MODERN THERAPEUTIC SYSTEMS

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Controlled Release Drug Delivery Systems According to Administration Route

- Parenteral
- Ocular
- Nasal
- Buccal
- Oral
- Rectal, vaginal, intrauterine
- Transdermal

Ocular Administration

DISADVANTAGES OF CONVENTIONAL DOSAGE FORMS	ADVANTAGES OF MODERN DOSAGE FORMS
Rapid precorneal elimination	Extended and/or controlled release
Drainage of solutions	Targeting
To be administered at frequent intervals	Protection of the APIs from chemical and enzymatic degradation
	Extending the time period of contact and thus increasing the bioavailability
	Increasing patient compliance

Modern therapeutic systems designed for the eye can be classified as follows according to the energy source that provides drug release:

1. **Diffusion controlled drug delivery systems**
2. **Dissolution controlled drug delivery systems**
3. **Osmotic controlled drug delivery systems**
   a. **Mini pump systems**
   b. **Micro-compartment systems**

Dissolution Controlled DDSs

They are inserts produced from synthetic material. They place in the conjunctiva and dissolve here.

SRAT® (Slow Release Artificial Tear)

- SRAT® was developed by MSD.

-It is a 6x2 mm cylinder made of hydroxypropyl cellulose (HPC).

-The cylinder is put into the lower eyelid and dissolves within 12-14 hours.

-As the HPC dissolves in the tear, the viscosity of the tear film increases.

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Osmotic Controlled DDSs

They are two-compartment systems. The first compartment comprises the API released from a single orifice (drug release opening), while the other compartment contains salt and is separated from the compartment containing the API by an elastic impermeable membrane.

While the API-containing compartment is surrounded by a impermeable membrane to water, the salt-containing compartment is surrounded by a semi-permeable membrane.

Classification of Ocular Modern Therapeutic Systems According to Dosage Form

1. Viscous solutions and hydrogels
2. Disperse systems
3. Inserts

1. Viscous solutions and hydrogels

For this purpose, viscous solutions and hydrogels obtained by the addition of hydrocolloids to the aqueous solutions are used. The most commonly used polymers for this purpose are cellulose derivatives, carbomers, polysaccharides, PVA, PVP and hyaluronic acid.

OCULAR INSERTS

- **Ocular inserts are thin, multi-layer, active substance loaded, solid or semi-solid sterile dosage forms.**
- **They are applied to the conjunctival fornix (Cul-de-sac) region of the eye.**

Advantages:

- **They increase bioavailability by extending contact time.**
- **They provide extended drug release.**
- **Systemic side effects are reduced.**
- **As the frequency of administration decreases, the patient compliance is increased.**

- **Lacrisert®**

-It was developed by MSD.

-It is made of hydroxypropylcellulose.

-It doesn’t contain API.

-It is a 24-hour system.

-It is used to treat dry eye syndromes.

-The energy source is the soluble system.

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SODI® (Soluble Ophtalmic Drug Insert)

-2.6 mg Pilocarpine, 1.5 mg Atropine or 1 mg İdoxurine containing forms were produced.

-Oval discs are 9 or 4.5 mm in diameter and 0.25 mm thick.

-Polyacrylamide methylmethacrylate and vinyl pyrolidone were used as polymeric material.

-It has been used in diseases such as glaucoma, corneal ulcer, conjunctivitis, trachoma.

-The energy source is the soluble system.

-In conjunctiva, when exposed to tears, the inert membrane dissolves and the API is released.

Buccal Route

Buccal Mucoadhesive Dosage Forms

- They are small disc or spherical.
- When exposed to mucus, they release the API locally.
- They are used in gingival diseases, aphthae and mouth sores.

Aftach®

Buccal bioadhesive system (Japan)

API: Triamcinolone acetonide (0.025 mg)

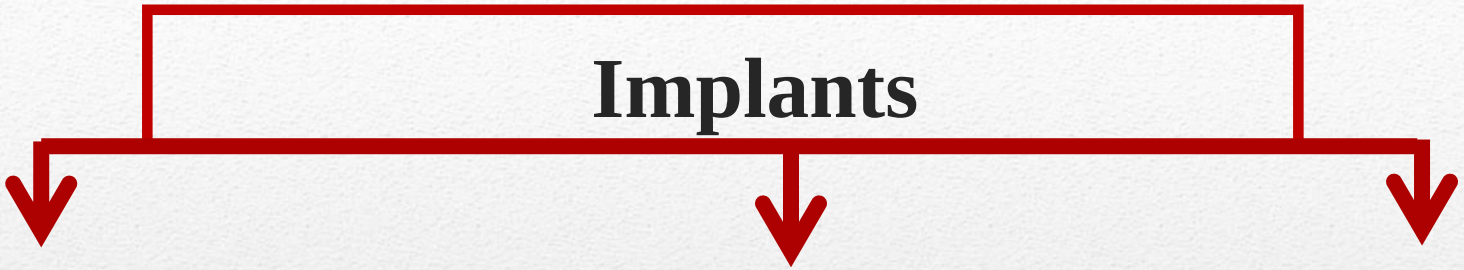
Indication: Aphthous stomatitis

Duration of use: 1 day

Implants

They are administered as controlled release drug delivery systems localized in various parts of the body through intravascular, intraperitoneal, intramuscular and subcutaneous ways.

- **Local drug release**
- **Controlled drug release**



Biodegradable & non-biodegradable polymeric implant systems

Implanted pump systems

Atypical implant systems

Non-biodegradable polymeric implants

-The release kinetics depend on the solubility of the API in the polymer and the diffusion coefficient and the amount of API that can be loaded in the implant.

-**Polymethyl methacrylate (PMMA)** is used as a polymer in matrix type systems.

-The API must be homogeneously dispersed in the matrix material.

-Slow diffusion provides extended effect.

- **Disadvantage:**

A surgical procedure is required to remove the implant.

NORPLANT®

-Subdermal implant

-API: Levonorgestrel (36 mg/capsule)

-Indication: Contraceptive

-Size: 2.4 mm x 34 mm 6 silicone capsule

-Once inserted, the contraceptive works within 24 hours and lasts up to 5 years.

NORPLANT II®

-Subdermal implant

-API: Levonorgestrel (75 mg/capsule)

-Indication: Contraceptive

-Size: 2.4 mm x 43 mm 2 silicone capsule

-The implant prevents pregnancy and is effective for 3 years.

Biodegradable polymeric implants

They are used for the delivery of proteins in skeletal-muscular system diseases, growth factors in bone regeneration and antibiotics in the treatment of osteomyelitis.

Zoladex® implant

- **Sterile**
- **It contains 3.6 or 10.8 mg goserelin acetate.**
- **Biodegradable D,L-lactic-co-glycolic acid copolymer (PLGA) was used as the polymer.**
- **It is subcutaneously implanted.**
- **It provides sustained release for 12 weeks.**

Implantable pump systems

-The velocity and volume are controlled from the outside.

-The release of the API from the reservoir is provided by mechanisms such as peristalsis, fluorocarbon propellant, osmotic pressure, piezoelectric effect or osmotic pressure with oscillating piston.

1. Infusion Pumps

-They were firstly developed for chronic pain and insulin treatment.

-They consist of disc-shaped titanium reservoir.

-Continuous infusion of the API into the bloodstream is provided with a silicone tube.

2. Osmotic pumps

ALZET®

- **The system has an API reservoir and is surrounded by a chemically inert and impermeable flexible membrane (hydrocarbon elastomer). It carries a orifice for the release of the API.**
- **Outside the API reservoir, there is an osmotic layer containing NaCl. There is a semipermeable membrane consisting of a mixture of cellulose esters outside the osmotic layer.**

Oral Systems

1) Dissolution Controlled DDSs
   A) Encapsulation Controlled DDSs
   B) Matrix Controlled DDSs
2) Diffusion Controlled DDSs
   A) Depot Systems
   B) Matrix Systems
3) Diffusion and Dissolution Controlled DDSs
4) İon Exchange Resin Technology for Oral Applications
5) pH Independent Systems
6) Osmotic Controlled DDSs
7) Low Density Controlled DDSs

Oral Osmotic Controlled DDSs

Osmotic pressure is the driving force that provides API release at constant rate in these systems.

Oros® Tablet

-It is a tablet form of osmotic systems developed by Alza Corporation.

-API release at constant rate for 24 hours can be achieved.

OROS Push-Pull® Tablet

-They have been developed for the delivery of water-soluble or insoluble APIs.

-They contain two compartment separated by elastic diaphragm.

-Upper compartment contains API with or without excipients.

-Lower compartment (push layer) contains a flexible hydrophilic polymer, osmogens (salts) and excipients.

PULSINCAP SYSTEM

-It was developed to provide targeting to the colon.

-The capsule consists of a enteric-coated capsule with water-soluble cap and a water-insoluble body.

-The API and the hydrogel plug are present in the body of the capsule.

-First enteric coating and then the water-soluble cap dissolve in the small intestine.

-The hydrogel plug absorbs water and swells up and releases the API after a delay of 4 hours.

TRANSDERMAL TERAPEUTIC SISTEMS (TTS)

- **TTSs are systems that deliver the API at constant rate (with controlled release) through the skin for a designed period.**
- **TTSs are systems that use diffusion as an energy source.**

Ideal Properties of API Used for TTS

Parameter	Properties
Dose	Should be low (>20 mg/day)
Half life in ‘h’	10 or less
Molecular weight	<400
Partition coefficient	Log P (octanol-water) between 1-4
Skin permeability coefficient	$>0.5x10^{-3}$ cm/hr
Oral bioavailability	Low
Therapeutic index	Low

Classification of TTSs

1) Depot systems
   - a) Rate controlled membrane systems
     - i) Single-depot systems
     - ii) Multi-depot systems
   - b) Systems without a rate controlling membrane
     - i) Depot systems containing orifice
     - ii) Rate controlled systems by adhesive layer
     - iii) Microcapsules
     - iv) Soluble membrane systems
2) Mikrosealed systems
3) Macromolecular systems
4) Poroplastic systems
5) Matrix systems
   - a) Adhesive matrix systems
   - b) Hydrophilic matrix systems
   - c) Polymeric matrix systems
   - d) Microporous matrix systems

Intravaginal Systems

Intravaginal systems can be used;

- **Locally as a contraceptive barrier,**
- **For protection or treatment of infection,**
- **In order to estrogenize the vaginal epithelium,**
- **In order to ensure controlled or sustained systemic delivery of certain therapeutic agents (eg sex hormones for the purpose of contraception or hormone replacement treatment),**
- **To provide non-parenteral administration of peptides and proteins.**

Classification of Intravaginal Systems

1. Mucoadhesive Semi-Solids
2. Vaginal Inserts, Tablets and Suppositories
3. Solid Polymeric Carriers
4. Intravaginal Peptide and Protein Carriers

1. Mucoadhesive Semi-Solids

The mucoadhesive formulations may contain one or more APIs for therapeutic purposes or may be used as moisturizers to prevent vaginal drying.

- **Polyacrylic acids**
- **Chitosan**

2. Vaginal Inserts

They are used for prenatal cervical maturation and for local drug delivery to the vagina.

Cervidil® vaginal insert

-It was developed by Forest Pharm.

-It contains 10 mg Prostoglandin E2 (Dinoprostone) as API.

-The API is dispersed in the hydrogel matrix.

-It is used to provide cervical ripening prior to the onset of labor contractions.

Intravaginal Rings (IVRs)

They are flexible, annular, local or systemic dosage forms that are inserted into the vagina once a year and which gradually release one or more APIs therein.

Intrauterine Devices (IUD)

-An intrauterine device (IUD) is a small, often T-shaped birth control device that is inserted into a woman's uterus to prevent pregnancy.

Copper-containing IUDs (1st Generation IUDs)

-Most copper IUDs have a plastic T-shaped frame that is wound around with pure electrolytic copper wire and/or has copper collars (sleeves).

-They work by damaging sperm and disrupting their motility so that they are not able to join an egg. Specifically, copper acts as a spermicide within the uterus by increasing levels of copper ions.

Hormonal IUDs (2nd generation IUDs)

Hormonal IUDs work by releasing a small amount of levonorgestrel, a progestin. Each type varies in size, amount of levonorgestel released, and duration.

Progestasert®

-It was developed by Alza Corp.

-The ethylene/vinyl coacetate polymer (EVA) T-shaped body has a 36 millimeter tubular vertical stem that contains a reservoir of 38 mg of microcrystallized progesterone (initially) and radiopaque barium sulfate (to monitor location) dispersed in silicone fluid; the horizontal arms measure 32 millimeters. In addition, the T-shaped body contains two blue-black monofilament threads (to monitor placement and aid in IUD removal).