Review Article

Recent Advances In An Emerging Novel Nanocarrier: Elastic Liposomes

ABSTRACT:

Elastic liposomes (ELs) are the flexible liposomes formulated using phospholipids as well as edge activators. Edge activators provide elasticity to the elastic liposomes. Elastic liposomes provide advantages over other formulations and have the ability to be delivered by different routes such as topical, transdermal, nasal, ocular, etc. Potential of encapsulating not only lipophillic but also hydrophillic drugs in a single vesicle, ability to pass through channels 1/10th of their diameter, increase in drug permeation, enhanced solubility of drug, patient compliance, prevention of degradation of drug makes them efficient carriers of drugs and leads to increased interest of researchers in them. This review provides understanding of composition of elastic liposomes, advantages, method of preparation and the adaptable role played by ELs in the administration of numerous drugs for different diseases.

Keywords: Elastic liposomes, advantages, composition, drug delivery

1. INTRODUCTION

Topical dosage form is a confined formulation, through which the drug can be administered anywhere in the body. Topical drug administration provides significant advantages over conventional systems, which include: direct availability of the drugs to the target sites, prevention of non compliance of patient due to painless administration, increased efficacy and tolerability, prevention of systemic toxicity, reduced fluctuations of drug in plasma, local delivery of drug which is also site-specific, avoidance of the first metabolism, and non intrusive administration [1].

Among the different carriers investigated for the topical delivery of drugs, elastic liposomes have been extensively investigated over the past few years due to their inherent advantages as compared to other vesicular carriers. Elastic liposomes (ELs), commonly known as transferosomes, are biologically compatible double layered vesicular systems [2]. They comprise of phospholipids, surfactants which acts as edge activator (EA), and an interior hydrous cavity surrounded by double layer of lipid competent of surrounding water loving and hydrophobic molecules. Furthermore, substances like cationic lipids or anionic lipids, polyethylene glycol (PEG), cyclodextrin complexes, ethanol as well as gelling agents can be used. Its constitution effect’s its physiochemical characteristics and afterwards, potency by changing skin invasion behaviour [3].

Els are colloidal lipid based nano sized carriers made up of special constituents with predictable ultradeformability and flexibility which help them to compress through microlamellar spaces (which have a size of 1/10th diameter of vesicle) between keratinocytes to travel undamaged beyond the layers of skin and enhance wetting of the skin to boost transepidermal water loss (TEWL) [4]. Owing to combined effect of elastic liposomes acting as a transporter and penetrant, there is increase in permeability of ELs. Magnificently EL can invade the skin without breaking or getting damaged [5].

They are known by other names such as ultradeformable liposomes, ultraflexible liposomes, transferosmes, etc. ELs have been prepared for nasal, topical, transdermal and biological (vaccines and toxoids) dosage forms. Owing to their improved physicochemical and pharmacokinetic characteristics, elastic liposomes can assist the problems associated with traditional drug delivery vehicles [2].

2. COMPOSITION OF ELASTIC LIPOSOMES (Els)

Major components of elastic liposomes are amphiphilic phospholipids with several/ numerous chemical structures, edge activator (such as sodium cholate, sodium deoxycholate, span, tween and dipotassium glycyrrhizinate) [6], and aqueous compartments [Figure 1]. By altering the type and concentration of each constituent, drug delivery system could be regulated [7].

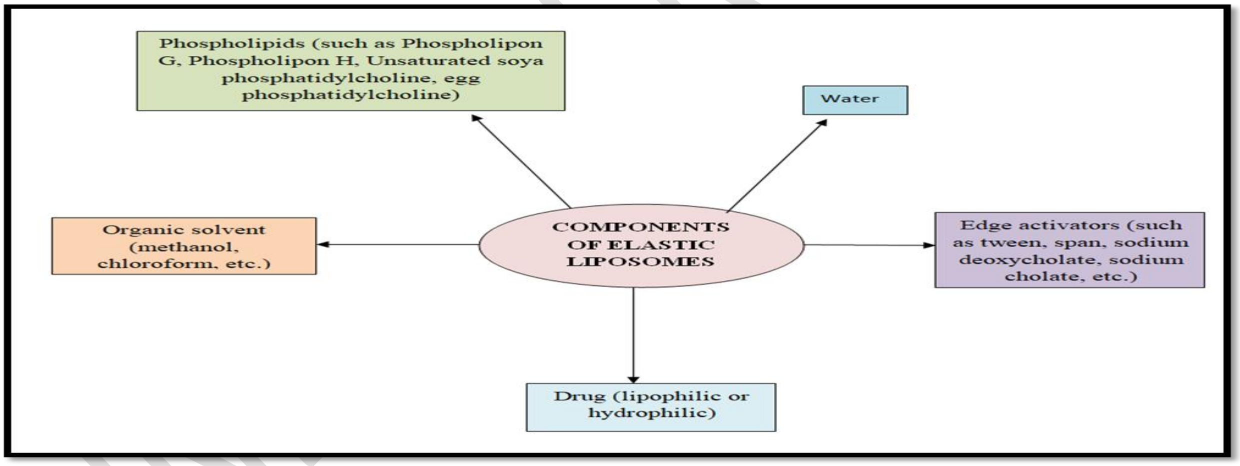

Fig. 1: Composition of Elastic Liposomes

2.1. Edge activators

Edge activator lowers the transition temperature of lipid and upset the double layer of lipid of elastic liposomes which increases the fluidity and governs the permeation behaviour of elastic liposomes across the skin. [8]

Several properties of edge activators that should be kept in mind before manufacturing EL are given in table 1.

Table 1: Properties of Edge Activator affecting characteristics of elastic liposomes.

Properties	Effect on characteristics of elastic liposomes
Elasticity	Increased elasticity results in increased leakage of drug [9].
Hydrocarbon chain (Non-bulky)	Edge activator having hydrocarbon chains which are non-bulky (Tween 80), are reported to be exhibit higher permeation flux as compared to other edge activators [15]. [9].
Transition temperature (T_m)	Addition of edge activator reduces the transition temperature and incite the fluidization of the double layer of lipid [10,11].
HLB value	Lower HLB values of edge activators result in the formation of vesicles of smaller size, the reason reported being reduction in surface energy due to enhanced hydrophobicity resulting from lower HLB values [9].
Affinity for lipid	Drug entrapment of hydrophobic drugs increases due to greater affinity of lipophilic EA with lipid bilayer [12].
Concentration	Edge activator when added in too low concentration, results in formation of extra inflexible vesicles and when added in excessive concentration will result in formation of mixed micelle, which exhibit smaller size, lesser entrapment efficiency, finite permeability, less flexibility, and little sensitivity to water activity gradients of the skin [13-16].

2.2. Phospholipids

Unsaturated soya phosphatidylcholine (PC) and egg phosphatidylcholine (~10% w/w) are the most preferred phospholipids. Normally lipids have unelevated transition temperature. At high temperatures, lipids are in a state of liquid crystal which results in leakage of drug (owing to enhanced permeability of confined therapeutic agent) at room temperature (25° C) and when administered to the skin (32° C). Storage stability can be prolonged by regulating the lipid double layer structure by setting its transition temperature between these temperatures [8]. Amphiphilic particles contain a glycerol bridge that forms a link between a pair of lipophillic acyl hydrocarbon chains and a hydrophillic head, which affects the lipid membrane phase transition for increased flexibility [17]. Table 2 contains summary of properties of lipids and their significant roles [17, 18-20]. Transportation of several challenging particles at elevated concentrations within and across the layers of skin by topical delivery is enabled by such systems.

Table 2: Characteristics of phospholipids and their noteworthy role.

Characteristics	Noteworthy role
Length of chain and saturation degree	Unsaturated phosphatidylcholine with a low transition temperature are mainly used for preparing ELs. Increased elastic and enhanced transdermal flux was shown by DLPC (C: 12) based ELs of sumatriptan as compared to DOPC (C: 18) composed vesicles [18].
Purity of lipid	The permeation behaviour of vesicles is affected by the purity of phosphatidylcholine. When the permeation behaviour of vesicles was studied with different purity concentrations, the finest result was acquired with 95% phosphatidylcholine [19].
Composition of	High membrane flexibility can be obtained by using unsaturated PC

Lipids	with lower $T_{m.}$ [17, 20].
Transition temperature (T_m)	The enhanced permeability of the encapsulated drug can be attributed to the lipids present in a liquid crystal state at room temperature (25° C). By altering the quantity of phosphatidylcholine in the EL bilayer, the transition temperature can be modified to set between the temperature at which they are stored and skin temperature (32° C). Furthermore, when applied to the skin, because of the temperature of the skin (32° C) being significant than its Tm, the state of vesicles turns into liquid, which eventually provides more elasticity [17].

For better elasticity and stability of ELs, the proportion of lipid to edge activator should be optimal, which helps in achieving long term storage stability and an efficient permeation potential, respectively. Constituents that can be used as carriers for vesicle formulation could be cationic lipids, PEGylated lipids, gels and complexing agents that encapsulate the drug. The complexing agents include cyclodextrine, ethyl alcohol (10% of aqueous volume) [17].

Figure 2 illustrates the composition of an elastic liposome.

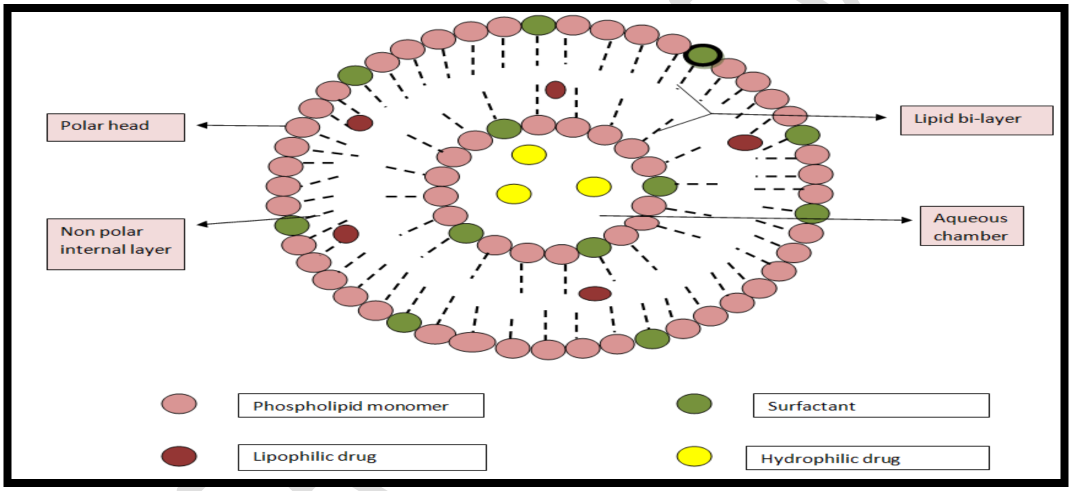

Fig. 2: The composition of an elastic liposome

3. MECHANISM OF PERMEATION OF ELASTIC LIPOSOMES THROUGH THE SKIN

Skin acts as a prominent barrier for many drugs after their administration through topical route. When suspension of ELs is applied topically, it interact with the skin and results in occurrence of many sequential events [17]. Initially, the concentration of non-volatile adjunct material increases on the skin due to immediate evaporation of water present in the suspension. After reaching the saturation level, the hydration gradient down the skin to elastic liposome vesicles are well maintained. Consequently, in the upper layer, there is increase in water content (10%-30%) in comparison to the internal living epidermis (75%) [21]. Transepidermal hydration gradients develop due to difference in water content in upper and lower layer. The vesicles are pulled towards the inner layer of the skin by water affinity of the vesicles, transepidermal hydration gradient, and high elasticity, until they have extended to the living epidermis rich in water. After liposomal vesicles have crossed the SC barrier by diffusion-mediated mechanism, the “pull” mechanism is substituted with a “push” mechanism on the vesicles. In living skin, the intracellular fluid motion may also be effectual. It is interesting that elastic liposomes cannot penetrate the SC layer without a transepidermal hydration gradient. Furthermore, the hydration gradient may be decreased when applied occlusively. So cannot be applied occlusively [21].

4. ADVANTAGES OF ELASTIC LIPOSOMES

Elastic liposomes have a number of advantages over other dosage forms. The advantages are compiled in Figure 3.

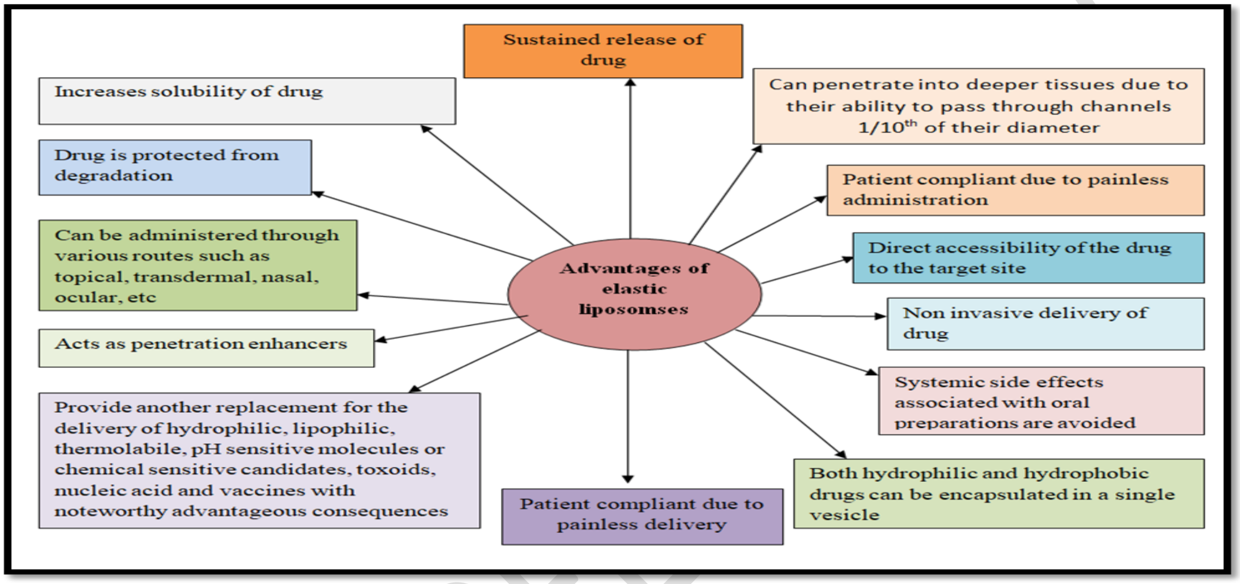

Fig. 3: Advantages of Elastic liposomes

5. PREPARATION OF ELASTIC LIPOSOMES

Conventional rotary evaporation method is used for preparing the elastic liposomes [22, 23]. Using different proportions of surfactants, phospholipid and potent drug, several batches of ELs are developed.

The various steps involved in the formulation of elastic liposomes are given in figure 4.

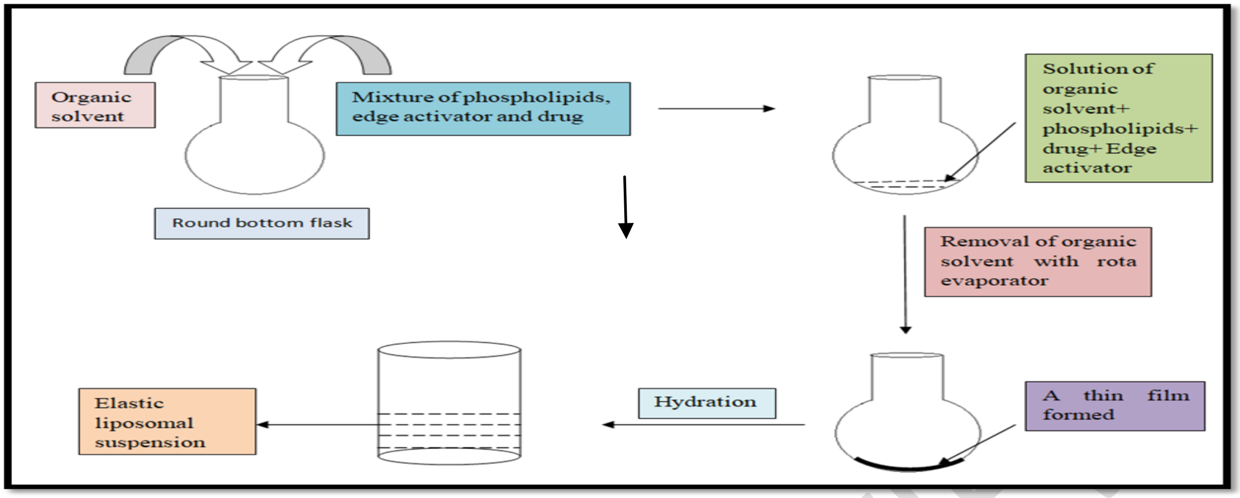

Fig. 4:The steps of formulation of elastic liposomes

6. CHARACTERIZATION OF PREPARED ELASTIC LIPOSOMES

6.1. Polydispersity index, vesicle size and zeta potential: Zetasizer is used for determining polydispersity index, vesicle size and zeta potential. After diluting each liposomal sample 30 times with HPLC Grade water, all the measurements are performed at 25ºC, a scattering angle of 90˚, and a laser wavelength of 633 nm. In order to figure out the values as a mean ± standard deviation, all the measurements will be repeated three times [24].

6.2. Percentage yield of elastic liposomes: For determining the %age yield of elastic liposomes, the developed ELs are weighed and the measured weight is divided by the total weight of drug and components utilized for the development of ELs [25].

%age yield = weight of prepared elastic liposomes / total weight of drug and excipients * 100

6.3. Drug entrapment efficiency (%EE): The drug entrapment efficiency is determined by isolating the unetrapped drug by using minicolumn centrifugation method. The pellet obtained is disrupted using suitable solvent (such as methanol, triton X, etc.) The solution is filtered and the amount of drug is quantified spectrophotometrically. The percentage entrapment is calculated using the following formula [26]:

$$\text{Percentage entrapment} = \frac{\text{entrapped drug}}{\text{Total drug added}} \quad *100$$

6.4. Vesicle morphology: Transmission electron microscope(TEM) is used for visualizing elastic liposomal formulations. A thin film is formed onto a grid coated with carbon after placing one drop of the sample on it. The film is negatively stained using 1% phosphotungastic acid before it gets dried on the grid. Onto the film, staining solution (one drop) is put and by using a filter paper, solution in excess is removed. Samples are observed under a TEM, after drying the grid in air [27].

6.5. Turbidity: Nephelometer is used for determining the turbidity of different formulations using suitable buffer as blank [27].

6.6. Elasticity: Elastic nature of the vesicles is measured by extruding the formulated vesicles at 2.5 bars through a polycarbonate millipore filter membrane which has 60–200 nm as the diameter of pores. After 10 minutes, the volume of the vesicle suspension is measured and the shape of vesicles and size is observed before and after the filtration. The following formula is used to measure the elasticity of the vesicle membrane:

$E= J^* (r_v/r_p)^2$

Where E= vesicle membrane elasticity; J = suspension amount, which will extrude during 10 min; r_v =size of vesicles size extrusion; and rp = barrier pore size [28, 7].

6.7. Viscosity: The viscosity of the prepared ELs suspension is measured using a viscometer at temperature 25º C [29]. The process is repeated three times on each sample to get a mean value [30].

6.8. Spreadability: The main factor of the formulations developed for topical application that provides advantage over formulations which are non-spreading or poorly spreadable is the degree of spreading capability of the formulation. To make sure that the dosage form applied topically leaves a fine film on skin, spreadability is an important parameter to acquit [30].

Between graduated flat glass surfaces, a weighed amount (1g) of the elastic liposome suspension is kept and pressed with weights which are increased (50-500g) after different time points. The developed diameter is estimated to determine the surface area (cm^2) at different time intervals. The procedure is carried out at 25º C [31].

6.9. *In vitro* drug release assessment: The test is performed in a Franz diffusion cell using a dialysis membrane, which is kept in between the donor and the recipient compartment of the diffusion cell and the sample is placed on it. The study is conducted under continuous stirring (100 rpm) using a magnetic bead and at a temperature of 37± 1º C. At predetermined time points, the samples are collected and the amount of sample collected is restored by adding fresh buffer. The samples collected are assessed spectrophotometrically to estimate the released drug content [32].

6.10. *Ex vivo* permeation study: The *ex vivo* permeation study is performed using the rat skin in a diffusion cell [33] after removal of unnecessary fatty debris and hairs. The cleaned skin is kept in between the compartments of the diffusion cell and the dosage form is applied onto the epidermal surface of the skin. The temperature is maintained at 37 ± 1º C and the release medium is continuously stirred at 50 rpm using a magnetic bead [34]. At given time intervals, the samples are withdrawn and the volume withdrawn is replaced by equal volume of fresh buffer. The amount of drug permeated is assayed spectrophotometrically [32].

7. APPLICATIONS OF ELASTIC LIPOSOMES IN THE TREATMENT OF DIFFERENT DISEASES

Elastic liposome's have been investigated extensively by researchers for delivery of drugs and other therapeutic agents for the effective treatment of many diseases. The common diseases for which the delivery of drugs by formulation of elastic liposomes has proven to be effective are given below.

7.1. Atopic Dermatitis

Goindi *et al.,* 2013 formulated nanosized elastic liposome based dosage form of cetrizine dihydrochloride for topical administration using phospholipon 90 G and surfactant to target peripheral H1 antihistaminic activity. The optimization of the prepared formulation was done on the basis of phospholipid/drug/charge inducer ratio and concentration of surfactant. The optimized dosage form was satisfactory in terms of stability, content of drug, pH, entrapment efficiency, size of vesicles, viscosity, spreadability as well as morphology. The *ex vivo* permeation study was carried out using franz diffusion cell and mice skin. The mean cumulative percentage of drug permeated in 8 hours was found to be approximately double (60.001±0.332) in comparison to commercially available cream (33.268±0.795) and drug solution (32.616±0.969), thereby recommending enhanced penetration as well as permeation of drug from the elastic vesicles. Additionally, oxazolone-induced atopic dermatitis in mice was used for assessing the therapeutic efficacy of optimized formulation. The developed formulation was found to be beneficial in lowering the itching score (4.75 itches per 20 min) in comparison to conventional cream (9.75 itches per 20 min) with marked decrease in count of eosinophils of dermis as well as erythema score. It was concluded that elastic liposomes were non toxic and safe for dermal application. The authors concluded that the formulated elastic liposomal formulation had potential for treating atopic dermatitis [35].

Lie and coworkers formulated tacrolimus loaded transfersomes (TFs) and evaluated their potential for treating atopic dermatitis in mice. A comparison of the formulation was done with commercial tacrolimus ointment (Protopic®) as well as liposomes-gel. Among the various carriers (sodium cholate, Tween 80 and Span 80) evaluated for the formulation of TFs, Tween 80 was chosen as the optimized carrier based on its highest deformability as well as maximum drug retentions. The optimized TFs were later converted into gel. The results of *in vitro* drug release of TFs-gel indicated a higher drug release after 24 h in comparison to the commercial ointment. The TFs-gel exhibited a *in vitro* drug release of 37.6% after 12 hours. Significantly higher drug retention in the skin was obtained for the optimized TFs-gel as compared to the liposomes-gel and ointment available commercially. The tacrolimus present in the epidermis as well as in the dermis after the application of TFs-gel was found to be 3.8 times and 4.2 times higher in comparison to the ointment. The liposomes-gel also exhibited higher levels of the drug in the epidermis and the dermis (1.7 times and 1.4 times respectively) as compared to the commercial ointment. The authors reported the developed formulation exhibited best curative action on 2,4-dinitrofluorobenzene induced atopic dermatitis in mice. Based on the results the authors suggested that TFs exhibited better performance as well as effective skin targeting of tacrolimus after topical application [36].

7.2. Hypertension

Manvir and coworkers formulated elastic vesicles of nifedipine for transdermal delivery. The vesicles containing nifedipine were developed by using rotary evaporator and different characteristics such as size, shape, size distribution, number of vesicles, entrapment efficiency, as well as stability were evaluated. Among the different formulations of elastic liposomes, one formulation was optimized on the basis of entrapment efficiency for the additional parameters. The entrapment efficiency was found to be higher in tranferosomal formulation as compared to the liposomal formulation. The number of vesicles formulated transferosomes was found to be more as compared to liposomal formulation. Franz diffusion cell was utilized for carrying out the *in vitro* drug release study. A lower release rate of nifedipine was found from elastic vesicles in comparison to liposomes. *Ex vivo* study was carried out on male albino rats and the results of *ex vivo* study were used to compare the performance of elastic liposomes and the liposomes solution. From the skin study, it was found that the skin permeation was higher for elastic liposomal formulation (76.41±0.9) in comparison to nifedipine loaded liposomal solution (71.44±0.9). No change was observed in the consistency of transferosomal formulation and no drug crystals appeared during the stability studies. Hence, the study concluded that transferosomal formulation of nifedipine have significant capability to enhance permeation of the entrapped drug across skin and prolong release of drug besides providing site specificity [37].

Ahad and coworkers formulated and evaluated the potential of eprosartan_mesylate (EM) loaded nanotransferosomes for transdermal delivery. Phospholipon 90G, sodium deoxycholate (SDC) and Span 80 (SP) were utilized for the formulation of nanovesicles. The formulation which was considered optimized exhibited 108.53 ± 0.06 nm as the size of the vesicles and 63.00 ± 2.76% as the entrapment efficiency. The authors reported that the formulated transferosomes exhibited a enhanced flux (27.22 ± 0.29 $\mu g/cm^2/h$) and enhancement ratio of 16.80 as compared to the conventional liposomes when evaluated using rat skin. The results of the confocal laser microscopy confirmed that the formulated dosage form successfully permeated and distributed through deep layers of rat skin. Based on the study results the authors also inferred that both the nature as well as the edge activator concentration and surfactants influenced the properties of transferosomes immensely. The authors confirmed that nano transferosomes are a potential drug delivery system for the delivery of EM through the rat skin [38].

7.3. Anti-histaminic activity

Elsayed and coworkers looked into feasible mechanisms through which transferosomes and ethosomes enhance delivery of ketotifen under non-intrusive state in skin. Rabbit pinna skin was used for studying the *in vitro* permeation as well as deposition studies of transferosomes and ethosomes, possessing ketotifen both within and externally on the vesicles, possessing ketotifen only within the vesicles and possessing ketotifen only on the outside of the vesicles. The authors proposed that the penetration increasing impact as the permeation of intact vesicle into the stratum corneum could enhance delivery of drugs in the skin by transferosomes, under non-intrusive state. Results concerning ethosomes showed that for the optimum delivery of the drug to the skin, the drug should be assimilated within the ethosomal vesicles. Ethosomes did not have the ability to improve the delivery of non-confined ketotifen to the skin [39].

7.4. Herpex Simplex infection

Jain and coworkers developed elastic liposomal formulation containing acyclovir sodium for its improved transdermal delivery by utilizing rotary evaporation method. The formulation was evaluated for shape as well as surface characteristics of the vesicles, size and size distribution, polydispersity index, entrapment efficiency, turbidity, elasticity as well as *in vitro drug* release. Artificial membranes and rat skin were used for carrying out permeability studies of drug loaded formulation. CLSM was used for assessing the capability of the developed dosage form to penetrate the skin. The results of CLSM revealed that the permeation was enhanced to the cavernous skin layers (up to 160µm) following pathways which were like channels. The authors concluded that the ELs were favorable vehicles for transdermal delivery of acyclovir sodium [27].

7.5. Gout

Singh and coworkers formulated a cyclodextrine- colchicines complex and examined its impact on permeation across skin as well as colchicines deposition in skin. Freeze- drying method was used for preparing the colchicines beta cyclodextrine (BCD) complex. NMR and *in vitro* drug release study were used for confirming the complex formulation. A enhanced transdermal flux (6 fold) was shown by formulation containing cyclodextrin drug complex in comparison to drug solution. The stored effect of transferosomes in skin was determined with the help of skin retention studies. A 12.4 times increase in the amount of drug deposition was observed in case of transferosomes of colchicines complex with cyclodextrin (567±1.5 mg) in comparison to solution of drug (46±1.1 mg). Air pouch model based on induction by monosodium urate was used for assessment of various elastic liposomal dosage forms and solution of drug. In rats, after administration of colchicines-BCD elastic liposomal formulation, superior anti-gout activity with biological effects which persisted for over 24 hours were observed in comparison to drug solution. The biological effects were calculated in terms of volume of exudates, decrease in count of leukocytes, reduction in accumulation of inflammatory cells and deposition of collagen. At the end, the study concluded that colchicines- cyclodextrin- transferosomes exhibited great ability to increase accumulation in skin, enhance release of drug and improvise the site specificity of colchicines [40].

Tiwari and co-workers loaded allopurinol in transferosomes and evaluated their efficacy in the treatment of gout. Thin film hydration process was used for the formulation of transfersosomes using soyalecithin, tween 80 and solvent. The results of characterizations done revealed that the formulation was spherical in shape, with a zeta potential and percentage entrapment efficiency of -11.4 mV to -29.6 mV and 52.4- 83.87% respectively. Absence of any interaction between the drug and other excipients during formulation of transferosomes was revealed by FTIR. The cumulative percentage drug release was between 51.87 to 81.87% from the formulations prepared. Further, the optimized drug containing dosage form was transformed into gel and evaluated for pH, rheological behaviour, permeation, irritation as well as *in vivo* studies in rabbit model. The results were better than the satandard allopurinol. The authors suggested the prepared transferosomal formulation to be a potential dosage form for the gout treatment [41].

7.6. Cutaneous Tuberculosis

Altamimi *and associates* developed isoniazid loaded elastic liposomes using phosphatidylcholine (PC) and surfactant having inherent anti-tubercular activity. The formulation was optimized using a full factorial design. The two factors were PC and surfactant which were considered as X1 and X2. The four variables which were dependent were Y1, Y2, Y3 and Y4 which corresponded to size, zeta potential, % entrapment and flux. In order to check and authenticate the mechanism of deposition and penetration of the formulation across the skin of rats, DSC, SEM and CLSM were utilized. In comparison to the formulations containing sodium deoxycholate and span 80, formulation F18 exhibited minimum size of vesicles (~ 78.6 nm) and optimal zeta potential (+ 25.31 mV). OEL (X1 ~ 82.5 mg and X2 ~ 30.5 mg) showed a good correlation between the observed and the predicted values with the maximum desirability (0.943) and absence of any interaction. The spherical shape and the deformability of the vesicles of the

OEL were ensured by the morphological and the extrusion studies. All the elastic liposomal formulations exhibited hemocompatibility with a sustained release of the drug. The OEL exhibited enhanced permeation flux which was 1.8-, 1.4-, 1.8-, 1.6- and 8.2 times more than formulations F3, F7, F11, F15, and drug solution, respectively. Reversible perturbation was shown by DSC and SEM whereas penetration into the skin was confirmed by CLSM. Based on the results the authors concluded that the formulated elastic liposomes could be successful approach for controlling cutaneous and systemic tuberculosis [42].

7.7. Cancer

Hussain and coworkers prepared elastic liposomes loaded with 5- fluorouracil (5-FU) by utilizing different surfactants and aimed to increase permeation of drug through stratum corneum (SC) layer of rat skin. The formulated elastic liposomes were evaluated for number and size of vesicles, their entrapment efficiency, turbidity, charge, morphological features, *in vitro* drug release, *in vitro* skin permeation as well as *in vitro* hemolytic ability and the results were compared with drug solution. The authors performed CLSM inorder to assess the *in vivo* skin irritation potential of the developed formulation. The elastic liposomal formulations EL3-S60, EL3-S80 and EL3-T80 exhibited drug permeation flux of 77.07 ± 6.34, 89.74 ± 8.5 and 70.90 ± 9.6 mg/cm2 /h respectively in comparison to drug solution (8.958 ± 6.9 mg/cm2 /h) and liposome (36.80 ± 6.4 mg/cm2 /h). Three fold higher drug deposition was shown by the optimized formulation EL3-S80 in comparison to the solution of drug. From the results of skin irritation and CLSM studies, it was proposed that the optimized gel was incapable of causing skin irritation and had ability of delivering 5-FU into the epidermis for increased topical delivery as compared to solution of drug. Minimum hemolysis was noticed in the case of optimized formulation during the *in vitro* study. The *in vivo* toxicity studies and histopathological evaluations indicated that the transferosome had ability of extracting SC to enhance permeation of drug without bringing about any alteration in the skins general anatomy [7].

7.8. Fungal Infections

Patel and parikh used Rotary Flask Evaporation -Sonication method for the formulation of transferosomes loaded with antifungal agent. The authors used Plackett-Burman Design to identify critical process and formulation parameters which affected the size of the vesicles. The authors concluded that lipid as well as surfactant amount, ethanol volume, hydration media and time of hydration had a significant effect on the size of the vesicles [43]

7.9. Wound Healing

Allaw and coworkers utilized the combined effect of glycerol (moisturizing ability), propylene glycol(enhanced permeation ability) and mucin (bioadhesive capability) to improve both the efficacy of transfersomes as well as the efficacy of the drug mangiferin in the skin lesion treatment. The authors formulated mucin modified transferosomes as well as glycoltransferosomes and evaluated their physicochemical properties as well as their their efficacy againt the treatment of oxidative stress an *in vitro* and *in vivo* skin wounds. The results confirmed enhanced deposition of the drug mangiferin in epidermis and dermis besides protection of fibroblasts from oxidative stress. The *in vivo* studies confirmed the anti-inflammatory efficacy as well as wound healing potential of the glycoltransferosomes [44].

Caddeoa and coworkers used Tween 20,40,60 and 80 for the formulation of tocopherol acetate loaded transferosomes. The formulated dosage form exhibited enhanced entrapment efficiency which increased with enhancement in fatty acid chain of Tween from 72% to 90%, small vesicle size of 85nm, were unilamellar and exhibited a polydispersity index of ≤0.27, which was low. The Turbiscan™ technology used for assessing the stability of the formulation indicated that the formulation was stable. The authors concluded that the vesicular carriers formulated were biocaompatible to fibroblasts as well as keratinocytes and delivered the encapsulated drug efficiently to the skin. Protection to skin cells against hydrogen peroxide induced oxidative damage was observed when drug loaded transferosomes were used. The authors reported speedy closure of skin wound after the application of formulation. This was attributed by authors to the promotion of cell proliferation as well as migration by transferosomes. The authors confirmed the wound healing potential of transferosomes [45].

7.10. Ocular diseases

González-Rodríguez and co workers optimized the timolol loaded transferosome formulation by utilizing Taguchi orthogonal experimental design and evaluated its efficacy in open angle glaucoma. The authors asserted that the ratios of lipid to surfactant as well as the surfactant type were the key variables which determined the bilayer flexibility of transferosomes. Based on the results of the study, the authors confirmed that the formulated transferosomes had the potentiaol to enhance the bioavailability of the drug [46].

7.11. Dental applications

Bnyan and coworkers designed and developed a transferosome formulation loaded with local anaesthetic (LA) for the treatment of buccal as well as dental pain. The formulation was developed with the aim to decrease the administration frequency and increase the safety of the administered LA by providing a local effect. A Taguchi design of experiment (DOE) was used to optimize the parameters. Size of the vesicles, polydispersity index (PDI), entrapment efficiency (EE) and charge were the parameters evaluated. The authors reported that the elastic liposomes exhibited a size less than 200nm and had a low PDI. The formulation which exhibited less size of vesicles with higher %EE was chosen for in vitro study, the results of which revelaed a sustained release of the LA from the formulation over a period of 72 hours [47].

Table 3 gives the applications of elastic liposomes in treatment of various diseases.

Table 3: Applications of Elastic liposomes in treatment of diseases

S. No.	Drug	Components	Method of preparation	Disease targeted	Reference
1	Cetirizine Dihydrochloride	Phospholipon 90G, Edge activators (Span 80, Tween 80, sodium deoxycholate), charge inducer (stearylamine)	Rotary evaporation method	Atopic dermatitis	[35]
2	Nifedipine	Soya phosphatidylcholine,	Rotary evaporation	Hypertension	[37]

		edge activator (span 80)	method		
3	Cyclodextrin-Colchicine Complexes	Soya phosphatidylcholine, Edge activators (Span 60, span 8- and cholesterol)	Conventional rotary evaporation sonication method	Gout	[40]
4	Isoniazid	Phospholipon 90H, Edge activators (Tween 80, span 80, sodium cholate and sodium deoxycholate)	Rotary evaporation method	Tuberculosis	[42]
5	5-fluorouracil	Soya phosphatidylcholine, Edge activator (Span-60, Span-80 and Tween-80)	Conventional rotary evaporation sonication method	Cancer	[7]
6	Ketotifen	Lipoid S100, Edge activator (Tween 80)	conventional mechanical dispersion method	Antihistaminic activity	[39]
7	Acyclovir Sodium	Soya phosphatidylcholine, Edge activators (Span 40, span 60, span 80)	Rotary evaporation method	Infections such as herpes, chicken pox, etc.	[27]
8	Clotrimazole	Soya phosphatidylcholine, Edge activators 9Span 80, Cholesterol)	Rotary evaporation method	Fungal infections	[26]
9	Naringenin	Epikuron-200, Edge activators (cholesterol, Tween 80)	Rotary evaporation method	Anti-oxidant activity	[48]
10	Curcumin	Phosphatidylcholine, Edge activators (Sodium deoxycholate, Polysorbate 80, Stearylamine)	Film hydration method	Wound healing	[49]
11	Acetazolamide	Phosphatidylcholine (PC), Edge activators (Tween 80, Span 60, and	Ethanol injection	Glaucoma	[50]

		Cremophor RH 40)	method		
12	Propranolol hydrochloride	Phosphatidylcholine, Edge activators (Span 40, Span 60 and span 80)	Conventional rotary evaporation sonication method	Anti-Hypertensive	[51]
13	Rifampicin	Phospholipon 90G, edge activator (Tween 80)	Rotary evaporation method	Anti-tubercular	[30]
14	Aceclofenac	Phospholipon 90G, Phospholipon 90H, Edge activator (stearylamine)	Thin film hydration	Against pain and inflammation	[52]
15	Ammonium glycyrrhizate	Phospholipon 90G, Edge activator (Sodium cholate)	Thin layer evaporation method	Anti-inflammatory	[53]
16	Lornoxicam	Phosphatidylcholine, Edge activators (Sodium deoxycholte, tween 80)	Thin film hydration method	NSAIDs	[54]
17	Sulforaphane	Phospholipon 90G, Edge activator (Sodium cholate)	Rotary evaporation method	Against skin cancer	[55]
18	4-OH Tamoxifen	soya phosphatidylcholine, Emu oil, sodium taurocholate	Thin film hydration method	Against Breast cancer	[56]
19	Carvedilol	Phospholipids (HEPC, SPC, DSPC), Edge activators (tween 80, sodium cholate)	Thin film hydration method	Against skin cancer	[57]
20	Ivabradine Hydrochloride	Soya lecithin, edge activators (Tween 80, Sodium Lauryl Sulphate or Cetrimide)	Ethanol injection method	Against stable angina pectoris	[58]
21	Pravastatin sodium and Naringin	Omega 3 phospholipid, edge activator (Sodium deoxycholate)	Thin film hydration method	Anti hyperlipidimic	[59]

22	Paclitaxel	Lactose monohydrate, microcrystalline cellulose, Starch, span 20, span 80 and Tween 80	Rotary evaporation method	Anti cancer	[60]
23	Voriconazole	Phosphatidyl choline from egg yolk, Brij S100	Ethanol injection method	Anti fungal	[61]
24	Allopurinol	Soya lecithin, Edge activator (Tween 80)	Thin-film hydration	Gout	[41]
25	Carnosine	Egg phosphatidylcholine (eggPC), Edge activator (Tween 80)	Extrusion method	Ischemic stroke	[62]

8. FUTURE PERSPECTIVE:

Elastic liposomes have been exploited extensively by researchers for enhancing the solubility, permeation and bioavailability with a reduction in side effects of many drugs used in the treatment of plethora of diseases. However, the commercialization of these products is still limited, due to their limited scale up by pharmaceutical industries. Besides this, there is scarcity of safety data pertaining to the clinical studies conducted using these vesicular carriers, which further limits their commercialization. Researchers should work towards establishing the cost/benefit ratio of using these vesicular carriers for delivery of drugs along with collecting information related to their safety which would contribute extensively to improving the commercialization as well as customer acceptance of these carriers. Besides this, optional ingredients added to the formulation to impart enhanced elasticity and stability need to be explored more for further improving the performance of these vesicular carriers.

9. CONCLUSION:

Elastic liposomes have been utilized for improving not only the physicochemical properties of the entrapped drugs but have also contributed in providing improvement in pharmacokinetic as well pharmacodynamic properties of drugs both in animal as well as in humans. They have extensively investigated for the treatment of numerous diseases. However, there is a need for the collaboration of researchers and pharmaceutical industries to improve their commercial viability.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors

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