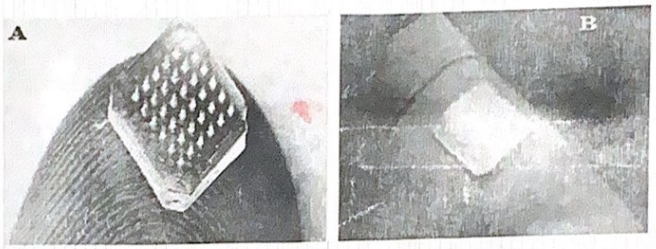
كلمة (Trans) يعني عابر يعبر الجلد ويوصل الـ Blood عشان يوصل الدماغ

Transdermal Formulations

بالصيدلية في منتجين فقط:

1) nitroglycerin
2) nicotin → للتوقف عن التدخين



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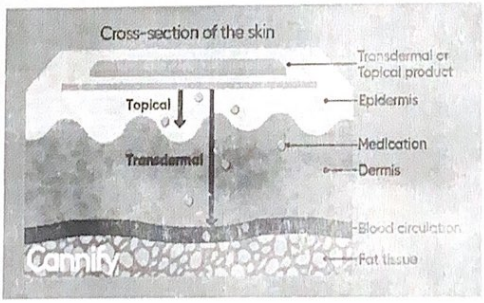
Introduction:

- Transdermal is a route of administration wherein active ingredients are delivered across the skin for systemic distribution.



- **Factors affecting transdermal bioavailability of the drug**
  - (A) Physicochemical factors → for drug
  - (B) Biological factors → for skin

2

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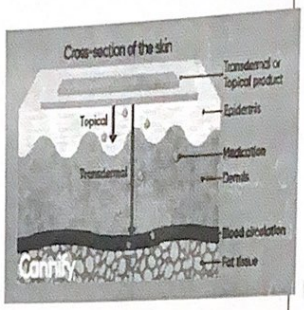
Introduction
Factors affecting transdermal bioavailability

Physicochemical factors:

- **Skin hydration:** In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectant is done in transdermal delivery.
- **Temperature and pH:** The permeation of drug increase ten folds with temperature variation.
- Weak acids and weak bases dissociate depending on the pH and pKa or pKb values.
- The proportion of unionized drug determines the drug concentration in skin.



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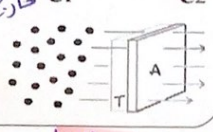
Introduction
Factors affecting transdermal bioavailability

Physicochemical factors:

- **Diffusion coefficient:** Penetration of drug depends on diffusion coefficient of drug. At a constant temperature, the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.
- **Drug concentration:** The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.
- **Partition coefficient** The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.
- **Molecular size and shape:** Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

$$dQ/dt = -DA(C_2 - C_1)/h$$



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Introduction
Factors affecting transdermal bioavailability

Biological factors:

A. Skin condition :Acids and alkalis, many solvents like chloroform, methanol damage the skin cells and promote penetration.

Diseased state of patient alters the skin conditions. The intact skin is better barrier

but the above mentioned conditions affect penetration.

B. Skin age: The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factor affecting penetration of drug in TDDS.

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Introduction
Factors affecting transdermal bioavailability

C. Blood flow: Changes in peripheral circulation can affect transdermal absorption. Regional skin sites Thickness of skin, nature of stratum corneum and density of appendages vary site to site.

D. Skin metabolism: Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin

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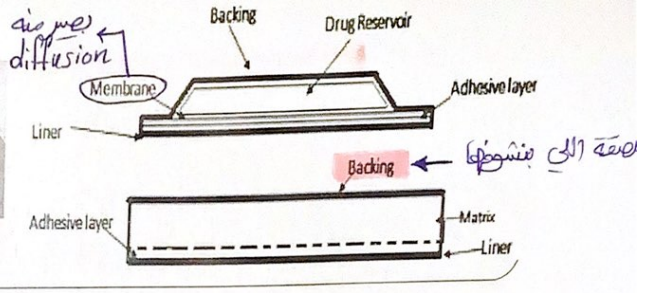
Transdermal Drug Delivery Systems (TDDS)
Transdermal Patches

- A transdermal patch is defined as adhesive medicated patch that is placed on to above skin to deliver an exact dose of drug through skin into the bloodstream with a predetermined rate of release to reach in the body.



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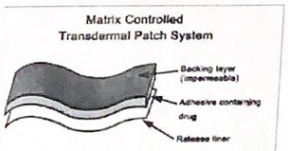
Components of Transdermal Patch

- **Backing Liner**- The film protects the patch from the outer environment. It protects the patch during storage. The liner should be removed before its use.
- **Adhesive**- It serves to adhere the components of the patch together along with adhering the patch to the skin. E.g.- Acrylic, polyisobutylene (PIB), and silicone are the adhesives have many pharmaceutical applications.
- **Drug reservoir** -Drug solution is in direct contact with release liner.
- **Membrane**- It controls the release of the drug from the reservoir and multi-layer patches.
- **Release Liner –**
- it allows drug release to skin.



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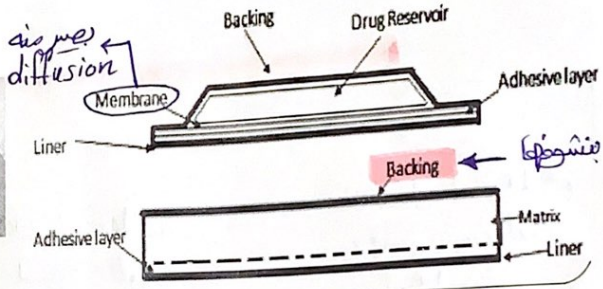

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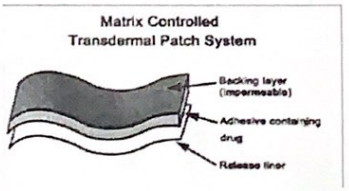

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Polymers used in TDDS

These polymers control the release of the drug from the drug reservoir:

A. Natural polymers: e.g. Shellac, gelatin, waxes, gums, starch

B. Synthetic polymers: e.g. Polyvinyl alcohol, polyethylene, polyamide, polypropylene, polyurea, polymethylmethacrylate

ومُمكن يكون عندي "Combination" (natural + synthetic) للوصول لـ release معين

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سلايد الحفظ

Table 1. Significant properties of TDDS

Properties	Comments
Shelf life	Up to 2 years
Patch size	< 40 cm^2 (مربع صغير)
Dose frequency	Once a daily to once a week (سعرها غالي)
Aesthetic appeal (من الناحية الجمالية)	Clear, tan or white color
Packaging (يكون ممتاز جدًا)	Easy removal of release liner and minimum number of steps required to apply
Skin reaction	Non irritating and non-sensitizing
Release (لازم يكون ثابت مش يطلع وينزل)	Consistent pharmacokinetic and pharmacodynamic profiles
Dose	Should be low
Half life (h) (تعتمد على metabolism of the drug)	10 or less
Molecular weight	< 400
Skin reaction	Non irritating and non sensitizer
Oral bioavailability	Low
Therapeutic index	Low

controlled release والـ release على فترات طويلة فما بتنفع التكرار.

لأنها بتظل ٢٤ ساعة أو أسبوع مش لازم تعمل أي تحسس ولو عملت بنشيلها.

الجرعة تكون صغيرة لكن بطء كمية كبيرة عشان تكفي ٢٤ ساعة (لما يصير الـ dose تكون كبيرة) لأنه مثلاً النيكوتين سام في لصقات النيكوتين

كلما كان الحجم كبير بيكون مروره أصعب

الأدوية اللي بتاخذ بالفم تروح عالـ liver وبتحطم حوالي 60% منه لهيك لجأت لـ system آخر

بالـ Toxicity السُمية

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Transdermal Patches -ADVANTAGES

a) Hepatic first pass metabolism, salivary metabolism and intestinal metabolism are avoided.

b) Ease of usage makes it possible for patients to self-administer these systems.

c) In case of an emergency, removing the patch at any point of time during therapy can instantly stop drug input

d) Since the composition of skin structurally and biologically is the same in almost all humans, (there is minimal inter and intra patient variation.)

e) Drugs showing gastrointestinal irritation and absorption can be suitably administered through skin.

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Transdermal Patches- Advantages

f) Due to reduced frequency of dosing there is better patient compliance.

g) Therapeutic failures associated with irregularities in dosing with conventional therapies can be avoided.

h. Adverse effects are minimized due to a steady and optimum blood concentration time profile.

i) Risks, pain and inconvenience associated with parenteral therapy are evaded. Release is more prolonged than oral sustained drug delivery systems.

j. Daily dose of drug required is lower than that with conventional therapies.

h. Drug release is such that there is a predictable and extended duration of activity

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Transdermal Patches- Disadvantages

- There is possibility of skin irritation due to the one or many of formulation components.
- It can be used only for chronic conditions where drug therapy is desired for a long period of time including hypertension, angina and diabetes.
- Lag time is variable and can vary from several hours to days for different drug candidates.
- Cutaneous metabolism will affect therapeutic performance of the system.
- Transdermal therapy is feasible for certain potent drugs only.
- Transdermal therapy is not feasible for ionic drugs.

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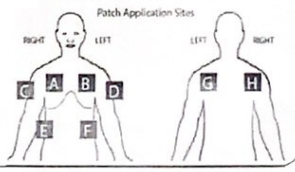
Useful considerations while applying transdermal patches

1. Before applying a new patch it should be made sure that the old patch is removed from the site
2. The part of the skin where the patch is to be applied should be properly cleaned
3. Patch should not be cut because cutting the patch destroys the drug delivery system
4. Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch
5. The patch should be applied accurately to the site of administration



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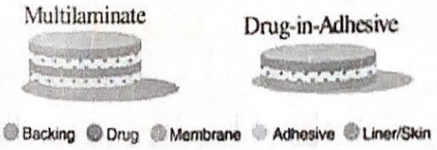
Types of transdermal patch

- **Single-layer Drug-in-Adhesive:** The adhesive layer of this system contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for releasing of the drug.
- **Multi-layer Drug-in-Adhesive:** The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different, that it adds another layer of drug-in-adhesive, usually separated by a membrane. This patch also has a temporary liner-layer and a permanent backing.



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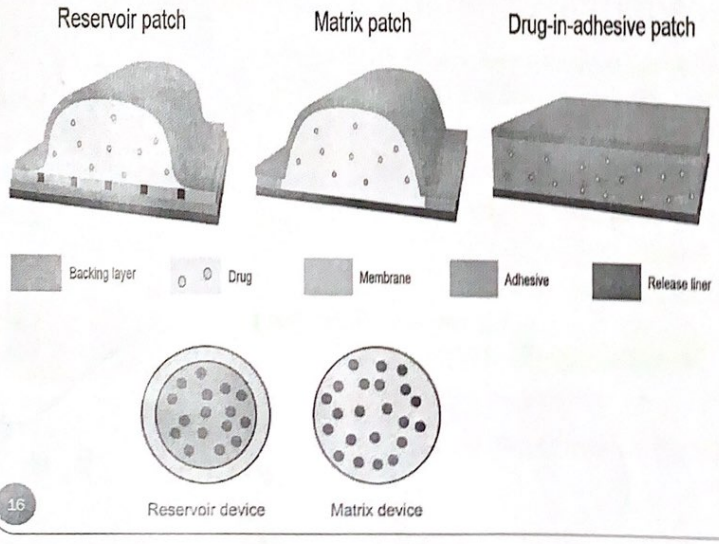
Types of transdermal patch



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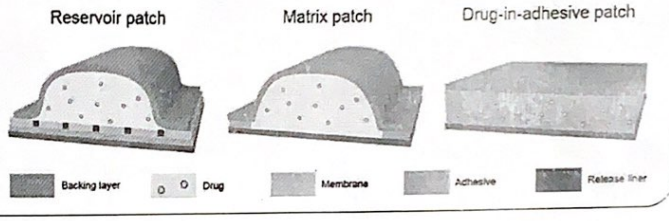
Types of transdermal patch

- **Reservoir:** In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be porous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix
- **Matrix:** The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it



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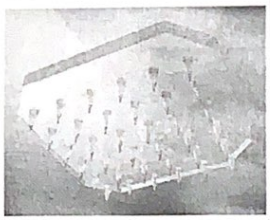
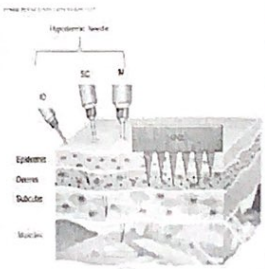
Transdermal Microneedles

- Microneedles can be defined as solid or hollow cannula with an approximate length of 50–900μm and an external diameter of not more than300μm.
- Microneedles can be fabricated within a patch for transdermal drug delivery.
- Patches containing microneedles have been used in the delivery of drugs, biopharmaceuticals, vaccines, etc.
- A quick response can be observed due to disruption of stratum corneum by microneedles





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Microneedle not painful

Blood و nerve ما بتوصل لهيك ما بتوجع

Supply

Stratum Cornea تتوزع

+ Epidermis + Dermis بداية

Transdermal Microneedles

- Microneedles have been designed to penetrate through the epidermis up to a depth of 70–200μm.
- Microneedles are thin and short and do not penetrate the dermis layer with its nerves; hence painless application is possible.
- Micro-needles are more capable of enhancing the transport of drug across the skin as compared with other transdermal delivery methods

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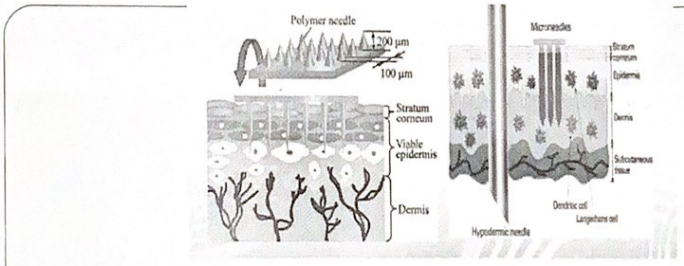

فارغين

والدواء بمرضهم

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Solid MN: الطبقة الخارجية بتضل موجود وتقطع الدواء

والـ Polymer تبعها رح تذوب بالجلد

Coated MN: الدواء خارج release ما needle الـ Coated

Dissolving M.N: كلها الـ needle رح تذوب بالجلد بعدين

المريض بطلعها

Microneedles- Advantages

Macromolecule — Protiens/Insulin

1. large molecules can be administered
2. painless **administration** of the active **pharmaceutical** ingredient
3. (first-pass metabolism) is avoided — in Liver
4. faster healing at injection site than with a hypo- dermic needle (مثل ابر فحص البنسلين)
5. no fear of needle
6. ease of administration
7. decreased microbial penetration as compared with a hypodermic needle, the microneedle punctures (only the epidermis) — not deep

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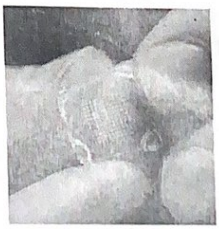
Microneedles- Advantages

8. specific skin area can be targeted for desired drug delivery
9. enhanced drug efficacy may result in dose reduction — ال dose لازم يكون قليل
10. rapid drug delivery can be achieved (by) coupling the microneedles with an electrically controlled micropump
11. the rate of drug delivery can be controlled more effectively by this system as compared with drug delivery via the stratum corneum

Stratum Corneum
طبقة عازلة ويصعب اختراقها
(الدواء يحتاج مدة أطول ليخترقها)
(microneedles) وهنا ال
مباشرة بتفوت على
(epidermis) ال



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note: always Injection parentral is most accurate.

Microneedles-Disadvantages

1. dosage accuracy may be less than with hypodermic needles
2. careful use of the device may be needed to avoid particles 'bouncing off' the skin surface; if the device is not held vertically, the dose may escape or can penetrate the skin to differing degrees,
3. The thickness of the stratum corneum and other skin layers varies between individuals and so penetration depth of particles could vary too
4. the external environment, like hydration of the skin, could affect delivery
5. repetitive injection may collapse the veins
6. the tip of the microneedle may break off and remain within the skin on removal of the patch
7. compressed dermal tissue can block hollow microneedles.

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Examples of TDDS

- *Transdermal scopolamine*

The first batch brought to market (for the treatment of motion sickness).

- *Transdermal nitroglycerin*

For the treatment of angina, congestive heart failure, etc

- *Transdermal to deliver female hormones*

For the treatment of menopausal symptoms and other results of oestrogen deficiency (hormone replacement therapy) → hormone supply

- As contraceptive: Such as ethinylestradiol and norelgestromin, one patch weekly for three weeks
- *Transdermal fentanyl*

Opioid analgesic patch for chronic pain such as that produced by cancer (72h).

- *Transdermal nicotine*
- Smoking cessation therapy
- Transdermal oxybutynin → البول الاارادي

For the treatment of bladder instability and incontinence

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