Biological Forum – An International Journal **15(5): 33-38(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

A Review on – Liposomes as a Novel Drug Delivery System: Marketed Products and Future Perspectives

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(Received: 25 February 2023; Revised: 15 April 2023; Accepted: 19 April 2023; Published: 20 May 2023)
(Published by Research Trend)

ABSTRACT: Liposomes are a drug delivery system that is adaptable and optimistic. The benefits of liposomes over other drug delivery systems include site-targeting, prolonged or controlled release, protection of drugs from degradation and clearance, higher therapeutic effects, and fewer toxic adverse effects. As effective drug carriers in pre-clinical and clinical studies, liposomes provide a wide range of benefits and uses. Additionally, issues pertaining to liposomal stabilization, efficient targeting techniques, and some of their drawbacks were discussed. Formulation of liposomes has enabled the modification of drug biodistribution of many drugs, hence improving the therapeutic properties of those compounds. In conclusion, this study aims to investigate the liposomes currently on the market that are used as a drug delivery method in various therapeutic uses.

Keywords: Liposomes, Drug delivery, Liposome Production, Applications, Commercialised products.

INTRODUCTION

The Greek term "liposome" is made up of two words: "Lipos" means fat and "Soma" means the flesh. Liposomes were first discovered in 1964 by Dr. Alec D. Bangham. A number of materials, including cholesterol, non-toxic chemicals, sphingolipids, glycolipids, long-chain fatty acids, and a layer of proteins, can be used to formulate liposomes, which are small, rounded spheres. In the recent past, a lot of research has been concentrated on the delivery of genes (Liu *et al.*, 2020), antifungal (Bezerra *et al*., 2020); de Oliveira *et al.* (2020), anti-inflammatory (Zhang and Michniak-Kohn (2020) and anti-cancer medications Lan Bai *et al.* (2020) as well as applied in various pharmaceutical, biological, and medical domains.

The phospholipid membrane of liposomes is 4-5 nm thick, and the liposome size varies i.e. 30 nm to micrometer scale. Monolayer and bilayer forms are referred to as micelles and liposomes, respectively. Because of their unique properties, liposomes are used in the distribution of drugs. A number of papers focus on biological applications, and new developments in liposomal methodology (Guimarães *et al.*, 2021).

They actually can entrap a huge range of hydrophobic and hydrophilic therapeutic or diagnostic agents, thereby increasing the quantity of medicine transported by each particle and protecting the entrapped agents from metabolic pathways.

A longer half-life in circulation (stealth liposomes), the ability to combine with nucleic acids to facilitate gene transport or genetic control, and the capacity to transport entrapped contents to the cytosol via the endosomal/lysosomal route are all possible changes that can be made to the lipid bilayer's structure (Wang, *et al*., 2017).

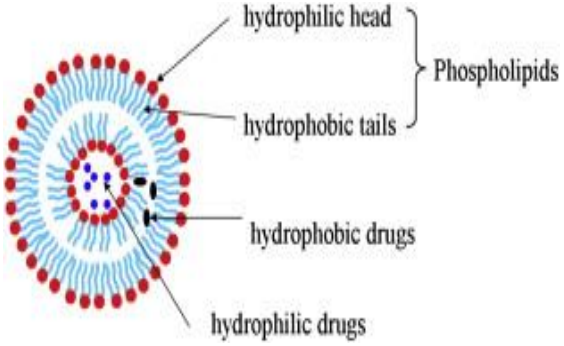

Fig. 1. Structure of Liposome.

COMPONENTS OF LIPOSOMES

The most common components are

- Phospholipids.
- Cholesterol.

Phospholipids:

Phospholipids are the main auxiliary components of natural films. The most prevalent phospholipid used in liposomal composition is phosphatidylcholine (PC).

An amphophilic molecule called phosphatidylcholine contain

- A hydrophilic polar head, phosphocholine
- A glycerol bridge
- A match of hydrophobic acyl hydrocarbon chain

Cholesterol: Almost all commercially available products can use cholesterol (Chol), another essential component of the liposome membrane. An increase in cholesterol can affect a variety of processes, including the compression of lipid chains and bilayer organization, modification of membrane fluidity/rigidity, progression of the effect on medication release, and solidity of liposomes.

The structure of these membranes is significantly altered when eight sterols are joined in a liposome bilayer.

- Cholesterol itself does not form a bilayer structure.
- Cholesterol acts as a buffer.

The membrane becomes more stable over the stage transition, while the film becomes less prevalent and slightly more porous beneath the stage shift. Exceptionally high concentrations of it can be integrated into phospholipid membranes, up to 1:1 or even 2:1 molar proportions of cholesterol to phospholipids (Martin, 1990).

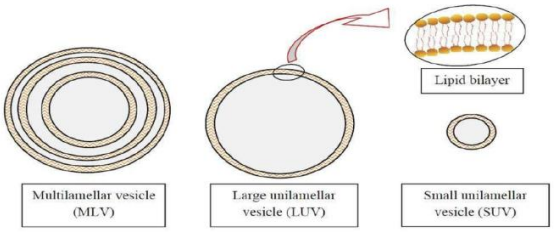

Fig. 2. Liposome classification based on dimensions and the number of bilayers.

METHODS OF PREPARATION

1. Passive loading technique
2. Active loading technique (Harada *et al.*, 2000).

A. Mechanical dispersion:

I. Lipid Film Hydration Method: The most typical and widely used method for MLV preparation is the hydration method. The method involves vortexing the dispersion and adding fluid buffer before hydrating the thin layer by dehydrating the lipid arrangement. The hydration phase is complete. Depending upon their solubilities substances that are to be enclosed are included either in a watery buffer or organic solvent containing lipids. The reduced application efficacy can be solved by hydrating the lipids adjacent to characteristic solvents that are immiscible, such as petroleum ether and diethyl ether. Then, sonication is used to emulsify it. By passing nitrogen, MLVs are formed by releasing a natural layer.

II. Micro emulsification: Small lipid spheres are commercially developed using this technique. This could be achieved by micro-emulsifying fatty mixes under shearing stress produced by a homogenizer. Microemulsion can be produced for natural purposes by increasing the rotation rate from 20 to 200.

III. Sonication: MLVs are sonicated using either a test (probe) sonicator or a shower (bath) sonicator in this technique. The primary drawbacks of this approach are its extremely low internal volume/encapsulation efficiency, phospholipid degradation, restriction on large particles, metal contamination of the test tip, and combination of MLV and SUV.

IV. French Pressure Cell Method: The release of MLV at a pressure of 20,000 psi and a temperature of 4°C through a small opening. The technique is easy to use, and quick to repeat, and it involves delicate manipulation of unstable materials. Compared to ultrasonic vehicles, the novel liposomes are bigger. The challenges include poor working conditions and inclement weather (at its most severe, about 50 mL) (Deamer and Bangham 1976).

V. Freeze-thawed liposomes: SUVs rapidly freeze and then progressively liquefy. Total elements are dispersed by the brief sonication to LUV. Unilamellar vesicles are produced as a consequence of the combination of Small Unilamellar vesicles during the phases of freezing and melting. This type of blend is unmistakably constrained by raising the phospholipid content and the ionic quality of the medium. 20% to 30% capsule efficacies were obtained.

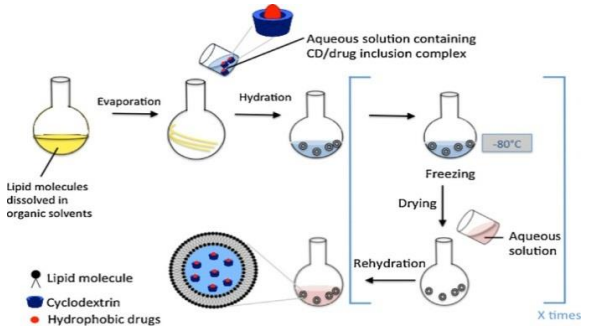

Fig. 3. Procedure for liposome preparation.

B. Solvent dispersion method:

1. Ether infusion: (Dissolvable vaporization) : An arrangement of lipids broken down in diethyl ether or a mixture of ether and methanol is progressively added to a fluid mixture of the material to be measured at 55°C to 65°C or under decreasing weight. As a consequence, liposomes are produced as the ether is expelled under pressure. The method's major disadvantages are the population's heterogeneity and the compounds that must be exposure to natural solvents at high temperatures (Szoka *et al.*, 1978).

2. Ethanol infusion: An ethanol lipid arrangement is quickly injected into a large amount of buffer solution. It is difficult to completely eliminate all of the ethanol because it makes an azeotrope with water, the group is heterogeneous, liposomes are very weak, and it is likely that many naturally active macromolecules will become inert in the presence of even small quantities of ethanol.

3. Double-Emulsification Strategy: Three commercial products, DepoCyte, DepoDur, and Eliminate, have adopted this process, also known as Depo Foam platform TM, to make MLVs. A "water-in-oil" emulsion's arrangement, and "water-in-oil-in-water" emulsion's arrangement (Ye *et al.*, 2000), dissolvable extraction with the assistance of stripping gas or vacuum weight, and Microfiltration for the concentration, exchange, and discharge of that free medication Mantripragada (2002). Since MLVs due to the smaller scale molecular measure cannot be

produced as sterile bunches through the 0.22 m filtration, aseptic proof should be provided during the manufacturing process.

For the second emulsion, a few MLVs break, and the medication leaks from the inner fluid stage, this reduces embodiment competence during the dissolvable evacuation. Additionally, the high temperature promotes lipid bilayer flexibility and modification, resulting in lipid combination and the closure of the fluid compartments (Sawant *et al.*, 2012).

4. Reverse phase evaporation technique: The water-in-oil emulsion is first formed by quickly sonicating a two-phase structure containing phospholipids in naturally dissolvable materials like isopropyl ether, diethyl ether, or a mixture of isopropyl ether and chloroform with aqueous buffer. A polymer is formed when natural substances break under lighter weights. The main benefit of method is that the liposomes were densely packed (about 80%) (Szoka *et al.*, 1978).

5. Detergent Solubilization Strategy: Micelles are the structures that are formulated as a consequence of its association. They are made up of a few hundred individual atoms. The CMC is the chemical concentration in water at which micelles begin to develop. As the detergent particle disintegrates in water at rates higher than the CMC, the micelle structure accumulates to significant levels. As the amount of detergent added increases, more cleanser is condensed into the bilayer up until a point at which the form of the detergent changes from lamellar to circular micellar. The micelles become smaller as cleaner content is promoted to be increased.

PURIFICATION OF LIPOSOMES

Liposomes are generally purified by Gel filtration Chromatography, Dialysis, and Centrifugation. In chromatographic separation, Sephadex-50 is the most widely used. In the dialysis method, a hollow fiber dialysis cartridge may be used. Whereas in the centrifugation method, SUVs in normal saline may be separated by centrifugation at 200000g, for 10-20 HOURS. MLVs are separated by centrifugation at 100000g for less than 1 hr. Sawant *et al.* (2012).

MECHANISM

Liposome-forming lipids have two different chemical structures. Their head groups are hydrophilic while their fatty acyl chains are hydrophobic. Phosphatidyl choline's Zwitter ionic head groups are thought to have around 15 weakly attached water particles, which accounts for its dominant affinity for the water stage. On the other hand, the toxic, oily bonds of hydrocarbons have a constant affinity for one another over water. This might be adopted if the CMC of P.C. is taken into consideration.

The Dipalmitoyl CMC was discovered to be 4.6–10 min in water, which may be a low value illustrating the PC's overwhelming preference for a hydrophobic environment like that found in the micelle or bilayer's core. For Dimyristoyl P.C. and Dipalmitoyl P.C., respectively, the free vitality of conversion from water to micelle is 13.0 Kcal/mol and 15.3 Kcal/mol. Because of the large difference in free energy between a water environment and an environment that repels water; normal lipids have a strong propensity to form bilayer structures by removing as much water as they can from the hydrophobic center to achieve the most reduced free energy level and, as a result, the highest stability for the entire structure.

TARGETING OF LIPOSOME

Passive Targeting: Consequently, when liposomes are targeted at the macrophages, the capability within the large phagocyte can be altered. The efficient delivery of liposomal antibacterial agents to macrophages serves as an illustration of this. As the first stage in the process of susceptibility, liposomes are currently used to target antigens to macrophages. For instance, in rats, intravenous administration of liposomal antigen-induced splenic phagocyte intervention and counteracting agent reaction, whereas intravenous administration of antigen not linked to liposomes resulted in counteracting agent reaction disappearing.

Active Targeting: A pre-requisite for focusing on this is the focus on specialists situated on the liposomal surface so that the receptor's contact with the target is arranged like a plug-and-attachment device. The liposome is literally set up so that the layer structure ties the fat-soluble part of the connector down into the film. The focusing agent must be held to the liposome's hydrophilic component in a sterically correct location in order to attach to the cell surface protein.

Advantages of Liposome: (Gulati *et al.*, 1998)

1. Liposomes are capable of forming complexes with negatively and positively charged substances.
2. Liposomes provide some protection for the DNA against deteriorating processes.
3. Liposomes can carry expansive pieces of DNA, conceivably as big as a chromosome.
4. Focused liposomes can be delivered to specific cells or organs.
5. Nonpolar
6. Liposomes help to reduce exposure of sensitive tissues to toxic drugs.
7. Prevention oxidation of drugs
8. Non-toxic
9. Biodegradable
10. Biocompatible

Disadvantages:

1. Allergic reactions may occur to the liposomal constituent.
2. Leakage and combination of typified medicate/ molecules.
3. Phospholipid experiences oxidation and hydrolysis-like reactions.
4. Short half-life.
5. Low solubility.
6. Less stable.

Application of liposome:

1. Liposomes for Respiratory System: Many categories of lung diseases extensively use liposomes for treatment. Liposomal pressurized canned products can be specified to maintain discharge, avoid adjacent disruption, reduce damage, and progress gradually.

Composition, estimate, price, drug/lipid percentage, and medication transportation strategy should all be taken into account when designing liposomes for lung delivery. During nebulization, the breathing form is either liquid or dry. Producing a medication powder liposome involves refining or spray drying.

2. Liposome in Ophthalmic Disorders: Endophthalmitis, proliferative vitreoretinopathy, eye irritation, keratitis, corneal implant failure, and uveitis retinopathy are examples of eye disorders against which liposomes have been found to be effective eye disorder has been recently approved as liposomal formulations.

3. Liposome as Vaccine Adjuvant: Liposomes have been firmly established as an immunoadjuvant that enhances both cell- and non-cell-mediated protection. Liposomes are targeted with the help of phosphatidyl serine in order to assemble to lymphoid cells. Liposomes for liposomal immunization can be produced by cytokinesis of damaging deoxyribonucleic acid, soluble antigens, and vaccine-eligible organisms.

4. Liposomes for Brain Targeting: Liposomes are used in brain sedative delivery systems because they are nontoxic and biodegradable. Liposomes that are large in thickness and only 100 nm across are freely dispersed through the BBB. Unilamellar vesicles (SUVs) linked to brain medication transport vectors can cross the BBB via transcytosis with the receptor or absorptive intervention. Mannose-coated liposomes enter the brain and aid in the transportation of layered drugs through the BBB. When administered directly, the neuropeptides leuenkephaline and met-enkephalin dynorphin typically do not penetrate the blood-brain barrier. Due to the adaptability of this approach, the antidepressant amitriptyline frequently enters the BBB.

5. Liposome as Anti-Infective Agent: Leishmaniasis, candidiasis, aspergillosis, histoplasmosis, erythrocytosis, giardiasis, digestive illness, and tuberculosis can all be treated by concentrating the medicine with a liposomal carrier.

6. Liposome in Cancer Therapy: On a long-term basis, all cancer medications produce clear negative impacts. The liposomal method targets the medication to the growth with less detrimental effects. Due to their ability to move for a lengthy period, the small, steady liposomes are latently targeted at various tumours.

7. Liposome in Cosmetics: Using them in cosmetics because their physiology is similar to the cell membrane, and they release materials to the cell.

8. Liposome in Intracellular Drug Delivery: Liposomal delivery of drugs that normally enter the cells by pinocytosis can be very effective because liposomes can contain greater drug concentration than extracellular fluid. Liposomes can be used to increase cytosolic delivery of certain drugs that are normally poorly taken into the cell.

9. Liposomes inDrug Distribution with Sustained Release: Sustain release systems are required to achieve and then maintain the concentration of drug administered within the therapeutically effective range needed for medication, it is often necessary to take this type of drug delivery system several times a day.

10. Liposomes in Gene Therapy: By introducing the appropriate foreign genes or DNA into cells, various attempts have been made to maintain gene activity in recent years.

Liposome characterization:

1. Visual Appearance: Based on the particle size and composition the appearance of the liposomal suspension may be varying from translucent to milky. The samples are homogeneous if the turbidity has a bluish shade; the presence of a non-liposomal dispersion is by flat, grey color and is most likely a disperse inverse hexagonal phase or dispersed micro crystallites. An optical microscope can detect liposomes of size greater than 0.3 µm as well as contamination with larger particles.

2. Determination of lamellarity: The lamellarity of liposomes can be measured by electron microscopy or spectroscopic techniques. The NMR spectrum of liposomes is recorded most frequently with and without the addition of a paramagnetic agent that shifts or bleaches the signal of the observed nuclei on the outer surface of the liposome (Gregoridis, 2004).

3. Liposome Stability: Liposomes should be physically, chemically, and biologically stable. Physical stability indicates the ratio of lipid to the therapeutic agent and the steadiness of the size. The chemical stability may be affected by two degradation pathways, oxidative and hydrolytic. Oxidation of phospholipids in liposomes mainly takes place in unsaturated fatty acyl chain-carrying phospholipids. These chains are oxidized in the absence of particular oxidants. Reduction of oxidation can be achieved by storage at low temperatures and protection from light and oxygen (Kapoor *et al.*, 2017).

4. Entrapped Volume: The entrapped volume of liposome (in µL/mg phospholipids) can often be deduced from measurements of the total quantity of solute entrapped inside liposome assuring that the concentration of solute in the aqueous medium inside liposomes is the same after separation from unentrapped material. For example, in the two-phase method of preparation, water can be lost from the internal compartment during the drying down step to remove the organic solvent (Sawant *et al.*, 2012).

% Entrapment Efficiency = Entrapped Drug/Added Drup * 100

5. Surface Charge: Liposomes are usually prepared using charge imparting constituting lipids and hence it is imparting to study the charge on the vesicle surface. The two methods used in general to assess the charge are free flow electrophoresis and zeta potential measurement (Kapoor *et al.*, 2017).

6. Drug-excipients interaction Study (FTIR Spectroscopy): The pure drug & excipients were mixed separately with IR grade KBr in the ratio 100:1 and corresponding pellets were prepared by applying 5.5 metric ton pressure with a hydraulic press. The pellets were scanned in an inert atmosphere over a wave number range of 4000-400cm-1.

7. Field Emission Scanning Electron Microscopic (FESEM) Study: The surface morphology of liposomes was investigated using Field Emission

Scanning Electron Microscope (FESEM). The prepared formulation samples were spread on a glass coverslip and mounted on the stubs using double-sided adhesive tapes. The stubs were then vacuum-coated with platinum using JEOL JFC 1600 (JEOL, Tokyo, Japan) Auto fine coater. Then the platinum-coated samples were observed and examined with the help of FESEM (JEOL JSM 6700F, Tokyo, Japan) and photographs were taken of different formulations.

8. Particle Size Distribution Study: The characterization of the size distribution of reconstituted lyophilized liposomes was determined by Dynamic Light Scattering (DLS, Zeta Sizer Nano ZS) and analyzed using DTS software (Malvern Instrument Limited, UK). This technique measures the time-dependent fluctuations in the intensity of scattered light which occur because the particles are undergoing Brownian motion. Analysis of these intensity fluctuations enables the determination of the diffusion coefficients of the particles which are converted into a size distribution. The average particle size was determined.

9. Polydispersity index: Intravenously injected liposomes must be stable to plasma proteins of the immune system, which adsorb onto the surface of liposomes and tag them for subsequent macrophage uptake. The stability depends upon two main factors namely: zeta potential and particle size. Based on the head group composition of lipids and the pH of a surrounding medium, liposome surface may bear negative, positive, or neutral charges. Liposomes with neutral charge showed lower tendency to be cleared by cells of RES (reticulo endothelial system) after systemic administration and highest tendency to aggregate. Also negatively charged liposomes containing PS and PG were observed to be endocytosed at a faster rate and to a greater extent than liposomes. Polydispersity was performed by the instrument Zetasizer nano ZS (0.6nm to 6 µm) using DTS software (Malvern instrument Limited, UK). NIBS technology was used for the measurements of particles. The lipid content of liposome dispersion was accessed by phospholipid quantification according to roscret radioactivity of the liposomes dispersion was assayed in ultima Gold Scintillation counter (Samad *et al.*, 2007).

10 Drug loading Study: Drug loading was determined spectrophotometrically. The drug quantification was confirmed by HPLC.

11. Lipid Quantification and Chemical Stability: Phospholipid concentration & Cholesterol concentration and purity were determined by HPLC or enzymatically by cholesterol oxidase. The purity of phospholipids as raw materials, and the extent of their hydrolysis during various steps of liposome preparation and liposome storage, was assessed by TLC and enzymatic determination of the increase in the level of non-esterified fatty acids.

12. Level of Free Drug: Two approaches were used: (i) the selective adsorption of free drug to dowexcation exchanges either in polycarbonate tips of pipetors (range 0.1-1.0ml) or in small glass columns (ii) small gel-exclusion chromatography).

13. Drug release determination: In-vitro drug release studies of drugs from liposomes were performed using a dialysis method. In a 250ml conical flask, 100ml of phosphate buffered saline was taken. 5mg lyophilized sample suspended in 1 ml of PBS was taken into a dialysis bag (Himedia dialysis membrane, 12000-14000 MW cut off). Two ends of the dialysis sac were tightly bound with threads. The sac was hung inside the conical flask with the help of a glass rod so that the portion of the dialysis sac with the formulation should dip into the buffer solution. The flask was kept on a magnetic stirrer. The content was stirred continuously at a controlled speed using a magnetic stirrer and the temperature. Sampling was done by withdrawing 1ml from the release medium with the help of a micropipette and 1ml of fresh PBS was added.Samples were analysed using a spectrophotometer at a specified wavelength. With the help of standard curve prepared earlier, drug concentration was determined (Nsairat *et al*., 2022).

Marketed Formulation of Liposome:

Table 1: Marketed Formulation of Liposomes.

Sr. No.	Drug	Application
1.	Amphotericin- B	Broad-spectrum antifungal agent
2.	Artemisinin	Treatment of malaria
3.	Doxophylline	Treatment of Asthma
4.	Gliclazide	Antidiabetic agent
5.	Rhodamine-conjugated liposomes	Treatment of uveitis

Table 2: Marketed Formulation of Liposomes.

Marketed product	Drug used	Target disease
Doxil	Doxorubicin	Kaposis sarcoma
Amphotec	Amphotericin b	Fungal infections leishmaniasis
Fungizone	Amphotericin b	Fungal infections leishmaniasis
Ventus	Prostaglandin- E1	Systemic inflammatory disease
Topex Br	Terbutaline sulfate	Asthma
Novasome	Smallpox Vaccine	Smallpox
Depocyte	Cytarabine	Cancer therapy

CONCLUSIONS

Liposomes are one of the unique drug delivery systems that played a significant role in the formulation of potent drugs, which can be of potential use in controlling and targeting drug delivery and improving their therapeutics. Drugs of both categories (hydrophilic/ lipophilic) are easily embedded in the liposomes. The liposomal formulation's effectiveness relies on its capacity to transport the molecules to the desired site over a lengthy duration of time, whereas minimizing the drug's adverse effects. The phospholipid bilayers contain the medicines, which are predicted to diffuse out of the bilayer gradually. When the development of liposomal drug therapy delivery methods, a number of variables, including drug quantity, the ratio of drug to lipid, capsule effectiveness, and in vivo drug release, must be taken into consideration. Liposomes are administrated orally,

parenterally, and topically as well as used in cosmetic and hair technologies, sustained release formulations, diagnostic purposes, and as good carriers in gene delivery various drugs with liposomal delivery systems have been approved. Nowadays liposomes are used as versatile carriers for targeted delivery of drug. The liposomal technique is used effectively to enhance the pharmacokinetics and therapeutic effectiveness while concurrently lowering the toxicity of different extremely potent medicines.

FUTURE SCOPE

Liposome-based formulations can be an ideal technique to deliver lipophilic bioactive, vitamins, minerals, and phytochemicals. Research into the targeted delivery of liposomes to a tumour or cancer cells has reported this as a potential application of liposomal drug delivery systems in the pharmaceutical sector.

Acknowledgment. The author is grateful to Honorable Shri. Sangramdada Thopte, Smt. Swarupa S. Thopte and the respected Principal of Rajgad Dnyanpeeth's College of Pharmacy, Bhor for providing an infrastructure facility for helping in the completion of the review article. The author is also extremely thankful to their teachers and friends for their continuous encouragement & support.
Conflict of Interest. None.

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How to cite this article: Deepak P. Kardile, Pravin B. Awate, Vishwas C. Bhagat, Aarti Y. Rajput, Rajkumar V. Shete, Mitali A.Aher, Priya R. Patil and Shraddha S. Pawar (2023). A Review on – Liposomes as a Novel Drug Delivery System: Marketed Products and Future Perspectives. *Biological Forum – An International Journal*, *15*(5): 33-38.