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Review Article

COLLOID MEDIATED DRUG TRANSPORT ACROSS DERMAL ROUTE: A CRITICAL REVIEW

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ABSTRACT
Pressure techniques or Focussed forces like sonic pulses, voltage pulses, ballistic treatment or optoporation by Laser beam and use of penetration enhancers are more often invasive to overcome the multiple barrier function of skin. Now, the colloidal systems are getting preference to be used transdermally. The colloidal systems include some basic structures like micelles, liposomes, nanoparticles, dendrimers, micro- and nanoemulsions etc. Again, for transdermal flux of any colloidal aggregate, the system must possess sufficient adaptability property depending upon the pore width, so to make a path way for its entry. The adaptability or deformability of the colloidal aggregate is a function of its composition. Micelles with long shape structures are flexible and depend upon binary phase composition. Vesicular or globular forms get the deformable nature by using lipid and membrane softener (bio surfactants) mixture. The diffusion or molecular barrier penetration of colloids need a driving force, which is provided by the trans-barrier hydration free energy gradient created internally or externally of and by the system. Some ultra deformable colloidal carriers like Transferosomes, Ethosomes, Aquasomes and Niosomes are potential systems for transport across the skin. However, this broad research area of colloids still needs much orientation and attention by researchers, rather than going for older invasive techniques.
Keywords: transmembrane barrier, binary phase, nano aggregates, water activity, transferosomes.

INTRODUCTION

Colloid by definition is a substance microscopically dispersed throughout another substance. The dispersed phase particles have a diameter range of 1-1000 nm. Colloidal drug delivery systems (CDDS) consist of therapeutic compounds present in the colloidal state. Many types of CDDS are available viz. micelles[1], liposomes[2], nanoparticles[3,4], dendrimers[5], liquid crystals etc[6,7]. These colloidal systems are popular for site specificity thus lending them to be used as targeted drug delivery devices[8,9]. The colloidal structures can be designed by suitably selecting the colloid components for effective drug delivery. Currently, the colloidal drug delivery systems are being highly preferred for administration through transdermal route, as this route provides a direct approach to the systemic environment for delivering the drug moieties. The transdermal drug delivery is a discrete mode of drug administration, by using the intact skin for delivering the drug through the skin in a controlled manner to the systemic circulation. A steady infusion of drug for a prolonged period by this route can be achieved, greatly dominating the intermittent dosing regimen. This provides an avoidance of variable rates of absorption and metabolism inherent with several oral drug delivery systems. Drugs of short biological half lives can be administered in a continuous and non-invasive mode. This route is indeed a preferable route, but the major and so to say the only obstacle for the drug to diffuse through the skin is its barrier function, which has the single agenda of keeping things out of the body. Achievement of a high and constant drug flux across the skin is a challenging assignment. Invasive methods are commonly used to overcome the barrier properties of skin. But use of colloids has created a new path in development of non-invasive techniques by using their excellent self-regulating properties, which are thoroughly discussed elsewhere in the text. The barrier function must be clearly understood before going for transdermal route. Hence, effort to critically represent the various aspects, starting from the barrier function of skin to the more sophisticated vesicular and other colloidal deformation behaviour has been made and given precisely.

Multiple Barrier Functions of Skin

The skin (or cutis in Latin) is the largest organ of the body [Figure 1], contributing around 4 % to a body weight. This largest organ is an excellent barrier too, though it is normally less than 2 mm thin. Regarding the permeability it is 10^2-10^4 times less permeable than a normal blood capillary wall. The skin imparts its barrier properties multi-directionally. It is an anatomical and biological barrier, preventing the diffusion of molecules and acts as semi-permeable nanoporous barrier. The different aspects of barrier functions are given below.

Anatomical and biological barrier function

The skin is one of the best biological barriers due to the outer most part of the epidermis, which is the outer skin region of 50-100 µm thickness. This outer most part is the horny layer called stratum corneum. This layer is very thin and measures 5-8 µm in thickness. It is quasi-passive anatomical barrier associated with intracutaneous molecular degradation, drainage through the blood and lymph capillaries in dermis and peripheral immune system. This layer is made by corneocytes, which are of 0.3-0.8 µm thickness in mammals. The total number of corneocyte layers in stratum corneum is around 15 and average number of corneocytes per unit area of stratum corneum is approximately 2×10^6 cm^{-2}. Hence, it is observed that the special anatomical organization provides mammalian skin a complex barrier property[10,11]. The individual corneocytes are merged together with desmosomes and sealed tightly with special intercellular lipids that are attached to plasma membranes. The quality, quantity and crystallinity of lipid provide the perfect barrier property to the

skin[12,13]. This refractiveness and fine structure of skin both vary between body sites, gender and species. It is higher in human and pigs than rodents.

Diffusion barrier function

The anatomical features suggested that the lateral overlapping of the quasi-columnar stacks of corneocytes are sealed tightly by densely packed lipid multi-layers, which are chemically attached to corneocyte envelope membranes. The in between space is hence filled up with the non-crystalline lipid domain. These are the major targets of the chemical skin permeation enhancers, which solubilise and partially extract the organized lipid in the skin there by increasing the numerosity of hydrophobic binding sites and regional lipid fluidity. As a consequence molecular partitioning and diffusion along the tortuous epidermal lipid layers become easier and permeation size limitation is overcome. The main factors for molecular permeation or diffusion across the horny layer of skin are molecular hydrophobicity, size and ability to interact with the other molecules, e.g. via H- bonding[14-16]. According to Cronin *et al*.[17] correlation between permeation coefficient, octanol-water partition coefficient and molecular weight of permeant suggested that the effective width of skin permeation pathway cannot be spoken strictly correct, due to the strong relative hydrophobicity effect, but the limit molecular weight is 328 and $K_{O/W}$ is 1, roughly corresponds to a pore size of approximately 0.5 nm. It can be drawn from the above description that no much larger colloids and colloidal components can enter the skin in a practically meaningful quantity, except through transport shunts.

Nanoporous barrier function

The focussed force or pressure techniques including iontophoresis, diffuse mechanical stress like Ultrasound, hypodermic needle, electroporation and local thermal and ballistic treatment are very often used to break the barrier properties of the skin over spots with a diameter, which is typically in the range of 50-100 μm [Table 1]. Apart from that the natural hydrophilic pores in the stratum corneum, like the hair follicles and glands in the skin are arguable shunts for colloid entry into skin. The size distribution and numerosity of artificially created nanoporous pathways through the skin is sparse [Table 2]. On the basis of reports of Anguilella[18], Pikal[19] and Ruddy and Hadzija,[20] the estimated hydrophilic pores width in intact mammalian skin treated with colloidal penetrants to be 20-30 nm on an average. However, the trans epidermal pathway may be a series of short, discontinuous channels possessing various diameters and the critical factors for hydrophilic entity penetration is molecular size rather than molecular weight. Moreover, the hydrophilic pore density in the stratum corneum is taken to be between 10^8 -10^9 cm^{-1}. This pore density corresponds to an effective porosity of approximately 0.5 % of total skin area assuming 25 nm path width. The funnel like geometry of inter-cellular junctions close to the skin surface weakens the impact of small porosity value.

The nature and location of hydrophilic pathways

The pathways with the lowest transport resistance lead between clusters of corneocytes in the stratum corneum. The cluster boundary parts do not have lateral overlapping and are surrounded by relatively weak packed and organized lipids. Such inter cluster space is therefore comparatively well accessible to the different colloid penetrants. Intercorneocyte pathways have a relatively high resistance to transport as it leads between the intercellular lipid lamellae and these are predominantly found near all edges. Corneocyte packing and the average number of open pathways through the horny layer of the skin are affected by organ hydration[21,22]. Water is hence an efficient skin permeation and possibly penetration enhancer. Additionally, binding of water to polar substances in the skin like proteins and natural humidifiers contributes to the permeation enhancement too.

Colloidal Binary Phases for Transdermal Application

Before we think of any carrier system for transdermal drug delivery, the goal or primary objective is to implement minimal invasiveness or non-invasiveness techniques, to improve the drug pharmacokinetic and to achieve a more target specificity. Solids or nearly incompressible particles consisting of stiff molecules cross linked or crystalline materials, all have a simple arrangement in a fluid forming a colloidal system [Figure 2]. Such colloids including dendrimers, latex or metallic particles either float or sediment, form a suspension or else organise in a colloidal crystal, if having sufficient monodispersity. Soft and complex colloids comprising of flexible molecules exhibit several polymorphic forms, which are generally allowed by molecular rearrangement and conformation adaptation. Oils and amphipats in polar solvents including water spontaneously form a long range colloid order like micelles, cubic phases, micro emulsions, hexagonal phases, vesicles etc[1]. Some of these groups have a potential to improve transdermal drug delivery, or even serve as drug carriers. Changing water concentration in a blend with one or more fatty molecules (oils, amphipats) yields different mesophases, among which only some are of nano- or submicron range. It should be therefore observed the structural changes followed by application on skin surface due to drying[23]. The ambient skin temperature must be kept in consideration as it varies between 25-30^oC in cold as well as warm climate. The structural changes in each phase region can be influenced by available water volume, presence of salt, temperature etc. Most lipid layers become thinner with increase in hydration due to imbibitions of more water into lipid lamellae, up to a certain characteristic limiting hydration value. The hydration value again depends upon the lipid polarity, hydrogen bonding ability, charge etc. Hydrophilic i.e. charged and flexible lipid bilayers swell more. Packed, uncharged, relatively unpolar and crystalline lipid multi-lamellae in the stratum corneum are therefore not suitable for ambient hydration. The lipid multi-lamellar phase can swell and break into individual lipid vesicles by means of mechanical or chemical energy, which may be produced by high pressure homogenization, agitation, pH jump or osmotic shock. Higher the lipid bi layer elasticity, lesser the energy demands for vesiculation. Addition of an unpolar fluid component (oil / a fluid drug) to a water-amphipat mixture can generate a microemulsion. Here, an oily and an aqueous sub-phase are separated by the extended lipid mono layers. Oil droplets of nano size range are produced from the micro emulsion after mechanical disruption or by thermal agitation in some rare cases[24,25]. Variation of concentration of the major system components relatively or absolutely, causes an isothermal phase transition and may also cause colloidal collapse of the system, which subsequently may hamper the drug diffusion from a colloidal system. This disturbance is caused by the coalesced material. It may be also possible that the effective permeant accumulation in one of the phase following phase segregation can subsequently increase the drug transport.

This enhancement of transport following colloidal collapse may be proved to be a danger or an opportunity, which is strong in case of an open application of complex colloid formulations on the skin. Though, solid particle suspensions have simple colloidal nature, the opportunity case is seldom found. Therefore, transdermal carriers must be small and discrete and must not cross any formulation phase boundary on skin in an uncontrolled pattern[26].

Penetration/Permeation of Basic Nanosized Colloidal Aggregates across Skin

Permeation/ penetration behaviour of some basic colloidal nano-aggregates are summarized below [Figure 3].

Liposomes

These are the most popular drug carrier aggregates well known for transdermal use. These are vesicular in nature comprising one or several lipid bilayers enclosing an aqueous core. The lipid bi layers are kept stiff in pharmaceutical liposomes to prevent drug leakage. The bilayer elastic energy keeps the shape of liposomes nearly spherical. To provide good encapsulation volume, liposomes have an average diameter above 75 nm. Conventional fluid bi layer liposomes hence cannot penetrate pores less than 30 nm and can be forced through wide pores by applying high pressure sufficient for vesicle fragmentation. The bi-layer stiffness in some cases in vesicles made up of the ordered chains lipid creates problem in trespassing through pores of size greater than 50 nm, even at a high pressure. Such vesicles are heated above their chains melting phase transition temperature before extrusion[27,28].

Micelles

Micelle formation is a spontaneous process and starts near and above the amphipaths solubility limit. Polar surfactants in water or non polar surfactants in oil produce variety of shapes, but all the shapes must be at least in one direction in the nano size range. The different shapes involve cylindrical, disc like, spheroidal, spherical etc. Micelles possess a size always smaller than liposomes. If micelles have fatty core separated from aqueous phase by the polar heads, the micelles are said to be normal and where aqueous core separated by the polar heads from a fatty solvent, it is called inverse micelle. Constant size micelles are incompressible, but long shape structures are having flexibility. Lower aggregation number micelles can be formed by either compressing or by more diluted surfaces, but such micellar suspension upon application on skin cause the aggregates to grow and micelles transform into vesicular structures[1].

Nanoparticles

Pharmaceutical nanoparticles range from the size and shape of a micelle to 1 μm. These are longer lived than micelles in suspension phase, due to polymeric conjugation or poor solubility of the components that form the core of nanoparticles. Metallic nanoparticles are naturally long lived and are having sound monodispersity and mechanical strength. So these particles cannot cross pores of comparable or smaller pore diameter than their own[29,30].

Micro emulsion

These are optically clear and contain droplets of size less than 300 nm. These droplets are structurally similar to micelles, except that they contain extra oily component. With an increase in oil content (decrease in water content), the original globular structure transforms into bicontinuous emulsion system generating a turbidity subsequently[31,32]. Hence, the composition and temperature play an important role in maintaining the characteristic structural length. Micro emulsion systems are now incorporated in conventional dermal preparations and are preferred in transdermal drug delivery. The popularity of micro emulsion for dermal application is second only to liposomes[33-35].

Nanoemulsions

The formerly called submicron emulsions have a droplet size range of 20-500 nm and the larger droplets are stabilized by surfactants. These differ from microemulsions in that, these are non-equilibrium structures and energetic input methods are utilized which makes nanoemulsion a metastable system[36]. Nanoemulsion survives for a longer period before being changed to coalesced form. Concentrated nanoemulsions on shearing deteriorate. Therefore, concentrated nanoemulsions when are squeezed through nanoporous structures of skin may create problem[37,38]. However, nanoemulsions are currently of great interest in transdermal drug delivery.

Dendrimers

These are nanosized, monodisperse, macromolecular structures proven to be effective for transdermal drug delivery. Lower generation cationic dendrimers were established to have better skin permeability than higher generation dendrimers. These can be designed to improve drug solubility in their core part or also the surface of dendrimers can be decorated with drug molecules as a surface attachment[39]. These are having viscosity imparting property which is helpful for easy handling. The dendrimers behave as unimolecular micelles. TDDS of different groups of drugs have been studied successfully by using PAMAM dendrimers[40]. However, molecular transport through intact skin is a function of molecular size, hence, these macromolecules sometimes face problem as a drug carrier to penetrate through skin.

Concept of Colloid Migration through Skin Barrier

Colloidal migration involves permeation and molecular penetration by a colloid. Permeability corresponds to the diffusion of a permeant through a barrier, whether penetrability corresponds to the molecular barrier penetration by a colloid.

Colloidal permeation/penetration

The driving force which drives the molecule across a semi-permeable and porous membrane/ barrier is strictly depends upon the permeant properties as well as concentration. For simple solutions the permeant activity is complementary to solvent/ water activity. The trans-barrier gradient in hydration free energy drives the permeant diffusion through barrier. The hydration free energy can be calculated from hydration potential, which is again a function of water activity. The hydration free energy is directly proportional to the number of water molecules associated with a permeant, average free energy of such solvent molecule and trans-barrier water activity difference[41]. This concept also resembles the electrostatic energy difference, which is proportional to the number of charges, unit charge and electrical potential difference. The trans-barrier flux value is proportional to the trans-barrier permeant concentration or activity difference. The flux decreases exponentially with time, from the

maximum initial value, with a time constant which is inversely proportional to the barrier permeability[26]. Hence, the transport process ceases when a steady state is achieved, where trans-barrier concentration and activity gradient are zero. Maintenance of the initial high trans-barrier flux can be achieved by applying an additional pressure on the donor or reservoir site. To ensure the gradient to be constant, the applied pressure must gradually increase with time. Practically this can be achieved by creating an external activity difference, which must rightly contribute to make up the disappearing trans-barrier drug and water activity difference. The concept is somewhat related to the transport enhancement achieved by drug super-saturated solution. The gradient matching option discussed in previous paragraph is proved to be of no use, when trans-barrier permeant concentration difference is nearer to zero always[27]. This particular case is encountered in permeant aggregation or encapsulation[42-45]. Higher number of drug molecule in an aggregate or capsule brings the trans-barrier diffusion to a standstill value. Externally created water activity difference is required to induce the transport. Hence, the rate of barrier penetration by permeant aggregates or capsule is proportional to external water activity difference, as no other flux driving gradients are there. The sensitivity of flux towards the water activity gradient in this case is such that, it is proportional to the drug cluster or carrier hydrophilicity, which linearly increases with the number of molecules in each aggregate. The process may go complicated when permeant aggregation is due to change in water activity or driving pressure, as seen in case of lipid vesicles that aggregate and fuse upon the application of external stress. To prevent such coalescence by resisting the external stress the colloids must have strong repellent property, which can be achieved by high surface hydrophilicity or charge. Inter-colloid repulsion must not hamper the colloid deformation during passage through a barrier from high stress zone to low stress zone. Any large aggregate must be highly adaptable to cross a barrier with pores smaller than the aggregate size. Such aggregates are insensitive towards the mismatch between vesicles and pore size[46-49].

Colloidal deformation and driving forces for transport

Incorporation of components that contribute towards the softness and surface fluidity of the colloid can be added, which enable the colloid to flow across the barrier. Hence, higher the particle adaptability, more will be the maximum trans-barrier suspension flow. A proper blend of components with different solubility and amphiphilicity complementing each other is must required to ensure a best aggregate adaptability. Upon the application of a non-uniform local stress the arrangement of the different component in the deformed system is such that the more soluble components accumulate at the site of greatest local deformation and less soluble ingredients remain in abundance in the less deformed parts[50] [Figure 4]. Here the role of membrane softener is pretty good to achieve optimum required deformability keeping the aggregate stability as such. Excessive use of softening agents (like surfactants, co-surfactants) leads to aggregate disintegration to mixed amphipat micelles. High surfactant or co-surfactant concentration on skin may damage the barrier too. Again, decrease in relative concentration of more soluble amphiphile decreases the deformability. Partially solubilised colloids and colloid stiffness over the skin greatly decreases the particle ability to cross nanoporous barriers on the skin, in contrast to stable and softer lipid aggregates[51,52]. The reported driving forces for barrier penetration are the hydration gradient or hydration potential difference across stratum corneum and by generating transepidermal electrical potential. For the former case, the colloid must be superficially hydrophilic in nature and the skin should be non-occluded. Penetration by electrical driving gradients needs the colloids to be charged, deformable and stable enough. The minimum required electrical potential difference depends on relative colloid size and more strongly on colloid deformability, which is again dependent on aggregate composition as discussed earlier. The transport of hydrophilic colloids through non-occluded stratum corneum is a kind of reverse osmosis, powered by the water activity gradient as well as penetrant deformability. Water evaporation from the non-occluded skin is a continuous process which pertains to the water activity gradient. But, the transdermal colloid flux is more influenced by the aggregate adapatability than the water activity gradient in case of skin and artificial nano-porous barriers. Transferosomes are the best examples for this phenomenon, which are more stable deformable vesicle and have sound transdermal flux[27,53].

Interactions between the Skin and Colloidal Systems

Epicutaneously applied aggregate colloids generally reduce the height of skin barrier by deteriorating inter-corneocyte lipid thickness by their aggregate components or by organ occlusion. This phenomenon significantly influences the drug partitioning or diffusivity or both in the stratum corneum. If the colloid dependent change of solvent activity exists on the skin surface, this can cause negative influence on drug diffusion, when superficial drug solubility consequently decreases due to the same[54]. When the colloid based drug formulation is applied on non-occlusive skin surface, the transdermal flux simply varies with a change in formulation composition. This phenomenon is commonly encountered in hydro-alcoholic drug carriers, where it is very difficult to maintain a constant formulation composition for a prolonged period on a non-occlusive skin surface[53]. In case of simple and highly adaptable vesicles, it has been reported that, the rate of highly adaptable colloid transport through the stratum corneum exceeds the rate of diffusion of the individual colloid components through the barrier. The flow of highly deformable aggregates across the stratum corneum is around 3 orders below in magnitude than the corresponding particle flux through an artificial semi-permeable barrier with 10^8 fixed size pores[55,56]. Hence, the path way for colloidal transport is created by the aggregates themselves and they penetrate as a whole entity when subjected to an external driving gradient. Moreover, the colloid mediated drug transport does not result from direct interactions of barrier components and colloid components, because such cases are never encountered, where, individual components or their clusters move across the barrier better than the whole mixed colloid. It is also improbable that the individualized, parallel, uncoupled action of more than one colloid component synergistically crack the skin barrier. If this were the case, the diffusion of each component must follow in a super additive manner according to individual component concentration gradient and partitioning behaviour[27].

Current Position and Future of Colloid Mediated Transdermal Drug Delivery

Three decades ago L' Oreal has filed the first patents on the preparation and usage of vesicles those were made from non-

ionic surfactants for application on skin. In 1980s, a number of patents covering specific use of vesicles were filed. Since then, the patenting in this field is running constantly covering various colloid drug combinations, preparation methodology or a specific application related with transdermal drug delivery. A major breakthrough in patenting was brought by IDEA AG and since 1991; it holds several patents covering all preparations based on mixed amphipat aggregates and formulations containing alcohols. Currently companies involved in developing transdermal nanocarriers are given in Table 3. Intact skin, as a largest drug delivery site in body has tremendously attracted researchers for drug delivery and also for cosmetics. The standard established pharmaceutical formulations including hydrogels, ointments, creams as well as the novel nanocarriers like liposomes, niosomes, micro emulsions are still not efficient enough to be used across the skin barrier for a systemic delivery. Ultra deformable hydrophilic colloids like transferosomes have succeeded in overcoming certain problems without compromising the barrier properties. The best transdermally given formulations to date are achieved with lipid and membrane softeners mixtures. The softeners may be a charged bio surfactant, a quasi-biological or synthetic surfactant or else an alcohol or a mixture. Some formulations include ethosomes, some niosomes, novosomes etc[56]. Ultra deformable, self-regulating vesicles are challenging carriers for transcutaneous delivery of highly potent drugs for a sustained action or also can be used for systemic delivery which usually needs a 100-1000 times higher dose than transcutaneous case. Ultra deformable carriers with high adaptability, self-regulating complex in form of mixed lipid vesicles do not obey simple concentration dependency relationship. Therefore, such drug carriers cannot be evaluated by conventional bio analytical methods like diffusion cell test and skin stripping, rather novel methods as well as open minded testing should be performed. Most of the research groups still rely on oldest or invasive transdermal drugs delivery and a few groups are involved in developing colloidal systems as tabulate above. A lot of opportunities are still waiting to be discovered in this area of transdermal drug delivery. However, this novel highly adaptable ultra deformable colloid mediated transdermal drug delivery systems are hoped to be in market in recent future.

Table 1: Commonly used techniques for enhancing Transdermal drug transport

Possible options	Methods
Regional Stratum corneum elimination	Abrasion (with sand paper), Ablation (RF or Ultrasonic field treatment)
Regional Stratum corneum perforation	Cutaneous micro needles, Sonoporation by sonic pulses, Electroporation by high voltage pulse, High velocity impact of particles/ballistic droplets, Optoporation by Laser beam
Stratum corneum perforation and Cutaneous depot formation	Hard Ballistic carriers, Soft Microinjected colloid carriers
Skin penetration without/ with depot formation	Penetration enhancer, Highly adjustable, soft carriers

RF = Radio Frequency

Table 2: Natural hydrophilic Transdermal penetration shunts

Pathway type	Average path width (nm)
Sweat duct	$> 5 \times 10^4$
Sebaceous duct	$5\text{-}15 \times 10^4$
Hair follicle	$5\text{-}70 \times 10^4$
Clusters junction	$3\text{-}8 \times 10^4$
Inter-corneocytes	0.5-7 (normal), 20-30 (widened)

Table 3: List of some leading pharmaceutical companies involved in development of colloid mediated TDDS

Name of company	Research field
Alza corporation	Lipid based systems
Helix Pharma	Biphasic vesicles
Idea AG	Ultra deformable carriers
Skye Pharma	Nanoparticles
Yamanouchi	Mixed lipid colloids

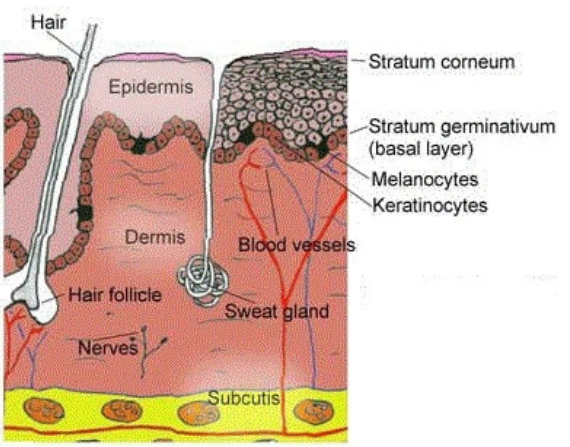

Figure 1: Different layers of skin along with the skin appendages

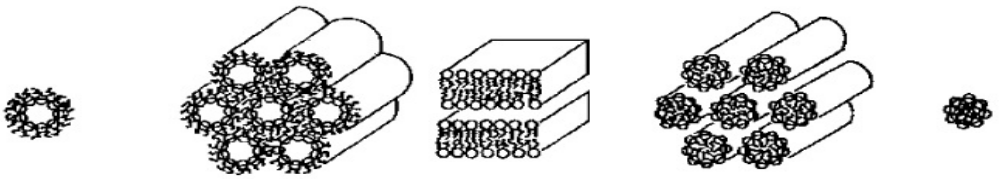

Figure 2: Sequential molecular arrangement in a Lipid-Water binary phase (% water content increases from left to right). From left to right: Inverse micelle, inverse hexagonal phase, Lamellar phase (can swell and break into individual lipid vesicles), normal hexagonal phase, normal micellar phase

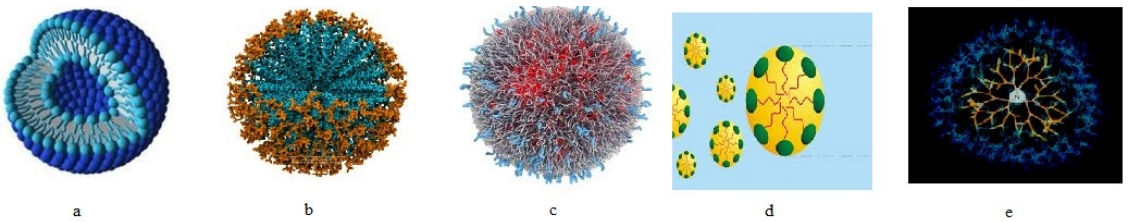

Figure 3: Pictorial representation of some colloidal systems showing Liposomes (a), Micelles (b), Nanoparticles (c), Globules of Nanoemulsion system (d) and Dendrimer (e)

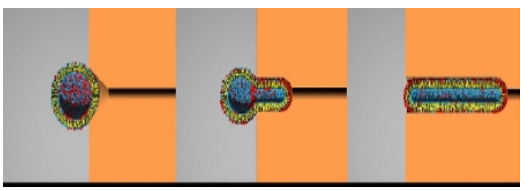

Figure 4: Distribution pattern of more soluble (Red part), Less soluble (Blue part) and Hydrophobic part (Yellow part) during barrier penetration, upon the administration of an external stress[26]

CONCLUSION

This paper highlights the sparse distribution of drug transport pathways in dermal route and the potential of some major colloidal systems to penetrate through this route. The skin barrier is generally breached by the use of substantially high forces, as in case of micro needles, ballistic treatments and local abrasion. The use of energetic and ultra deformable colloidal systems is the only left option for transdermal application, apart from the invasive methods. Transferosomes are the newer colloidal systems with better deformability are having appreciable spontaneous barrier penetration. Colloidal nano-devices with particle size below 150 nm with no local dehydration on skin surface are requisite for a system to achieve an enhanced transdermal penetration.

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