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An Updated Review on Formulation, Characterization and Evaluation of Herbal and Synthetic Liposome

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ABSTRACT

Liposome are microscopic spherical vesicles together of one or more outer shell consisting of lipid arranged in bilayers configuration .which are under extensive investigation as drug carrier for improving the delivery of bioactive agent and many different compound in biological ,pharmaceutical, medical and nutritional research .it also utilized in a broad range of pharmaceutical application .liposome were first describe in 1965 and initially as model for studying the biological membrane as drug carrier for several drug to reduce side effect or to deliver the drug at the site of action. Liposome are considered as superior carriers having ability to encapsulated hydrophilic and lipophilic drugs and protect from the degradation. topical liposome formulation might be simpler and fewer toxic than conventional formulation, as a prolonged and controlled drug release. topical dosage form, which may be lead to improved efficiency and better patient compliance. But they have less half-life and poor solubility. The amount of phospholipid and cholesterol, are taken and formulated by using different method like thin film hydration method, sonication method, reverse phase evaporation method, ethanol injection method etc. the liposome formulation characterized by their vesicles size, shape, pH, solubility studies, % of encapsulation efficiency, % of drug content, stability studies, zeta potential, rheology study, *in vitro* drug release study of liposome formulation.

Keywords- Liposome, Topical Liposome Formulation, Pharmaceutical Application, Stability Studies, *In Vitro* Drug Release.

INTRODUCTION

Liposome formulations are widely used in the pharmaceutical field as drug delivery system due to their versatility and clinical efficacy and they have been used to administer drug by several routes. Liposome are having the higher diffusivity in the skin compared to other most formulation, so the liposome formulation is widely used as topical drug delivery system.

Liposomes are microscopic spherical vesicles together of one or more outer shell consisting of lipid arranged in a bilayer's configuration. Liposome have been used in a broad range of pharmaceutical application. Liposomes are also considered as superior carriers due to their ability to encapsulate hydrophilic and lipophilic drugs. Liposomes are also found to have crucial in medical, cosmetic, and industrial application. liposome can practicably improve drug loading, drug delivery and sustained release, thereby offering advantages over traditional dosage form.

Liposomes were first produced in England in 1961 by Alec D. Bangham, who was studying phospholipids and blood clotting. It was found that phospholipids combined with water immediately formed a sphere because one end of each molecule was water soluble, while the opposite end is water insoluble. Water soluble medications added to the water were trapped inside the aggregation of the hydrophobic ends; fat-soluble medications were incorporated into the phospholipid layer

Topical drug delivery is an attractive route for local and systemic treatment .it also has affinity to keratin of horny layer of skin and can penetrate deeper tissues into skin and hence give better absorption .In the

formulation of topical dosage forms, attempts are being made to utilize drug carriers that ensure adequate localization or penetration of drug within or through the skin in order to enhance the local and minimize the systemic effects or to ensure adequate percutaneous absorption .when applied on the skin, liposome act as a solubilizing matrix for poorly soluble drug ,penetration enhancer and local depot at the same time reducing the side effect of these drugs thereby topical liposome formulation could be more effective and less toxic than conventional formulations.

Liposomes are incorporate into gel to enhance the skin retention of drugs and provide higher and sustained concentrations of drug in skin at the same time do not enhance the systemic absorption of drugs. They act as drug reservoir that provides a localized and controlled drug delivery. By the liposomal gel approach enough drug can be delivering into skin so that the adverse effects of drug can be minimize. Carbopol is used as hydro gel which acts as a vehicle for liposomes have ability to enhance local delivery of drugs. The release of drug is controlled by degradation of hydro gel matrix [1-2].

STRUCTURE OF LIPOSOME AND COMPOSITION

The main structural components of liposome are phospholipid and cholesterol. Phospholipid is the main structural component of the biological membrane such as the cell membrane. The main sources of natural phospholipids are yolk egg and soya bean although they can be obtained from plant oils such as olive oil. Phospholipids can be classified by two categories like phosphoglycerides and sphingolipids. phosphatidylcholine is mainly used for the preparation of liposomes due to its amphipathic molecules having hydrophilic polar head group phosphocholine, a glycerol bridge and pair of hydrophobic acryl chains.

Another structural component of liposome is the cholesterol. Incorporation of the sterol in the lipid bilayers brings about major changes in the preparation of the membrane. Cholesterol acts as a fluidity buffer. below the phase transition temperature, it marks the membrane less ordered and slightly more permeable and above the phase transition temperature the membrane more ordered and stable [3].

The mainly common phospholipids used in preparation of liposome

Phosphatidylcholine(Pc),phosphatidylserine(Ps),phosphatidyletanolamine(PE),phosphatidylinositol(Pi),dipalmitoylphosphatidylcholine(Dppc)dipalmitoylphosphatidyl glycerol,dioleoylphosphatidyletanolamine(Dopa),1,2-dioleoyl-sn-glycero-3phospho-l-serine,distearoylphosphatidylcholine(Dspc),dipalmitoylphosphatidylserine.There are following advantage and disadvantages of liposome formulation [4]

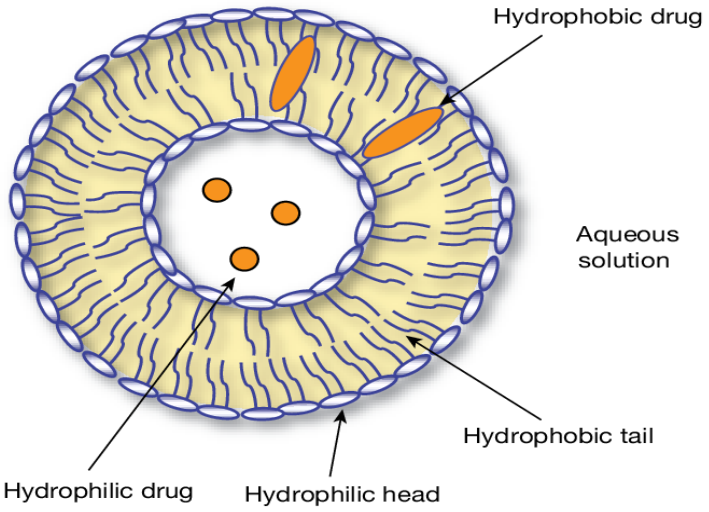

Figure:1 basic structure of liposome

Table 1: Advantages and Disadvantages of Liposome Formulation

S.no	Advantages	Disadvantages
1	Biocompatible, biodegradable	Low solubility
2	Reduced the systemic toxicity of drug	Short half life
3	It can carry both lipid and water molecules	Sometimes phospholipid undergoes oxidation and hydrolysis like reaction
4	Amphiphilic	Leakage and fusion of encapsulated drug molecules
5	Non immunogenic, not toxic formulation	Production cost is high
6	It helps in reduced the exposure of sensitive tissue to toxic drug	Fewer stable
7	Possibility of several routes of administration (intravenous, inhalator,)	
8	Can be delivered different forms suspension, cream powder, gel	

SIGNIFICANT PROPERTY OF DRUG FOR LIPOSOME FORMULATION

For preparation of liposome some drugs having properties like

- Poor solubility
- They are permeable in water.
- They are osmotically sensitive.
- lesser half-life,
- less oral bioavailability,
- less biodegrability,

Low toxicity; make them undesirable to conventional dosage forms. To overcome such limitations, the novel drug delivery systems came in pharmaceutical practice, particularly the vesicular systems like liposomes, ethosomes, niosomes, etc.

- **The liposome formulation is classified by different parameter**

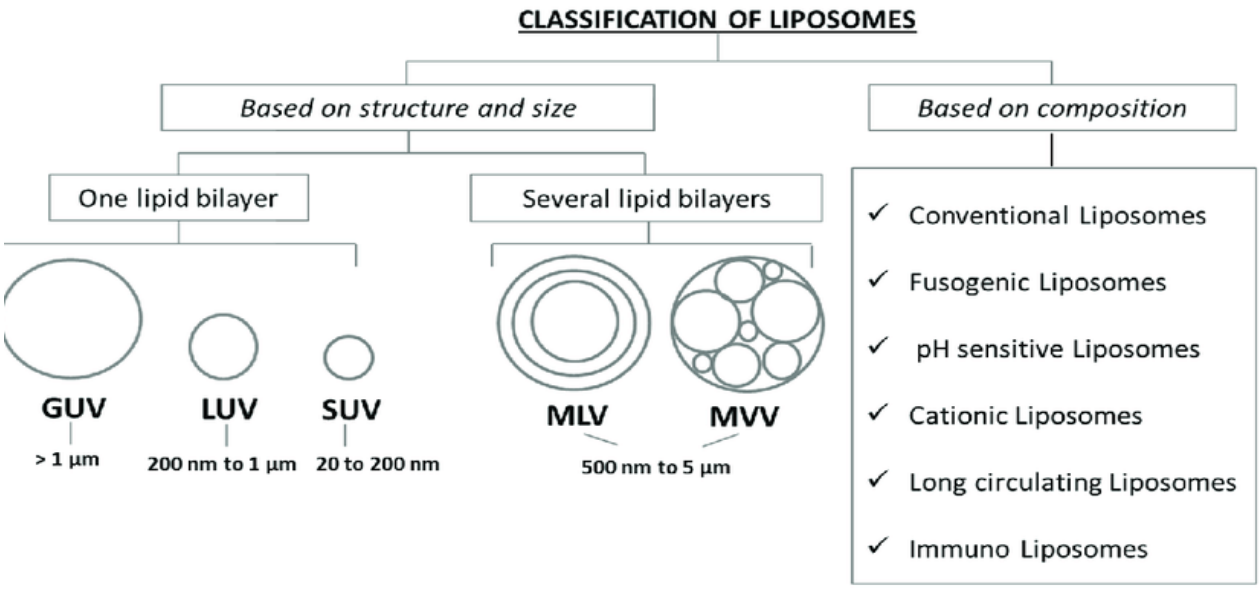

Figure 2: Different classification of liposome

Where as

GUV (Giant unilamellar vesicles) > 1 micrometer
LUV (Large unilamellar vesicles)>10nm
SUV (Small unilamellar vesicles) 20-100nm
MLV (Multi lamellar large vesicles) >0.5
MVV (Multivesicular vesicles) 1micro meter [5].

APPLICATION

Applications of liposomes in medicine and pharmacology can be divided into diagnostic and therapeutic applications of liposomes containing various markers or drugs, and their use as a tool, a model, or reagent in the basic studies of cell interactions, recognition processes, and mode of action of certain substance[6]

- Chelation therapy for treatment of heavy metal poisoning.
- Liposome as protein carriers in immunology
- Sustained or controlled delivery
- Diagnostic imaging of tumors
- Intracellular drug delivery
- Site avoidance delivery
- Site specific targeting
- Enzyme replacement
- Study of membranes
- Oral drug delivery
- Gene therapeutics
- Formulation aid
- cosmetics

METHOD FOR PREPARATION OF LIPOSOME

[A] Multi lamellar vesicles method

1. Thin film hydration method

This is the most widely used for the research of MLV. The method involves drying a solution of lipid so that a thin film is formed at the bottom of round bottom flask and then hydrating, the film by adding aqueous buffer and vertexing the dispersion for a short time. The hydration step is done at a temperature above the gel-liquid crystalline transition temperature Tc of the lipid or above the Tc of the maximum melting component in the lipid mixture. the compounds to be encapsulated are added either to aqueous buffer or to organic solvent containing lipid depending upon their solubilities. MLV are simple to organize by this method and a variety of substances can been encapsulated in these liposome figure:3.

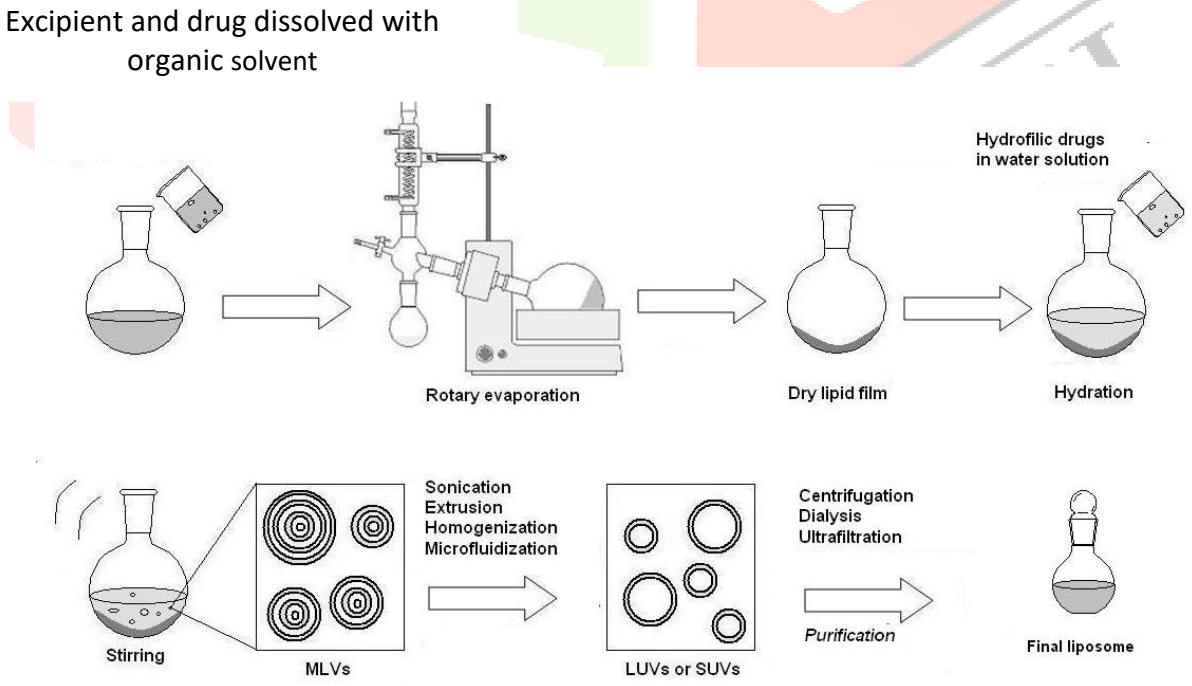

Figure 3: thin film hydration method for the preparation of liposome

Drawback

The process is low internal volume, low encapsulation efficiency and the size distribution is heterogeneous [3,7,8].

2.Solvent spherule method

A process for the preparation of MLVs of homogeneous size distribution. the procedure involved dispersing in aqueous solution the small spherules of volatile hydrophobic solvent in which lipids had

been dissolved. MLVs were created when controlled evaporation of organic solvent occurred in a water bath [8].

[B] **Small unilamellar vesicles**

1. Sanitation method

This method reduced the size of the vesicles and impart energy to lipid suspension .this can be achieved by exposing the MLV to ultrasonic irradiation .there are two method of sonicated (A) using bath sonicator(B) probe sonicator .the probe sonicator is used for suspension which require high energy in small volume (e.g. high concentration of lipid or viscous aqueous phase)the bath sonicator is used for large volume of dilute lipid. The disadvantages of probe sonicator is contamination of preparation with metal from tip of probe. by this method small unilamellar vesicles are formed and they are purified by ultra-centrifugation.

Drawback

the main drawback of this method is this method are very low interior volume /encapsulation efficiency, possibly degradation of phospholipid and compounds to be encapsulate, exclusion of large molecules, metal pollution from probe tip and existence of MLV along with SUV [4].

2. French pressure cell membrane method

French pressure cell method involves the extrusion of MLV at 20000 psi at 4 c through a small orifice. An important feature of the French press vesicles method is that the proteins do not seem to be significantly protenious during the procedure as they are in sonication's method has advantages over sonication method the method is simple, rapid and reproducible, the liposome formed by this method is quite larger than sonicated method.

Drawback

This method is mainly difficult to achieve, and the working volume are relatively small [9].

[C] Large unilamellar vesicles'

In this method they have high internal volume and encapsulation efficiency and are now days being used for the encapsulation of drugs and macromolecules.

1.**Solvent injection method**

[a] Ether injection method-

A solution of lipids dissolved in diethyl ether or ether/methanol mixture Is slowly injected to an aqueous solution of the material to been capsulated at 55-65c or under reduced pressure. the subsequent removal of ether under vacuum leads to the formation of liposomes.

Drawback

In this method, the population is heterogeneous (70-190nm) and the exposure of compound to be encapsulated to organic solvent or high temperature.

[**b] Ethanol injection method-**

A lipid solution of ethanol is injected to a buffer solution. the liposome is formed rapidly.

Drawback

This method is same as a ether injection method and also the liposome are very dilute, it is difficult to remove all ethanol because it forms azotrope with water and the possibility of various biologically active macromolecules to inactivation in the presence of even low amounts of ethanol[9-10].

[**c] Reverse phase evaporation method-**

First water in oil emulsion is formed by brief sonication of a two-phase system containing phospholipid in organic solvent (diethyl ether or mixture of isopropyl ether and chloroform), and aqueous buffer. The organic solvent removed under reduced pressure, resulting in the formation of a viscous gel. the liposome is formed when residual solvent is removed by continued rotary evaporation under reduced pressure. the high encapsulation efficacy can be achieved by this technique. the several macromolecules are encapsulated by this method.

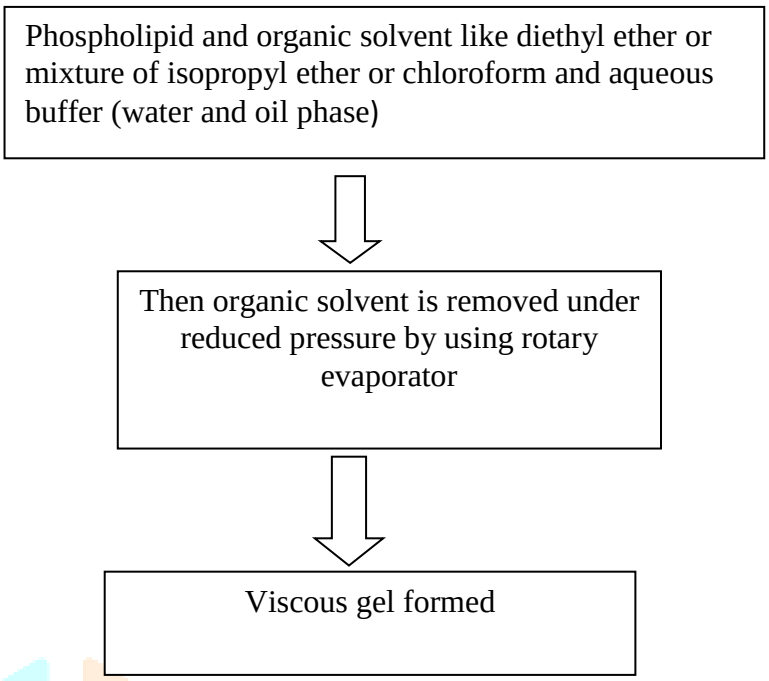

Figure 4: Reverse phase evaporation method

Drawback-

This method is required brief sonication. But this condition may possibly cause the denaturation of some proteins or breakage of DNA stands [8].

The exposure of material to be encapsulated in the organic solvent.

[d] Calcium induced fusion method-

This method is used to prepare LUV from acidic phospholipids. This procedure is based on addition of calcium to SUV induces fusion and result in the formation of Multilamellar structure in spiral configuration (cochleate cylinder) the addition EDTA to these preparations results in the formation of LUVs. The main advantage of this method is that macromolecules can be encapsulated under gentle condition

Drawback-

The LUVs can only be obtained from acidic phospholipid [2]

[e]freeze thaw method

SUVs are rapidly frozen followed by slow thawing. The formation of unilamellar vesicles is due to the fusion of SUVs during the processes of freezing and or thawing. This type of fusion is strongly inhibited by increasing the ionic strength of the medium and by increasing the phospholipid concentration.

Drawback-

The encapsulation efficiencies from 20-30% ware obtained [2-3].

[F]Giant liposome-

This method for the formulation of giant liposome involves the dialysis of a methanol solution of phosphatidylcholine in the presence of methyl glycoside detergent against an aqueous solution containing up to 1M NACL. The liposome range in diameter from 10to 100mm [2].

There are following liposome formulations of herbal and synthetic drug shown in below

Table 2: Herbal liposome formulation

s.no	Formulation	Biological activity	Application of liposome formulation	Method of preparation	References
1	Quercetin	Antioxidant and anti-inflammatory and anti-cancer	Reduced dose, and side effect enhance penetration in BBB and bioavailability	By using mixture of egg phosphatidylcholine quercetin and dispersion in polyethylene glycol	[11]
2	Cur cumin liposome	Antioxidant and anticancer	Long circulating with high entrapment	Ethanol injection method	[12]
3	Myrtle liposome	Antibacterial and antioxidant	Increase its activity	Thin film method	[13]
4	Rutin	Antiaging antioxidant	Good entrapment efficiency, prolong drug release, enhance skin hydration	Thin film hydration technique	[14]
5	Eugenol	Moisturizer, skin care	High entrapment efficiency value	Ethanol injection method	[15]
6	Black pepper	anti-inflammatory antibacterial	Enhancement of anti-inflammatory effect.	Rotary flush evaporator method	[16]
7	Ketoconazole	Antifungal activity		Thin film hydration technique	[17]
8	Triptolide	Anti-inflammatory	Increase stability and reduce side effect	Thin film depression method	[18]
9	Resveratrol	Treatment of acne	Maximum entrapment efficiency, reduced the side effect	Thin fil hydration method	[19]
10	Silymarin extract	Hepatoprotective antioxidant property for the liver and skin	Increase stability anti-hepatic activity, enhance penetration into cytoplasm tic barrier	Reverse evaporation method	[20]
11	Usnic acid with beta cyclodextrin	Antimycobacterial activity	Increase solubility and localization with prolonged release.	Thin lipid hydration method with sonication.	[21]
12	Emodin	Anti-inflammatory Antioxidant antibacterial	,	Thin film hydration method	[22]
13	Capsaicin liposome	Treat Muscles/joint pain,	Increase in skin permeation as well as prolongation of duration of action	Reverse evaporation technique	[23]
14	Garlicin	Antioxidant	Increase efficiency	Reverse phase evaporation method	[24]

15	Artemisia	Antiviral	Increase stability, anti-hepatic activity enhance penetration into cytoplasmatic barrier	Film method and sonication method	[25]
16	Diospyrin liposome	Antibacterial anti-tumor	Enhancement its anti-tumor effect	Reveres evaporation technique	[26]
17	paclitaxel	Anti-tumor	High entrapment efficiency (94%)	Thin film hydration method	[27]
18	Catechin liposome	Antioxidant and chemo preventive	Increase permeation through skin	Rotary evaporation sonication method	[28]
19	Colchicine's	Antigout	Enhance skin accumulation. prolong drug release and improve site specificity	Rotary evaporation sonication method	[29]
20	Magnolol liposome	Antioxidant inhibiting vascular smooth muscles cell proliferation	Enhance therapeutic efficiency.	Magnolol and phospholipidixed by ultrasonic facilitation	[30]

Table 3: Synthetic liposome formulation

s.no	Drug	Biological Activity	Application of liposome	Method	Ref.
1	Triamcinolone acetonide	Skin inflammation skin allergic	Reduced the side effect of drug prolong release	Thin film method	[31]
2	ketoconazole	Antifungal activity	Maximum entrapment efficacy and reduced side effect	Thin film hydration method	[7]
3	clotrimazole	Antifungal activity	Controlled and prolonged release of drug from veginal local treatment	Thin lipid evaporation method	[32]
4	doxibuprofen	Anti-inflammatory, Pain killer	Improved therapeutic efficacy, bioavailability for long period,	Rotary evaporator method	[33]
6	Lornoxicam	Anti-inflammatory activity, antipyretic, anti-analgesic	High therapeutic benefit and low toxicity	Thin film hydration method	[34]
7	Tazoretin	Antibacterial activity	Minimize the adverse effect	Lipid film hydration method using the rotary vacuum evaporator	[35]
8	Itraconazole	Antifungal activity	Reduced the side effect	Thin film hydration method	[7]

9	Fluconazole	Antifungal activity	Maximum entrapment efficiency prolong action	Thin film hydration method	[36]
10	isoniazid	Anti-tuberculosis activity	Prolong stability	Thin film hydration method	[37]
11	croconazole	Antifungal activity	stable	Dry film method	[38]
12	Diclofenac	Anti-inflammatory activity, anti-analgesic	Entrapment efficiency less	Reverse evaporation method	[39]
13	Amphotericin-B	Sever fungal infection	Stable	Film hydration method	[40]
14	vincristine	For cancer treatment	Increase the therapeutic value	Solvent evaporation method	[41]

CHARACTERIZATION AND EVALUATION OF LIPOSOME GEL PREPARATION

1.Structure characterization

physical characterization was evaluating the vesicles size, shape and size distribution by light microscopy, florescent microscopy, electron microscopy, laser light microscopy, photon correlation spectroscopy, field flow fractionation, gel permeation and gel extrusion. In the electron microscopic like scanning electron microscopy (SEM) and transmission electron microscopy (TEM), the size of the liposome vesicles can precisely characterize. Laser light scattering is one of the simplest methods to determine the size and the size distribution of the vesicles. The only drawback is the average property of bulk of the liposome cannot be determined [1,42].

2. Measurement of pH

The amount of gel formulation was taken 25ml in volumetric flask and then volume was made up with double distilled water to 25ml.the pH of gel was determined using a digital pH meter. the electrode was immersed in the gel and reading were recorded from pH meter [34].

3. Viscosity studies

Viscosity was determined by Brookfield viscometer by selecting spindle number and rpm. 30grm of gel preparation was kept in 50ml beaker, which was set till spindle groove was dipped and rpm was set, and reading was measured after five min. viscosity was calculated. the procedure was repeated three times and observations are recorded as mean [43].

4. Spread ability

Gel sample of 0.1g of each formula was pressed between 2 slides and left for about 5min.it's no more spreading was expected. The diameters of spreader circles were measured in c.m.it was taken as comparative value for spread ability.

$$S = ML/T$$

Whereas.

S= spread ability M= weight tied to upper slide,

L=length of glass slide, T= time taken by the slide to separate from [43].

5. Drug content and content uniformity

the drug content was determined using UV spectrophotometer.0.5gm of gel was taken in test tube and diluted up to 5ml with methanol and centrifuged at 18000 rpm for 30 min at 4 ◦c. Supernatant was taken and checked its absorbance[19].

6. Rheology studies

It is important and controls the flow properties to ensure product quality effectiveness of the production.it help in selection of dermatological formulation that will progress to clinical efficacy. In present study liposomal gel were prepared using Carbopol as gelling agent .rheology analysis of liposome loaded Carbopol gel were performed using a stress control rheometer (viscometer, rheological instrument AB, Lund, Sweden),equipped with stress rheologic basic software, version 5cone-plate geometry with diameter of the cone being 25mm and a cone angle of 10,operating in the oscillation and static mode. Rheological analysis was performed at room temperature. the following parameter were carried out for Rheology measurement.

Oscillation stress sweep:

Dynamic oscillation stress sweep was performed to determine the linear viscoelastic region (LVR). LVR is the region where the elastic modulus (g) was independent of applied stress because destruction in the structure of gels occurs at high shear stress. "Analysis of viscoelastic material was designed not to destroy the structure so that measurement can provide the information about intramolecules and inter particles forces in the material. this test gives idea about the critical stress beyond which the sample may show significant structural changes, and therefore the consequent choice of the stress valve to be used in other oscillation tests. the samples were exposed to increasing stress (0.5 to 150pa) at a constant frequency 0. g 0.Hz.

The three main parameter determines in this test were the storage modulus G ,loss modulus G ,and loss tangent tan δ .the end point of the linear viscoelastic region was determine as a stress ,when the G value was dropped 10% from the linear level that indicated a significant changes in the structure gel samples" .

Oscillation frequency sweep

The sample were exposed to stepwise increasing frequency (01to 100H2) at a constant stress in the field of LVR and elastic moduli (G) as viscous modules were recorded against frequency

Creap recovery

The creap recovery test was used to determine the visco elastic properties of the selected silk fibrain gel sample [36].

7.Entrapment Efficiency

Drug associated with liposome was separated from unentrapped drug using centrifugation method. Liposome were centrifuged at 20000rpm for 1hrs at controlled temperature of 4 ·c. supernatant containing unentrapped drug was withdraw and measured UV spectrophotometrically against phosphate buffer saline (pH7.4). the amount of drug entrapped in liposome was determined as follows

$$EE = [(CD-CF)/CD]\ 100$$

Where as

Cd-is concentration detected of total drug and

Cf- is concentration of free drug

The entrapment efficiency was obtained by repeating the experiment and the values were expressed as mean standard deviation [44].

8. Zeta potential (Z) determination

The potential difference existing between the surfaces of solid particle immersed in a conducting liquid (e.g. water) and the bulk of the liquid. That mean charge on empty and drug loaded vesicles surface was determined using zetasizer300HSA (Malvern instruments, Malvern, UK). analysis time was kept for 60s and average zeta potential and charge on the liposome was determine [33].

9. Stability Studies

The ability of vesicles to contain the drug (i.e. drug retentive behavior) was measured by keeping the liposomal suspensions at the 4-8 ·c and room temperature for period of 60day. Sample was withdrawn periodically and analyzed the physical examination, drug content and particle size distribution studies for liposomal suspension [42].

10. skin irritation studies

Skin irritation studies was used for determining the effect of drug in the skin. It was carried out on five human volunteers. A half gram of gel F2 was applied in the hand of each volunteer for 24 hours. After removal of gel, the resultant skin effects were examined for the sign of erythema or itching. The effects were classified into 5 scores depending on the degree of erythema as follows: 0 (no erythema), 1 (slight erythema-light pink), 2 (moderate erythema-dark pink), 3 (moderate to severe erythema-light red), and 4 (severe erythema extreme redness)[34] .

10. *In vitro* drug studies

In vitro drug studies are the important parameter for the evaluation of drug release from the carrier. in this study we are using cell membrane as a model membrane for the skin permeation study because of its similarity to human skin in lipid content and permeability. The membrane was sandwiched between the lower cell reservoir and the glass top containing the sample and secured in place with pinch clamp. the receiver compartment was filled with a pinch clamp. the receiver compartment was filled with pH 6 phosphate buffer. the system was maintained at 37 +/- 0.5 ^{0}C on the thermostatic controlled magnetic stirrer with continue stirring ,to avoid diffusion layer effect .multiple of 1ml from the receptor compartment were withdrawn at different hours respectively and replaced with equal amount of fresh buffer medium. After suitable dilution, the sample were analyzed spectrophotometrically by using UV spectrophotometer at specific wavelength [7]

FUTURE PROSPECTIVE

Liposomes have some advantages which make them look interesting as drug carriers for topically applied drugs. First, they are variable concerning size and surface properties and Second, they can act as sustained release depots, releasing encapsulated drugs of half-lives ranging from 0.6 to 11 days. Moreover, a new generation of liposomes, the so-called “collagen modified liposomes” can moderate the liposome and the liposome-cell interaction due to their collagen surface properties. This indeed might mean a greater possibility to control the drug release. The topically applied liposomal formulations, particularly those prepared from lipid mixtures of composition similar to the stratum corneum, would be an effective delivery system for the treatment of skin diseases. In the future the liposome gel is prepared in liposome hydro gel in the form of injectable for the treatment of breast cancer.

CONCLUSION

This study was done for herbal formulation for liposome gel topical delivery of therapeutic agent at the time of injury to accelerate skin repair within shortest time possible. By the above study we will conclude that hydrophilic as well lipophilic drugs can be easily encapsulated in liposomal formulation and dispensing in the form of Carbopol gel was found to be well suited and sound approach to get stable liposome formulation and variables like amount of phospholipid ,amount of stabilizers have a profound effect on the vesicles size and entrapment efficiency. Liposome dispersion and gels were found to extend the skin permeation and deposition compared to other conventional forms. Liposome gel technology offers entrapment of ingredient and thus reduced side effect, improved stability, increase elegance and enhanced formulation flexibility.

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