Development in natural polymer based drug delivery in transdermal therapeutics

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***Abstract*- Transdermal drug delivery systems (TDDSs) offer several advantages over other routes of drug administration, contributing to their popularity and utilization in various medical contexts. It offers several advantages, such as non-invasive administration, avoidance of first-pass metabolism, prolonged therapeutic effect, and improved patient compliance. The efficacy and performance of transdermal drug delivery systems can indeed be influenced by various biological factors, which in turn affect the integrity and barrier qualities of the skin. These factors contribute to the variations in the amount of drug absorbed through the skin.Some Barrier properties of the skin reduce with recent advances of polymers in transdermal therapeutics. Polymers play a pivotal role in transdermal drug delivery by controlling drug release, enhancing permeation, providing stability, ensuring biocompatibility, and enabling the formulation of effective and patient-friendly transdermal patches or other systems.This review would aim to highlight the key advancements, innovations related to the use of polymers in transdermal formulations.**

Keywords: **Transdermal route, Chitosan, Hyaluronic Acids, Cellulose, Collagen, Alginate.**

INTRODUCTION

Transdemal route is substitute for oral and Parentral drug delivery system. TDDS ignores the pre systemic Metabolism which leads to improve in Bioavailability.Common formulation given through Transdermal Route to the systemic circulation in the form of Gel ,Transdermal Patches,Lotion and creames in harmless and effortless manner.

Skin act as barrier for the protection of interior layers of tissues cover area of around 1.5 to 2.0 m2 and makes up 15% of an adult's total body mass. .it act as largest tissue .epidermal and dermal segment useful for delivery of medication and denoted as transdermal drug delivery system.Transdermal DDS has numerous advantages as they are useful for self administration, By Pass-First Pass metabolsm, immunovigilance.Different ways designed for the absorption of drug which depend on the nature of the drug either its hydrophilic or hydrophobic.Transcellular way contribute for hydrophilic drugs (water soluble) and intercellular way involve for hydrophobic drugs [1-4]. Three tissues—the epidermis, dermis, and subcutaneous layers—make up the human skin. In which epidermis is the top layer of skin and is made up of five layers:

1) stratum corneum, stratum corneum is responsible for enhancement of permeation has composition of protein such as keratin,Lipids,ceramides,cholestrols esters,free fatty acids, squalene, wax esters and triglycerides with thickness 10-20 µm [1,5-8].
2) Stratum lucidum has keratine layer (2-3) hence it seems as thin layer located at several parts such as palm, sole and digits [9].
3) Stratum granulosum are thicker as compared to stratum corneum or lucidum.keratohyalin a protein synthesised from granules form stratum granulsum [10].
4) Stratum spinosum is known as the "spiny layer" because it contains connections to cells termed desmosomes connecting the cells formed by 8–10 layers of keratinocytes [9].
5) Stratum germinativum formed by a single layer of cuboidal cells, or more or less columnar cells.

Barriers involve for transdermal

1) Partition cofficient (logP)-Less value of logP has limitation for the permeation of drug due to little partitioning in the layer of skin .The drug with high logP also face the same problem of permeation as it can not partition out the stratum corneum layer of epidermis.the optimum logP value for permeation of dug sucessfully [11-13].
2) Diffusion –Stratum corneum has thickness of approximtely 20 µm hence it not allows to across the skin layer easily due to unappropriate chemical structure of drug. .Intercellular lipids interacton with hydrogen bond resulted functional group in chemical structure of drug cause less diffusivity [14-17].

Variability in drug delivery using the transdermal route:

1 Age factor

The aging process can impact the permeability of hydrophilic substances across the skin. This is thought to be linked to the decreased natural moisturizing factor, which leads to a lower water content in the stratum corneum (SC). As a result of this reduced water level in the SC, the pathway for polar movement across the lipid lamellae is disrupted, hindering the transport of hydrophilic compounds through the skin [18, 19].

2 Variances based on ethnic background

Research endeavors have frequently involved the comparison of Caucasian and Afro-Caribbean skin, revealing that permeation across Afro-Caribbean skin has commonly been observed to be less pronounced [20-23].

3 Skin permeability increases as its temperature rises, as higher temperatures cause greater fluidity in the lipid domain of the stratum corneum (SC). This increased fluidization leads to a higher diffusion coefficient for the drug, ultimately resulting in enhanced drug permeation [18].

4 Medical Conditions

Evidence suggests that skin that is damaged or affected by disease exhibits significantly higher permeability when compared to skin that is undamaged and healthy [24].

5 Variations among Anatomical Sites

Permeability across distinct anatomical locations can be categorized, where skin in the epigenital region is recognized for its highest permeability, succeeded by skin in the head and neck region, the trunk (encompassing chest, stomach, and back), the arms, and finally, the skin on the legs[18,19].

Advantages of natural polymer

1. Natural polymers are biodegradable as they have been been produced by natural sources and living things.
2. Plant has sugar polysaccharides due to which Polymers are biocompatable and non hazardious
3. May be easily acquired since it tends to be less expensive than synthetic polymers.
4. Can collect easily due to its simple production process.
5. Formulation produced by natural polymer has no risk for patients [25].

Natural polymer in transdermal drug delivery and formulations

1 Chitosan

N-deocetylation of chitin synthesized the chitosan a natural cationic polymer has functional groups of amino, acetamide, and hydroxyl [26,27].Chitosan has potential to interact with negatve charged protein whch leads to the drug encapsulation [26,28].Chitosan has potential to interact with negative charged protein which leads to the drug encapsulation[29].Transdermal delivery of drug has many limitations such kertin(a protein), intercellular lipid,stratum corneum,keratinocytes.Chitosan and chitosan derivatives has shown variety of approches for delivery of drug across the skin.Keratinocytes ,intercellular lipids interact with keratin make a brick wall as protecting wall to protect outer substance to reach systemic circulation through the skin.Chitosan derivatives N-trimethyl chitosan,N-carboxymethyl chitosan make changes in keratins and enhance the permeation across the skin for transdermal drug delivery[30].

Chitosan in transdermal formulation:

Chitosan Emulsion free from agglomeration, chitosan provide a coat at the outer layer of emulsion and make it more stable [31].

Transdermal microneedles-Microneedles insertion enhance the permeation of drug across the skin.Transdermal microneedles prepared by water soluble polymer such as Polyvinylpyrrolidone,Polyvinyl alcohol,Carboxymethyl cellulose leads to extreme release of drug ,this issue may be avoided using chitosan and its derivatives due to its low water solubility as well as they have biocompatable and biodegradable characterisation[26,32].

Chitosan hydrogel has characterisation such as biocompatibility and ability to degrade make it more perfect for the formulation of hydrogels these gels do gas exchange at the site of wound and provide a favourable atmosphere its antimicrobial capability do wound repaire.

Case study

The experiment focused on assessing how substances permeate the skin over a 24-hour period. After this timeframe, the chitosan nanoparticles containing tacrolimus exhibited a permeability rate of 24%, whereas the tacrolimus cream showed a higher rate of 61%. This suggests that the chitosan nanoparticles effectively delayed the release of tacrolimus, potentially reducing its systemic toxicity. Additionally, within the first 24 hours, the cream deposited 11.4% of tacrolimus onto the skin, while the chitosan nanoparticles achieved a substantially greater deposition rate of 75%. This highlights the advantage of using chitosan nanoparticles for delivering tacrolimus to the skin, especially relevant for psoriasis treatment where skin thickening hinders drug penetration. In this study, the chitosan nanoparticles demonstrated an ability to enhance the passage of tacrolimus through the skin, prolong its presence in the skin layers, extend its effectiveness at targeted areas, and minimize its overall impact on the body. Rada Al-Kassas et al. developed a method for delivering transdermal propranolol in their research [26].

2 Hyaluronic Acids

Hyaluronic acid, also known as hyaluronan (HA), is a water-soluble polymer that is found in significant amounts in the extracellular matrix (ECM) of all connective tissues in humans and other animals. It is the only nonsulfated GAG made up of many glucuronic acid and nacetylglucosamine disaccharide units [33,34]

According to reports, medium (100-300 kDa) and high (600-1200 kDa) molecular weight Polymer show smaller permeability whereas HA enhancing effects due to low molecular weight of (5-50 kDa).To increase the effectiveness of administration, HA has become commonly included in transdermal formulations recently[35,36].

The coiling of HA allows it to hold 1,000 times its weight in water. Due to these qualities, it has particular physicochemical properties and biological activities. HA is able to moisturise both the SC and the dermis because of its great hygroscopic ability. Excessive moisture will cause corneocytes to swell, break intercorneocytes, alter the microstructure of intercellular lipids, and finally make the skin more permeable [35, 37].

Hyaluronic Acid in transdermal formulation:

Hydrogel (of indomethacin) include polymer Hyalauronic Acid which shows high and easy permeation across the skin with high concentration.

Hyaluronic acid Microneedle Patch is great at holding onto water, which helps keep our skin hydrated and our tissues strong. When it's used in a microneedle patch, it could make our skin even more hydrated and help medicines get in better [38].

Hyaluosomes have demonstrated remarkable advantages as a transdermal liposomal system, surpassing other liposomal variants in terms of transdermal permeation. They exhibited a threefold increase in both flux and permeability coefficient compared to alternative liposomal systems. This study suggests that hyaluosomes hold substantial promise for transdermal drug delivery due to their favorable rheological properties and exceptional permeation abilities, outperforming both traditional and unconventional liposomal systems. This advancement underscores the potential significance of hyaluosomes in enhancing skin-permeating substance delivery [39].

Case study

SU Son, J Lim, T Kang, J Jung, EK Lim conducted a study on Pig Skin that Nanohydrogel Transdermal Penetration Franz diffusion cells and confocal laser scanning microscopy (CLSM) pictures were used in an ex vivo skin permeation investigation to verify the impact of HA-Do on the enhancing of nanohydrogel skin permeation. Used nanohydrogel (A) for this investigation on skin permeation since it was an appropriate size to be carried in by cells. Researchers measured the skin penetration level of the nanohydrogels by fluorescence using ICG as a model lipophilic component (Figure 6). Free ICG without HA-Do was only found in the epidermis' top layer after 24 hours of penetration; While examined,it had not reached the stratum corneum. The stratum corneum, epidermis, and dermis layers of the ICG-containing nanohydrogel (A) showed higher fluorescence due to diffusion from the stratum corneum to the dermis [40-44].

3 Cellulose

Cellulose is a renewable and eco-friendly natural polymer with added benefits like its lightweight nature, high porosity, and extensive specific surface area. As a result, it finds versatile applications in areas such as adsorption, oil/water separation, thermal insulation, biomedical uses, and numerous other fields [45-47].

Natural cellulose, primarily sourced from bacteria (BC) and plants (PC), offers substantial potential as a scaffold material for diverse regenerative purposes. The distinct advantages of natural cellulose in comparison to synthetic alternatives have captured the attention of researchers. These benefits encompass its abundant supply, cost-effectiveness, ease of use, biocompatibility, low toxicity, minimal immune response, and ability to mimic native tissues.Bacteria within the Gluconacetobacter genus are responsible for producing an exceptionally pure form of bacterial cellulose (BC), which manifests as a significantly swollen membrane [45].

Cellulose in transdermal formulation:

The advantages associated with BC films could also find application in the realm of transdermal drug delivery systems. Many conventional transdermal patches are constructed through the assembly of various materials. In contrast, a design utilizing BC films with fewer layers, or even a single layer, has the potential to simplify the manufacturing process and decrease production costs [48].

In drug formulations as gel, cellulose derivatives such as HPMC and CMC are widely preferred as gelling agents. These polymers display a reduced susceptibility to microbial contamination when compared to natural gelling agents like tragacanth, acacia, sodium alginate, agar, pectin, and gelatin [49-50].

HydroxyPropyl methylcellulose HPMC allow continuous and extended drug release from the patches. The process that predominantly controls drug release in the majority of controlled or sustained release devices, such as transdermal patches.

Case study

Orally ingested Clopidogrel bisulfate has a brief elimination half-life (approximately 7-8 hours) and limited oral bioavailability (50%). It goes through significant first-pass metabolism (85%), leading to the need for frequent administration of high doses (75 mg) to achieve therapeutic levels, which can result in potential toxicity. To address these challenges, a transdermal drug delivery system (TDDS) for Clopidogrel bisulfate was created and assessed using various polymers like HPMC, PVP, and EC through the solvent evaporation technique. The goal was to enhance the drug's bioavailability and reduce potential toxicity.

The diffusion study outcomes revealed that the formulation denoted as F2 (comprising HPMC and PVP) demonstrated the highest release rate, achieving a maximum release of 90.06% within 24 hours. Considering drug release patterns and physicochemical characteristics, formulation F2 was identified as the optimized choice; exhibiting a significant drug release of 90.06% in a 24-hour timeframe.These newly developed transdermal patches hold the promise of improving therapeutic effectiveness while mitigating potential toxicity of Clopidogrel bisulfate [51-52].

4 Collagen

Collagen stands as the most abundant protein in mammals, serving as a primary source of tissue strength. A typical collagen molecule comprises three interwoven protein chains that form a helical shape. This molecular structure is responsible for its pivotal role in providing resilience and structure to various bodily tissues, including skin, bones, tendons, and more. Collagens form the primary structural components of vertebrate connective tissues, constituting approximately 30% of the overall protein content. They are also present in the interstitial tissues of nearly all parenchymal organs, where they play a role in maintaining organ stability [53-54]

Collagen in transdermal formulation:

Polyvinylpyrrolidone microneedle deliverd Collagen use for cosmetic maintenance, wound recuperation, and potentially heightened immune prowess, and treat dystrophic epidermolysis bullosa [55].

A collagen-infused microemulsion that enhances and Restores the protective barrier of old or compromised skin [56].

Collagen hydrogel has been investigated as a potential material for wet wound dressings with the ability to promote the formation of new skin appendages as Collagen, a natural protein found in various tissues including skin, plays a significant role in providing structural support during wound healing [57].

Case study

In their research, Borumand and Sibilla focused on investigating the impact of a supplement containing collagen hydrolysates sourced from tilapia and pangasius fish, along with hyaluronic acid, vitamins, and minerals, on skin properties. This study involved 294 participants aged 18 to 74, recruited by 40 dermatologists across five countries. Participants were instructed to consume 50 mL of the supplement once daily. The study was organized into three segments. The initial segment indicated that after 60 days of treatment, 69% of participants witnessed noticeable or significant improvement in their facial lines. The volunteers experienced enhancements in facial photoaging issues and skin dryness. The subsequent section revealed an increase in dermal collagen density, with the degree of increase being more pronounced on the face compared to the forearm after 12 weeks of treatment. Lastly, the third segment demonstrated that skin firmness witnessed a remarkable up to 94% increase by the time the treatment period reached 130 days [58].

5 Alginate

Alginate, derived from brown algae, is a polysaccharide characterized by varying ratios of (1–4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) components. The α-L-guluronic acid (G) content enables alginate to form gels upon exposure to divalent ions like calcium (Ca^2+), resulting in the creation of gel-type nanoparticles. Alginate and its derivatives exhibit hemostatic and regenerative attributes that find application in wound dressings. These substances facilitate the movement of cells, promote the development of new blood vessels (angiogenesis), and diminish the levels of proinflammatory cytokines in persistent wounds.

Alginate in transdermal formulation:

Wound dressings made from alginate are commonly employed for the coverage and safeguarding of wounds. The gel-forming property of alginate contributes to the creation of a moist environment that fosters the healing process. These dressings are particularly valuable for wounds that exhibit a moderate to significant excretion (fluid drainage).

Alginate's ability to form gel-like structures, along with its hemostatic, regenerative, and anti-inflammatory properties, makes it a valuable material for wound care applications.Due to their hydrophilic properties, alginate dressings create a moist environment, absorbing wound exudate and preventing bacterial infections at the site of the wound [59].

Alginate hydrogels exhibit a high degree of versatility and adaptability as biomaterials, offering significant potential for utilization in diverse biomedical contexts. Their resemblance to the extracellular matrix plays a crucial role in their selection as carriers for strategies involving cell delivery, with a focus on facilitating tissue regeneration [60].

Case study

In 2010, Borselli and colleagues developed an injectable alginate gel containing insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF), which was administered to ischemic mice. The results demonstrated that only the IGF-1 treatment was effective in reducing apoptosis, promoting cell activation and proliferation, and significantly aiding in the regeneration of muscle fibers at the wound site. However, it should be noted that IGF-1 exhibited an initial burst release of around 80% within the first 24 hours in vitro, whereas VEGF exhibited a more sustained release profile, releasing approximately 40% during the same timeframe [105]. While natural polymers offer benefits such as biocompatibility and biodegradability, synthetic polymers provide an advantage in terms of controlled structural design, enabling the customization of material properties [61].

Conclusion

Transdermal drug delivery systems (TDDSs) offer advantages that can help overcome some of the drawbacks associated with other drug delivery routes, such as oral and parenteral administration. Review Highlight the importance of polymers in enhancing transdermal drug delivery. the polymers is modifying drug release and permeation kinetics.The recent innovations and advancements in polymer-based transdermal systems improving patient care and therapeutic outcomes.

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