

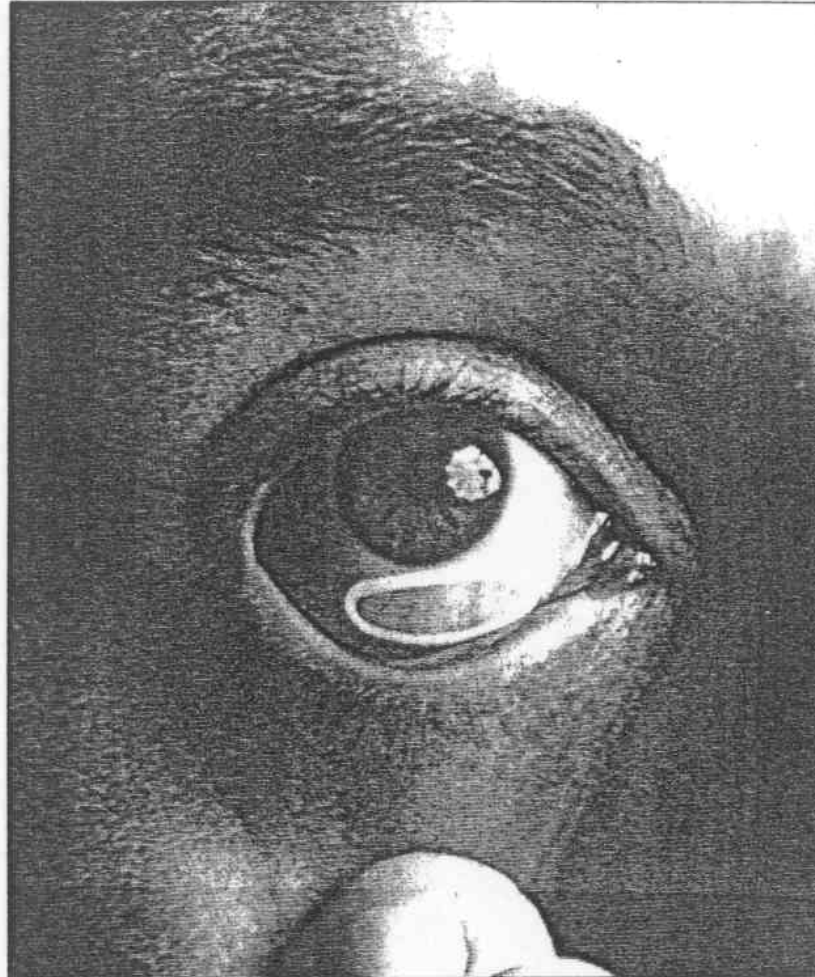
# POSEBNI PRIPRAVKI (SPECIAL DEVICES)

Gre za sproščanje, ki preprečuje fluktuacije med minimalno in maksimalno krvno koncentracijo, povezane z večkratnim doziranjem.

## **OKULARNI SISTEMI:**

- samo lokalna terapija (visoke koncentracije – nevarno za oko)
- očesne kapljice (2 gtt = 50 – 100  $\mu$ L; večina se izgubi oziroma se razredči s solzno tekočino, volumen solzne tekočine = 7 – 8  $\mu$ L). V prvih 5-ih minutah se tako izgubi 75 – 80% doze.
- kontaktne leče hidrogelskega tipa, prepojene z učinkovino, npr. Bionite leče iz hidrofilnega polimera (2 hidroksimetil-akrilat); Sauflon hidrofilne kontaktne leče iz vinilpiridon-akrilnega kopolimera.
- novi okularni inserti iz matriks jedra z zdravilom, obdani s parom fleksibilnih, transparentnih, biokompatibilnih, polimernih membran, netopni v solzni tekočini (membrane omejujejo hitrost sproščanja). Insert se namesti v konjunktivalno vrečko. Inserti s pilokarpinom, prednizolon acetatom in hidrokortizon acetatom. Izdeluje ALZA korporacija – “Ocusert system”.

**Figure 1: Ocusert (pilocarpine) ocular therapeutic system is used to treat glaucoma for 7 days with a single application. When placed in the cul-de-sac of the eye, the Ocusert system is not visible (reproduced with permission of ALZA Corporation).**



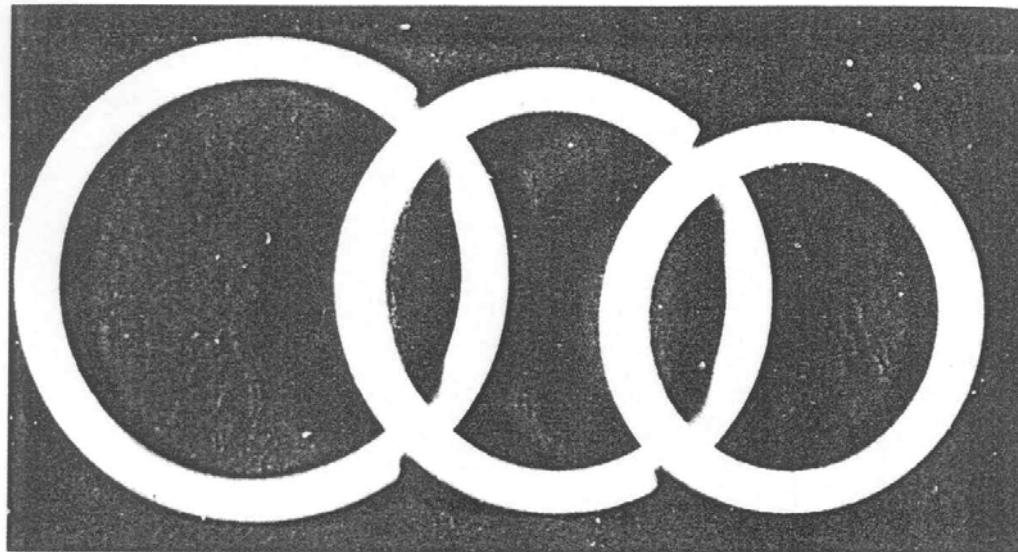
## **INTRAUTERINI SISTEMI:**

- intrauterini kontracepcijski sistemi (Intrauterine contraceptive devices – IUDs). Začetek v dvajseta leta – iz fleksibilne kovinske žice in svilenih niti.
- kasneje raznovrstni in biokompatibilni polimeri
- intrauterina plastična spirala in zanka

**Učinek – MEHANSKI!**

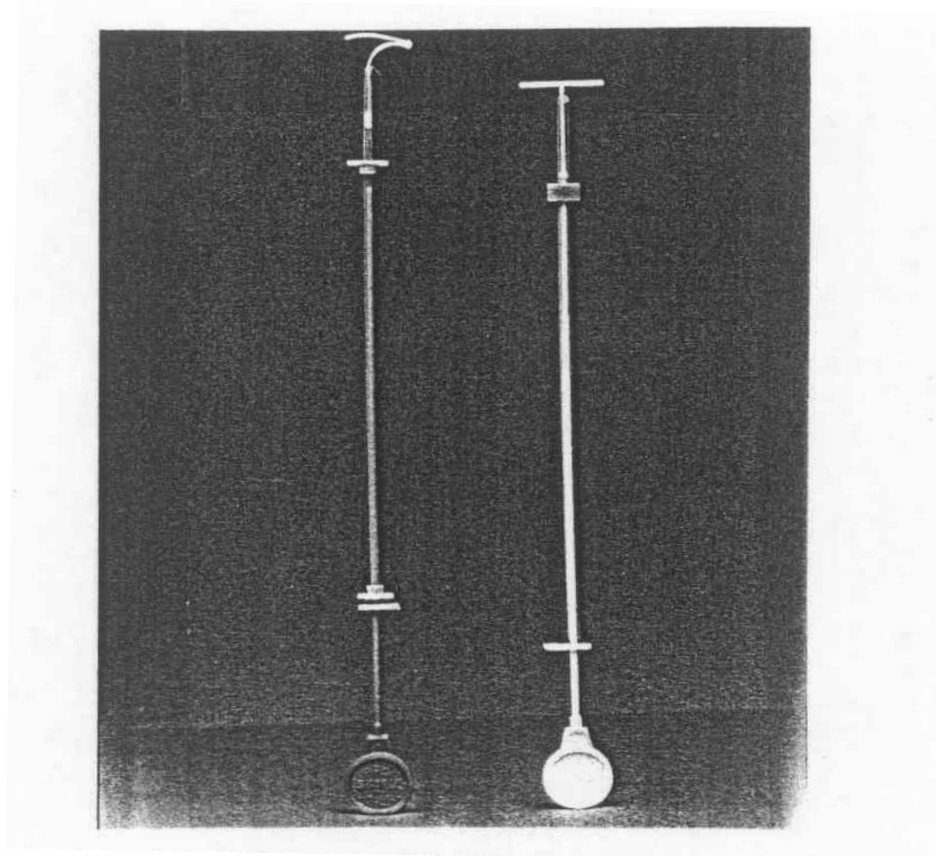
- leta 1968 – IUDs s kontroliranim sproščanjem učinkovine – baker (kontracektivna kovina). Zipper et al. ter progestrin IUD (Doyle in Clewe).

**Figure 2: Contraceptive vaginal rings fabricated from silicone medical grade Elastomer. (From Ref. 33).**

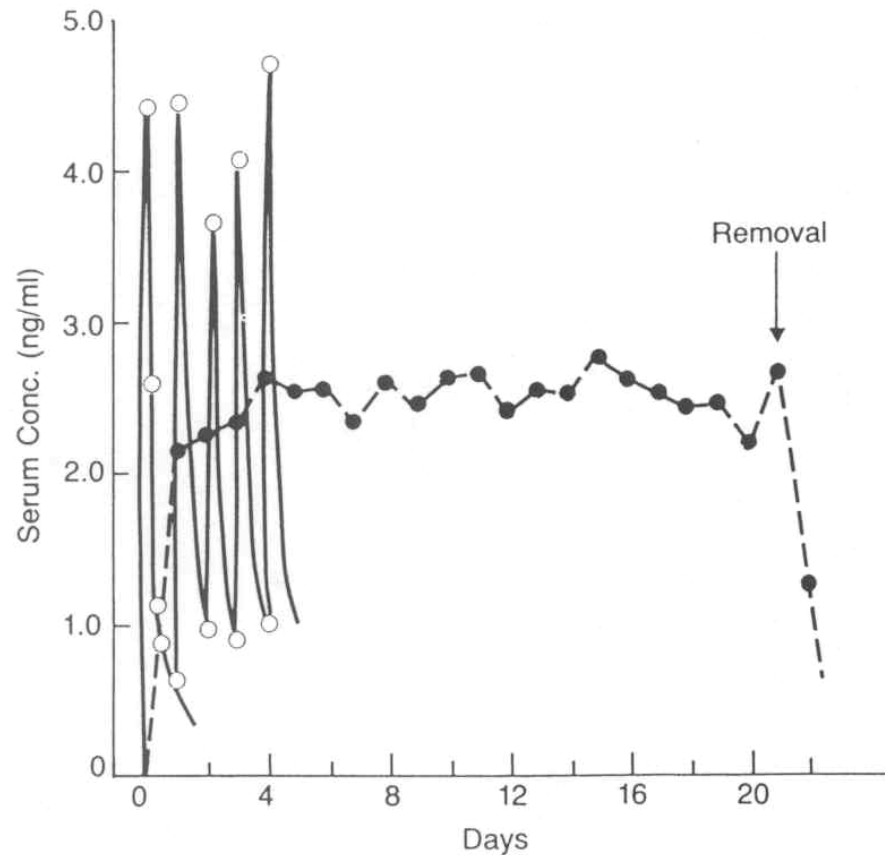


- FDA odobri prvi IUD z bakrom za triletno intrauterino uporabo – Cu 7 IUD (89 mg Cu žica) – G.D. Searle&Co.
- IUD s progesteronom – lokaliziran učinek v maternici (1 leto terapije).

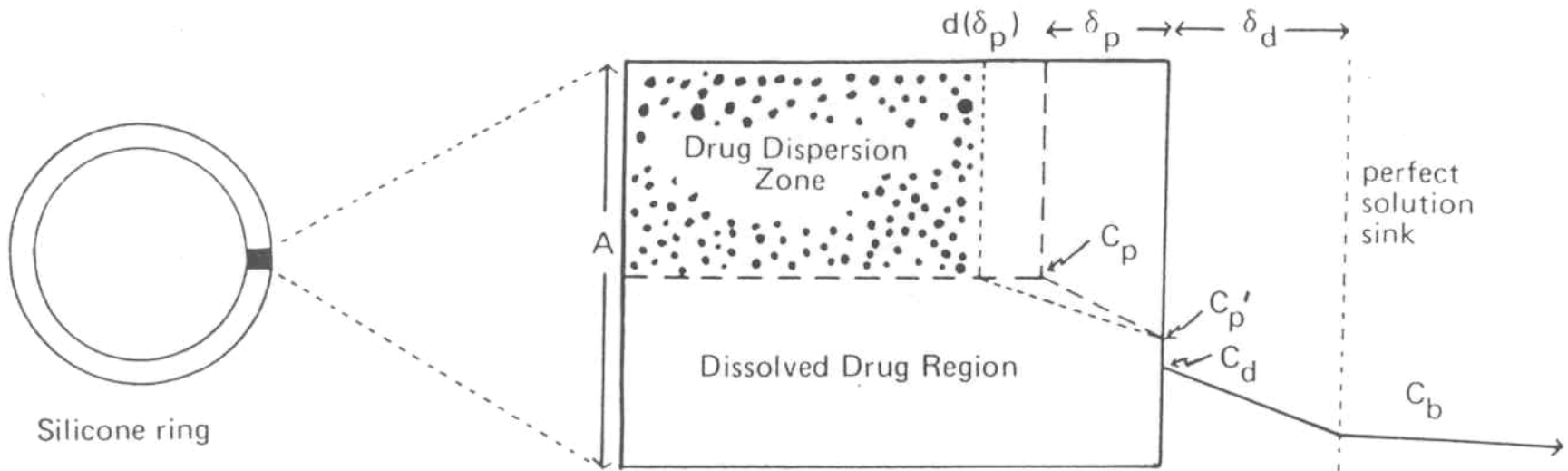
**Figure 5: Copper-bearing CU-7 (left) and Tatum-T (right) intrauterine devices (courtesy G.D. Searle&Company)**



**Figure 3: Comparative serum concentration profiles of medroxyprogesterone acetate in humans resulting from continuous delivery of medroxyprogesterone acetate from intravaginal administration of one unit of contraceptive vaginal ring (each ring contains 100 mg of medroxyprogesterone acetate) for 21 days (●) and from daily oral intake of one Provera tablet (each contains 10 mg medroxyprogesterone acetate) for 5 consecutive days (○). [Plotted from the data by Hiroi et al., *Steroids* 26, 373 (1975) and by Thiery et al., *Contraception* 13, 605 (1976).]**



**Figure 4: Schematic illustration of the controlled release of drug molecules from a matrix diffusion-controlled drug delivery device (such as the vaginal ring in Fig. 2). A is the initial amount of drug solids impregnated in a unit volume of polymer matrix;  $C_p$  is the solubility of drug in the polymer phase;  $C_p'$  is the conc. of drug at the polymer/solution interface;  $C_d$  is the conc. of drug at the solution/polymer interface;  $C_b$  is the conc. of drug in the bulk of elution solution;  $\delta_p$  and  $\delta_d$  are the thicknesses of the drug depletion zone in the matrix and of the hydrodynamic diffusion layer on the immediate surface of the device, respectively; and  $d(\delta_p)$  is the differential thickness of the depletion zone formed after more drug solids elute out. [ From Y. W. Chien, H. Lambert and T. Lin, *J. Pharm. Sci.* 64, 1643 (1975). ]**



## **TRANSDERMALNI SISTEMI:**

- 70 kg odrasla oseba – 1,8 m<sup>2</sup> kože; na 1 cm<sup>2</sup> – 10 dlačnih foliklov, 12 živcev, 15 lojnic in 100 žlez (za izločanje pota), 1/3 celokupne telesne cirkulacije.

- sestava: 2 ločeni tkivi – večplastni neprekrvavljeni celični *epidermis* (0,8 – 0,6 mm) ter *dermis* (3 – 5 mm, vezna tkiva – kolgen, elastin, retikulin; krvne žile, živci, limfne žleze). Pod dermisom je maščobno tkivo.

### **Classes of drugs used for topical administration**

<b>Antibacterials</b>	<b>Astringents</b>	<b>Keratolytics</b>
<b>Antibiotics</b>	<b>Cytotoxic agents</b>	<b>Keratoplastic agents</b>
<b>Antifungals</b>	<b>Depigmenting agents</b>	<b>Local anesthetics</b>
<b>Antihistamines</b>	<b>Depilatories</b>	<b>Parasitocides</b>
<b>Antiinflammatory agents</b>	<b>Epilatories</b>	<b>Pigmenting agents</b>
<b>Antiperspirants</b>	<b>Germicides</b>	<b>Rubefaciants</b>
<b>Antipruritics</b>	<b>Insect repellents</b>	<b>Sunscreening agents</b>

- dvig “bariernih lastnosti” kože: kreme za sončenje, topikalni antibiotiki, antibakterijski agensi, vlažilna mazila idr.
- lokalna aplikacija zaradi bolezni kože (učinkovina se koncentrira v koži)
- sistemska aplikacija

**Table 1: Routes of drug penetration through the skin**

<b>Interfacial Skin Boundaries</b>	<b>Mechanism</b>	<b>Treatment</b>
<b>Surface</b>	<b>Dissolution and diffusion</b>	<b>Antifungals and antimicrobials</b> <b>Cosmetics</b> <b>Insect repellents</b>
<b>Stratum corneum</b>	<b>Partition and dissolution</b>	<b>Emollients</b> <b>Exfolients</b>
<b>Viable epidermis and dermis</b>		<b>Anesthetics</b> <b>Antihistamines</b> <b>Antiinflammatories</b> <b>Antipruritics</b>
<b>Circulation</b>		<b>Drugs for systemic absorption</b>



**Table 2: Factors affecting transdermal absorption**

<b>Factor</b>	<b>Example</b>
<b>Physicochemical properties of the drug</b>	<b>Partition coefficient of the drug molecule Concentration of drug in the delivery system pH of the delivery system pH of the skin</b>
<b>Physicochemical properties of the drug delivery system</b>	<b>Affinity of the vehicle for drug molecules Composition for the delivery system Presence of permeation promotor in the delivery system</b>
<b>Physiologic and pathologic conditions of the skin</b>	<b>Nature and thickness of the barrier layer Reservoir effect of the horny layer Cutaneous drug metabolism Moisture balance in the stratum corneum Lipid film on the skin surface Temperature of the skin Pathologic injury to the skin</b>

## Transdermalni obliž

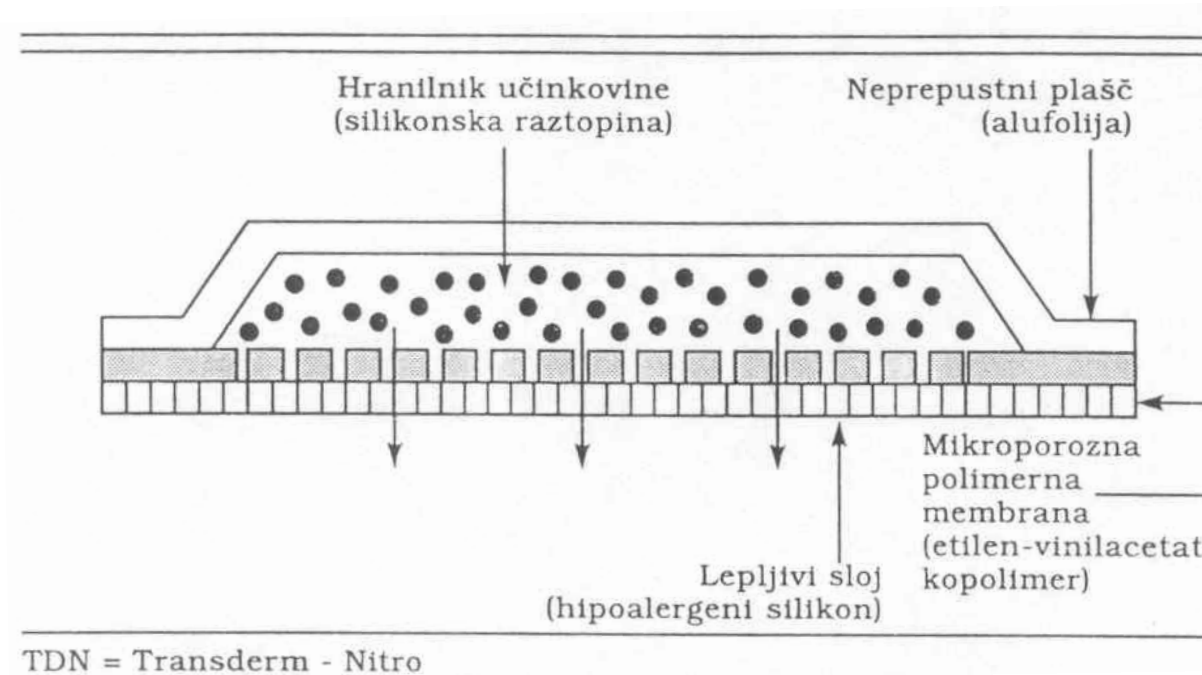
- nitroglicerina in skopolamin (prva uporabljena)
- sestava: zaščitni zunanji sloj; rezervoar učinkovine, membrane in adhezivna plast z začetnim odmerkom učinkovine
- počasno sproščanje nitroglicerina: postopna difuzija (vezanega) nitroglicerina skozi gel – matriks iz polivinilalkohola, laktoze, glicerola, vode, povidona in Na-acetata
- rezervoar v Searle Nitrodisc je trdno-silikonski polimerni matriks

**Table 3: Transdermal nitroglycerin products**

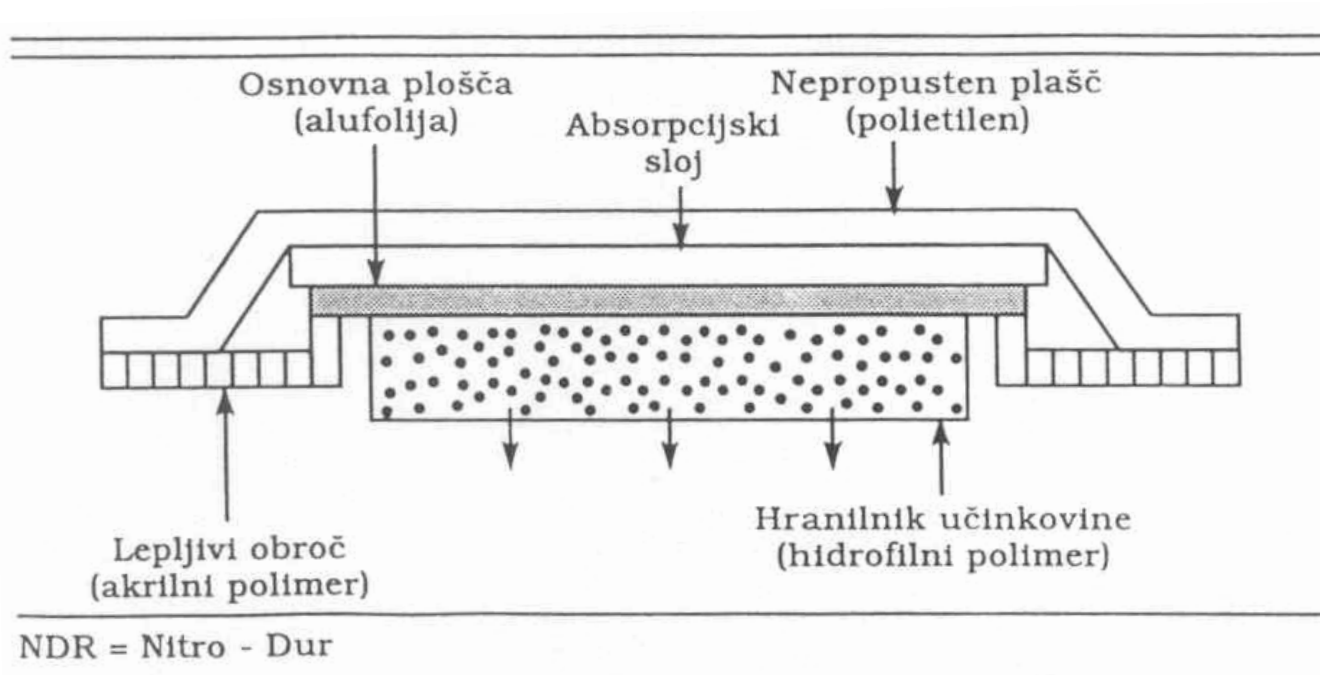
<b>Manufacturer and Product</b>	<b>Product Size, cm<sup>2</sup></b>	<b>Total Drug Content, mg</b>	<b>Drug Delivered in 24 Hours, mg</b>
<b><i>Ciba-Geigy:</i></b>			
<b>Transderm-Nitro 2.5</b>	<b>5</b>	<b>12,5</b>	<b>2,5</b>
<b>Transderm-Nitro 5</b>	<b>10</b>	<b>25,0</b>	<b>5,0</b>
<b>Transderm-Nitro 10</b>	<b>20</b>	<b>50,0</b>	<b>10,0</b>
<b>Transderm-Nitro 15</b>	<b>30</b>	<b>75,0</b>	<b>15,0</b>
<b><i>Key Pharmaceuticals:</i></b>			
<b>Nitro-Dur 5 cm<sup>2</sup></b>	<b>5</b>	<b>26,0</b>	<b>2,5</b>
<b>Nitro-Dur 10 cm<sup>2</sup></b>	<b>10</b>	<b>51,0</b>	<b>5,0</b>
<b>Nitro-Dur 15 cm<sup>2</sup></b>	<b>15</b>	<b>77,0</b>	<b>7,5</b>
<b>Nitro-Dur 20 cm<sup>2</sup></b>	<b>20</b>	<b>104,0</b>	<b>10,0</b>
<b><i>G.D. Searle:</i></b>			
<b>Nitrodisc 5 mg/24h</b>	<b>8</b>	<b>16,0</b>	<b>5,0</b>
<b>Nitrodisc 10 mg/24h</b>	<b>16</b>	<b>32,0</b>	<b>10,0</b>

1. Učinkovina se izogne razpadu v prebavnem traktu oziroma vplivu prvega prehoda jeter
2. Krvne koncentracije učinkovine so manjše in brez večjih nihanj
3. Biološka uporabnost se med posamezniki ne razlikuje veliko
4. Ni potrebno večkratno odmerjanje zdravila na dan
5. Učinkovine s kratko biološko razpolovno dobo imajo daljši čas delovanja
6. Učinkovitost zdravila se poveča, ker se izognemo težavam, povezanim z napačnim odmerjanjem

**Slika 6: Transdermalni sistem z mikroporozno polimerno membrano**



## Slika 7: Transdermalni sistem s hidrofilnim ogrodjem



**Tabela 4 prikazuje različne transdermalne sisteme, ki so že v uporabi. Vsi imajo več prednosti pred običajnimi zdravili ne glede na uporabljeni sistem.**

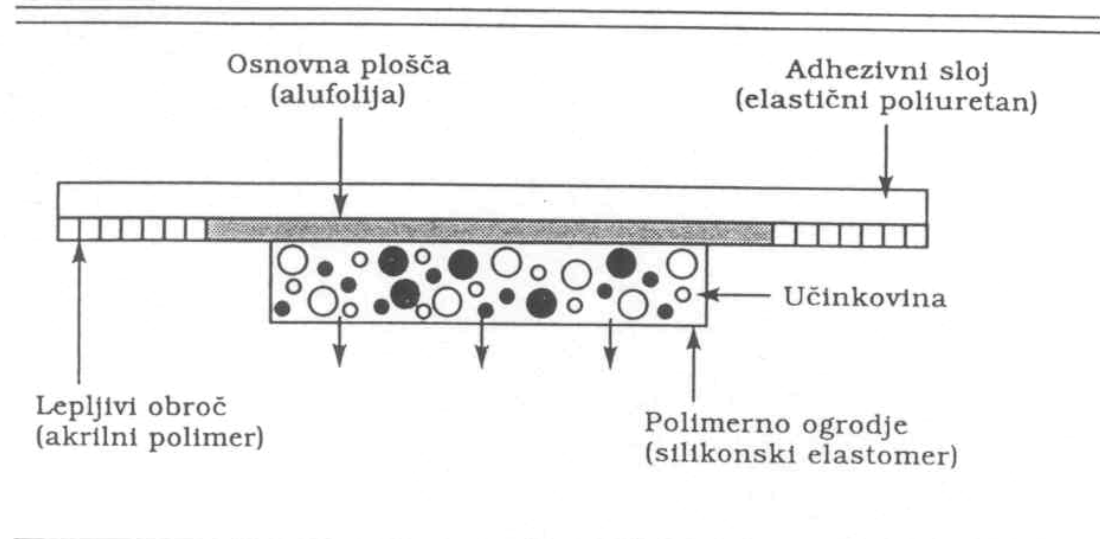
## Tabela 4: Transdermalni sistemi sproščanja učinkovine

- ❖ Adhezivni pripravki
- ❖ Monolitni pripravki
- ❖ Pripravki s hranilnikom učinkovine
- ❖ Pripravki s sproščanjem skozi membrano
- ❖ Adhezivni pripravki z difuzijo
- ❖ Pripravki z učinkovino, vgrajeno v ogrodje
- ❖ Pripravki z učinkovino v mikrokapsulah

## Tabela 5: Absorpcija hidrokortizona skozi kožo na različnih predelih človeškega telesa

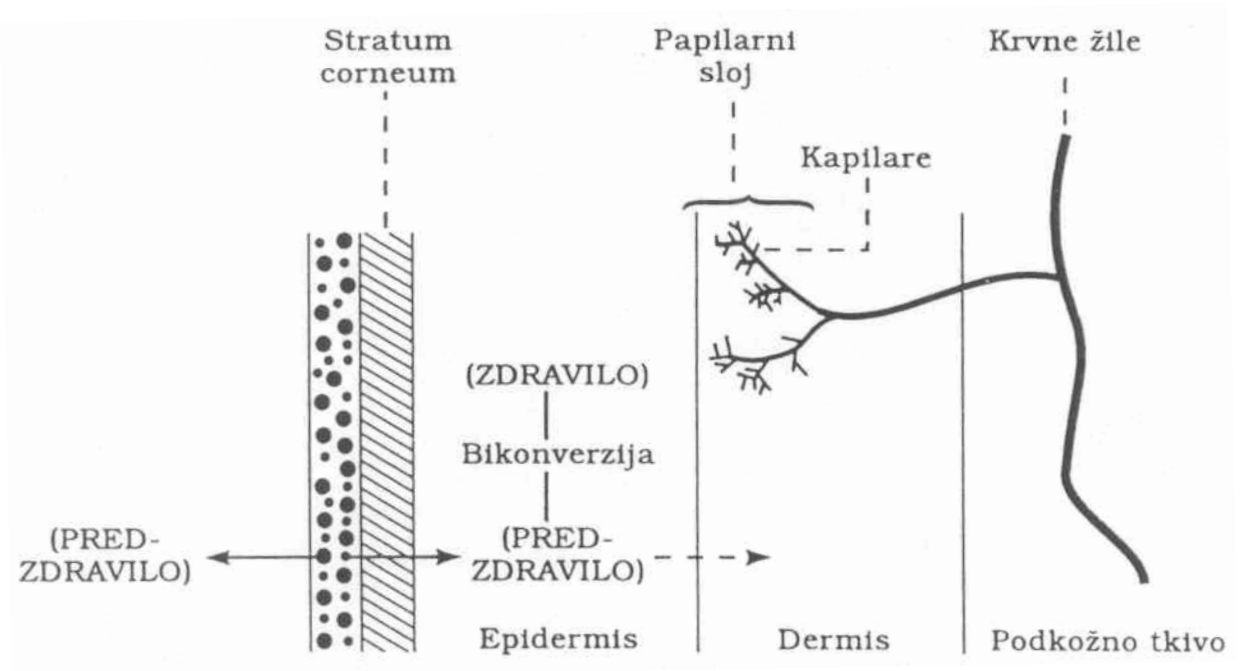
<b>Mesto uporabe</b>	<b>Absorpcijski indeks</b>
Nadlahtnica	1,1
Stopalo	0,14
Hrbet	1,7
Lasišče	3,5

**Slika 8: Transdermalni sistem z učinkovino v silikonskem ogrodju**



DS = Nitrodisc

**Slika 9: Transdermalni sistem z vgrajenimi predzdravili**



# TRANSDERMALNI PRIPRAVKI

- stratum corneum – glavna bariera

Možnosti difuzije (permeacije):

- skozi intaktni stratum corneum
- v območju okoli lasnega folikla
- izvodila žlez za potenje

Pomemben je porazd. koeficient stratum corneum/vehikel z učinkovino.

## Absorpcija alkanalov

$$\log(P_s)_n = \log(P_s)_0 + (\Pi)_{\text{CH}_2} \cdot (n)_{\text{CH}_2}$$

$(P_s)_n$  – permeabilnostni koeficient alkanola ( z n CH<sub>2</sub> skupinami) skozi kožo

$(P_s)_0$  – permeabilnostni koeficient hipotetičnega alkanola z 0 C-atomi

$(\Pi)_{\text{CH}_2}$  – konstantna vrednost za metilensko skupino

$(n)_{\text{CH}_2}$  – število CH<sub>2</sub> skupin v alkanolu

Enačba velja:  $C_3 \leq n \leq C_8$  (Figure 10)

$$\log P_n = \log P_0 + (\Pi)_{\text{CH}_2} \cdot (n)_{\text{CH}_2}$$

$P_n$  – porazd. koef. stratum corneum/vehikel za alkanol z n CH<sub>2</sub> skupinami



# STANDARDNA PROSTA GIBBSOVA ENTALPIJA

$$\Delta G^{\circ} = RT \ln P$$

**P** – porazdelitveni koeficient stratum corneum/vehikel

**$\Delta G^{\circ}$**  – energija, ki jo prejme topljenec, ko gre za desorpcijo s strani stratum corneum/vehikel

$$\Delta G^{\circ} = \Delta G_{OH}^{\circ} + n\Delta G_{CH_2}^{\circ} \Rightarrow \log P = \text{konst.} + \frac{n\Delta G_{CH_2}^{\circ}}{2,303RT}$$

Izračun  $\Delta G_{CH_2}^{\circ}$  (za homologno serijo alkanolov, za P med strat.corn./voda):

$$\Delta G_{CH_2}^{\circ} = 241 \text{ cal/mol} \quad n < 3$$

$$\Delta G_{CH_2}^{\circ} = 448 \text{ cal/mol} \quad n > 3$$

$n < 3 \rightarrow$  mešanje z vodo; ker je strat. corn. tudi dobro hidratiran  $\rightarrow \downarrow \Delta G_{CH_2}^{\circ}$

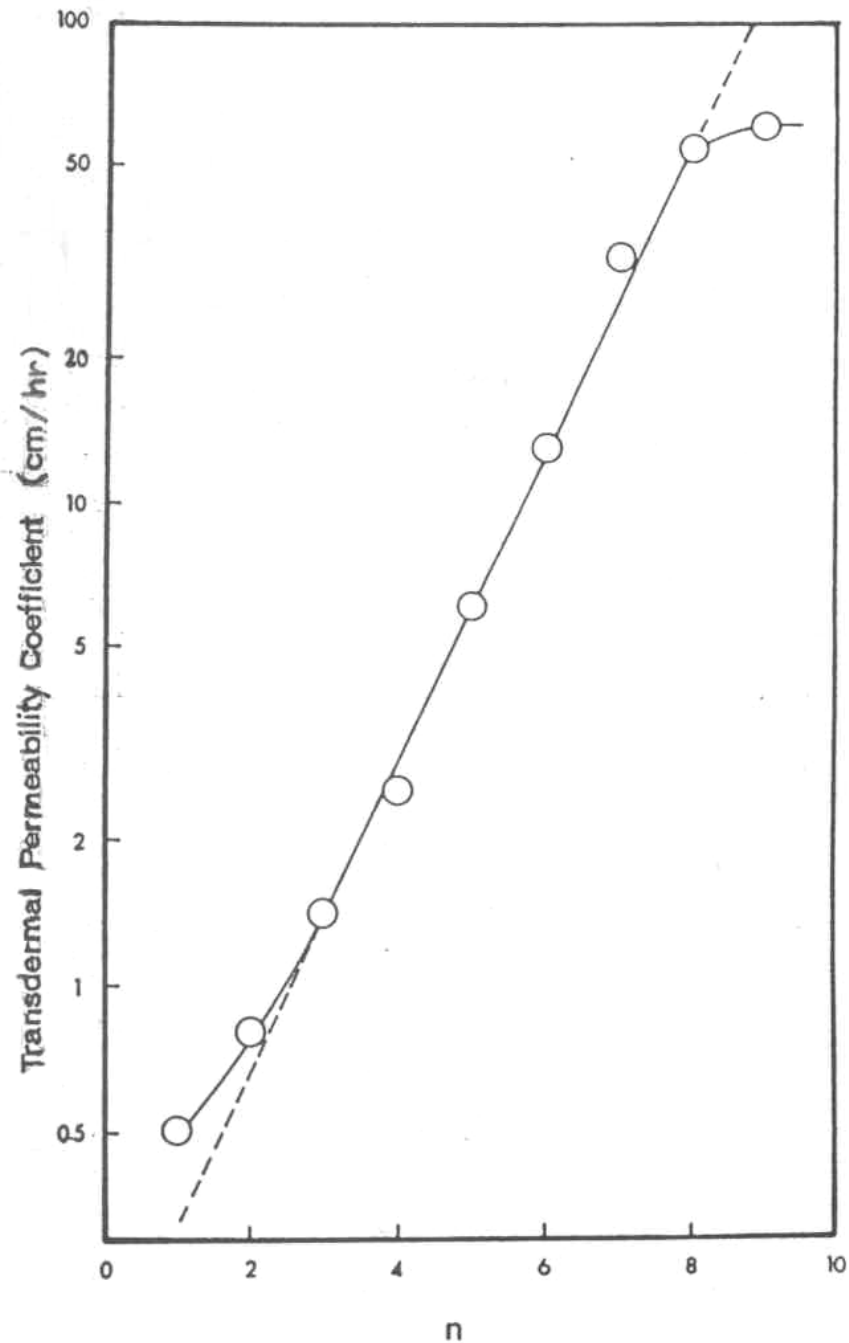
1) Vehikel ima podobne lastnosti kot stratum corneum  $\rightarrow \Delta G^{\circ} = 0$  in  $P = 1$ , permeabilnost kože je neodvisna od dolžine verige ( $n \text{ CH}_2$ ) alkanola

2) Vehikel – bolj lipofilen kot stratum corneum  $\rightarrow \Delta G^{\circ} < 0$  in  $P < 1 \rightarrow$  permeabilnost kože  $\downarrow$  z daljšanjem alkilne verige

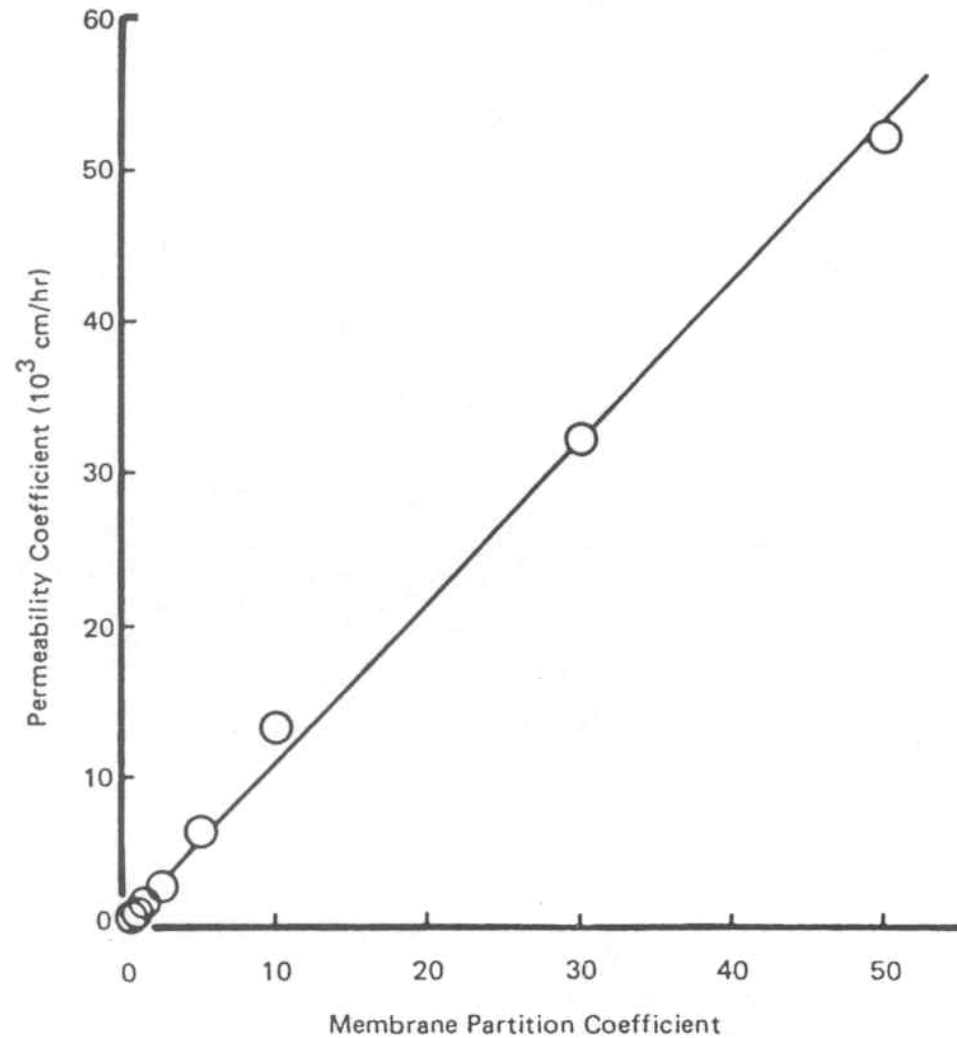
Primer: vehikel izopropil palmitat

$$\Delta G_{CH_2}^{\circ} = -326,5 \text{ cal/mol}$$

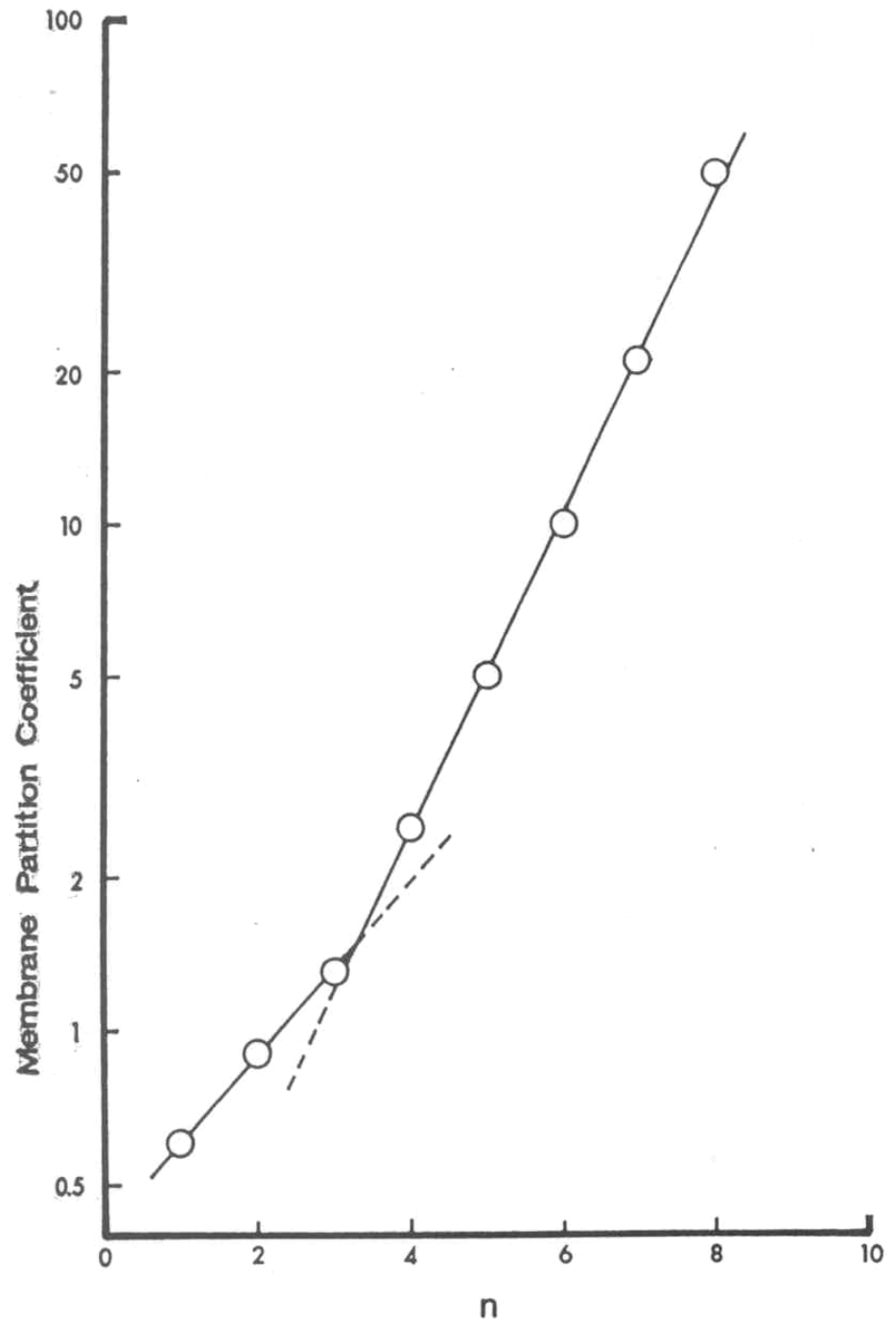
**Figure 10: Dependence of skin permeability coefficients on the alkyl chain length  $n$  of alkanols in aqueous solution. (Plotted from the data by Scheuplein and Blank, 1971.)**



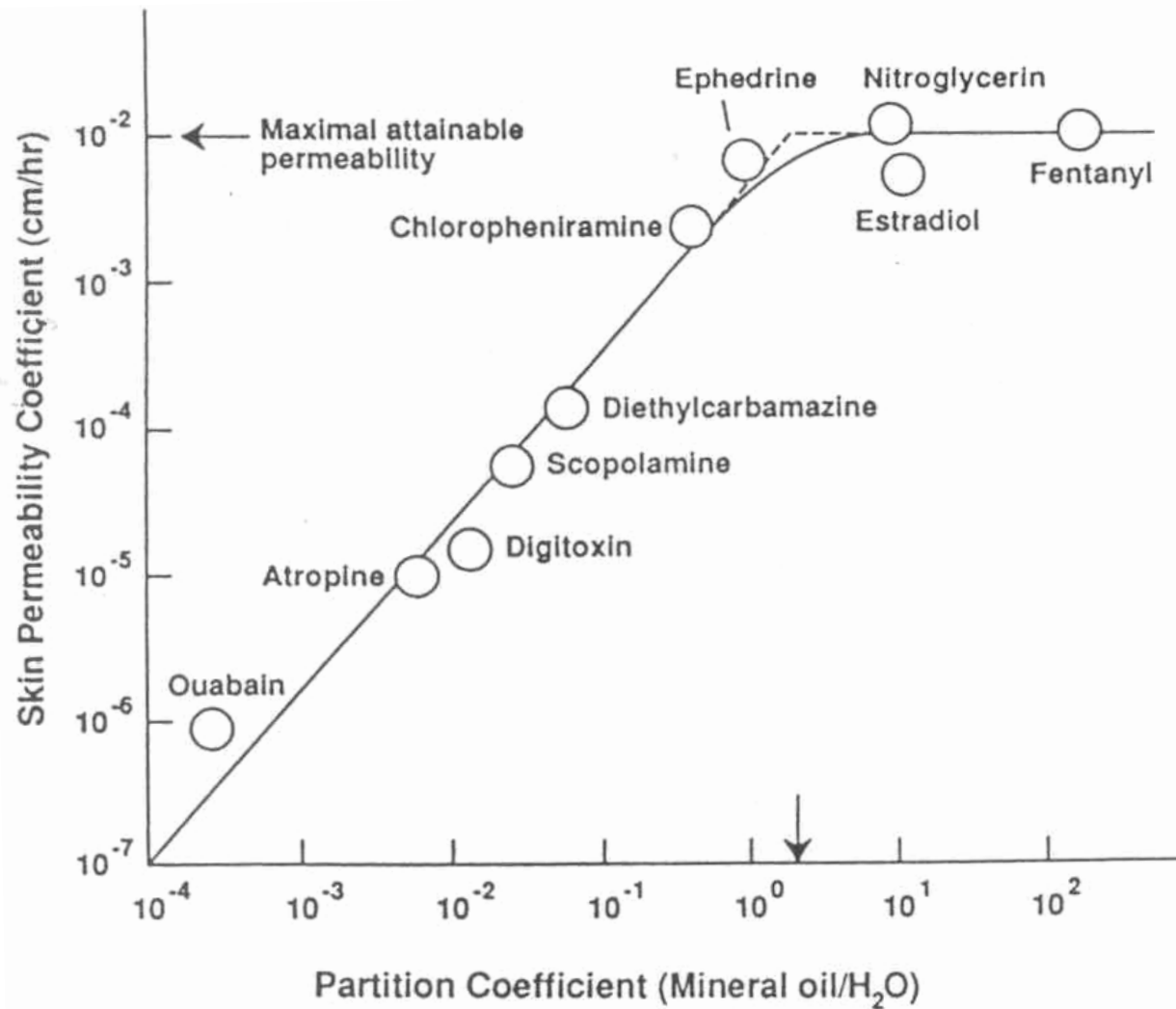
**Figure 11: Linear relationship between the skin permeability coefficient and the stratum corneum/aqueous vehicle partition coefficient (or membrane partition coefficient). (Plotted from the data by Scheuplein and Blank, 1971.)**



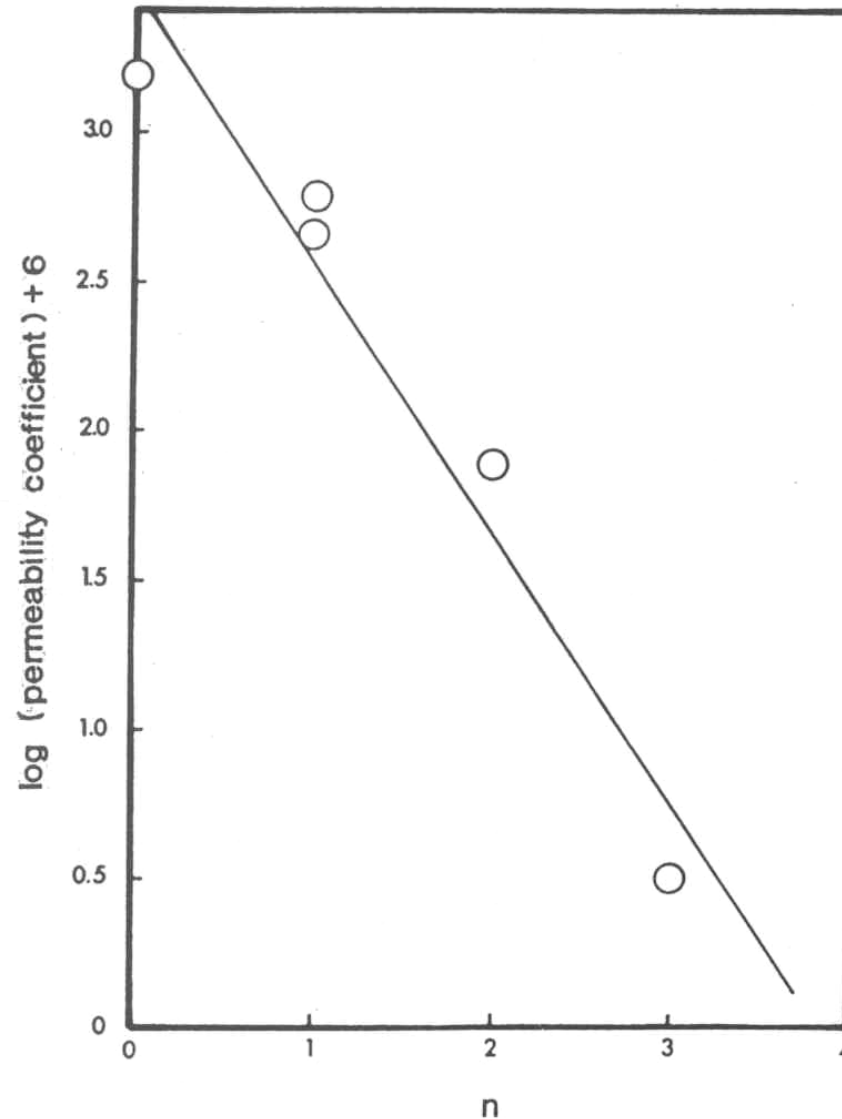
**Figure 12: Effect of the alkyl chain length  $n$  of alkanols in aqueous solution on the partition coefficient for the interfacial partitioning of alkanols from aqueous phase to stratum corneum. (Plotted from the data by Scheuplein and Blank, 1971.)**



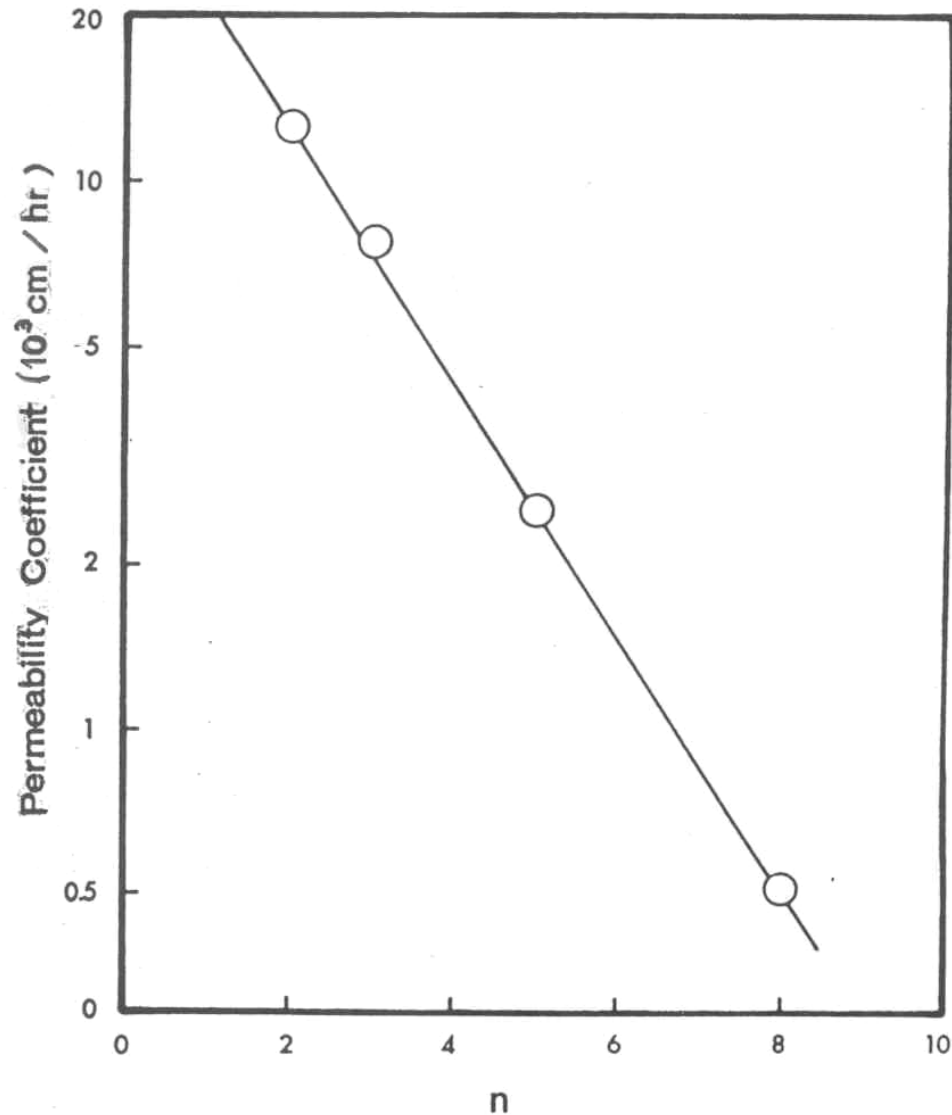
**Figure 13: Dependence of the skin permeability coefficients of a series of drugs on their partition coefficients determined in a mineral oil – water system. (Plotted from the data by Michaels et al., 1975.)**



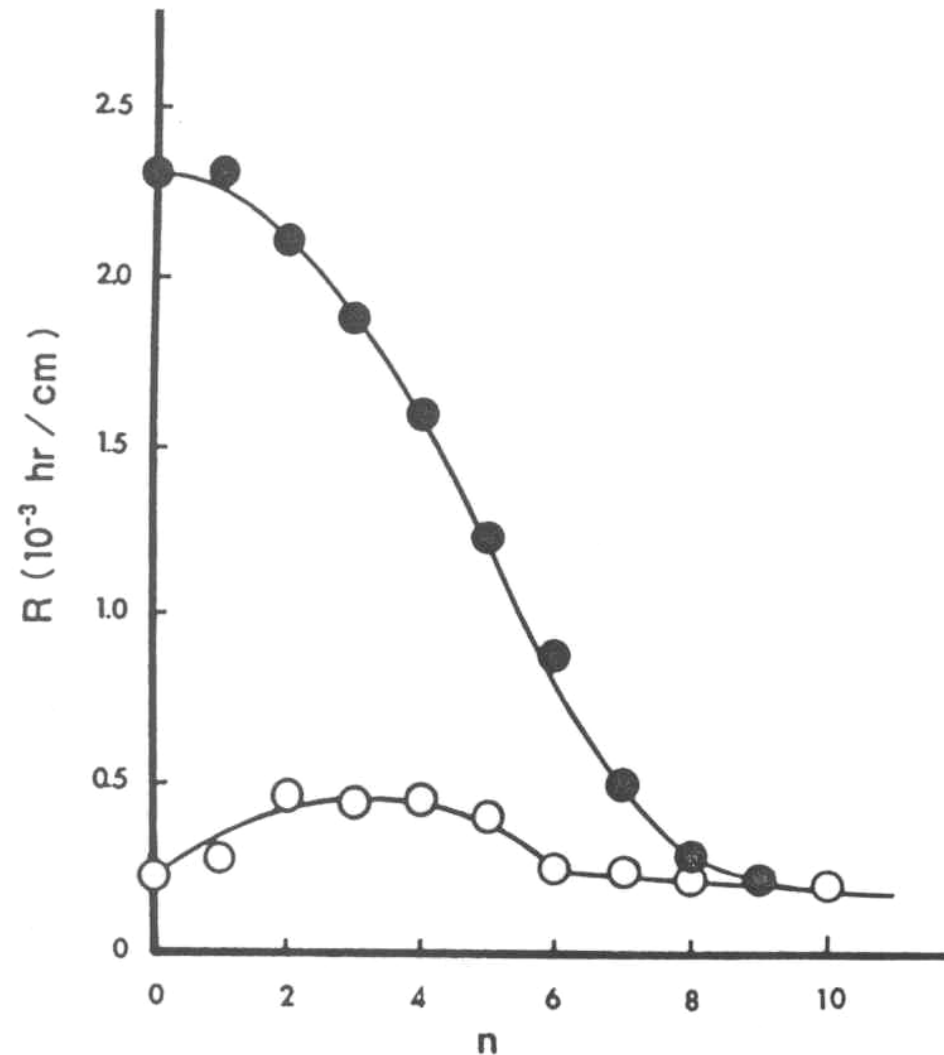
**Figure 14: First-order dependence of the transdermal permeability coefficients of progesterone and its derivatives on the number  $n$  of hydroxy groups. (Plotted from the data by Scheuplein et al., 1969.)**



**Figure 15: Effect of alkyl chain length  $n$  on the skin permeability coefficients of alkanols from a lipophilic vehicle of isopropyl palmitate. (Plotted from the data by Scheuplein and Blank, 1971.)**



**Figure 16: Effect of alkyl chain length  $n$  on the diffusional resistance  $R$  of isolated epidermis ( $\bullet$ ) and dermis ( $\circ$ ) to alkanols. (Plotted from the data by Scheuplein and Blank, 1971.)**





# BIOADHEZIVNI SISTEMI

- ↑ BU
- ↑ lokalno delovanje
- daljše zadrževanje učinkovine v krvi
- ↑ BU predzdravil (vezanje na polimere)
- učinek na encime

Peptidi, proteini (vgradnja inhibitorjev encimov)

## BUKALNA, SUBLINGVALNA APLIKACIJA

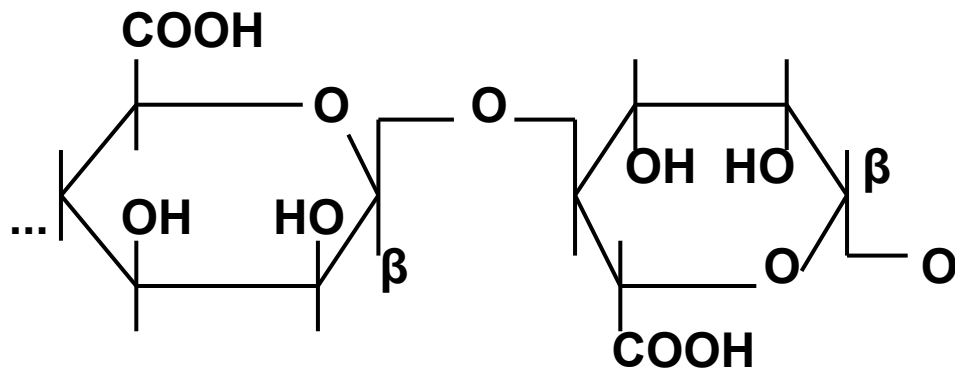
- mikrokapsule (polimerni plašč iz HPC in pektin – adheziv)
- adhezivne pastile: učinkovina + polimer (npr. hidroksipropil + etil celuloza)

**OSTALE SLUZNICE:** nazalna, vaginalna, rektalna (problem BU – sistemska in “portalna” absorpcija).

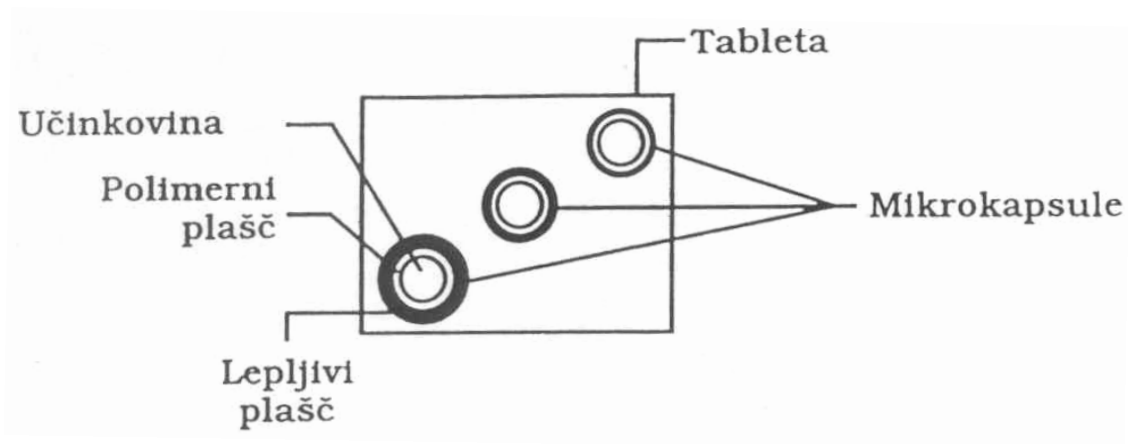
## POLIMERI (bioadhez.):



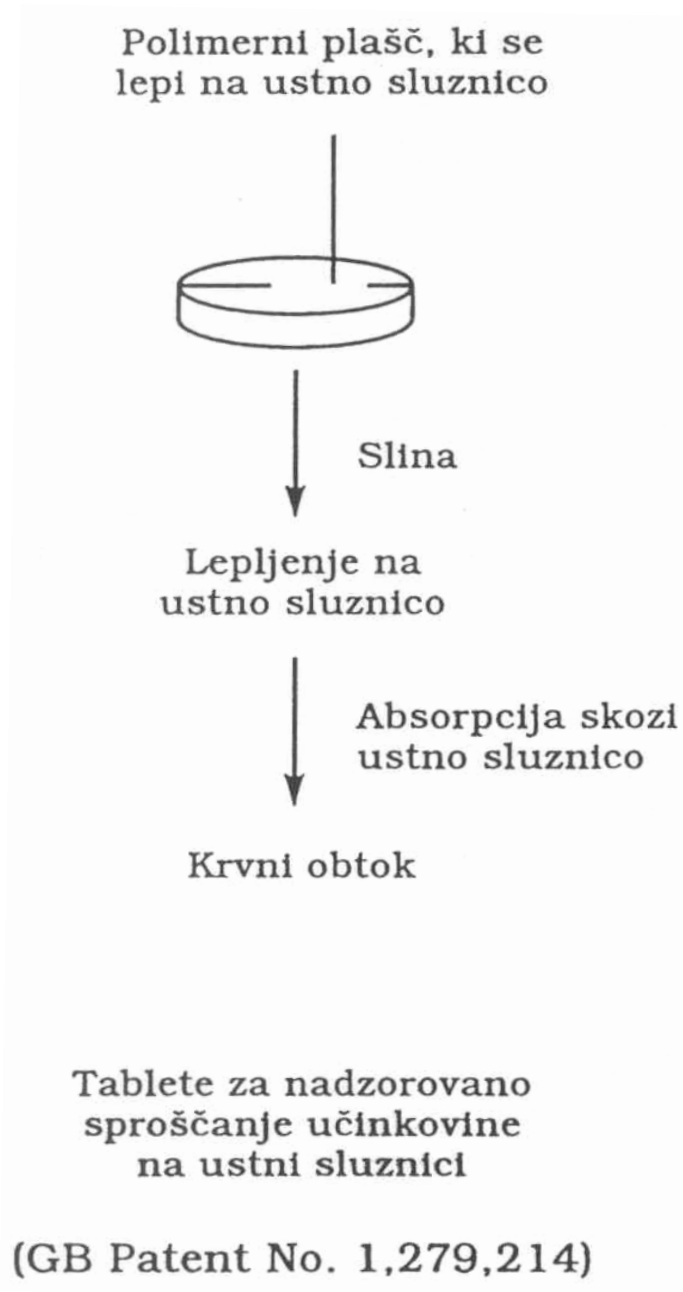
## ALGINATI (iz manuron – in guluronske kisline):



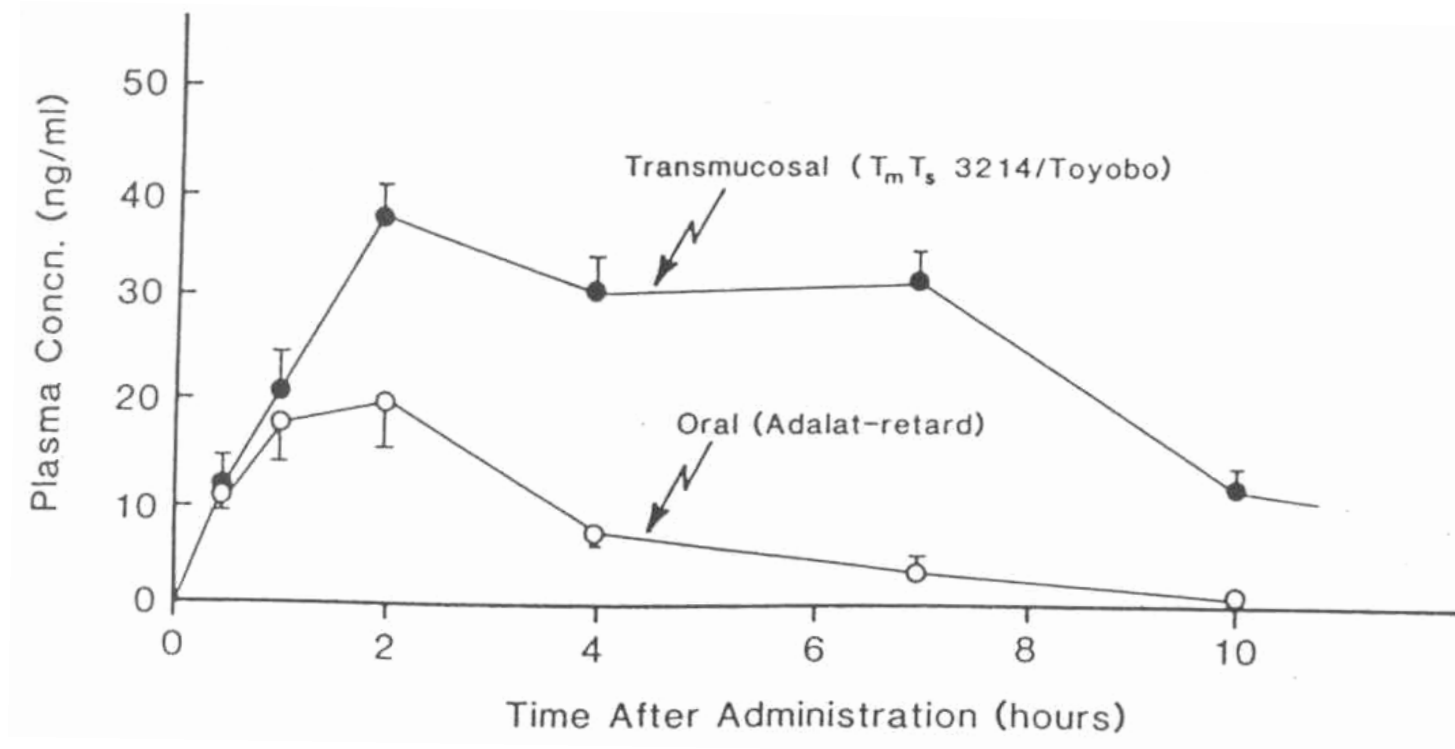
## Slika 17: Mikrokapsule z nadzorovanim sproščanjem učinkovine



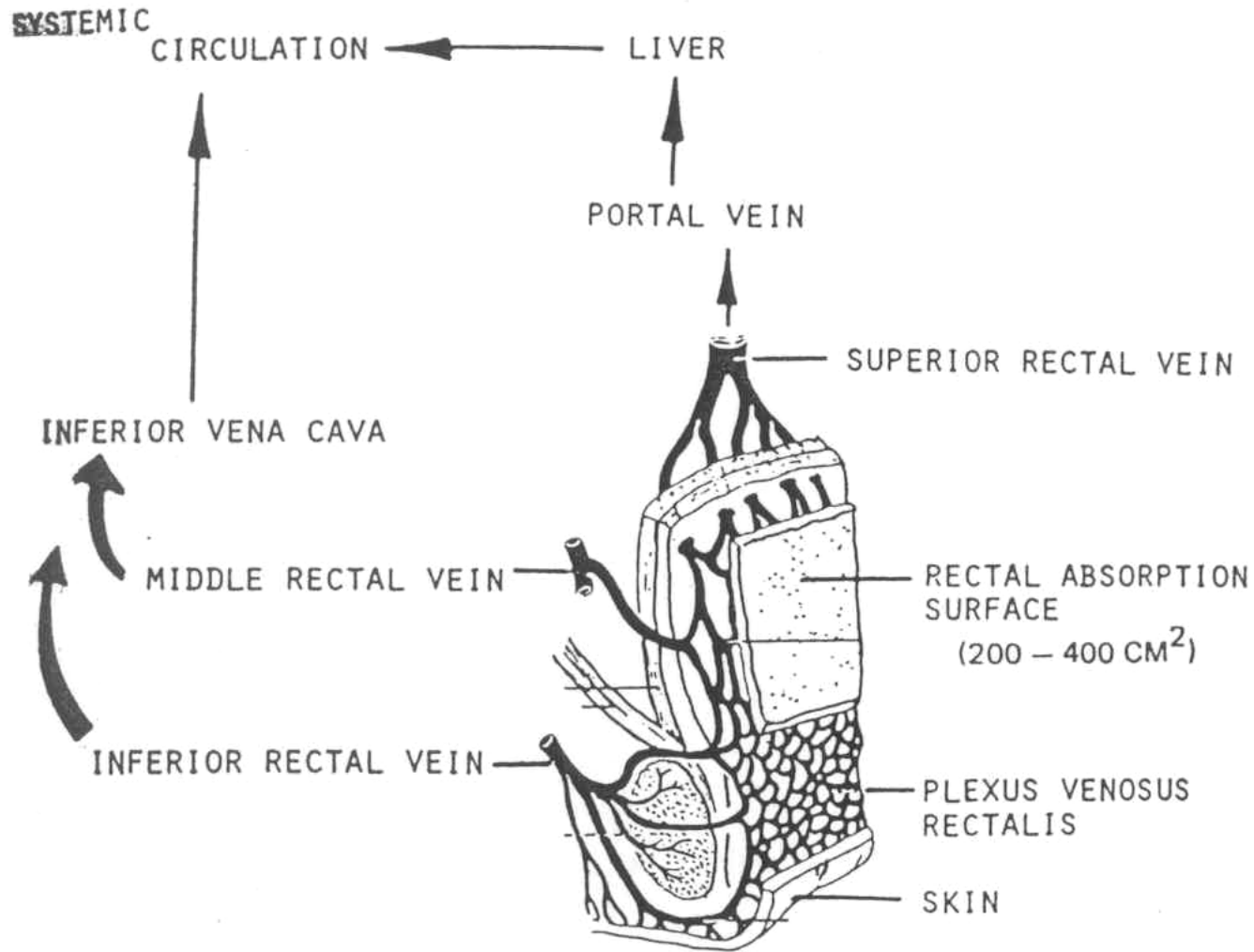
## Slika 18: Princip delovanja adhezivnih plasti



**Figure 19: Comparative plasma profiles of nifedipin delivered either transmucosally by a Toyobo oral mucosa bioadhesive drug delivery system or orally by sustained-release oral tablet (Adalat-retard) in beagle dogs ( $n = 8$ ). (Courtesy of Yukimatsu, 1989.)**



**Figure 20: The Venous drainage network in human rectum. (Chien, 1983.)**



# PROGRAMIRANI SISTEMI ZA VSAJEVANJE

## - Biološko razgradljivi polimerni sistemi:

polimlečna, poliglikolna kislina; kopolimeri → hitrost razpada  
drugi polimeri

## - Sistemi nadzorovanega sproščanja za vsajevanje:

programirani vsadki (peristaltična črpalka → sproščanje  $0,025 - 0,9 \text{ mL/h} \pm 15\%$ )

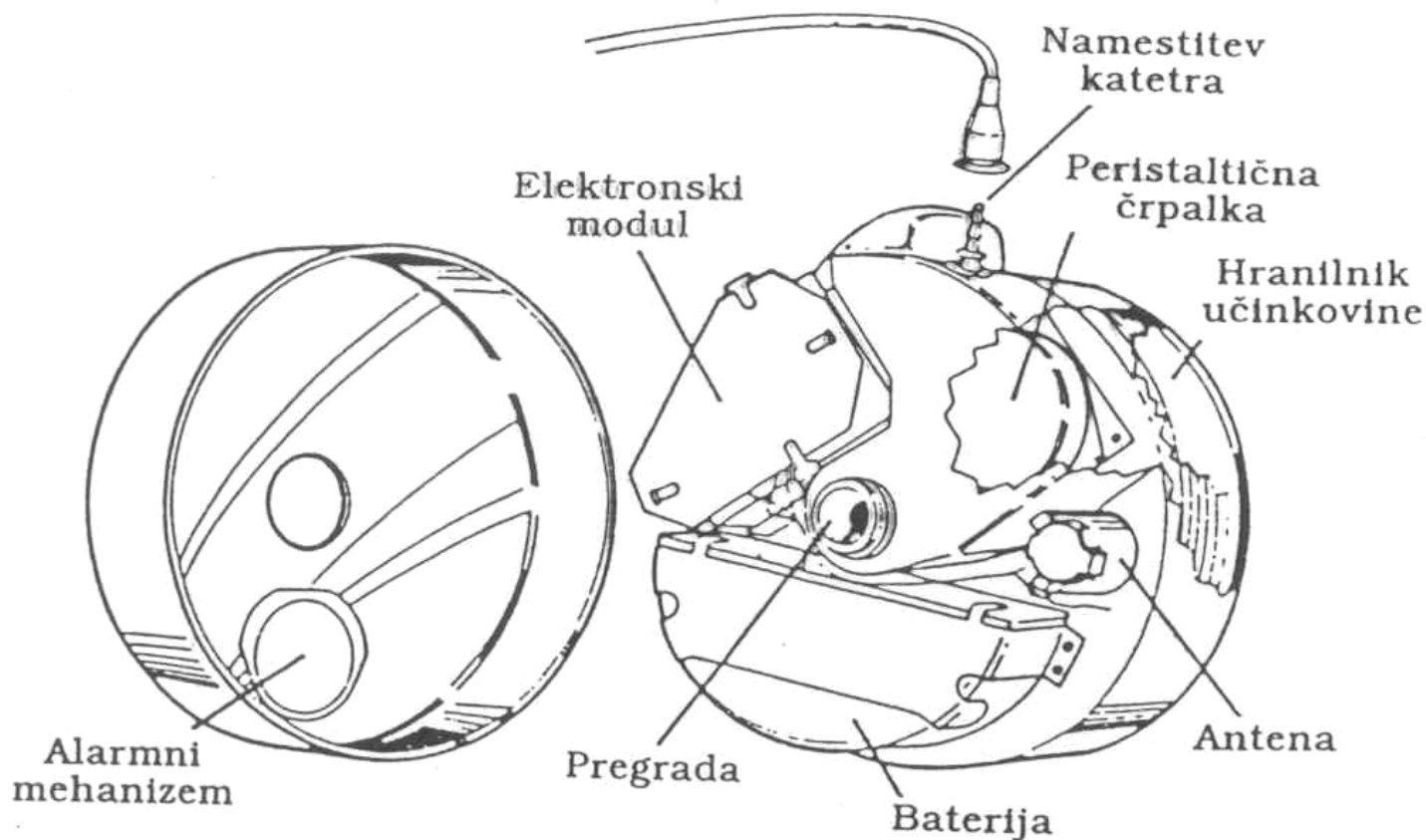
## - Sistemi sproščanja na osnovi magnetnega polja:

namagneteni delci; ciljano mesto – magnetno polje. Delci iz biološko kompatibilne snovi (npr. albumini). Rakava obolenja.

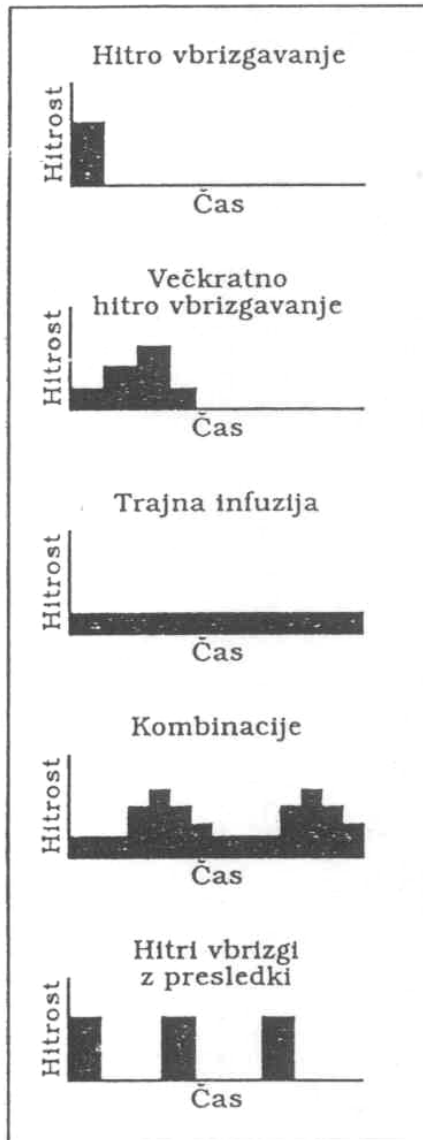
## - Sistemi nadzorovanega sproščanja na osnovi kemijskih reakcij

(“sinonim” – biorazgradljivi sistemi); na osnovi osmoze ...

**Slika 21: Shematični prikaz sistema za implantacijo s programiranim sproščanjem učinkovine**



**Slika 22: Način sproščanja iz vsadka**



**Slika 23: Shematični prikaz usmerjanja mikrodcelcev z vgrajeno učinkovino na mesto delovanja z magnetno silo**

