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Comparative Study of Conventional and Fatty Acid Vesicular Systems – An Overview

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ABSTRACT: Fatty acid vesicles are suspensions of closed lipid bilayers that are composed of fatty acids and their ionized species which are restricted to a narrow pH range. The fatty acid molecules are oriented in such a way that their hydrocarbon tails are directed toward the membrane interior and the carboxyl groups are in contact with water. Recent innovations provide an opportunity to formulate fatty acid vesicles with distinguishing features such as extension of pH range, insensitivity toward divalent cations, easy alteration in membrane composition, very simple systems in terms of chemical nature and enhanced stability properties. This review contains detail about the present stature of fatty acid vesicles, comparative study of fatty acid vesicles with conventional liposomes, unique features of fatty acid vesicles (dynamicity, stability, matrix effect etc.,) and key evaluation parameters of fatty acid vesicles. Fatty acid vesicles were found to have high penetration capacity, good bio-distribution properties, increased diffusion rate and optimum drug deposition nature than other vesicular forms. They have various applications in transdermal delivery, follicular delivery and in brain targeting drug delivery systems (drugs that are unable to cross blood brain barrier due to high solubility). This review focuses on various researches conducted on fatty acid vesicles with reference to its formulation and evaluation parameters.

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INTRODUCTION

In recent years, vesicular systems became formulator's choice of drug delivery. Plethora of drug related problems such as drug insolubility, instability, and rapid degradation can be solved by vesicular drug delivery system [1]. Despite liposomes are available in the market, other lipid vesicles have not reached on large scale due to various disadvantages. But lipid vesicles were found to be of value in immunology, membrane biology and diagnostic techniques along with targeted drug delivery systems (especially brain) [2]. Vesicular drug delivery systems are useful in improving bioavailability of medication (especially for poorly soluble drugs), incorporate both hydrophilic and lipophilic drugs and delay drug elimination of rapidly metabolized drugs [3]. They enhance effective drug permeation into cells, prolonged existence of drugs in systemic circulation, selective uptake by reducing toxicity, effective for treating intracellular infections due to enhanced permeation of drugs into cells which is not possible by conventional chemotherapy, sustains drug release and lessens the therapeutic cost [4]. Vesicular system solves the drug related problems like drug insolubility, instability, and rapid degradation [5].

Fatty acid vesicles are colloidal suspensions of closed lipid bilayers which are composed of fatty acids along with their ionized species having 2 types of amphiphiles, one is non-ionized neutral form and the other is ionized form [6]. The ratio of non-ionized neutral form and the ionized form plays a key role in vesicular stability. Fatty acid vesicles are observed in a small region within the fatty acid-soap-water ternary phase diagram above the chain melting temperature (Tm) of the corresponding fatty acid-soap mixture. Fatty acid vesicles stability depends on selection of fatty acid, type of buffer used, pH range and the presence of divalent cations [7]. Recent innovations give opportunity to formulate fatty acid vesicles with essential features like extension of pH range,

insensitivity toward divalent cations, and enhanced stability. They are useful as carriers for the oral administration of poorly absorbable drugs, drugs which are unable to cross BBB [8], drugs having hinderance for passing through stratum corneum and for the horizontal transfer of genes from plants [9].

Unsaturated fatty acids such as oleic acid and linoleic acid are having ability to form vesicles in the aqueous environment. After about a decade of research it was conferred that saturated fatty acids with carbon atoms in the range of 8–12 undergo self-assemblage into vesicles in a pH-dependent manner in broad sense [10]. As fatty acids are highly soluble, they tend to partition into artificial as well as natural membranes rapidly compared to other vesicular systems [11]. Fatty acid vesicles enhance the absorption of therapeutic molecules through the GIT by forming mixed micelles or chylomicrons, thus increase the bioavailability of the bioactives [12]. Free fatty acids serve as penetration enhancers for the bioactives through the stratum corneum [13]. Skin permeation potential of fatty acids differs with the chain length and branching [14]. The penetration enhancement effect of fatty acid is directly proportional to the chain length. The skin permeation property of unsaturated fatty acids is high compared to saturated fatty acid [15]. Fatty acids containing Cis double bond exhibited higher penetration property compared to Trans form [16].

PRESENT STATURE OF FATTY ACID VESICLES

Fatty acid vesicles now-a-days are widely used for the transdermal drug delivery systems (mostly in case of fungal infections on skin), Follicular delivery in case of minoxidil, and brain targeting drug delivery systems mainly for the drugs that are unable to cross the BBB due to their physical characteristics [17]. For diseases like alopecia areata which is specifically restricted to hair follicles, it is essential to enhance drug absorption into the hair follicles for effective and safe treatment. So, the ideal formulation for hair follicle targeting should include a composition and physical properties which facilitate the fusion of fatty acid molecules in sebum making fatty acid vesicles an attractive delivery system for targeted drug delivery to the hair follicles. Surfactant is also used along with fatty acid to enhance flexibility of skin and improves the passage of drug through skin membrane [18]. In general, long chain fatty acids along with water form two types of systems called Homogeneous systems and Heterogeneous systems [19].

Homogeneous systems: They are more of diluted systems with neutral pH. In this type of systems, soap-ions and various acid-soap complexes are formed. As the pH of these systems increases, the soap formation also increases.

Heterogeneous systems: These are mainly concentrated systems which form either Emulsions (ions associate and form micelles) or Fatty acid vesicles (fatty acid molecules are organized to form membrane enclosing sealed aqueous spaces mostly at low pH) under certain conditions.

Table 1: List of various drugs used as fatty acid vesicular systems

S.No	Vesicular carrier	Drug	Route of administration	BCS class	Method of preparation	References
1	Oleic acid containing deformable liposomes	Methotrexate	Transepidermal delivery	III	Thin film hydration method	[20]
2	Oleic acid based unsaturated fatty acid liposomes	Oxiconazole	Topical delivery	II	Vortex method	[21]
3	Oleic acid vesicles	Minoxidil	Follicular delivery	III	Vortex method	[22]
4	Oleic acid vesicles	Clotrimazole	Topical delivery	II	Thin film hydration method	[23]
5	Unsaturated fatty acid vesicles	Dexamethasone	Cutaneous delivery	I	Thin film hydration method	[24]
6	Unsaturated fatty acid vesicles	methotrexate	Dermal administration	III	Thin film hydration method	[25]

Table 2: Evaluation parameters of some drug loaded fatty acid vesicles

S.No	Formulation	Drug	Fatty acid used	Drug:fatty acid	Particle size (nm)	Zeta potential (mV)	PDI	EE%	References
1	Oleic acid vesicles	Methotrexate	Oleic acid	3:7	632±17	-	0.262±0.037	51.0±2.2	[25]
2	Oleic acid vesicles	Oxiconazole	Oleic acid	1:2	215	-	-	61.05	[21]
3	Oleic acid vesicles	Minoxidil	Oleic acid	-	317±4	13.97±0.45	0.203±0.016	69.08±3.0	[20]
4	Oleic acid vesicles	Clotrimazole	Oleic acid	4:6	455±22	-22.5±0.25	0.210±0.035	49.5±1.0	[23]
5	Unsaturated fatty acid vesicles	dexamethasone	Oleic acid	2:8	631±15	-11.8±0.9	0.534±0.026	65.2±3.8	[24]
6	Unsaturated fatty acid vesicles	Methotrexate	Oleic acid	-	149±39	-	0.37±0.05	-	[22]

Table 3: Comparison of fatty acid vesicles with conventional liposomes

S.No	Liposomes	Fatty acid vesicles
1	Tolerate wide range of ph and ionic strength of the medium.	Very sensitive to pH and ionic strength of the medium.
2	Extensively prepared by both Thin film hydration method and Probe sonication method.	Extensive sonication results in the formation of non-uniform vesicular suspension.
3	Strong light scattering property per mole.	Weak light scattering property per mole.
4	Size distribution is two folds high than fatty acid vesicles.	Size distribution is lower compared to liposomes.
5	Vesicular size is large and so entraps more amount of glucose.	Vesicular size is comparatively small and thus entraps less amount of glucose.
6	Chemically complicated systems.	Chemically very simple systems than all vesicular forms.
7	Not used as prototypes for simple cells.	Used as prototypes for simple cells.
8	Membrane composition cannot be changed by simple procedures.	Membrane composition can be changed easily by simple procedures like alteration of fatty acid components or addition of lipid soluble substances.
9	Stability is less compared to fatty acid vesicles.	Have long-term stability than all vesicular types.
10	Shorter retention in brain after crossing BBB. Clearance, bioavailability, residence time and sustained release are comparatively weak than the fatty acid vesicles.	Longer retention in brain after crossing BBB. Less clearance, more bioavailability, prolonged residence time and sustained release are more than for liposomal formulations.

UNIQUE FEATURES OF FATTY ACID VESICLES

Dynamic nature

They are composed of single chain amphiphiles. This dynamic feature places them in between conventional vesicles formed from double-chain amphiphiles (phospholipids) and micelles formed from single-chain surfactants [26]. The fact is that a range of fatty acid aggregates are formed just by changing the protonation/ionization ratio of the terminal carboxylic acid.

Matrix effect

They are having ability of forming self-reproducing molecular assemblies (spontaneous formation of fatty acid vesicles from micelles which are diluted in buffer solution) It is an autocatalytic process. Fatty acid vesicles, after a significant lag time, increase the rate of vesicle formation in this process. The lag time in this process can be eliminated by adding preformed vesicles (seed vesicles) which increases the rate of vesicular formation instantly without any delay [27].

Protocell model

These are used to investigate vesicle self-reproduction by cell mimicking behavior by dynamic properties like rapid exchange of fatty acid molecules between vesicles & across the vesicular membrane due to relative high monomer concentration and various aggregate structures can be formed by changing ratio of fatty acids and soap [28].

Effect of pH

The pH of the fatty acid vesicles is restricted to a narrow pH range (7-9). The pH range broadly depends on the chemical structure of the fatty acid. For long chain fatty acids, vesicles will be formed at higher pH. The membrane surface pH should be less compared to fatty acid vesicular dispersion for local action. In dilute systems, transitions in vesicle shapes can be done by changing pH. It influences the drug diffusion across the skin, stability of the formulation and vesicular size in general [29].

Expansion to mixed vesicular systems

The narrow pH range of the fatty acid vesicles can be extended by adding amphiphilic additives like sulfonate groups or surfactant with a sulfate or linear alcohols [30].

Stability

They are more stable compared to the other vesicular systems because of reduction in the free energy of fatty acid-water system during its formation. The low ionic strengths, stabilizing buffers and slightly alkaline pH also makes them quite stable compared to other liposomes. To enhance the stability of the fatty acid vesicles, the fatty acids should be cross linked by chemical bonds (fatty acid + polymerizable moiety). The stability of oleic acid vesicles can be adding antioxidants/chelating agents/inert gases [31]. Fatty acid vesicular membrane stability can be stabilized by head group H-bonding with water, complex formation between ionized and neutral acid molecules and by hydration of dissociated carboxyl groups [32].

EVALUATION PARAMETERS OF FATTY ACID VESICLES

Vesicle size and shape

The vesicles formed by the fatty acids are uniform in size with spherical smooth surface and homogeneous in nature [33]. The vesicular shape becomes non uniform on extensive sonication. The vesicles formed by the fatty acids are small compared to the vesicles formed by other lipids.

Skin permeability

The fatty acid vesicles with oleic acids and linoleic acids shows enhanced skin permeability compared to the other conventional liposomes due to the flexibility of the fatty acid, having the advantage of penetration capacity into the skin pores which are much smaller than the vesicles of the fatty acid vesicles. Oleic acid has selective perturbation of the intracellular lipid bilayers present in the stratum corneum, which dramatically change the density and morphology of epidermal Langerhans cells and results in the generation of pores on the surface of the epidermal corneocytes [34].

Entrapment efficiency

The entrapment efficiency holds well for the fatty acid vesicles in general manner. In case of oleic acid vesicles, if the drug molecules are negative, the entrapment efficiency decreases because of the negative charge of the oleic acid which repels the negatively charged drug molecules and decrease the drug loading capacity [35]. As the concentration of oleic acid increases, the entrapment efficiency also increases.

Release kinetics

Diffusion rate is high for the fatty acid vesicles compared to the conventional liposomes due to the good penetration capacity of fatty acids compared to other lipids [36].

Drug deposition

Fatty acid vesicles have more depoting property of drug in the epidermal layers of skin compared to the conventional liposomes as the fatty acids have more retaining property in the epidermis than other lipids [37].

Compatibility studies

The DSC and FTIR studies prove that there is good compatibility property between drug molecules and excipients in the formulation of fatty acid vesicles than the conventional liposomes. The fatty acid vesicles do not show any peaks related to the drug substances indicating that vesicles fully encapsulation of the drug and other solutes. In case of conventional liposomes, the peaks more or less related to the drug molecules are observed indicating the free drug present on the vesicles even after the encapsulation [38].

Bio-distribution study

In case of brain targeting experiments, fatty acid vesicles showed enhanced efficiency to cross BBB and presence of more amount of drug in the brain (high retention) compared to the normal conventional liposomes. High retention indicates sustained release of the drug, less clearance through liver and kidney, longer blood residence time than liposomes and ability to tackle short elimination half-life and low bioavailability [39].

CONCLUSION

Fatty acid vesicles are now-a-days widely used due to their dynamic nature of changing their membrane composition easily. They are useful in delivery of anti-inflammatory drugs by encapsulation of drug in the fatty acid vesicle and thus they act as potential carriers. Sustained release of drug, drug deposition, more stability, good bio-distribution properties and high rate of diffusion are the benefits through these fatty acid vesicular drug delivery systems compared to conventional liposomes. They increase the permeation of the drug molecule by avoiding the stratum corneum barrier potential and hence increase the in-vitro skin delivery of drug compared to conventional liposomes.

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CONFLICT OF INTEREST

There is no conflict of interest regarding the research article.

DATA AVAILABILITY

Not declared.

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