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Review on Assesment of Permeability of Enhancement Property of Hyaluronic Acid as Compare to Peg in Core Gel Liposome

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ABSTRACT

New controlled transdermal drug delivery systems (TDDS) technologies (electrically-based, structure-based and velocity-based) have been developed and commercialized for the transdermal delivery of troublesome drugs. The use of solvents that affect the skin barrier function is one of the classic strategies of penetration enhancement. The liposomes as a delivery system for hydrophobic and hydrophilic drugs is well recognized Standardized poly(ethylene glycol)-modified (PEGylated) liposomes, which have been widely used in research as well as in pre-clinical and clinical studies. The aim of present work was to investigate the potential utility of novel carrier gel core liposomes. This delivery system is capable of transporting the drug or macromolecules painlessly through skin into the blood circulation at fixed rate. The study includes the development of liposomal and ethosomal gels for transdermal delivery to overcome the side effects associated with oral route and comparing the latest gel-core liposomes (hyaluosomes) with non-conventional liposomal systems such as propylene glycol (PG)-liposomes, ethosomes, transferosomes and conventional liposomes. With the advancement in liposomal sciences, it warrants that hyaluosomes as a promising transdermal liposomal system for favourable rheological characteristics as well as superior transdermal permeation that proved greater capacity than conventional and other non-conventional liposomal systems.

1. INTRODUCTION

Drug delivery to skin includes a wide array of therapeutic technologies and pharmaceutical applications. In spite of their victory and showcase development as it were a modest bunch atoms have been endorsed for transdermal delivery. This is mainly because skin forms a very effective barrier against drugs and to passively transport drugs across this barrier drugs must be in a narrow window of physicochemical properties. Also skin barrier properties can change significantly based on age, race, location of application etc[1]. Since the primary FDA endorsement of a transdermal pharmaceutical item in 1979, transdermal medicate conveyance frameworks have pulled in the consideration of the detailing researchers [2]. Usually since sedate conveyance to skin incorporates a wide cluster of helpful innovations and pharmaceutical applications and the transdermal course can offer more focal points compared with the verbal and parenteral routes of drug organization[3]. To overcome the confinement a few procedures have been presented which run from utilizing entrance enhancers to assist the drug penetrate into the skin by tweaking . The obstruction work of the stratum corneum sc to physically by passing the sc utilizing procedures such as microneedles laser removal etc. Benefits of near by conveyance are legitimately archived which incorporates focused on conveyance, lower systemic presentation and lower harmfulness than verbal drugs. Preferences of topical medicate conveyance over verbal conveyance incorporate, quick onset of activity and Sedate input can be halted at any point after expulsion of the fix from the location[4]. Gives unfaltering plasma levels. Makes strides bioavailability and approaches to entrance improvement have been created to overcome these challenges. Best route for pediatrics patients. Suitable route for unconsious or vomiting patient. Lesser chances of overdose and simple discovery of medicate.

Classic physical infiltration upgrade methodologies incorporate iontophoresis[5], sonophoresis [6], penetration enhancers[7] and vesicular medicate conveyance frameworks[8-9]. Electroporation[10], phonophoresis [11-13] or supersaturated arrangements[14-15], but as of late novel approaches have been created such as compressed gas drive[16] and the utilize of microfabricated microneedles to puncture the stratum corneum , laser removal etc[17]. Among these conveyance modules, the vesicular frameworks are possibly useful as vesicles tend to fuze and follow to the cell surface; usually accepted to extend the thermodynamic movement angle of the sedate at vesicle stratum corneum interface hence driving to improved penetration rate [7]. A few chemical substances have been appeared to have the capacity to upgrade penetration over the skin, and are hence commonly included in transdermal frameworks. These incorporate moo atomic weight alcohols [18] alkyl methanol sulphoxides [19] non ionic surfactants [20] (polysorbates, polyethoxylated alkyl ethers and esters and poloxamers),

oleic corrosive in collaboration with propylene glycol [21-22] and azone [23-24]. And planning, characterizing different phospholipid, vesicles to be specific liposomes, ethosomes, propylene glycol (PG)-liposomes, ethosomes, transferosomes and hyaluosomes. The liposomes and ethosomes are not elective to each other. Their whole physicochemical properties and sedate penetrability components are very diverse from each other [8-9]. Broad investigate has been done on the application in TDDS of liposomes and ethosomes. Routine liposomes cannot enter into profound layers of the skin, but they can adsorb on the upper layer of the SC. The reason being, customary liposomes are less deformable, get dried out totally, fuze and limited to the skin surface [25]. Liposomes don't have capacity to penetrate the phycocyanin into the profound layers of the skin and embodiment productivity of liposomes was found less than 50% [26]. To overcome the destitute penetrability of liposomes through the skin, ethosomes were to begin with created for transdermal conveyance by Elka Touitou. Ethosomes are delicate liable vesicles implanted with tall alcoholic substance (up to 45% v/v). The ethosomal molecule estimate was exceptionally moo compared to liposomes due to the interpenetration of lipid bilayers. It is proposed that synergetic movement of lipid and ethanol alter the warm properties of stratum corneum by fluidization[24]. They detailed that ethosomes kept up the skin fluidized situation by interaction with hydrophilic portions of lipids within the SC[28]. The polysorbate 80 and turpentine was utilized as the saturation enhancers for the liposomes and ethosomes, separately. The turpentine contained ethosomes appeared higher skin penetration after 24 h compared to liposomes separately .To kill these side impacts, transdermal course can be chosen for organization. Among these physicochemical criteria are appropriate atomic estimate and ideal medicate lipophilicity in arrange to pick upget to through the greatly lipophilic stratum corneum boundary[3]. Over the past three decades, lipid-based nano-sized vesicles have been utilized effectively for transdermal medicate conveyance frameworks; these nano-sized conveyance frameworks incorporate liposomes, ethosomes and transferosomes have been utilized for hydrophilic and lipophilic sedate conveyance over the skin obstructions[29]. Numerous reports have pointed out that not all lipid-based vesicles are similarly competent of accomplishing adequately tall and steady penetrability through the impressive obstructions of the skin. For illustration, transferosomes and ethosomes epitomizing edge activators and certain sum of liquor individually illustrated predominant skin penetrability compared with ordinary liposomes[30]. While the writing has barely said how these fluid liposomal scatterings might conceivably follow to the skin surface to permit adequate time for medicate saturation over the skin. On the drawback, these non ordinary liposomes might have dejected rheological characteristics and adherence to the skin. This conceivably requires the utilize of extra gooey vehicle or joining of the liposomal frameworks into suitable patches for the ease of application and spreading the managed dosage on the skin. More as of late, gel core-filled liposomes have been utilized viably for transdermal medicate conveyance of little and macromolecules such as curcumin and hyaluronic corrosive[31-32]. These novel liposomes are composed of phospholipid vesicles entrapping gel material in their core. Therefore, they can combine the advantages of liposomes and gel formulations in one drug delivery system[33]. The following section will focus on structure of the skin and understanding the role of core gel liposomes after liposomes in the grand theme of drug delivery to the skin.

2. SKIN

2.1 Human skin: penetration barrier

Skin is the biggest organ of the human body weighing at approximately 10 % of the body weight in adults and with an impressive surface region of around 20,000 cm^2[34]. the essential work of the skin is to preserve the body hydration[35]. Skin forms a vital obstruction between the environment and our organs. This barrier function protects us from hurtful impacts of chemicals, microorganisms, allergens and UV radiation. Skin barrier is 100 – 10,000 times less penetrable compared to a blood capillary divider[36]. Other major functions of the skin include homeostasis by thermoregulation and sensory function by detecting heat, pressure, pain and allergen mediated stimuli. Thickness of skin shift between 0.5 – 4 mm depending upon the anatomical location, which subsequently means based on the location, skin barrier can also vary considerably.

Briefly, skin can be considered to be divided in four layers, outermost stratum corneum (non-viable epidermis), viable epidermis, dermis, and bottom most subcutaneous tissue. Apart from different layers, skin also contains appendages like hair follicles sweat organs and sebaceous glands.(Figure1)

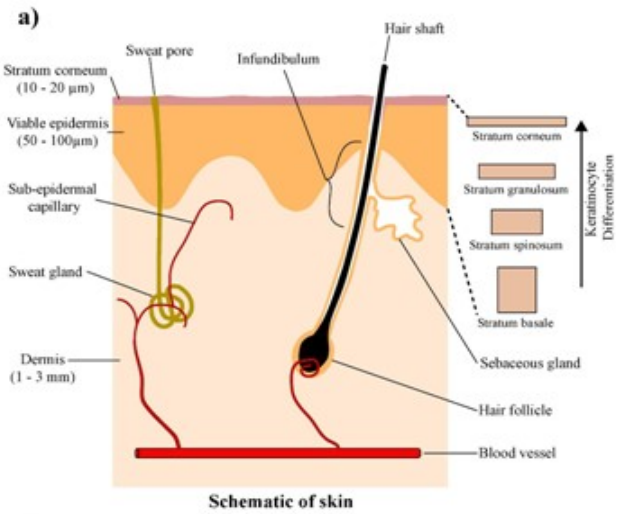

Figure:- 1 Shows a schematic representation of the human skin.

2.1.1 Stratum corneum (SC):-

The exposed layer of the skin (also termed as horny layer) which is approximately 10mm thick and formed by 10-15 layers of highly flattened, highly differentiated, non-nucleated cells called corneocytes. It has barrier property due to presence of 79–90% of protein and 5–15% of lipids. The multilayered epidermis shifts in thickness which basically depends upon cell thickness and layers of epidermis, body site, age, gender and race[36]. it is well built up that the SC is responsible for a major fraction of the boundary to the percutaneous retention of topically applied compounds. . A strong evidence for this was given within the shape of increased transdermal flux for different penetrating compounds when the SC was physically removed by tape stripping[37-42]. Removal of the SC can increase transdermal permeability by a factor of 10 – 20[34]. Although SC is the major skin barrier, deeper layers also possess a small barrier function.

2.1.2 Viable epidermis

Viable epidermis is the layer directly below SC and is mindful for producing the highly differentiated corneocytes of the SC. Viable epidermis is typically 50 – 100µm thick and contains three distinct layers based on the state differentiation of keratinocytes. Apart from keratinocytes viable epidermis moreover contains Langerhans cells responsible for immune response, melanocytes which produce melanin and Merkel cells which are involved in the somato sensory functions[43]. Viable epidermis does not contain any blood capillaries but does contain nerve fibers[44]. Due to a lack of vascular network, nutrients are delivered to the keratinocytes by inactive is semination through the interstitial liquid.

2.1.3 Hypodermis

It holds the fat tissues and acts as a back memberane for both epidermial and dermal layer of skin. It has its claim significance in transdermal medicate conveyance. Sedate might enter through all three layers to reach systemic circulation[45].

2.1.4 Dermis

Thickness of this layer is 3–5 mm. It mainly consist of connective tissues obligatory in direction of body temperature, oxygen supplements to the skin and evacuating poisonous items[45]. Dermis is divided in to outer *papillary dermis* and inner *reticular dermis*. A large proportion of the dermis by weight contains a relatively loose fibrous connective tissue matrix. Cellular component of the dermis comprises of fibroblasts, epithelial cells, mast cells and cells of immune system such as lymphocytes and leukocytes. Dermis also provides physical support for skin appendages, nerve fibers and network of lymphatic and blood vessels. Microvasculature of the dermis is responsible for maintaining the sink conditions for the drug molecules that have penetrated through the primary skin barrier into the dermis[47]. Dermis does not posture as a major barrier to drugs unless drugs are susceptible to enzymatic degradation then dermis can pose as a relevant barrier for absorption of drugs into systemic circulation.

2.1.5 Skin appendages

Most important skin appendages include, sweat organs, hair follicles and sebaceous glands. These appendages originate from lower dermis and reach the skin surface by penetrating through viable epidermis and the *stratum corneum*. Skin appendages occupy about 0.1 % of the total skin area[48]. Amongst all appendages *sweat glands* are the most abundant with approximately 400 glands/cm^2[34]. Hair follicles are the second most abundant skin appendages. Entire human body is covered with hair follicles except on the palms and soles. Due to secretion of sweat, pH of the skin surface is mildly acidic and can be in the range of 4 – 7.0[49]. As variation in pH could affect the stability of the formulation or even irritate the skin. Hair follicles are related with one or more sebaceous organs towards the mouth of the hair follicles. Sebaceous glands are holocrine glands which secrete an oily fluid called sebum.. Sebum typically is composed of mixtures of triglycerides free greasy acids squalene, squalene and waxes. Excretion rate of sebum averages around 0.1 mg/cm^2/h[50]. It is a common consensus that sebum does not have a skin barrier function. However, it may have a beneficiary or a retarding effect on the percutaneous penetration of the drug applied to the skin, depending on the nature of formulation and physicochemical properties of the sedate.

3. TRANSDERMAL DRUG DELIVERY SYSTEM

Among all strategies utilized for discharging drugs in a controlled way into the human body, transdermal sedate conveyance (TDD) is presently broadly recognized as one of the foremost promising ones, with a expansive number of commercialized applications. The foremost common transdermal frameworks display on the advertise are based on semi-permeable films (the so-called ‘‘patches). Transdermal medicate conveyance medications final a few hours a day, since they are regularly required to preserve a consistent concentration of medicate in blood. As a result, an perfect TDD framework ought to be compact and versatile. The TDD framework combines created parts with a commercially accessible micromotor and changeless magnets.

4. FACTORS AFFECTING TRANSDERMAL DRUD DELIVERY

4.1 Physiochemical properties of active moiety[51-52]

4.1.1 Partition coefficient

Medicate have both water and lipid solvency. Perfect segment coefficient for middle transdermal conveyance is log K 1–3. For exceedingly lipophillic medicate (log k43), intracellular course is positive, while for hydrophillic drugs (log k51), it is saturated by means of transcellular course.

4.1.2 Molecular size

Atomic measure of the medicate is inversaly corresponding to transdermal flux. The perfect atomic estimate of sedate atom for transdermal conveyance is 400.

4.1.3 Solubility/melting point

Most natural solutes have tall dissolving point and moo dissolvability at ordinary temperature and weight. Lipophillic sedate penetrates speedier than hydrophillic substances, but it ought to more over have watery dissolvability as required in most of topical definitions.

4.1.4 Ionization

Unionized drug permeates the skin as according to pH-Partition hypothesis.

4.1.5 Diffusion coefficient

Entrance of sedate depends on dissemination coefficient of medicate. At a steady temperature, the dissemination coefficient of medicate basically depends on properties of medicate, dissemination medium and their interaction.

4.2 Physiochemical properties of the drug delivery system[53-54]

4.2.1 Release characteristics

Medicate discharge instrument primarily depends on medicate atoms which are broken up or suspended within the conveyance framework and on interfacial segment coefficient or pH of the sedate from conveyance framework to the skin tissue. On the off chance that the medicate is effectively discharged from the conveyance framework, the rate of transdermal saturation will be higher.

4.2.2 Composition of drug delivery system

Composition may not influence discharge properties but may influence its penetrability usefulness. For case, methyl salicylate is more lippophilic than parent corrosive, i.e. salicylic corrosive, and its percutaneous retention is tall when connected to skin in a lipoidal vehicle.

4.2.3 Enhancement of transdermal permeation

Lion's share of drugs will not saturate into skin for theraputic utilize. A few enhancers are utilized for synergistic activity without showings its properties (e.g. dimethyl sulphoxide, acetone, propylene glycol and tetradihydrofuryl liquor).

4.3 Physiological properties[55-56]

Skin obstruction properties within the neonate and youthful newborn child the skin surface of the infant is marginally hydrophobic, generally dry and unpleasant when compared to that of more seasoned newborn children. Stratum corneum hydration stabilizes by the age of 3 months. Skin boundary properties in matured skin. There are a few changes within the physiology of matured skin (465 a long time). The moisture content of human skin diminishes with age. There's a pulverization of the epidermal intersection and thus, the region accessible for transmission into the dermis is reduced.

4.3.1 Race

Racial contrasts between dark and white skins have appeared a few anatomical and physiological capacities of the skin. In dark skin, there's expanded intracellular saturation due to higher lipid substance and higher electrical skin resistance levels when compared to whites, but this contrast isn't identified in stripped skin.

4.3.2 Skin temperature

The human body maintains a temperature of 32–37°C across the skin. Hence, increase in temperature leads to increase in diffusion through the tissue.

5. TYPES OF TRANSDERMAL DRUG DELIVERY

Formulation	Mechanism	Conclusion	Reference
Liposomes	Permeation enhancer effect and direct vesicle fusion with stratum corneum	Ability to modulate drug delivery without toxicity and makes the two vesicles useful to formulate topical route.	[114]
Cationic Transferosomes	Inducing strong humoral and cellular immune response	Inducing strong humoral and cellular immune response	[115]
Ethosomes	Lipid perturbation and increasing the intercellular lipid lamellae space of stratum corneum	Lipid perturbation along with elasticity of ethosomes vesicle seems to be the main contributor for improved skin permeation	[116]
Invasomes	Synergistic effect of liposomes, terpenes and ethanol	Invasomes containing 1% of terpenes mixture present an effective drug carrier system for delivering the highly hydrophobic drug Temoporfin into the stratum corneum and deeper layers of skin.	
Niosomes	No absorption due to large molecular structure of Gallidermin as well as the large niosomal structure	Gallidermin loaded in anionic niosomes and incorporated in gel is the superior topical anti-bacterial formulation because of high accumulation in the skin with no risk of systemic effect.	[117]
Deformable liposomes	By transcutaneous hydration Force	Deformable liposomes improve in vitro skin delivery compared to either aqueous solution or normal liposomes.	[118]
Ethosomes	Increase in thermodynamic activity due to evaporation of ethanol, increases penetration of drug molecule due to reduction in barrier property of stratum corneum by ethanol.	Ethosomes bearing melatonin offered a suitable approach for transdermal delivery when compared to liposomes and hydroethanolic solution.	[119]
Elastic liposome	IL-13 antisense oligonucleotide (ASO) was designed and formulated with cationic elastic liposome (cEL)	IL-13 ASO/cEL-treated AD mice showed reduced infiltration of inflammatory cells into the epidermal and dermal areas, with concomitant reduction of skin thickness.	[120]
SPACE ethosome	The peptide was conjugated to phospholipids and used to prepare an ethosomal carrier system (_110 nm diameter), encapsulating HA (200– 325 kDa)	Concentrations of HA in skin were 1000-fold higher than those in blood; confirming the localized nature of HA delivery into skin. The SPACE ethosomal delivery system provides a formulation for topical delivery of macromolecules.	[121]

Table:-1 Types of Transdermal delivery system

5.1 LIPOSOMES

Liposomes are an alluring candidate as pharmaceutical novel nanocarriers that have as of now been utilized clinically[57-58]. Liposomes have been extensively used as carriers for hydrophilic drugs for many reasons. First, they can protect the core-incorporated hydrophilic drug from degradation. Second, they aid this kind of drugs in crossing several biological membranes. Finally, they are sought of amongst the safest types of drug delivery systems due to their high biocompatibility and biodegradability properties originating from their main components which are the phospholipids vesicles bilayered structures. The advancement of sterically stabilized liposomes that decrease the location and ensuing take-up of the liposomes by the resistant framework, presently appears to have satisfied the requests of a long circulating medicate conveyance framework[59-62].Within the field of topical vehicles for dermal/transdermal conveyance *ultra adaptable liposomes* are frequently considered the vehicle of choice basically since of their tall performance as transdermal penetration enhancers and their good stability in suspension[63-68]. It is composed by a blend of lipids with moo stage move temperatures and an fitting sum of a cleanser. The cleanser acts as a film destabilizer creating an increment in layer deformability. Its tall deformability has been proposed to be the cause of their capacity to enter the skin and indeed permit for proteins to reach systemic circulation [69-75]. It is totally biocompatible additionally investigated by many specialists within the frame of polymeric *microparticle* and *hydrogel* for conveyance of protein and peptide[76-81].*Gel center liposomes* are the progressed liposomal build bearing center of biocompatible polymer interior the lipid vesicle. This system is the combination of polymer and lipid based delivery system, in which core of polymer serves function of skeleton and provides mechanical support to vesicles and in this way gelling will be actuated after division of unentrapped polymer. It is stabilized liposome with all of the advantage of liposome imitating cell layer focusing on controlled discharge interaction with particular cells with elimination of single drawback of instability and with added advantage of controlled release for prolonged period of time. It contain three unmistakable situations for drugs to break up within the water lipid interface the hydrophobic center and the watery insides. Within the show work of it was arranged by turn around stage vanishing strategy and optimized by implies of different in vitro considers The most common polymer used is polyethylene glycol polymer (PEG). There's a reported increment of in vivo solidness of liposomes containing peg lipids is likely due to the arrangement of a steric obstruction which ruins the approach of various blood proteins[82]. It is in this manner of awesome significance to extend the information of the physical impacts of peg lipid on liposomal properties pH or temperature in the presence of specific ions or low molecular weight cross-linking agents. Thus, *gel core liposomes* can act as a novel controlled release system[83-89]. The objective of this study was to prepare a modified liposomal carrier with a gelatinized core aiming for higher entrapment efficiencies of hydrophilic molecules and to develop a stabilized liposome by imparting a core of polymer in it and its comparison with conventional liposomes (liposomes prepared by 7 : 3 ratio of soya PC and cholesterol) for better controlled and sustained release properties of such molecules.

6. DRUG PENETRATION PATHWAY

Sedate can be entered by three pathways such as transcellular course, paracellular lipid course and transappendgeal course (Figure 2).

Transcellular Course:- Moeity passes through both keratinocytes and lipids (straight way to the dermis)[90]

Paracellular Course:-The foremost common entrance pathway of sedate atoms. In this pathway, medicate remains in lipid moeity and remain around keratin (simple for lipid solvent sedate instead of proteins)[91].

Transappendgeal Course:- It makes proceeds channel for sedate saturation but it ruined effectively due to nearness of hair follicles and sweat conduits.

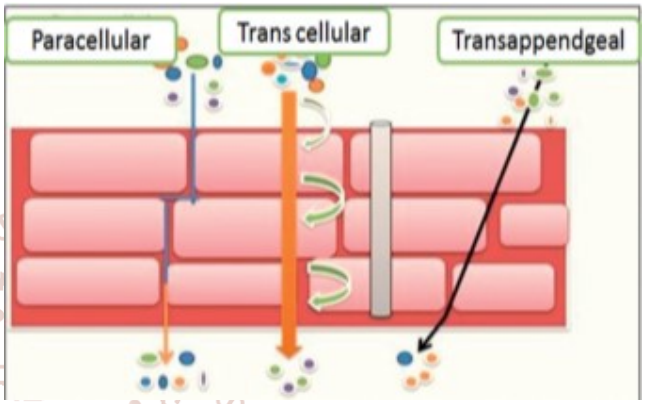

Figure :-2 Drug permeation pathway through skin.

7. STRATEGIES APPLIED FOR PERMEATION ENHANCEMENT

A very small number of drugs have the ability to effectively cross the skin barrier and reach target sites in therapeutic concentrations and Drawback of transdermal Conveyance is penetration of dynamic moeity through skin. So, various studies are done for enhancing its permeability percutaneously and therefore various strategies can be employed to help the drug cross the skin barrier effectively. They act by three mechanisms:

1. By altering physicochemical properties of stratum corneum.
2. By changing hydrating property of stratum corneum.
3. By altering structure of lipids and protein in intercellular channel via carrier mechanism

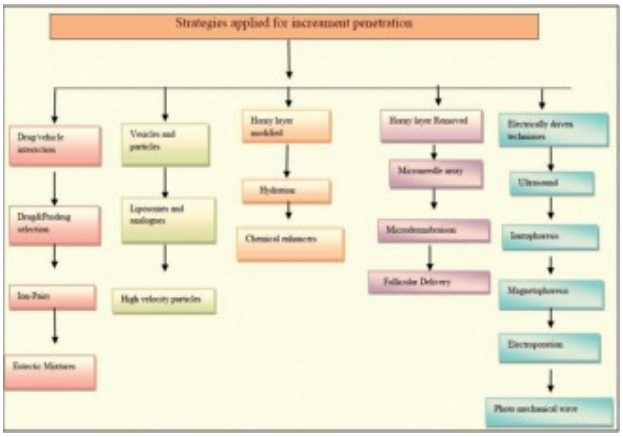

Figure:- 3. Advance strategies to overcome problems related to transdermal delivery.

Chemical class	Compounds
Water	Water
Hydrocarbons	Alkanes, alkenes, squalene, mineral oil, halogens
Alcohols	Glycerols, glycols, polyglycol, ethanol, caprylic alcohol
Acids	Oleic acid, Undecanoic acid and other fatty acids
Amines	Primary, secondary and tertiary, cyclic and acyclic amines
Amides	Pyrrolidone(N-methyl-2-pyrrolidone 2-pyrrolidon)azones (Azone (1-dodecylazacycloheptan-2-one))urea _
Esters	Isopropyl myristate
Surfactants (anionic cationic,monolaurate non-ionic, Zwitterionic)	Sodium lauryl sulfate, cetyltrimethyl ammonium bromide, sorbitan polysorbate 80,dodecyl dimethyl ammoniopropane sulfate
Terpenes, terpenoids and essential oils	Menthol, limonene
Sulfoxides	Dimethyl sulfoxide, dodecyl methyl sulfoxide
Lipids	Phospholipids

Table 2. Classification of percutaneous chemical enhancers on the bases of their structure.

7.2 Additional methods:-

A. Photomechanical wave

It is additionally named as laser-generated stretch weight wave, which is produced by cut of the focused on substance polystyrene. It has no particular component of activity, but it changes the lacnuar framework within the epidermis as appeared in(Figure 3). This procedure is able in conveying of macromolecules (40 000 Da)

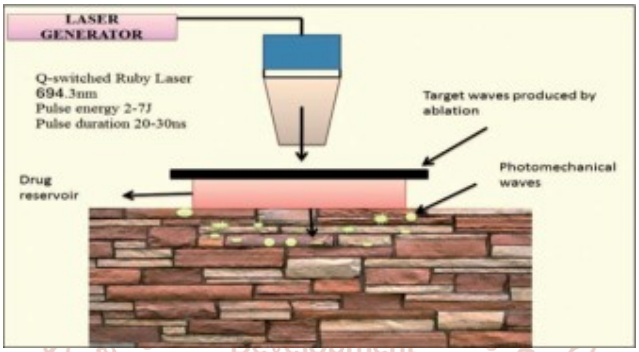

Figure:-3 Showing Photomechanical Wave

B. High-velocity particles

Powderject device

It consist of propulsion of solid drug into skin by gas (helium) as medium with a speed of 600–900 m/s (Figure 4). This technique is painless and non-invasive. This system ruptures the epidermal layer which is reversible in nature.

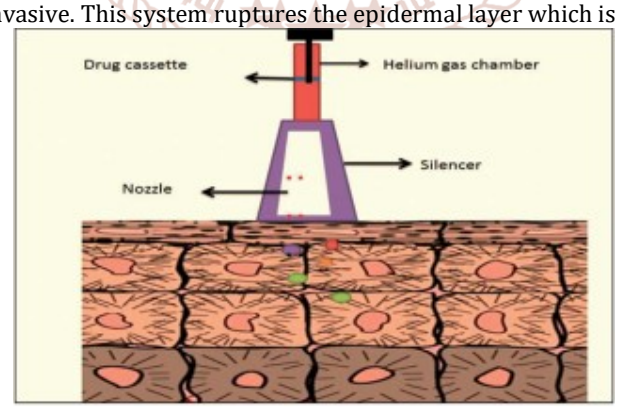

Figure:-4 Shows powderjet device

C. Needle-free injections

This method consist of non-invasive technique which is boon over conventional dosage form. Some of its injectors are as follows:

Intrajet: It uses nitrogen propelled gas. Patient breaks up the tip and presurized gas forces the liquid drug into generated small pores.

Implajet: It pushes a fine needle into the skin with opens channels and drug permeates immediatly.

Jet-syringe: This is capable of delivering 0.5 ml dose into the skin. It is best for short therapies

Iject: It is capable of delivering drug upto 0.1–1 ml drug and it is needle-free therapy.

Miniject: This velocity injector uses polycarbonate syringe which can deliver drug subcutaneously as well as intramusculary.

Cross-ject: This needle-free device uses gas source to propelled drug into subcutaneous tissue with the help of polycarbonate nozzle[92].

Technique	Trans ort	Sustained delivery	Pain	Cost
Chemical enhancer	Good	Moderate	Limited	Good
Iontophoresis	Limited	Good	Moderate	Good
Electroporation	Moderate	Good	Moderate	Limited
Ultrasound	Moderate	Good	Good	Limited
Microneedles	Moderate	Good	Good	Limited
High-velocity particles	Good	Limited	Limited	Limited

Table 3. Comparison between different transdermal drug delivery systems on the basis of various pharamceutical aspects.

8. MECHANISMS OF DRUG PENETRATION IN SKIN FROM LIPOSOMES

Liposomes with rigid bilayers tend to confine the drug locally in the skin. For deeper penetration, liposomes with flexible bilayers perform better. This flexibility is often induced by incorporation of surfactants often termed as 'edge activators' which reduce the elastic modulus of the phospholipid bilayer.

Liposomal drug delivery to the skin can be classified in five different mechanisms or pathways as shown in Figure 5[93].

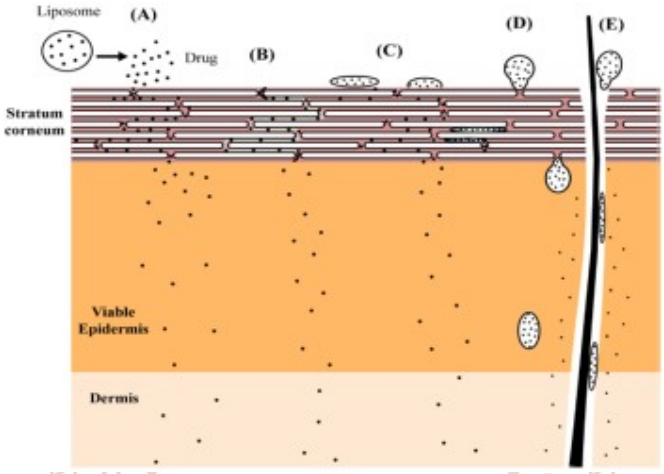

Figure 5: Schematic showing various mechanisms by which liposomes can facilitate drug delivery to skin.

According to this classification:- (1) liposomes can either act as drug carriers bringing different lipophilic and hydrophilic drugs in close proximity to the SC from where drug partitions into the SC independent of the liposomal components. (2)It recommends that components of the liposomes act as entrance enhancers which facilitate in the penetration of the drugs. (3) It suggests that liposomal bilayers can fuse or get adsorbed on the surface of the SC where they release their drug cargo. (4) The most controversial mechanism suggests that flexible liposomes such as Transfersomes can penetrate the SC intact and therefore taking the drug cargo along with them. (5) The transfollicular mechanism, where liposomes can enter the hair follicles which typically penetrate the dermis and release the drug in the hair follicles which can diffuse out in the dermis or viable epidermis from within the hair follicle. Which mechanism or combination of two or multiple mechanisms dominate in any given drug liposomal system combination would depend on the physicochemical properties of the drug and liposomal system.

9. CURRENT STATUS OF LIPOSOMES IN TRANSDERMAL DRUG DELIVERY SYSTEMS

This section will take a closer see at the liposomal formulations for drug delivery to skin. Liposomes were to begin with recommended by mezei and gulasekharam in 1980 as a medicate conveyance framework for depositing triamcinolone in skin[94]. Liposomes are phospholipid vesicles containing one or more bilayers containing an aqueous core. A point by point survey for diverse planning strategies characterization and properties of liposomes can be found somewhere else[95-97]. Liposomes in skin drug delivery applications have a rather controversial history. Ambiguity originates from the wide array of results that have been reported by various work groups. Liposomes have been even shown to accumulate in the hair follicles[98-100]. Liposomes have also shown the ability to improve transdermal delivery of small molecules as well as peptides and proteins[101,93]. Reasons for the disparity between different results of different studies likely originate from; differences in composition of liposomes, different physicochemical Properties of the liposomal vesicles added substances to the liposomes such as ethanol edge activators entrance enhancers more over adjust the bilayer characteristics and drug transfer from the liposomal bilayer, use of different animal models etc. Intuitive of liposome with the skin and sedate exchange from liposome to skin are impacted by the thermodynamic state of the liposomal bilayers and so influenced by the nature of phospholipids used in the preparation of the liposomes. Depending on the composition liposomal bilayers can exist in gel state characterized by inflexible and unwavering bilayers or fluid crystalline state where bilayers or *liquid crystalline state* where bilayers are flexible and accommodating. Liposomal details in gel state are more often than not related with medicate amassing within the upper layers of the skin and indeed diminished transdermal medicate infiltration[102-103,94]. For skin application, liposomal definitions can be isolated in two wide categories as customary liposomes and novel liposomes(deformable or ultra deformable or elastic liposomes)[104]. Ordinary liposomes are basically composed of pure or mixtures of phospholipid(s) and may or may not contain cholesterol.

In spite of the fact that a couple of considers have recommended plausibility of transdermal sedate conveyance utilizing customary liposomes a tremendous number of thinks about suggest conventional liposomes are more suitable for topical or local delivery of drug in the skin[105-106]. Second category represents an array of different liposomal systems which apart from phospholipids contain other additives which essentially imparts the liposome bilayer deformability or elasticity which has been correlated to increased drug permeability in skin[107-111].

Formulations Work group	Bilayer forming lipid and other additives
Transfersomes® Cevc *et al.*	Soya phosphatidylcholine (S100, Lipoid GmbH). See table 3 for composition. Edge activators, sodium cholate, polysorbate 80, sorbitan monooleate 80 etc.
Ethosomes Touitou *et al.*	Soya phosphatidylcholine (S100, Lipoid GmbH) 10-50% ethanol by weight which fluidizes the phospholipid bilayers
Invasomes Fahr et al	Soya phospholipid (NAT 8539, Lipoid GmbH) See table 4 for composition. Lyso phosphatidylcholine as an edge activator, 1% terpenes and 10% ethanol by weight as penetration enhancers
Niosomes	Non-ionic surfactants such as dicetylphosphate, hexadecyl diglycerol ether, polysorbates, sorbitan monooleates etc and cholesterol

Table 3: A brief description of the liposomal systems for skin drug delivery

10. FUTURE ASPECTS

Hyaluronic acid

More as of late gel center filled liposomes have been utilized effectively for transdermal medicate conveyance of little and macromolecules such as curcumin and hyaluronic acid[31-32]. These novel liposomes are composed of phospholipid vesicles entangling gel fabric in their center. Therefore, they can combine the advantages of liposomes and gel formulations in one drug delivery system[33].There were no measurably critical contrasts $p > 05$ among normal estimate breadths for ethosomes pg liposomes transferosomes and hyaluosomes. Further, the effect of PG and ethanol concentrations had no statistically significant ($P > 0.05$) effects on the average diameter. Comparable comes about were detailed somewhere else with cinchocaine PEG liposomes, ethosomes and transferosomes[112].

Liposomal Systems	Z average diameter (nm)	PDI	Zeta potential (mV)	EE% (w/w)	Release rate Q2h (% w/w)	Release rate constant (K; h-1)	Release exponent (n)	Correlation coefficient (r)
Conventional liposomes	700±10	0.5±0.1	-28±3	55±4	47±3.5	1.6±0.2	0.43	0.997
PG-liposomes (10% v/v)	160±6.0	0.2±0.03	-33±3	86±1.5	29±1.5	1.38±0.1	0.35	0.994
PG-liposomes (20% v/v)	175±4.0	0.22±0.04	-35±2	84±2	31±3.0	1.40±0.12	0.44	0.992
Ethosomes (20% v/v)	166±5.0	0.17±0.02	-34±3	82±2.4	28±2.0	1.20±0.8	0.45	0.995
Ethosomes (30% v/v)	177±6.0	0.23±0.04	-35±2	80±3.6	38±1.5	1.50±0.13	0.43	0.992
Transferosomes (5% v/v)	180±3.5	0.22±0.03	-34±3	81±3.2	26±1.5	1.34±0.13	0.42	0.990
Transferosomes (10%)	188±5.5	0.22±0.02	-35±2.5	79±3.5	29.5±3	1.42±0.12	0.45	0.992
Hyaluosomes	180±4.5	0.15±0.03	0.15±0.03	82±2	17±1.5	1.0±0.4	0.46	0.995

Table 4 Size, PDI, zeta potential, entrapment efficiency (EE %), release kinetics for the prepared liposomal systems. Results are expressed as mean ± standard deviation.

The zeta potential recorded for the prepared liposomal systems was negative and ranged from -28 to -40 mV (Table 1). Zeta potential is the magnitude of the electrostatic charge and it gives an idea about the stability of the colloidal system. The greater the zeta potential, the more stable the colloidal system and the lower tendency of the particles to aggregate and lower PDI. The zeta potential (-28 mV) recorded for the conventional liposomes was the lowest. This may incompletely clarify their generally tall PDI, compared with other non-conventional liposomes. It is worth specifying that hyaluosomes recorded the biggest zeta potential and this might be attributed to consolidation of the anionic hydrophilic polymer hyaluronic acid that exists overwhelmingly in ionized shapes at pH 7.4[113]. EE% evaluated for the arranged diverse liposomal frameworks extended from 55% to 84% while the routine liposomes appeared altogether $p < 05$ lower EE%; no statistically significant ($P > 0.05$) Contrasts were recorded among EE% for the distinctive non ordinary liposomal frameworks pg liposomes, ethosomes, transferosomes and hyaluosomes. Nearness of the film added substances eminently pg ethanol

tween 80 and hyaluronic acid appears to create more steady vesicles with less inclinations to total and become less leaky to the entrapped drug molecules, compared with the conventional liposomes.

11. CONCLUSIONS

Skin saturation upgrade innovation may be a quickly developing field which would expressively increment the

number of drugs which is appropriate for transdermal medicate conveyance. Approaches the investigation for the perfect skin entrance enhancer has been the accentuation of critical inquire about exertion over a number of times. We hypothesize that the developed new liposomal carrier system possessing a gelatinized core can contribute in the successful delivery of hydrophilic drugs. The characterization of the prepared liposomes and the results of the hydrophilic molecule-release experiments showed favorable rheological properties, high entrapment efficiencies and sustained drug release and better stability. Ultra-flexible Liposomes improve the infiltration independent of the drug's measure compared to liquid liposomes. This data proposes that liposomes can either improve or decrease skin entrance depending on the atomic weight of the sedate and the liposome composition. All deformable liposomes displayed tall hEGF substance with a somewhat higher stack for anionic deformable liposomes. hEGF containing anionic deformable liposomes shown the foremost maintained hEGF in vitro discharge and guaranteed a station on the ex vivo human skin as compared to impartial and cationic deformable liposomes. . The novel gel center phospholipid vesicles hyaluosomes as a promising transdermal definition framework since they illustrated ideal rheological characteristics such as thermal gelation and shear-thinning behaviours for better retention at the site of application on the skin and spreading ability respectively.

12. REFERENCES

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