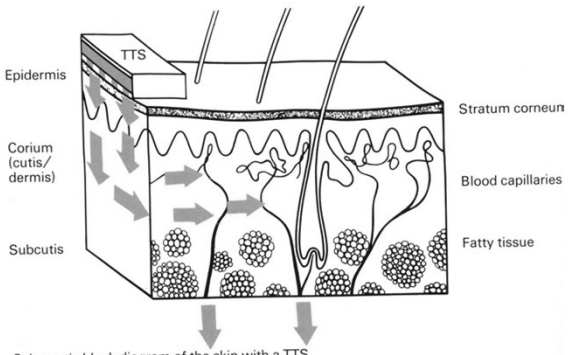
تقديم الدواء عبر الجلد
Transdermal Drug Delivery



Schematic block diagram of the skin with a TTS (transdermal therapeutic system) applied for systemic therapy

د. مصطفى عبد الإله بيش

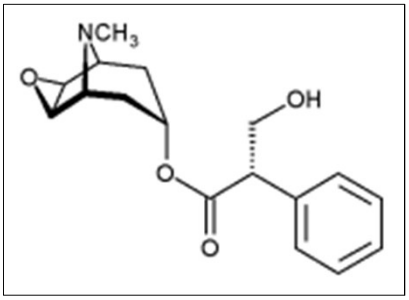
دكتوراه في التكنولوجيا الصيدلية

محتوى المقرر	
القسم النظري: 1- تكنولوجيا المستحضرات الجلدية 2- فكرة عامة عن بنية الجلد 3- امتصاص الدواء من خلال طبقات الجلد المختلفة 4- تعزيز إمتصاص الدواء عبر الجلد 5- تصنيف و مزايا المستحضرات نصف الصلبة 6- المواد الأولية الأساسية المستخدمة في تصنيع المستحضرات نصف الصلبة 7- آلية عمل المواد الفعالة على السطح في المستحضرات الجلدية 8- تركيب المراهم المحبة للماء و المحبة للزيت 9- تركيب الكريمات المحبة و الكارهة للماء 10- تكنولوجيا صناعة الهلامات المحبة والكارهة للماء 11- البوليميرات المستخدمة في عملية التهليم، العامل المصالب 12- دراسة انسيابية المستحضرات الجلدية 13- التصنيف الدستوري للتحاميل 14- أشكال تطبيق التحاميل 15- بنية المستقيم و العوامل المؤثرة على التوافر الحيوي 16- الأسس المستخدمة في صناعة التحاميل 17- طريقة تحضير التحاميل الشرجية و البولية والبويضات المهبلية 18- تكنولوجيا لمستحضرات الجلدية للعبور عبر الجلد. 19- الواقيات الشمسية أنواعها و آلية عملها و تركيبها و استخدامها	Theoretical section: - Skin products technology. - A general idea about the anatomical skin structure. - Drug absorption via the various layers of the skin. - Enhancement of drug absorption through the skin. - Semi-solid preparations - Raw material used in the manufacture of semi-solid preparations. - mechanism of action of surfactants contained in skin preparations. - Formulation development and ingredients of oleaginous and hydrophilic ointments bases. - Formulation considerations and ingredients of oil/water and water/oil creams. - Manufacturing technology of aqueous and oily gels. - Gelling agents and cross-linking agents. - rheology and flow behavior of the skin preparations. - Classification of suppositories - Applications of suppositories. - the structure of the rectum and the factors affecting drug bioavailability through the rectal route. - Suppositories bases. - The preparation methods of urethral, rectal and vaginal suppositories - Skin preparations technology and skin penetration. - Mechanism of action, formulation ingredients

تقديم الأدوية عبر الجلد

1. **تعريف: حامل يحتوي كمية من المواد الفعالة والذي عندما يطبق على سطح الجلد سيحرر محتواه من المادة الفعالة إلى الدوران الجهازي بمعدل مضبوط (Controlled rate),**
   - **أول لصاقة دواء عبر الجلد تم المصادقة عليها من قبل الـ FDI عام 1981,**
   - **كانت موجهة لمعالجة دوار وإقياء السفر (Scopolamine)**
   - **حالياً يوجد أكثر من 35 نوع من اللصاقات الجلدية و تحمل أكثر من 13 مادة فعالة**

- ***Scopolamine***
- Works as competitive antagonist of acetylcholine at the muscarinic receptor
- Product Name = Transderm Scop®
- Used for: **Motion Sickness**



تكنو 2- د. بيش 5

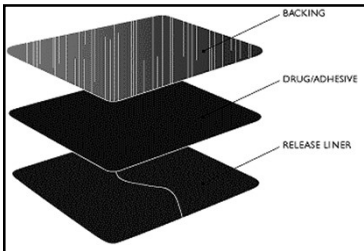
POTENTIAL BENEFITS OF TRANSDERMAL DRUG DELIVERY (ADVANTAGES)

- **Easy** to use.
- Avoid GIT **absorption problems** for drugs.
- Avoids FP **hepatic metabolism** of drugs.
- More improved and convenient patient compliance.
- Rapid **termination in case of toxicity** is possible.
- Self medication is possible.
- **Reduces frequency** of dosing.
- Maintains therapeutic level **for 1 to 7 days**.
- Controlled delivery resulting in more reliable and predictable blood levels.

تكنو 2- د. بيش 6

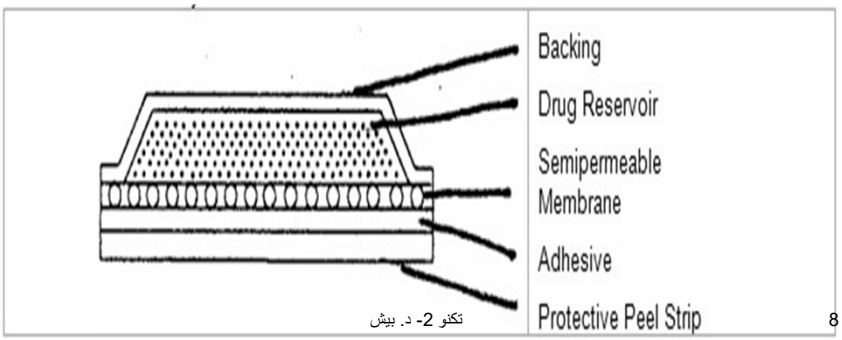
DISADVANTAGES

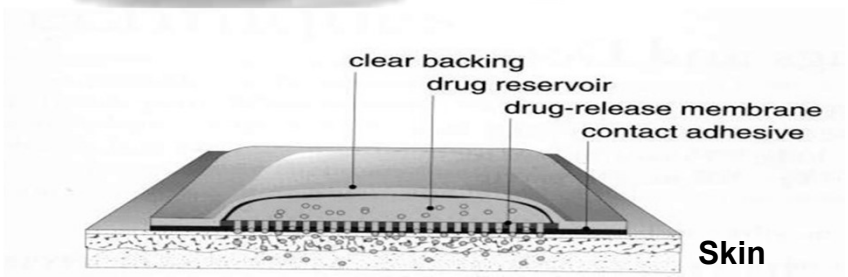
- Daily dose of **more than 10mg** is **not possible**.
- **Local irritation** is a major problem.
- Drug requiring **high blood levels are unsuitable**.
- Drug with **long half life** can not be formulated in TDDS.
- Uncomfortable to wear.
- May **not** be economical.
- Barrier **function changes** from person to person and within the same person.
- Heat, cold, sweating (perspiring) and showering prevent the **patch from sticking** to the surface of the skin for more than one day. A new patch has to be applied daily.



يتكون بشكل عام من عدة طبقات:

1- طبقة حماية خارجية للتغليف
2- طبقة المادة الفعالة
3- غشاء أو فلتر
4- شريط لاصق
5- شريط الأغلاق (ينزع قبل التطبيق)





أقسام اللصاقات الجلدية

تغليف
طبقة الدواء
الغشاء ضابط التحرر
اللاصق
طبقة عازلة تنزع قبل الاستخدام

الجلد

TDD Patches: A System of Components

- **Components must be chemically and physically compatible**
- **Drug formulation may or may not include excipients**
- **Backing: provides protection from external factors during application period**
- **Membrane: moderates rate of drug release**
- **Adhesive: maintains contact with patient's skin; incorporates drug and excipients in drug-in-adhesive TDD systems**
- **Liner: protects patch during storage; is removed prior to application**

Component/Composition

- **Matrix devices (Skin control systems)**

  Active agent in polymeric membrane, adhesive, solvent, penetration enhancer, backing,

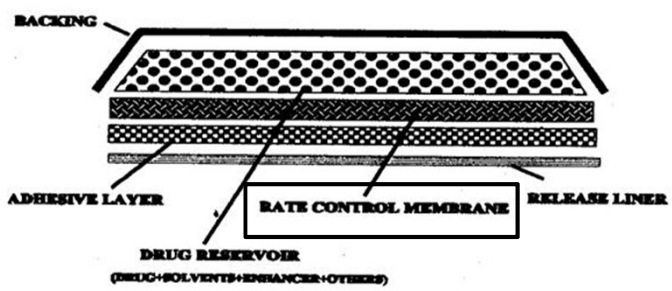
- **Reservoir devices (Membrane control systems)**

  Active agent, gelling agent or excipient, solvent, penetration enhancer, adhesive, **membrane**, backing, release liner

TDD Patch Construction

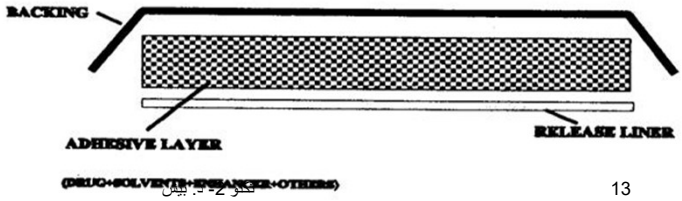
Reservoir
مستودع

I.



Matrix
قالب

II.



تكنو 2- د. بيش 13

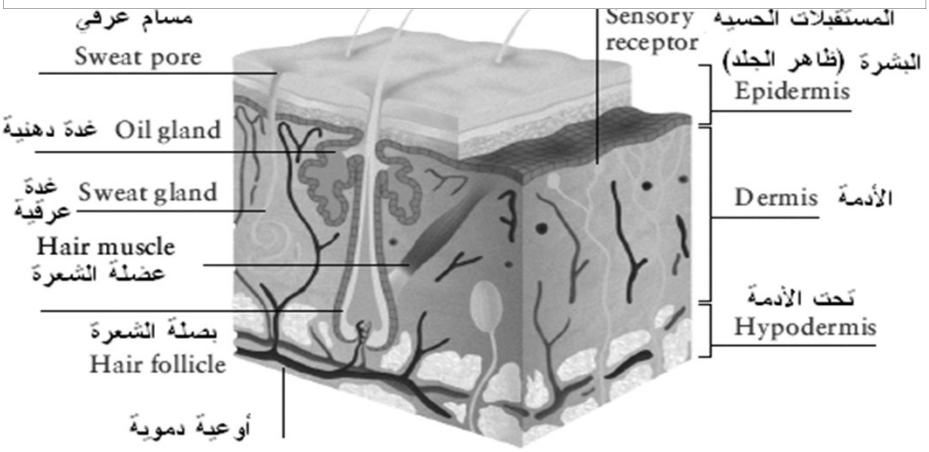
System-controlled drug delivery requires a rate-controlling element such as a polymeric membrane (Fig. 13). The membrane allows measured release of drug throughout the wearing period and provides more protection from potential drug overdose than skin-controlled delivery. Drug delivery with a system that incorporates a rate-controlling membrane produces less variability in drug input, yielding a more predictable and reproducible pharmacokinetic profile (75).

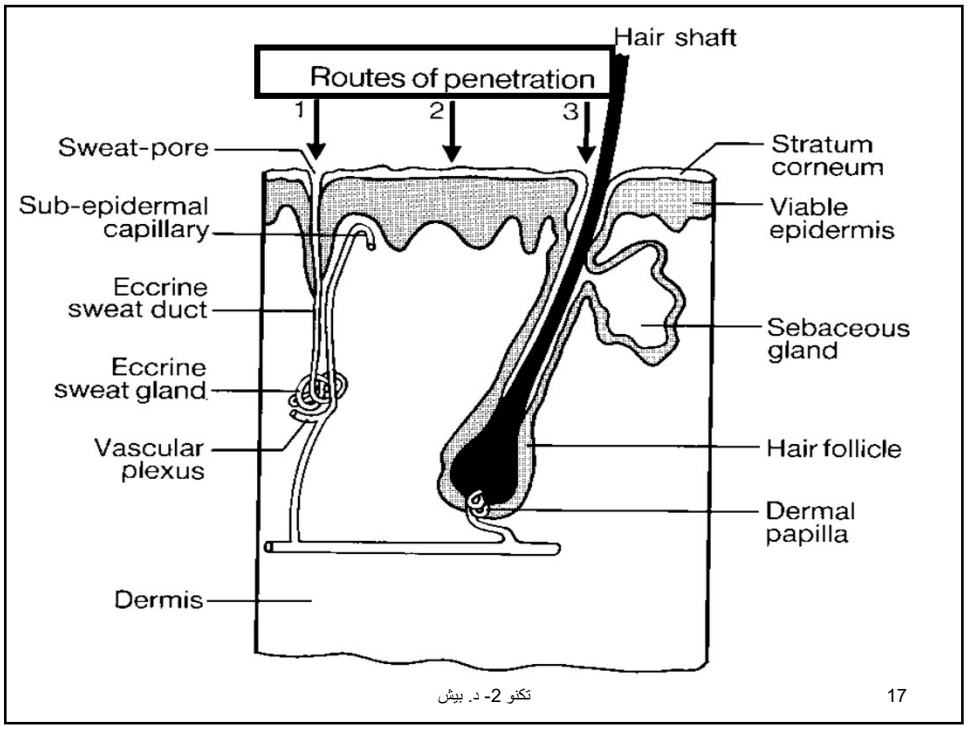
تكنو 2- د. بيش 14

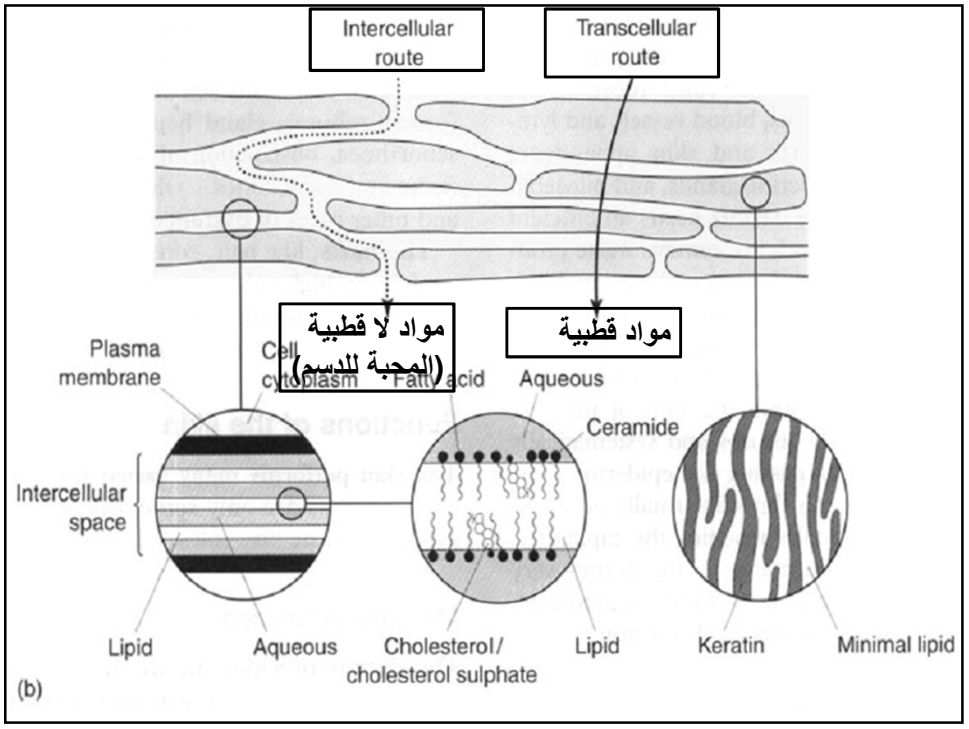
Skin-controlled drug delivery devices rely on the skin's barrier properties to control the rate of drug input to the body. These devices may include a matrix or multilaminate design to act as a carrier that maintains drug in contact with the surface of the skin. Drug diffuses through the skin at a rate dictated by the concentration of drug on the skin and by the permeability of the skin to the drug. Because rate control relies completely on the skin's diffusive properties, variations in skin permeability (e.g., at different sites) may have variable effects on the delivery rate of systems without built-in control mechanisms (75).

الجلد

Human skin contains **40-70 hair follicles**, **200 to 250** sweat glands on every **sq.cm. of skin area**.




Hair shaft
Routes of penetration
1
2
3
Sweat-pore
Sub-epidermal capillary
Eccrine sweat duct
Eccrine sweat gland
Vascular plexus
Dermis
Stratum corneum
Viable epidermis
Sebaceous gland
Hair follicle
Dermal papilla
تكنو 2- د. بيش
17


Intercellular route
Transcellular route
مواد لا قطبية (المحبة للدسم)
مواد قطبية
Plasma membrane
Cell cytoplasm
Fatty acid
Aqueous
Ceramide
Intercellular space
Lipid
Aqueous
Cholesterol / cholesterol sulphate
Lipid
Keratin
Minimal lipid
(b)

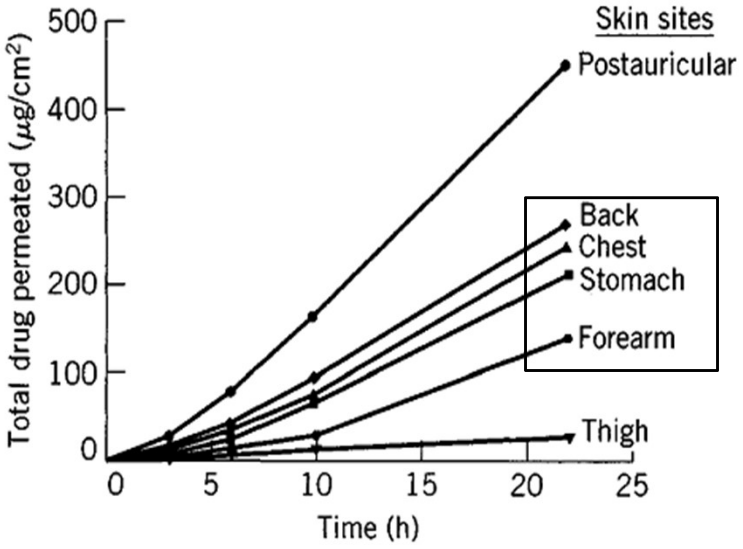


Figure 5. Variation in cumulative scopolamine flux as a function of skin site.

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Skin Metabolism

The metabolic activity of the skin can alter the delivery profile and pharmacologic effects of substances that undergo percutaneous absorption. A topically applied drug can be transformed into either active or inactive metabolites that are capable of different levels of toxicity than the parent compound (27). For example, epidermal keratinocytes have the potential to metabolize propranolol via a pathway that includes formation of an aldehyde intermediate (49). Changes in the pharmacologic or toxicologic profile that result from skin metabolism may have local as well as systemic effects.

أهم التفاعلات الاستقلابية في العضوية والأعضاء المسؤولة عنها

التفاعل العضو	أكسدة	إرجاع	إماهة	ألكلة	أستلة	انضمام غلوكوروني	انضمام سلفوني	انضمام غلوتاتيوني	انضمام للحمض الأميني	نزع كربوكسيل	نزع ألكيل
رئتين	++	+	+	+	+	-	-	-	-	-	-
كبد	+	+	+	+	+	++	+	+	+	-	-
مخاطية أمعاء	+	+	+	+	+	+	+	-	-	-	-
لمعة أمعاء	-	+	+	-	+	+	+	-	-	+	+
كليتين	-	-	-	-	-	-	-	+	+	-	-
بلازما	-	-	+	-	-	-	-	-	-	-	-
جلد	+	-	-	-	-	-	-	-	-	-	-

The need for permeation enhancers is determined by the nature of the drug intended for use in the transdermal delivery system. Highly skin-permeable drugs agents, such as nicotine, do not require a permeation enhancer. The transcutaneous flux of most hormones, however, is low, requiring the use of a permeation enhancer such as ethanol or triethanloamine. These solvents permeate the skin but without rate control or occlusion, their effectiveness is brief and limited. The use of certain types of permeation enhancers has been associated with skin irritation.

العوامل المؤثرة على سرعة النفوذية عبر الجلد

1- تركيز الدواء المطبق

2- المساحة المطبقة

3- الخواص الفيزيائية والكيميائية للمادة الفعالة

4- الوزن الجزيئي

5- ترطيب الجلد

6- مكان التطبيق

7- المدة الزمنية

مكونات ادوات التقديم عبر الجلد تتضمن:

1- بوليميرات حاملة (POLYMER MATRIX)

2- المادة الفعالة (THE DRUG)

3- محسنات النفوذية (PERMEATION ENHANCER)

4- سواغات أخرى

1-POLYMER MATRIX

Following criteria to be considered in selection a polymer:

- Molecular weight, physical of polymer must allow **diffusion of drug at desired rate**.
- Polymer must be **non-reactive, inert, non-toxic, easy to manufacture, inexpensive**.
- It should **not decompose on storage** of the device & not deteriorate when large amount of active ingredient is **in corporated into it**.

LIST OF POLYMERS USED

NATURAL POLYMERS:

Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Gums & Natural rubber

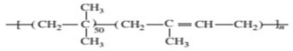
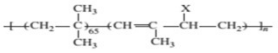
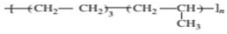
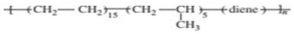
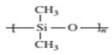
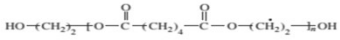
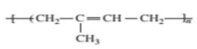
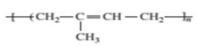
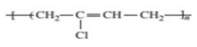
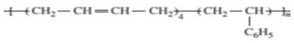
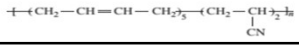
SYNTHETIC ELASTOMER POLYBUTADIENE:

Polysiloxane, Silicon rubber, Acrylonitryle, Butyl rubber, Styrene butadiene rubber.

SYNTHETIC POLYMER

Poly vinyl alcohol, Poly vinyl chloride, Polyethylene, Poly propylene, Poly urea, PVP, Polymethacrylate

Table 3 Chemical structures of common elastomers

Common name	Chemical name	Structure
Butyl rubber	Poly(isobutylene-isoprene)	
Halobutyl rubber[a]	Halogenated poly(isobutylene-isoprene)	
Ethylene-propylene rubber	Poly(ethylene-propylene)	
Ethylene-propylene-diene rubber	Poly(ethylene-propylene-diene)	
Silicone rubber	Polydimethylsiloxane	
Urethane rubber	Adipic acid-ethylene glycol polyester	
Fluoroelastomers	Polytetrafluorethylene	
Natural rubber	*cis*-(1.4-Polyisoprene)	
Polyisoprene rubber	*cis*-(1.4-Polyisoprene)	
Neoprene rubber	Polychloroprene	
Styrene-butadiene rubber	Poly(butadiene-styrene)	
Nitrile rubber	Poly(butadiene-acrylonitrile	

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POLYMER MEMBRANE PERMEATION CONTROLLED SYSTEM

- Rate controlling membrane **made up of ethylene vinyl acetate EVA copolymer**
- A thin layer of drug compatible, **hypoallergenic** adhesive polymer **e.g. Silicon or polyacrylet** adhesive may be applied to the external surface.
- **Rate of drug** release affect by **varying** the polymer composition, **permeability coefficient and thickness** of rate limiting membrane and adhesive.

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POLYMER MEMBRANE PERMEATION CONTROLLED SYSTEM

- **Accidental breakage** of the rate controlling membrane can result in **dose dumping** or a rapid release of the entire drug content.

E.g.

- Nitroglycerine releasing trans dermal system for once a day medication for **angina**

2- المواد الفعالة المفضلة للإيتاء عبر الجلد (Drug):

1- التي تتخرب ضمن جهاز الهضم

2- التي تتخرب بالمرور الكبدي الأول

3- المواد الفعالة القطبية

4- غير النفوذة عبر جهاز الهضم

5- ذات الأوزان الجزيئية الكبيرة (أقل من 1000 دالتون)

يجب ان تكون المادة الفعالة محبة للماء وللدسم معاً وذات درجة انصهار منخفضة (أقل من 200 م°)

Ideal properties of drug candidate

PARAMETER	PROPERTIES
Dose	Sh'd be low(< 20mg/day)
Half life	10 or less
Molecular weight	< 800
Skin permeability co- efficient	> 0.5 X 10^{-3} cm/ hr
Skin reaction	Non irritating & non sensitizing
Oral Bioavailability	low
Therapeutic index	low
Partition coefficient (Log P)	1-3

Partition coefficient

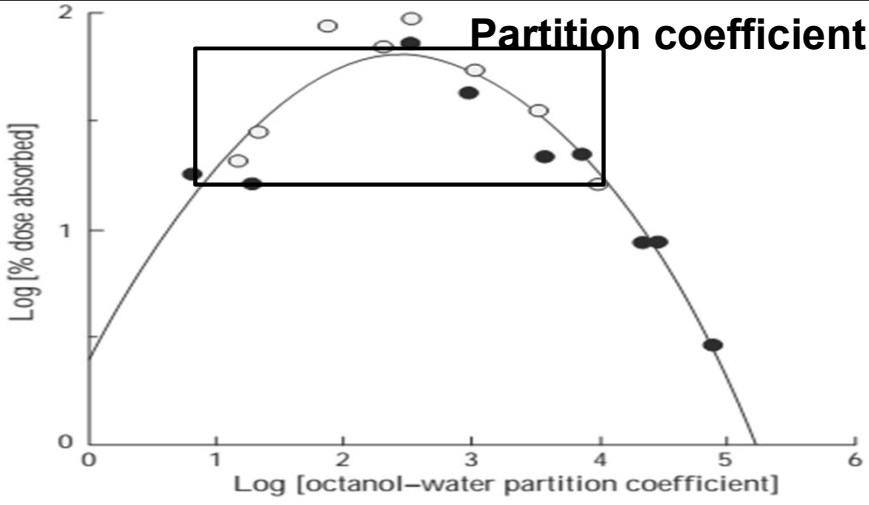


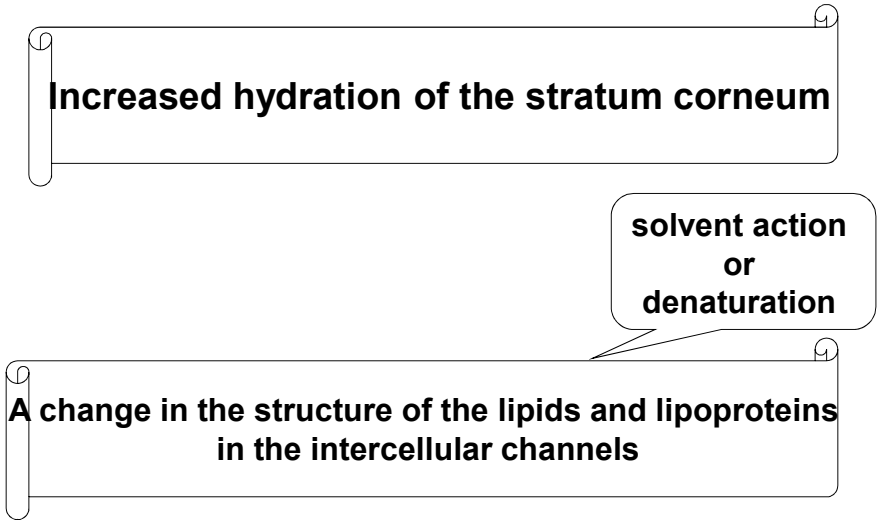
Fig. 1 Relationship between amount of drug absorbed though skin and compound octanol–water partition coefficient (increasing lipophilicity). ○: salicylates; ●: other non-steroidal anti-inflammatory agents. (Redrawn from Ref.[32].)

3- محسنات النفوذية (PERMEATION ENHANCER)

مواد تضاف لزيادة وتحسين نفوذية المواد الفعالة عبر الجلد :

A. محسنات نفوذية كيميائية: (Chemical Enhancers)

- **تعمل طريق التحريض العكوس أو تبديل الخواص الفيزيوكيميائية الطبيعية للطبقة المتقرنة لتقليل مقاومتها لنفوذ المواد الفعالة:**
  1. **زيادة ترطيب البشرة**
  2. **تغيير في بنية اللبيدات والبروتينات بين الخلايا باستخدام محلات**
- **أكثر من 275 مادة استخدمت لتحسين النفوذية عبر الجلد**



More than 275 chemical compounds have been cited in the literature as skin penetration enhancers; they include :

- **Acetone, Azone ,**
- **Dimethyl Acetamide , Dimethyl Formamide**
- **Dimethyl Sulfoxide (DMSO),**
- **Ethanol,**
- **Oleic Acid,**
- **Polyethylene Glycol, Propylene Glycol ,**
- **Sodium Lauryl Sulfate .**

Transdermal Controlled-Release Products and Devices

Drug	Trade Name	Type of Devices	Indication
Scopolamine	Transderm-Scop	Reservoir	Motion sickness
Nitroglycerine	Transderm-Nitro	Reservoir	Angina
	Nitro-Dur	Monolithic	
	Nitrodisc	Monolithic	
Estradiol	Estraderm	Reservoir and ethanol enhancer	Hormone treatment

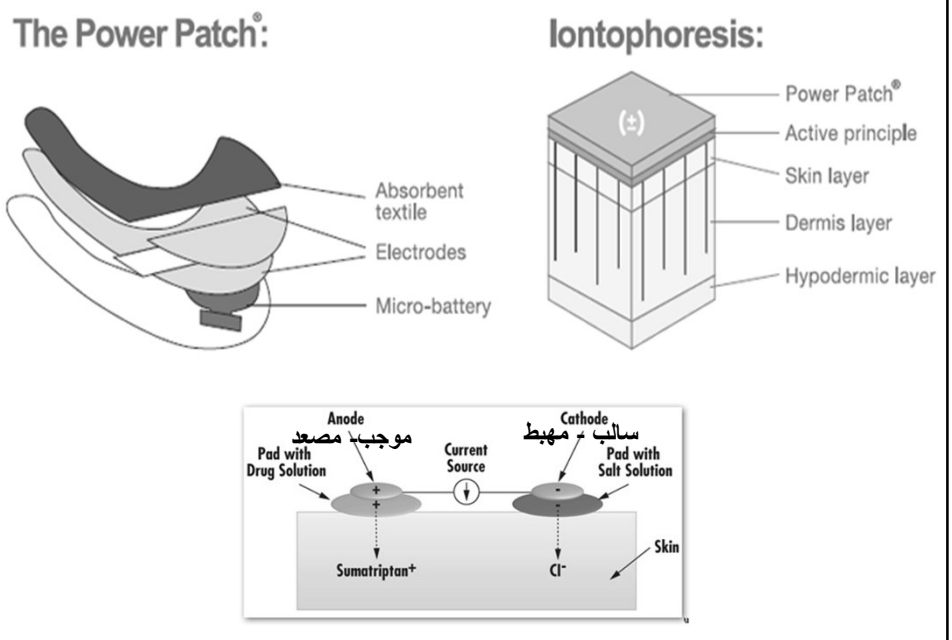
B. محسنات نفوذية فيزيائية: (Physical Methods)

1- ترحال أيوني (Iontophoresis)

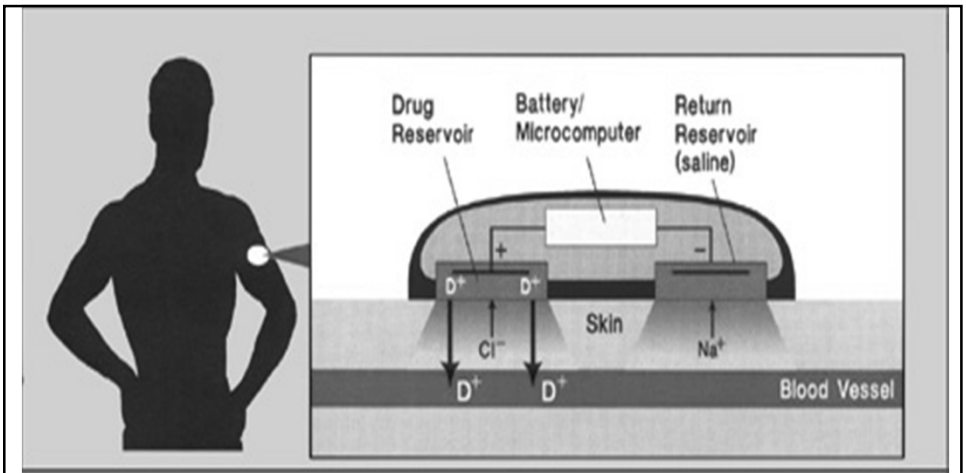
استخدام حقل كهربائي, دراسات لمواد مثل ليدوكائين- ديكسامستازون- امينو أسيد- ببتيدات- انسولين، لتقدم عبر الجلد.

- **حالياً جميع هذه المواد تقدم بالحقن, لأنها تستقلب بسرعة وضعيفة الامتصاص فموياً,**
- **أيضاً هي ضعيفة الامتصاص عبر الجلد لأنها ذات اوزان جزيئية كبيرة وشاردية وأيضاً غير نفوذة عبر الجلد**

تكنو 2- د. بيش 37



تكنو 2- د. بيش 38



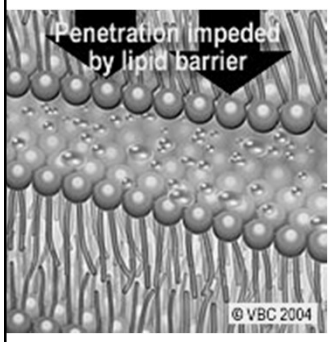
- Drug ions are delivered from the reservoir of similar polarity
- Drug flux increases with applied current
- Drug ions compete for current with extraneous ions

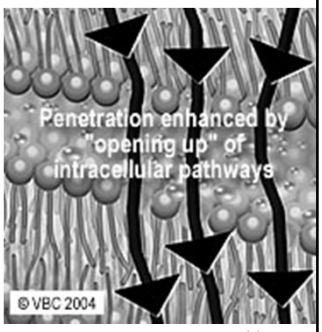
B. محسنات نفوذية فيزيائية: (Physical Methods)

2- ترحال بالموجات فوق الصوتية (Sonophoresis)

دراسات لتقديم الهيدروكورتيزون والليدوكائيين بشكل جل أو كريم أو لوسيون عبر الجلد باستخدام الموجات فوق الصوتية التي تقلل تماسك وصلابة الطبقة المتقرنة وبالتالي تعزيز الامتصاص عبرها

How it works



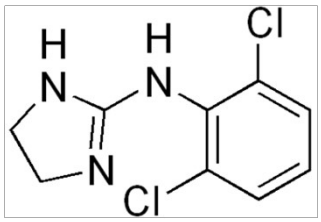


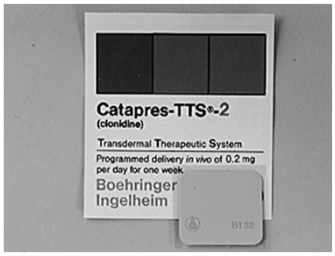
Iontophoresis vs Phonophoresis

- Both Techniques Deliver Chemicals To Biologic Tissues
- **Phonophoresis** Uses **Acoustic Energy (Ultrasound) To Drive Molecules** Into Tissues
- **Iontophoresis** Uses Electrical Current To Transport **Ions** Into Tissues

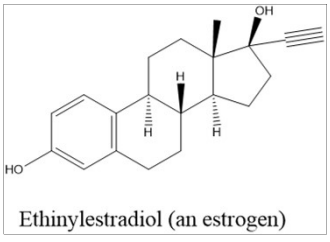
Products on the market, or in development include:

- **Clonidine**
- Works as an agonist of adrenaline at the presynaptic α_2 adrenergic
- Product name = Catapres-TTS®
- used to treat ***hypertension***

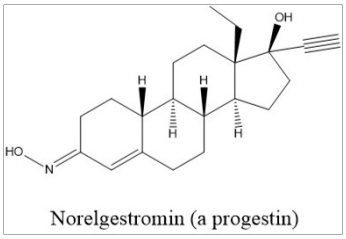




- **Ethinylestradiol** (EO) and norelgestromin (N)
- Product name = Ortho-Evra®
- Used for **Contraception**
- Type of patch = Drug-in-Adhesive
- Frequency of application = **weekly**

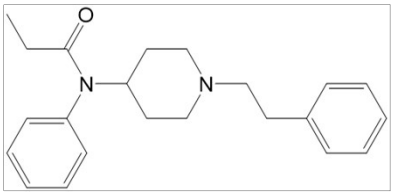


Ethinylestradiol (an estrogen)



Norelgestromin (a progestin)

- Fentanyl
  - Product Name = Duragesic®
  - Used for: **Analgesia**
  - Type of Patch = Drug-in-Adhesive
  - Frequency of Application = **Weekly**



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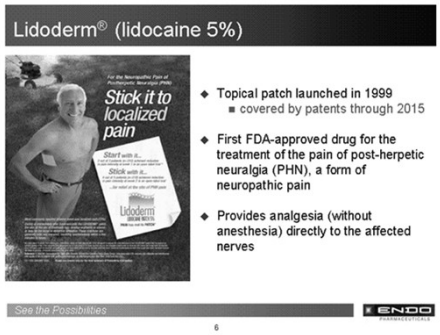
- **Lidocaine**
- Product Name = Lidoderm®
- Used for: analgesia of postherpetic neuralgia (PHN), a painful condition caused by the varicella zoster virus (herpes zoster = shingles)



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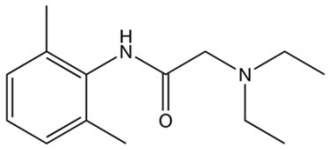
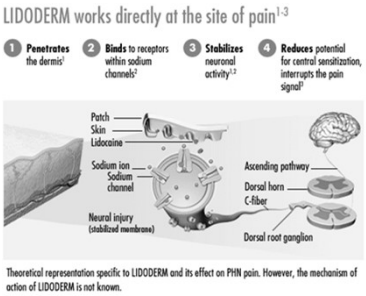
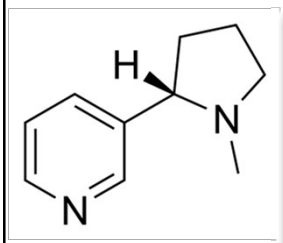
Lidoderm Patch

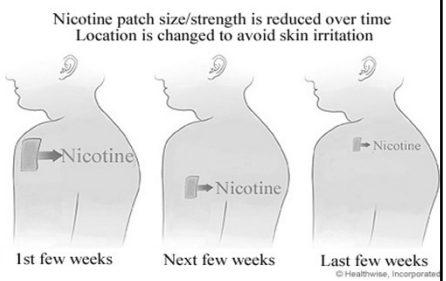




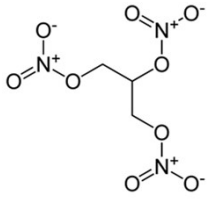
- Type of Patch = Reservoir
- Frequency of Application = Daily

- **Nicotine**
- Product name = Habitrol®, Nicoderm – CQ®, Nicotrol®, Prostep®
- Used for: **Smoking cessation**
- Frequency of administration = **Daily**





- **Nitroglycerin**
- Works by producing nitric oxide (NO), which then acts as a vasodilator
- Product Names = Nitro-Dur®, Transderm-Nitro®
- Used for: **Angina**
- Type of Patch = Nitro-Dur is Drug-in-adhesive
  Nitrodisc is reservoir
- Frequency of administration = **Daily**



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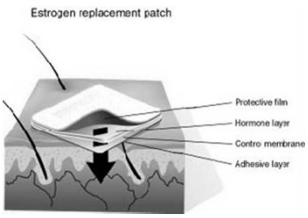
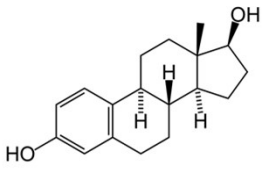
- **Estradiol**
- Product Name = Alora®, Climara®, Esclim®, Estraderm®, FemPatch®, Vivelle®, Vivelle-DOT®
- Used for: **Hormone replacement**
- Type of Patch: Drug-in-adhesive
- Frequency of application = **weekly**





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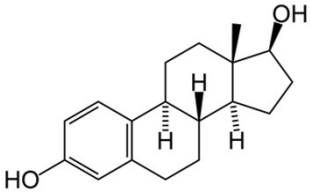
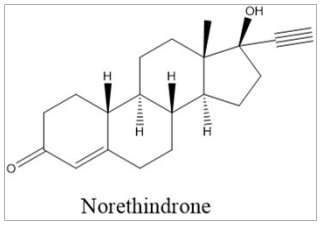
- Estradiol + Norethindrone
- Product name = CombiPatch®
- Used for: **Hormone Replacement**





Iontophoretic Patches

- Iontophoretic patches use a tiny electrical current to promote flow of the drug (usually charged) through the skin.