraxis oncology
Nanoparticle	Combidex®/ Ferumoxtran-10	Iron oxide nanoparticles	MRI contrast agent	AMAG Pharmaceuti-cals
Nanobubble	MRX 815	Nanobubble technology	Treatment of in-travascular clots	IMA Rx Therapeutics
Dendrimer	VivaGel®	Dendrimer based microbicide gel	HSV prevention	Star pharma Pvt. Ltd.
Nanoparticle	INGN 401	Nanoparticle formulation of tumour suppression gene FUS1	Lung cancer	Introgen Therapeutics Inc.
Dendrimer	Dendrimer-magnevist#	PMMAM dendrimers	MRI imaging agent	Dendritic Nanotech-nologies Inc.
Nanoshell	Aurolase™	Gold nanoshell	Head and neck cancer	Nanospectra Bio-sciences Inc.
Nanoparticle	Targeted Nanotherapeutic (TNT)™ sys-tem	TNT with polymer coated iron oxide magnetic particle	Solid tumour	Triton Biosystems
Nanoparticle	MRX 952	Nanoparticle preparation to encapsulate camptothecin analogues	Tumours	IMA Rx Therapeutics

Table 3. Marketed products or products in clinical trials with their indications.

	Compound	Product	Status	Indications	Ref.
Liposomes	**Liposomal Doxorubicin**	Daunoxome	Market	Kaposi's sarcoma	[65]
	Stealth Liposomal Doxorubicin	Doxil/Caelyx	Market	Kaposi's sarcoma, refectory ovarian cancer, refectory breast cancer	[66, 67]
	Liposomal Doxorubicin	Myocet	Market (Europe)	Metastatic breast cancer in combination with cyclo-phosphamide	[68, 69]
	Liposomal lurtotecan	OSI-211	Phase-II	Recurrent ovarian cancer, recurrent small-cell lung cancer	[70]
	Liposomal paclitaxel	LEP ETU	Phase-I/II	Advanced solid tumors	[71]
	Liposomal oxaliplatin	Aroplatin	Phase-II	Advanced colorectal cancer	[72]
	Liposomal interleukin-2	Oncolipin	Phase-II	Immune stimulant for use with a liposomal vaccine against non-small cell lung cancer	[73]
Polymeric Nanoparticles	**Albumin-Paclitaxel**	Abraxane/ ABI-007	Market	Metastatic breast cancer	[74]
	Paclitaxel-Poliglumex	CT-2103; Xyotax	Phase-III	Non-small cell lung cancer, ovarian cancer	[75, 76]
	HPMA-copolymer-doxorubicin	PK1; FEC28069	Phase-II	Lung cancer, breast cancer and various other cancers	[77, 78]
	HPMA-copolymer-doxorubicin-galactosamine	PK2; FEC28069	Phase-I/II	Particularly hepatocellular carcinoma	[79]
	PEG-aspartic acid-doxorubicin micelle	NK911	Phase-I	Pancreatic cancer	[80]
	HPMA copolymer-paclitaxel	PNU166945	Phase- I	Various cancers	[81]
	PEG-camptothecin	Prothecan	Phase-II	Various cancers	[82, 83]
	HPMA copolymer-camptothecin	MAG-CPT	Phase-I	Various cancers	[84, 85]

Table 4. Examples of nanocarriers as drug delivery vehicle for cancer treatment.

	Drug Type	Cancer Type	Formulation	Remarks	Ref.
Carbon Nanotubes	Cisplatin	Lung cancer	Injectable chemotherapeutics with cisplatin entrapped in amino-functionalized multiwalled carbon nanotubes	Functionalization of carbon nanotubes with amino moiety enhances the drug accumulation in tissues such as- lung, and reduces drug accumulation in kidney & liver. It does not affect the biodistribution of cisplatin.	[86]
	Oxaliplatin	Metastatic and advanced colorec-tal cancer	Oxaliplatin is incorporated into the inner cavity of multiwalled carbon nanotubes, and polyethylene glycol 600 is used to surface functionalize the nanotubes to enhance their water solubility and reduce cytotoxicity.	The carbon nanotubes selectively deliver oxaliplatin to tumor tissues and enhance the overall efficacy of drug.	[87]
	Paclitaxel	General cancer	Paclitaxel is incorporated into differ-ent carbon allotropes like graphene oxide, carbon nanotubes, and nano-diamonds	The delivery systems own adequate surface-to-volume ratio, thermal conductivity and rigid struc-tural properties.	[88]

(Table 4) contd….

	Drug Type	Cancer Type	Formulation	Remarks	Ref.
	Doxorubicin	Breast cancer	A steroid-macromolecular bioconjugate based on polyethylene glycol-linked 17β-estradiol is appended to intrinsically cell-penetrable multi-walled carbon nanotubes.	The developed delivery system initiates intranuclear drug delivery and is effective against breast cancer *in-vivo*.	[89]
	Doxorubicin	Breast cancer cell line MCF-7	Folic acid-appended polyethylene glycol engineered multiwalled carbon nanotubes are loaded with doxorubicin.	The nanoconjugate is more effective in tumor growth suppression because of its stealth nature and taken up by the cultured MCF-7 *via* caveolae-mediated endocytosis when compared to free drug.	[90]
	Tamoxifen	4T1 cells	An aspargine-glycine-arginine peptide modified single-walled carbon nanotube system is developed by a simple noncovalent approach, and loaded with tamoxifen.	In the developed system, the optical property of single-walled carbon nanotubes and the cytotoxicity of tamoxifen are retained. The tamoxifen loaded, aspargine-glycine-arginine modified single-walled carbon nanotubes exhibit enhanced cellular uptake, antitumor effects, and cell apoptosis when given in combination.	[91]
Quantum Dotsnt	Herceptin	Breast cancer cells SK-BR3	Herceptin, a typical monoclonal antibody, is immobilized on the surface of cadmium selenide/zinc sulphide core-shell quantum dots.	The growth of breast cancer cells is completely inhibited through specific binding of herceptin to Her-2 receptor of SK-BR3 membrane and causes interaction between quantum dots and breast cancer cells.	[92]
	Busulfan	Lung cancer	The inorganic imaging agent SPIONs, manganese-doped zinc sulphide quantum dots and busulfan are encapsulated in poly (lactic-co-glycolic acid) vesicles *via* emulsion-evaporated method.	The biodegradable polymeric vesicles are presented in the form of the nanocarrier which affords multimodal bioimaging and anticancer drug delivery.	[93]
	Doxorubicin	General cancer cell	Positively charged copper indium disulfide quantum dots electrostatically interact with negatively charged poly (L-glutamic acid) conjugated with doxorubicin.	The nanocarrier affords multimodal bioimaging and anticancer drug delivery.	[94]
Dendrimers	Methotrexate	Somatostatin receptor-overexpressed tumor	The octreotide is conjugated to polyamidoamine dendrimer and is used as the nanocarrier of methotrexate.	Specific receptor-mediated endocytosis is induced by octreotide to allow target drug delivery.	[95]
	Cisplatin	Ovarian, head, neck, and testicular cancer	Dendrimer-cisplatin complex is prepared by composite method.	The dendrimer-cisplatin complexes demonstrate relatively slow release of cisplatin due to the formation of strong bonds between cisplatin and dendrimer.	[96]
	Acetylshikonin	Leukemia K562 and breast cancer SK-BR3	Polyamidoamine dendrimers and their polyethylene glycol-grafted derivatives are employed to load the drug through strong intermolecular interaction.	The solubility of acetyl shikonin increases and formed nanoparticles can effectively inhibit the growth of tumor cells.	[97]
	Curcumin	Breast cancer cell line T47D	Polyamidoamine dendrimers encapsulate curcumin.	The curcumin-loaded polyamidoamine dendrimers show no cytotoxicity on cancer cells. Additionally, they increase the inhibitory effect on telomerase activity and decrease the IC_{50} for proliferation.	[98]
Gold and Iron Oxide	Cisplatin	SKOV3 ovarian cancer cells and tumor xenograft	The gold nanorod is stabilized with polyethylene glycol.	The mild hyperthermia (42-43°C) effect induced *via* treating tumor the gold nanorods with free cisplatin at a cytostatic concentration of 5μM.	[99]

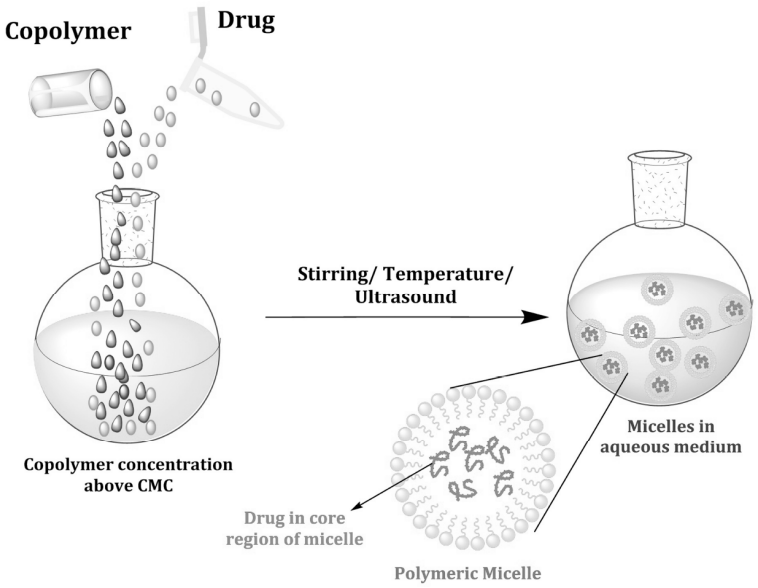

Fig. (7). Direct dissolution method for preparation of micelles.

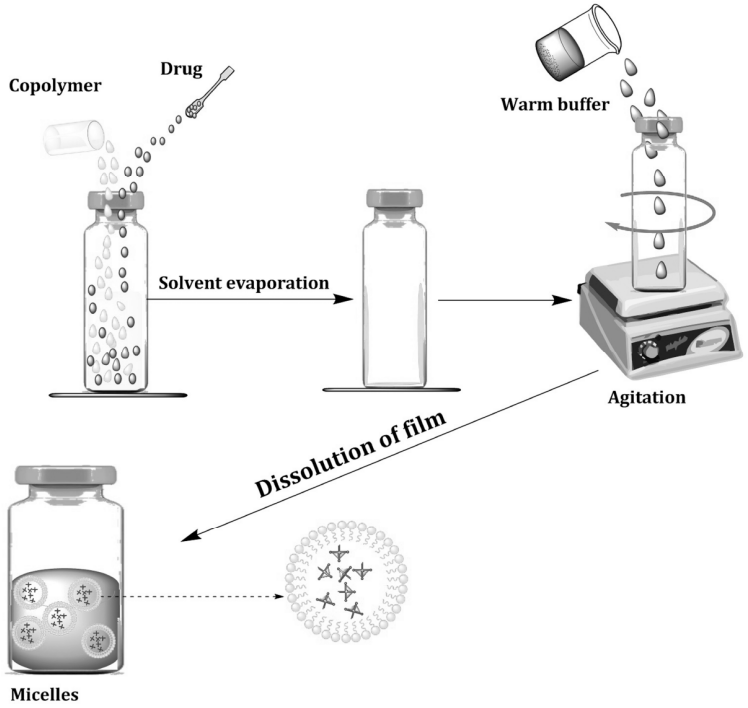

Fig. (8). Film casting method for the preparation of micelles.

2.2.6. Nanotubes, Nanowires and Fullerenes

Nanoconstructs that have earned much attention are hollow, carbon based case like structures-nanotubes and fullerenes. Nanotubes and nanowires are the self-assembling sheets of atoms arranged in the form of tubes and thread like structures of nanoscale range [116]. Nanotubes are of two types- single walled and double walled carbon nanotubes. Single walled nanotubes have an internal diameter of 1-2 nm and multi-walled nanotubes have an internal diameter of 2-5 nm with 0.36 nm distances between the layers of multi-walled carbon nanotubes, and these vary in their length ranging from 1μm to a few micrometers. The solubility of carbon nanotubes can be enhanced by incorporation of carboxylic or ammonium groups to their structure, and it could be utilized for transporting the peptides, nucleic acids and other drug molecules. For example, Indium-111 radionuclide labeled carbon nanotubes are under investigation for destroying the cancer cells selectively [117].

Fullerenes possess spherical structures which are called as "Bucky balls", and the soluble derivatives of fullerenes, like C-60 a soccer ball shaped arrangement of 60 carbon atoms per molecule, are promising pharmaceutical agents. The most common form of fullerenes is Buckminster fullerene, measuring about 7Å in diameter with 60 carbon

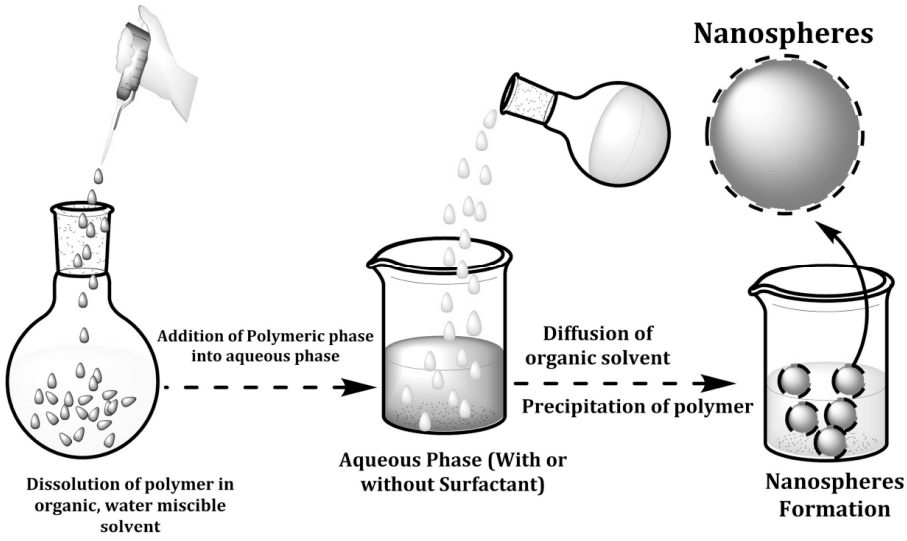

Fig. (9). Solvent displacement method (nanoprecipitation method) for the preparation of nanospheres.

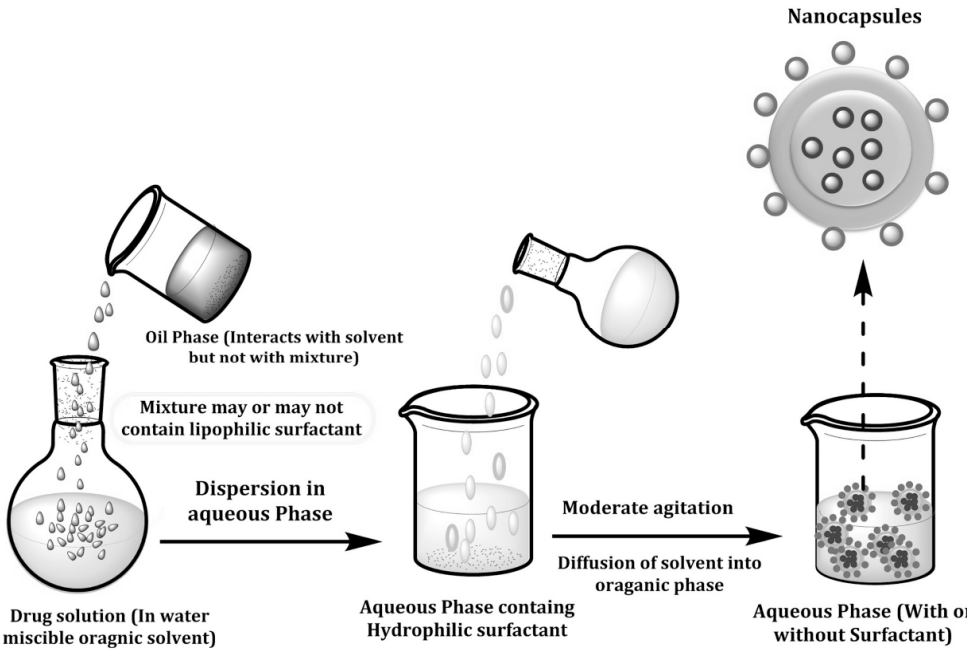

Fig. (10). Method of preparation of Nanocapsules.

atoms arranged in a shape known as truncated isosahedrons. Fullerenes are very effective in tissue selective and intracellular targeting of mitochondria and used for drug transport of antiviral drugs, antibiotics and anti-cancer agents [118]. Fullerenes and carbon nanotubes are prepared by several techniques like electric arc discharge, laser ablation, chemical vapor deposition or combustion processes [119].

2.2.7. Nanocrystals, Quantum Dots and Nanosuspension

Nanocrystals are aggregates of about hundreds or thousands of molecules that are combined in a crystalline form, composed of pure drug with only a thin coating constituted of surfactant. Nanocrystal production technique is called as "Nanonisation" [120]. To formulate nanosuspensions, the drug is dispersed in aqueous surfactant solutions by high speed stirring, and the obtained microsuspension is then homogenized to nanosize by wet milling [121], high-pressure homogenization [122], nanocrystallization from super saturated solution [123] and spray drying [124].

Quantum dots are nanocrystals around 2-10 nm which can be made to fluoresce when induced by light. It comprises of an inorganic core, the size of which influences the color emitted by an organic shell and an aqueous organic coating to which bio-molecules are conjugated. Quantum dots could also be utilized for the imaging of sentinel node in patients suffering from cancer for tumor staging and planning of therapy, and it can be utilized for different malignancies like – melanoma, breast, lung and gastrointestinal tumors [125].

2.2.8. Nanoshells, Nanopores and Nanosponges

Nanopores comprise of wafers with high density of pores (20 nm in diameter). The pores permit the entry of oxygen,

glucose and few other products like insulin, but it does not permit immunoglobulin and cells to pass through them. It is employed as a device to protect transplanted tissues from the host immune system, at the same time, employing the profit of transplantation. Nanoshells consist of nanoparticles with a core of silica and a coating of thin metallic shell. This technology is being evaluated for cancer therapy [22]. Various drug carrier systems which are based on magnetic nanocomposites have gained attention in cancer therapies for enhancing the bioavailability and minimizing the adverse effects. For example, pH sensitive core-shell magnetic nanoparticles (NPs) are synthesized by several methods like coprecipitation, microemulsion, sol–gel reactions, aerosol/vapor processes and sonolysis *etc*. [126, 127]. (Fig. **11**) shows a scheme representing the synthesis of gold nanoshells. pH responsive core-shell magnetic NPs are envisaged for controlled release of drugs into the tumor site by pH change:

- magnetite@silicon dioxide (Fe_3O_4@SiO_2),
- Fe_3O_4@titanium dioxide (TiO_2),
- β-thiopropionate–polyethylene glycol (PEG)-modified Fe_3O_4@$mSiO_2$,
- Fe_3O_4 NPs core coated with SiO_2 with an imidazole group modified PEG-polypeptide (mPEG-poly-L-Asparagine),
- polyacrylic acid (PAA) and folic acid (FA) coating of the iron oxide NP core,

PEG-modified polyamidoamine (PAMAM) dendrimer shell with Fe_3O_4 core [128].

Current researches which have been conducted in drug delivery have introduced mesoporous and nanoporous structures as nanocarriers, like inorganic or organic-based nanosponges. Amongst them, very less toxicity and low biodegradability were depicted *in vivo* by the inorganic systems based on metal. Due to this outcome, researches have shifted their focus from the organic nanosystems. In cyclodextrin-based nanosponges, the building blocks consist of hypercross-linked polymers with cyclodextrin units [129]. Poor water solubility is one of the major drawbacks of anticancer drugs. Nanosponges can play a major role in enhancing the wetting property and solubility of molecules that possess very low aqueous solubility. The complexation of drugs with nanosponges will disperse the drug molecules within the nanosponge structure to evade crystallization. Cyclodextrin-based nanosponges can provide protection to anticancer drugs, a slow and prolonged release, enhanced oral bioavailability, and trigger drug release using an internal or external stimulus upon suitable modification [2, 130].

Amongst numerous sub-areas in drug delivery, major nanotechnology research has been concentrated on tumor targeted drug delivery. This field can be utilized in defining a goal and in assessing the progress of nanotechnology in the past few years. Often, Doxil® and Abraxane® have been employed as examples of nanotechnology-based drug-delivery systems, mainly due to their size range lying within nanometers. Doxil (a PEGylated liposome formulation) was developed and commenced in the early 1980s, and it was approved by the US Food and Drug Administration (FDA) in 1995. It was approved due to its equivalent efficacy and decreased cardiotoxicity or enhanced safety profiles in comparison to free doxorubicin. The nanotechnology in drug delivery is aimed at delivering the drug the target site for increased efficacy and decreased side effects. Liposomes have been exploring for the last six decades followed by PEGylation technology for the last four decennia [131]. Earlier methods of preparation were employed for preparing them before the evolution of the concept of modern nanotechnology. There arises a question that only due to the size at nanoscale level did the drug delivery formulation became a nanotechnology system, disregarding how it is prepared? This would depict that the existing nanotechnology in drug-delivery systems has no advancements in its technology instead it is only a modification in its name [85]. Nanoscale

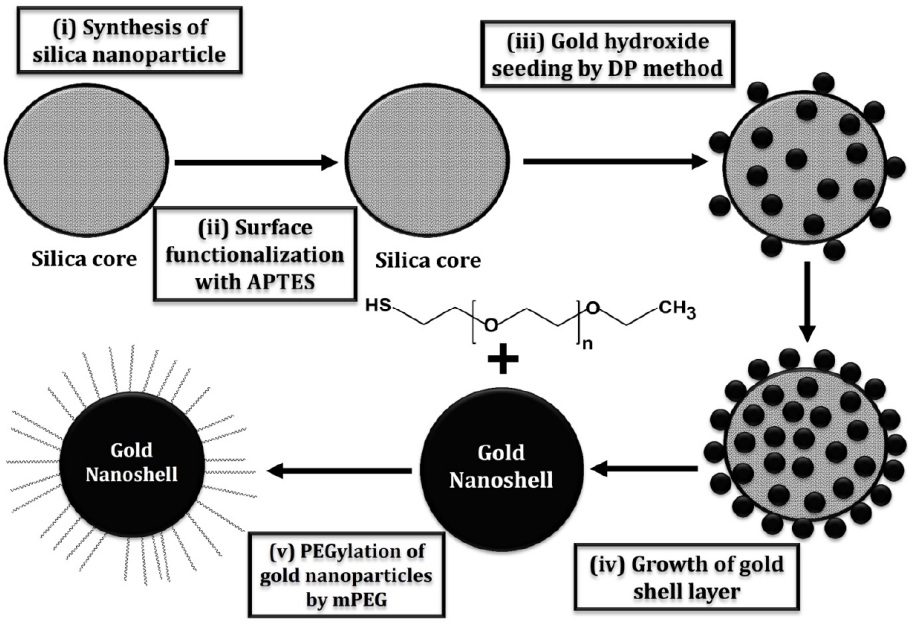

Fig. (11). Scheme representing synthesis of gold nanoshell.

drug delivery systems like nanoparticles, nanoliposomes, dendrimers, fullerene, nanopores, nanotubes, nanoshells, quantum dots, nanocapsules, nanospheres, nanocrystals, and nanosponges *etc*. are considered to possess a potential to bring a revolution in the field of nanotechnology. Nanomaterials could be employed for the development of novel drug delivery systems and reformulating the existing drugs to increase the effectiveness, patent protection, patient-compliance, safety of drugs and to make it economic [132]. (Table **5**) summarizes the typical representative targets employed in ligand-mediated drug delivery and (Table **6**) shows targeting strategies used for drug delivery to sub-cellular compartments. (Fig. **11**) depicts a scheme of receptor mediated endocytosis (RME) of a tumor targeted ligand coupled nanocarrier.

3. RECENT ADVANCEMENTS

Various nanocarriers have shown good potential in drug and gene delivery. Numerous nanosystems like nanostructured lipid carriers (NLCs), liposomes, niosomes and transfersomes have been employed in cancer targeting of dug/gene cargoes. siRNA/miRNA and small molecule co-delivery has demonstrated a better therapeutic result. Few challenges, like hostile bioenvironment, have precluded systemic delivery and thus clinical applications of this method. An ideal carrier system ought to efficiently load these agents, protect them from degradation *in vivo* and deliver to the target site. Besides, they need to be non-toxic and non-immunogenic. A promising option has been given by various nanocarriers for co-loading these agents and achieving efficient transfection *in vivo* with high specificity. Nanocarriers like lipidic and polymeric nanoparticles, SNALPs, micelleplexes, dendriplexes and inorganic nanoparticles have demonstrated their potential to simultaneously deliver the siRNA/miRNA and hydrophobic small molecule. Various factors like physicochemical properties such as molecular weight, solubility profiles and stability *etc*. and pharmacokinetic properties like absorption, bioavailability, half- life, biodistribution, metabolism, excretion, and stability in biological environment) govern the selection of a nanocarrier for co-delivery of small molecule and miRNA/siRNA. An adequate cationic charge is needed for loading miRNA/ siRNA, whereas, a hydrophobic small molecule necessitates a hydrophobic environment in the nanocarrier to get

Table 5. Few targets employed in ligand-mediated drug delivery.

Targeting Ligands	Affinity Moiety	Target Location	Application	References
Folate receptor	Folate	Cell surface, caveoli	Cancer and Inflammation	[133]
VEGF receptor	Ab (Avastin®), peptides, aptamers	Cell surface	Vasculature in solid tumors	[134, 135]
Transferrin receptor	Transferrin, Ab, aptamers	Cell surface	Cancer and blood-brain barrier	[132, 136]
MUC1	Antibody and aptamers	Cell surface	Breast and bladder cancer	[137]
MMPs	Antibody and peptides	Extra cellular matrix	Cancer and inflammation	[138, 139]
Selections	Antibody, oligosaccharides, aptamers	Cell surface	Tumor vasculature and inflammation	[140]
IL-2 receptor	Antibody and peptides	Cell surface	Cancer and immunity	[141, 142]
IGF-1 receptor	Antibody and Ab-derived peptides	Cell surface	Cancer	[143]
αvβ3 and αvβ5 integrins	RGD peptides, aptamers	Cell surface and lipid rafts	Vasculature in solid tumors	[144, 145]
EGF receptor (ErbB1)	Antibody (Erbitux®), aptamers	Cell surface and lipid rafts	Metastatic colorectal cancer	[146]
Endoglin	Antibody, Ab-derived peptides, aptamers	Cell surface-caveoli	Vasculature in solid tumors	[147]
ErbB2	Ab (Herceptin®) and aptamers	Cell surface	Breast and ovarian cancer	[148]
EDB-Fn	Antibody	Extracellular matrix	Cancer	[149]
LHRH receptor	Peptides (Lupron®, Zoladex®)	Cell surface	Prostate cancer	[150]
Insulin receptor	Antibody, Ab-derived peptides, aptamers	Cell surface-caveoli	Cancer and LSDs	[151, 152]
gp60	Albumin and antibody	Caveoli	Vascular targeting	[153]

Ab = antibody; Aptamer = only nucleic acid-based affinity molecules are shown; VEGF = vascular endothelial growth factor; MUC1 = mucin 1; VCAM-1 = vascular cell adhesion molecule 1; gp60 = albumin receptor glycoprotein 60; LHRH = luteinizing hormone-releasing hormone; EDB-Fn = extradomain B fibronectin; IL = interleukin; MMC = matrix metalloprotease; IGF-1 = insulin-like growth factor; EGF = epithelial growth factor.

Table 6. Targeting strategies used for drug delivery to sub-cellular compartments.

Sub-cellular Target	Targeting Moiety	References
Membrane anchors	Human low-affinity nerve growth factor	[154]
	Acylation	[155]
	Palmitoylation	[156]
Cell penetration	TAT peptide	[157]
	Penetratin	[158]
	Peptoids	[159]
Lysosomes	Integrins	[144, 145]
	EGF receptor	[146]
	Folate receptor	[133]
	ICAM-1	[160, 161]
	LHRH receptor	[150]
	LFA-1	[161]
	Mannose-6-phosphate receptor	[151, 152]
	MUC1	[137]
	VCAM-1	[162]
	VEGF receptor	[134, 135]
	Selectins	[140]
	TMEM192	[163]
Endosomal escape	TAT peptides	[157]
	Hemagglutinin	[164]
	GALA & KALA peptides	[165]
Golgi & ER	Cholera toxin	[166]
Mitochondria	Cytochrome oxidase subunits	[167]
	Proteins	[167]
Transcytosis	Transferrin receptor	[4]
	IGF-1 receptor	[143]
	ICAM-1	[168]
	gp60	[153]
	Amino peptidase P	[169]
	Insulin receptor	[170]
	LDL	[171]
	Glycosphingolipid globotriaosylceramide (Gb3)	[172]
	Glycoprotein-2 (GP-2)	[173]

efficiently encapsulated. On co-loading the drug and miRNA in the nanocarrier, a better pharmacokinetics can be attained specifically for the siRNA/miRNA which is highly prone to degradation by the nucleases found in the biological milieu. Moreover, combination chemotherapeutics offer various advantages like reversal of drug resistance, synergistically acting drugs, and improved efficacy in comparison to single drug therapy [174-176]. Although, each drug possesses its

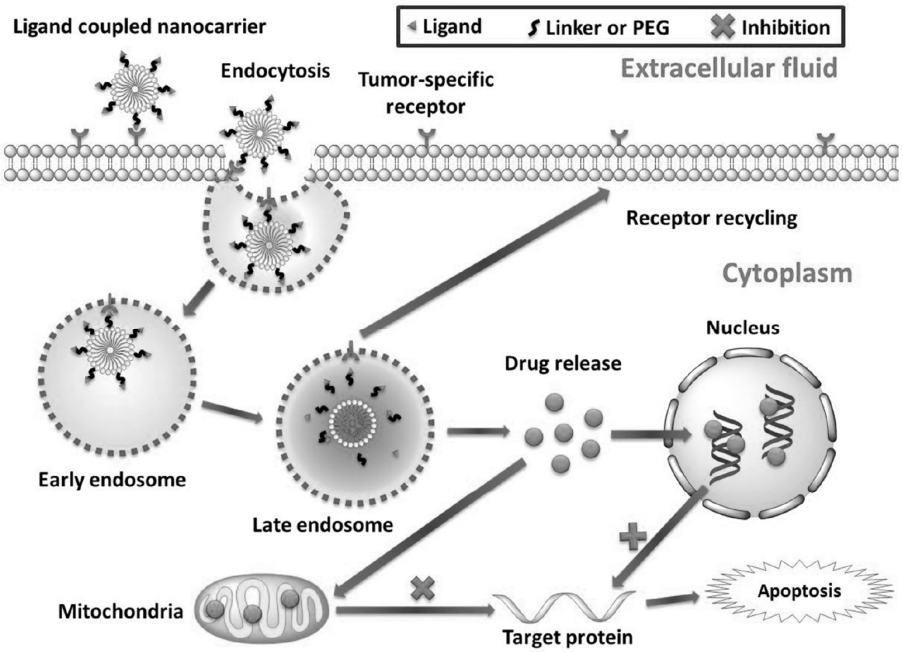

Fig. (12). Schematic representation of the Receptor Mediated Endocytosis (RME) of a tumor targeted ligand coupled nanocarrier.

unique pharmacokinetics, the administration of drug in conventional way will alter the optimized synergistic drug ratio for analysis which may further lead to inadequate therapeutic results *in vivo* [14]. Polymer and/or lipid-based nanosystems which have been designed for single drug therapy are currently being used for the co-delivery of multiple drugs [11]. Further, pharmacokinetics of the loaded molecules can be altered by modifying the surface characteristics of the nanocarriers. PEG has been widely employed for enhancing the surface hydrophilicity which renders stealth effect to the nanocarriers and raises their residence time of the blood circulation. Moreover, the surface of these systems can be modified to achieve active targeting to the tumors [175]. The application of miRNAs for cancer therapy is based on the findings that miRNA expression is deregulated in cancer tissues and the ability of miRNAs to target multiple genes and modify the cancer phenotypes. Cancer is a complex disease which involves dysregualtion of multiple genes, whereas miRNAs can regulate different disease pathways and reduce the chances of cancer. Moreover, distinctive miRNA expression profiles have been found to link with specific cancer types, allowing for the discrimination and identification of poorly differentiated tumours. Thus, miRNAs have depicted applicability as cancer therapeutics [177].

CONCLUSION AND FUTURE PROSPECTS

Nanotechnology is the main driving force behind various revolutionary changes taking place in the field of medicine. Nanotechnology and its application to nanomedicine have resulted in technological advancements across myriad fields of materials technology and have ameliorated the biomedical understanding. Nanocarriers such as liposomes, transfersomes, polymersomes, functionalized nanoparticles, fullerenes, nanotubes *etc*. are few examples of advances in nanotechnology that are currently being applied for the treatment of various diseases including cancer. These nanocarriers with advancing nanotechnology based tactics in drug delivery have emerged as promising cargoes to deliver bioactive to sub-cellular compartments at pathophysiological sites. Current research is in quest to achieve better safety and efficacy of the existing therapeutics, and it will lead to the development of newer therapeutic tools with the desired patient compliance, cost-effectiveness and ease in regulatory approval in the near future.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Nikalje AP. Nanotechnology and its applications in medicine. Med Chem 2015; 2015.

[2] Kumari A, Jain A, Hurkat P, Verma A, Jain SK. Microsponges: A Pioneering Tool for Biomedical Applications. Crit Rev Ther Drug Carrier Syst 2016; 33(1): 77-105.

[3] Sharma VK, Jain A, Soni V. Nano-aggregates: emerging delivery tools for tumor therapy. Crit Rev Ther Drug Carrier Syst 2013; 30(6): 535-63.

[4] Jain A, Jain SK. Brain Targeting using Surface Functionalized Nanocarriers. In: Singh B, Jain NK, Katare OP, Eds. Drug Nanocarriers, 2014 (ISBN no. 1-62699-052-2): 203-55.

[5] Sahoo SK, Parveen S, Panda JJ. The present and future of nanotechnology in human health care. Nanomedicine 2007; 3(1): 20-31.

[6] Jain SK, Jain A. Ligand mediated drug targeted liposomes. Liposomal Delivery Systems: Advances and Challenges. Future Science Book Series: Future Science Ltd; 2016. p. 144-58.

[7] Dangi R, Hurkat P, Jain A, Shilpi S, Jain A, Gulbake A. Targeting liver cancer *via* ASGP receptor using 5-FU-loaded surface-modified PLGA nanoparticles. J Microencapsul 2014; 31(5): 479-87.

[8] Jain A, Jain SK. Smart liposomes: Multifaceted approach to target ovarian cancer. Pharm Anal Acta 2015; 6(1): 157.

[9] Devi R, Jain A, Hurkat P, Jain SK. Dual Drug Delivery Using Lactic Acid Conjugated SLN for Effective Management of Neurocysticercosis. Pharm Res 2015; 32(10): 3137-48.

[10] Jain A, Gulbake A, Jain A, Shilpi S, Hurkat P, Jain SK. Dual drug delivery using "smart" liposomes for triggered release of anticancer agents. J Nanopart Res 2013; 15(7): 1-12.

[11] Jain A, Jain SK. Chapter 9: Application Potential of Engineered Liposomes in Tumor Targeting. Multifunctional Systems for Combined Delivery, Biosensing and Diagnostics: Elsevier - Health Sciences Division, https://www.elsevier.com/books/multifunctional-systems-for-combined-delivery-biosensing-and-diagnostics/grumezescu/978-0-323-52725-5; 2017. p. 171-92.

[12] Roco MC. Nanotechnology: convergence with modern biology and medicine. Curr Opin Biotechnol 2003; 14(3): 337-46.

[13] Caruthers SD, Wickline SA, Lanza GM. Nanotechnological applications in medicine. Curr Opin Biotechnol 2007; 18(1): 26-30.

[14] Jain A, Jain SK. Multipronged, strategic delivery of paclitaxel-topotecan using engineered liposomes to ovarian cancer. Drug Dev Ind Pharm 2016; 42(1): 136-49.

[15] Vyas A, Jain A, Hurkat P, Jain SK. Targeting of AIDS related encephalopathy using phenylalanine anchored lipidic nanocarrier. Colloids Surf B Biointerfaces 2015; 131(0): 155-61.

[16] Wang MD, Shin DM, Simons JW, Nie S. Nanotechnology for targeted cancer therapy. Expert Rev Anticancer Ther 2007; 7(6): 833-7.

[17] LaVan DA, McGuire T, Langer R. Small-scale systems for *in vivo* drug delivery. Nat Biotechnol 2003; 21(10): 1184-91.

[18] Boisseau P, Loubaton B. Nanomedicine, nanotechnology in medicine. Comptes Rendus Physique 2011; 12(7): 620-36.

[19] Sahoo SK, Labhasetwar V. Nanotech approaches to drug delivery and imaging. Drug Discov Today 2003; 8(24): 1112-20.

[20] Gopal V, Karthik A, Ranjith Kumar A, Udupa N. Regulatory Considerations of Nanotechnological Products in Developed Countries.

[21] Zhang G, Zeng X, Li P. Nanomaterials in cancer-therapy drug delivery system. J. Biomed. Nanotechnol 2013; 9(5): 741-50.

[22] Surendiran A, Sandhiya S, Pradhan SC, Adithan C. Novel applications of nanotechnology in medicine. Indian J Med Res 2009; 130(6): 689-701.

[23] Roco M, Williams R, Alivisatos P. Biological, medical and health applications."Nanotechnology Research Directions," Chap. 8. Kluwer Academic Publishers, Boston; 2000.

[24] Kipp JE. The role of solid nanoparticle technology in the parenteral delivery of poorly water-soluble drugs. Int J Pharm 2004; 284(1-2): 109-22.

[25] Ould-Ouali L, Noppe M, Langlois X, *et al.* Self-assembling PEG-p(CL-co-TMC) copolymers for oral delivery of poorly water-soluble drugs: a case study with risperidone. J Control Release 2005; 102(3): 657-68.

[26] Arbos P, Campanero MA, Arangoa MA, Irache JM. Nanoparticles with specific bioadhesive properties to circumvent the pre-systemic degradation of fluorinated pyrimidines. J Control Release 2004; 96(1): 55-65.

[27] Yamamoto H, Kuno Y, Sugimoto S, Takeuchi H, Kawashima Y. Surface-modified PLGA nanosphere with chitosan improved pulmonary delivery of calcitonin by mucoadhesion and opening of the intercellular tight junctions. J Control Release 2005; 102(2): 373-81.

[28] Lobenberg R, Kreuter J. Macrophage targeting of azidothymidine: a promising strategy for AIDS therapy. AIDS Res Hum Retroviruses 1996; 12(18): 1709-15.

[29] Brannon-Peppas L, Blanchette JO. Nanoparticle and targeted systems for cancer therapy. Adv Drug Deliv Rev 2004; 56(11): 1649-59.

[30] Rawat M, Singh D, Saraf S, Saraf S. Nanocarriers: promising vehicle for bioactive drugs. Biol Pharm Bull 2006; 29(9): 1790-8.

[31] Jain A, Jain SK. *In vitro* Release Kinetics Model Fitting of Liposomes: An Insight. Chem Phys Lipids 2016; 201: 28-40.

[32] Jain A, Jain SK. Liposomes in Cancer Therapy. Nanocarrier Systems for Drug Delivery: Nova Science Publishers, https://www.novapublishers.com/catalog/product_info.php?products_id=59761&osCsid=e7d370318f328e75748328a1e44e48aa; 2016. p. 1-42.

[33] Akbarzadeh A, Rezaei-Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y, *et al.* Liposome: classification, preparation, and applications. Nanoscale Res Lett 2013; 8(1): 102.

[34] Discher DE, Eisenberg A. Polymer vesicles. Science 2002; 297(5583): 967-73.

[35] Discher BM, Won Y-Y, Ege DS, *et al.* Polymersomes: tough vesicles made from diblock copolymers. Science 1999; 284(5417): 1143-6.

[36] Bermudez H, Brannan AK, Hammer DA, *et al.* Molecular weight dependence of polymersome membrane structure, elasticity, and stability. Macromolecules 2002; 35(21): 8203-8.

[37] Photos PJ, Bacakova L, Discher B, Bates FS, Discher DE. Polymer vesicles *in vivo*: correlations with PEG molecular weight. J Control Release 2003; 90(3): 323-34.

[38] Ahmed F, Discher DE. Self-porating polymersomes of PEG-PLA and PEG-PCL: hydrolysis-triggered controlled release vesicles. J Control Release 2004; 96(1): 37-53.

[39] Letchford K, Burt H. A review of the formation and classification of amphiphilic block copolymer nanoparticulate structures: micelles, nanospheres, nanocapsules and polymersomes. Eur J Pharm Biopharm 2007; 65(3): 259-69.

[40] Vyas SP, Katare YK, Mishra V, Sihorkar V. Ligand directed macrophage targeting of amphotericin B loaded liposomes. Int J Pharm 2000; 210(1-2): 1-14.

[41] Barenholz Y, Crommelin D. Liposomes as pharmaceutical dosage forms. Encyclopedia Pharm Technol 1994; 9: 1-39.

[42] Hamilton R, Goerke J, Guo L, Williams MC, Havel RJ. Unilamellar liposomes made with the French pressure cell: a simple preparative and semiquantitative technique. J. Lipid Res 1980; 21(8): 981-92.

[43] Huang C. Studies on phosphatidylcholine vesicles. Formation and physical characteristics. Biochemistry 1969; 8(1): 344-52.

[44] Mayhew E, Lazo R, Vail W, King J, Green A. Characterization of liposomes prepared using a microemulsifier. Biochim Biophys Acta 1984; 775(2): 169-74.

[45] Kirby C, Gregoriadis G. Dehydration-rehydration vesicles: a simple method for high yield drug entrapment in liposomes. Nat Biotechnol 1984; 2(11): 979-84.

[46] Mayer LD, Hope MJ, Cullis PR, Janoff AS. Solute distributions and trapping efficiencies observed in freeze-thawed multilamellar vesicles. Biochim Biophys Acta 1985; 817(1): 193-6.

[47] Ohsawa T, Miura H, Harada K. Studies on the effect of water-soluble additives and on the encapsulation mechanism in liposome preparation by the freeze-thawing method. Chem Pharm Bull 1985; 33(12): 5474-83.

[48] Batzri S, Korn ED. Single bilayer liposomes prepared without sonication. Biochim Biophys Acta 1973; 298(4): 1015-9.

[49] Baillie A, Coombs G, Dolan T, Laurie J. Non-ionic surfactant vesicles, niosomes, as a delivery system for the anti-leishmanial drug, sodium stibogluconate. J Pharm Pharmacol 1986; 38(7): 502-5.

[50] Szoka F, Jr., Papahadjopoulos D. Procedure for preparation of liposomes with large internal aqueous space and high capture by reverse-phase evaporation. Proc Natl Acad Sci USA 1978; 75(9): 4194-8.

[51] Buboltz JT, Feigenson GW. A novel strategy for the preparation of liposomes: rapid solvent exchange. Biochim Biophys Acta 1999; 1417(2): 232-45.

[52] Cevc G, Gebauer D. Hydration-driven transport of deformable lipid vesicles through fine pores and the skin barrier. Biophys J 2003; 84(2): 1010-24.

[53] Verma A, Jain A, Hurkat P, Jain S. Transfollicular drug delivery: current perspectives. Research and Reports in Transdermal Drug Delivery 2016; 5: 1-17.

[54] Kumar R, Philip A. Modified transdermal technologies: Breaking the barriers of drug permeation *via* the skin. Trop J Pharm Res 2007; 6(1): 633-44.

[55] Azmin MN, Florence AT, Handjani-Vila RM, Stuart JF, Vanlerberghe G, Whittaker JS. The effect of non-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice. J. Pharm. Pharmacol 1985; 37(4): 237-42.

[56] Kiwada H, Niimura H, Fujisaki Y, Yamada S, Kato Y. Application of synthetic alkyl glycoside vesicles as drug carriers. I. Preparation

and physical properties. Chem Pharm Bull (Tokyo) 1985; 33(2): 753-9.

[57] Zeng F, Zimmerman SC. Dendrimers in Supramolecular Chemistry: From Molecular Recognition to Self-Assembly. Chem Rev 1997; 97(5): 1681-712.

[58] Mohanraj V, Chen Y. Nanoparticles-a review. Trop J Pharm Res. 2006; 5(1): 561-73.

[59] Vanderhoff JW, El-Aasser MS, Ugelstad J. Polymer emulsification process. Google Patents; 1979.

[60] Rao JP, Geckeler KE. Polymer nanoparticles: preparation techniques and size-control parameters. Prog Polym Sci 2011; 36(7): 887-913.

[61] York P. Strategies for particle design using supercritical fluid technologies. Pharm Sci Technolo Today 1999; 2(11): 430-40.

[62] Quintana A, Raczka E, Piehler L*, et al.* Design and function of a dendrimer-based therapeutic nanodevice targeted to tumor cells through the folate receptor. Pharm Res 2002; 19(9): 1310-6.

[63] Padilla De Jesus OL, Ihre HR, Gagne L, Frechet JM, Szoka FC. Polyester dendritic systems for drug delivery applications: *in vitro* and *in vivo* evaluation. Bioconjugate chemistry 2002; 13(3): 453-61.

[64] Kihara F, Arima H, Tsutsumi T, Hirayama F, Uekama K. Effects of structure of polyamidoamine dendrimer on gene transfer efficiency of the dendrimer conjugate with alpha-cyclodextrin. Bioconjug Chem 2002; 13(6): 1211-9.

[65] Fassas A, Anagnostopoulos A. The use of liposomal daunorubicin (DaunoXome) in acute myeloid leukemia. Leuk. Lymphoma 2005; 46(6): 795-802.

[66] Charrois GJ, Allen TM. Drug release rate influences the pharmacokinetics, biodistribution, therapeutic activity, and toxicity of pegylated liposomal doxorubicin formulations in murine breast cancer. Biochim Biophys Acta 2004; 1663(1-2): 167-77.

[67] Allen TM, Cullis PR. Drug delivery systems: entering the mainstream. Science 2004; 303(5665): 1818-22.

[68] Sapra P, Tyagi P, Allen TM. Ligand-targeted liposomes for cancer treatment. Curr Drug Deliv 2005; 2(4): 369-81.

[69] Jain A, Jain S. Ligand-mediated drug-targeted liposomes. UK: Future Medicine; 2016.

[70] Seiden MV, Muggia F, Astrow A, Matulonis U, Campos S, Roche M. A phase II study of liposomal lurtotecan (OSI-211) in patients with topotecan resistant ovarian cancer. Gynecol Oncol 2004; 93(1): 229-32.

[71] Guo W, Johnson JL, Khan S, Ahmad A, Ahmad I. Paclitaxel quantification in mouse plasma and tissues containing liposome-entrapped paclitaxel by liquid chromatography-tandem mass spectrometry: application to a pharmacokinetics study. Anal Biochem 2005 ; 336(2): 213-20.

[72] Dragovich T, Mendelson D, Kurtin S, Richardson K, Von Hoff D, Hoos A. A Phase 2 trial of the liposomal DACH platinum L-NDDP in patients with therapy-refractory advanced colorectal cancer. Cancer Chemother Pharm 2006; 58(6): 759-64.

[73] Neville ME, Boni LT, Pflug LE, Popescu MC, Robb RJ. Biopharmaceutics of liposomal interleukin 2, oncolipin. Cytokine 2000; 12(11): 1691-701.

[74] Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005; 23(31): 7794-803.

[75] Boddy AV, Plummer ER, Todd R, *et al.* A phase I and pharmacokinetic study of paclitaxel poliglumex (XYOTAX), investigating both 3-weekly and 2-weekly schedules. Clin. Cancer Res 2005; 11(21): 7834-40.

[76] Albain KS, Belani CP, Bonomi P, O'Byrne KJ, Schiller JH, Socinski M. PIONEER: a phase III randomized trial of paclitaxel poliglumex *versus* paclitaxel in chemotherapy-naive women with advanced-stage non-small-cell lung cancer and performance status of 2. Clin Lung Cancer 2006; 7(6): 417-9.

[77] Thomson AH, Vasey PA, Murray LS, *et al.* Population pharmacokinetics in phase I drug development: a phase I study of PK1 in patients with solid tumours. Brit J Cancer 1999; 81(1): 99-107.

[78] Bilim V. Technology evaluation: PK1, Pfizer/Cancer Research UK. Curr Opin Mol Ther 2003; 5(3): 326-30.

[79] Seymour LW, Ferry DR, Anderson D, *et al.* Hepatic drug targeting: phase I evaluation of polymer-bound doxorubicin. J Clin Oncol 2002; 20(6): 1668-76.

[80] Matsumura Y, Hamaguchi T, Ura T, *et al.* Phase I clinical trial and pharmacokinetic evaluation of NK911, a micelle-encapsulated doxorubicin. Brit J Cancer 2004; 91(10): 1775-81.

[81] Terwogt JMM, ten Bokkel Huinink WW, Schellens JH, *et al.* Phase I clinical and pharmacokinetic study of PNU166945, a novel water-soluble polymer-conjugated prodrug of paclitaxel. Anti-Cancer Drugs 2001; 12(4): 315-23.

[82] Greenwald RB, Choe YH, McGuire J, Conover CD. Effective drug delivery by PEGylated drug conjugates. Adv Drug Deliv Rev 2003; 55(2): 217-50.

[83] Rowinsky EK, Rizzo J, Ochoa L, *et al.* A phase I and pharmacokinetic study of pegylated camptothecin as a 1-hour infusion every 3 weeks in patients with advanced solid malignancies. J Clin Oncol 2003; 21(1): 148-57.

[84] Bissett D, Cassidy J, de Bono JS, *et al.* Phase I and pharmacokinetic (PK) study of MAG-CPT (PNU 166148): a polymeric derivative of camptothecin (CPT). Br J Cancer 2004; 91(1): 50-5.

[85] Saraf S, Jain A, Hurkat P, Jain SK. Topotecan Liposomes: A Visit from a Molecular to a Therapeutic Platform. Crit Rev Ther Drug Carrier Syst 2016; 33(5): 401-32.

[86] Li J, Pant A, Chin CF, *et al. In vivo* biodistribution of platinum-based drugs encapsulated into multi-walled carbon nanotubes. Nanomedicine 2014; 10(7): 1465-75.

[87] Lila ASA, Kiwada H, Ishida T. Selective delivery of oxaliplatin to tumor tissue by nanocarrier system enhances overall therapeutic efficacy of the encapsulated oxaliplatin. Biol. Pharm. Bull 2014; 37(2): 206-11.

[88] Lim DJ, Sim M, Oh L, Lim K, Park H. Carbon-based drug delivery carriers for cancer therapy. Arch Pharm Res 2014; 37(1): 43-52..

[89] Das M, Singh RP, Datir SR, Jain S. Intranuclear drug delivery and effective *in vivo* cancer therapy *via* estradiol-PEG-appended multi-walled carbon nanotubes. Mol Pharm 2013; 10(9): 3404-16.

[90] Mehra NK, Jain NK. Development, characterization and cancer targeting potential of surface engineered carbon nanotubes. J Drug Target 2013; 21(8): 745-58.

[91] Chen C, Hou L, Zhang H, *et al.* Single-walled carbon nanotubes mediated targeted tamoxifen delivery system using asparagine-glycine-arginine peptide. J Drug Target 2013; 21(9): 809-21.

[92] Han S-J, Rathinaraj P, Park S-Y, *et al.* Specific intracellular uptake of herceptin-conjugated CdSe/ZnS quantum dots into breast cancer cells. Biomed Res Int 2014; 2014.

[93] Ye F, Barrefelt A, Asem H, *et al.* Biodegradable polymeric vesicles containing magnetic nanoparticles, quantum dots and anticancer drugs for drug delivery and imaging. Biomaterials 2014; 35(12): 3885-94.

[94] Gao X, Liu Z, Lin Z, Su X. CuInS(2) quantum dots/poly((L)-glutamic acid)-drug conjugates for drug delivery and cell imaging. Analyst 2014; 139(4): 831-6.

[95] Peng J, Qi X, Chen Y, *et al.* Octreotide-conjugated PAMAM for targeted delivery to somatostatin receptors over-expressed tumor cells. J Drug Target 2014; 22(5): 428-38.

[96] Kulhari H, Pooja D, Singh MK, Chauhan AS. Optimization of carboxylate-terminated poly(amidoamine) dendrimer-mediated cisplatin formulation. Drug Dev Ind Pharm 2015; 41(2): 232-8.

[97] Peng J, Zhou W, Xia X, *et al.* Encapsulation of acetylshikonin by polyamidoamine dendrimers for preparing prominent nanoparticles. AAPS PharmSciTech 2014; 15(2): 425-33.

[98] Mollazade M, Nejati-Koshki K, Akbarzadeh A, *et al.* PAMAM dendrimers augment inhibitory effects of curcumin on cancer cell proliferation: possible inhibition of telomerase. Asian Pac. J. Cancer Prev 2013; 14(11): 6925-8.

[99] Mehtala JG, Torregrosa-Allen S, Elzey BD, Jeon M, Kim C, Wei A. Synergistic effects of cisplatin chemotherapy and gold nanorod-mediated hyperthermia on ovarian cancer cells and tumors. Nanomedicine 2014; 9(13): 1939-55.

[100] Jones M, Leroux J. Polymeric micelles - a new generation of colloidal drug carriers. Eur. J. Pharm. Biopharm 1999; 48(2): 101-11.

[101] Savic R, Luo L, Eisenberg A, Maysinger D. Micellar nanocontainers distribute to defined cytoplasmic organelles. Science 2003; 300(5619): 615-8.

[102] Nakanishi T, Fukushima S, Okamoto K, *et al.* Development of the polymer micelle carrier system for doxorubicin. J Control Release 2001; 74(1-3): 295-302.

[103] Nishiyama N, Kataoka K. Polymeric micelle drug carrier systems: PEG-PAsp (Dox) and second generation of micellar drugs. Polymer Drugs in the Clinical Stage: Springer; 2004. p. 155-77.

[104] Kataoka K, Matsumoto T, Yokoyama M, *et al.* Doxorubicin-loaded poly (ethylene glycol)–poly (β-benzyl-l-aspartate) copolymer micelles: their pharmaceutical characteristics and biological significance. J Control Release 2000; 64(1): 143-53.

[105] Wang X, Li S, Wan Z, Quan Z, Tan Q. Investigation of thermosensitive amphiphilic micelles as drug carriers for chemotherapy in cholangiocarcinoma *in vitro* and *in vivo*. Int J Pharm 2014; 463(1): 81-8.

[106] Kabanov AV, Alakhov VY. Pluronic® block copolymers in drug delivery: From micellar nanocontainers to biological response modifiers. Crit Rev Ther Drug Carrier Syst 2002; 19(1).

[107] Burt HM, Zhang X, Toleikis P, Embree L, Hunter WL. Development of copolymers of poly (D, L-lactide) and methoxypolyethylene glycol as micellar carriers of paclitaxel. Colloids and Surfaces B: Biointerfaces 1999; 16(1): 161-71.

[108] Liu J, Xiao Y, Allen C. Polymer-drug compatibility: a guide to the development of delivery systems for the anticancer agent, ellipticine. J Pharm Sci 2004; 93(1): 132-43.

[109] Park EK, Kim SY, Lee SB, Lee YM. Folate-conjugated methoxy poly (ethylene glycol)/poly (ε-caprolactone) amphiphilic block copolymeric micelles for tumor-targeted drug delivery. J Control Release 2005; 109(1): 158-68.

[110] Marty JJ, Oppenheim RC, Speiser P. Nanoparticles--a new colloidal drug delivery system. Pharmaceutica Acta Helvetiae 1978; 53(1): 17-23.

[111] Malyankar UM. Tumor-associated antigens and biomarkers in cancer and immune therapy. Int Rev Immunol 2007; 26(3-4): 223-47.

[112] Na K, Lee KH, Lee DH, Bae YH. Biodegradable thermo-sensitive nanoparticles from poly (L-lactic acid)/poly (ethylene glycol) alternating multi-block copolymer for potential anti-cancer drug carrier. Eur J Pharm Sci 2006; 27(2): 115-22.

[113] Galindo-Rodriguez S, Allemann E, Fessi H, Doelker E. Physicochemical parameters associated with nanoparticle formation in the salting-out, emulsification-diffusion, and nanoprecipitation methods. Pharm Res 2004; 21(8): 1428-39.

[114] Reis CP, Neufeld RJ, Ribeiro AJ, Veiga F. Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles. Nanomedicine 2006; 2(1): 8-21.

[115] Fessi H, Puisieux F, Devissaguet JP, Ammoury N, Benita S. Nanocapsule formation by interfacial polymer deposition following solvent displacement. Int J Pharm 1989; 55(1): R1-R4.

[116] Martin CR, Kohli P. The emerging field of nanotube biotechnology. Nat Rev Drug Discov 2003; 2(1): 29-37.

[117] Reilly RM. Carbon nanotubes: potential benefits and risks of nanotechnology in nuclear medicine. J Nucl Med 200; 48(7): 1039-42.

[118] Ala'a K. Isolation, separation and characterisation of the fullerenes C 60 and C 70: the third form of carbon. J Chem Soc Chem Commun 1990; (20): 1423-5.

[119] Mamalis A, Vogtländer L, Markopoulos A. Nanotechnology and nanostructured materials: trends in carbon nanotubes. Precision Engineering 2004; 28(1): 16-30.

[120] Rabinow BE. Nanosuspensions in drug delivery. Nat. Rev. Drug Discov 2004; 3(9): 785-96.

[121] Merisko-Liversidge E, Liversidge GG, Cooper ER. Nanosizing: a formulation approach for poorly-water-soluble compounds. Eur J Pharm Sci 2003; 18(2): 113-20.

[122] Müller R, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy: rationale for development and what we can expect for the future. Adv Drug Deliv Rev 2001; 47(1): 3-19.

[123] Sarkari M, Brown J, Chen X, Swinnea S, Williams RO, Johnston KP. Enhanced drug dissolution using evaporative precipitation into aqueous solution. Int J Pharm 2002; 243(1): 17-31.

[124] Chow LC, Sun L, Hockey B. Properties of Nanostructured Hydroxyapatite Prepared by a Spray Drying Technique. J Res Natl Inst Stand Technol 2004; 109(6): 543-51.

[125] Iga AM, Robertson JH, Winslet MC, Seifalian AM. Clinical potential of quantum dots. J Biomed Biotechnol 2007; 2007(10): 76087.

[126] Verma A, Jain A, Tiwari A, Jain SK. Emulgels: Application Potential in Drug Delivery. Functional Biopolymers: Springer; 2018. p. 343-71.

[127] Jain A, Tiwari A, Verma A, Jain SK. Ultrasound-based triggered drug delivery to tumors. Drug Deliv Transl Res 2017:1-15.

[128] Lungu II, Radulescu M, Mogosanu GD, Grumezescu AM. pH sensitive core-shell magnetic nanoparticles for targeted drug delivery in cancer therapy. Rom J Morphol Embryol 2016; 57(1): 23-32.

[129] Trotta F, Dianzani C, Caldera F, Mognetti B, Cavalli R. The application of nanosponges to cancer drug delivery. Expert Opin. Drug Deliv 2014; 11(6): 931-41.

[130] Sherje AP, Dravyakar BR, Kadam D, Jadhav M. Cyclodextrin-based nanosponges: a critical review. Carbohydr Polym 2017; 173: 37-49.

[131] Park K. Facing the truth about nanotechnology in drug delivery. ACS Nano 2013; 7(9): 7442-7.

[132] Jain A, Jain SK. Ligand-Appended BBB-Targeted Nanocarriers (LABTNs). Crit Rev Ther Drug Carrier Syst 2015; 32(2): 149-80.

[133] Xia W, Low PS. Folate-targeted therapies for cancer. J Med Chem 2010; 53(19): 6811-24.

[134] Brekken RA, Overholser JP, Stastny VA, Waltenberger J, Minna JD, Thorpe PE. Selective inhibition of vascular endothelial growth factor (VEGF) receptor 2 (KDR/Flk-1) activity by a monoclonal anti-VEGF antibody blocks tumor growth in mice. Cancer Res 2000; 60(18): 5117-24.

[135] Binetruy-Tournaire R, Demangel C, Malavaud B, *et al.* Identification of a peptide blocking vascular endothelial growth factor (VEGF)-mediated angiogenesis. Embo J 2000; 19(7): 1525-33.

[136] Pardridge WM. Brain drug development and brain drug targeting. Pharm Res 2007; 24(9): 1729-32.

[137] Ren J, Agata N, Chen D, *et al.* Human MUC1 carcinoma-associated protein confers resistance to genotoxic anticancer agents. Cancer Cell 2004; 5(2): 163-75.

[138] Vartak DG, Gemeinhart RA. Matrix metalloproteases: underutilized targets for drug delivery. J. Drug Target. 2007; 15(1): 1-20.

[139] Koivunen E, Arap W, Valtanen H, *et al.* Tumor targeting with a selective gelatinase inhibitor. Nat Biotechnol 1999; 17(8): 768-74.

[140] Everts M, Koning GA, Kok RJ, *et al. In vitro* cellular handling and *in vivo* targeting of E-selectin-directed immunoconjugates and immunoliposomes used for drug delivery to inflamed endothelium. Pharm Res 2003; 20(1): 64-72.

[141] Schrama D, Reisfeld RA, Becker JC. Antibody targeted drugs as cancer therapeutics. Nat. Rev. Drug Discov 2006; 5(2): 147-59.

[142] Lamaze C, Dujeancourt A, Baba T, Lo CG, Benmerah A, Dautry-Varsat A. Interleukin 2 receptors and detergent-resistant membrane domains define a clathrin-independent endocytic pathway. Mol Cell 2001; 7(3): 661-71.

[143] Weroha SJ, Haluska P. IGF-1 receptor inhibitors in clinical trials—early lessons. J Mammary Gland Biol Neoplasia 2008; 13(4): 471-83.

[144] Ruoslahti E, Rajotte D. An address system in the vasculature of normal tissues and tumors. Annu Rev Immunol 2000; 18(1): 813-27.

[145] Kumar CC, Malkowski M, Yin Z, *et al.* Inhibition of angiogenesis and tumor growth by SCH221153, a dual αvβ3 and αvβ5 integrin receptor antagonist. Cancer Res 2001; 61(5): 2232-8.

[146] Graham J, Muhsin M, Kirkpatrick P. Fresh from the pipeline: Cetuximab. Nat Rev Drug Discov 2004; 3(7).

[147] Fonsatti E, Nicolay HJ, Altomonte M, Covre A, Maio M. Targeting cancer vasculature *via* endoglin/CD105: a novel antibody-based diagnostic and therapeutic strategy in solid tumours. Cardiovasc Res 2010; 86(1): 12-9.

[148] Noonberg SB, Benz CC. Tyrosine kinase inhibitors targeted to the epidermal growth factor receptor subfamily: role as anticancer agents. Drugs 2000; 59(4): 753-67.

[149] Menrad A, Menssen HD. ED-B fibronectin as a target for antibody-based cancer treatments. Expert Opin Ther Targets 2005;9(3):491-500.

[150] Schally AV, Comaru-Schally AM, Plonowski A, Nagy A, Halmos G, Rekasi Z. Peptide analogs in the therapy of prostate cancer. Prostate 2000; 45(2): 158-66.

[151] Desnick RJ, Schuchman EH. Enzyme replacement and enhancement therapies: lessons from lysosomal disorders. Nature Rev Genet 2002; 3(12): 954-66.

[152] LeBowitz JH, Grubb JH, Maga JA, Schmiel DH, Vogler C, Sly WS. Glycosylation-independent targeting enhances enzyme delivery to lysosomes and decreases storage in mucopolysaccharidosis type VII mice. Proc Natl Acad Sci USA 2004; 101(9): 3083-8.

[153] Tiruppathi C, Song W, Bergenfeldt M, Sass P, Malik AB. Gp60 activation mediates albumin transcytosis in endothelial cells by ty-

rosine kinase-dependent pathway. J Biol Chem 1997; 272(41): 25968-75.
[154] Hildinger M, Dittmar MT, Schult-Dietrich P, *et al.* Membrane-anchored peptide inhibits human immunodeficiency virus entry. J Virol 2001; 75(6): 3038-42.
[155] Petersen J, Dandri M, Mier W, *et al.* Prevention of hepatitis B virus infection *in vivo* by entry inhibitors derived from the large envelope protein. Nat Biotechnol 2008; 26(3): 335-41.
[156] Covic L, Gresser AL, Talavera J, Swift S, Kuliopulos A. Activation and inhibition of G protein-coupled receptors by cell-penetrating membrane-tethered peptides. Proc Natl Acad Sci USA 2002; 99(2): 643-8.
[157] Frankel AD, Pabo CO. Cellular uptake of the tat protein from human immunodeficiency virus. Cell 1988; 55(6): 1189-93.
[158] Elliott G, O'Hare P. Intercellular trafficking and protein delivery by a herpesvirus structural protein. Cell 1997; 88(2): 223-33.
[159] Schröder T, Niemeier N, Afonin S, Ulrich AS, Krug HF, Bräse S. Peptoidic amino-and guanidinium-carrier systems: targeted drug delivery into the cell cytosol or the nucleus. J Med Chem 2008; 51(3): 376-9.
[160] Muro S, Muzykantov VR. Targeting of antioxidant and anti-thrombotic drugs to endothelial cell adhesion molecules. Curr Pharm Des 2005; 11(18): 2383-401.
[161] Dunehoo AL, Anderson M, Majumdar S, Kobayashi N, Berkland C, Siahaan TJ. Cell adhesion molecules for targeted drug delivery. J Pharm Sci 2006; 95(9): 1856-72.
[162] Nahrendorf M, Keliher E, Panizzi P, *et al.* 18F-4V for PET-CT imaging of VCAM-1 expression in atherosclerosis. JACC Cardiovasc Imaging 2009; 2(10): 1213-22.
[163] Nguyen TL, Schneppenheim J, Rudnik S, *et al.* Functional characterization of the lysosomal membrane protein TMEM192 in mice. Oncotarget 2017; 8(27): 43635-52.
[164] Mastrobattista E, Koning GA, Storm G. Immunoliposomes for the targeted delivery of antitumor drugs. Adv Drug Deliv Rev 1999; 40(1-2): 103-27.
[165] Li W, Nicol F, Szoka FC, Jr. GALA: a designed synthetic pH-responsive amphipathic peptide with applications in drug and gene delivery. Adv Drug Deliv Rev 2004; 56(7): 967-85.
[166] Rajendran L, Knolker HJ, Simons K. Subcellular targeting strategies for drug design and delivery. Nat. Rev. Drug Discov 2010; 9(1): 29-42.
[167] Muratovska A, Lightowlers RN, Taylor RW, Wilce JA, Murphy MP. Targeting large molecules to mitochondria. Adv Drug Deliv Rev 2001; 49(1-2): 189-98.
[168] Ghaffarian R, Bhowmick T, Muro S. Transport of nanocarriers across gastrointestinal epithelial cells by a new transcellular route induced by targeting ICAM-1. J Control Release 2012; 163(1): 25-33.
[169] Oh P, Borgstrom P, Witkiewicz H, *et al.* Live dynamic imaging of caveolae pumping targeted antibody rapidly and specifically across endothelium in the lung. Nat Biotechnol 2007; 25(3): 327-37.
[170] Boado RJ, Zhang Y, Zhang Y, Xia CF, Wang Y, Pardridge WM. Genetic engineering of a lysosomal enzyme fusion protein for targeted delivery across the human blood-brain barrier. Biotechnol Bioeng 2008; 99(2): 475-84.
[171] Molino Y, David M, Varini K, *et al.* Use of LDL receptor–targeting peptide vectors for *in vitro* and *in vivo* cargo transport across the blood-brain barrier. FASEB J 2017; 31(5): 1807-27.
[172] Müller SK, Wilhelm I, Schubert T, *et al.* Gb3-binding lectins as potential carriers for transcellular drug delivery. Expert Opin. Drug Deliv 2017; 14(2): 141-53.
[173] Khan IU, Huang J, Liu R, Wang J, Xie J, Zhu N. Phage Display-Derived Ligand for Mucosal Transcytotic Receptor GP-2 Promotes Antigen Delivery to M Cells and Induces Antigen-Specific Immune Response. SLAS Discov 2017; 22(7): 879-86.
[174] Greco F, Vicent MJ. Combination therapy: opportunities and challenges for polymer-drug conjugates as anticancer nanomedicines. Adv Drug Deliv Rev 2009; 61(13): 1203-13.
[175] Chitkara D, Singh S, Mittal A. Nanocarrier-based co-delivery of small molecules and siRNA/miRNA for treatment of cancer. Ther Deliv 2016; 7(4): 245-55.
[176] Jain A, Jain SK. P-gp inhibitors: A potential tool to overcome drug resistance in cancer chemotherapy. Nanomedicine and Tissue Engineering: State of the Art and Recent Trends 2016: 247.
[177] Fernandez-Piñeiro I, Badiola I, Sanchez A. Nanocarriers for microRNA delivery in cancer medicine. Biotechnol Adv 2017.

PMID: 29384060