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Formulation Based Technology Advancements in Transdermal Drug Delivery System

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Authors' contributions

This work was carried out in collaboration among all authors. The author SM designed the project, conducted literature searches and wrote first draft. The author MAT managed the material of manuscript and finalized it with technical assistance of author MSAA. So the work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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Review Article

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ABSTRACT

Transdermal drug delivery is the safest and convenient delivery system for numerous drugs. Different types of transdermal patches are used for specific targeted drug delivery. Conventional transdermal patches have disadvantage that drugs with larger molecular size have difficulty in absorption. Stratum corneum is the primary barrier layer for many drugs permeation. Several methods are employed for the penetration enhancement and successful penetration of many drugs has been observed. The objective of this article is to explore the potential of different formulation based technology advances in this respect. The drug delivery systems are divided into vesicular and non vesicular drug systems like liposomes, hydrogels, dendrimers etc. and then further their individual role in transdermal drug delivery is discussed. These systems act as carrier for both low as well as high molecular weight drugs, thus resulting in improved stability, solubility and effective delivery of drug molecules. This review articles covers the individual role of these delivery systems along with some examples of drugs.

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1. INTRODUCTION

Transdermal drug delivery system (patches) is a non-invasive route of delivering therapeutically active drug at a predefined rate [1]. The major purpose of this delivery system is to control the drug in the body with least variation among the individuals (Fig. 1). The rate and extent of drug absorption is dependent on different parameters like nature of drug, the amount of drug in the patch and the skin region where the patch is applied [2].

In all the controlled release techniques, the transdermal is the most interesting, efficient and convenient technique during last twenty years [3]. When compared to other drug delivery systems, transdermal drug delivery system decreases the frequency of dosing, avoids the first pass effect and the chances of adverse effects are also reduced. It has also an ease of removing the patch when the drug therapy is no longer required [4].

The transdermal patch is composed of different parts named as drug substance, drug reservoir components, penetration enhancers, polymer matrix, adhesives and backing membrane [5]. The skin of human beings is composed of different layers. So, it is a selective barrier for many drugs. Many approaches have been employed to enhance the skin permeation. Enhancers change the skin structure and solubility of the penetrate thus increase the drug penetration through skin [6].

The important classes of enhancers are:

1. Physical enhancers (ultrasound, electroporation, magnetophoresis, microneedle, iontophoresis).
2. Vesicles particulate systems (liposome, transfer some, micro emulsion, niosome, nanoparticle).
3. Chemical enhancers (sulphoxides, azones, alkanols, terpenes, glycols) [7,8].

There are a lot of novel delivery technologies used in transdermal drug delivery system including liposomes, niosomes, hydrogels, dendrimers etc. Few are discussed here with their applications in the field of transdermal drug delivery.

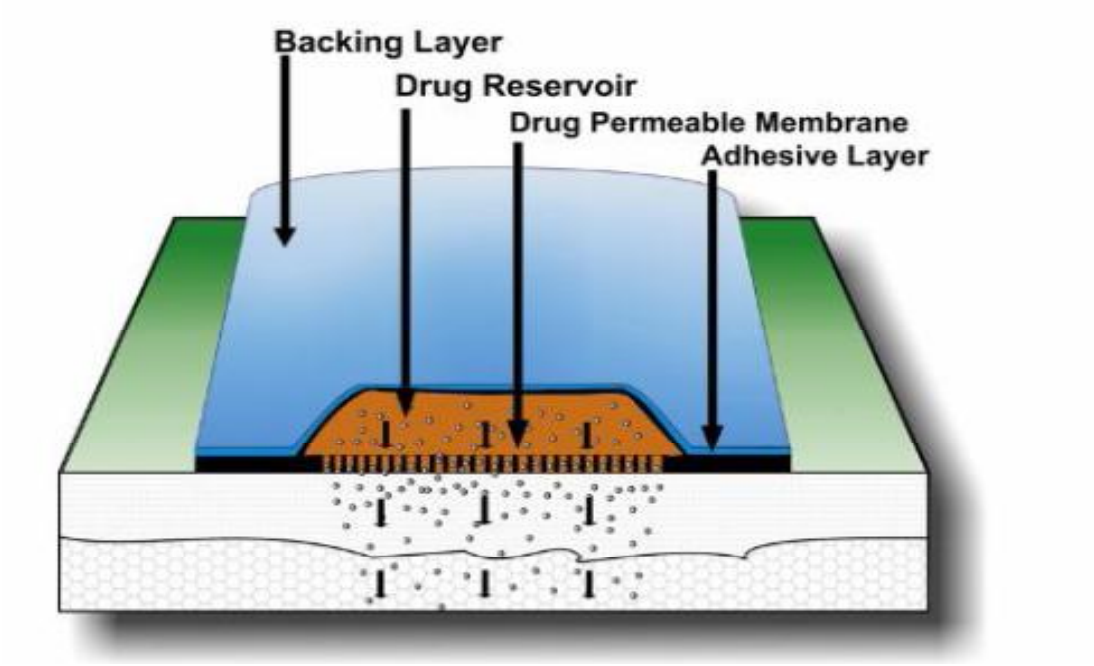

Fig. 1. Transdermal route of drug delivery

2. ADVANCEMENT IN TRANSDERMAL FORMULATIONS

A selected group of delivery systems is shown in the Fig. 2.

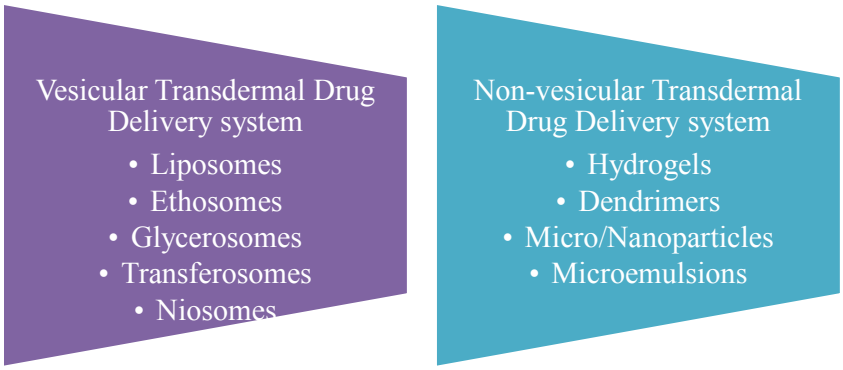

Fig. 2. Classification of delivery system

3. VESICULAR SYSTEM

Vesicular systems are colloidal particles having aqueous core and bilayer amphiphilic molecular shell [9]. Vesicular system in transdermal drug delivery system acts as a drug vehicle to transport drug molecules across the skin. It is able to deliver hydrophilic, hydrophobic as well as amphiphilic drugs through the skin into the systemic circulation [10].

Vesicular drug delivery is advantageous in transdermal delivery due to their composition, as they act drug carriers as well as penetration enhancers. They act as rate limiting membrane barrier and hence the sustained release of drug molecule is also achieved [11]. It has become evident that physicochemical properties like size, charge, lamellarity, elasticity, thermodynamic phase changes and etc., is affected by the composition of vesicular system. So, numerous materials have been utilized to develop modified vesicular drug delivery system. Many of these systems have proven to enhance the penetration of drug through the skin hence, increase the bioavailability [12].

Some vesicular system can be employed for localized treatment of diseases where the systemic release of drug should be avoided [13]. Over the last decade various new classes of vesicular systems has been introduced. These are categorized into two major classes (Table 1).

3.1 Liposomes

Liposomes are lipid bilayer vesicular systems ranging from micrometer to nanometer in size. They can entrap hydrophilic drugs inside central aqueous core and lipophilic drugs between bilayer [14]. Liposomes are highly compatible in nature. Phospholipids and cholesterol are major components of liposomes [15]. The lipids of liposomes might interact with the lipids of stratum corneum which promotes the penetration of drug through stratum corneum [16].

In respect to the interaction of liposomes with human skin, it is concluded that liposomes diddolve in the skin and make a unit membrane structure with the skin [17]. There are several types of liposomes depending upon its

Table 1. Classification of vesicular system

Lipid based vesicular system	Liposomes Ethosomes Transferosomes Glycerosomes
Non- lipid based vesicular system	Ufasomes Sphingosomes Niosomes

composition and application like temperature or heat sensitive liposomes, pH sensitive liposomes, magnetic liposomes and etc. Materials used in manufacturing and method of manufacture affect the physicochemical properties of liposomes [18].

Transdermal penetration of liposomes affects by physical state of stratum corneum, presence by penetration enhancers as well as liposomal characteristics like its charge, lamellarity, composition and concentration of lipids [19].

Liposomes are successfully applied in antifungal and anticancer treatment as well as in skin melanoma [20]. Liposomes of melatonin [21], indinavir [22], methotrexate [23], amphoteracin B [24], ketoprofen [25], estradiol [26], and benzocaine [27] were formulated with improved clinical effectiveness. Major drawback of liposomes is its physical instability. They undergo chemical degradation such as oxidation and hydrolysis of ester linkage [15].

3.2 Ethosomes

Ethosomes are lipid based vesicular system. It is composed of hydro alcoholic or simply alcoholic or glycolic or hydro phospholipids having high concentrations of alcohol. Commonly used phospholipids in Ethosomes are propylene glycol, iso-propylene alcohol, phosphatidic acid, phosphatidylcholine, hydrogenated phosphatidylcholine, phosphatidylinositol, phosphatidylethanolamine [28]. It is approved safe and effective in pharmaceutical and cosmetic transdermal drug delivery system [29].

Ethosomes enhances the permeation of drug through the skin by increasing the fluidity of cell membrane lipids by high content of alcohol present in Ethosomes [30]. Ethosomes are capable to carry the drug into deeper layers of skin and systemic circulation [31].

Ethosomes having zidovudine is capable to maintain the prolonged release of drug by increasing the transdermal flux [32].

Ethosomes having testosterone has been observed 30 times higher permeation potential of testosterone as compared to marketed transdermal patch of testosterone [33]. Ethosomes having erythromycin (antibacterial drug) has been reported to decrease the minimum inhibitory concentration of erythromycin and improved efficacy of drug to eradicate staphylococcal infections in skin [34].

Ethosomes having trihexyphenidyl hydrochloride has enhanced drug delivery into systemic circulation as well as long term stability as compared to conventional liposomes containing trihexyphenidyl hydrochloride [35].

Ethosomes having cyclosporine A [36] and ammonium glycyrrhizinate [37] have been reported with enhanced dermal delivery in various skin diseases. Transethosomal gel loaded with colchicine was formulated for transdermal delivery. The ex-vivo skin permeation studies showed the enhanced permeation of Transethosomal gel when compared to non-ethosomal gel [38].

3.3 Transferosomes

Transferosomes are highly flexible and deformable lipid based vesicular system having aqueous core surrounded by phospholipid bilayer shell having edge activators which is mostly surfactant [39]. Transferosomes is able to change their shape in response to external stimuli. That's why they are proved to be efficient in the delivery of drugs having small as well as large molecular size.

Through electron and fluorescence microscopy presence of vesicles was evident between the cells of stratum corneum [40]. While the Transferosomes can penetrate into skin having pore size less than their own size because of their deformability [41].

Transferosomes can squeeze up to 500nm in size to pass through the stratum corneum. It can penetrate the skin without causing any change in stratum corneum. Double label confocal laser scanning microscopy (CLSM) studies indicated after topical application 50% of peptide was penetrated into the skin within 30 minutes [42].

The nano-transferosomes are more flexible and able to transport across the intact stratum corneum without rupture as a result of hydro taxis. The penetration of Transferosomes across the epidermis relies on transpore hydrostatic pressure difference [43].

A novel Transferosomes of Diclofenac diethyl amine (DDEA) and Curcumin (CRM) was prepared which provided a large surface area

with higher penetration potential of 1.39 folds for DDEA and 1.43 folds for CRM. These Transferosomes gives high bioavailability and sustained release drug delivery [44].

Transferosomes in combination with physical penetration enhancers has been reported i.e., microneedles for Transferosomes containing docetaxel [45] and iontophoresis for Transferosomes containing estradiol [26].

Another study reported deformable liposomes prepared by soybean phosphatidylcholine (PC) or dimyristoylphosphatidylcholine (DMPC) and sodium deoxycholate added as edge activator to increase encapsulation efficiency and percent drug diffusion. These new vesicular systems exhibited enhanced encapsulation efficiency, good stability and higher in vitro percent drug diffusion as compared to non-deformable liposomes [46]. Diclofenac sodium loaded in transferosomal transdermal patches was observed to enhance the penetration of drug through skin [47].

3.4 Glycerosomes

Glycerosomes is novel approach to enhance properties of liposomes in dermal and transdermal drug delivery systems.(Fig. 3) The fluidity of bilayer is modified by using high concentration of glycerol and variety of phospholipids. Glycerosomes have high ability to squeeze through skin pores. Glycerol is quite acceptable chemical in transdermal drug delivery. They can be prepared by any technique used to prepare conventional liposomes [48-51].

Glycerosomes were formulated using dipalmitoyl-glycerophos-phatidylcholine cholesterol, and different amounts of glycerol. Glycerosomes were loaded with diclofenac which is commercially successful non-steroidal anti-inflammatory drugs (NSAIDs) and has been used as model drug in variety of transdermal vesicular carriers [52].

In particular, DSC results indicate that when the amount of glycerol is appropriate (20 or 30%) DPPC Glycerosomes are in a fluid state, with an increased capacity to penetrate the skin carrying their payload. Glycerosomes toxicity was very low and this is a very important advantage for this new vesicular system. Overall results suggest that 20 and 30% Glycerosomes are good candidates for improving topical DCFN an anti-inflammatory efficacy [53].

3.5 Sphingosomes

Sphingosomes are vesicular carriers having natural or synthetic sphingolipid bilayer enclosing aqueous volume. They are named due to the presence of sphingolipids instead of phospholipid in liposomes. They are physically more stable than liposomes as ether or amide linkages of sphingolipids are more resistant to chemical degradation as well as acid hydrolysis [54]. Sphingolipids are more resistant to hydrolysis than the phospholipids as they have only amide and ether linkage [55].

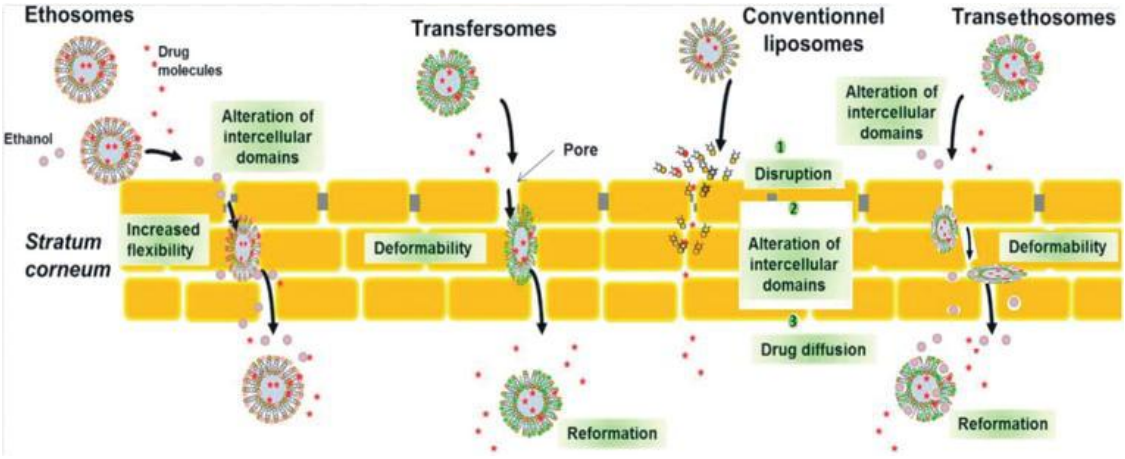

Fig. 3. Possible mechanism of action of vesicles in transdermal delivery

They can also enhance in-vivo delivery of chemotherapeutics, macromolecules and various other agents. Shingolipids are used in transdermal drug delivery systems to increase efficacy and active targeting. Most commonly utilized sphingolipids are Sphinganines, Hexadecasphinganine, Lysosphingomyelins, and lysoglycosphingolipids, N-Acylsphingosines, Gangliosides, Glucuronosphingolipids, Phosphoglycosphingolipids. These are quite expensive and have low entrapment efficiency [56]. Beclomethasone has been incorporated in Sphingosomes resulted in enhanced penetration of drug [57].

3.6 Ufasomes

Ufasomes have been developed for efficient drug delivery through stratum corneum by exchanging lipids between the outermost layers of the stratum corneum and ufasomes. Ufasomes are unsaturated fatty acid vesicles. Its lipid bilayers are composed of fatty acids and ionic surfactants. In ufasomes, fatty acid molecules are organized in such a way that their hydrophobic portion is directed toward the inside of the layer and the hydrophilic portion remains in contact with water. They are more stable, economical and have better entrapment efficiency for both hydrophilic and hydrophobic drugs than liposomes [58].

Oleic acid based ufasomal vesicular suspension of dexamethsone has been formulated and evaluated. When applied topically, enhanced anti inflammatory activity was observed. Ufasomes are economical and therapeutically stable. Oleic acids are observed to be penetration enhancer and form drug depot in deeper parts of skin resulting in sustained release behavior [59].

Ufasomes obtained containing methotrexate has been observed to improve in vitro skin delivery of methotrexate and enhance accumulation of methotrexate within the skin make it valuable in the treatment of rheumatoid arthritis [60].

3.7 Niosomes

Niosomes are made of lipids (like cholesterol) and nonionic surfactants, which are biodegradable and have low toxicity. Niosomes are soft malleable highly flexible than conventional liposomes [61]. They have ability to encapsulate both types of drugs hydrophilic as well as lipophilic. Niosomes are versatile vesicular carrier systems that can be utilized through various routes, including dermal and transdermal drug delivery [62].

Niosomal dermal and transdermal drug delivery system has been observed to decrease the systemic absorption of drug and improve penetration of drug across the skin resulted in increased residence time of drugs in the skin [63].

(Fig. 4) Niosomes formulated by sorbitan monoesters (Span) with cholesterol observed to enhance topical delivery of minoxidil in treatment

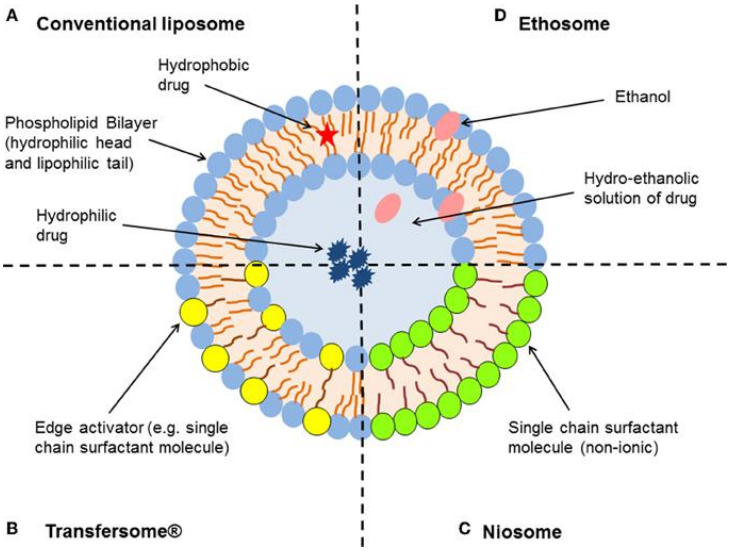

Fig. 4. Structural composition of different vesicular systems

of alopecia [64]. Niosomes formulated by Span 60 and Tween 60 niosomes may be a promising carrier for dermal delivery of ellagic acid [65]. In another study, the central composite design was applied for optimizing diacerin noisome by film hydration method. The drug was successfully delivered with increased entrapment efficiency, low particle size and polydispersity index [66].

4. NON-VESICULAR SYSTEM

4.1 Hydrogels

Hydrogels are in the form of a network of water soluble polymers, sometimes also form a colloidal gel. They can have more than 99% of water contents therefore they are superabsorbent. Due to having such a large amount of water, they are flexible like natural tissues. They have a three dimensional structure [67]. When they are placed in a biological condition, they remain immiscible with water and swell. That is why they are used in the delivery of different drugs and also in the immobilization of proteins, peptides and many other biological compounds [68].

The polymers used in the preparation of hydrogels can be natural gyms, cellulose derivatives, gelatin and polycrylates. They are prepared by different methods of crosslinking.

- Crosslinking of polymers
- Crosslinking by enzymes
- Copolymerization
- Crosslinking using high energy radiations

As hydrogels contain high water contents and swell, so they are better as compared to other topical dosage forms like ointment and conventional patches and also give a better sensation on skin[69]. It is suggested after in vivo studies, that 20% w/w aqueous gel can be more useful as a base in topical drug delivery [70].

Transdermal patches were prepared by mixing the pectin and gelatin. It was done by a two gelation step, first(thermal) in the presence of gelatin and second(ionic) by the formation of a egg box structure of pectin. When the in vitro release of the patches were studied, the patches gave the reproducible and reliable results [71].

The in situ hydrogels prepared by curcumin and its inclusion complex of hydroxypropyl-β-cyclodextrin showed a transdermal effect in the treatment of melanoma. The in vitro release of drug is dependent on the dissolution of drug [72]. Transdermal formulations of antihypertensive drug diltiazem hydrochloride using different techniques like hydrogels, organogels and bigels. When the three were compared, the hydrogels gave the best transdermal delivery among all [73].

4.2 Dendrimers

Dendrimers are macromolecules having tree shaped structure having a central core and inside the core, there are terminal groups and interior branches. The reactivity of the dendrimers is based on the chemical composition of the core and branches. The branched polymers have diameter of size ranging from 5-50nm. There properties can be tailored so they are an ideal carrier for the delivery of small molecules and biomolecules [74].

Dendrimers have a starting atom like nitrogen and further carbon and other atoms are attached to it by chemical reactions and a final sphere like shape is attained. By the repetition of the process, the sphere can be expanded up to the required size. The dendrimer surface contains sites for drug attachment and also other materials (polyethylene glycol) can be attached and the property of interacting with body can be changed [75].

4.3 Types of Dendrimers

- Poly amide amine (PAMAM) Dendrimer monodisperse
- Poly propylene Imine (PPI) Dendrimer polymers
- Poly amid amine-organosilicon (PAMAMOS) Dendrimers
- Chiral Dendrimer
- Hybrid Dendrimer
- Amphiphilic Dendrimer
- Multilingual Dendrimer
- Tecto Dendrimer
- Frechet-Type Dendrimer
- Peptide Dendrimer [74].

Dendrimers are useful as a transdermal drug delivery carrier for different drugs like Non-Steroidal anti-inflammatory drugs (NSAIDS), antihypertensives, antivirals and anti-cancer drugs [76]. PAMAM dendrimers enhance the water solubility and stability of lipophilic drugs. They are used some penetration enhancers for

transdermal drug delivery system. Three types of PAMAM dendrimers have been studied which includes G 4NH2, G 4OH and G 4.5 COOH. Indomethacin was used as model drug and enhanced steady state flux of drug was achieved [77].

The solubility and in vitro diffusion of transdermal patches of vitamin B2 was improved by using different PAMAM dendrimers in an order G2_G2.5 > G3_G3.5 > G4 [78].

PAMAM dendrimers G2.5 and G 3.5 were also studied as effective in the transdermal delivery of 8 methoxypsoralene (8MOP). *In vitro* Franz diffusion studies by using polyvinyl diflurise membrane with pig ear skin and *in vivo* studies with rat skin were done. Half generation dendrimers were found more effective when compared to full generation dendrimers [79].

4.4 Micro Emulsions

Micro emulsion is a spontaneously forming system combining the oil, water and surfactant sometimes also co-surfactants in the form of a single liquid solution with droplets of an average diameter ranging in 10-140nm. These are optically isotropic and have a thermodynamic stability. The surfactant is at the boundary present in between the aqueous and oily phases. These systems can be used as a carrier to deliver a hydrophilic substance into lipoidal medium and in the same manner lipophilic substance into aqueous medium [80].

They are having some definite advantages over other dosage forms. These are in the form of stability, transparent, spontaneous formation, increased penetration, greater drug loading capacity, improved bioavailability and the most importantly less variability in drug pharmacokinetic data [81].

Micro emulsions have wide applications in the transdermal, parenteral, oral, nasal, topical and ocular administration of drugs. By this route of administration, the therapeutic activity and target specificity of the drug is increased and toxicity of drug is decreased. In topical administration they are used as vehicles for drugs but some micro emulsion based gels are also formulated [82].

According to the structure micro emulsions are of three types that are: water in oil(w/o), oil in water(o/w) and bicontinuous (both water and oil are in the similar amounts). The main components are oil, water, primary surfactant, co-surfactant and co-solvent. Depending upon the characteristics of the components, micro emulsions shows a diversity of structure and phases [80].

Micro emulsions are used in skin products as a vehicle because they are thermodynamically stable and can immediately permeate into the skin. But the droplet size is an important factor which affects the skin permeation [83].

As micro emulsion can solubilize both types of drugs that is hydrophilic and lipophilic so it is used as a vehicle in cutaneous delivery. Many drugs are used like ascorbic acid(antioxidant), diclofenac(NSAIDs), lidocaine (local anesthetic and cardiac suppressant)and prilocaine hydrochloride, triptolide (immunosuppressive, anti-fertility, and anti-cancer drug), 5-fluorouracil(antineoplastic) [84].

The mechanism of skin penetration of micro emulsions is due to the smaller particle size and greater surface area. The skin penetration is also related to the individual components of the systems. Micro emulsions also increase the hydration of the skin so it increase the permeation of drug through the skin [85].

The drug delivery from micro emulsion is dependent on the composition of the micro emulsion e.g. when the water contents are increased, the drug penetration also increases. The effect of penetration of micro emulsion with different concentrations of monoacyl phosphatidylcholine(surfactant) was evaluated and it was concluded that by changing the type of excipient, the drug penetration in the skin can be changed [86].

Surfactant rich micro emulsions of theophylline and theobromine were formulated and successfully be evaluated for their response of cutaneous delivery [87]. transdermal delivery of ropivacaine was successfully evaluated by using the techniques of micro emulsions as well as micro emulsion based gels. Both formulations showed analgesic effect but the micro emulsion showed greater permeation of drug even after 12h of application [88].

The in vitro studies were performed for the evaluation of liposomal and micro emulsion gel of clonazepam by using methylated β-cyclodextrin for the enhancement of penetration. The micro emulsion based gels showed enhanced

penetration of clonazepam when compared to liposomal gel [89].

Micro emulsion of beta histidine hydrochloride was successfully formulated and evaluated for their transdermal effect. The components used were ethyl oleate, transcutol, Capriol and water [90]. Micro emulsion of diclofenac epolamine was compared with the poloxamer micro emulsion based gel of diclofenac epolamine for transdermal drug delivery and micro emulsion showed increased release of drug even after removing the formulation [91].

Curcumin was successfully evaluated for their transdermal delivery by using the technique of micro emulsion with different types of terpenes and co-surfactants [92].

4.5 Micro/Nano Particles

Particles with size range one micron to few mms are included in micro particles. They improve the bioavailability of drugs and reduce the side effects of the drug [93]. The main advantages of micro particles include improved solubility of poorly soluble drugs, targeted and controlled drug delivery [94]. A wide variety of drugs are encapsulated like vitamins, aspirin, antihypertensives, theophylline and certain hormones [95].

Drug release from micro particle is by the phenomenon of erosion and then diffusion. The release of drug can be controlled by controlling the molecular weight, particle size and nature of polymer. Micro particles are classified into microcapsules and microspheres [96]. There is an interaction of skin and particles at the cellular level of skin which is responsible for the penetration of Nano and micro particles in the skin [97].

In transdermal drug delivery, three different types of Nano carriers are being used: solid, liquid or liquid crystalline phase Nano carriers. They show targeted drug delivery as well as increased skin penetration [98]. The combination of solid lipid nanoparticles and Nano structured carriers are more favorable for dermal and transdermal delivery [99].

Transdermal delivery of rabeprazole was successfully evaluated by ex vivo studies using rat skin rabeprazole alginate coated chitosan nanoparticle (RP-NP). Rabeprazole is degraded by stomach enzymes but by this technique the enhanced permeation and controlled delivery of the drug was examined with minimum patch to patch variability [100].

Transdermal delivery of warfarin-β- cyclodextrin loaded nanoparticles with enhanced permeation was evaluated by *in vitro* Franz diffusion as well as *ex vivo* permeation studies [101]. Hydrocortisone succinic acid chitosan microcapsules were successfully formulated and all the release parameter were evaluated for their topical delivery [102].

Nanoparticles with two different types of starch derivatives were formulated and both the formulation showed their transdermal delivery with great efficiency [103]

4.6 Future Aspects

Transdermal therapy was started with the nicotine patch then different drugs were used like scopolamine, clonidine, estradiol, nitroglycerine etc. Only a few number of drugs were formulated as transdermal patched during past decades. The reason was the limitation of molecular weight of drug for successful transdermal absorption [104].

A variety of novel drug delivery systems are being evaluated continuously for the transdermal delivery of drug. A number of new skin penetration mechanisms are also being explored to overcome the cutaneous barrier and to enhance the penetration of skin e.g. electrophoresis, sonophoresis etc. When compared to other routes, skin seems to be the safest and the suitable route of administration. And these new techniques will explore a new visions for enhanced transdermal drug delivery[105].

5. CONCLUSIONS

Transdermal route of drug delivery seems to be the safest and the most convenient route of drug administration. From all the above mentioned formulation advancements in transdermal, it is exploring the new eras of success. By combining different drug delivery systems in patches, the permeation problem of drugs can be overcome. It is concluded that transdermal may be the most widely used drug delivery system in the future if more and more clinical trials done using these latest techniques.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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