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Modern approaches in creating forms for delivery of medicinal products

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Definitions

According to Federal Law No. 61-FZ dated April 12, 2010 (amended January 30, 2024):

- * **Medicinal product**: Substances or their combinations that come into contact with human or animal bodies, enter organs and tissues, are used for prevention, diagnosis, treatment, rehabilitation, preservation, interruption, or termination of pregnancy, obtained from blood, plasma, organs, tissues, plants, minerals using synthesis methods or biological technologies. Includes pharmaceutical substances and medicinal preparations.
- * **Pharmaceutical substance**: A medicine consisting of one or more pharmacologically active ingredients regardless of origin, intended for manufacturing medicinal preparations determining their effectiveness.
- * **Medicinal preparation**: Medicine in specific dosage forms used for prevention, diagnostics, treatment, rehabilitation, preservation, interruption, or termination of pregnancy.
- * **Dosage form**: The state of a medicinal preparation corresponding to its administration route ensuring necessary therapeutic effect.

Importance and Objectives of New Form Development

- Problems with traditional delivery forms include:

* Distribution throughout the body
* Lack of targeted delivery
- Non-specific effects

Goals of new delivery systems development include enhancing bioavailability, efficacy, prolongation of effect, reduction of side effects, optimization of therapy costs.

In 1951, the first prolonged-action medication was developed and patented. Multilayer tablets containing drugs and gastrointestinal soluble coatings significantly extended the pharmacological effect and reduced dosing frequency. Later, spansules were introduced as another modified-released formulation.

Classification of New Delivery Systems

Medications can be classified based on modification type:

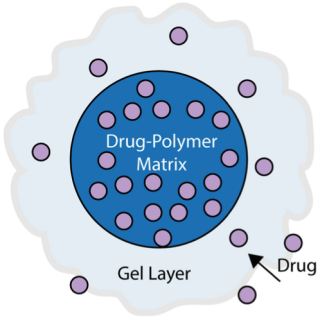
Examples include:

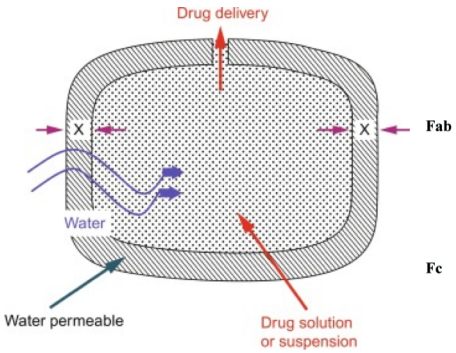
- liposomes,
- antigen-binding sites,
- polymeric matrices, etc.

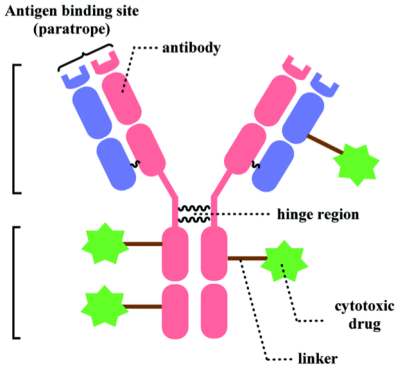
By kinetic release mechanism: diffusion-programmed, solvent-activated, chemically programmed, self-regulating (“smart”).

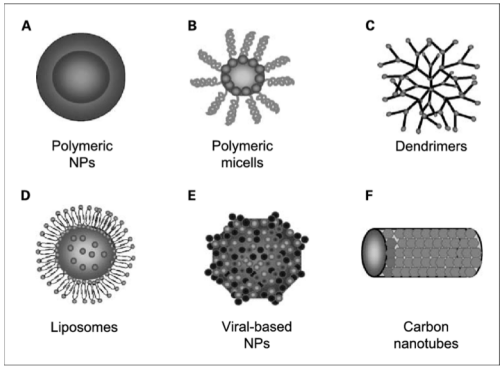
Carrier-based systems:

- cellular,
- macromolecules,
- antibodies,
- micro-particles (liposomes & microspheres),
- nanoparticles.









Dosage Forms with Modified Release

These involve altering the release profile and mechanism through various modifications such as:

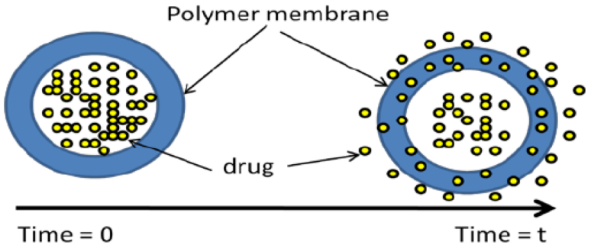
- Physical: coating granules, particles, cores with membranes forming durules, lontabs, retards, microencapsulation.
- * Technological: multilayer structure, use of resins, ion-exchange materials, hydrophilic base like floating tablets, Oros technology.
- * Chemical: producing poorly-soluble salts, replacing functional groups, introducing new chemical groupings within molecules.

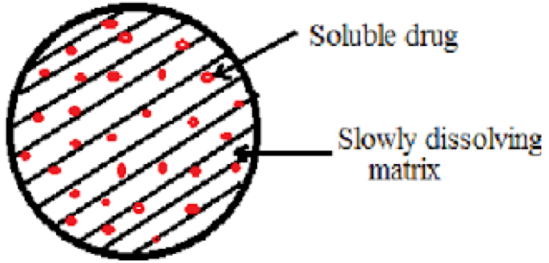
There are three main types:

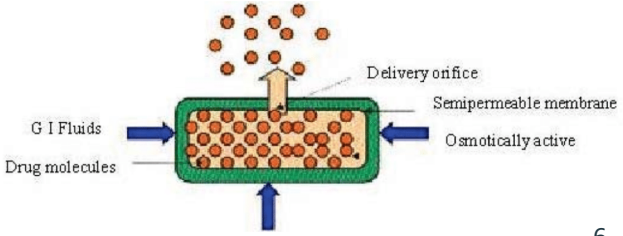
reservoir,

matrix,

pump-like (osmotic) systems.







Examples of Modified-Release Systems

		example drugs
ER, XR	Extended release	Felodipine (Plendil ER)
SR	Sustained (slow) release	Clarithromycin (Clarithromycin SR)
CR, RR	Controlled (regulated) release	Diltiazem (Altiazem RR)
CD	Controlled delivery	Methylphenidate (Metadate CD)
CC	Coat-core system	Nifedipine (Adalat CC)
LA	Long-acting	Tolterodine (Detrol LA)
PA	Prolonged action	
SL	Short-long form	Nifedipine (Adalat CC)
XL	Extra-long	Doxazozin (Cardura XL)
ZOK	Zero-order kinetics	Metoprolol (betalok ZOK)
OROS	Oral osmotic system	Nifedipine (Adalat OROS)
GITS	Gastrointestinal therapeutic system	Nifedipine (Adalat GITS)

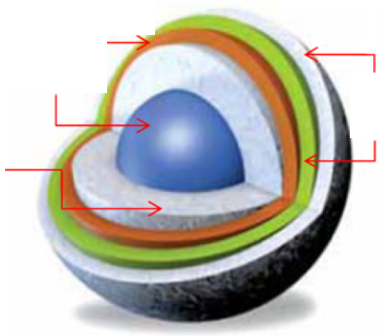
Reservoir-Type Drug Delivery Systems

- The reservoir system consists of an outer shell (membrane) forming a reservoir and a core containing the active pharmaceutical ingredient (API).

Mechanisms of API release:

- - Passive diffusion along concentration gradients.
- - Biodegradation through dissolution processes such as:
- * Bio-destruction—rapid penetration of environmental fluids into the polymeric structure leading to degradation throughout its volume.
- * Bio-erosion—surface erosion followed by solubility of oligomers.
- * Bio-resorption—polymeric breakdown via enzymatic and cellular processes (e.g., multinucleated foreign body cells).

SODAS is composed of spherical granules measuring 1–2 mm in diameter that contain APIs and auxiliary substances. Upon contact with water, these granules swell and dissolve, allowing for diffusion of the dissolved API outwards.



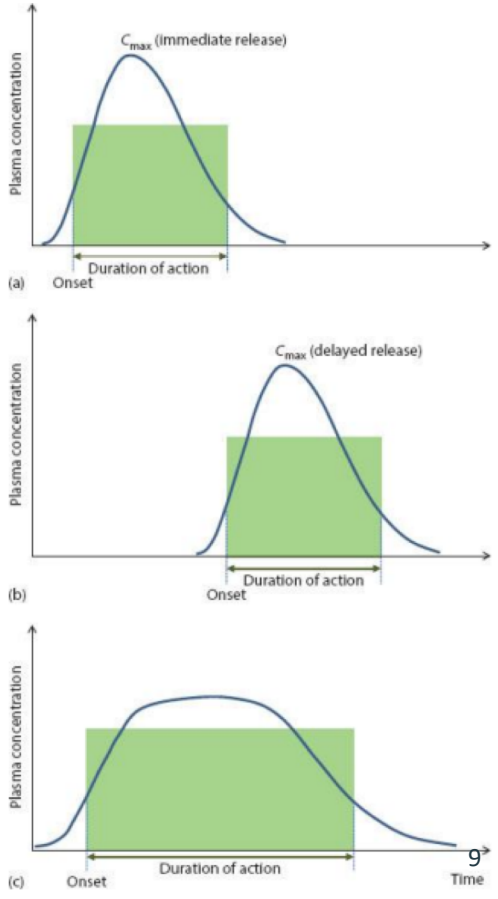
Modified Drug Delivery Systems

Immediate-release formulations where the API is released immediately after administration.

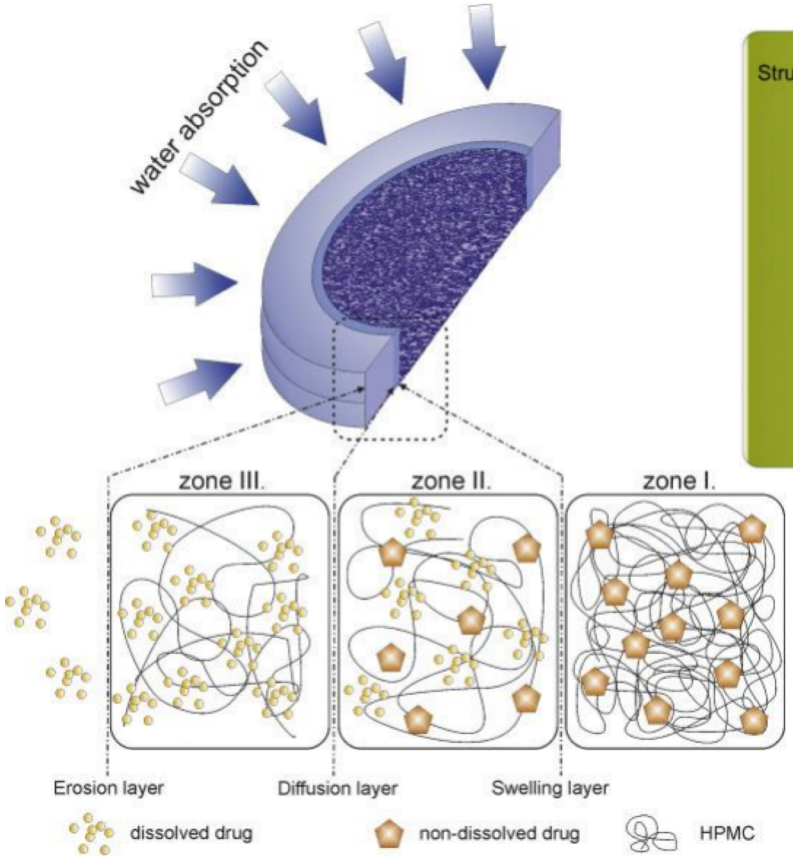
Sustained-release formulations providing prolonged release over time.

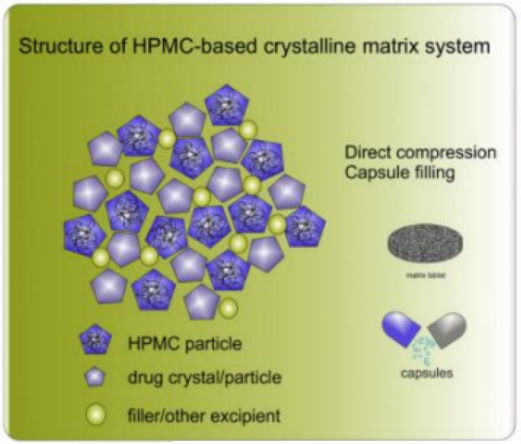
Delayed-release systems delivering the API at a later point post-administration.

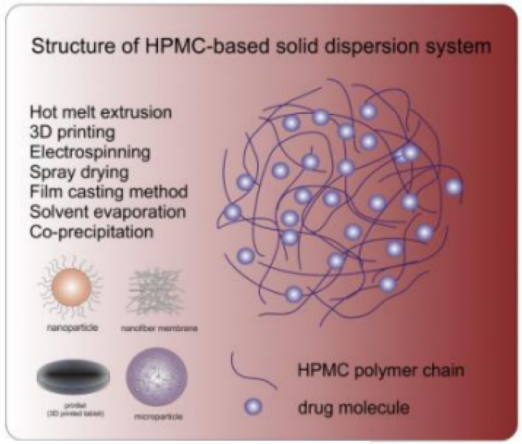
Controlled-release systems designed
to deliver precise amounts of API
within specific therapeutic ranges



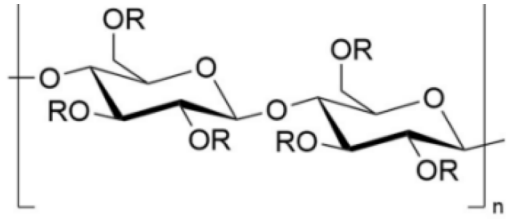
Matrix-Based Drug Delivery Systems







Hydroxypropyl methylcellulose (HPMC)

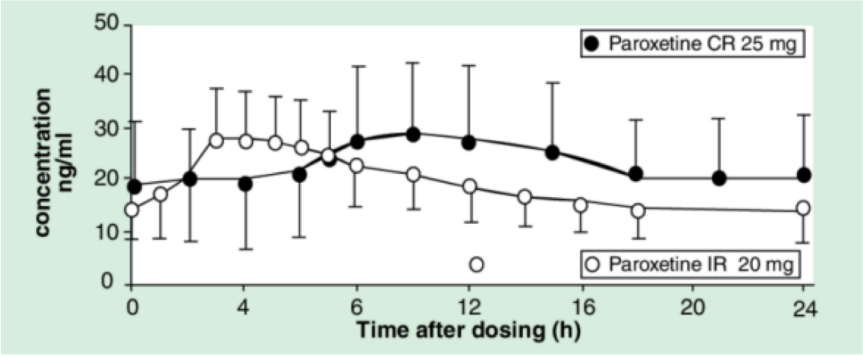


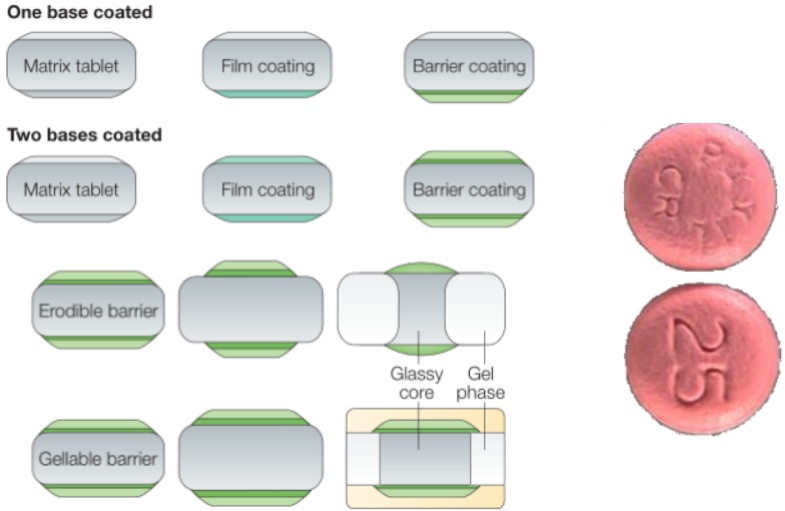
HPMC: R = H, CH_3, $CH_3CH(OH)CH_2$

Multilayer Matrix Tablets

(Geomatrix®; SkyePharma)

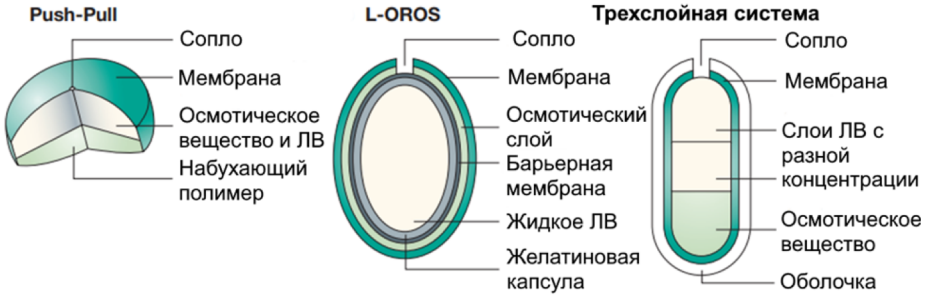
Technology using high viscosity HPMC barriers to control API diffusion from inner cores. This technology has been applied to reformulate immediate-release drugs like Dilacor XR (Watson Labs), Paxil CR (GlaxoSmithKline), and Voltaren XR (Novartis).

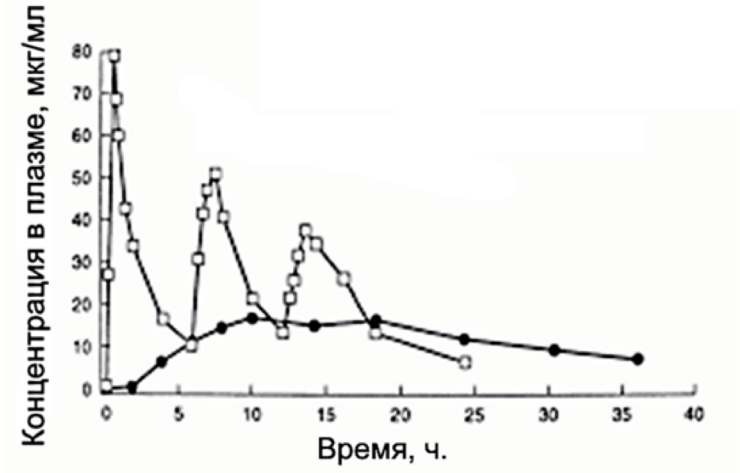




Osmotic Drug Delivery Systems

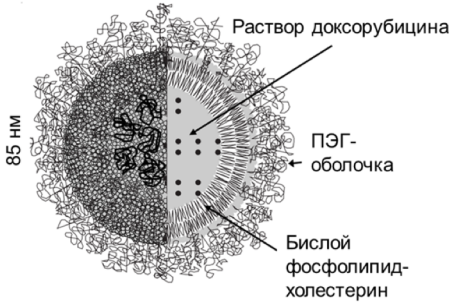
- Advantages:
- - Constant zero-order kinetics independent of gastrointestinal conditions (pH variations, pressure changes, mixing effects).
- - Disadvantages:
- - Complex manufacturing process.
- - Risk of complete dose leakage if membrane integrity fails.

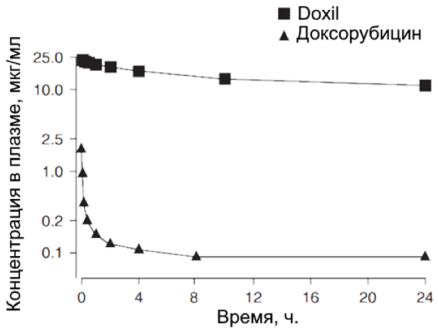


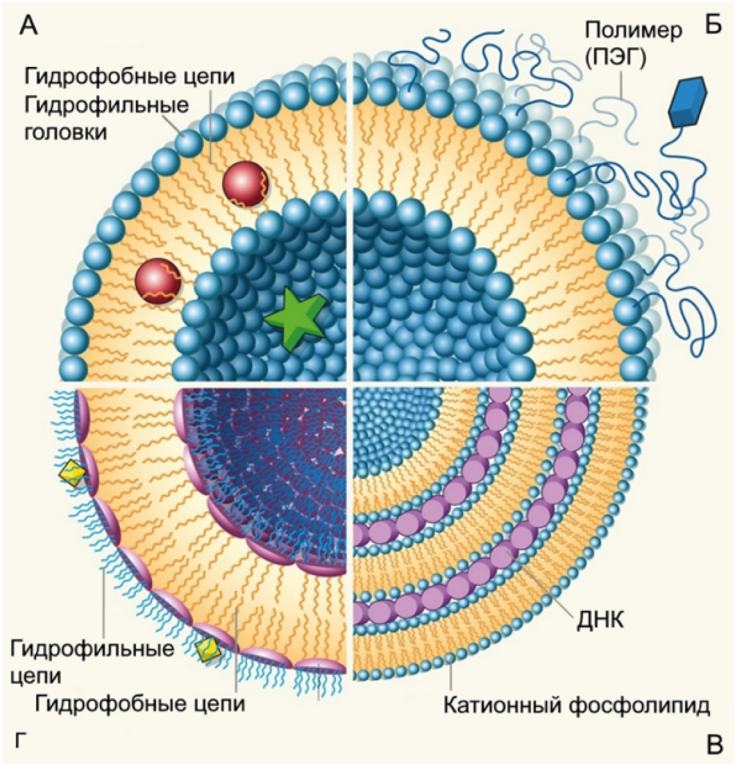


Liposomes

- Liposomes are microscopic vesicles consisting of one or more phospholipid bilayers enclosing aqueous compartments. They may have additional surface-active agents altering their properties and pharmacokinetic behavior.







Pulmonary Delivery of Drugs

Advantages:

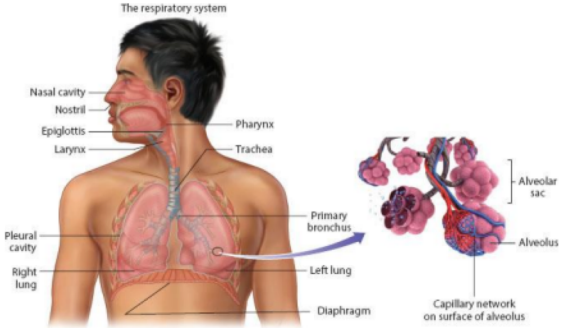
- - Large absorption area (80–150 m^2)
- - Thin epithelium that is easily permeable
- - Intensive blood supply
- - No first-pass effect
- - Lower activity of hydrolytic enzymes compared to the gastrointestinal tract

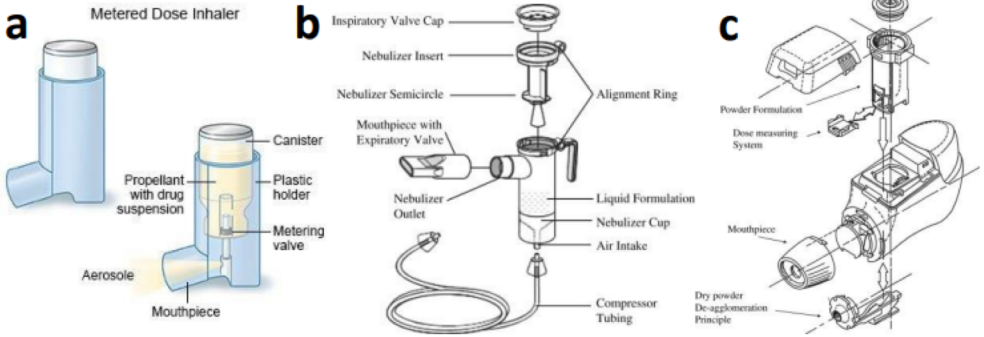
Limitations:

Geometric structure of airways
- Mucociliary transport and mucus secretion
- Clearance by alveolar macrophages
- Importance of proper application technique

Delivery Devices:

- Metered-dose inhalers (propellant-based)
- Nebulizers (compressed air)
- Dry powder inhalers (patient's inspiration)





Transdermal Delivery. Iontophoresis

Advantages of Transdermal Delivery:

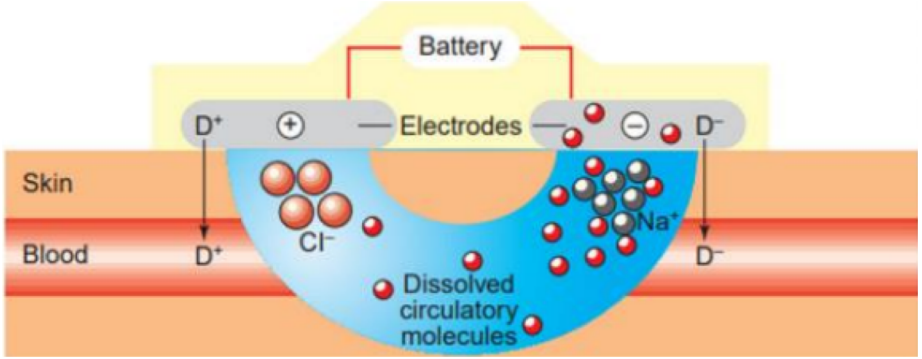
- Non-invasiveness
- - Controlled delivery
- - Localized or systemic action

- Iontophoresis increases skin penetration for macromolecules and hydrophilic molecules using low-intensity electric current, especially effective for cationic compounds.

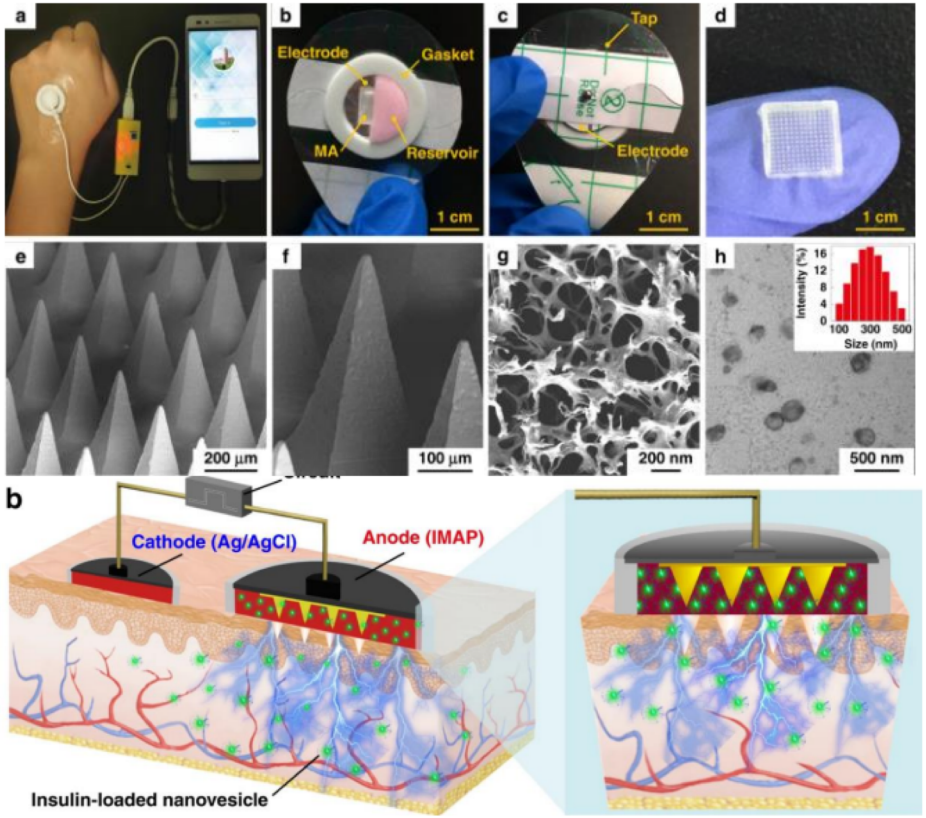
- - Avoids first-pass metabolism
- - Enables delivery of peptides, vaccines, and cells unavailable via oral route

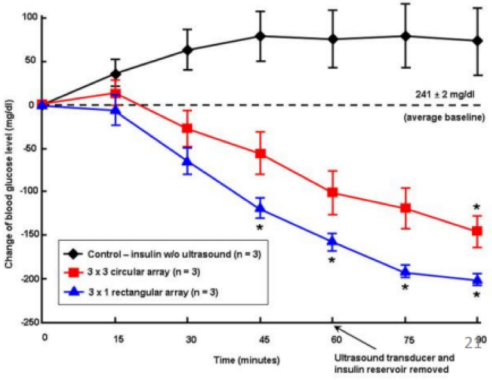
Limitations:

- Traditional methods are applicable only for small water-soluble compounds (<500 Da), lipophilic substances, and high logP values
- May cause local irritation



Sonophoretic





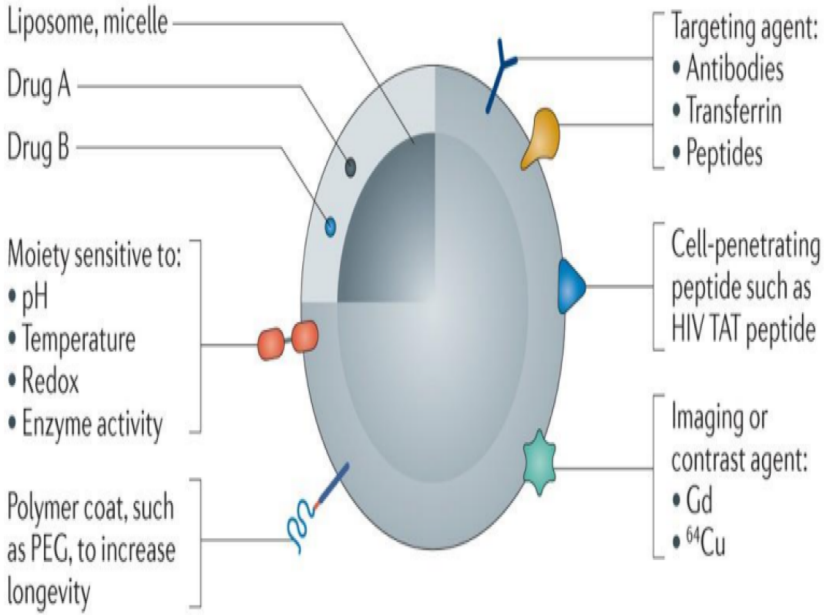
- llustrates an applicator equipped with micro needles and iontophoresis technology for controlled transdermal insulin delivery. Shows changes in glucose levels in rats after sonophoretic insulin administration over time.

Targeted Delivery and Regulated Specificity Using Nanoparticles

Targeted Delivery Achieved Through Surface Modification With Ligands:

- React to various pathological site-specific stimuli
- Can be supplemented with contrast agents for monitoring distribution and therapeutic efficacy
- Release drugs in response to diverse stimuli (internal or external) such as pH, temperature, redox state, enzyme activity, magnetic fields, ultrasound, etc.

Relevant for cancer, cardiovascular diseases, infections, etc.



Stimuli-Responsive Nanoparticle Systems

Mechanisms of Stimulus-Controlled Drug Release:

- - External stimuli include heat, light, ultrasound, magnetic field
- - Internal stimuli involve lower pH, enzymatic activities within tumors, reductive environments
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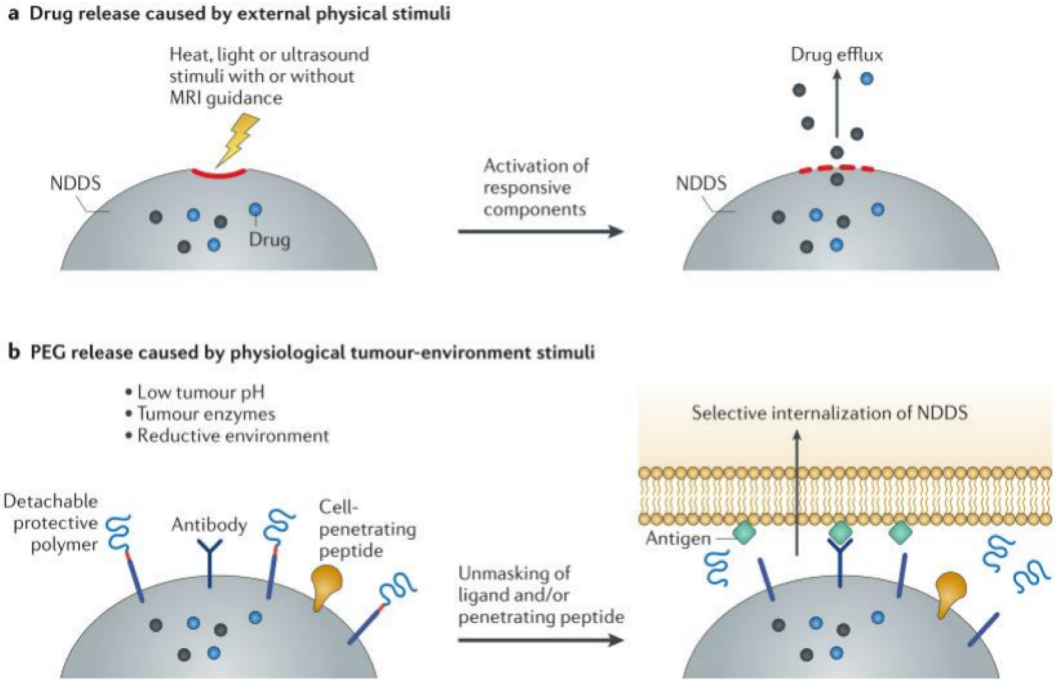
- Illustrated mechanisms show detachment of polyethylene glycol (PEG) layers from nanoparticles under tumor environmental conditions.



Conclusion

Optimization of currently practiced medications should focus on enhancing their effectiveness, tolerability, and ease of administration. Preferred approaches include controlled-release systems offering advantages like:

Delivering poorly soluble compounds, peptides, and cells

Decreasing dosing frequency and improving patient adherence
- Minimizing fluctuations and maintaining therapeutic concentrations

These slides provide an overview of stimulus-driven drug delivery strategies and key requirements for developing efficient drug delivery systems.