CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

http://doi.org/10.5281/zenodo.5136410

Online at: http://www.iajps.com *Review Article*

NANOPARTICLES AND LIPOSOMES PAVING A WAY FOR SMART DRUG DELIVERY SYSTEM

Hindavi C. Deshmane, Saurav S. Kawale, Saiee P. Joshi, Kaustubh A. Kasture, Prashant L. Pingale*

GES's Sir Dr. M. S. Gosavi College of Pharmaceutical Education and Research, Nashik-422005, Maharashtra, India

Corresponding Author email: prashant.pingale@gmail.com

Article Received: June 2021 **Accepted:** June 2021 **Published:** July 2021

Abstract:

There are exponential developments in nanotechnology and its medical applications over the past few years, traditional drug delivery systems have been encompassed in smart, stimulus-responsive drug delivery systems. Using the reaction to particular stimuli, known nano-platforms may improve the effectiveness of drug targeting by minimising side effects and the toxicity of payload, which are important factors to enhance patient conformity. Various advanced drug delivery systems are widely used for various interesting structures, such as stimuli-triggered nanoparticles, liposomes. However, these nano-programmes do not have a standardised manufacturing process, toxicity evaluation expertise and clear applicable significance between pre-clinical (diagnostic) and therapeutic studies.

A smart drug delivery system (SDDS), a newly developing therapeutic method, is now becoming a traditional drug delivery prototype for particular locations or targets. Drug-targeted delivery (DT) systems sustain the concentration of drugs at required doses in the human body and reduce the necessity for frequent doses. The DT system has some unique features like self-regulation, pre-programming, multi-targeted, timely response control, mapping of targeted drug delivery, response to pH, and spatial targeting. The DT system uses biological membrane modifications in the structure of malicious cells to improve the incorporation or entry of drug-coated nanoparticles into targeted tissues. This device provides a certain amount of the medicinal substance for the longevity of its operation to a targeted region within the human tissue; this increases the effectiveness of the procedure by decreasing the side effects of the drug.

Keywords: *Smart Drug Delivery System, Microelectromechanical systems, Nanoelectromechanical systems, Nano-carriers, Liposomes.*

Corresponding author:

Prashant L. Pingale*,

GES's Sir Dr. M. S. Gosavi College of Pharmaceutical Education and Research, Nashik-422005, Maharashtra, India

Corresponding Author email: prashant.pingale@gmail.com

QR code

Please cite this article in press Prashant L. Pingale et al., ***Nanoparticles and liposomes paving a way for Smart drug delivery system****.., Indo Am. J. P. Sci, 2021; 08(07).*

INTRODUCTION:

The Smart Drug Delivery System (SDDS) is an innovative form of drug targeting (DT) delivery [1,2]. The smart drug delivered by this method should meet the following criteria:

- ✓ increase the dosage of the drug delivered to the target body of interest (tissue/cells/organs)
- ✓ not degrade any of the body fluids
- ✓ decrease the side effects by increasing the effectiveness of the drug treatment
- ✓ absorption of the drug delivered must cross the biological membrane
- ✓ release of the drug in an acceptable manner and
- ✓ should not be toxic to the host

The ultimate aim of the DT delivery system is to pinpoint, preserve drug properties, ensure a clear route for drug delivery, target the desired location only, minimise drug side effects, and prolong drug interactions with diseased tissue. Targeted delivery system retains the necessary concentration of the drug in plasma and tissues at the target sites, thus preventing damage to normal tissue/cells caused by the drug [3,4,5]. This system is very complex and requires knowledge and application of multiple areas like chemistry, biology and also engineering [2].

Out of many problems with the administering drugs like chemotherapy, is that the drug affects the whole body and not merely the diseased cells, and the side effects can be very serious. Hence the need to use SDDS so that the drug only reaches the diseased cells.

Nanoparticles: Nanoparticles are most prominently used owing to their utilization of size and surface properties. Because of this atypical biological nature of these nanoparticles, they can very effortlessly cross the barriers in the cell. Given their targeting properties, they have been used in the treatment of cancer and tumour alike [6]. Various drugs can be integrated with these nanoparticles. The drugs are released to the target cells by certain triggers. Some are discussed below. Figure 1 indicates development and current status of nanoparticle-based drugs and formulations and their current market in comparison with conventional drugs.

pH trigger: Most widely used method [7,8,9]. Different organs are known to have different levels of pH, which makes the drug delivery easy to the wanted site, for example the pH of duodenum is approximately 6 and appx. 6.7 in the rectum. For example, 5-Fluorouracil (5-FU) [10] is an antineoplastic agent used to treat tumours in colon, rectum, etc. With 5-FU, for colon targeting, E-CPN i.e., Eudragit S100 nanoparticles with coated with citrus pectin are used.

The pH-responsive Nano carriers for solid tumour targeting are a typical example [11]. Extracellular pH in normal tissues and blood is normally maintained at about 7.4. In some tumours given their high glycolysis rate, the average extracellular pH is lower than 7.0 [12,13]. Lower pH levels in the extracellular tumour matrix can be manipulated as a precise stimulus in Controlled Drug Delivery Systems. The pH variance can also be observed in organelles like mitochondria and endoplasmic reticulum. Some organelles like lysosomes have lower pH value (within 4.5 to 5.5) [7,13] as compared to other cell organelles. The pH dissimilarity is therefore the main reasoning for the production of advanced drug delivery systems.

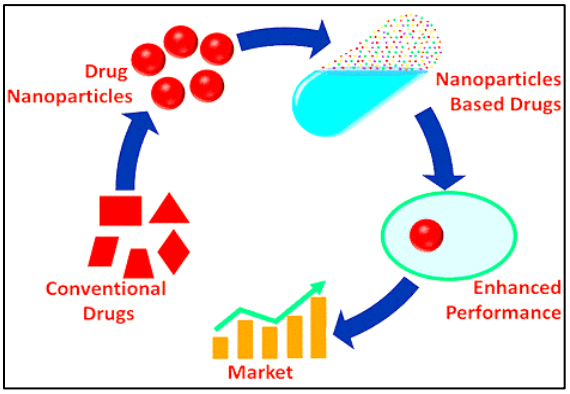

Figure 1: Development and current status of nanoparticle-based drug formulations

Temperature Responsive: Disease conditions like tumours and inflammation have different temperature as compared to normal tissues [14] in the body hence temperature seems effective and easy tool as a trigger. This way the cancerous tissue can be easily identified by specialized nanoparticles. If not for natural temperature, the temperature of site of target can be excited by external influences like magnetic field [1,15].

Light Response: Light-triggered system is a technique to activate the transport of drugs to the desired target through external light luminance. The on and off drug transport occurrence can be accomplished by photosensitive carriers, as the nanostructure can open or close when stimulated by either one-time or repeatable light irradiation [16]. However, given the restriction of light wavelength for practical treatment, light penetration depth currently limits non-invasive deep tissue applications [1,17].

Enzyme Responsive: There are various enzymes present in the human body. Enzymes like lipase, phospholipases, proteases, etc. are related to metabolic activities. Thus, nanoparticles can be functioned to capitalize enzyme-mediated drug release by the bio-catalytic action at the tumour or inflammation tissues [18]. Innovative projects are currently developing some advanced drug delivery systems. Research undertaken by Ben-Gurion University of Negev's Chemical Engineering Department Yosi Kost et al., of the Laboratory for Controlled Release, Gene Therapy, Biomaterials and Medical Technologies are developing systems to sneak drugs like chemo or genes past the body's defence mechanism and straight to their destination, including a cell organelle like a nucleus inside the cancer cell. Scientists are also attempting to develop nanoparticles made of a distinctive polymer and a dosage form that can separate between a healthy cell and a cancerous cell. The nanoparticle is tiny enough to pass across the microscopic holes that exist only in the blood vessels adjoining the cancerous growth. For example, when nanoparticles identify a malignant cell, their external receptors attached to the cell, but not all of them, are capable of crossing the cell membrane. Researchers are now using ultrasound in an incredible way: they rely on low-frequency ultrasound waves to form a small, temporary opening that facilitates the particles to penetrate [19,20]. Next the particles need to get to the nucleus to release the drug. The smart polymer knows how to identify particular intracellular proteins that migrate through the nucleus and reaches the nucleus with it. Once the particle meets its target, it requires help to free the medicine from the polymer, and the scientist employ ultrasound waves again. These waves target the target cells and the drug is released, and the rest of the body's cells are protected from side effects. This research incorporates the use of ultrasound that detects the diseased cells and smart guidance to get to the target location. As a result, ensuring optimal healing without adverse side effects.

Marketed Formulations using Nanoparticle:
Depending on their site of action and application different types of nanoparticles are used. They are broadly classified into two types: organic and inorganic nanoparticles. Organic nanoparticles constitute of liposomes, carbon nanomaterials, polymeric micelles and dendrimers. Quantum dots, gold and silver nanoparticles and fullerenes comprise of inorganic nanoparticles.

Tricor®: Brand name for the drug fenofibrate which came into medical use in 1975. It is administered orally. It is used to treat Dyslipidemia which is abnormal amounts of lipids in the blood. Fenofibrate belongs to group of drugs called fibrates that work by breaking down fats in the blood [21].

Amphotec®: This formulation is used to treat various serious fungal infections and is injected into the veins by the physician. It simply works by stopping the growth of fungi. It works by mononuclear phagocyte system targeting. This drug is Manufactured by Sequus Pharmaceuticals, Inc. It contains amphotericin B complex along with cholesteryl sulfate in the ratio of 1:1 [22].

Cimzia®: Certolizumab pegol is sold under the brand name of Cimzia. Used in the treatment of Crohn's disease and rheumatoid arthritis among many others. In 2008, FDA approved the use of certolizumab pegol to treat Crohn's disease. It is an anti-TNF drug known to reduce inflammation [21].

Emend®: It is the trade name for drug Aprepitant. This is an antiemetic medication which means it prevents nausea. Emend is generally given with nausea causing medications like in chemotherapy. This drug is given orally (by mouth) and is manufactured by Merck and Company [21, 22].

Liposomes: The word liposome comes from two Greek words: "lipos" which means fat and "soma" which means body. Liposomes simply are spherical vesicles which may have a unilamellar or multilamellar structure. This means that they have either they have only one lipid bilayer or multiple bilayers of phospholipids. They generally have a size of 30nm to several micrometres. A drug is added to the core for the liposome for drug targeting. Liposomes are considered to be included in Advance drug delivery systems for drug targeting and various formulations have already been introduced into the market successfully. Furthermore, there is advancement in liposomal technology which helps the liposomes to circulate longer in the system. A diagrammatic representation of benefits of drug formulation in liposomes shown in figure 2.

It is to be noted that there are three things that influence the stability and the efficacy of the liposomes the most:

- Lipid Composition,
- Surface Charge,
- Method of Preparation.

Liposomes are vesicles which can be prepared via the help of cholesterol and other phospholipids which are not harmful. The bilayer component that is the

phospholipids highly affect the rigidity or the flexibility of the liposomes [23]. For example, if we choose unsaturated phosphatidyl choline from sources such as eggs, it would make a flexible liposome wherein the absorption of the formulation is good but has some stability problems as compared to other liposomes. While when we use saturated liposomes with long acyl chains as a phospholipid it brings about sturdiness in the structure and therefore leading to increase stability but the permeability is not that good.

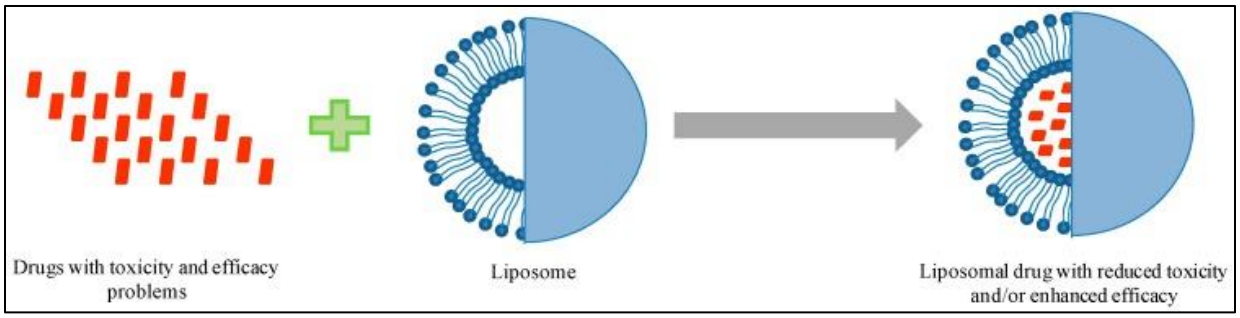

Figure 2: Diagrammatic representation showing the benefits of drug formulation in liposomes

Liposomes can carry out both hydrophilic and lipid drugs. They consist of a polar and a nonpolar region. They have a feature wherein they can orient themselves as per the environment. As soon as the liposomes are hydrated the liposomes form a closed structure. When the liposomes are introduced in the aqueous media the polar region of the liposome is outward whereas the nonpolar region gets oriented inwards forming a spherical structure. The core consists of the lipid drug.

Advantages of Liposomes as a SDDS:

- Charge of the drug is not the limiting factor, can carry both negatively and positively charged molecules.
- In gene therapy, large pieces of DNA or gene can be carried. Liposomes offer protection to the DNA.
- Increased efficacy of the drug and therefore decreased toxicity and increased therapeutic index.
- Targeted drug delivery leads to less exposure of toxic drugs to sensitive tissues.
- Nontoxic. Made from natural sources hence biodegradable and does not incite any immunogenic response.

Disadvantages of Liposomes as a SDDS:

- Expensive to produce.
- Lipoidal barrier may break or get fused with other liposome.
- Phospholipids may undergo oxidative degradation and hydrolysis of phospholipids may occur.
- Has lower solubility as well as lower half life.
- It is very difficult to formulate stable liposomes.

Classification of Liposomes:

Liposomes can be classified with size as the parameter. The size determines the amount of drug it can carrier. The classification also distinguishes between unilamellar and multilamellar systems [24]. Both the size of the vesicles and the number of bilayers affects the half-life of the vesicle. Thus, these can be categorised as:

- Unilamellar: Unilamellar systems can be further categorised into: -

1. Giant Unilamellar Vesicles
2. Large Unilamellar Vesicles
3. Small unilamellar Vesicles

- Multilamellar Vesicles (MLV)

Preparation of Liposomes:

Due to large applications in various fields, it is now more than ever necessary to develop procedures to prepare liposomes which are highly efficient, reproducible and simple to follow. Due to the ease and simplicity of the thin film hydration method it is generally preferred even though being the first method to be introduced in 1965. In Thin film hydration method, you take lipids in a round bottom flask and dry it to form a thin layer. Then you need to hydrate it with the help of aqueous buffer and vortex the mixture. The temperature should always exceed the gel liquid crystal transition temperature of the lipid and care should be taken that this temperature is maintained even while adding the aqueous buffer. The compound to be encapsulated can be added either to the lipid or the aqueous buffer as per its solubility. Various forms of methods such as sonification, homogenization and extrusion can be used to decrease the particle size [24].

Sonification can form Unilamellar vesicles from multilamellar vesicles with the size range of 15-50nm

diameter. Bath tip and Probe tip are the most widely used sonicators used for this purpose. Generally, homogenization occurs by high velocity collisions.

Mayhew had developed a micro emulsifier wherein the large vesicles rich lipids are cut down two streams are forced to collide and to form monodisperse liposomes which has a size range of 100nm. In Membrane Extrusion method the size reduction is done by passing the liposomes across a membrane filter. The membrane filter is made up of polycarbonate which has straight holes and exact diameter with offering less resistance [24].

In Reversed Phase evaporation method first the lipids are mixed with the aqueous phase. This brings about formation of inverted micelles. As we bring about heating and evaporation of the organic phase there is destruction of the micelles and the formation of liposomes thereof [24].

Detergent dialysis generally used when the compound to be encapsulated is sensitive to degradation, compounds such as DNA or proteins. In this method lipid is mixed with aqueous media which contains surfactant which leads to formation of micelles. These micelles upon dilution or removal of the detergent lead to the formation liposomes containing proteins [24].

There are various other methods as well when it comes to preparation of liposomes such as double emulsion method, freeze thaw method, dehydration-rehydration and supercritical carbon dioxide method. In this method the phospholipids solution is sprayed onto the supercritical carbon dioxide which leads to the evaporation of the solvent and formation of the phospholipid hollow vesicles which can be rehydrated with various aqueous buffers [24]. Therapeutic areas covered by liposome-based products and their brand names/innovator products are depicted in figure 3.

Figure 3: Therapeutic areas covered by liposome-based products and their brand names/innovator products

Marketed formulations using Liposomes [21]
Various liposomes have been formulated wherein the conventional liposomes consist of negative or neutral charged lipids with the mixture of cholesterol as a source of phospholipids to formulate. Following is the list of some of the approved liposome's formulations:

Doxorubicin Liposomes: Doxil® is the trade name for this active ingredient. Doxorubicin (liposomal) is a drug that is encapsulated in a Stealth® liposome. Liposomes are small spherical particles found in human cells. They have the ability to encapsulate solvent or a fraction of it in which they are diffused. This type of liposome has a substance on its surface to protect it from recognition by the body's immune

system [25]. This maximizes the time it circulates in the blood in body. When the drug/medication is given through this liposome, research has shown that this way, the drug can reach the tumour. It is used to treat variety of diseases including Breast cancer and Kaposi's sarcoma [26].

Vincristine Liposomes: This active ingredient is marketed under the name Marqibo®. Used in treatment of Acute lymphoid leukemia. Vincristine Liposomal belongs to the category of Antimicrotubular agents. Their function is to inhibit the microtubule structures contained by the cell. Microtubules are part of the cell that help in moving of the chromosome during the process of cell division for dividing and copying itself. Inhibition of these structures eventually marks the cell death [27].

Cytarabine Liposomes: Sold under the trade name DepoCyt ™, is used to treat lymphomatous meningitis, a type of cancer found in the lining of brain and spinal cord. Another name for this is Liposomal Ara-C. This drug is administered directly into the spinal fluid and given via intrathecal or intraventricular infusion. The drug cytarabine is encapsulated in liposomes and thus provides a sustained release [28].

Visudyne®: Visudyne® is a drug that is activated by light. Lipoproteins transfer verteporfin (verteporfin for injection), directly to the plasma. The Visudyne therapy is a two-step process that entails administration of the drug as well as a nonthermal red light [29].

Devices: There are various devices available to administer drugs via SDDS. Biological information perceived by biological sensors is deduced and the drug delivery system is used to administer the medication on the basis of data. The technique uses MEMS (Microelectromechanical systems) or NEMS (Nanoelectromechanical systems) equipment (Microelectromechanical systems, penned as micro-electro-mechanical systems and correlated micro-mechatronics and microsystems, encompass the technology of microscopic equipment, especially those with shifting parts. They integrate into nano-electro-mechanical systems and nanotechnology) centred on drug pumps, micro-pumps, micro-osmotic pumps, micro-needles and nano-pumps [30]. Drug delivery based on MEMS include improved drug therapy that enables more efficient and effective precise dosing. The use of MEMS for the transport of drugs through microneedles, bio-capsules and micro-pumps provides less intrusive drug therapy and enhances the quality of life of patients. It also comprises of devices or communication devices for remote activation or control of pumps [31].

CONCLUSION:

Due to recurring problems with other conventional drug delivery methods, smart drug delivery system (SDDS) was introduced. While drugs delivered by other drug delivery systems targeted not only the diseased cells but also the healthy cells, with SDDS there is hope that the drug will reach successfully to only the needed site. The most fundamental benefit of using SDDS is that there is fast absorption which is proportional to rapid onset of action. There are also several ways to inject or introduce the drug acting by smart drug delivery method to the body and this can be achieved with the help of devices like micro-needles, nano-pumps, etc. Some studies have shown that these nanocarriers sometimes get amassed in vital body organs like kidney, spleen and liver. Hence it means that extensive research and studies are needed regarding these nanocarriers. There are also various instances of toxicity caused by them. This unwanted is toxicity is an enormous barrier in the way of SDDS. However, there is still scope for research and development for smart drug delivery systems as there are far too many advantages of SDDS to be overshadowed by obstacles that can be overcome with research as well as extensive studies.

REFERENCES:

1. Liu D, Yang F, Xiong F, Gu N. The smart drug delivery system and its clinical potential. Theranostics. 2016; 6(9):1306-1323.
2. Dhanasekaran S, Chopra S. Getting a Handle on Smart Drug Delivery Systems–A Comprehensive View of Therapeutic Targeting Strategies. Smart drug delivery system. InTech, Croatia. 2016:31-62.
3. Pierigè F, Serafini S, Rossi L, Magnani M. Cell-based drug delivery. Advanced Drug Delivery Reviews. 2008; 60(2):286-295.
4. Schmidt JJ, Rowley J, Kong HJ. Hydrogels used for cell-based drug delivery. Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials. 2008; 87(4):1113-1122.
5. Walker PA, Aroom KR, Jimenez F, Shah SK, Harting MT, Gill BS, Cox CS. Advances in progenitor cell therapy using scaffolding constructs for central nervous system injury. Stem Cell Reviews and Reports. 2009; 5(3):283-300.

6. Hossen S, Hossain MK, Basher MK, Mia MN, Rahman MT, Uddin MJ. Smart nanocarrier-based drug delivery systems for cancer therapy and toxicity studies: A review. Journal of Advanced Research. 2019; 15:1-8.
7. Liu J, Huang Y, Kumar A, Tan A, Jin S, Mozhi A, Liang XJ. pH-sensitive nano-systems for drug delivery in cancer therapy. Biotechnology Advances. 2014; 32(4):693-710.
8. Yu P, Yu H, Guo C, Cui Z, Chen X, Yin Q, Zhang P, Yang X, Cui H, Li Y. Reversal of doxorubicin resistance in breast cancer by mitochondria-targeted pH-responsive micelles. Acta Biomaterialia. 2015; 14:115-124.
9. Gao W, Chan JM, Farokhzad OC. pH-responsive nanoparticles for drug delivery. Molecular Pharmaceutics. 2010; 7(6):1913-1920.
10. Subudhi MB, Jain A, Jain A, Hurkat P, Shilpi S, Gulbake A, Jain SK. Eudragit S100 coated citrus pectin nanoparticles for colon targeting of 5-fluorouracil. Materials. 2015; 8(3):832-849.
11. Stubbs M, McSheehy PM, Griffiths JR, Bashford CL. Causes and consequences of tumour acidity and implications for treatment. Molecular Medicine Today. 2000; 6(1):15-19.
12. Neri D, Supuran CT. Interfering with pH regulation in tumours as a therapeutic strategy. Nature Reviews Drug discovery. 2011; 10(10):767-777.
13. Lee ES, Oh KT, Kim D, Youn YS, Bae YH. Tumor pH-responsive flower-like micelles of poly (L-lactic acid)-b-poly (ethylene glycol)-b-poly (L-histidine). Journal of Controlled Release. 2007; 123(1):19-26.
14. Danhier F, Feron O, Préat V. To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. Journal of Controlled Release. 2010; 148(2):135-146.
15. Torchilin VP. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. Nature Reviews Drug Discovery. 2014; 13(11):813-827.
16. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nature Materials. 2013; 12(11):991-1003.
17. Lal S, Clare SE, Halas NJ. Nanoshell-enabled photothermal cancer therapy: impending clinical impact. Accounts of Chemical Research. 2008; 41(12):1842-1851.
18. De La Rica R, Aili D, Stevens MM. Enzyme-responsive nanoparticles for drug release and diagnostics. Advanced Drug Delivery Reviews. 2012; 64(11):967-978.
19. Shen N, Lei B, Wang Y, Xu S, Liu H. Redox/ultrasound dual stimuli-responsive nanogel for precisely controllable drug release. New Journal of Chemistry. 2018; 42(12):9472-9481.
20. Weissig V, Pettinger TK, Murdock N. Nanopharmaceuticals (part 1): products on the market. International Journal of Nanomedicine. 2014; 9:4357-4373.
21. Barua S, Mitragotri S. Challenges associated with penetration of nanoparticles across cell and tissue barriers: a review of current status and future prospects. Nano Today. 2014; 9(2):223-243.
22. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y, Samiei M, Kouhi M, Nejati-Koshki K. Liposome: classification, preparation, and applications. Nanoscale Research Letters. 2013; 8(1):1-9.
23. Nimtrakul P, Williams DB, Tiyaboonchai W, Prestidge CA. Copolymeric Micelles Overcome the Oral Delivery Challenges of Amphotericin B. Pharmaceuticals. 2020; 13(6):121.
24. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: an updated review. Pharmaceutics. 2017; 9(2):12.
25. Daraee H, Etemadi A, Kouhi M, Alimirzalu S, Akbarzadeh A. Application of liposomes in medicine and drug delivery. Artificial Cells, Nanomedicine, and Biotechnology. 2016; 44(1):381-391.
26. Makwana V, Karanjia J, Haselhorst T, Anoopkumar-Dukie S, Rudrawar S. Liposomal doxorubicin as targeted delivery platform: Current trends in surface functionalization. International Journal of Pharmaceutics. 2020:120117.
27. Olusanya TO, Haj Ahmad RR, Ibegbu DM, Smith JR, Elkordy AA. Liposomal drug delivery systems and anticancer drugs. Molecules. 2018; 23(4):907.
28. Douer D. Efficacy and safety of vincristine sulfate liposome injection in the treatment of adult acute lymphocytic leukemia. The oncologist. 2016; 21(7):840.
29. Salehi B, Selamoglu Z, S Mileski K, Pezzani R, Redaelli M, C Cho W, Kobarfard F, Rajabi S, Martorell M, Kumar P, Martins N. Liposomal Cytarabine as Cancer Therapy: From Chemistry to Medicine. Biomolecules. 2019; 9(12):773.
30. Wei C, Li X. The Role of Photoactivated and Non-Photoactivated Verteporfin on Tumor. Frontiers in Pharmacology. 2020; 11:1626.
31. Villarruel Mendoza LA, Scilletta NA, Bellino MG, Desimone MF, Catalano PN. Recent advances in micro-electro-mechanical devices for controlled drug release applications. Frontiers in Bioengineering and Biotechnology. 2020; 8:827.