Liposomes and Nanoemulsions : A Brief Review on Approved Products

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***Abstract*—This review gives a brief overview of the advantages and disadvantages of liposomes and nanoemulsions used in drug delivery systems. Due to unique features liposomes and nanoemulsions attained much attention of companies for their utilization in pharmaceutical, cosmetics, food science and agriculture sector. Currently, the number of formulations are approved by Food and Drug Administration (FDA) and are already available in the market where are some are under review. This paper summarizes the list of approved products of liposomes and nanoemulsions.**

***Keywords*—Liposomes, Nanoemulsions, Vyxeos®, Liple®, Ropion®, Limethason®**

I. INTRODUCTION

Drug delivery has evolved over the last several decades to become more sophisticated platform for treating diseases of interest in humans or animals. In the early days, when simple dosage forms such as tablets and topical creams were in use, more advanced systems, such as injections, infusions, and implants, have been developed for treating the critical diseases with different routes and mechanisms of action [1]. In the several past decades, there has been tremendous progress in development and utilization of nanotechnology based therapeutic products for the treatment of various diseases like cancer, diabetes, asthma, infectious diseases, skin problems, etc [2]. These nanotechnology based therapeutic delivery systems, more precisely target the site, improve their solubility, increase their half-life and reduce their immunogenicity [3]. Nanotechnology based systems can also protect the drugs from degradation, reduction in number of doses, make treatment patient convenience and reduce overall treatment cost [4]. Commonly used nanocarriers include liposome's, solid lipid nanoparticles, polymeric nanoparticles, polymeric micelles, protein nanoparticles, ceramic nanoparticles, metallic nanoparticles viral nanoparticles and nanoemulsions, dendrimers and carbon nanotubes for biomedical applications.

II. LIPOSOMES

The concept of liposomes described by Dr. Alec D Bangham in 1961 and received a wide spread attention in various areas of biomedical research and drug delivery system [5]. Liposomes are spherical lipid vesicles, have an inner hydrophilic core and outer lipophilic phospholipid bilayer that resemble with cells as illustrated in Fig. 1 [6].

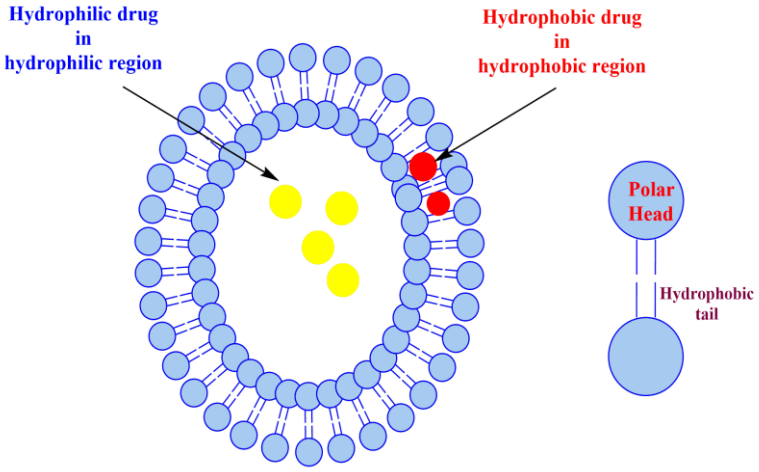

Fig. 1: Schematic diagram of drug entrapped in Liposomes

They are composed from natural or synthetic amphiphilic lipid molecules, mainly phosphatidylcholine derived from egg or soybean lecithin [7]. Further, liposomes are stabilized by use of cholesterol or mixture of stabilizer to increases the in vivo and in vitro stability [8]. Several liposome based formulation are under clinical trials and while some are already approved by FDA for clinical use [9-10]. They are suitable for both hydrophilic and hydrophobic drugs without any stability issues. They are biodegradable, compatible with immune system and suitable for targeted delivery with low toxicity [11]. Hydrophilic drugs are generally entrapped in central aqueous cores while lipophilic drugs are in outer lipid bilayers. The drug encapsulation capacity of liposomes depends on the bilayer composition and preparation method of the liposomes [12]. They can be classified into several types according to their size and lamellarity as summarized in Table 1 [13-14]. The method of preparation play a significant role in formation of unilamellar vesicles (ULVs) or multilamellar vesicles (MLVs) liposomes and as illustrated in Fig. 2. They have different drug release kinetics, ULVs release drug faster than MLVs due to the number of phospholipid bilayer [15].

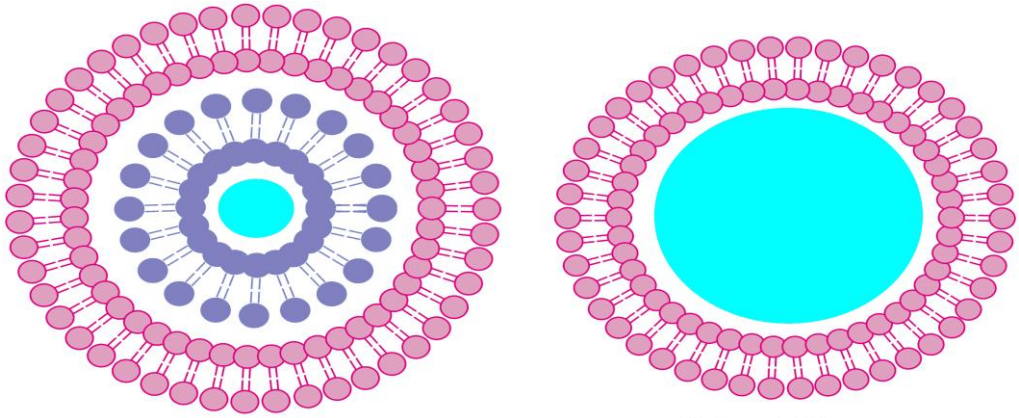

Fig. 2: Representation of liposomes lamellarity

Table 1: Size and layer of different liposomes

Type of vesicles	Number of layers	Diameter (μm)
Multilamellar large	5-25	>0.5
Oligolamellar	0.5	0.1-1
Unilamellar	1	all sizes
Small unilamellar	1	0.02-0.1
Medium unilamellar	1	-
Large unilamellar	1	>0.1
Giant unilamellar	1	>1
Multivesicular	Multi compartmental	usually >1

Advantages of liposomes [6], [16]

1. Suitable for hydrophilic and hydrophobic drugs
2. They are prepared from biocompatible and biodegradable lipids
3. Specific drug targeting functionalized with specific ligands to tissues or individual cellular compartments
4. Surface modification, prolonging the bio-distribution as stealth liposomes®
5. Minimize the reticuloendothelial system (RES) uptake
6. Improved therapeutic index of drug
7. Suitable for various routes of administration

Disadvantages of liposomes [17-18]

1. High production cost
2. Leakage of drug/molecules
3. Short half life, uptake of liposomes from the circulation by Kupffer cells
4. Allergic reactions may occur due lipids
5. Rancidity during storage, susceptible to oxidation and hydrolysis reactions

FDA approved several kinds of therapeutics drugs which have been formulated in liposomal formulations and commercialized a brief summary listed in Table 2 [19-21]. Among them, Doxil® is first approved formulation containing pegylated liposomal doxorubicin in 1995. Liposomes play a great role in cosmetic, pharmaceutical industries, food and farming industries to encapsulate antimicrobials, antioxidants, flavors and bioactive elements and protect their functionality [22-23].

Table 2: List of liposomal formulations approved by FDA

S. No	Product	Approval year	Active ingredients	Administration route	Name of company	Main indication
1.	Doxil®	1995	Doxorubicin	Intravenous	Ortho Biotech, Schering-plough	Ovarian, breast cancer
2.	Abelcet®	1995	Amphotericin B	Intravenous	Enzon	Invasive severe fungal infections
3.	DaunoXome®	1996	Daunorubicin	Intravenous	Gilead Sciences	AIDS-related Kaposi's sarco
4.	Amphotec®	1996	Amphotericin B	Intravenous	Alkopharma USA	Fungal infections
5.	Ambisome®	1997	Amphotericin B	Intravenous	Astellas/Gilead Sciences	Presumed fungal infections
6.	Inflexal® V	1997	Inactivated hemaglutinine of Influenza virus strains A and B	Intramuscular	Crucell (Berna Biotech Ltd.)	Influenza Crucell
7.	Depocyt®	1999	Cytarabine/Ara-C	Spinal	Pacira Pharms Inc.	Neoplastic meningitis
8.	Myocet®	2000	Doxorubicin	Intravenous	Zeneus	Metastatic breast cancer
9.	Visudyne®	2000	Verteporphin	Intravenous	Valeant Luxembourg, Novartis	Choroidal neovascularisation
10.	DepoDur™	2004	Morphine sulfate	Epidural	Skye Pharma Inc.	Pain management
11.	Exparel®	2011	Bupivacaine	Intravenous	Pacira Pharmaceuticals	Postsurgical analgesia
12.	Marqibo®	2012	Vincristine	Intravenous	Talon Therapeutics	Acute lymphoblastic leukaemia
13.	Onivyde™	2015	Irinotecan	Intravenous	Merrimack	Metastatic pancreatic cancer
14.	Vyxeos®	2017	Combination of daunorubicin and cytarabine	Intravenous infusion	Jazz Pharma	Acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes

III. NANOEMULSIONS

Nanoemulsions are prepared from oil, water and an emulsifier with droplet size of 100 nm. The amount and type of an emulsifier added to the system, plays a critical role in the formation of small sized droplets of emulsions. The emulsifier decreases the interfacial tension between the oil and water phases [24]. Commonly, emulsifiers are surfactants in nature which are used in preparation of nanoemulsions, alternatively proteins and lipids can also be used for same purpose [25]. On the basis of energy utilized, the methods of preparation can be classified as high and low energy methods [26] . Microfluidization and high-pressure homogenization and ultrasonification are the most preferable methods for production nanoemulsions for laboratory and manufacturing scale due to the small droplets size [27] . Nanoemulsions are getting great attention in recent years in the field of personal care, diagnostics, agrochemical, food and in pharmaceutical industries [28]. These have excellent safe profile, as they are made up from FDA approved surfactants which are recognized as safe for use human use. In pharmaceutical research, they are being evaluated as a ideal formulation for various routes of administration such as topical, transdermal, parenteral, oral, ocular, pulmonary and nasal [29-30].

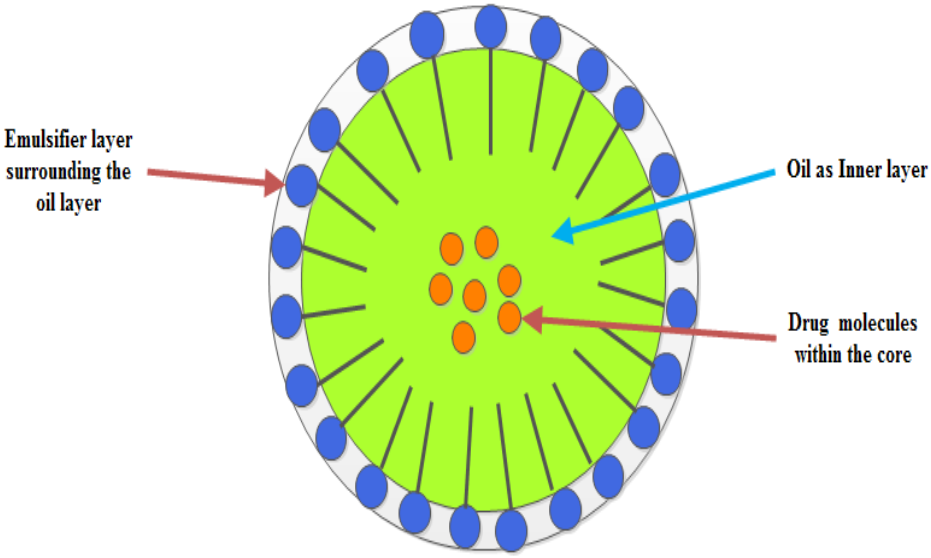

Fig.2 :Structure of nanoemulsion

Advantages of nanoemulsions [31-34]

1. More surface area and free energy than emulsions
2. Stability towards creaming, flocculation, and sedimentation than emulsions
3. Formulate in various forms such as foams, creams, liquids, and sprays
4. Non-toxic and non-irritant, for skin and mucous membranes
5. Improve the water solubility of lipophilic drugs
6. Suitable for sustained as well as targeted drug delivery system
7. Protection from hydrolysis and oxidation
8. Alternative for liposomes and vesicles
9. Long shelf life

Disadvantages of nanoemulsion system [29], [30]

1. Solubility issue for high-melting substances
2. Required large concentration of surfactant and co-surfactant
3. Susceptible to pH and temperature change during storage
4. Size reduction required special instruments and process methods

Factors to be considered for optimization of nanoemulsion [35-36]

1. Capability of surfactant to produce an ultra low interfacial tension system
2. Suitable concentration of surfactant for stability of microdroplets to produce nanoemulsion
3. Suitable oil/surfactant ratio

Now, pharmaceutical industries are focusing on R&D as well as manufacturing aspects of a formulation to achieve higher efficiency with lower risks and low cost as compared to traditional drugs. Nanoemulsions have attracted considerable attention due to their versatile nature and wide range of applications. Several nanoemulsion formulations that have been approved by FDA are manufactured and marketed by different companies for various indication are summarized in Table 3 [21], [37-39]

Table 3: List of Nanoemulsion based commercialized formulations

S. No	Drug	Brand Name	Route	Manufacture	Year	Indication
1.	Alprostadil	LIPLE®	Intravenous	Mitsubishi Tanalo Pharma Corp.	1988	Vasodilators, Erectile dysfunction
2.	Dexamethasone-21-Palmitate	LIMETHASON®	Intravenous	Mitsubishi Tanabe Pharma Corp. (Green Cross Corp.).	1988	Rheumatoid arthritis
3.	Flurbiprofen axetil	ROPION®	Intravenous	LTT Bio-Pharma/ Kaken Pharmaceutical Co., Ltd.	1992	Postoperative pain or pain due to cancer
4.	Soybean oil	NUTRILIPID®	intravenous	B. Braun Medical Inc	1993, 2014	Parenteral nutrition
5.	Propofol	DIPRIVAN®	Intravenous	AstraZeneca LP	2001	General anaesthetic
6.	Vitamin A, D2, E, and K1	VITALIPID®	Intravenous	Fresenius Kabi	2012	Multivitamin preparation
7.	Aminolevulinic acid hydrochloride	AMELUZ®	Topical gel	Biofrontera Bioscience GmbH	2016	Actinic keratosis

IV. Conclusions

In clinical practice, several liposomal and nanoemulsions based products have been approved by regulatory bodies. The most difficult tasks for pharmaceutical researcher is to develop an effective nano drug delivery system which is capable of carrying drugs, specifically to a desired site of action. Attempts have been made to reformulate the existing conventional formulations into nano delivery systems for better therapeutic use and positive scientific breakthroughs. Future perspective of liposomes and nanoemulsion as efficient carrier is very promising in the field of drug delivery or development of various topical formulations. However, the development of such systems requires safety, efficacy, ease of handling, and cost effectiveness.

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