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Original Research Paper

Transdermal drug delivery through skin barrier using different devices

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ABSTRACT:
A transdermal patch is a medicated patch use on the skin to deliver medicine through the skin into the bloodstream. Oral, topical, intravenous, intramuscular are the different others medication system. Transdermal drug delivery system have an advantages over other system as it delivers medicine through the skin by controlled release. Drug deliver either through a porous membrane into the skin or it melted by the body heat and passes through the skin. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variations.

Keywords: Stratum Corneum, Transdermal Drug Delivery, Hydrophilic Drugs, Cystemic Circulation, Capillaries

INTRODCUTION:

Transdermal drug delivery is an alternative to oral drug delivery. It is also an alternative to hypodermic injection [1,2,3,4]. In the earlier people placed substances on the skin for therapeutic effects. In the modern time it is modified and uses as transdermal patches. In 1979 in the United States scopolamine drug was used as first transdermal system for systemic delivery. It was used as a three-day patch to treat motion sickness. After a decade nicotine patches was used as a transdermal patches and deliver medicine through the skin. Estradiol, fentanyl, lidocaine and testosterone were used for 19 transdermal drug delivery systems. Between 1979 and 2002 a new patch was approved on average every 2.2 years. In between 2003-2007 a new transdermal delivery system tripled in every 7.5 months. In comparison to the oral route transdermal drug delivery system has a variety of advantages. In developing countries transdermal drug delivery has an advantages over hypodermic injections. Hypodermic injections are painful and poses risk of disease transmission by needle use [5]. Transdermal drug delivery system has an advantage that it can release drug in our body for a long period of time more than one week. It is inexpensive and has lesser side effects. The greatest disadvantages of transdermal drug delivery system is that very lesser drugs can show delivery through skin. Hydrophilic drugs can not be deliver through this route. The transdermal delivery of peptides and macromolecules, including new genetic treatment employing DNA or small-interfering RNA has posed particular challenges [6]. Another area of great interest is the delivery of vaccines [7]. An analgesic patch has approved by the United States. In Europe it deliver fentanyl modulated by iontophoresis [8]. Drug is not only deliver but molecules also extracted through skin [9]. This has already been achieved for glucose monitoring by extracting interstitial fluid using electrical means and is in clinical trials using other approaches, such as ultrasound. So in this journal we mainly focus on transdermal drug delivery of drug through the skin. Disrupting stratum corneum but remain intact of epidermis. So we discuss here structure of skin so can easily understand the mode of drug delivery. Advantages and disadvantages of drug delivery also discuss here. Also the structure and mode of delivery of different device discuss here.

1. Structure of skin:

The structure of skin can be categorised in mainly three parts. The three parts are (1) Epidermis (2) Dermis (3) Hypodermis

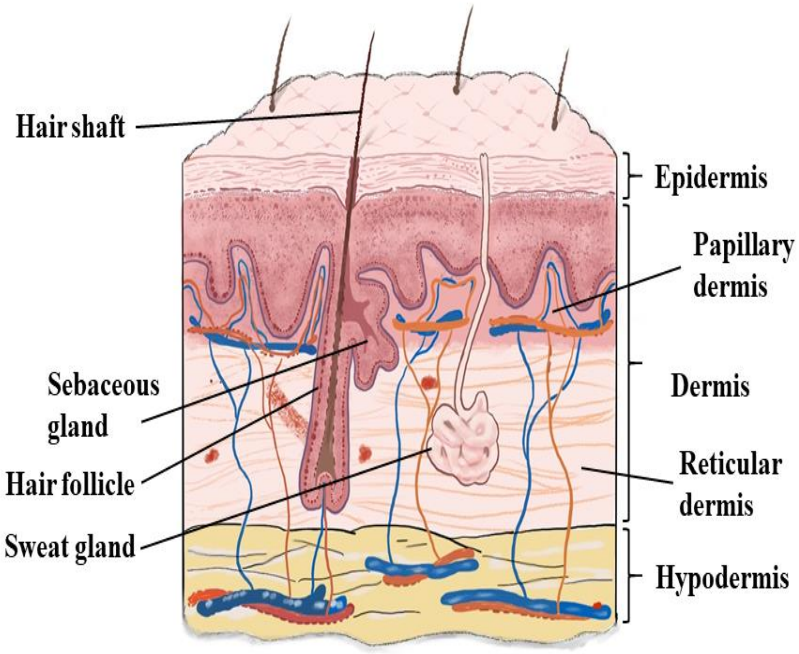

Figure: 1. The schematic structure of the three layer of the skin

(1) Epidermis:

The epidermis cover the entire outer surface of the body and it is a self-renewing squamous epithelium part of the body. It contains two parts. The two parts are (1) Viable epidermis and the (2) stratum corneum. Inside the stratum corneum it is located from 0.06mm on the eyelids to 0.8 mm on the palms. It consists of *stratum lucidum*, *stratum granulosum*, *stratum spinosum*, and the *stratum basale*. The dead horny cell from the skin surface can be replenished by mitosis of the cells in the basale layer of the epidermis. The basale layer continually move outward and keratinaized to form the outermost layer of stratum corneum [10].

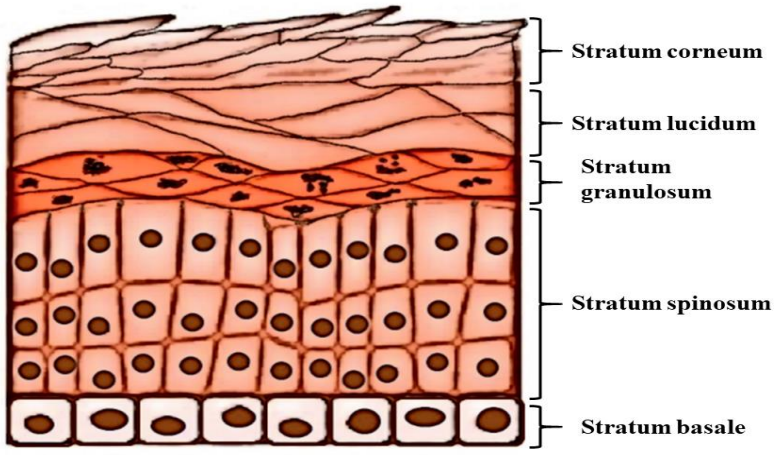

Figure: 2. The schematic structure of the epidermis

The outermost horny layer of the skin is known as stratum corneum. It acts as a barrier and limits the movement of chemical substances. 75-80% proteins, 5-15% lipids, and 5-10% ondansetron material decides the horny nature of the outermost layer. *Stratum corneum* is approximately 10 mm thick when dry but swells to several times when fully hydrated. It is flexible but relatively impermeable. In Figure 1 the structure consist of a wall-like structure with protein bricks and lipid mortar. It consists of horny skin cells (corneocytes) which are connected via desmosomes (protein-rich appendages of the cell membrane). The permeability of substance across the skin determined by the embedded corneocytes of the lipid matrix [11].

(2) Dermis:
Dermis is a 3 to 5 mm thick layer of connective tissues, blood vessels, lymph vessels and nerves. It is located just below the epidermis. It removes toxins and waste products and provides nutrients and oxygen to the skin. Capillaries present on skin surface provides sink conditions for most molecules across the skin barrier. The fluid concentration across the epidermis is very low. This difference in concentration across the epidermis allow blood supply through the transdermal barrier. The gelled water cross the transdermal barrier during transdermal delivery of drugs. The lipophilic molecules felt difficulty to cross the transdermal barrier [12].

(3) Hypodermis:
The hypodermis layer consist of maximum fat tissue and it located just below the dermis. This layer helps to regulate temperature, provides nutritional support and mechanical protection. Maximum blood vessels , nerves, sensory pressure organs located in this layer. Ultimately during transdermal drug delivery, drug reaches in systemic circulation through penetrating all the three layers [10].

2. Absorption through the skin:
During transdermal drug delivery drug should penetrate through stratum corneum and spread locally. This type of absorption is well known as percutaneous absorption. In this type of absorption drugs penetrates into different layer of skin and ultimately enter into systemic circulation [11]. Percutaneous absorption of drug molecules is of particular importance in transdermal drug delivery system because the drug has to be absorbed to an adequate extent and rate to achieve and maintain uniform, systemic, therapeutic levels throughout the duration of use. Once the drug penetrate the stratum corneum layer it passes into the blood quickly through the dermal layers[13].

3. Drug penetrate through skin route:
In Figure it is clear that widely distributed hair follicles and eccrine glands act as shunts for percutaneous absorption. In this type of absorption drug molecules passes through this shunt. At first drug molecules penetrate through the skin along the hair follicles or sweat ducts then take entry through the follicular epithelium and the sebaceous glands. The primary pathway for transdermal permeation after steady state is through the stratum corneum [11]. For any molecules applied to the skin, two main routes of skin permeation can be defined: Transepidermal route Transfollicular route.

3.1. Transepidermal route:
Drugs can penetrate the horny layer either by intracellular or intercellular pathway (Figure 7 and 8). Both polar and non-polar substances diffuse via intracellular and intercellular routes by different mechanisms. The polar molecules mainly diffuse through the polar pathway consisting of “bound water” within the hydrated stratum corneum whereas the non-polar molecules dissolve and diffuse

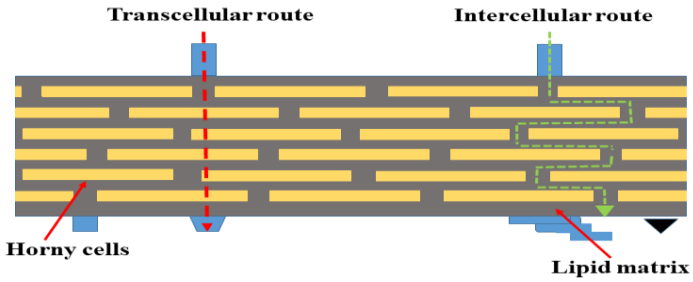

Figure: 3. Presentation of schematic image of transepidermal route

through the non-aqueous lipid matrix of the stratum corneum. The value of the partition coefficient (logK) determined the principal pathway of the penetrant. Hydrophilic drugs can easily penetrate into the intracellular domains through stratum corneum via the intercellular route. Most molecules past through the stratum corneum by both routes [14].

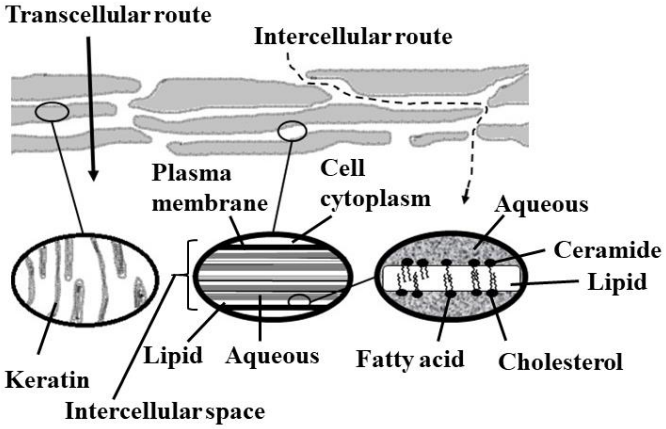

Figure: 4. Intercellular entry of drug through the human skin

3.2 Transfollicular route (Shunt pathway):
In transfollicular route sweat glands, hair follicles associated with sebaceous glands help in the transport of drugs.Although these routes offer high permeability, they are considered to be of minor importance because of their relatively small area, approximately 0.1% area of the total skin. Ions like large polar molecules can penetrate through stratum corneum [14].

4. Skin act as a barrier:
The top layer of the skin act as most important barrier in case of transdermal drug delivery. The tight construction of skin is due to overlying of individual cells. This structure prevent bacteria from entry and maintain water balance of the skin [10]. Water percentage in stratum corneum is less in comparison to other components of the skin. Keratinized dead cells are most important components of this layer [15]. Lipids are secreted from the base layer of the skin to the top. These lipid molecules together connectively form a concrete layer which act as a mortar between the bricks of a wall.

5. Transdermal permeation:
Passive diffusion through skin expressed as transdermal permeation [16]. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network [17]. The release of drug from skin surface to the blood circulation system occur in a multistep process are described below
(1) It is release on the membrane (2) Then the drug release from the formulation (3) It is absorb through stratum corneum and penetrate through viable epidermis (4) Through capillary network drug take entry to the papillary layer. (5) Effect on the target organ. (6) Take entry into the skin's outermost layer stratum corneum (7) Diffusion through the stratum corneum.
Properties that influence transdermal delivery:
1. Medicament release from the vehicle. 2. Drug Penetrate through the skin barrier.
3. Activation of the pharmacological response [18].

6 Advantages of transdermal drug delivery: [16,19,18,20,21,22]

 Transdermal drug delivery overcome the problem of pitfalls of enzymatic and pH associated deactivation related to gastrointestinal absorption.

 Avoidance of first pass metabolism.

 Lesser peak in plasma levels decrease the risk of side effects. So the plasma with lesser peak is appropriate for transdermal drug delivery.

 As a substitute for oral route.

 The patch also permit constant dosing rather than the peaks and valley in medication level associated with orally administered medication.

 In case of emergency drugs from the transdermal patches spread rapidly and in case of side effects it is removed easily.

 As it is not pass through gastrointestinal tract we can avoid gastro intestinal incompatibility.

 Drugs in transdermal patches once applied it will last for one week. So patient have an adherence for this therapy.

 Minimizing undesirable side effects.

 Provide utilization of drug with short biological half lives, narrow therapeutic window.

 Avoiding in drug fluctuation drug levels.

 Inter and intra patient variation.

Termination of therapy is easy at any point of time.

 Provide suitability for self administration.

 They are non invasive, avoiding the inconvenience of parentral therapy.

 Drugs having short half life choose for the therapeutic delivery system and its controlled release.

 Patients those who have nausea or unconsciousness find great advantages in transdermal patches.

 Substances that are broken down by stomach are not easily absorbed by the gut and liver, deliver by transdermal patches.

 Transdermal patches are cost effective.

7. Disadvantages of transdermal drug delivery: [19,20,22]]

 Transdermal drug delivery system cannot deliver ionic drugs.

 It cannot achieve high drug levels in blood.

 It cannot develop for drugs of large molecular size.

 It cannot deliver drugs in a pulsatile fashion.

 It cannot develop if drug or formulation causes irritation to skin.

 Possibility of local irritation at site of application.

 May cause allergic reaction.

Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's impermeability.

 Long time adherence is difficult

8. Skin permeability increases by the following techniques:

Passive/chemical or active/physical methodologies are two methods used to modify the barrier properties of the stratum corneum. In order to modify the stratum corneum structure passive methods influence drug and vehicle interaction and optimization [23,24,25]. Passive methods like chemical enhancers and emulsions are incorporated into transdermal patches [26]. The main drawback of passive methods is negative influence on delay drug release like insulin. Chemical penetration enhancers is facilitate drug permeation across the skin by partitioning into the stratum corneum [27,28]. Penetration enhancers have several mechanisms of action such as: increasing the fluidity of the stratum corneum lipid bilayers, interaction with intercellular proteins, disruption or extraction of intercellular lipids, increase of the drug's thermodynamic activity and increase in stratum corneum hydration [27,28,29]. In case of most of the penetration enhancers, based on the structure they are divided into several groups [30,28]. chemical penetration enhancers. Most of the enhancers have mixed modes and it is very difficult to classify them according to their characteristic. Alcohols, sulphoxides, azone, pyrrolidones, essential oil, terpenes and terpenoids,fatty acids, water and urea are examples of penetration enhancers[28,29]. Skin irritation is the major problem arises due to side effects of penetration enhancers [30,29]. New variants of semisolid like proniosomes and microemulsion gels used in transdermal drug delivery [31]. To enhance the drug permeation through the skin barrier penetration

enhancers like Proniosomes used in transdermal drug delivery [31,32]. Upon hydration proniosomesare converted into niosomes which are capable of diffusing across the stratum corneum and then adhere to the cell surface which causes a high thermodynamic activity gradient of the drug at the vesicle/stratum corneum surface, thus acting as the driving force for the penetration of lipophilic drugs across the skin (Figure 6) [31,32]. The use of penetration enhancers are limited due to poor efficacy and safety. Due to slow skin disruption it is transport across the skin in low and variable rate [32,33]. Local inflammation, erythema, swelling and dermatitis [33].The active methods for skin permeabilisation include ultrasound, electrically assisted methods (electroporation and iontophoresis), velocity based devices *(*powder injection, jet injectors), thermal approaches (lasers and radio-frequency heating) and mechanical methodologies such as microneedles (MN) and tape stripping [34,35-38]. With the help of these methodologies a large class of drugs can be delivered into the skin. The active methods lead in the disruption of stratum corneum by using external energy as driving force for drug transport across the skin [35,36]. Wide range of drugs deliver across the skin by this methods.This in turn will significantly enhance the value of the transdermal delivery market and will be increasingly important over the coming years as the number of new drugs of biological origin continues to increase. Some of these active methodologies will be described in detail below.

9.1. Ultrasound Devices:

In the field of physics, chemistry, biology and engineering ultrasound can be used in a wide range of frequencies [34,37]. Ultrasound, sonophoresis, or phonophoresis can be defined as the transport of drugs across the skin by application of ultrasound perturbation at frequencies of 20 kHz–16 MHz which has a sufficient intensity to reduce the resistance of skin [34,39]. Various different categories and classes of drugs can take entry through the skin by the use of ultrasound devices . Hydrophillic and large molecular weight drugs are permeable through the skin by ultrasound devices [40].The proposed mechanisms by which ultrasound effects tissues and cells it include thermal effects and cavitation effects caused by collapse and acoustic streaming which can be explained as oscillation of cavitation bubbles in the ultrasound field [39]. When the skin absorb ultrasound waves with greater frequency than sound waves automatically its temperature increase [37]. Transdermal drug delivery system can be increased by ultrasound system [37]. In 1950 Fellinger and Schmidt both scientist reported that polyarthritis can be treated by hydrocortisone ointment combination with sonophoresis [41-43]. Before the commercial acceptance of the devices many challenges we have to overcome.Some of these challenges include: availability of easy-to-use devices; the determination of the duration of treatment required; gaining a full understanding of how the technology functions; broadening of the range of drugs that can be delivered and evaluation of the safety profiles of the devices [39,40,44,45].

9.2. Electrical Techniques:

9.2.1. Electroporation:

Iontophoresis and electroporation are two major means of electrically-facilitated transdermal drug delivery [34,46]. High intensities of electric pulses in electroporation result in the formation of aqueous pores in the lipid bilayers of the stratum corneum and allow drugs to diffuse across the skin [39, 47-49]. Neumann and his collaborators in 1982 describes the above technique [49]. Fentanyl, timolol, orcalcein, to high molecular weight drugs such as LHRH, calcitonin, heparin or FITC–dextran with molecular weights up to 40 kD transport across the skin on the application of high voltage pulses (50–500 V) for short times of only one second [50,51,52,53,54-57]. However, the main drawbacks are the lack of quantitative delivery, cell death with high fields and potential damage to labile drugs, e.g., those of protein origin [47,58].

9.2.2. Iontophoresis:

Electrostatic effects can make ionic drugs pass through the skin across the potential gradient [39,59,53,60-63]. With the help of electroosmosis uncharged particles can also cross the transdermal barrier [62].Several factors affect iontophoretic TDD, including pH of the donor solution, electrode type, buffer concentration, current strength and the type of current employed [59,61,64,65]. For successful iontophoretic delivery across the skin molecular size of the drug is also an important factor. The smaller size hydrophilic ions can also cross the skin in comparison to larger size ions [64-66]. The transport of compounds decreased with increase in molecular weight (chloride > amino acid > nucleotide > tripeptide > insulin) [66,64,67-70]. In a limited supply of current 1 mA there is a linear relationship between the current and drug flux across the skin [64]. 3 min is the maximum time consider in order to prevent local skin irritation or burns. The maximum physiologically acceptable iontophoretic current is 0.5 mA/cm2 [71]. Current can apply to increase the flux rate but it should not irritate the skin [72]. Due to the polarization effect on the skin drug current can decrease the drugs flux [61].In order to overcome this problem, pulsed current has been used [73]. A few studies has been carried out in comparison to current iontophoresis *vs.* continuous direct current

iontophoresis. Recently, Kotzki *et al*. 2015 showed that pulsed iontophoresis of treprostinil significantly enhanced cutaneous blood flow compared with continuous iontophoresis [72]. The most common electrodes that are used in iontophoresis are aluminium foil, platinum and silver/silver chloride electrodes [64]. The most used electrode is the Ag/AgCl which changes in pH. The electrode materials used for iontophoretic delivery is harmless to the body and can applied closely to the body surface [65]. Molecules of molecular weight less than 12,000 Da may be successfully delivered across skin via iontophoresis [71]. In order to deliver molecules greater than 12,000 Da, an alternate means of overcoming the barrier properties of the stratum corneum must be sought. However, it was found that a small protein, cytochrome *c* (12.4 kDa) was delivered non-invasively across intact skin [74,75]. Afterwards, ribonuclease A, with isoelectric point of 8.64 (13.6 kDa), was successfully delivered across porcine and human skin [76,77]. More recently, it was shown that transdermal iontophoresis was also able to deliver biologically active human basic fibroblast growth factor (hbFGF; 17.4 kDa) in therapeutically relevant amounts corresponding to those used in clinical trials and animal studies [77,78]. Iontophoresis can be easily applied in diagonostic cystic fibrosis and in monitoring blood glucose levels [79,80]. The applications of iontophoresis can be classified into therapeutic and diagnostic applications. No mechanical penetration or disruption of the skin are the main advantages of iontophoresis [81,82].

9.3. Velocity Based Devices:

Using power source liquid or powder jet injections can inject drug using a power source with a velocity range between 100 to 200 m/s [83]. In 1930s, Arnold Sutermesiter discover the concept of jet injectors [27]. Single-dose jet injectors (disposable cartridge jet injectors) and multi-use-nozzle jet injectors (MUNJIs) are two types of liquid jet injectors use in drug delivery [83]. More than 50 years Jet injections can be used for parenteral delivery of vaccines, as well as small molecules, such as anesthetics and antibiotics [27]. A jet injector is a needle free device capable of delivering electronically controlled doses of medication which result in improved consistency of delivery and reduced pain for the patient [35,84]. In comparison between liquid-jet injectors (50 to 360 μm) and standard hypodermic needle (810 μm for a 21G needle) the orifice of the nozzle is smaller than the later [59,85,86]. Changing the jet velocity and orifice diameter, jet can deliver drug in three different layer {intradermal (i.d.), subcutaneous (s.c.) or intramuscular (i.m.)} [59]. To avoid accidental needle stick injuries and safe disposal of needle, needle free devices are used [59]. In cross contamination intestinal liquid from the skin may contaminate the nozzle [87]. Powder jet injectors have an advantage over liquid jet injectors as it deliver drug across the skin by avoiding the use of cold storage which minimizes the cost of drug delivery [59,88]. In spite of many advantages like bioavailability for a number of drugs pain and bruising are some disadvantages of jet injectors [83]. The basic design of solid jet injectors consists of compressed gas as the power source, drug loaded compartment containing solid drug formulation, and a nozzle to direct the flow of particles towards the skin [89]. When compressed gas expands it allow drug powder to move through a nozzle into the skin. Then powder particles create micronsized holes and deposit in the stratum corneum or viable epidermis.

9.4. Thermal Approaches (Lasers and Radio-Frequency Heating):

In thermal ablation stratum corneum selectively depleted without damaging other tissues. So drug can be easily deliver through the skin by heating the skin surface [36,90]. Laser, radiofrequency, electrical heating are some methods of thermal ablation [91,36,92]. The short time thermal exposure can disrupt the stratum corneum but not the underlined epidermis. The temperature of the epidermis is not high enough but the temperature of the stratum corneum is high enough [93].

9.5. Mechanical Approaches to Mediate Skin Permeation:

Macromolecular compounds can be injected through needles though risk of needle-stick injuries can be overcome on use of hypodermic needles [94,95]. Some innovative methodologies have been explored to overcome these issues and include the use of micro needle arrays and tape stripping [95,96].

10. CONCLUSION:

So transdermal drug delivery have wide application in the field of medicine. In the prevention and diagnosis of disease the modern technology in transdermal drug delivery is necessary. To this end, this review has charted the development of numerous novel TDD methodologies, highlighting the advantages and disadvantages of each approach.

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