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TOPICAL SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM: A NOVEL APPROACH FOR TOPICAL DELIVERY OF DRUG

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ABSTRACT

Topical or dermal drug delivery system is the approach of delivering the drug onto the skin for protection of skin or for local and systemic effect. Dermal delivery system is although a conventional method but research is still continuing to find its applicability in various aspects of latest pharmaceutical investigations as delivery system. Skin is a multi-layered structure that is easily accessible organ for drug delivery and has the potential of delivering drugs with better efficacy and overcoming the disadvantages associated with other routes of drug delivery. SMEDDS traditionally originated as oral lipid based systems with the purpose of delivering lipophilic drugs. However, new approaches are presented by utilising this simplified system of drug delivery. Although routes such as topical, rectal, nasal and vaginal have gained lesser attention but the delivery of drug containing SMEDDS topically is noteworthy. Topical SMEDDS has the potential of delivering lipophilic drug with high efficacy topically in a cost effective manner. This article reviews the topical drug delivery system, self-microemulsifying drug delivery system and the concept of topical SMEDDS with their potential advantages in pharmaceutical industries. An overview of reviews was conducted to locate published literature between 2000 and 2020.

KEYWORDS: Dermal drug delivery, SMEDDS, Lipophilic drugs, Topical delivery, Prolonged release, Effective delivery.

INTRODUCTION

Dermal drug delivery system is although a conventional approach of delivering the drug via skin but it has been an attractive approach since then. Dermal products are applied topically/ on skin for either local or systemic effect or are categorised on same basis. The one applied on skin to give local effect are known as topical formulation and those giving systemic effect

on skin application are known as transdermal formulations.[1-3] Drug molecules with low doses can be easily and effectively delivered through topical route. Topical drug delivery systems are applied to treat cutaneous disorders. Topical drug delivery systems are localized drug delivery system generally applied for local skin infection. Dermatological formulations are available in different forms, like solid, liquid and semisolid. These formulations are available in different consistencies but the semi-solid formulations are most popular in derma products.[1] The drug absorption in drug substances having favourable lipid/ water partition coefficient is enhanced via the skin.[4] Topical delivery includes two basic types of product: External topical products and internal topical products. The external topical products are the one that are sprayed, spread or dispersed on cutaneous tissues in order to cover the affected area. Internal topical products are applied on the mucous membrane orally, vaginally and rectal tissues for local activity.[5]

Rationale for topical preparation

Various factors have to be considered in order to formulate an efficient and effective topical preparation. The topical preparations are used to produce effects on surface and stratum corneum. These effects include:

On skin surface

a. Cleansing effect of removing dirt and germs
b. Improves the appearance
c. Protects the skin surface either from excess dryness or moisture
d. Pharmacological effect such as anti-microbial effect

On stratum corneum

a. Protective action
b. Provide moisture
c. Keratolytic effect
d. Effect on viable epidermis and dermis: Anaesthetic, anti-histamine, anti-inflammatory anti-pruritic etc.
e. Provide systemic effect: The drugs include nitroglycerin, scopolamine, clonidine, estradiol
f. Additional effects: anti-microbial effect, emollient, anti-perspirant effect [6]

Advantage of topical drug delivery systems[7,8]

☆ Bypass the first pass metabolism as well as GIT metabolism

- ☆ Very convenient to use
- ☆ Easy to apply
- ☆ Self medication is possible
- ☆ Shows patient compliance
- ☆ Easy to terminate the therapy or medication
- ☆ Can be applied to specific/ targeted site
- ☆ Incompatibility in GIT is avoided
- ☆ Maximum drug utilization even with short half life and narrow therapeutic window
- ☆ Effective in low dose and by continuous drug input
- ☆ No risk of fluctuation in drug concentration
- ☆ Can be applied to large area
- ☆ Offers an alternative pathway for patients who have oral dosing issues, such as in unconscious patients
- ☆ Fewer side effects related to systemic toxicity compared to other routes of administration
- ☆ Painless and non-invasive technique
- ☆ Higher drug bioavailability
- ☆ Higher physiological and pharmacological response
- ☆ Minimum systemic toxicity and exposure of drug to non-infectious tissue/sites
- ☆ Prolonged duration of action

The introduction of drug onto the surface of the skin in a topical formulation is typically formulated for better drug absorption. When this formulation is applied on the skin, it interacts which the skin environment and further influence the rate of release of drug compound in order to achieve sufficient skin absorption.[9] Topical drug formulations are applied for various purposes such as antiseptics, anti-fungal, skin emollients and protectants etc.[10] Skin is the main and most accessible route of topical drug delivery system and has the tendency to facilitate the drugs to specific site with better efficacy as compared to other routes of administration.[11] The drug reaches the specific or targeted site of action via diffusion and their absorption takes place on skin.[12] The major goal of drug delivery system is to get the right dosage at right place.[13] Some topical formulations contain API as such with excipients but other preparations contain API dissolved or dispersed in topical base. This has direct impact on release rate and it depends solely on physical and chemical properties of the carrier or topical base and medications used.[14-16] The drug absorption from topical

preparations solely depends upon physiological and physiochemical factors. These factors include:

Physiological factors

a. Thickness of skin
b. pH of skin
c. Temperature of skin
d. Lipid content
e. Hydration of solvent
f. Density of solvent
g. Inflammation of skin
h. Blood flow

Physiochemical factors

a. Partition co-efficient
b. Molecular weight of drug
c. Degree of ionization
d. Vehicle effect

Many different factors are considered during the development of ideal dosage form and these include the retention of dosage form, patient acceptability and the flux of drug across the skin.[17-19] The topical formulation includes multiple components and in an ideal formulation these components must be compatible with each other and should have stable environment for all the ingredients.[8,9] Topical drug delivery system allows optimum penetration of the drug into the skin membrane.

A topical dermatological product must have the following properties

a. Aesthetically pleasing
b. Physically and chemically stable
c. Have an adequate shelf life[20]
d. Releases drug from the formulation and delivers it into the skin as required for the target indication[21]
e. Elegant in appearance and cosmetically acceptable to patients[22]
f. Contains only FDA-approved or acceptable excipients that are necessary from a regulatory perspective[23]
g. Acceptable for the disease state[24]

h. Easy to apply
i. Compatible with the desired packaging
j. Scalable manufacturing processes on a commercial level[25]

Skin, as drug carriers

Skin is the largest organ of human body that represents the first complex barrier between the human body/ biological system and exogenous/ external substances.[26] The multi-layered structure of skin not only influence physiological activities but also regulates the internal homeostasis by means of active metabolic pathways. The enzymatic profile of skin is very similar to that of liver and hence considered as metabolically active part of human body.[27] The various layers of skin such as the epidermis, dermis and the outermost stratum corneum (SC) have enzymatic activity and this activity intensifies within the deeper skin layers. Stratum corneum is composed of lipids, proteins and water. The high lipoidal content in SC makes it lipid-rich in nature. The stratum corneum of the skin is very selective as it permits selectively due to which the drug transport through skin becomes limited. The topical delivery of lipophilic drugs is possible and is aided by dissolution into intracellular lipids around the cells of stratum corneum. But the transport of hydrophilic drug components is quite difficult because of low water content in stratum corneum. These hydrophilic molecules are transported from skin through presence of pores or openings of hair follicles and sebaceous glands on skin that restrict the drug absorption. There are three different pathways namely transcellular, transappengeal and intracellular that are involved in the transportation of drug across the stratum corneum.[28] The epidermal layer of skin contains highly hydrated keratins and hydrophilic drugs tends to pass through this keratins through transcellular pathway.[29] The lipophilic drugs are transported through intercellular pathway via lipid matrix. The drug transport to dermal layer occurs via transappengeal pathway, where less that 0.1% of hair follicles and sebaceous glands are present.[30] Percutaneous absorption is also an ideal factor responsible for achieving and maintaining uniform systemic and therapeutic levels throughout the duration of use. During the delivery of drug through topical route should have adequate lipophilic character and molecular weight less than 500Da. Drugs applied topically reaches the area in optimum concentration by reducing the side effects and by increasing bioavailability and patient compliance.[31]

Self-micro emulsifying drug delivery system (SMEDDS)

Although the concept of lipid drug delivery system was applied commercially for the efficacious transport of hydrophobic pesticides or herbicides. This same principle was then used in pharmaceutical industries in the form of SEDDS, SMEDSS, etc. This type of delivery system are frequently used to improve solubility, bioavailability of Biopharmaceutical Classification System (BCS) class II drugs, and also enhance the delivery of BCS Class III & IV drugs.

Self micro-emulsifying drug delivery systems are isotropic, transparent mixtures of oil, hydrophilic surfactant and/or a cosurfactant, and a solubilized drug. This combination has been attributed to the drugs with poor solubility. SMEDSS are physically stable formulations which possess particle size less than 500ŋm.[32] SMEDDS have attained more attention due to its efficiency in solubilizing the drug and enhancing the bioavailability. Apart from adding oil, surfactant and co-surfactants other excipients such as permeation enhancers, co-solvents, and viscosity builders are also added in the formulation.[33] The important feature of SMEDDS is their stability. SMEDDS have the ability to self emulsify in aqueous solution. During emulsification with aqueous solution it forms small oil droplets and also increases the rate of diffusion and bioavailability. Self-micro emulsifying drug delivery systems being the novel approach are extensively used for the enhancement of solubility and bioavailability of Biopharmaceutical Classification System Class II, III & IV.

SMEDDS is a drug delivery system that uses a microemulsion achieved by chemical rather than mechanical means. That is, by an intrinsic property of the drug formulation, rather than by special mixing and handling. Microemulsions have significant potential for use in drug delivery, and SMEDDS are the best of these systems identified to date. SMEDDS are thermodynamically stable as compared to emulsions. Typically, lipid based formulation is categorized into four types based on their specific material used and characteristics.[34] The Type I of lipid formulation is composed of oils with least concentration of surfactants and is considered as safe, simple and compatible. The type II is usually composed of oils and hydrophobic surfactants and Type III is composed of oils, surfactants and co-solvents. Lastly type IV lipid formulations are composed of hydrophilic surfactants and co-solvents. Traditionally SMEDDS, SEDDS have been extensively used for oral delivery but topical route of SMEDDS is least approached. The SMEDDS have many advantages as oral route but it has pit falls too. Liquid SMEDDS filled in soft gelatin capsules has disadvantages of

incompatibility, drug leakage and similarly forming tablets for SMEDDS are expensive and not easy to formulate. Nowadays, researchers have demonstrated the potential for improving drug delivery via diverse pathways for both SEDDS and SMEDDS. These pathways include vaginal, ocular, rectal, topical and nasal. For example a study was published demonstrating SEDDS as oral vaccination vehicle and SMEDDS as topical gel. These approaches are very much welcoming in pharmaceutical industries not only on novelty point but also these are easy to formulate and less expensive. Hence, these approaches can be considered as ground-breaking commercially in pharmaceutical industries.

Advantages of Topical SMEDDS

a. Ease of formulation
b. Suitable for lipophilic drugs
c. No adverse effects
d. Cost effective
e. Suitable for both local and systemic effect
f. Higher rate of diffusion
g. Increased bioavailability

Transport of SMEDDS through skin: The skin is highly accessible route for drug administration, especially due to various advantages such as hepatic metabolism being circumvented, reduced side effects of drugs, enhanced drug bioavailability, allowing immediate drug withdrawal, and improved patient compliance.[35] However, despite being advantageous for many reasons, it has been a challenge due lipophilic nature of outermost layer and followed by hydrophilic nature of deeper skin layers.[36] The SMEDDS being lipophilic in nature containing fine-oil droplets has potential for topical route of drug delivery due to lipid rich sebum present in sebaceous glands on skin.[37] However, sweat can be a minute obstacle due to its hydrophilic nature and lipophilic drug. Topically applied SMEDDS can portray robustness to dilution. The obstacle created by sweat can also act as agent slowing dermal permeation rather than mediator-blocking dermal permeation.[38] In addition, it was previously researched by scientists that drugs that are to be applied topically should possess both lipophilic as well as hydrophilic character. The lipophilic character of formulation enables the drug to cross the outermost skin layer and similarly the hydrophilic character enables to cross the hydrophilic epidermis and dermis layer.[39] Furthermore, the lipophilic nature of SMEDDS can be utilised to reach lymph nodes that are located within the

epidermis and dermis layer in order to target the dermal drug delivery system.[40,41] The researchers found that drug metabolism occurs within deeper layer of dermis and the dermal lymphatic uptake of SMEDDS can successfully protect the drug from dermal metabolism[42, 43] Consequently, special consideration must be taken when choosing excipients included in topical SMEDDS, as these compounds will be the decisive factor in terms of optimised topical drug delivery across the multiple layers of the skin.

CONCLUSION

Most of the researchers working on lipophilic drug products including herbal extracts face a challenge of finding suitable/ appropriate solvent or formulation system because of limited solubility. Hence, the concept of oral SMEDDS is utilized in topical route. Here, the topical SMEDDS would have the potential of overcoming the disadvantages of oral SMEDDS such as decreased dissolution, bioavailability, and difficulty of formulating and higher cost. The lipophilic drugs can be formulated into SMEDDS and further into topical gel. This topical formulation can be effective for both local and systemic effect. Topical SMEDDS formulation provides a great scope in future for the delivery of hydrophobic drugs with high efficacy and cost effectively.

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