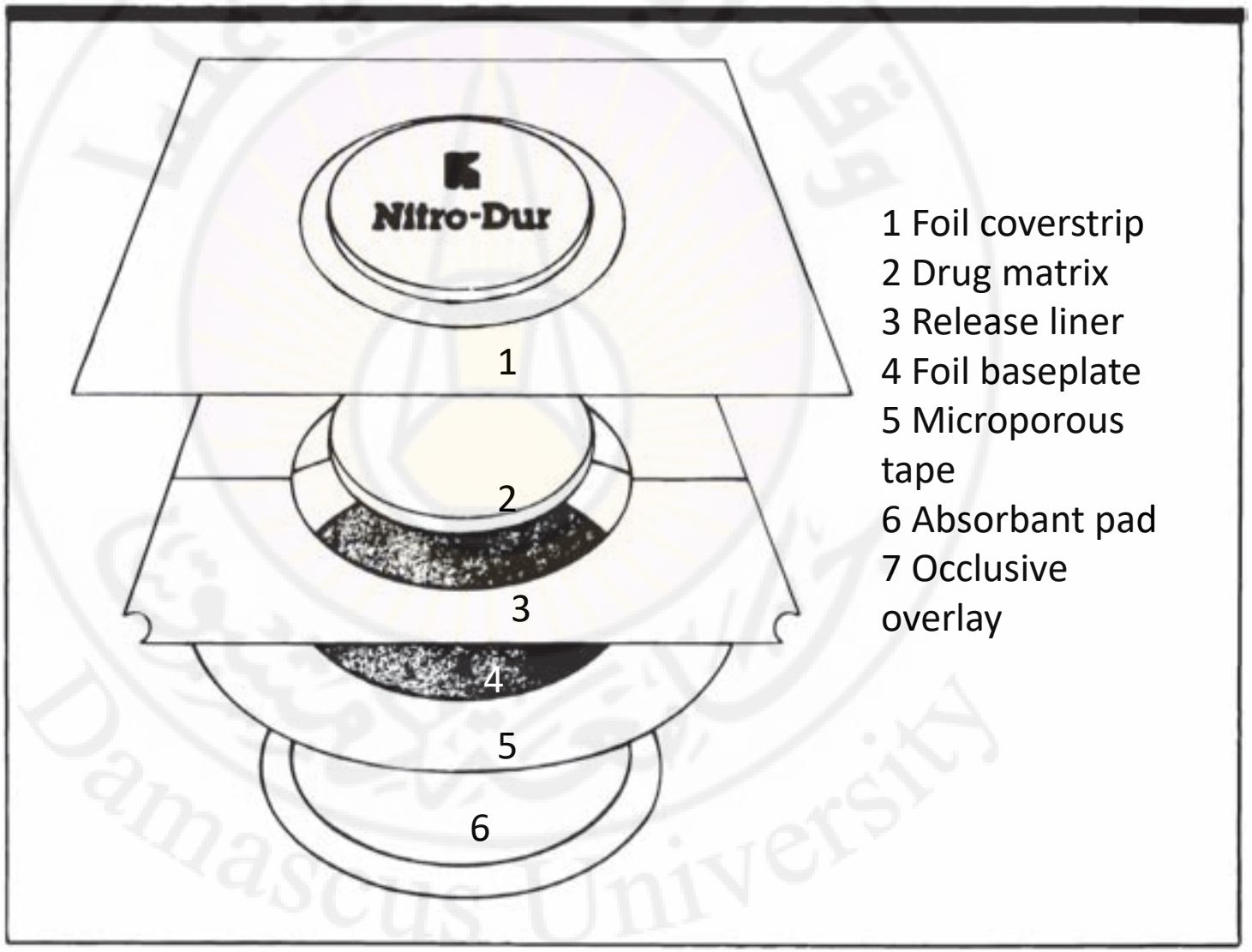
Transdermal Drug Delivery Systems (TDDSs)

TDDSs also often called **transdermal patches**

designed to support the passage of drug substances from the surface of the skin through its various layers and into the systemic circulation.

تصمم اللصاقات الجلدية لدعم مرور الدواء من سطح الجلد وعبر طبقاته المتعددة الى جهاز الدوران.



1 Foil coverstrip
2 Drug matrix
3 Release liner
4 Foil baseplate
5 Microporous tape
6 Absorbant pad
7 Occlusive overlay

Transdermal Scop



In 1965, Stoughton first conceived of the *percutaneous absorption of drug substances. The* first transdermal system, Transderm Scop (Baxter), was approved by the Food and Drug Administration (FDA) in 1979 for prevention of nausea and vomiting associated with travel, particularly at sea.

1965 اول من درس ايتاء الدواء عبر الجلد هو Stoughton

1979 وافقت منظمة الغذاء والدواء FDA على ايتاء السكوبولامين عن طريق الجلد بشكل لصاقات جلدية لعلاج الغثيان و الإقياء أثناء السفر بالبحر.




NDC 10019-553-01
NDC 10019-553-02
TRANSDERM SCŌP
scopolamine 1.5 mg
TRANSDERMAL THERAPEUTIC SYSTEM
Programmed delivery of approximately
1.0 mg over three days
℞ only
24 Patches
Multipack
TRANSDERM SCOP

الأفضل هو مرور الدواء عبر الجلد الى الدم من غير أن يتراكم في طبقات الأدمة .

For transdermal drug delivery, it is considered ideal for the drug to migrate through the skin to the underlying blood supply without buildup in the dermal layers.

ADVANTAGES AND DISADVANTAGES OF TDDSs

1. Avoiding gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
2. Oral rout is unsuitable, as with vomiting and diarrhea.

Damascus University

3. They avoid the *first-pass effect*
4. They are noninvasive, avoiding the inconvenience of parenteral therapy.
5. Improving compliance over other dosage forms requiring more frequent dose administration.

.

6. The activity of drugs having a short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
7. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
8. They are easily and rapidly identified in emergencies

(e.g., unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings

The disadvantages of TDDSs

1. Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
2. Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.

Skin layers طبقات الجلد

يتألف الجلد من
الطبقة المتقرنة، فوق الأدمة الحية، والأدمة التي تشكل طبقات حاجزية تتحكم بمرور العوامل الخارجية.

The skin is composed of the

stratum corneum (the outer layer), the living epidermis, and the dermis, which together provide the skin's barrier layers to penetration by external agents.

The stratum corneum is the major rate-limiting barrier to transdermal drug transport

الطبقة المتقرنة هو الحاجز المحدد لسرعة نقل الدواء عبر الجلد

تتصرف مثل غشاء صنعي نصف نفوذ وينفذ الدواء بالانتشار المنفعل.

تتألف الطبقة المتقرنة من 15-25 طبقة من الخلايا المتقرنة المسطحة وبسماكة 10 ميكروميتر.

The stratum corneum is the major rate-limiting barrier to transdermal drug transport

The stratum corneum, being keratinized tissue, behaves as a semipermeable artificial membrane, and drug molecules penetrate by passive diffusion. It is the major rate-limiting barrier to transdermal drug transport. Over most of the body, the stratum corneum has 15 to 25 layers of flattened corneocytes with an overall thickness of about 10 µm.

Substances with both aqueous and lipid solubility characteristics are good candidates

ان سرعة مرور الدواء عبر الطبقة المتقرنة يعتمد على

1- تركيز المادة الفعالة في السواغ

2- ذوبانية المادة الفعالة في الماء

3- معامل التوزع بين الماء والزيت

المادة التي تملك ذوبانية في الماء والدسم هي مرشح جيد للعبور عبر الطبقة المتقرنة وطبقة فوق الأدمة والأدمة.

Damascus University

Substances with both aqueous and lipid solubility characteristics are good candidates

- The rate of drug movement across this layer depends on
- 1- its concentration in the vehicle,
- 2- its aqueous solubility,
- 3-The oil–water partition coefficient between the stratum corneum and the vehicle. Substances with both aqueous and lipid solubility characteristics are good candidates for diffusion through the stratum corneum, epidermis, and dermis.

العوامل المؤثرة بامتصاص الدواء عبر الجلد

لايمكن ايتاء كل الأدوية عن طريق الجلد فمن العوامل التي تلعب دورا في الايتاء عبر الجلد:

تركيزالمادة الفعالة

الوزن الجزيئي

الذوبانية

معامل التوزع

ثابتة التشرد

طبيعةالسواغ

حالة الجلد

العوامل المؤثرة بامتصاص الدواء عبر الجلد

1-تركيز المادة الفعالة تزداد كمية الدواء الممتصة من خلال واحدة السطح خلال فاصل زمني مع ازدياد تركيز الدواء اللصاقة الجلدية.

1. Drug concentration is an important factor. Generally, the amount of drug percutaneously absorbed per unit of surface area per time interval increases with an increase in the concentration of the drug in the TDDS.

العوامل المؤثرة بامتصاص الدواء عبر الجلد

2- كلما زادت مساحة التطبيق (مساحة اللصاقة) زادت كمية الدواء الممتصة.

3- يجب أن يملك الدواء انجذابا فيزيوكيميائيا نحو الجلد أعلى منه تجاه السواغ فيغادر السواغ نحو الجلد.

2.The larger the area of application (the larger the TDDS), the more drug is absorbed.

3. The drug should have a greater physicochemical attraction to the skin than to the vehicle so that the drug will leave the vehicle in favor of the skin.

العوامل المؤثرة بامتصاص الدواء عبر الجلد

The ideal molecular weight 400 or less

4- الأدوية التي لها وزن جزيئي من 100-800 وذوبانية كافية في الدسم والماء يمكن أن تنفذ عبر الجلد

4. Drugs with molecular weights of 100 to 800 and adequate lipid and aqueous solubility can permeate skin..

العوامل المؤثرة بامتصاص الدواء عبر الجلد

5- اماهة الجلد بشكل عام الجلد المميه هو المفضل للامتصاص الجلدي.
اللصاقة الجلدية تعمل كحاجز تمنع مرور العرق مما يزيد اماهة الجلد.

5. Hydration of the skin generally favors percutaneous absorption. The TDDS acts as an occlusive moisture barrier through which sweat cannot pass, increasing skin hydration.

العوامل المؤثرة بامتصاص الدواء عبر الجلد

6- سماكة الطبقة المتقرنة كلما كانت الطبقة المتقرنة رقيقة كلما زاد الامتصاص عبر الجلد.

7- بشكل عام كلما طالت فترة تطبيق الدواء كلما زاد امتصاص الدواء الكلي.

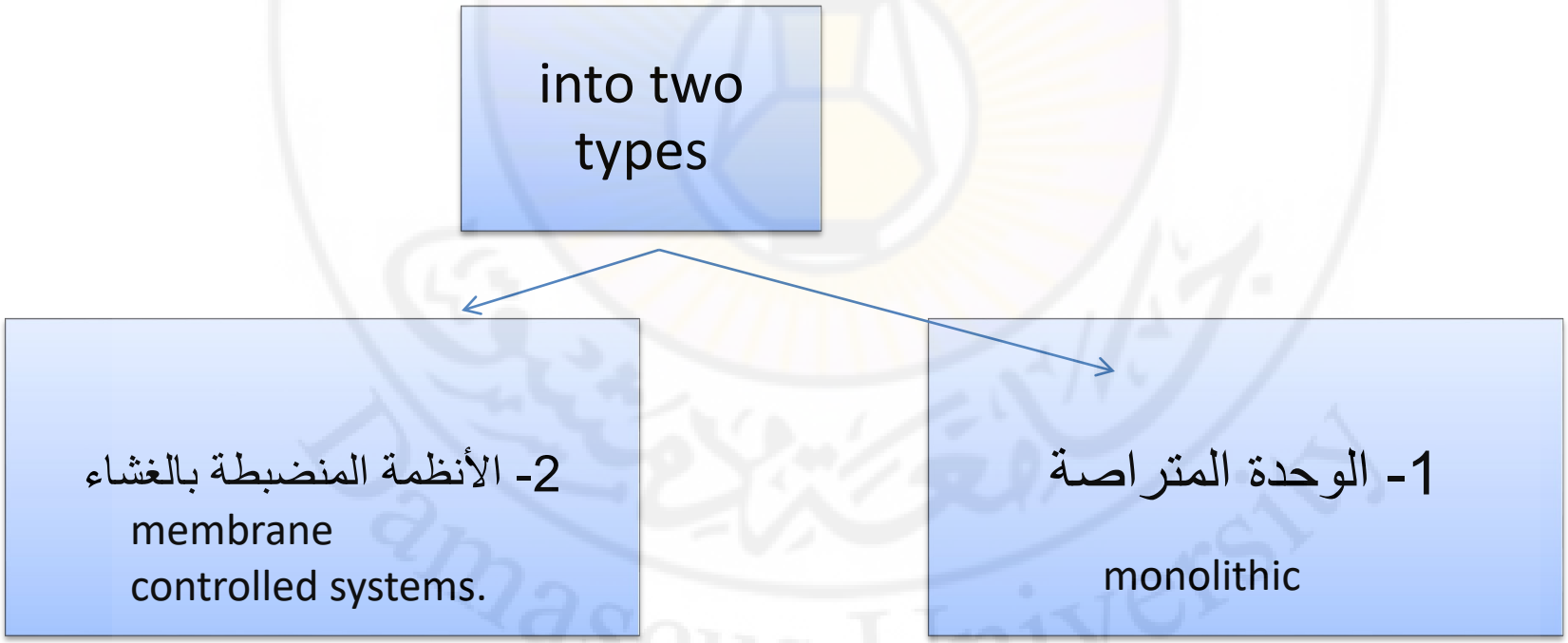
6. Percutaneous absorption appears to be greater when the TDDS is applied to a site with a thin horny layer than with a thick one.
7. Generally, the longer the medicated application is permitted to remain in contact with the skin, the greater is the total drug absorption.

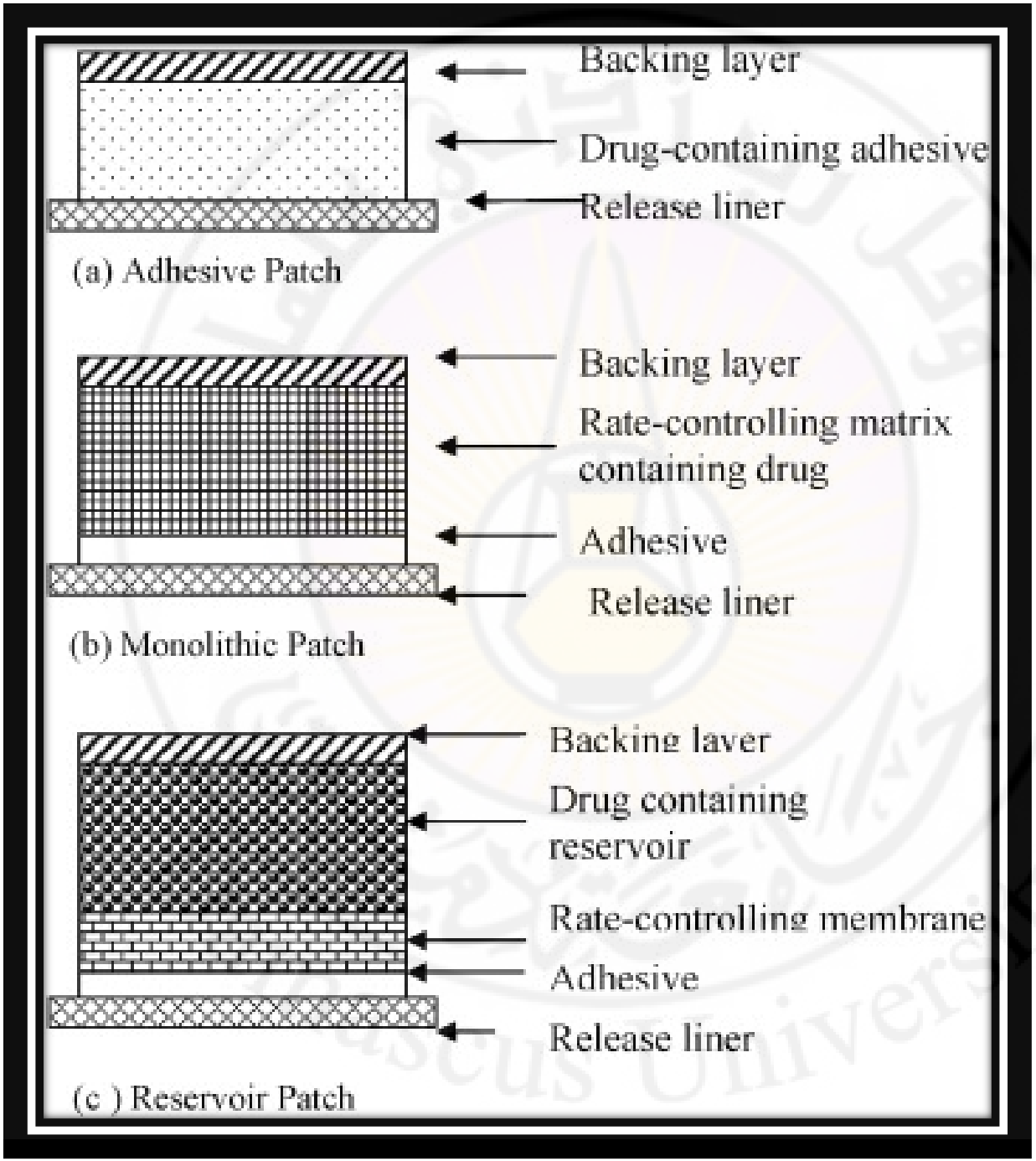
الجلد المصاب (المجروح) يسمح للأدوية أن تمر مباشرة الى الدم ويفشل دور اللصاقة في ايتاء الدواء بمعدل منضبط الجلد في التحكم في معدل المرور.

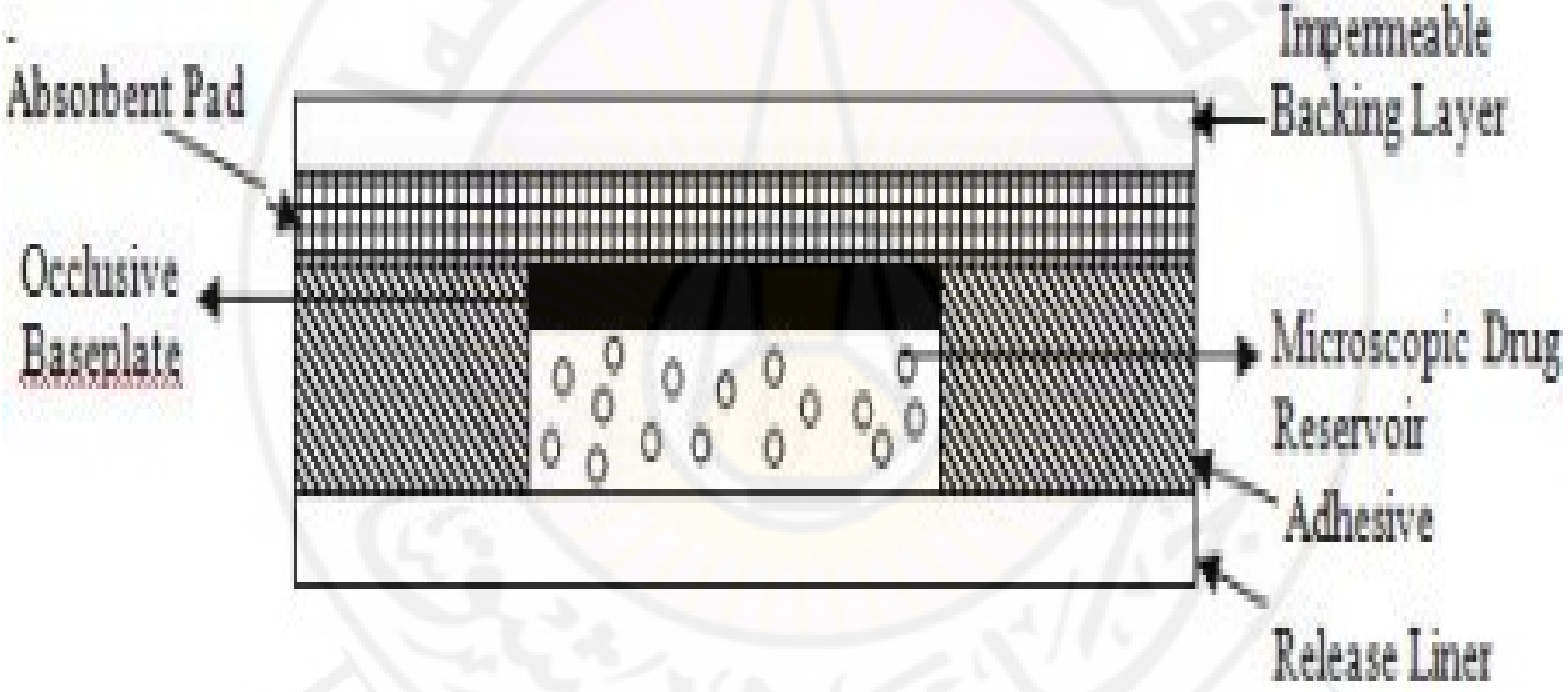
Skin that is injured or cut permits drugs to go direct to the subcutaneous tissues and the capillary network, defeating the function of the TDDS.

معالم تصميم أنظمة ايتاء الدواء عبر الجلد

يمكن تصنيف اللصاقات الجلدية تقنيا في نوعين




Backing layer
Drug-containing adhesive
Release liner
(a) Adhesive Patch
Backing layer
Rate-controlling matrix containing drug
Adhesive
Release liner
(b) Monolithic Patch
Backing layer
Drug containing reservoir
Rate-controlling membrane
Adhesive
Release liner
(c) Reservoir Patch


Absorbent Pad
Occlusive Baseplate
Impermeable Backing Layer
Microscopic Drug Reservoir
Adhesive
Release Liner

1-أنظمة الوحدة المتراصة

1-Monolithic systems

1-في هذه الأنظمة يوضع مطرس الدواء بين الطبقتين الأمامية والداعمة (الخلفية).

2- تتألف طبقة المطرس من جزيئات الدواء موزعة بين سلاسل البلمر .

1-Monolithic systems incorporate a drug matrix layer between the backing and the frontal layers

2-The drug–matrix layer is composed of a polymeric material in which the drug is dispersed.

3- يتحكم مطرس الدواء بمعدل تحرر الدواء لأجل الامتصاص الجلدي.

4- في نظام الوحدة المتراصة يوجد نوعين:

أ- نوع لا يحوي زيادة من الدواء

ب- نوع يحوي زيادة من الدواء مع الأخذ بعين الاعتبار لذوبانية الدواء ومدروج تركيز حالة الثبات في الطبقة المتقرنة.

3-The polymer matrix controls the rate at which the drug is released for percutaneous absorption.

4- The matrix may be of two types, either with or without an excess of drug with regard to its equilibrium solubility and steady-state concentration gradient at the stratum corneum

أ- النوع الذي لا يحوي زيادة من الدواء ، وهنا يتوافر الدواء ليحافظ على اشباع الطبقة المتقرنة

طالما أن مستوى الدواء في اللصاقة يزيد عن حدود ذوبانيته في الطبقة المتقرنة.

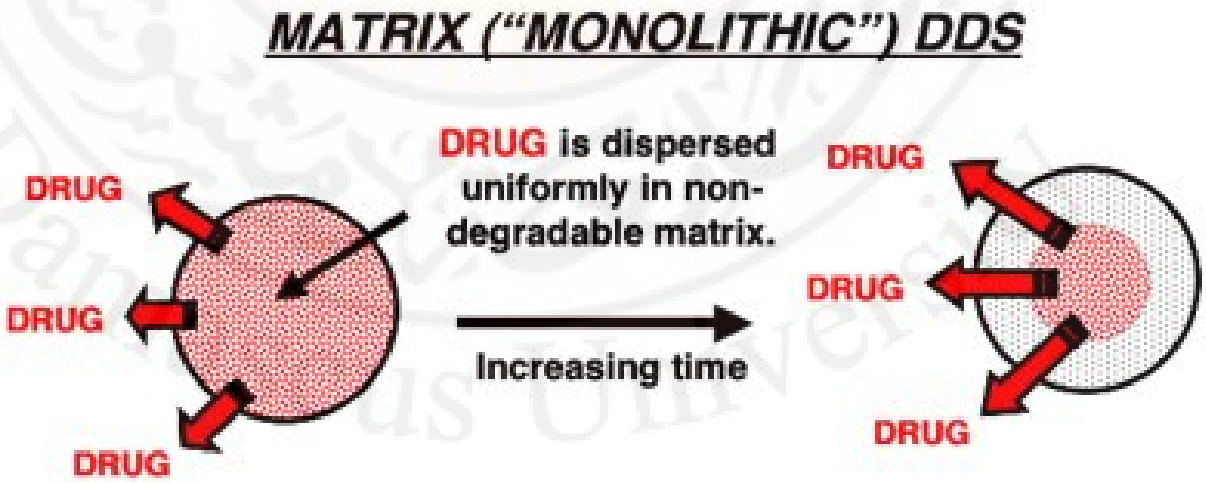
4-a In types having no excess, drug is available to maintain the saturation of the stratum corneum only as long as the level of drug

in the device exceeds the solubility limit of the

stratum corneum.

As the concentration of drug in the device diminishes below the skin's saturation limit, the transport of drug from device to skin declines.

ما ان ينقص تركيز الدواء في اللصاقة تحت حد اشباع الطبقة المتقرنة حتى يتناقص نقل الدواء من اللصاقة الى الجلد.



ب-النوع الذي يحوي زيادة من الدواء في المطرس، توجد هذه الزيادة لتؤمن اشباع مستمر للطبقة المتقرنة وهنا تناقص معدل ايتاء الدواء يكون أقل من النوع الأول.

4-b In systems with excess drug in the matrix, a drug reserve is present to ensure continued saturation at the stratum corneum.

In these instances, the rate of drug decline is less than in the type having no reserve.

تحضير أنظمة الوحدة المتراصة
Preparation of monolithic systems

تحضر أنظمة الوحدة المتراصة:

1- يذاب البلمر والدواء أو يمزجان معا فتتشكل المطرس

2 - يصب المطرس

3- يجفف ويشكل المطرس على شكل صفيحة أو اسطوانة تحوي الجرعة المحددة وتجمع بين الطبقات الداعمة (الخلفية) و الأمامية.

In the preparation of monolithic systems,

1-The drug and the polymer are dissolved or blended together,

2-cast as the matrix,

3- and dried.

The gelled matrix may be produced in sheet or cylindrical form, with individual dosage units cut and assembled between the backing and frontal layers.

تصمم معظم اللصاقات الجلدية لتحوي زيادة من الدواء وبالتالي تملك قدرة على تحرير الدواء الى ما بعد الاطار الزمني الموصى به لأجل الاستبدال. مما يضمن توافروامتصاص مستمر للدواء.

Most TDDSs are designed to contain an

excess of drug and thus have drug-releasing

capacity beyond the time frame recommended for replacement. This ensures continuous drug availability and absorption.

أنظمة الايتاء الجلدي المنضبط بالغشاء

Membrane-controlled transdermal systems

تصمم هذه الأنظمة لتحوي مخزن للدواء(كيس)،الدواء بشكل سائل أو هلامة، غشاء يتحكم بمعدل الايتاء ، طبقة الظهارة، الطبقة اللاصقة، الطبقات الداعمة.

Membrane-controlled transdermal systems are designed to contain a drug reservoir, or pouch, usually in liquid or gel form, a rate controlling membrane, and backing, adhesive, and protecting layers.

يتم ايتاء النتروغليسرين والسكوبولامين بأنظمة الايتاء الجلدي المنضبط بالغشاء.

Transderm- Nitro (Summit) and Transderm-Scop (Baxter)are examples of this technology.

تتميز أنظمة الايتاء الجلدي المنضبط بالغشاء عن أنظمة الايتاء بالوحدة المتراصة بأن معدل تحرر المادة الفعالة عبر الغشاء يبقى ثابتا طالما أن محلول المادة في المخزن مازال مشبعا.

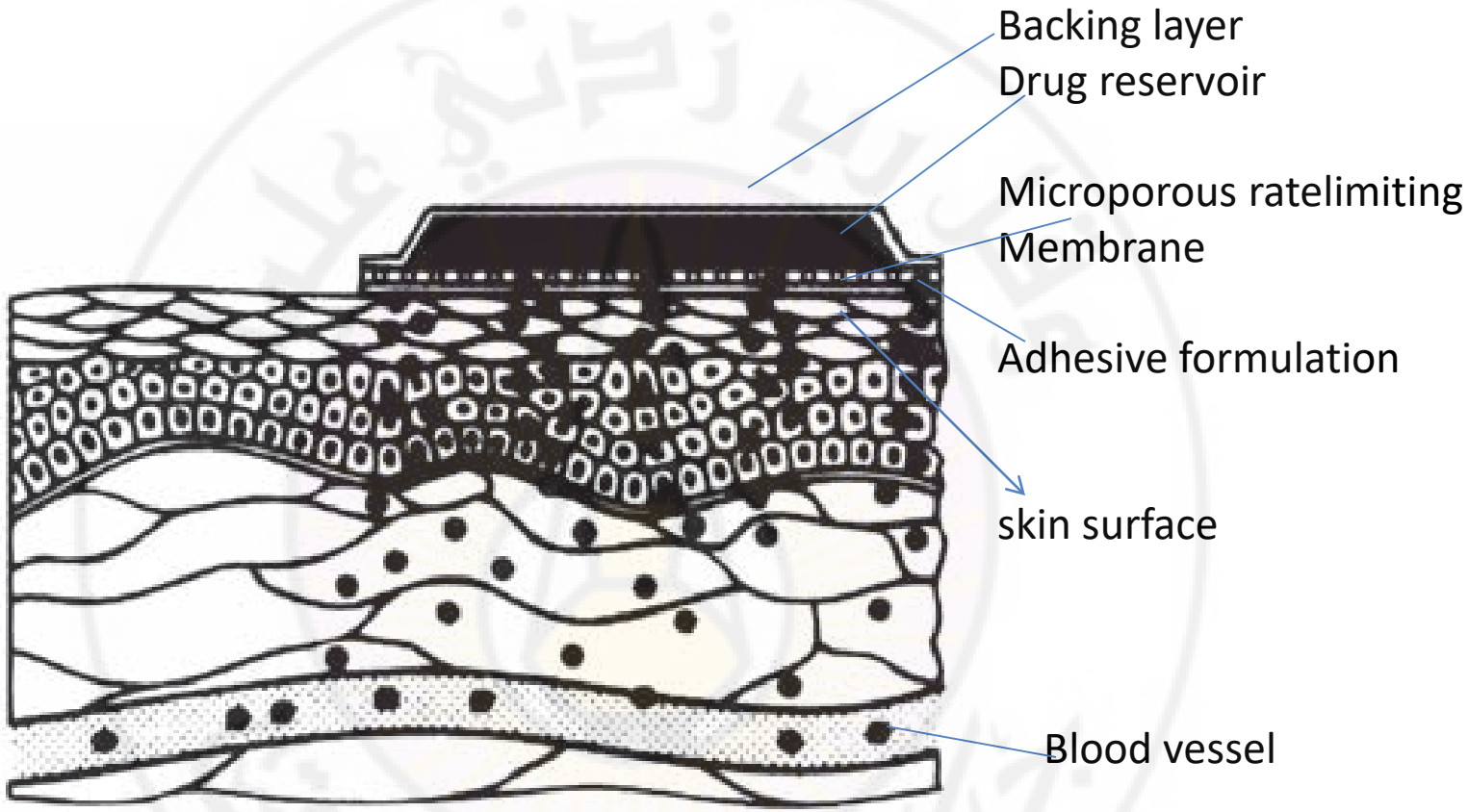
Membrane-controlled systems have the advantage over monolithic systems in that as long as the drug solution in the reservoir remains saturated, the release rate of drug through the controlling membrane remains constant.

في كل أنظمة الايتاء عبر الجلد يتم ضبط الايتاء اما عن طريق غشاء صناعي

Membrane-controlled transdermal systems

أو غشاء طبيعي هو الجلد monolithic

Thus, the rate of drug transport in all TDDSs, monolithic and membrane, is controlled by either artificial or natural (skin) membranes.


Backing layer
Drug reservoir
Microporous ratelimiting
Membrane
Adhesive formulation
skin surface
Blood vessel

تتركب TDDSs من عدة طبقات:

أ- طبقة ظهارة سادة لحماية اللصاقة من العوامل الخارجية ومنع ضياع الدواء أو ماء الجلد

ب- مخزن أو مطرس للدواء لادخار الدواء وتحريره في الجلد

ج-بطانة التحرر تزال قبل التطبيق مباشرة

د-طبقة لاصقة

TDDSs may be constructed of a number of layers, including

*(a) an occlusive backing membrane*to protect the system from environmental entry and from loss of drug from the system or moisture from the skin;

(*b) a drug reservoir or* matrix system to store and release the drug at the skin site;

(*c) a release liner, which is removed* before application and enables drug release; and

(*d) an adhesive layer to maintain contact with* the skin after application.

TDDSs are packaged in individual sealed packets to preserve and protect them until use.

The backing layer must be occlusive to retain skin moisture and hydrate the site of application, enabling increased drug penetration.

Backing materials

Preferred backing materials are approximately 2 to 3 mm thick and have a low moisture vapor transmission rate, less than about 20 g/m^2 in 24 hours.

Transparent or pigmented films of polypropylene, polyethylene, and polyolefin are in use in TDDSs as backing liners.

Transderm-Scop system

لصاقة دائرية مسطحة سماكتها 0.2ملم ومساحتها 2.5 سم مربع .

تتألف من أربع طبقات:

مصممة لتحوي 1.5ملغ من السكوبولامين وتؤتي 1ملغ الى الدوران العام بمعدل ثابت لمدة 3 أيام . توضع كمية قدرها 200مكغ من السكوبولامين في الطبقة اللاصقة لتشبع مواقع الارتباط في الجلد ويدخل تركيز الدواء سريعا في البلازما في مرحلة الثبات.

The Transderm-Scop system is a circular flat patch 0.2 mm thick and 2.5 cm2 in area . It is a four-layer system .The TDDS contains 1.5 mg of scopolamine and is designed to deliver approximately 1 mg of scopolamine at an approximately constant rate to the systemic circulation over the 3-day lifetime of the system. An initial priming dose of 200 µg of scopolamine in the adhesive layer of the system saturates the skin binding sites and rapidly brings the plasma concentration to the required steady-state level.

. The continuous release of scopolamine through the rate-controlling microporous membrane maintains the plasma level constant.

The rate of release *is less than* the skin's capability for absorption, *so the membrane, not the skin*, controls the delivery of the drug into the circulation.

Scopolamine Transderm Scop (Baxter)

Four-layer patch: (*a) backing layer of* aluminized polyester film; (*b) reservoir* of scopolamine, mineral oil, polyisobutylene;

(*c) microporous polypropylene* membrane for rate delivery of scopolamine;

(*d) adhesive of polyisobutylene,* mineral oil, scopolamine continuous release of drug over 3 days to prevent nausea and vomiting of motion sickness.

Patch is placed behind the ear. For repeated administration,

first patch is removed and second placed behind the other ear. Also approved to prevent nausea of certain anesthetics and analgesics used in surgery.

Testosterone patch

The testosterone transdermal systems Testoderm (Alza) and Androderm (Watson) are available with various delivery rates as hormone replacement therapy in men who have an absence or deficiency of testosterone.

Testosterone Testoderm (Alza)

Three-layer patch: (*a) backing layer of* PET;

(*b) matrix film layer of testosterone,* ethylene–vinyl acetate copolymer;

(*c) adhesive strips of polyisobutylene,*

colloidal silicon dioxide.

Androderm

Five-layer patch: (*a) backing film of* ethylene–vinyl acetate copolymer, polyester laminate;

(*b) reservoir of* testosterone, alcohol, glycerin, glyceryl monooleate, methyl laurate gelled with acrylic acid copolymer;

(*c) microporous* polyethylene membrane;

(*d) acrylic* adhesive;

(*e) adhesive polyester laminate.*

Patch is placed on back, abdomen, upper arms, or thighs for treatment of testosterone deficiency.

Nitroglycerin

It is used widely in the prophylactic

treatment of angina. It has a relatively low

dose, short plasma half-life, high peak plasma

levels, and inherent side effects when taken sublingually, a popular route.

It is rapidly metabolized by the liver when taken orally; this first-pass effect is bypassed by the transdermal route.

Nitroglycerin Deponit (Schwarz)

Three-layer system: (*a) covering foil;*

(*b) nitroglycerin matrix with polyisobutylene*

adhesive, plasticizer, release membrane;

(*c) protective foil, removed before use*

Nitroglycerin Nitro-Dur (Key)

Nitroglycerin in gel-like matrix of glycerin water, lactose, polyvinyl alcohol, povidone, sodium citrate sealed in polyester, foil, polyethylene laminate.

Nitroglycerin Transderm-Nitro (Summit)

Four-layer patch: (*a) backing layer of*

aluminized plastic; (*b) reservoir of* nitroglycerin adsorbed on lactose, colloidal silicon dioxide, silicone medical fluid; (*c) ethylene–vinyl acetate copolymer* membrane; (*d) silicone adhesive.*

Each of these products maintains nitroglycerin drug delivery for 24 hours after application. Tolerance, however, is a major factor limiting the effectiveness of these systems when used continuously for more than 12 hours per day. Hence, an appropriate dosing schedule would include a daily “patch on” period of 12 to 14 hours and a “patch off” period of 10 to 12 hours.

Gels

الهلامات أشكال صيدلانية نصف صلبة تتألف من بلمرات محبة للماء مبعثرة في حامل مائي مناسب . عندما يذوب البلمر المحب للماء في الطور المائي يتصرف هذا البلمر كغرويد محب للماء وتأتي الصفات الفيزيائية المتميزة التي يتمتع بها من التجمع الذاتي للبلمر المنحل وتداخله مع الوسط المائي.

Pharmaceutical gels are most commonly (but not exclusively) manufactured by dispersing hydrophilic polymers within an appropriate aqueous vehicle. When dissolved within an aqueous phase, hydrophilic polymers behave as lyophilic colloids and their unique physical properties result from the self-association of the dissolved polymer and its interaction with the aqueous medium.

يوجد نوعين للتجمع الذاتي (عكوس وغير عكوس) الذي تبديه الغرويدات المحبة للماء وهذا يجعل الهلامات المحضرة من الغرويدات المائية تصنف في نمطين : النمط الأول و النمط الثاني.

- There are two types of self-association (termed irreversible and reversible) that may be demonstrated by lyophilic colloids and this allows gels that are manufactured from lyophilic colloids to be classified as either type 1 or type 2 gels.

النمط الأول (وتسمى الهلامات المائية) حيث الترابط بين سلاسل البلمر يتم

بروابط تساهمية وتتوسطه جزيئات تربط بشكل متصالب السلاسل القريبة.

Type 1 gels

In type 1 gels (often termed *hydrogels) the interaction between* the polymer chains is covalent and is mediated by molecules that

cross-link the adjacent chains (termed cross-linkers).

تملك هذه الهلامات صفات فيزيوكيميائية فريدة

- تمتص كمية كبيرة من الماء تصل الى 100 مرة من الوزن الأصلي وتحافظ على بنيتها ثلاثية الأبعاد
- تملك خواص ميكانيكية قوية ،لاتتجزأ وان طبق عليها جهد كبير وتبدي مرونة ممتازة

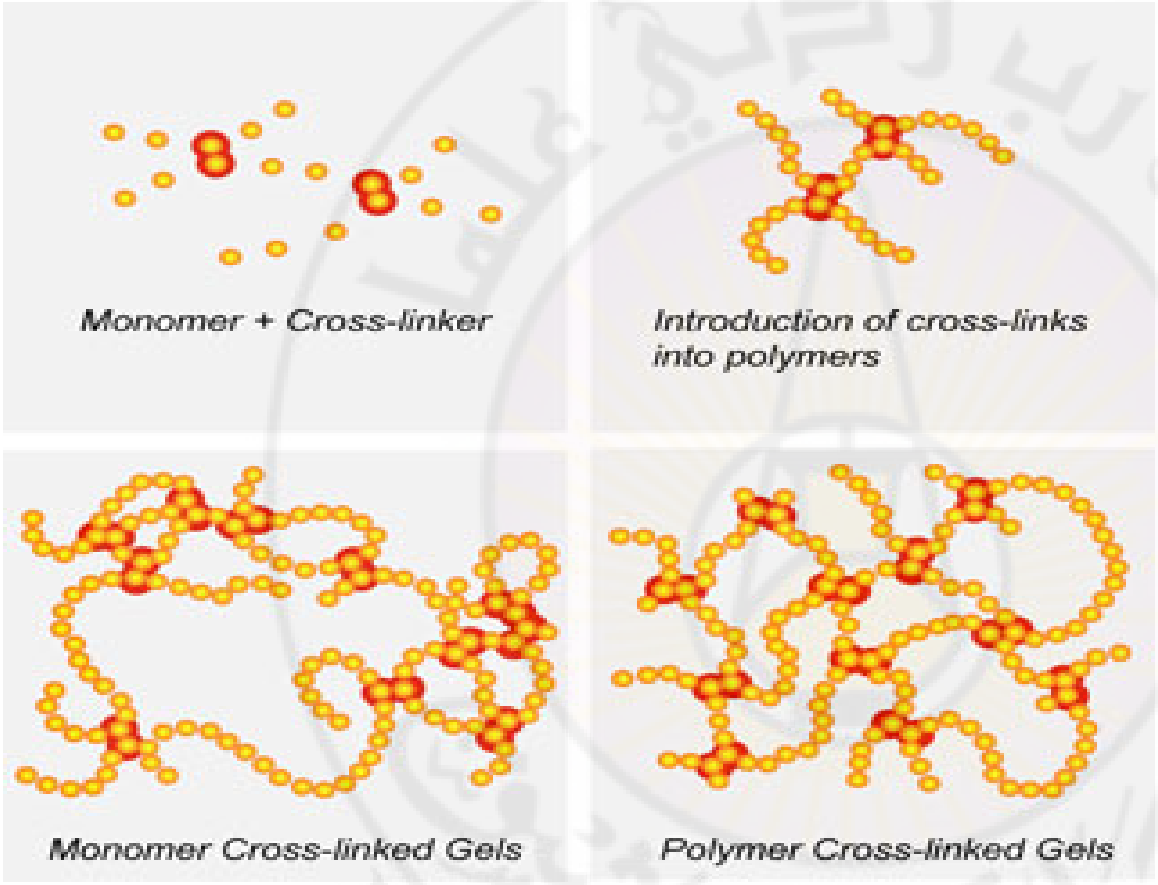
These gels exhibit unique physicochemical properties, including:

- The ability to absorb a considerable mass of aqueous fluid (often 100 times the original mass) whilst still retaining a three-dimensional structure.
- Hydrogels exhibit robust mechanical properties, being resistant to fracture following exposure to stresses frequently up to 1 kPa. Moreover, hydrogels exhibit excellent flexibility.

الهلامات من النمط 1 لاتنساب عندما تتعرض للجهد بسبب عدم قدرة الجهد التغلب على الروابط التساهمية . الجهد المقدم (الطاقة المقدمة) للهلامة يخزن ويستعمل فيما بعد في اعادة سلاسل البلمر الى وضعها المتوازن.

هذه الخواص مكنت من استخدام هذه الهلامات كضمادات للجروح.

- type 1 gels do not exhibit flow when exposed to an applied stress due to the inability of the stress to overcome the covalent bonds. Under these conditions, the elastic properties of type 1 gels enable the applied energy to be stored and utilised (after the stress is removed) to return
- the polymer chains to their equilibrium position.
- Due to this ability to absorb a large mass of fluid (whilst retaining their mechanical properties), hydrogels are clinically used as wound dressings



مثال على الهلامات المائية المرتبطة بالتصالب

هيدروكسي ميثيل أكريلات (المونومير) ودي ميثاأكريلات ايثيلين غليكول(الكروس لينكر)

An example of the chemical structures of a cross-linked hydrogel and the monomer (hydroxyethylmethacrylate) and crosslinker

(ethyleneglycol dimethacrylate) used in the synthesis of the hydrogel . In this diagram the points of intersection of the polymer chains are covalent cross-links.


476139
KENDALL
AQUAFLO
Hydrogel Wound Dressing
3 in. (7.6 cm)
Pansement pour plaie Hydrogel
Nicht-haftender chirurgischer Verband
Medicazione con idrogel per ferite
Apósito para heridas de Hidrogel
Hydrogel Sårförband
Hydrogel wondverband
5

هلامات النمط 2التداخل بين سلاسل البلمر عكوس بسبب الروابط الضعيفة:

Hydrogen bonding, ionic association or van der Waals interactions

وبتطبيق جهد على الهلامة تتحطم الروابط وتنساب الهلامة ويشار الى هلامات النمط الثاني أنها من الأنظمة شبه البلاستيكية.

Type 2 gels

In type 2 gels the interactions between the polymer chains are reversible and are facilitated by weaker bonds, e.g. hydrogen bonding, ionic association or van der Waals interactions. The application of stresses to type 2 gels will end in the temporary destruction of these bonds, thereby enabling the formulation to flow.

As a result, type 2 gels are rheologically referred to as *pseudoplastic (shear-thinning) systems.*

معظم الهلامات الصيدلانية من النمط الثاني والبلمرات المستعملة في تصنيعها:

1-مشتقات السللولوز

2-عديدات السكاريد الطبيعية

3-حمض عديد الأكريليك

The overwhelming majority of pharmaceutical gels are type 2 gels and typically the following polymers are employed in the formulation of these systems: (1) cellulose derivatives;

(2)polysaccharides derived from natural sources;

and (3) polyacrylic acid.

Cellulose derivatives مشتقات السللولوز

The cellulose derivatives represent a family of chemically related polysaccharides that are structurally derived from cellulose (following the appropriate chemical substitution). The most commonly used examples from this series that are used to formulate pharmaceutical gels include:

- methylcellulose
- hydroxyethylcellulose
- hydroxypropylcellulose
- sodium carboxymethylcellulose.

Polysaccharides عديدات السكاريد

Polysaccharides derived from natural sources

Polysaccharides that have been derived from natural sources are commonly used as the basis for pharmaceutical gels.

Examples of these include:

(1) carrageenan; and

(2) alginic acid/sodium alginate.

Carrageenan الكاراجينان

- This is a family of polysaccharides that is derived from red
- seaweed. There are three chemically related carrageenans, termed
- lambda, iota and kappa which differ according to the location of
- sulphate groups and the presence or absence of anhydrogalactose.
- Kappa carrageenan exhibits excellent gelling properties (due to
- the presence of a tertiary helical structure); iota carrageenan (but
- not lambda carrageenan) also displays gelling (albeit weaker)
- properties. The typical range of concentrations of kappa
- carrageenan used to form pharmaceutical gels is 0.3–1.0% w/w.

Damascus University

الطحالب الحمراء

الطحالب الحمراء أو رودوفيتا = نبات، ومن ثم فإن الاسم يعني (النبات الأحمر) تعد واحدة من أقدم مجموعات الطحالب حقيقيات النوى، كما أنها واحدة من أكبر تلك المجموعات حيث تضم حوالي 5000 إلى 6000 نوع طحالب بحرية متعددة الخلايا.

الطحالب الحمراء



حمض الألجيني وألجينات الصوديوم
Alginic acid/sodium alginate

المصدر من الطحالب

باضافة شوارد الكالسيوم بتركيز قليل الى محلول حمض الألجيني يحدث تبادل شاردي يرفع اللزوجة .

يتنافر حمض الالجيني مع الادوية الاساسية

Alginic acid is a polysaccharide that is derived from algae (Phaecophyceae family). Addition of calcium ions to a solution of alginic acid will result in an electrostatic interaction, producing a viscous gel at low concentrations of calcium and a cross-linked polymer at higher concentrations. Alginic acid is incompatible with basic drug molecules.

Polyacrylic acid الكاربوبول

متماثر حمض الأكريليك

Polyacrylic acid is a synthetic polymer that is

produced following the polymerisation of acrylic acid and crosslinking with either allyl sucrose or allyl ethers of pentaerythritol.

الكاربوبول

In water polyacrylic acid exists as aggregated (coiled) colloidal particles of minimal viscosity (pH circa 3). However, if the pH of the system is neutralised by the addition of an appropriate base, e.g. triethanolamine, triethylamine or sodium hydroxide, the pendant carboxyl groups will ionise, resulting in expansion of the polymer chains due to repulsion of the adjacent ionised groups. In so doing the viscosity of the formulation is dramatically increased. Typically pharmaceutical gels are produced using 0.5–2.0% w/w poly(acrylic acid) that has been neutralised with an appropriate base. Incompatibilities exist between poly(acrylic acid) and basic therapeutic agents.

Multiple Choice Questions

1. Regarding parenteral formulations, which of the following are true

a. Parenteral formulations are sterile products.

b. Parenteral formulations must be pyrogen-free.

c. The majority of parenteral formulations for human administration are multidose formulations.

d. The vehicle of choice for human parenteral formulations is water.

INJECTIONS





Sterility in these preparations (injections) is ESSENTIAL because they are placed in direct contact with internal body fluids or tissues where infections can easily arise .

Ophthalmic preparations are also prepared to be sterile.

3. Regarding the intramuscular route of parenteral administration, which of the following are true?

a. Large-volume parenteral formulations are routinely administered intravenously.

b. Solution parenteral formulations may be administered intramuscularly.

c. Emulsion parenteral formulations may be administered intramuscularly.

d. Intramuscular administration of parenteral formulations provides a rapid onset of drug action

2. Regarding the intravenous route of parenteral administration, which of the following are true?

a. Large-volume parenteral formulations may be administered intravenously.

b. Intravenous administration results in a rapid onset of drug action.

c. Emulsion parenteral formulations must never be administered intravenously.خ

d. The intravenous route of parenteral administration provides limited drug bioavailability



- Injections are sterile, pyrogene-free preparations intended to be administered parenterally.
- Pyrogenes are fever producing organic substance, coming from microbial contamination, responsible for many of the febrile reactions in patients following intravenous injections.

Damascus University

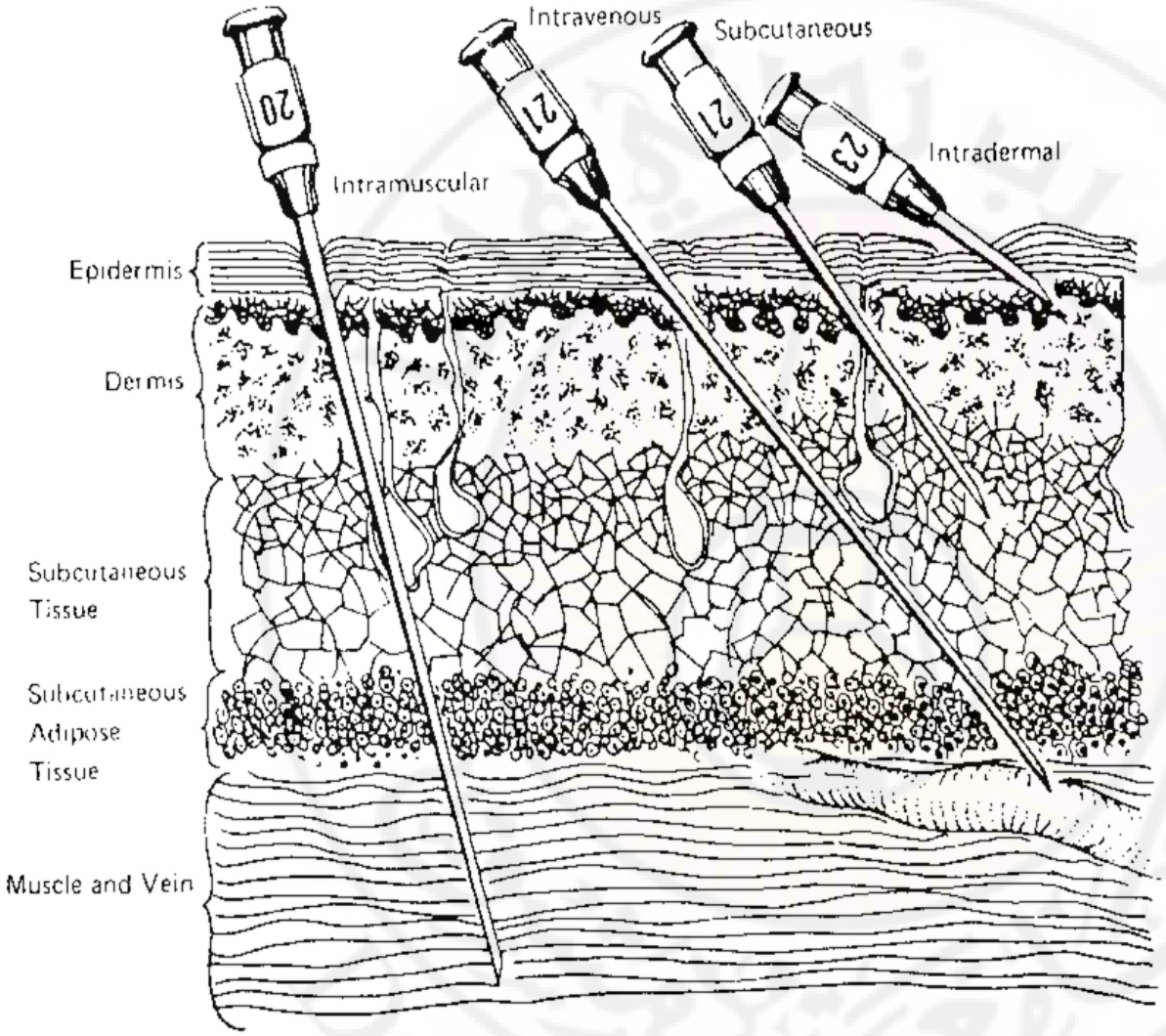
Parenteral formulations are extensively used in the treatment and control of numerous disease states, e.g. diabetes, infection, pain.

Parenteral formulations can be subdivided into three categories, namely solutions, suspensions and emulsions. Furthermore parenteral formulations may be defined as either large-volume or small-volume parenterals.

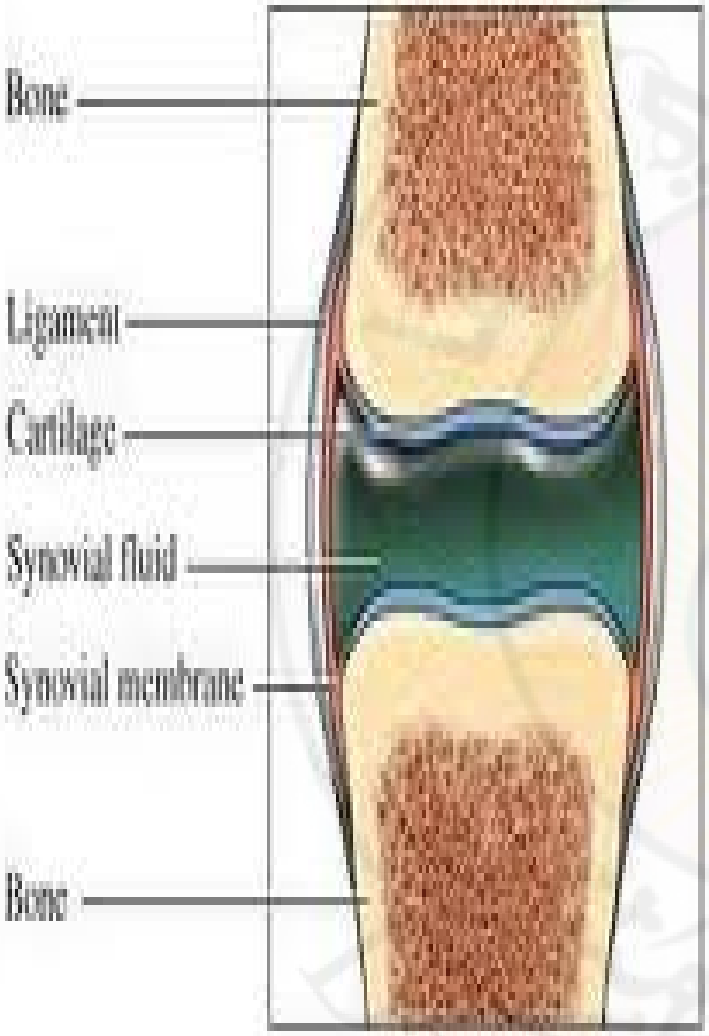
- When do you use parenteral route?
- Rapid drug action is desired .
- In emergency.
- Patient unable to accept or to tolerate oral medication.
- The drug itself is ineffective by other routes.
- Most injections are administered by the physician, physician assistant ,and nurse.

- In 1874 hypodermic morphine solution was the first drug who received approval to be administered parenterally and recognized in British Pharmacopeia and then in USA.
- Now there are hundreds of parenteral drugs.

- Drug can be injected in any organ or area of the body even intra-articular, and intrasynovial . Intraspinal, intrathecal, intraarterial, intracardiac.
- The most common routs are
- Intravenous.
- Intramuscular.
- Intradermal.
- Subcutaneous or Hypodermic.



E 15.1 Routes of parenteral administration. Numbers on needles indicate gauge of needle (outside diameter of
Presented with permission from Turco S, King RE. Sterile dosage forms: their preparation and clinical applica-
ed. Lea & Febiger, 1987.)



Cross section of a healthy joint



Damascus University

Intravenous route

- This involves administration of the parenteral formulation into a vein, usually a large proximal vein. The veins are located beneath the subcutaneous tissue, embedded within the muscle.
- IV administration achieves a rapid and predictable response.

Damascus University

Intravenous route

- It ensures 100% drug bioavailability.
- Both large- (up to 500 ml) and small- (up to 10 ml) volume formulations may be administered intravenously.
- Large volumes are infused into the vein at a controlled rate, e.g total parenteral nutrition, infusion of solutions of electrolytes/nutrients either containing or devoid(empty) of drugs.

Damascus University

Intravenous route

- Formulations are usually solutions or emulsions (in which the size of the disperse phase is small, 1 um).
- Suspensions(or solutions that precipitate within the blood stream) must not be administered IV due to disruption of blood flow.

Damascus University

Intravenous route

- Care must be taken regarding the rate of administration of the parenteral formulation. If the administration is performed too quickly, an excessive concentration of drug at the target organ may result, leading to drug-induced shock.
- Training is required to ensure that the dosage form is actually administered to the vein and that puncture of the vein is avoided.

Damascus University

- Administration of drug intravenously is of great risk.
- The risk could be formation of thrombus.
- Great care is necessary .
- IV administration produces rapid effect especially in case of emergency.
- The negative thing about IV rout that when it is given it cant be retrieved.
- Antecubital area is the best area for IV injection.

- In hospitals big volumes solutions can be given intravenously (1000 ml) .
- These big volume solutions could be blood extenders, electrolytes, amino acids.
- Infusion rate could be modified according to physician decision.

Formation of thrombus (clots) could happen when:

1. Catheter contacts vein walls .
2. Infused solution has irritating effect on tissue.
3. The clot circulates in the blood and blockage any small vessel which is very dangerous.
4. Solutions shouldn’t precipitate in blood vessels.

- **Intravenous of fat emulsions have gained acceptance for use as a source of calories and essential fatty acids for patients requiring parenteral nutrition.**

Damascus University

Intramuscular Route IM

- IM injections provides effects that are less rapid but generally longer than those obtained from IV administration.
- Aqueous, oleaginous solutions or suspension of drugs can be administered IM.
- The physical type of preparation is based on the properties of the drug itself and on therapeutic goals.

Intramuscular Route

- Intramuscular injections are performed deep into muscles.

-The point of injection should be as far as possible from nerves and blood vessels.

-The volume of injection is small, usually 1–3 ml or up to10 ml in divided doses.

Intramuscular Route

This involves administration into a muscle, usually the buttocks, lateral thigh or upper arm muscles. The musculature resides below the subcutaneous tissue (which itself lies beneath the epidermis and the dermis).

Intramuscular Route

-IM injection results in relatively rapid absorption, second only to IV with respect to the time taken for the onset of action.

-The nature of the formulation directly affects the rate of absorption of drugs administered by the IM route..

Damascus University

Intramuscular Route

■ Drug absorption from aqueous solutions is greater than from aqueous suspension or non-aqueous (oil-based) solutions of drugs. •

■ IM injections are usually used for controlled-release formulations.

Damascus University

- IM injections usually are related to the point at which the needle entered and where the medication was deposited.
- Such injuries include:
- Paralysis
- Abscess
- Cysts
- Embolism
- Scar

- Subcutaneous Route
- It can be used for small amount of drugs.
- Arm, thigh, and lower abdomen are the main sites for subcutaneous injections.
- The maximum amount is 1.3 ml ,insulin is an example.

- Intradermal Route
- This layer in skin is rich of blood vessels.
- It is used for diagnostic determination, allergy treatment, immunization.
- Volume 0.1 ml.

- According to USP, injections are devided into 5 types and they could contains buffers, preservatives, and other substances.
- 1-liquid products such as insulin.
- 2-solid dry products with suitable vehicle produce suitable solution.
- 3- Injectable emulsion.
- 4-Injectable suspension.
- 5-Dry solid products with suitable vehicle to produce injectable suspension.
-

The solutions and suspensions of drugs intended for injection are prepared in the same general manner as solutions and disperse systems with the following differences:

1- solvents or vehicles must meet special purity and other standards ensuring their safety by injection.

2- the use of added substances, such as buffers, stabilizers, and antimicrobial preservatives, fall under specific guidelines of use and are restricted in certain parenteral products .

The use of coloring agents is strictly prohibited.

3- parenteral products are always sterilized, meet sterility standards , and must be pyrogen free.

4-parenteral solutions must meet compendial standards for particulate matter.

5- Parenteral products must be prepared in environmentally controlled areas, under strict sanitation standards, and by personnel specially trained and clothed to maintain the sanitation standards.

6- parenteral products are packaged in special hermetic container of specific and high quality.

7- each container of an injection is filled to a volume in slight excess of the labeled volume to be withdrawn.

This overfill permits ease of withdrawal and the administration of the labeled volumes.

8- The volume of injection permitted in multiple-dose containers is restricted, as are the types of the containers(single –dose or multiple dose) that may be used for certain injections.

9-Specific labeling regulations apply to injections.

10- sterile powders intended for solution or suspension immediately prior to injection are frequently packaged as lyophilized or freez-dried powders to permit ease of solution and suspension upon the addition of the solvent or vehicle.

Solvents and Vehicles for Injections

Water for injection:

- According to USP:
- It is distilled water purified by distillation or reverse osmosis..
- solid particles not more than 1mg/100ml water for injection.
- No pyrogene.

- The water used for injectable products should be sterilized after preparation.
- Water for injection should be stored in containers tightly closed in temperature less or more than that suitable for microbial growth.

- It should be used within 24 hours after collecting.
- The containers should be sterile, free of pyrogenes.
- It should be made of glass.

Sterile water for injection

- According to USP it is a sterile water in single dose container with volume not more than 1 liter.
- It is free from pyrogene.
- It may have amount of solid particles slightly more than water for injection because of leaching from glass container during sterilization.
- 1 liter vial is not for intravenous use because it lacks tonicity.
- It is used for solving and diluting sterile and packaged drugs and also for reconstitution of antibiotics.

Bacterostatic water for injection:

- It is sterile water for injection with one antimicrobial agent or more.
- It is packaged in 30 ml vials.
- It is for multidose containers.
- The maximum amount used is 5 ml, otherwise sterile water for injection is used because the amount of preservative could be toxic.

- Bacteriostatic water for injection containing benzyl alcohol labeled by “Not for use for Newborn “which may cause gasping syndrome which means multi-organ failure.

- **Nonaqueous Vehicles**
- Aqueous vehicle is preferable but sometimes it is not possible to use water because the active substance does not dissolve in water or may exposed to hydrolysis.
- The selective vehicle should be nonirritating, nontoxic, not causing allergy, no therapeutic effect, compatible with the active substance .
- According to physical and chemical considerations the solvent should be stable in different pH, its viscosity should be suitable for injection, its boiling point should be high enough to allow heat sterilization, it should have low steam pressure to prevent problems during heating, pure and its purity should be stable and easy to pure it.

The most famous nonaqueous solvents are fixed vegetables oils.

Glycerin

Glycols such as ethyl oleat, isopropyl myristate, dimethyl acetate.

According to USP fixed vegetables oils should stay clear when exposed to cooling 10 ºC.

It should have no mineral oil or paraffin because tissues does not absorb these substances.

The fluidity of these oils depends on the ratio of unsaturated fatty acids and saturated acids.

These oils should verify the conditions mentioned in pharmacopeias about iodine number and saponification number.

Some patients may suffer from allergic reactions to some oils so the kind of oil should be labeled.

The most common used oils are corn oil, cottonseed oil, peanut oil, sesame oil, castor oil, and olive oil, but the last one its use is limited.

Oil injection is administered IM but not IV because oily drops may block blood vessels in lung.

Added substances

Preservatives, antioxidants, solubilizers, and other substances, but no coloring agents.

The concentration of the preservative should be very accurate because it may cause toxic effect in large concentration:

Mercury substance and cationic substance 0.01 %.

Chlorobutanol, cryzol, phenol 0.5 %

Sulfer dioxid as anti oxidant., sulfite, or bisulfite, or metabisulfite sodium 0.2 %

N_2 is used to prevent O_2 in the air from oxidizing the active substance.

Methods of sterilization

1- steam sterilization.

2- dry heat sterilization.

3- sterilization by filtration.

4- gas sterilization.

5- sterilization by ionizing radiation.

The method used depends on the product nature and its ingredients.

Sterilization mean complete destruction for all living organism and their spores and removing completely from the product.

Steam sterilization: It is conducted in autoclave using steam under pressure.

It is better than dry heat because in presence of moist, bacteria are coagulated and destroyed at a considerably lower temperature than when moisture is absent.

The hot moist inside the bacteria allows denaturation and coagulation of some essential proteins and as a result killing the bacteria. Pressure is used to get high temperature only.

Time is another important factor in this method:

Damascus University



- Pressure 10 pound (115.5°C) for 30 min.
- Pressure 15 pound (121.5°C) for 20 min.
- Pressure 20 pound (126.5°C) for 15 min.
- This method is applicable to pharmaceutical preparations and materials that can withstand the required temperature and are penetrated by moisture and not affected adversely by both.

- This method is used for aqueous solutions where the moisture is already present, it is also for ampuls, bulk solution, glassware, surgical dressing, and instruments.
- It is not useful for oils, and fat preparations.



FIGURE 15.3 Autoclaving of intravenous electrolyte solutions. (Courtesy of Abbott Laboratories.)

- Dry heat sterilization:
- It is carried out in sterilizing ovens.
- The oven may be heated either by gas or by electricity and are generally thermostatically controlled.
- Dry heat is less effective in killing microorganism than moist heat
- Higher temperature and longer periods of exposure are required.

- These must be done individually for each product with consideration to the size and type of product and the container and its heat distribution characteristics.
- In general, individual units to be sterilized should be as small as possible. Dry heat sterilization is usually conduct at temperatures of 160 to 170ºC for periods of not less than 2 hour.
- Higher temperature permit shorter exposure times for a given articles, conversely lower temperature requires longer exposure times.

- For example, if a particular chemical agent decomposes at 170ºC, but is unaffected at 140ºC, the lower temperature would be employed in its sterilization, and the exposure time would be increased over that required to sterilize another chemical that may be safely heated to 170ºC.
- Fixed oils, glycerin, mineral oil, paraffin,

and various heat-stable powders such as zinc oxide. It is also used for sterilizing glassware, and surgical instruments.

Dry heat is the method of choice when dry apparatus or dry containers are required.

- Sterilization by filtration:
- It is a physical removal of microorganism by adsorption on the filter medium or by sieving mechanism .
- It is used for the sterilization of heat sensitive solution.
- Commercially available filters are produced with a variety of por-size specification.
- Millipore filters are thin plastic membrane of cellulosic ester with millions of pores per square inch of filter surface.
- They are available in pore size from 14 to 0.025μm.

- Commercially available filters are produced with a variety of pore-size specification.
- Millipore filters are thin plastic membrane of cellulosic ester with millions of pores per square inch of filter surface.
- They are available in pore size from 14 to 0.025μm.
- The size of the smallest particle visible to the naked eye is about 40μm, red blood cell is about 6.5μm, the smallest bacteria is about 0.2μm, and a poliovirus, about 0.025μm.

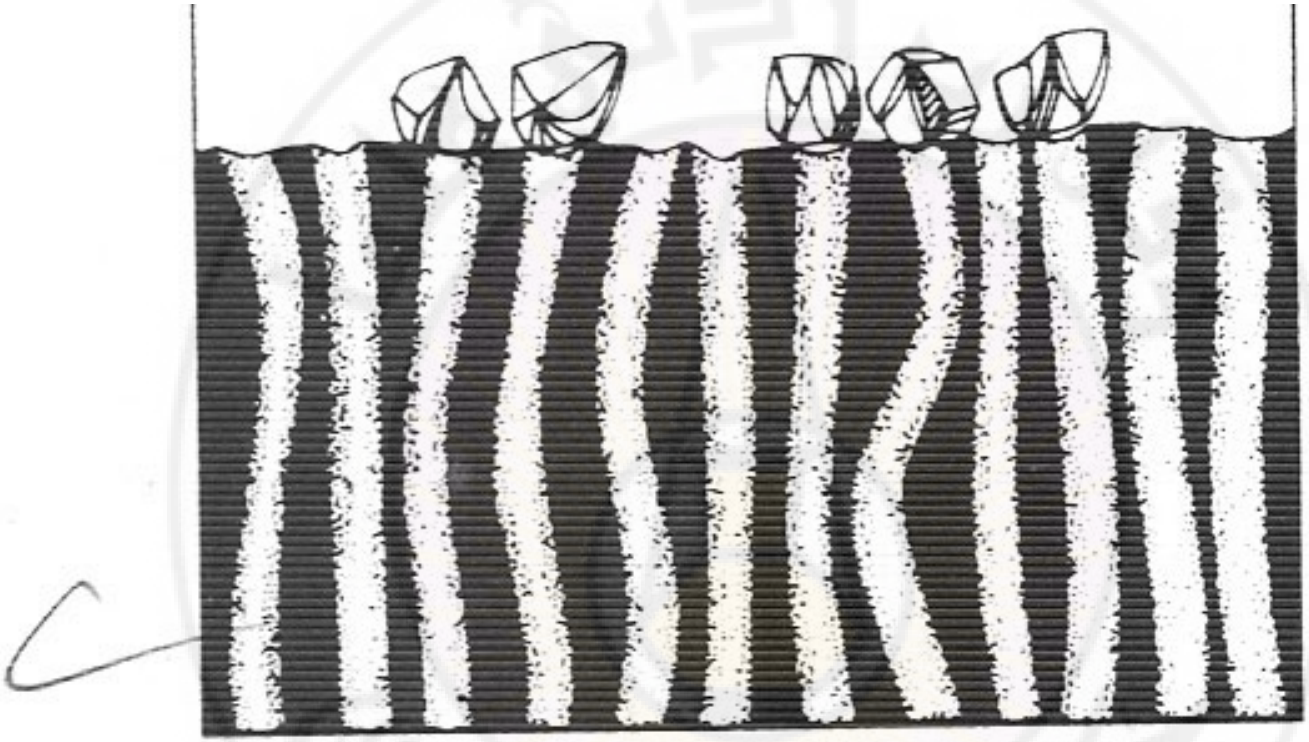


FIGURE 15.5 Membrane filters act as microporous screens that retain all particles and microorganisms larger than the rated pore size on their surface. (Courtesy of Millipore Corporation.)

- *Advantageous of filtration method:*
- It is a speed sterilization method for small volume solution.
- For thermolabile material.
- Inexpensive.
- Complete removal of living and dead microorganism and other particulate matter from solution.

- ***The disadvantage of filtration method:***

- The membrane tends to be fragile, so it is essential to determine that the assembly was properly made and that the membrane was not ruptured during assembly, sterilization, or use.
- Drug adsorption to membrane filter:0.22µm filters reduce the activity of amphotericin B (suspension) while filtration of the amphotericin B through 0.85µm and 0.45µm did not.

  Low doses drug may show this problem.

Damascus University

- Filters made of acetate or nitrate cellulose are polar and may adsorb drug by their hydroxyl group. Also hydrocabons portions of drug may interact with cellulose molecules of filter and drug may adsorbed.
- Membrane filter made of cellulose acetate,cellulose nitrate,acrylic polymers, polyster, nylon, vinyl.

Damascus University

- Gas sterilization
- Ethylene oxide,
- and propylene oxide are gases used for sterilization.
- Sterilization with gas enhanced by increasing humidity of the system to 60% and by increasing the exposure temperature to 50-60ºC.
- If the material being sterilized cannot tolerate either the moisture or the elevated temperature , so exposure time must be increased.

- Generally ,sterilization with ethylene oxide gas requires 4 to 16 hours of exposure. Ethylene oxide is thought to sterilize by interfering with the metabolism of the bacteria cell.

- Ethylene Oxide is useful in sterilizing medical and surgical supplies such as catheter, needles, plastic disposable syringes in their final plastic packaging.
- It is also used to sterilize heat-labile enzyme preparation, certain antibiotic and other medicines.



- Sterilization by Ionizing Radiation
- By gamma rays and cathode rays .
- Application is limited: highly specialized equipment is required,
- the effect of rays on the drug and container.

- Validation of sterility:
- Regardless of the method, pharmaceutical preparations required to be sterile must undergo tests to confirm the absence of microorganism.
- The USP contains monographs and standards for biologic indicators of sterilization.

- Biologic indicators are generally of two main forms. In one, spores are added to a carrier ,packaged to maintain physical integrity while allowing the sterilization effect.
- In the other, the spores are added to representative units of the product being sterilized, with assessment of sterilization based on these samples.

- In steam and ethylene oxide sterilization, spores of Bacillus stearothermophilus are commonly used because of their resistance to these modes of sterilization.

- In dry heat, spores of Bacillus subtilis are commonly used.
- With ionizing radition, spores of suitable strains Bacillus pumilus, Bacillus stearothermophilus, Bacillus subtilis.

- F values may be computed from biologic data derived from the rate of destruction of known numbers of microorganisms.
- $F=D_{121}(\log A-\log B)$
- D_{121} is the time required for a one log reduction in the microbial population exposed to a temperature 121ºC.
- A is the initial microbial population, and B the number of microorganisms that survive after a defined heating time.
-

- ***Pyrogene and pyrogene test :***
- It is thought to be a lipopolysacchride from the outer cell wall of the bacteria .
- Because the material is thermostable and water soluble, it may remain in water even after sterilization by autoclaving or by bacterial filtration.
- One of the more common means of removing pyrogene is by oxidizing them to easily eliminated gases or to nonvolatile solids, both of which are easily separated.

- Potassium permanganate is usually employed as the oxidizing agent, with its efficiency increased by addition of a small amount of barium hydroxide to the solution and to make nonvolatile barrium salts of any acidic compound that may present.
- These two reagents are added to water that has been distilled several times to get highly pure, sterile, and pyrogene free water.

Pyrogene test

- In each instance the official pyrogene test must be performed to ensure absence of these fever-producing materials.
- The USP pyrogene test uses rabbits that have been properly maintained in suitable environment and on suitable diet.
- Temperatures are measured for each animal to be used in the test. These temperatures are used as the base for determination of any increase resulting from injection of a test solution.

- The procedure of the test is as follow:
- Heat the syringes, needles, and glassware to 250ºC for not less than 30 minutes.
- Warm your product to 37ºC .
- Inject into ear vein of each three rabbits 10 ml of the product per kilogram of body weight.
- Record the temperature at 30-minute intervals1 to 3 hours after injection.

- If no rabbit shows an individual rise in temperature of 0.5ºC or more , the product meets the requirements for the absence of pyrogens.
- If any rabbit shows an individual temperature rise of 0.5ºC or more, continue the test using five other rabbits.
- If not more than three of the eight rabbits show individual rises in temperature of 0.5ºC or more and if the sum of the eight individual maximum temperature rise dose not exceed 3.3ºC, the material under examination meets the requirements for the absence of pyrogens

Limulus amebocyte lysate (LAL)

This discovery led to the development of the *Limulus amebocyte* lysate (LAL) test for the presence of bacterial endotoxins. The Bacterial Endotoxins Test, USP, uses LAL, and is considered generally more sensitive to endotoxin than the rabbit test.

Limulus amebocyte lysate (LAL)

An extract from the blood cells of the horseshoe crab *contains an enzyme* and protein system that coagulates in of low levels of the presence lipopolysaccharides.

Damascus University

When you add a solute to solvent the boiling point of the solution increases, while the vapor pressure, freezing point decreases. Osmotic pressure also changed because:

Osmotic pressure and freezing point are two physical constants relate to each other, because both of them proportional to number of molecules or ions in solution.

It is easy to measure the decrease in freezing point but difficult to measure the osmotic pressure.

Colligative properties of drugs

- Colligative properties depend primarily on the number of particles in solution. These properties include changes in vapor pressure, boiling point, freezing point, and osmotic pressure.
- these values should be approximately equal for equimolar concentrations of drugs.
-

- Raoult law allows to measure the decrease in freezing point which is proportional to the number of the molecules dissolved:

$$F = \frac{c.w}{M.w_s}$$

- Each substance in solution contributes in decreasing the freezing point of the solution:
- F=f1+f2+f3…..
- After knowing the decrease in freezing point, you compare it with the freezing point of the serum or tear solution

- If the decrease in freezing point is less than 0.52 so it is a hypotonic solution and it needs to isotonic with the serum
- If the decrease in freezing point is more than 0.52 so it is hypertonic and it needs dilution.

- If the solution is hypotonic you should add substance which is inactive to make the injected solution isotonic to serum.
- Nacl is usually added unless it is incompatible with any other active substance. In this case sodium nitrate, potassium nitrate, and lactose or glucose.

Osmolality and Tonicity

- Iso-osmotic and isotonic solutions are solutions contain the same number of solute particles per unit volume.
- If solutions contain more (hypertonic) or fewer (hypotonic) dissolved species, it may be necessary to alter the composition of the solution to bring them into an acceptable range.

Damascus University



- One mole of glucose (180g) dissolved in 1000 g of water has an osmolality of 1osmol or 1000mOsm/kg of water.
- One mole of sodium chloride (23+35.5=58.5 g) dissolved in 1000g of water has an osmolality of almost 2000 mOsm, since sodium chloride dissociate into almost two particles per molecule.
- In another word, a 1-mole solution of sodium chloride is equivalent to a 2-molal solution of dextrose.

Damascus University

- Normal serum osmolality values are in the vinicity of 285mOsm/kg.
- Ranges may include values from about 275 to 300 mOsm/L .
- Pharmaceutical forms should be close to this value to minimize discomfort on application to the eyes or nose or on injection.

- Some solutions are iso-osmotic but not isotonic. This because the physiology of the cell membranes must be considered.
- For example , the cell membrane of the red blood cell is not semipermeable to all drugs.
- It allows ammonium chloride, alcohols, boric acid, glycerin, propylene glycol, and urea to diffuse freely.

Comparison between eye and red blood cell

- In the eye, the cell membrane is semipermeable, to boric acid, and a 1.9% solution of boric acid is an isotonic ophthalmic solution. But even though a 1.9% solution of boric acid is isotonic and iso-osmotic, it is not isotonic with blood – since boric acid can freely diffuse through the red blood cells- and it may cause hemolysis.

- Pharmacists are often called upon to calculate the quantity of solute that must be added to adjust a hypotonic solution of a drug to isotonic.
- This can be done by several methods: including L, sodium chloride equivalent, and cryoscopy.
-

- A sodium chloride equivalent is the amount of sodium chloride that is osmotically equivalent 1 g of the drug.
- For example, the sodium chloride equivalent to ephedrine sulfate is 0.23, that is, 1g of ephedrine sulphate is equivalent to 0.23 g of sodium chloride.

- How much sodium chloride is required to make the following prescription isotonic?
- Rx Ephedrine sulphate 2%
- sterile water, qs 30ml
- M. isoton with sodium chloride.
- 30 ml X 0.009= 0.270 g Nacl if only Nacl is present in 30 ml solution.
- 30 ml X 0.02= 0.6 g ephedrine sulphate is to be present.
- L=0.23
- 0.6 X 0.23 = 0.138 g is the quantity of sodium chloride represented by ephedrin sulphate.
- , then 0.270- 0.138 =0.132g of sodium chloride is
- Required to make to make the solution isotonic.
- The solution needs 0.6 ephedrine sulphate, 0.132 g Nacl and serile water to make 30 ml.
-

Calculations using freezing point

- If we go back to tables we find that the decreasing in freezing point for 1% ephedrin sulphate is 0.13 and as a result for 2% solution it is 0.26 which means that it is a hypotonic solution so
- 0.52 -0.26/0.58=0.44 g Nacl for 100 ml solution .
- For 30 ml: 0.44X30/100=0.132 g of Nacl.

What about the pH of the injection?

What about the pH of the injection?

pH of the body is 7.35-7.4

The solution given should have the same physical and chemical properties.

It is important to make the pH of the injection close to the pH of the biological fluids, but

It is impossible to do that because it dose not agree with the stability of many active substances

Adrenalin injection should have the pH between 3.5-4,

Atropine sulphate hydrolysis in pH 7.

Tolerance of body tissues to pH changing

- Body tissues and blood can tolerate injected solution with pH between 4-10.
- Pain can be tolerated in this range.
- Body tissues and blood buffering capability, so they can easily change the pH of the injected solution to the physiological one.
- In case of buffered injected solutions, the presence of strong buffer may retard the work of buffering capability of tissues or blood and the pain felt in this case is great.
-

- The pH of injection should grantee the stability of the active substance first without being not tolerated from the body.

The Industrial preparation of parenteral products

- After determination of the formula :proper solvent and additives, the pharmacist should follow rigid aseptic procedures in preparing the products.
- In most manufacturing plants the area in which parenteral products are made is maintained bacteria free by use of UV lights, a filtered air supply, sterile manufacturing equipment, such as flasks, connecting tubes, and sterilizing work clothing.



Preparation of parenteral solutions

- The required ingredient are dissolved in water for injection, in another solvent, or in combination of solvents.
- The solutions are usually filtered through a membrane.
- After filtration, the solution is transferred as rapidly as possible to its final container.
- The product is then sterilized by autoclave.

- Samples of finished product are tested for sterility and pyrogene.
- If sterilization by autoclaving is impractical then each component is sterilized by appropriate mean then added aseptically to the sterilized solvent.
- Autoclave is not used for suspension parenteral, because it may alter viscosity of the product, change the particle size of the suspending particles, altering both the pharmaceutical and therapeutic characteristics.

- Some injections are packaged as dry solids, the solid powder is sterilized by dry heat.

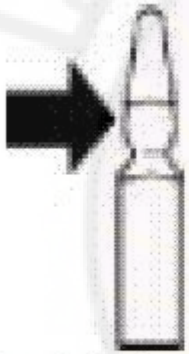
Packaging, labeling and storage of injections

- Containers for injections, including the closures, must not interact physically or chemically with the preparation.
- If the container is made of glass, it must be clear and colorless or light amber to permit inspection of its contents.
- The type of the glass is usually stated in the monograph.

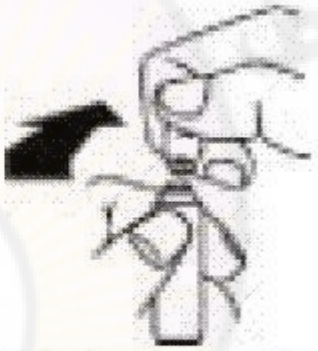
Types of containers

- 1- single-dose container: hermetic container when opened can`t maintain its sterility. It could be ampules or single dose vials.
- 2- multiple-dose container: hermetic container permits withdrawal of successive portions without changing the strength, quality, or purity.

Instructions for Use



One-point-cut ampule with cut below colored line.



To break, place thumb on the color line and snap back.

Damascus University



- Ampules are sealed by fusion, the neck of the ampule is easily separated without breaking the glass.
- The contents of the ampule should be withdrawn into a syringe with a 5μm filter needle to trap any glass particles.
- If there is no filter needle syringe the ampul is hold upright, tilted slightly and with avoid the outer surface of the neck of the ampule.
- The needle should not be lowered to the bottom.





Damascus University




labphoto.tumblr.com
Kristof Hegedüs


labphoto.tumblr.com
Kristof Hegedüs


SCIENCE PHOTO LIBRARY

- Clarity is one of the prime requisites of parenteral solutions
- No dust, no cloth fibers, no glass fragments,no material leached from the glass container or seal.
-

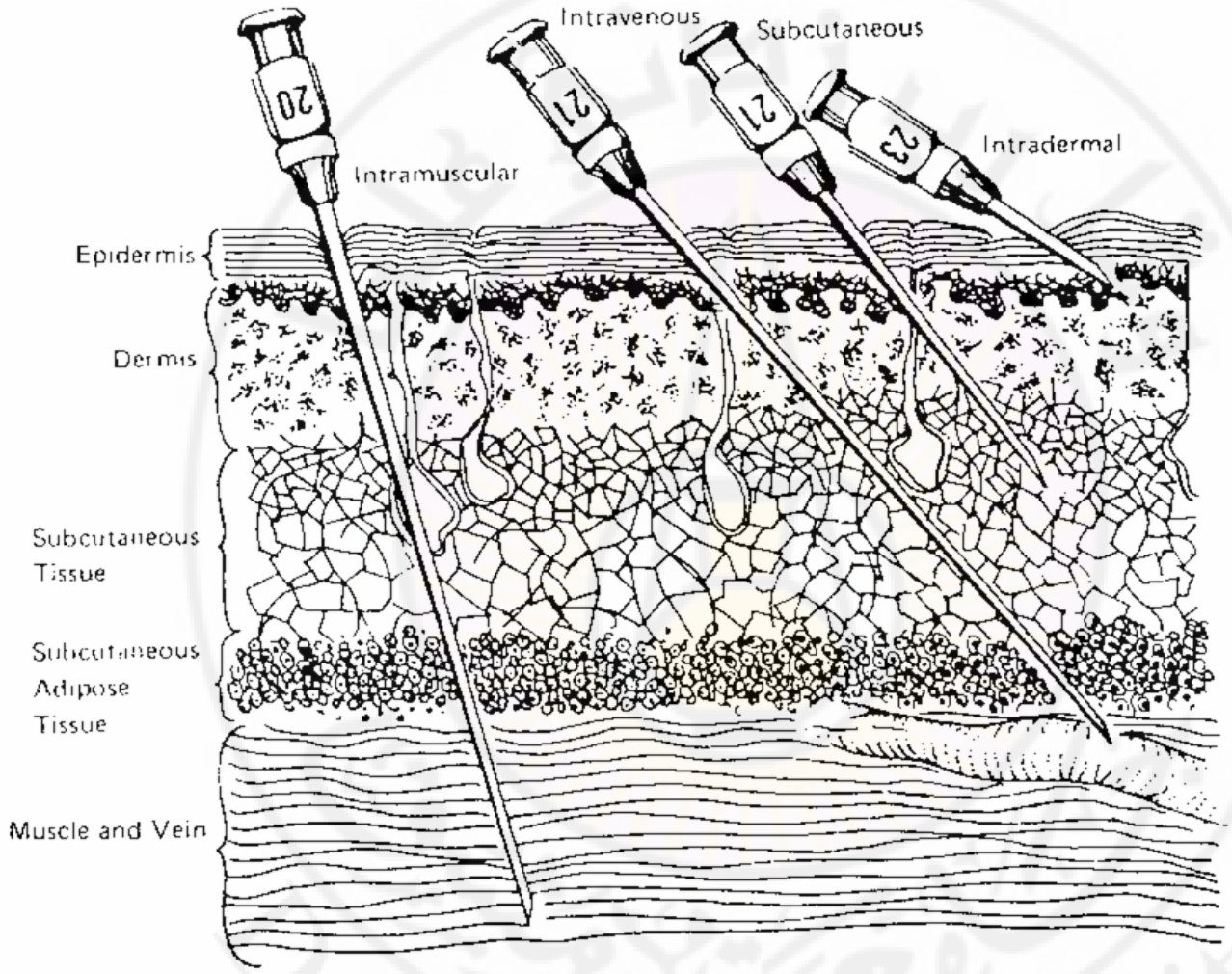
Precautions

- The container is carefully selected.
- The container should be carefully cleaned.
- During filling laminar flow hoods allow for draft-free flow of clean filtered air over the work area.
- The worker should be aware of the importance of cleanliness and aseptic techniques.
- They wear face hoods,caps, gloves, and disposable shoe cover to prevent contamination.
- After filling and sealing the containers are visually or automatically inspected for solid particles and by this method 50μm particle can be discovered .
- Coulter counter can count the particles electronically.

- Single dose products can be administered rapidly.
- Other products are infused slowly in circulatory system for hours.
- In markets there is several strength injections for certain drugs so the doctor can choose the dose he needs.
- Single dose and big volume product are used to expand blood volume or to replenish nutrients or electrolytes and they infused slowly.
- The biggest single dose container for withdrawal and injection is not more than 1000 ml.
- If the doctor wants to add additional substance to big volume injectable solution for infusion he should be sure of the aseptic conditions and substance added is compatible with the other ingredients.

Multiple dose container are closed by rubber closures allow the needle to penetrate without destroying the rubber closure, and when the needle is withdrawn the closure resealed again and protect the ingredients from contamination





15.1 Routes of parenteral administration. Numbers on needles indicate gauge of needle (outside diameter of
ted with permission from Turco S, King RE. Sterile dosage forms: their preparation and clinical applica-
ed. Lea & Febiger, 1987.)

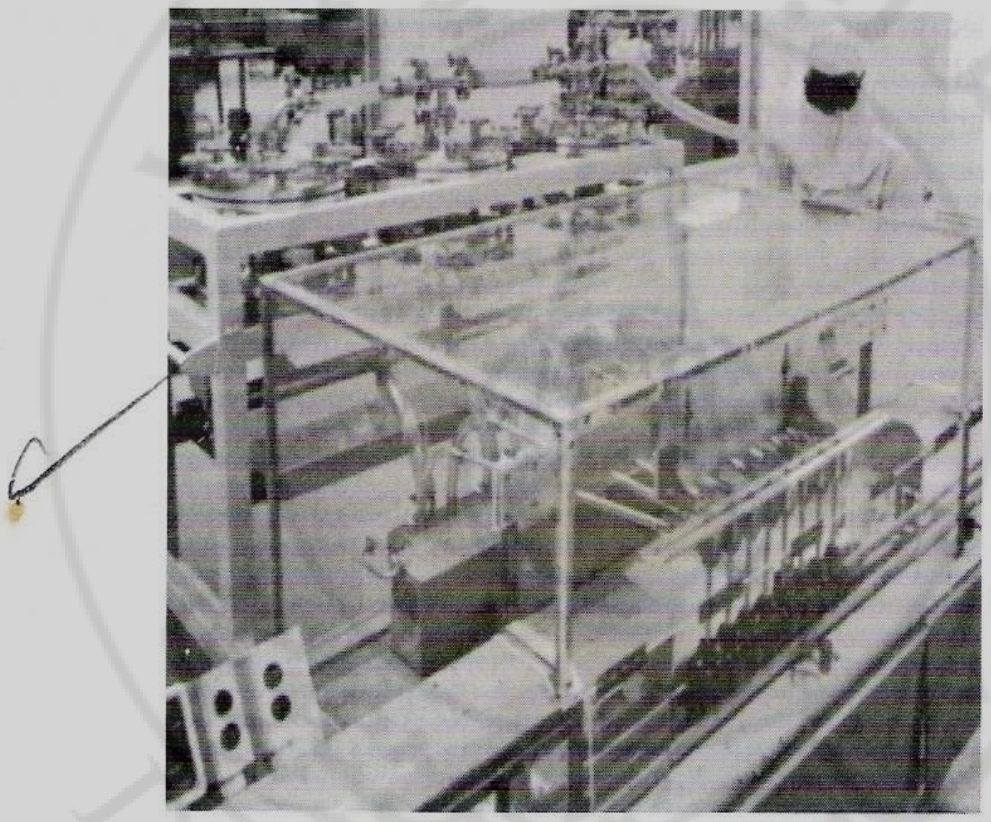


FIGURE 15.4 Sterilization by filtration. An eight-head bottle-filling machine using three large filters in large-scale pha maceutical production. (Courtesy of Millipore Corporation.)

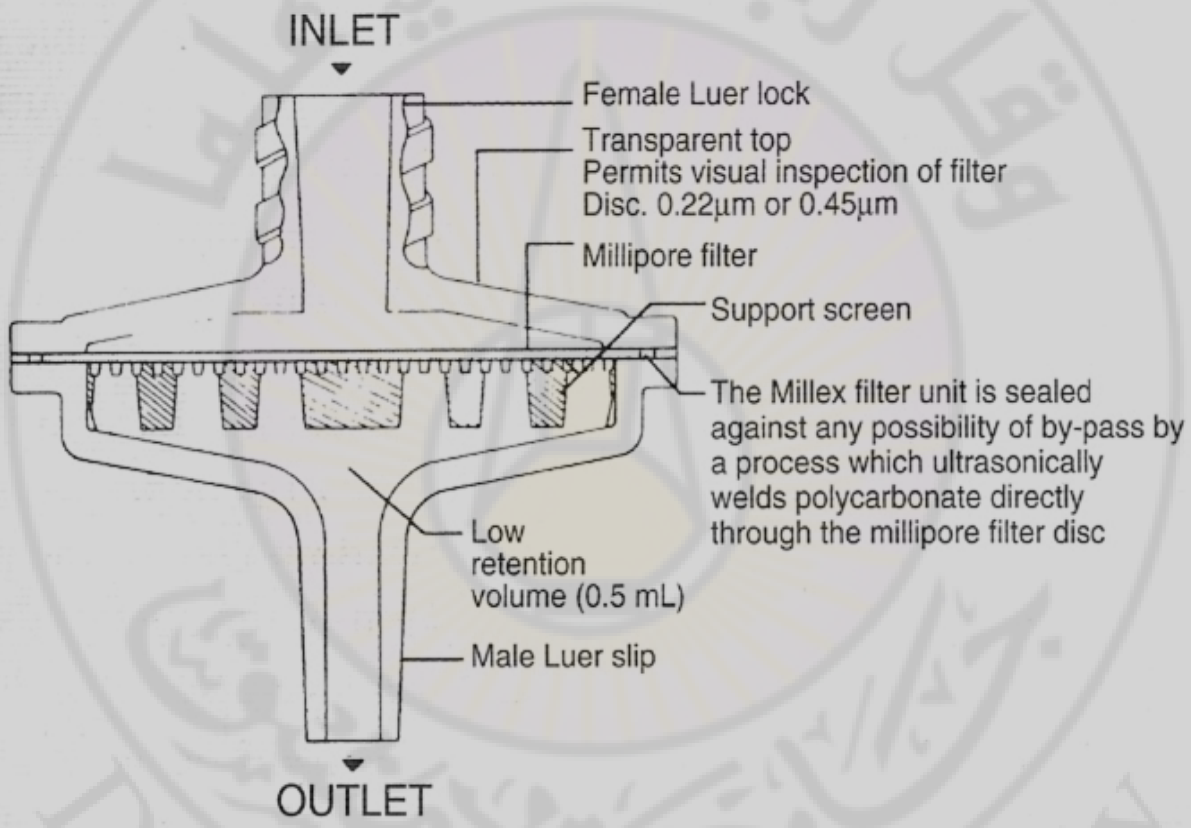


FIGURE 15.7 Cutaway showing composition of the Millex filter unit. (Courtesy of Millipore Corporation.)



FIGURE 15.6 Luer-Lock syringe adapted with a Millex Filter Unit and hypodermic needle. (Courtesy of Millipore Corporation.)

Container properties

Containers should have good resistance and not broken during filling, transporting and handling.
Container should protect the liquid injection from leakage.
Containers should protect the drug from the effect of air, humidity and light.
Containers should not react with active substance or the excipients.
Containers should be easily used
Glass and plastic containers are available to contain injections.
Glass composition is Ca and Na selenium SiO_2 plus boric acid, zinc, or Mg, Al, pb oxide.

.

- Glass can't be considered inactive – substance because ions could be exchanged (Na+, Ca++) between glass and alkaline solution.

- On the other hand the bonds between – selenium and O2 could be broken and this reaction increase in presence of alkaline solution.

- In this case some active substance could – precipitate, and other may loose their activity, oxidized like adrenaline.

Types of glass

First type I glass it contains less percent of alkaline substance and more percent of anhydrous boric acid.
Second-type II glass it is called a modified glass, the surface of the glass painted with silicon and this will facilitate the flow of the solution .

Third- type III glass is selenium-Ca glass.

Type one and two are used for aqueous solutions, type three is for oil solutions.

Colored glass is used for light sensitive products.

Fe_2O_3 and MnO are used in fabricating this type of glass.

Available Injections

1-small volume parenterals

a-solutions

b-suspensions

2-big volume parenterals

Small volume parenterals

Insulin injection is the most famous used small volume injection.

Insulin injection is available in 2 strength : 40 U/ml, 100U/ml.

Now the strength 100U/ml is the strength used by patients at their homes.

Insulin Injection (Regular)

It is sterile aqueous solution prepared from the pancreas of pork or beef .

The first developed insulin used to be amorphous but now there is the pure crystalline insulin consists of zinc- insulin crystals with neutral pH.

It is available now by two strengths 100U/ml and 500U/ml.

The strength (potency) of insulin injection should be labeled and the expiry date should not be more than 24 month after distributing from the manufacturing store.

The container color changes according to strength: 100U/ml orange

500U/ml brown

- 500U/ml insulin injection is a solution which is free from turbidity , it contains glycerin 1.4-1.8% as stabilizer, phenol or cryzol 0.1- 0.25% as preservative.
- It is preferable to store insulin injection in refrigerator, or in room T 15-30ºC but for one month only. it is not for freezing.
-

Insulin injection, the solution form is a prompt acting insulin while the suspension form is a slow acting one.

Insulin injection alone can be given intravenously .

Normally insulin injection is given subcutaneously half to two hours before the meal.

Dose is determined individually , it could be 5 to 100 U/ml according to USP.

500U/ ml insulin injection is used in insulin resistance cases.

Patient should learn how to rotate the insulin injection site continously.

Rotating the injection site will help avoiding lipohypertrophy by tissues fibrous.

One site injection will develop spongy and avascular tissues.

Absorption of insulin in this site would be erratic.

Patient should learn how to use insulin injection properly :

No shaking

Rotating slowly between two hand`s palms several times.

Suitable storage : no heating, no freezing.

Human Insulin

The first product prepared by DNA recombinant techniques.

Approved by FDA.

It is produced by Lilly and Humulin companies.

It has been in the market since 1983.

It is prepared from Escherichia coli strain .

- The recombined plasmid by DNA coding for human insulin is entered into the bacteria.
- Cultured by fermentation to give the two chains A and B from human insulin.
- The two chains released and purified before binding both by disulfide bridges.
- Pharmacokinetics studies refer to human insulin formulations have faster onset but shorter effective duration in comparison with pork insulin.

In the market now two products for human insulin : neutral normal human insulin which is a solution of insulin-zinc crystal (Humulin R, Lilly),and human insulin suspension (Humulin N,Lilly) and it is called isophan insulin suspension (NPH).

Large volume parenterals

These large volume products are given by IV infusion.

Volume 100 ml to 1liter.

Contains no bacteriostatic agents or other pharmaceutical additives.

They used to replenish body fluids, electrolytes, or to provide nutrition.

Two patients died

Calcium phosphate precipitate was found in the microvascular of patient lung causing pulmonary emboli.

FDA – safety alert advices to use millipore filters for TNA solutions.

Large volume parenterals are used in maintainace therapy for patient recovering from surgery or will undergoing a surgery.

For maintenance therapy : water, dextrose, small amount Na, K.

Oral nutrition is impossible for more than one week so Total Nutrient Admixture (TNA) or Total Parenteral Nutrition (TPN) is needed.

It contains carbohydrates, proteins, fats and electrolytes and trace elements.

It is called also three-in-one.

Replacement therapy

- In case of sever diarrhea or vomiting may bigger amounts elctrolytes, protein, carbohydrates are needed .
- Crohn`s disease , and AIDS patients , burn patients and those suffering from trauma all need replacement therapy before maintenance therapy.

Damascus University

GARAMYCIN Injection •

DESCRIPTION •

Gentamicin sulfate, USP, a water-soluble antibiotic of the aminoglycoside • group.

GARAMYCIN Injection is a sterile, aqueous solution for parenteral • administration.

Each mL contains gentamicin sulfate, USP equivalent to 40 mg gentamicin • base;

requires no refrigeration. 1.8 mg methylparaben and 0.2 mg propylparaben ; •

3.2 mg sodium bisulfite and 0.1 mg edetate disodium. •

GARAMYCIN Injection may be given intramuscularly or intravenously. •

GARAMYCIN Injection, 40 mg per mL, for parenteral administration, is • supplied in 2 mL (80 mg) vials.

GARAMYCIN Injection is a clear, stable solution that •

الأشكال الصيدلانية نصف الصلبة

الأستاذة المساعدة الدكتورة هند الزين

رئيسة قسم الصيدلانيات والتكنولوجيا الصيدلية

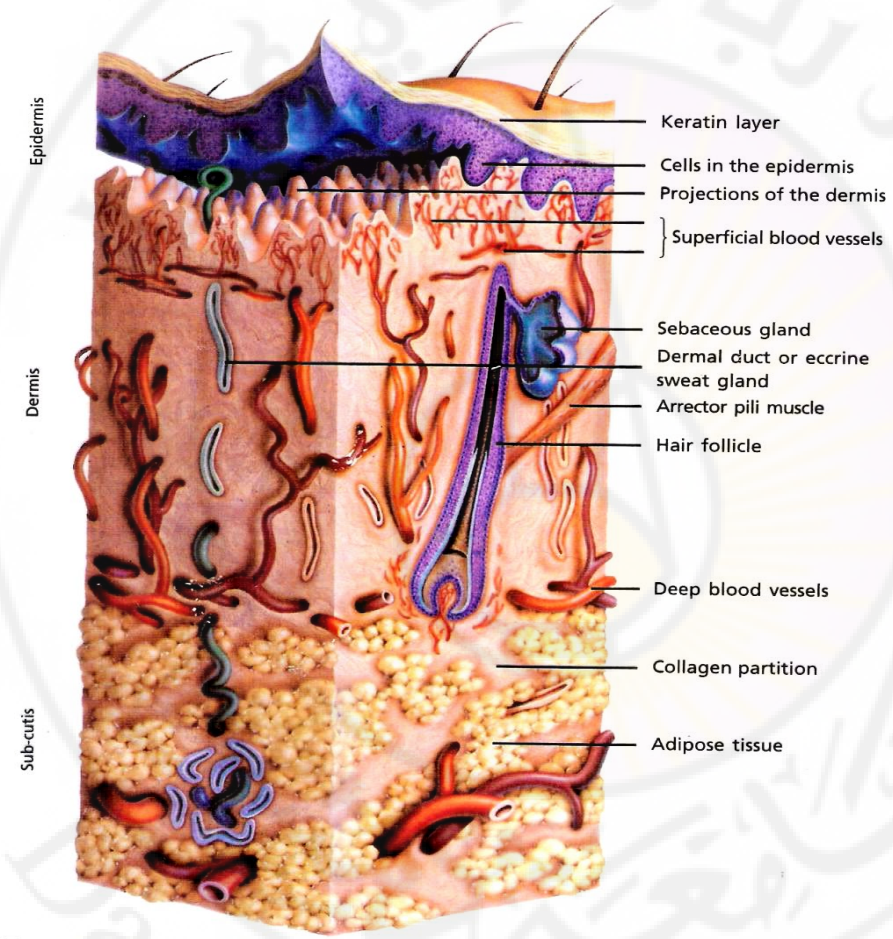
كلية الصيدلة - جامعة دمشق

بنية الجلد Skin Structure

يتألف الجلد من الطبقات الرئيسية:

1. فوق الأدمة Epidermis
2. الأدمة Dermis
3. تحت الأدمة Sub-cutis

Damascus University



Transverse section through the skin.

1- طبقة فوق الأدمة أو طبقة الخلايا المتقرنة

وهي الطبقة السطحية التي سماكتها بين 20-40 ميكرو متر تقي الجلد من العوامل الخارجية تتكون بشكل عام من مادة الكيراتين. في أسفل هذه الخلايا توجد الخلايا القاعدية basal layer حيث تتشكل الخلايا الجديدة وتدفع نحو الأعلى حيث تصل إلى الأعلى وتتقشر. هذه العملية تحدث باستمرار في كل لحظة من حياتنا حيث يتجدد جلدنا باستمرار.

عندما تتجه هذه الخلايا نحو الأعلى فإنها تفقد حيويتها وماءها وعندما تصل السطح تكون قد ماتت.

في هذه الطبقة أيضاً توجد الخلايا الميلانية melanocytes والتي تنتج صباغ الميلانين melanin الذي يعطي الجلد اللون الداكن dark color.

•تغطي الطبقة المتقرنة طبقة رقيقة واقية تتكون من مستحلب ينتج من المفرزات الدهنية والعرقية ذو درجة حموضة 5 يحتوي الطور الدهني في تركيبه على:

1- مركبات هيدروكربونية 15% أهمها السكوالين وهو هيدروكربون غير مشبع.

2- ستيرولات 5% أهمها الكوليسترول وطليعة الكولكالسيفرول الذي يعطي بفعل الطاقة الضوئية فيتامين D3

3- حموض دسمة حرة 20 % وبخاصة غير مشبعة

4- غليسيريدات ثلاثية 25%

5- استيرات لحموض دسمة مع أغوال مختلفة من الغليسرين 25%

والحموض الحرة أو المرتبطة بشكل غليسريدات وشموع فوسفوليبيدات تشبه حموض اللانولين وأغواله.

الطور المائي يفرز من منتجات الغدد العرقية خارجية الافراز المكونة من سائل ملحي بدرجة حموضة 3.8 – 5.6 ومفرزات الغدد العرقية داخلية الإفراز المكونة من سائل حليبي غني بالدسم والبروتينات والشوارد (الصوديوم، البوتاسيوم، والمغنزيوم، والكالسيوم) وكميات قليلة من الأمونياك وشوارد الكلور وآثار من الفسفات والسلفات والبولة والغلوكوز وحمض اللبن.

أما العوامل الاستحلابية فتتكون من الكولسترول واستراته واسترات حموض دسمة طويلة السلسلة تأتي من الغدد الدهنية وكذلك الفوسفوليبيدات القادمة من الخلايا الدهنية المتقرنة.

ويمكن تقسيم فوق الآدمة الى طبقتين هامتين:

الطبقة المتقرنة وطبقة مالبيكي

1- الطبقة المتقرنة كما تحدثنا عنها. ويتواجد الماء فيها بكمية تتراوح بين 7 – 20% من كمية الماء التي تتواجد في الطبقات السفلى

2- طبقة اجسام مالبيكي المخاطية تتكون من ثلاث طبقات:

أ- الحبيبية: وهي خلايا السيتوبلاسما فيها بشكل حبيبات ضخمة مكونة من مادة ليبوبروتينية.

ب- طبقة مالبيكي وهي خلايا في حالة انقسام مستمر ويوجد بينها العديد من ألياف الكولاجين

ت- الطبقة القاعدية فهي صف من الخلايا المكعبية نواتها في حالة انقسام كما تتضمن الخلايا الميلانية.

Skin color

The differences in skin color between different individuals and between races are determined genetically by the amount of melanin produced by the melanocytes and its distribution through out the skin.

In fact, differences in skin shade and color are determined not by the number and density of the melanocytes but by their degree of activity.

Exposure to sun light stimulates the production of melanin.

2- طبقة الأدمة Dermis

وتتألف من :

- خلايا الأدمة dermis cell
- ألياف مرنة وكولاجين collagen and elastin fibers
- أوعية دموية blood vessels
- أعصاب وأجسام حسية nerves and sensory organ
- غدد دهنية sebaceous glands
- أشعار hairs
- الغدد العرقية sweat glands
- الكولاجين والألياف المرنة هي المسؤولة عن متانة strength ومرونة elasticity الجلد.

أما الغدد الدهنية فإنها تفرز الدهن sebum إلى الجريب الشعري hair follicle الذي يقودها إلى سطح الجلد فتغلفه بطبقة دهنية oily layer. وكذلك الغدد العرقية eccrine sweat glands تفرز العرق عبر أنبوب شديد الالتفاف يعبر طبقتي الأدمة وفوق الأدمة ليصل إلى سطح الجلد بمسام ضيق tiny sweat pore، تنظم الغدد العرقية درجة حرارة الجسم.

Dermis cell خلايا الأدمة

The basic cell of the dermis is the fibroblast.

This cell produces collagen fibers.

Other cells within the dermis include white blood cells(leukocytes) which defense against infection.

ألياف الكولاجين والالاستين Collagen and elastin fibers:

Collagen and elastin are proteins in form of fibers.

The fibers are intertwined throughout the intercellular substance and provide the dermis with its strength and elasticity.

- The collagene fibers give the skin its strength.
- The elastin fibers are thinner than the collagen fibers .
- They are responsible for the skin elasticity.
- If these fibers are damaged (as a result of ageing or from excessive cumulative exposure to the sun), the skin becomes losse, thin and wrinkled.

مكونات الزهم

1-هيدروكربونات Hydrocabons 15%
squalene(unsaturated hydrocarbon)

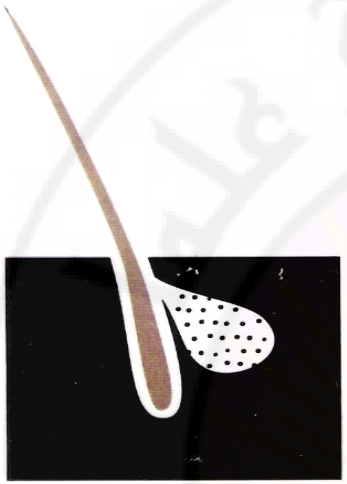
2- ستيرولات :sterols 5%

cholestrol and cocalciferol light energy
vit D

3- حموض دسمة حرة free fatty acid 20%

4- غليسيريدات glycerides 25%

5- استرات لحموض دسمة وأغوال غير الغليسرين



1 Cross-section of a hair follicle: normal sebaceous gland.



2 The duct leading from the sebaceous gland is blocked by sebum and keratin.



3 The sebum, produced in the sebaceous gland, accumulates behind the area of blockage.



4 The accumulated sebum distends the sebaceous gland and its duct.

Damascus University

Clogged pores cause acne itself.
These may be attributed to:
excess production of oil (sebum)
bacteria
hormones
dead skin cells
ingrown hairs

Acne may be noninflammatory or inflammatory.
Subtypes of acne within these two categories include:
blackheads
whiteheads
papules
pustules
nodules
Cysts

قد يكون حب الشباب غير التهابي أو التهابي. تشمل الأنواع الفرعية لحب الشباب ضمن هاتين الفئتين ما يلي:
الرؤوس السوداء
الرؤوس البيضاء
حطاطات
بثر
العقيدات
الخراجات

Noninflammatory acne

Noninflammatory acne includes blackheads and whiteheads.
These normally don't cause swelling. They also respond relatively well to over-the-counter (OTC) treatments.
Salicylic acid is often marketed for acne in general, but it usually works best on noninflammatory acne. It naturally exfoliates the skin, removing dead skin cells that can lead to blackheads and whiteheads.

Inflammatory acne

Pimples (البثور) that are red and swollen are referred to as inflammatory acne.

Although sebum and dead skin cells contribute to inflammatory acne, bacteria can also play a role in clogging up pores. Bacteria can cause an infection deep beneath the skin's surface. This may result in painful acne spots that are hard to get rid of.

Products containing benzoyl-peroxide may help reduce swelling and get rid of bacteria within the skin. These can also remove excess sebum. Your doctor may prescribe either an oral or topical antibiotic along with the benzoyl-peroxide to treat your inflammatory acne. Topical retionoids are also an important part of combatting inflammatory papules and pustules.

Papules الحطاطات

Papules occur when the walls surrounding your pores break down from severe inflammation. This results in hard, clogged pores that are tender to the touch. The skin around these pores is usually pink.

Pustules البثور

Pustules can also form when the walls around your pores break down. Unlike papules, pustules are filled with pus. These bumps come out from the skin and are usually red in color. They often have yellow or white heads on top.

Treating papules

To clear this type of acne blemish, try washing your face twice daily with an acne face wash that contains benzoyl peroxide or salicylic acid. If you have a lot of papules, it can be helpful to see a dermatologist

Treating pustules

To treat, wash your face with an acne product that contains benzoyl peroxide or salicylic acid. Resist the temptation to pop these. It can worsen acne. If you don’t see results from treatment in six to eight weeks, see a dermatologist.

Nodules العقيدات

Nodules occur when clogged, swollen pores endure further irritation and grow larger. Unlike pustules and papules, nodules are deeper underneath the skin.

Because nodules are so deep within the skin, you can't typically treat them at home. Prescription medication is necessary to help clear these up.

Your doctor or dermatologist will likely prescribe the oral medication isotretinoin .This is made from a form of vitamin A and is taken daily for four to six months. It can treat and prevent nodules by decreasing oil gland size within the pores.

Cysts

Cysts can develop when pores are clogged by a combination of bacteria, sebum, and dead skin cells. The clogs occur deep within the skin and are further below the surface than nodules.

These large red or white bumps are often painful to the touch. Cysts are the largest form of acne, and their formation usually results from a severe infection. This type of acne is also the most likely to scar.

The prescription medication isotretinoin is commonly used to treat cysts. In severe cases, your dermatologist may surgically remove a cyst.

Damascus University

Acne nodules and cysts

These acne blemishes penetrate deep into the skin, and often cause permanent acne scars when they heal. If you have acne that looks like this, you'll need a dermatologist's help to treat it. The sooner you start treatment, the fewer permanent scars you'll have

- Sweat glands regulate the body temperature:
- The main function of the sweat glands is to regulate body temperature.
- As sweat evaporates from the surface of the skin, it lowers the skin temperature, with a subsequent decrease in the body`s temperature

Eccrine sweat glands الغدد العرقية الخارجية الافراز

They secret sweat through extensively convoluted tube passes all the way up through the dermis and the epidermis to reach the skin surface by tiny sweat pore.

There are between two and three million eccrine sweat glands in the body but they are not distributed evenly .

There are more eccrine sweat glands in the areas of the face , the palms, and the soles.

The amount of the sweat also varies considerably from day to day, but can reach several liters a day.

Sweat glands regulate the body temperature.

- The secretion of the sweat is controlled through nerve endings attached to sweat glands.
- Physical efforts, warm weather, fever or emotional stress stimulates the sweat glands, which secret sweat.
- Sweat is largely water, with small amounts of salts, pH=3.8-5.6.
- Usually, the sweat secreted by the eccrine sweat glands does not cause body odor.

Apocrine sweat glands الغدد العرقية داخلية الافراز

These glands, unlike the eccrine sweat glands, are not distributed on most of the skin surface (armpits).

They develop and start to secret during adolescence.

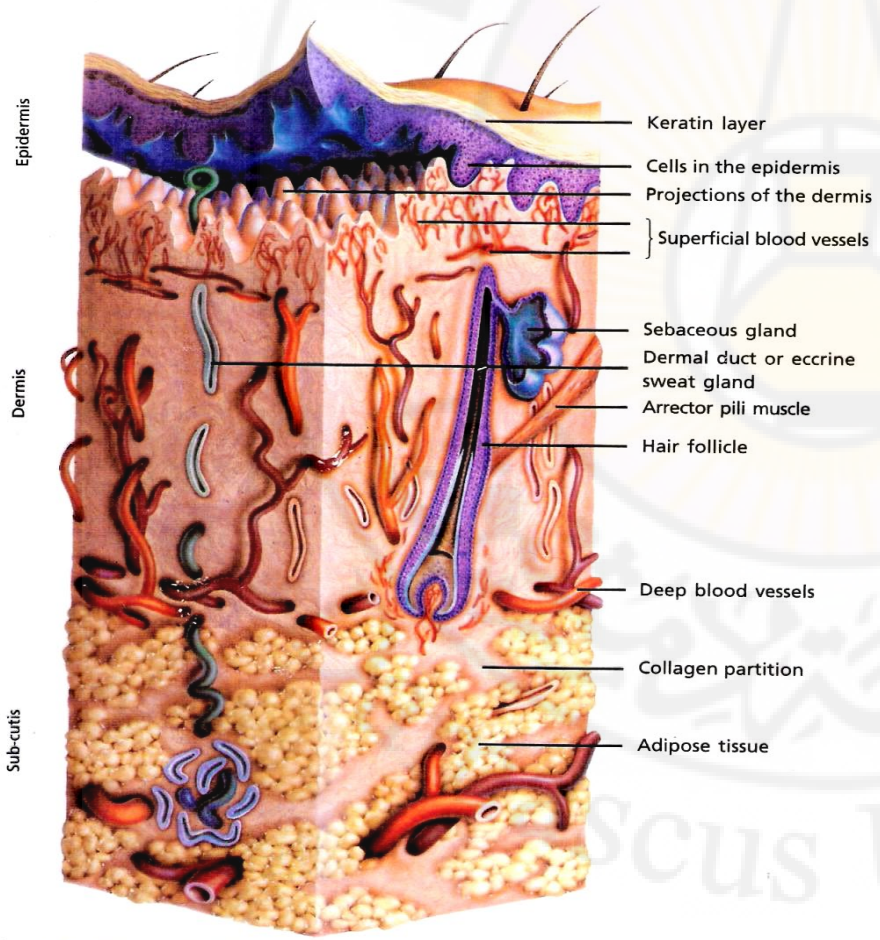
The secretion from the apocrine glands is relatively thick and has milky consistency.

It contains: proteins, fats, ions(Na, K, Mg, Ca), small amounts of amonia,and Cl and very small amounts of phosphate,sulphate, glucose, and lactic acids.

In the form in which it is secreted , it has no smell, however, subsequently, the organic compounds in it are broken down by bacteria, and the products of this breakdown are characterized by an unpleasant smell.

3- طبقة تحت الأدمة Sub-cutis

وهي طبقة من الخلايا الدسمة تعمل على حماية الأعضاء الداخلية من الصدمات الخارجية ومصدر هام للطاقة.



Transverse section through the skin.

Absorption of امتصاص الأدوية عبر الجلد drugs through skin

1- طريق المرور عبر فوق الأدمة: تشكل الخلايا الكيراتينية طبقة تشبه الاسفنج قادرة على امتصاص كميات كبيرة من الماء والمواد القطبية.

2- الامتصاص بواسطة الغدد الدهنية والجريبات الشعرية وهو ذو أهمية بالغة بالنسبة للمواد المحبة للدسم حيث أنها تنحل بالمفرز الدهني وتبلغ الأدمة حيث الأوعية الدموية بسهولة.

السواغات الدسمة القادرة على الامتزاج مع المفرزات الدهنية تحسن الامتصاص عبر الجلد للعديد من المواد الدوائية

العوامل المؤثرة في الامتصاص عبر الجلد

Factors affecting absorption through skin

1- **حالة الجلد ونوعه**: الجلد المحروق أو المرضوض المجروح يمتص المواد الدوائية بشكل أكبر من الجلد السليم.

نوع الجلد: دهني، جاف

2- **شروط التطبيق**: تركيز المواد الفعالة والإطالة في فترة التطبيق الجلدي واستخدام ضمادات جلدية محكمة.

3- **الخصائص الفيزيوكيميائية للمواد الفعالة**

- الوزن الجزيئي
- أبعاد أجزاء المواد قليلة الانحلال

Damascus University

4- خصائص السواغات

- أن تكون قادرة على الاختراق بسهولة لطبقات الجلد
- أن تكون قادرة على تحرير المادة الفعالة في مستوى المنطقة المصابة.
- السواغات الدسمة القادرة على الامتزاج مع المفرزات الدهنية تحسن الامتصاص عبر الجلد للعديد من المواد الدوائية.
- الأسس الاستحلابية ز/م أو م/ز من السواغات الأكثر قدرة على تحسين الامتصاص عبر الجلد للعديد من المواد الدوائية.
- المواد المحبة للماء مثل الغليسرول والبروبلين غليكول تعمل على منع تجفاف المستحضر وعلى إماهة الجلد hydration وبذلك تحسن الامتصاص.

Hydration of keratinous layer increases the absorbance through skin since it widen the pores and the channels so drugs can reach deep layers.

Example: salicylate esters

Ethyle salicylate p.c =1170 O/W

Methyl salicylate p.c =343 O/W

Glycol salicylate p.c =7.7O/W

Damascus University

- **To get hydration :**
- Occlusive dressing
- Fatty bases
- Emulsions leaving fatty layer on the skin
- Humectants.

2-Application conditions: concentration of active substance, time for application, using occlusive dressing.

Psoriasis was treated using corticoids and using occlusive dressing may decrease the dose by 100 times.

- Increasing temperature decreases the viscosity sebum and increases absorption.
- The thickness of the keratinous layer.

- Estradiol in ocalyptus has been absorbed 4 times more than estradiol in alcohol(as if it was given intramuscularly).
- The most important excipients from hydrocabons C8-C10.
- alcohols C7-C8.
- Esters with long chain hydrocarbns acids and alcohols.
-

3-Physiochemical properties of the active substance

- Molecular weight
- Particle size of insoluble substances:

  17-betametathone valerate
- Solubility of the active substance in fats.
- methyl and ethyl nicotin p.c=1

3-Physiochemical properties of the active substance

- Molecular weight
- Particle size of insoluble substances:

  17-betametathone valerate
- Solubility of the active substance in fats.
- methyl and ethyl nicotin p.c=1

4-Excipient properties -

- Excipient should be able to penetrate through the skin layers.
- Excipient should be able to release the active substance in the injuried layer.
- Fatty excipients mix easily with sebum which mean enhancing for many susbtances absorption.

- Estradiol in ocalyptus has been absorbed 4 times more than estradiol in alcohol(as if it was given intramuscularly).
- The most important excipients from hydrocabons C8-C10.
- alcohols C7-C8.
- Esters with long chain hydrocarbns acids and alcohols.
-

- Vegetable oils penetrate easier than mineral oils.

.In markets now many synthetic excipients:

Penetrates easily, and with low viscosity such as:

Isoprpyl merystate

Glycerol caprate

Hexyl laurate

Deceyl oleate

المستحضرات الجلدية
Skin products

للمستحضرات الجلدية أنواع متعددة تختلف باختلاف السواغ والهدف من التطبيق:

- **المراهم Ointments**: وهي شكل صيدلاني نصف صلب يتألف إضافة إلى المواد الدوائية من أسس دسمة كارهة للماء (الفازلين) أو محبة للماء (اللانولين). تترك السواغات الدسمة طبقة رقيقة على الجلد غير غسولة بالماء. أما اللانولين فيتميز بقدرته على امتصاص الماء تبعاً لتركيبه وبقدرته الاختراقية العالية.
- **الكريمات Creames**: وتتكون من أسس استحلابية من نمط ز/ م أو م / ز إضافة إلى المواد الدوائية التي تتوضع في أحد الطورين حسب ذوبانها.


fougera
NITROGLYCERIN
OINTMENT, USP 2%
BACTROBAN
MUPIROCIN OINTMENT 2%
15 gram

أنماط الكريمات:

1- ***الكريمات المختفية vanishing creams***: تحتوي نسبة عالية من الماء سهلة الغسل، لها تأثير مبرد cooling effect، ليس لها تأثير حاجزي.

2- ***الكريمات الليلية nighty creams***: تحوي نسبة عالية من الزيت فهي دهنية وحاجزية أكثر من المختفية وأقل من المراهم. تطبق على الجلد الجاف وغالباً ما تحوي مواد مغذية nourishing cream.

3- ***الكريمات المنظفة cleansing cream***: كريمات تحوي صوابين.

4- كريمات مرطبة moisturizing cream: تعمل على زيادة رطوبة الجلد عن طريق تشكيل طبقة حاجزية تمنع تبخر الماء إضافة إلى احتوائها على مرطب humactant يمتص الماء.

5- ***كريمات الأساس foundation cream***: وهي كريمات مرطبة تحوي عامل ملون أو واقي شمسي تعمل على إخفاء بعض العيوب الجلدية.

6- ***الكريمات الباردة cold creams***: هي مزيج من المواد الدسمة والماء عند التطبيق على الجلد يتبخر الماء ويعطي الشعور بالبرودة مثل شمع النحل وزيت الزيتون مع الماء وعطر الورد.

- **المعاجين Pastes**: وهي عبارة عن أمزجة لأجسام دسمة تختلف في حبها للماء تضاف إليها كميات كبيرة من المساحيق. إن إضافة المساحيق تضفي على المستحضرات تأثيراً امتصاصياً.
- **الكولوديون Collodion**: هي مستحضرات سائلة تحوي بحالة محلول لمحل عضوي، عدة أدوية مخصصة للتأثير السطحي مثال ذلك المطهرات التي تحوي مشتقات سللوزية وتترك على سطح الجلد طبقة رقيقة واقية.
- **اللوسيونات Lotions**: (سواغات مائية): وهي محاليل أو أمزجة من الماء والغول مضافاً إليها عوامل رافعة للزوجة (غليسيرين، بروبيلين غليكول، مثيل سللوز، CMC) وذلك لتسهيل الالتصاق وعوامل فعالة على السطح متنوعة وذلك لضمان بعثرة جيدة للمواد الفعالة غير المنحلة.
- **الهلاميات المائية Hydrogels**: وهي ذات قوام أعلى من قوام اللوسيونات وهي مستحضرات غنية جداً بالماء تتمتع ببنية متغيرة القوام لدى الرج texotropic وذلك لتجنب حدوث الترسب أثناء التخزين ولتسهيل مدها على الجلد.
- **مستحضرات PEG** التي تتكون من أمزجة PEG السائلة والنصف صلبة والصلبة.

هذا وتعد الأسس الاستحلابية نموذج ز/م أو م/ز من السواغات الأكثر قدرة على تحسين الامتصاص عبر الجلد للعديد من المواد الدوائية.

هذا وقد اعتمد المؤلف Harry التصنيف التالي للسواغات الجلدية تبعاً لدرجة اختراقها:

- سواغات شديدة الاختراق: كاللانولين، كريمات نموذج ز/م موادها الدسمة ذات منشأ طبيعي (حيواني أو نباتي)
- سواغات متوسطة الاختراق: الزيوت النباتية (زيت الزيتون، زيت الأراشيد، مستحلبات نموذج ز/م ذات زيوت معدنية، مستحلبات نموذج م/ز ذات دسم حيوانية أو نباتية.
- سواغات ضعيفة الاختراق: الزيوت المعدنية ومستحلبات نموذج م/ز ذات زيوت معدنية

ويختار الأطباء سواغات المستحضرات الجلدية تبعاً لتطور الإصابة الجلدية وتبعاً لبعض التأثيرات العلاجية المرغوب فيها كالتأثير المنعش، والتأثير المضاد للالتهاب.

وعلى سبيل المثال لدى المعالجة بالكوريتكوئيدات corticoeides باستعمال 0.02% بيفالات الفلوميتازون، استعملت خمسة أشكال جلدية مختلفة وذلك تبعاً للحالة المرضية:

- التهاب جلد حاد قيحي ناز مع شعور بالحكة ⇦ **يستعمل اللوسيون** ز/م فهو نفوذ تجاه الافرازات ويتبخر الطور المائي ⇦ تسكين الإحساس بالحكة.
- التهاب جلد وقروح نازة ⇦ **معجون مائي** ز/م يحوي كمية كبيرة من أكسيد التيتان (مساحيق) لتجفف القروح ويتمتع بتأثير منعش.
- التهاب جلد حاد قيحي وأكزيما غير نازة وجلد دهني حساس تجاه المواد الدسمة نستخدم **كريم** ز/م الذي له تأثير منعش و لا يترك طبقة دسمة.
- التهاب مزمن جلد جاف يستعمل **كريم نموذج م/ز** المواد الدسمة فيه ذات قدرة اختراقية عالية.
- جلد جاف وخشن يعاني من التهابات مزمنة يستعمل مرهم يحوي الفازلين ليشكل طبقة واقية تمنع جفاف الجلد وتحفظ رطوبته أو يستعمل في المراحل الأخيرة بعد أن يكون قد عولج التهاب جلد حاد ناز بكريمات ز/م أو معجون مائي ولا تستعمل المراهم في التهابات الجلد الحادة في شكلها النضحي ولا تستعمل في التهاب الجلد الدهني.

- Emulsion systems
- They are the best excipients which can enhance the absorption through skin for many drugs.
- Study showed the absorption of dexamethasone from w/o emulsion was maximum but from o/w emulsion, aqueous excipients, veegum gel,and PEG it was minimum.
- It showed also that the absorption of diphenhydramine hydrochloride is maximum from veegum gel, PEG, aqueous excipients.
- W/o emulsions can give water soluble drugs extended release system.

أهم المواد الأولية المستخدمة في المستحضرات الجلدية والتجميلية:

- ***الفازلين petrolatum*** : وهو من الفحوم الهيدروجينية المشبعة الذي يستحصل من نواتج البترول وهو نوعين أبيض وأصفر، خامل كيميائياً، لا يزنخ ويتوافق مع العديد من المواد، لاتؤثر به الحموض والقلويات. غير ممتص من قبل الجلد، قدرته الاختراقية ضعيفة، ولا يمتص الماء.

- ***البارافينات paraffins***: وهي أيضاً أمزجة معقدة لفحوم هيدركربونية مشبعة، البارافين السائل liquid petrolatum أو زيت الفازلين يستخدم في تنعيم مساحيق المواد الدوائية قبل إضافتها إلى المراهم، يشارك عادة مع الفازلين لتحسين سيولته. البارافين الصلب solid paraffine كتل بيضاء، صلبة، ينصهر بين 50 – 60° م له بنية بلورية، يستخدم كرافع قوام.

- **الغليسريدات طبيعية المنشأ *Natural glycerides*:**

1- **الزيوت النباتية vegetables oils**: وتتكون غالباً من غليسريدات ثلاثية لحموض دسمة عالية الوزن الجزيئي مشبعة saturated وغير مشبعة unsaturated لحمض الشحم، حمض النخيل، وحمض الزيت ويجب أن تتصف بما يلي:

أ- ذات قرينة حموضة ضعيفة.

ب- خالية من الحموض الدسمة ذات السلاسل القصيرة سريعة التزنخ.

أشهرها: زيت اللوز الحلو amande oil، زيت الأراشيد، زيت الأفوكاة avocats oil، زيت الرشيمات، زيت القطن، زيت الكتان، زيت الزيتون، زيت الخروع، زيت السمسم.

2- **الغليسريدات الحيوانية animal glycerides**: أشهرها زيت كبد الحوت الغني بفيتامين A، D .

- **الشموع النباتية** V.waxes :

وأشهرها شمع الخرنوبا الذي يتميز بدرجة انصهار عالية 80م فيستعمل في تحضير حمرة الشفاه .يستحصل عليه من أشجار النخيل في البرازيل

الشموع الحيوانية Animal waxes:

1. **شمع النحل Bees Wax**: ويؤخذ من أقراص العسل ويستخدم في تحضير الكولد كريم كرافع قوام وعامل استحلابي ضعيف: م/ز.
2. **أبيض البال spermaceti** : يستحصل من المادة الزيتية في رأس الحوت يستخدم أيضاً كرافع قوام.
3. **اللانولين lanolin**: شحم الصوف وهو قريب جداً في تركيبه من تركيب دسم المفرز الدهني البشري لذا ذو قدرة اختراقية عالية وعامل استحلابي نموذج م/ز يستخدم في تحضير كريمات نموذج م/ز

الحموض الدسمة ومشتقاتها Fatty acids & Derivatives:

1. **حمض الشحم**: $C_{17}H_{35}COOH$ ويستخدم كرافع قوام وفي الكريمات الصابونية حيث يتفاعل مع الصود أو البوتاس ويشكل صابون عامل استحلابي ز/م.
2. **استرات الحموض الدسمة**:

أ- **ميريستات الإيزوبروبيل Isopropyl Myristate** سائل زيتي حال للعديد من المواد الدوائية يستخدم في مواضع استعمال الزيوت النباتية، لا يتأكسد، ممتص جيداً ومحتمل من قبل الجلد.

ب- **لورات الهكزيل (استر هكزيلي لحمض اللوريك) Cetiol A، زيتات الديسيل Cetiol V (استردبسيلي لحمض الزيت)** وهما استرات لأغوال ذات وزن جزئي متوسط وذات قدرة اختراقية عالية وحال للعديد من المواد الدوائية.

3. استرات حموض مع أغوال عالية الوزن: أهمها

Amphocerin ، de hymulus F, de hymulus E

وتستخدم كعوامل استحلابية م/ز

أ- استرات الغليسرول وأشهرها الكوتينا cutina وحيد شمعات الغليسرول mono stearate glycerol وهي تستعمل كرافع للقوام، ممتصة من الجسم وعامل استحلابي م/ ز ويضاف لها صابون سترات البوتاسيوم أو في نوع آخر لوريل سلفات Na فنحصل على عوامل استحلابية محبة للماء ز/ م.

ب- زيت الميغليول: ثلاثي الغليسريدات لحموض دسمة مشبعة ذات منشأ نباتي C8 – C12 يمتد بسهولة عبر الجلد، سهل الاختراق ، حال للعديد من المواد الدوائية.

- ***الأغوال الدسمة Fatty alcohols:***

1. الغول السيتلي $C_{16}H_{33}OH$ Cetyl alcohol
2. الغول الستئريلي $C_{18}H_{37}OH$ Stearyl alcohol
3. الغول السيتوسيتريلي مزيج من السيتلي والستئريلي وتستخدم كعوامل استحلابية ضعيفة م/ز ورافعة للقوام، وتدخل في تركيب الشموع ذاتية الاستحلاب مثل لانيت W الذي يتركب من 90% غول سيتوستيريلي + 10% غول لوريل سلفات Na.

ناقش الصيغ التالية

كريم ستئرات البوتاسيوم:

حمض الشمع 10.9 غ ، أبيض البال 1.9 غ ، K2Co3 0.55 غ ، غليسرين 22 غ، ماء 64 غ.

كريم ز/م لا يترك طبقة دسمة على الجلد :

غول ستئريلي 15 غ، شمع النحل 8 غ، سبان80 1.25 غ، توين 80 3.75 غ، محلول السوربيتول 70% 7.5 غ، ماء 64.5 غ.

كريم زيت السيليكون:

DIMETHICONE 350 10 غ، غول سيتو ستئريلي 5 غ، بارافين سائل 40 غ، CETRIMIDE 0.5 غ، كلور كريزول 0.1 غ، ماء 44.4 غ.

كريم مطري للجلد:

كوتينا MD 4 غ، كوتينا CP 4 غ، إيمولجين B1 1 غ، إيمولجين B2 1 غ، ميريستات وبالميتات الايزوبروبيل 5 غ، كاربوبول 940 0.5 غ، تري ايتانول أمين 0.5 غ، غليسرين 3 غ، ماء 81 غ.

حليب للأيدي (مقاوم للحموض الضعيفة):

غول سيتيلي 0.5 غ، حمض الشمع 5 غ، غليسرين 2 غ، ألجينات الصوديوم 0.3 غ، تري ايتانول أمين 0.5 غ، ماء م .ك حتى 100.

و من المواد المستخدمة أيضاً في تحضير المستحضرات الجلدية

- **السيليكونات Silicones** : توجد بحالة زيوت مختلفة اللزوجة و يشار الى اللزوجة برقم يعبر عنه بالسنتي ستوك . من خواصها أنها مقاومة جيدة للحرارة فتطرأ عليها تبدلات طفيفة تبعاً لتبدلات درجة الحرارة، خاملة كيميائياً ، تتمتع بمقاومة كبيرة تجاه التبدلات ذات المنشأالجرثومي، محتملة من قبل الجلد، ذات قدرة طاردة للماء . تستعمل في تحضير المراهم الحاوية المواد الفعالة قليلة الثبات مثل المضادات الحيوية .
- **المواد المرطبة أو المطرية Humectants and emollient substances** :

الغاية من اضافة هذه المواد هي :

1. منع تجفاف المستحضرات الجلدية بخاصة كريمات نموذج ز/م بفضل قدرتها على الإمساك بالماء
2. منع تشكل طبقة رقيقة دسمة مستمرة على سطح الجلد لدى تطبيق كريمات دسمة وبالتالي منع تخرب الجلد و التهابه
3. تقوم بفعل مطري للجلد وذلك بسبب احتفاظها في مستوى الطبقات السطحية للجلد بدرجة عالية من الاماهة .

أهم العوامل المستخدمة : الغليسرين، الغليكولات ، السوربيتول 70% وتستخدم بتركيز 3-٥% للحصول على التأثير المرطب ، وبتركيز 10-20% للحصول على التأثير المطري.ولكن يجب الانتباه الى محذور تجفيف الجلد والأغشية نتيجة جذب الماء بكميات كبيرة من طبقات الجلد العميقة . والمواد المرطبة الأكثر تجفافا للجلد هي الغليكولات ثم الغليسرين أما السوربيتول فلايبدي هذا المحذور .

كما تدخل الهلاميات المائية في تحضير المستحضرات الجلدية ، بعضها ذات منشأ طبيعي مثل الأغار، ألجينات الصوديوم وغيرها وبعضها مواد اصطناعية وأشهرها الكاربوبول: وهو متماثر حمض الأكريلي ويستخدم بخاصة الكاربوبول 940، قليل الانحلال في الماء ولكنه ينتبج ليعطي هلاميات قليلة اللزوجة ذات pH حامضية . ان التعديل الجزئي لهذه المواد بماءات الصوديوم يسمح بزيادة لزوجيتها ويمكن للكاربوبول أ، يهلم محلات أخرى غير الماء مثل الغول. ويوجد أيضاً السلولوز ومشتقاته و اللابونيت .

- **المواد المهلمة للمحلات وللمواد الدسمة**
- **الايروزيل** : وهو عبارة عن حمض السيليس ذو النعومة العالية جداً ، يملك الايروزيل خاصة تثبيت الماء بوساطة الروابط الهيدروجينية أو تثبيت مواد عضوية مختلفة الاستقطابية وذلك لتشكيل هلامة . لايناسب الايروزيل مستحلبات من نمط م/ز بسبب ألفته العالية لماء هذه المستحلبات مما يخرب البنية الهلامية . ويوجد أيضاً البنتون 38 وستئرات الألمنيوم وشموع مجهرية التبلور مثل Esma M وEsma P,
- **البولي ايثيلين غليكول**: وهي مواد متماثرة تنتج عن تكاثف أكسيد الايثيلين والماء .
- متعددات البولي ايثلين غليكول ذات الوزن الجزيئي أقل من 600 سائلة أما ذات الوزن الجزيئي أعلى من 1000 فهي صلبة ، تزداد قساوة مع ازدياد درجة التماثر .

ميزات المراهم المكونة من PEG ومساوئها :

1. انحلاليتها في الماء تجعلها سهلة الغسيل والازالة
2. تمتص الماء بسهولة كبيرة مما يؤدي الى تجفيف جلد المريض
3. تجف بسرعة اذا لم تكن محمية من التبخر
4. اختراقها ضعيف

Table 3.B Determine the activity of some surfactants according to their HLB

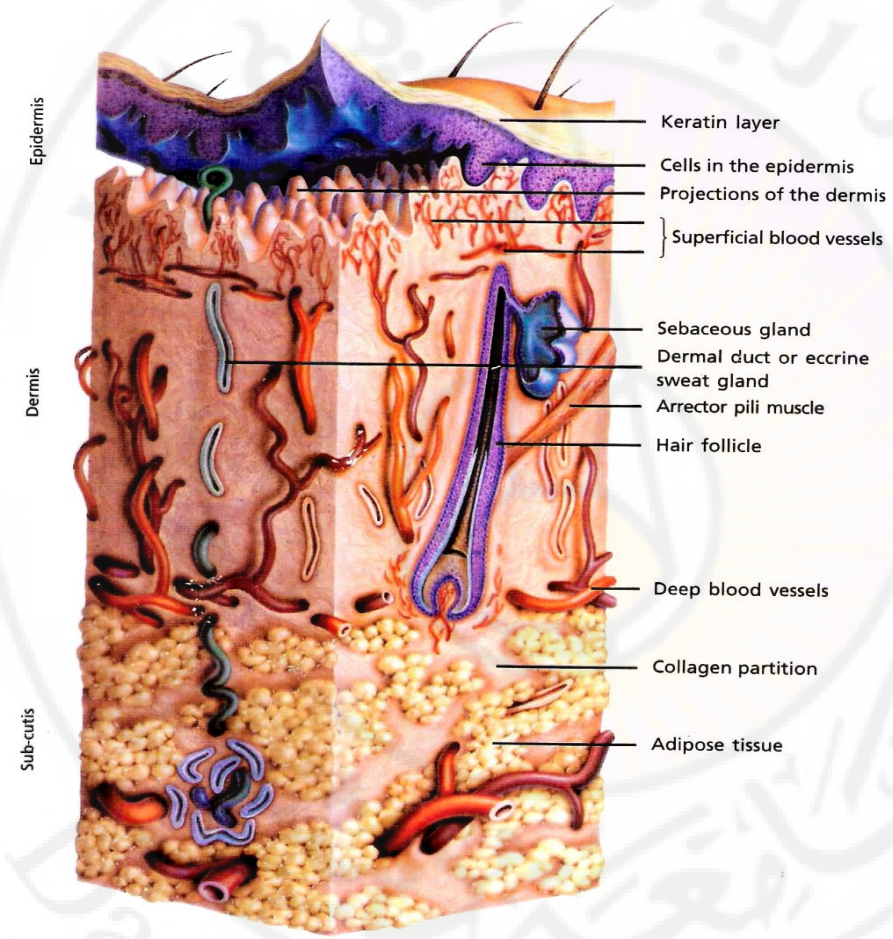
Activity	HLB
Antifoaming	1 – 3
Emulsifiers (w/o)	3 – 6
Wetting agent	7 – 9
Emulsifiers (o/w)	8 – 18
Solubilizers	15 – 20
detergents	13 - 15

بنية الجلد Skin Structure

يتألف الجلد من الطبقات الرئيسية:

1. فوق الأدمة Epidermis
2. الأدمة Dermis
3. تحت الأدمة Sub-cutis

Damascus University



Transverse section through the skin.

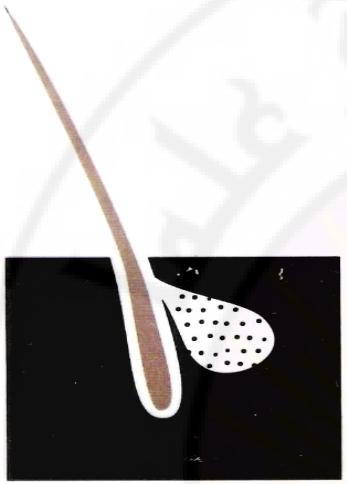
ملحقات الجلد

- 1- الجريبات الشعرية: وهي انخماص لطبقة وحيدة من البشرة يمتد لأسفل طبقة الأدمة
- 2- الغدد الدهنية: 90% من هذه الغدد مفتوحة على الجريبات الشعرية
- 3- الغدد العرقية

حب الشباب

- في سن البلوغ فرط نشاط الغدد الدهنية يؤدي الى امتلاء الجريبات الشعرية بالزهم
- الخلايا الميتة تسد مسام الجريبات الشعرية
- تتكاثر الجراثيم اللاهوائية وتفرزانزيم الليباز الذي يؤدي الى ارتفاع نسبة الحموض الحرة وتخريش البشرة.
- تستدعى الكريات البيضاء الى المنطقة ويظهر حب الشباب بشكل بثورحمراء متورمة ممتلئة بالقيح وقد يتطور الى عقيدات و خراجات.
- ليس بالضرورة أن يتطور حب لشباب الى حالة البثور المتقيحة وإنما قد تقف عند اندفاعات جلدية طفيفة ذات رؤوس سوداء أوبيضاء.

حب الشباب Acne



1 Cross-section of a hair follicle: normal sebaceous gland.



2 The duct leading from the sebaceous gland is blocked by sebum and keratin.



3 The sebum, produced in the sebaceous gland, accumulates behind the area of blockage.



4 The accumulated sebum distends the sebaceous gland and its duct.

Damascus University

مكونات الزهم Sebum composition

1- مركبات هيدروكربونية 15% أهمها السكوالين وهو هيدروكربون غير مشبع.

2- ستيرولات 5% أهمها الكوليسترول وطليعة الكولكالسيفرول الذي يعطي بفعل الطاقة الضوئية فيتامين D3

3- حموض دسمة حرة 20 % وبخاصة غير مشبعة

4- غليسيريدات ثلاثية 25%

5- استيرات لحموض دسمة مع أغوال مختلفة من الغليسرين 25%

والحموض الحرة أو المرتبطة بشكل غليسريدات وشموع فوسفوليبيدات تشبه حموض اللانولين وأغواله.

مسام البشرة المسدودة تسبب حب الشباب.
قد يعزى ذلك إلى:
فرط إنتاج الزهم
البكتيريا
الهرمونات
خلايا الجلد الميتة
نمو الشعر تحت الجلد ingrown hairs

قد يكون حب الشباب

1-غير التهابي **Noninflammatory acne**

2- التهابي **Inflammatory acne**

تشمل الأنواع الفرعية لحب الشباب ضمن هاتين الفئتين ما يلي:

الرؤوس السوداء blackheads

الرؤوس البيضاءwhiteheads

حطاطات papules

بثورpustules

العقيدات nodules

الخراجات Cysts

Noninflammatory acne حب الشباب اللالتهابي

Noninflammatory acne includes blackheads and whiteheads.
These normally don't cause swelling.
They also respond relatively well to over-the-counter (OTC) treatments.
Salicylic acid is often marketed for acne in general, but it usually works best on noninflammatory acne.
It naturally exfoliates the skin, removing dead skin cells that can lead to blackheads and whiteheads.

Damascus University

جل (هلامة) حمض الصفصاف

حمض الصفصاف	2 غ
كاربوبول 940	4غ
محلول ماءات الصوديوم 10%	16 مل
EDTA	0.05 غ
ماء م.ك مع مواد حافظة	100مل

Penzoyl peroxide

- It works as an antiseptic to reduce the number of germs (bacteria) on the surface of your skin. It's usually one of the first treatments recommended for mild to moderate acne. It comes as a gel or face wash containing 5% benzoyl peroxide.

جل الفيغم لحمل مادة البنزويل بيروكسيد

- الفيغم هو سيليكات الألمنيوم والمغنزيوم

الفيغم عالي اللزوجة H V	1 غ
كاربوكسي ميثيل سللولوزصودي (متوسط اللزوجة)	0.85 غ
غليسرين	3 غ
محلول دي اوكتيل سلفوسوكسينات الصوديوم	5غ
عامل حافظ	م.ك
ماء مقطر م.ك	90.5 غ

Inflammatory acne حب الشباب الالتهابي

Pimples (البثور) that are red and swollen are referred to as inflammatory acne.

Although sebum and dead skin cells contribute to inflammatory acne, bacteria can also play a role in clogging up pores. Bacteria can cause an infection deep beneath the skin's surface. This may result in painful acne spots that are hard to get rid of.

Products containing benzoyl-peroxide may help reduce swelling and get rid of bacteria within the skin. These can also remove excess sebum. Your doctor may prescribe either an oral or topical antibiotic along with the benzoyl-peroxide to treat your inflammatory acne.

أنماط الكريمات:

1- ***الكريمات المختفية vanishing creams***: تحتوي نسبة عالية من الماء سهلة الغسل، لها تأثير مبرد cooling effect، ليس لها تأثير حاجزي.

2- ***الكريمات الليلية nighty creams***: تحوي نسبة عالية من الزيت فهي دهنية وحاجزية أكثر من المختفية وأقل من المراهم. تطبق على الجلد الجاف وغالباً ما تحوي مواد مغذية nourishing cream.

3- ***الكريمات المنظفة cleansing cream***: كريمات تحوي صوابين.

4- كريمات مرطبة moisturizing cream: تعمل على زيادة رطوبة الجلد عن طريق تشكيل طبقة حاجزية تمنع تبخر الماء إضافة إلى احتوائها على مرطب humactant يمتص الماء.

5- ***كريمات الأساس foundation cream***: وهي كريمات مرطبة تحوي عامل ملون أو واقي شمسي تعمل على إخفاء بعض العيوب الجلدية.

6- ***الكريمات الباردة cold creams***: هي مزيج من المواد الدسمة والماء عند التطبيق على الجلد يتبخر الماء ويعطي الشعور بالبرودة مثل شمع النحل وزيت الزيتون مع الماء وعطر الورد.

- Topical retionoids are also an important part of combatting inflammatory papules and pustules.
- **Topical retinoids** are prescribed to control blackheads and whiteheads, or comedonal **acne**. They also called retinoic acid or vitamin A acid.

Tretinoin 0.025% creme

- Each gram contains: Tretinoin 0.025%, stearic acid 7%, isopropyl myristate 5%, polyoxyl 40 stearate 6%, stearyl alcohol 5%, xanthan gum 0.5%, sorbic acid, butylated hydroxytoluene, and purified water.

Papules الحطاطات

Papules occur when the walls surrounding your pores break down from severe inflammation. This results in hard, clogged pores that are tender to the touch. The skin around these pores is usually pink.

Pustules البثور

Pustules can also form when the walls around your pores break down. Unlike papules, pustules are filled with pus. These bumps come out from the skin and are usually red in color. They often have yellow or white heads on top.

Treating papules

To clear this type of acne blemish, try washing your face twice daily with an acne face wash that contains benzoyl peroxide or salicylic acid. If you have a lot of papules, it can be helpful to see a dermatologist

Treating pustules

To treat, wash your face with an acne product that contains benzoyl peroxide or salicylic acid. Resist the temptation to pop these. It can worsen acne. If you don’t see results from treatment in six to eight weeks, see a dermatologist.

Nodules العقيدات

Nodules occur when clogged, swollen pores endure further irritation and grow larger. Unlike pustules and papules, nodules are deeper underneath the skin.

Because nodules are so deep within the skin, you can't typically treat them at home. Prescription medication is necessary to help clear these up.

Your doctor or dermatologist will likely prescribe the oral medication isotretinoin .This is made from a form of vitamin A and is taken daily for four to six months. It can treat and prevent nodules by decreasing oil gland size within the pores.



Tablet coating

Tablet coating process have occurred over the past thousand years, one of the references to coated solid dosage forms appears in 850-923, probably on the basis of food preservation methods. In French at 1600s, coating described as a means of masking the taste of medicines.

Sugar coating of pills were developed in the mid 1800s and patent issued in 1837-1840 (In French), subsequently got rapid acceptance in USA & Europe for the next 75 years, on a large scale production on coating pans with unchanged formula.

In 1953, A dramatic change was made on tablet coating when Abbott Laboratories marketed the first film coated pharmaceutical tablets. This stimulated interest in tablet coating technology for the next 12-15 years and several patents & a series of coating pans have been developed.

WWW.BDTECHIE.COM



Coating of tablets

Reasons for tablet coatings:

- to protect the drug from **degradation in the stomach** (an enteric coating)
- to prevent drug-induced irritation at a specific site within the gastrointestinal tract, e.g. the stomach for non-steroidal antiinflammatory drugs
- to provide controlled release of the drug throughout the gastrointestinal tract
- to target drug release to a specific site in the gastrointestinal tract, e.g. the delivery of drug to the colon for the treatment of inflammatory conditions
- to mask the taste of drugs
- to improve the appearance of the tablet.

General description of tablet coating

- The tablets (or granules) are placed within the coating apparatus and agitated.
- The coating solution is sprayed on to the surface of the tablets.
- Warm air is passed over the tablets to facilitate removal of the solvent from the adsorbed layer of coating solution on the surface of the tablets.
- When the solvent has evaporated, the tablets will be coated with the solid component of the original coating solution.

Coating methods

- 1-Sugar coating method
- 2-Film coating method

- The sugar coating tablet may be divided into the following steps:

a) Water proofing and sealing coats

b) sub coating

c) smoothing and final rounding

d) finishing and coloring

e) Imprinting

f) polishing

a) Waterproofing and sealing coats: the solution of pharmaceutical shellac or other polymer is poured or sprayed on the compressed tablet rotating in the coat pans.

Warm air is blown into the pan during the coating to hasten the drying and to prevent tablets from sticking together

b)Subcoating**: three to five subcoats of a sugar-based syrup are applied. This bound the sugar coating to the tablet and provides rounding.**

The syrup also contains gelatin, acacia, or polyvinylpyrrolidone (PVP) to enhance coating.

- when the tablets are partially dry, they are sprinkled with a dusting powder usually mixture of powdered sugar and starch but sometimes talc, acacia or precipitated chalk as well.
- Warm air is applied to the rolling tablets and when they are dry, the process is repeated until the tablets are of the desired shape and size.
- The tablets are gently shaking on a cloth screen.

- c)Smoothing and final rounding

Five to ten additional coatings of a thick syrup are applied to complete the rounding and smooth the coatings.

As the syrup is applied the operator moves his hand through the rolling tablets to distribute the syrup and to prevent the tablet from sticking to one another.

A dusting powder is often used between syrup applications . Warm air is blown to hasten the drying time of each coat

d) Finishing and coloring

Thin syrup containing suitable color is used.

It is applied many times to get several layers .

This step is carried out in clean pan empty of any coating substances used in the previous steps.

e) Imprinting

Using special machine to give tablets identification codes.

The imprinting could be engraved.

f) Polishing

Carnuba wax is used

Sugar coating method

The sugarcoating process is

- tedious
- time-consuming,
- requiring the expertise of highly skilled technicians
- also results in coated tablets that may be twice the size and weight of the original
- From a patient's point of view, large tablets are not as easily swallowed as are small tablets.

Film coating process

The film-coating process, was developed to produce coated tablets having essentially the same weight, shape, and size as the originally compressed tablet.

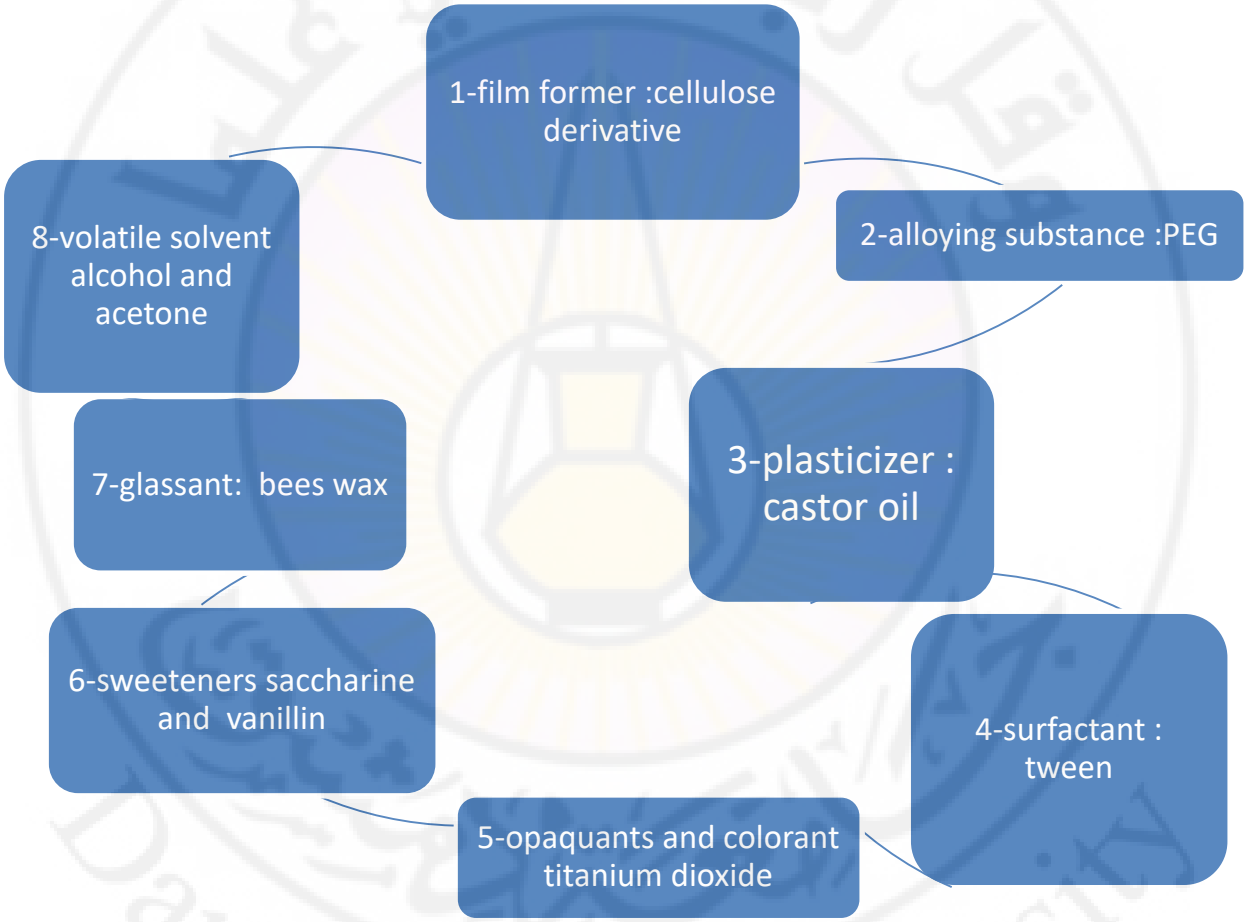
Also, the coating is thin enough to reveal any identifying monograms embossed in the tablet during compression by the tablet punches.

Film-coated tablets also are far more resistant to destruction by abrasion than are sugarcoated tablets. However, like sugarcoated tablets, the coating may be colored to make the tablets attractive and distinctive.

Kinds of Film-Coating solutions

- Film-coating solutions may be
- 1- nonaqueous solution
- 2- aqueous solution.

Non aqueous coating solution



Damascus University

polymers that are used to film-coat

In addition to improving the appearance of conventional tablets, film coatings are employed to control the rate and duration of drug release or to target drug release to certain regions of the gastrointestinal tract tract.e.g. the colon.

Note: If the film coating is insoluble, the tablet will retain its shape during transit along the gastrointestinal.

polymers that are used to film-coat

Examples of polymers that are used to film-coat tablets dissolve in the stomach to enable tablet disintegration and drug dissolution) include:

- hydroxypropylmethylcelluose
- hydroxypropylcellulose
- Eudragit E100 (a co-polymer of butylmethacrylate, 2-dimethylaminoethylmethacrylate and methylmethacrylate, 1:2:1)

polymers that are used to film-coat

Drug release occurs by diffusion through the insoluble coating and subsequent partitioning into the gastrointestinal fluids. Examples of polymers that may be used for this purpose include: (1) ethylcellulose; and (2) Eudragit RS and RL.

polymers that are used to film-coat

Ethylcellulose

Ethylcellulose is an ethyl ether of cellulose in which there is complete substitution of the hydroxyl groups with ethyloxygroups. It is insoluble in aqueous solutions at all pH

values. When used as a coating, a plasticiser (e.g. tributyl citrate, triethyl citrate) is required to lower the glass transition temperature of the polymer and hence to enhance the flexibility of the coating.

polymers that are used to film-coat

Eudragit RS and RL

Eudragit RS and RL are methacrylate co-polymers that are insoluble, with the RL grade being more permeable than the RS grade. Chemically the RL grade is composed of poly(ethyl acrylate-co-methyl methacrylate-co-triethylammonioethyl methacrylate chloride), the ratios of the three monomers being 1:2:0.2, respectively. Similarly, the RS grade is a co-polymer of the above three monomers, with a different ratio of monomers (1:2:0.1, respectively).

pH dependent polymers

The use of film coatings to target drug release within the gastrointestinal tract requires the use of polymers that dissolve within certain pH ranges. For example, enteric coatings offer drug targeting to regions of the gastrointestinal tract in which the pH is greater than 5.5 (e.g. Eudragit L-100). Targeting drug release to the colon involves the use of polymer coatings that dissolve at higher pH values (7), e.g. Eudragit S-100.

- 2-alloying substance, to enhance the penetration of body fluids through the tablet, like PEG.
- 3. A *plasticizer to produce flexibility and elasticity* of the coating and thus provide durability. Example: castor oil.
- 4. A *surfactant to enhance spreadability of the* film during application. Example: tweens

- 5. *Opaquants and colorants to make the appearance* of the coated tablets handsome and distinctive. Examples: titanium dioxide; colorant, FD&C or D&C dyes.
- 6. *Sweeteners, flavors, and aromas to enhance* the acceptability of the tablet by the patient.
- Examples: sweeteners, saccharin; flavors and aromas, vanillin.

7. A *glossant to provide luster to the tablets* without a separate polishing operation.

Example: beeswax.

8. A *volatile solvent to allow the spread of the* other components over the tablets while allowing rapid evaporation to permit an effective yet speedy operation.

Example: alcohol mixed with acetone.

Aqueous film coating

A typical aqueous film-coating formulation contains the following

1. *Film-forming polymer (7% to 18%). Examples:* cellulose ether polymers such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, and methylcellulose.
2. *Plasticizer (0.5% to 2.0%). Examples: glycerin,*

propylene glycol, polyethylene glycol, diethyl

phthalate, and dibutyl subacetate.

3. *Colorant and opacifier (2.5% to 8%).* Examples: FD&C or D&C lakes and iron oxide pigments.
4. *Vehicle (water, to make 100%).*

Problems associated with film coating

- 1-*picking* :small film fragments flaking from the tablet surface.
- *2-peeling: large* film fragments flaking from the tablet surface.
- 3-*orange peel effect* :roughness of the tablet surface due to failure of spray droplets to coalesce.
- 4-*mottling* :an uneven distribution of color on the tablet surface.
- *5-bridging:* filling-in of the score line or indented logo on the tablet by the film.
- 6-tablet *erosion* disfiguration of the core tablet when subjected for too long to the coating solution.









Damascus University

1-*picking* :small film fragments flaking from the tablet surface



2-peeling: large film fragments flaking from the tablet surface



3-*orange peel effect* :roughness of the tablet surface due to failure of spray droplets to coalesce



5-bridging: filling-in of the score line or indented logo on the tablet by the film



6-tablet *erosion* disfiguration of the core tablet when subjected for too long to the coating solution



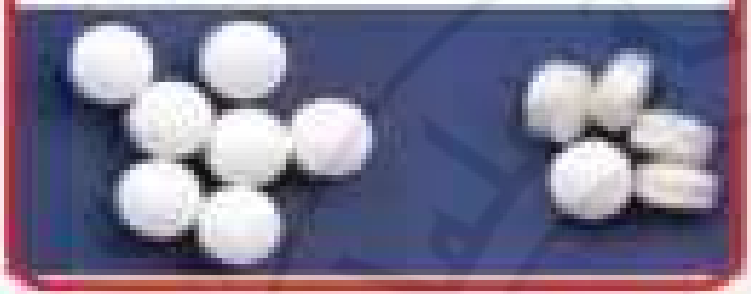








Picking and sticking



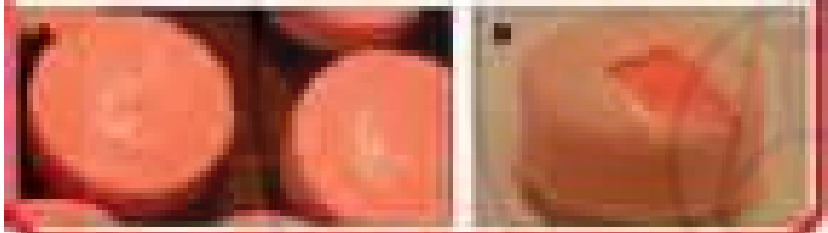
Capping and Lamination



Twinning



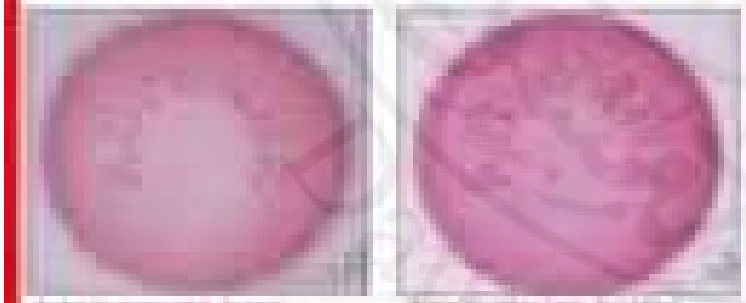
Orange Peel



Erosion



Roughness



Bridging



Coating formation

- Coating solutions are available in two main formulation types:
- (1) solutions: aqueous or non aqueous
- (2) emulsions.

Tablet coating in practice

- There are several designs of systems that are used in industrial practice to coat tablets (or granules).
- 1-Pan coater
- 2-Fluid-bed processor

1-Pan coater

The pan coating system is generically composed of a metal

1-The tablets are placed in the pan (drum)

2-The drum rotates at a range of speeds.

3- The coating solution is sprayed on to the surface of the tablets within the pan whilst the drum is rotated.

4-Simultaneously warm air is passed over the surface of the tablets to facilitate the evaporation of the solvent in which the coating material has been dissolved.

Control of the coating process

It is obtained by modifying the following parameters:

- rotation rate of the drum/pan
- airflow rate
- temperature of the air
- concentration of polymer within the coating solution/emulsion.

- Coating solutions contain the coating material (polymers or sugar), the coating solvent and other excipients that are required to improve the formulation or performance of the tablet coating, e.g. colourants/opacifiers, plasticisers (to render the film flexible).

More recently, pan coaters have been developed in which the pan is perforated (e.g. the Accela-Cota and Hi-Coater systems).

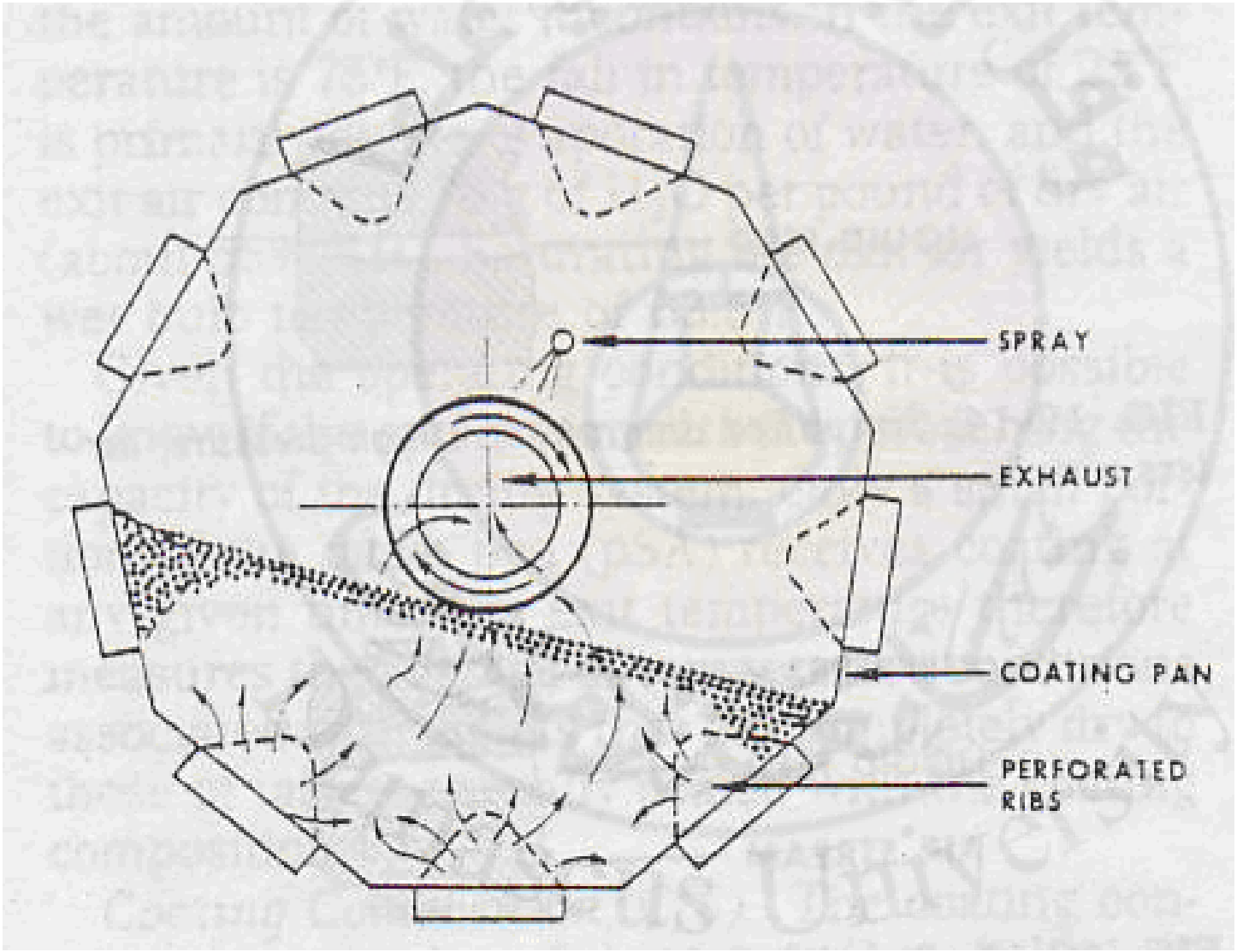
In these systems the warmed air is passed into the drum and through the tablet bed before being exhausted (with the solvent from the coating solution) via the perforated drum.

In the Driacoater system, the drum is composed of a serious of perforated fins (typically 8 per drum) from which the warmed air is provided. As the drum rotates, the tablets in the tablet bed are

mixed by and collected on the fins before being suspended in the warmed air.

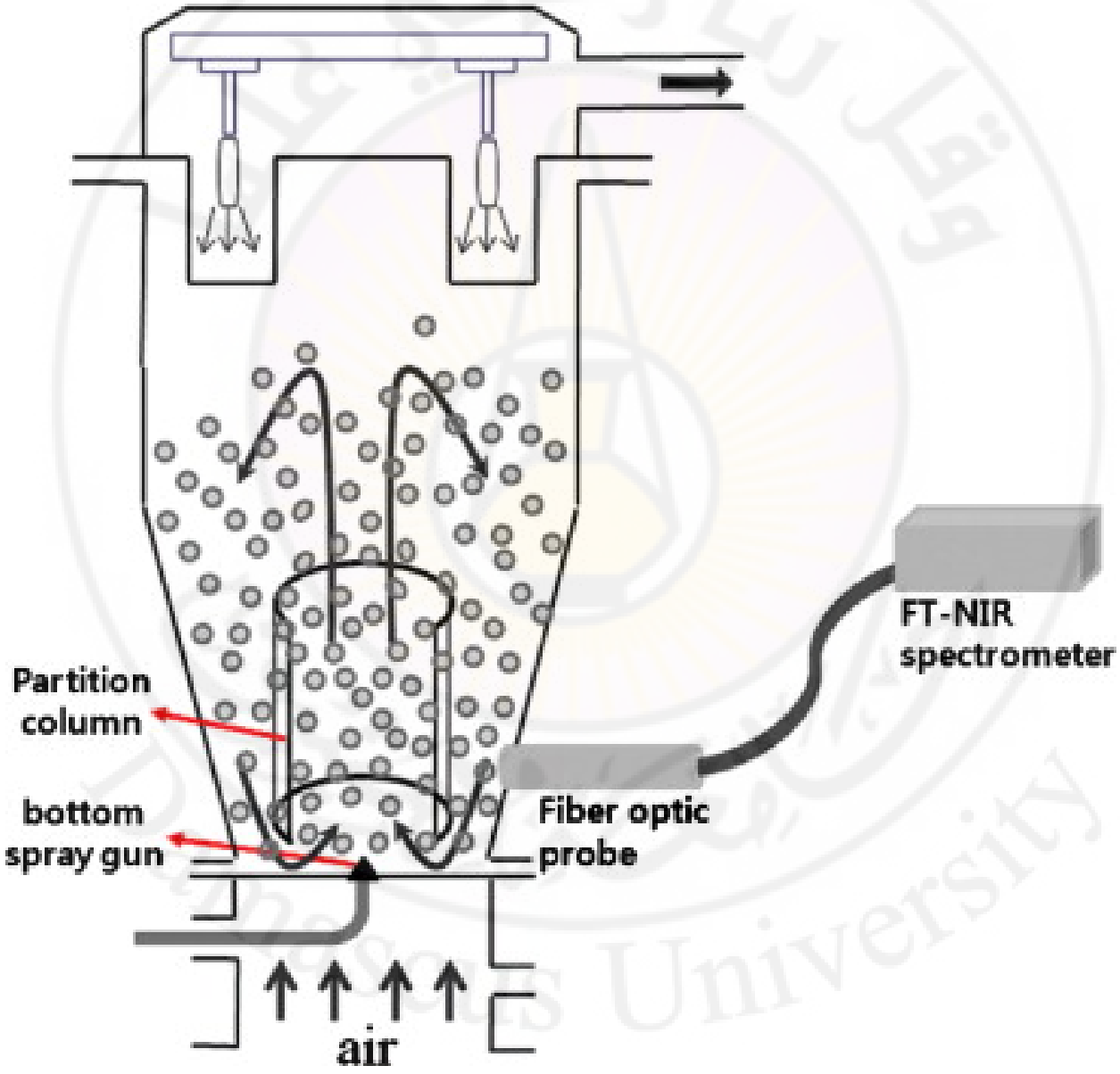
The tablets are then dropped into the tablet bed and the process is repeated. The warmed air is then exited from the rear of the pan.




SPRAY
EXHAUST
COATING PAN
PERFORATED
RIBS

2-Fluid-bed processor

- 1-The tablets are initially suspended in the centre of the chamber then move to the periphery of the chamber before falling to the bottom (stage the process is continuously repeated).
- 2-The coating solution is fed into the fluidisation chamber usually at the bottom of the chamber.
- 3- Coating solution is sprayed on fluidized tablets through a nozzel.


FT-NIR
spectrometer
Partition
column
bottom
spray gun
Fiber optic
probe
air

Vector/Freund Flo-Coater production system. A fluid bed system used to apply coatings to beads, granules,powders, and tablets. Capacity of models ranges from 5 to 700 kg. (Courtesy of Vector Corporation.



Process variables in fluidised air coating

- There are several process factors that control both the efficiency of the coating process and the quality of the formed coat.
- (1) evaporation rate of the solvent
- (2) fluidised air volume
- (3) specific humidity
- (4) coating spray rate and duration.

If solvent evaporation rate is too rapid, the mechanical properties of the films will be compromised due to the adverse effects on polymer interactions.

Fluidised air volume

The fluidised air volume will affect both the velocity of the droplets of coating solutions and their fluidised pattern within the coating chamber.

Control the relative humidity

If the relative humidity in the coating chamber is high this will lower the temperature of the air to below the dew point, resulting in the condensation of water on to the tablet surface. This will interfere with the coating process, resulting in poor adhesion of hydrophobic coatings to the tablet surface and visual imperfections in the formed coating.

Therefore, control (but not elimination) of the relative humidity within the coating process is required.

Coating spray rate and duration

In addition, it is important to ensure droplet integrity (i.e. minimise droplet aggregation) during the process.

It should be noted that excessive spray rates will produce coatings that exhibit poor adhesion to the tablet surface.

Therefore one method by which the thickness of the coating on the tablet may be modified is to increase the time spent within the coating chamber.

Alternatively, the concentration of coating material may be increased within the coating solution.

The viscosity of the solution must be considered

to ensure that the increased viscosity does not compromise the atomisation process, and specifically the droplet size.

Irregular tablet shape

Irregular tablet shapes are more prone to abrasion than regular tablet shapes. This problem may therefore be overcome by changing the tablet shape.

Poor adhesion of the coating to the tablet

This phenomenon may be due to:

- high relative humidity within the coating chamber when coating tablets using an organic solvent system
- high coating spray rate
- concentration of polymer in the coating solution/emulsion is too low
- temperature of air is too low, resulting in a slow rate of solvent evaporation (particularly valid for coating systems that employ solvents of low vapour pressure, e.g. water)
- air fluidisation rate or pan rotation rate is too slow
- the tablet substrate has minimal curvature. Typically curved surfaces are easier to coat than flat surfaces.

Tablet abrasion

- The coating process involves exposing the tablets to shearing stresses that are generated as a result of collisions with other tablets and also with the walls of the coating chamber. This may result in damage to the tablet surface.

Tablet abrasion problem may occur due to

- (1) inappropriate tablet hardness; (2) irregular tablet shape; (3)tablet bed is too heavy during coating; and (4) the speed of rotation of the pan or the air fluidisation rate is excessive.



Tablet abrasion

Filling tablet markings



Markings performed by using a tablet punch.

If the coating conditions are unsuitable, the coating will excessively deposit within the mark/name

. This may occur due to:

- the use of deep markings
- use of an excessive volume of coating solution
- air temperature is too low
- pan rotation speed/fluidisation flow rate is too low.

Rough surface

- The problem: tablets that exhibit a rough surface.
- The reason : this phenomenon is often associated with drying of the coating droplets prior to reaching the surface of the tablet.
- The solution: To correct this problem the spray rate may be increased and the inlet air temperature decreased.

Formation of cracks in the coating

- The problem: cracking in the coating polymer
- The reason :The platiciser used in coating solution
- The solution: the plasticiser concentration should be increased or, alternatively, a different plasticiser that is more compatible with the polymer chosen for the coating should be considered.

Variations in the color of the coating

Coated tablet should have uniform color

. Variations in the color of a tablet coating may be due to:

- improper mixing of the colour within the coating formulation
- uneven coating process, resulting in regional differences in the thickness of the applied coating
- migration of coloured components within the tablet core into the coating.

The solution: by the use of a colored coating that will mask the effects of the migration or by the use of a coating in which the components within the table core are insoluble.

1. Concerning roller compaction as a method for tablet manufacture, which of the following statements are true?

a. Roller compactions requires the application of heat.

b. Roller compaction is suitable for the manufacture of tablets containing high-potency (i.e. low-dose) drugs.

c. Roller compaction produces soft tablets.

d. Roller compaction requires only conventional excipients.

Concerning direct compression as a method for tablet manufacture, which of the following statements are true?

a. It is a simple process, involving a lower number of unit operations in comparison to wet granulation.

b. The morphology of particles is not important in direct compression.

c. Direct compression employs spray-dried excipients only.

d. Coloured tablets may be easily produced by direct compression.

- **Concerning wet granulation, which of the following**
- **statements are true?**
- a. Alcohol may be employed as a granulating fluid.
- b. Only spray-dried excipients may be used.
- c. Wet granulation may be unsuitable for thermolabile drugs or drugs that are prone to hydrolysis.
- d. Tablets produced by this method are prone to capping.

Concerning pharmaceutical tablets, which of the following statements are true?

a. Pharmaceutical tablets may include a disintegrant to improve tablet strength.

b. Pharmaceutical tablets may include magnesium stearate to prevent tablet adhesion to punches.

c. Pharmaceutical tablets include diluents such as colloidal silicone dioxide.

d. Pharmaceutical tablets may involve a granulation stage in order to prevent segregation of the powder mix.

6. The dissolution rate of drugs from tablets may be increased by:

a. Increasing the compression stress during tableting.

b. Increasing the concentration of lubricant.

c. Increasing the concentration of disintegrant.

d. Film-coating tablets with ethylcellulose.

- **9. The following excipients are employed in tablets for the stated reasons:**

a. Lactose – as a diluent.

b. Sucrose – as a binder.

c. Hydroxypropylmethylcellulose – as an enteric coating.

d. Polyethylene glycol – as a lubricant.

- **Regarding the various types of tablets, which of the following**
- **statements are true?**

a. Enteric-coated tablets release the therapeutic agent within the small intestine but not in the stomach.

b. Effervescent tablets are used to enhance the dissolution rate and hence absorption rate of poorly soluble drugs.

c. Sugar-coated tablets are employed to reduce drug degradation within the stomach.

d. Film-coated tablets may be used to target drug release to the Colon.

Cysts

Cysts can develop when pores are clogged by a combination of bacteria, sebum, and dead skin cells. The clogs occur deep within the skin and are further below the surface than nodules.

These large red or white bumps are often painful to the touch. Cysts are the largest form of acne, and their formation usually results from a severe infection. This type of acne is also the most likely to scar.

The prescription medication isotretinoin is commonly used to treat cysts. In severe cases, your dermatologist may surgically remove a cyst.

Damascus University