Hitrost absorpcije

Biofarmacija s farmakokinetiko

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Biološka uporabnost

- hitrost in obseg absorpcije (F)

- mesto aplikacije → CKO
- ekstravaskularna aplikacija

- Razlogi za nepopolno absorpcijo:
  - ZU se ne sprosti popolnoma iz FO
  - razpad ZU v GIT
  - absorpcijsko okno
  - predsistemski metabolizem

Biofarmacevtska klasifikacija učinkovin

ZU v FO $\xrightarrow{\text{topnost}}$ ZU v raztopini $\xrightarrow{\text{permeabilnost}}$ ZU v plazmi

GIT

- BCS

    topnost / hitrost raztapljanja

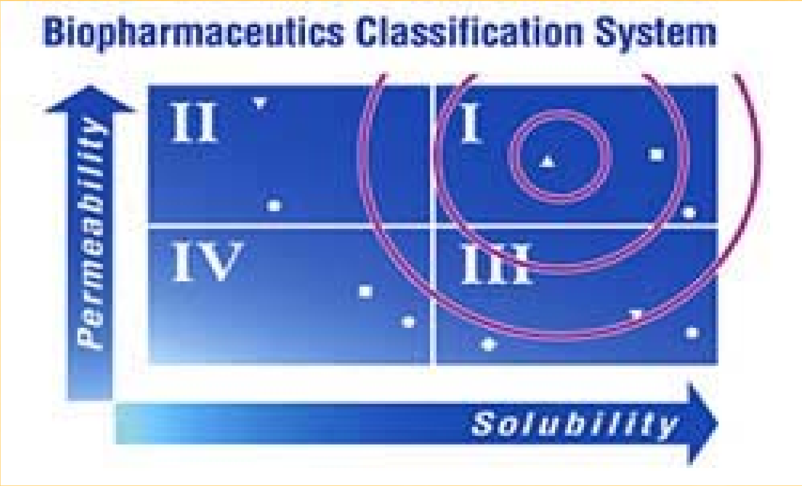
    permeabilnost

- dobra permeabilnost →

  raztapljanje ZU je omejujoč faktor absorpcije

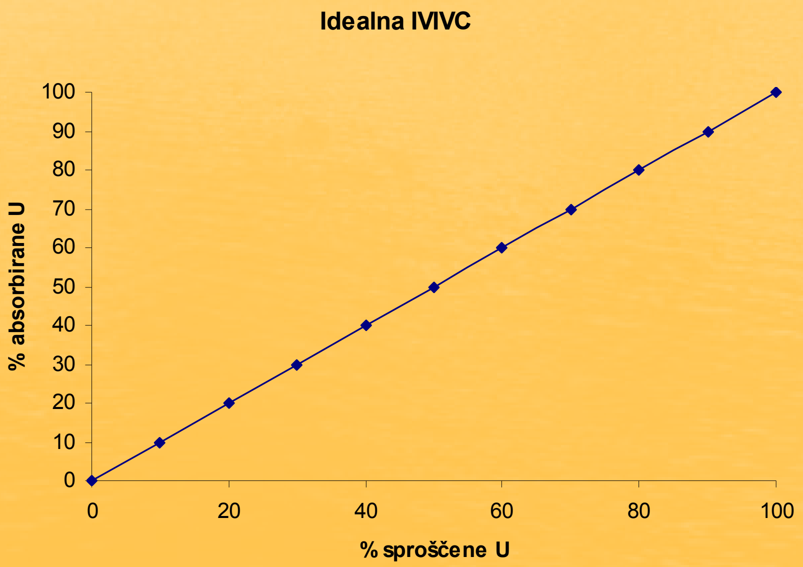
- slaba permeabilnost →

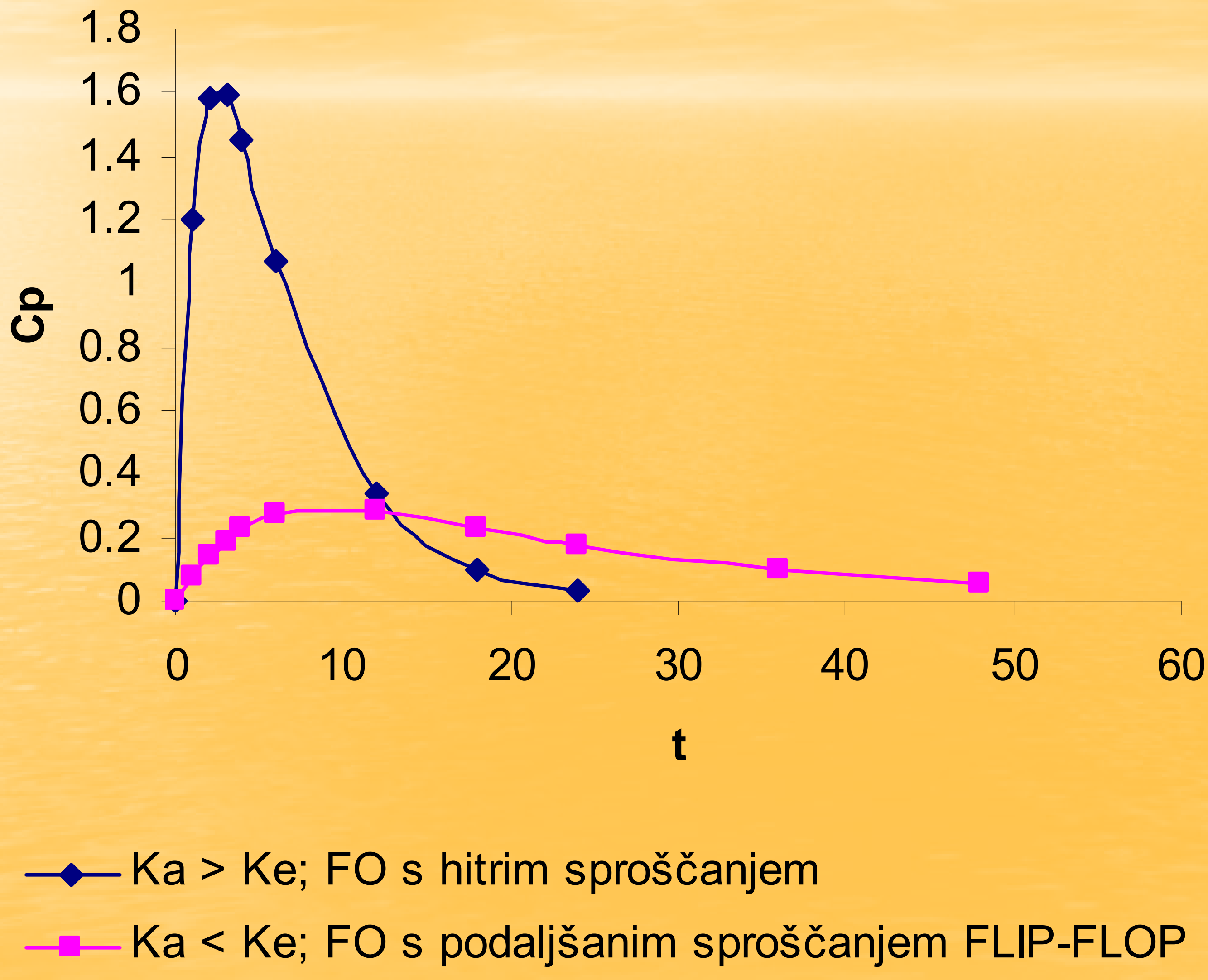
  C_p je neodvisna od hitrosti raztapljanja



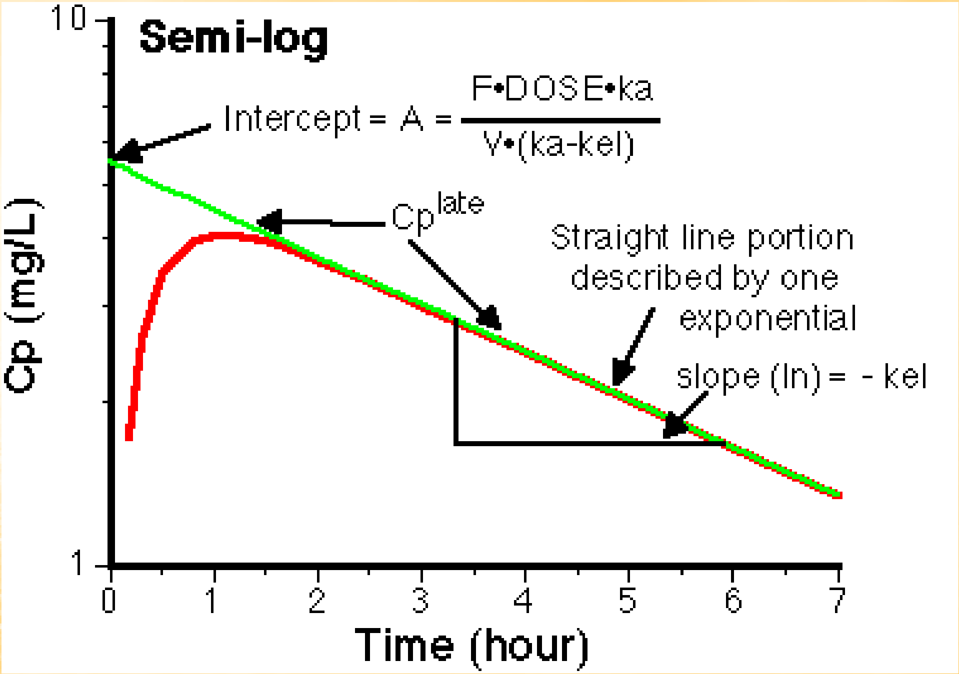
In vitro-in vivo korelacija

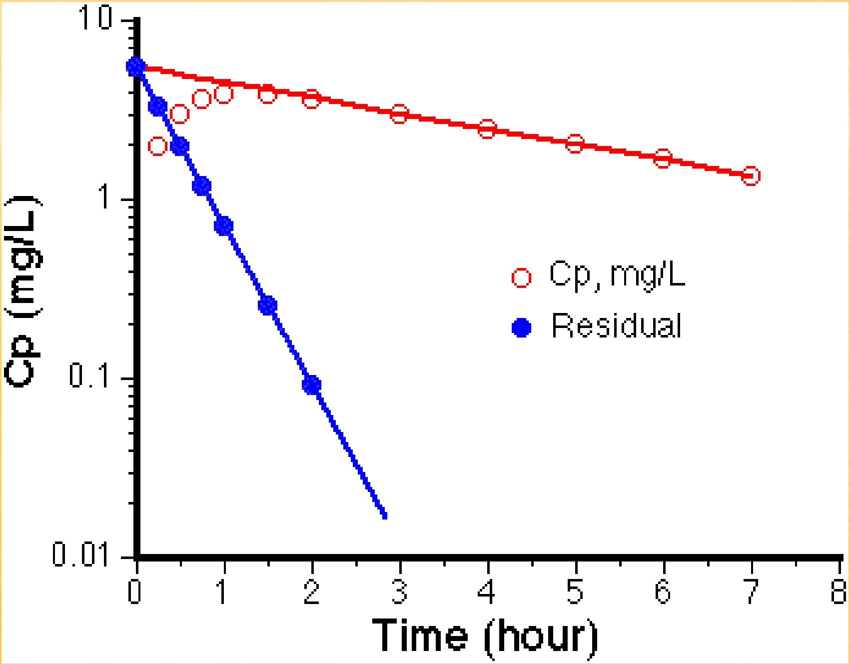
- odnos med biološkimi in fizikalno-kemijskimi lastnostmi
  - in vitro: testi raztapljanja
    - kontrola kakovosti
    - dogajanje s FO v GIT
  - in vivo: absorpcijski profil




1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Cp
0
10
20
30
40
50
60
t
Ka > Ke; FO s hitrim sproščanjem
Ka < Ke; FO s podaljšanim sproščanjem FLIP-FLOP

Določanje hitrosti absorpcije - k_a





- Metoda rezidualov
- Wagner-Nelsonova enačba (plazma)
  Nelsonova enačba (urin)

Predpostavke

- Metoda rezidualov:
  - vsi procesi so 1. reda
  - utemeljena predpostavka za eliminacijo, zlasti v območju terapevtskih koncentracij (M.M. kinetika)
- Wagner-Nelson/Nelson:
  - enoprostorni model
  - kinetika eliminacije 1. reda (absorpcije NE!) → **za ugotavljanje kinetike absorpcije**

Plazemski koncentracijski profil
Wagner-Nelsonova enačba

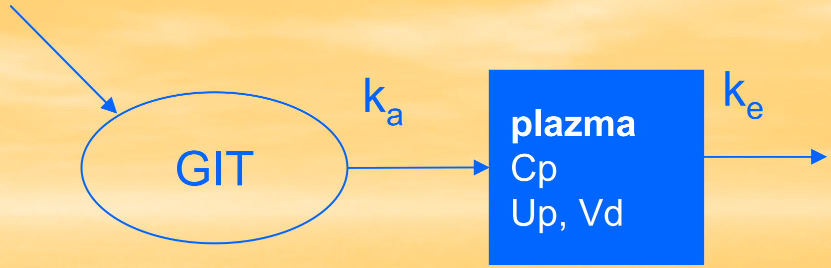
$$f_a = \frac{U_A^t}{U_A^\infty} = \frac{C_p^t + k_e \int_0^t C_p \cdot dt}{k_e \int_0^\infty C_p \cdot dt}$$

Urinski kumulativni količinski profil
Nelsonova enačba

$$f_a = \frac{U_A^t}{U_A^\infty} = \frac{\left(\frac{dU_{eu}}{dt}\right)_t + k_e \cdot U_{eu}^t}{k_e \cdot U_{eu}^\infty}$$

Izpeljava Wagner-Nelson

$$\frac{dU_p}{dt} = \frac{dU_A}{dt} - \frac{dU_e}{dt}$$



$$\frac{dU_e}{dt} = k_e \cdot U_p$$

$$dU_A = V_d \cdot dC_p + k_e \cdot V_d \cdot C_p \cdot dt$$

$$U_A^t = V_d \cdot C_p^t + k_e \cdot V_d \cdot \int_0^t C_p \cdot dt$$

$$U_A^\infty = k_e \cdot V_d \cdot \int_0^\infty C_p \cdot dt$$

$$f_a = \frac{U_A^t}{U_A^\infty} = \frac{V_d \cdot C_p^t + k_e \cdot V_d \cdot \int_0^t C_p \cdot dt}{k_e \cdot V_d \cdot \int_0^\infty C_p \cdot dt} = \frac{C_p^t + k_e \int_0^t C_p \cdot dt}{k_e \int_0^\infty C_p \cdot dt}$$

Analiza – plazemski vzorci

osnovni podatki

naklon iz terminalnega dela ln(Cp)=f(t) → β

površina pod plazemsko krivuljo

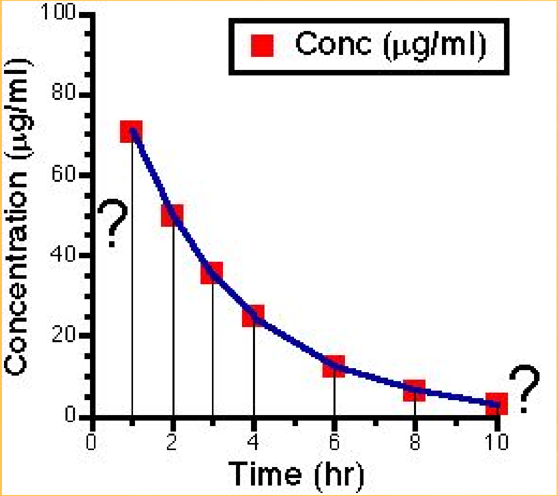
$$f_a = \frac{U_A^t}{U_A^\infty} = \frac{C_p^t + k_e \boxed{\int_0^t C_p \cdot dt}}{k_e \boxed{\int_0^\infty C_p \cdot dt}}$$

$$P = (a+c) \cdot \frac{v}{2}$$

$$AUC_{t1 \to t2} = (C_1 + C_2) \cdot \frac{(t_2 - t_1)}{2}$$

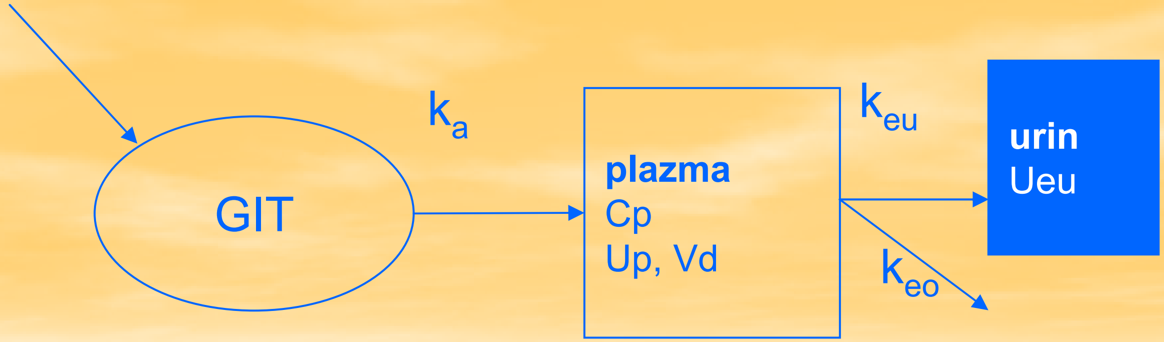
$$AUC_{0 \to \infty} = AUC_{0 \to t^*} + \frac{C^*}{\beta}$$

METODA TRAPEZOV



$\beta \neq k_e$; FLIP-FLOP ($k_a < k_e$)

Izpeljava Nelson



$$\frac{dU_p}{dt} = \frac{dU_A}{dt} - \frac{dU_e}{dt}$$

$$\frac{dU_e}{dt} = k_e \cdot U_p$$

$$\frac{dU_{eu}}{dt} = k_{eu} \cdot U_p = k_{eu} \cdot V_d \cdot C_p \longrightarrow C_p = \frac{1}{k_{eu} \cdot V_d} \cdot \frac{dU_{eu}}{dt}$$

$$dU_A = V_d \cdot dC_p + k_e \cdot V_d \cdot C_p \cdot dt$$

$$dU_A = \frac{d\left(\frac{dU_{eu}}{dt}\right)}{k_{eu}} + \frac{k_e}{k_{eu}} \cdot dU_{eu}$$

$$U_A^t = \frac{1}{k_{eu}} \cdot \left(\frac{dU_{eu}}{dt}\right)t + \frac{k_e}{k_{eu}} \cdot U_{eu}^t$$

$$U_A^\infty = \frac{k_e}{k_{eu}} \cdot U_{eu}^\infty$$

$$f_a = \frac{U_A^t}{U_A^\infty} = \frac{\frac{1}{k_{eu}} \cdot \left(\frac{dU_{eu}}{dt}\right)t + \frac{k_e}{k_{eu}} \cdot U_{eu}^t}{\frac{k_e}{k_{eu}} \cdot U_{eu}^\infty} = \frac{\left(\frac{dU_{eu}}{dt}\right)t + k_e \cdot U_{eu}^t}{k_e \cdot U_{eu}^\infty}$$

Analiza – urinski vzorci

METODA SREDIŠČENJA

1. Določimo intervale s srednjim časom v časih vzorčenja
2. Hitrost izločanja učinkovine v urin

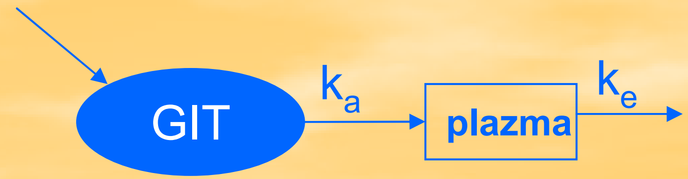
osnovni podatki

$$f_a = \frac{U_A^t}{U_A^\infty} = \frac{\left(\frac{dU_{eu}}{dt}\right)_t + k_e \cdot U_{eu}^t}{k_e \cdot U_{eu}^\infty}$$

naklon iz terminalnega dela

$\ln(U_{eu\infty} - U_{eut}) = f(t) \rightarrow \beta$

Kinetika absorpcije – 1. red



$$\frac{dU_{gi}}{dt} = -k_a \cdot U_{gi} \quad \rightarrow \quad \frac{dU_{gi}}{U_{gi}} = -k_a \cdot dt$$

$$\ln \frac{U_{gi}^t}{U_{gi}^0} = -k_a \cdot (t - 0) \quad \rightarrow \quad \ln U_{gi}^t - \ln U_{gi}^0 = -k_a \cdot t$$

$$\ln U_{gi}^t = \ln U_{gi}^0 - k_a \cdot t \quad \rightarrow \quad U_{gi}^t = U_{gi}^0 \cdot e^{-k_a \cdot t}$$

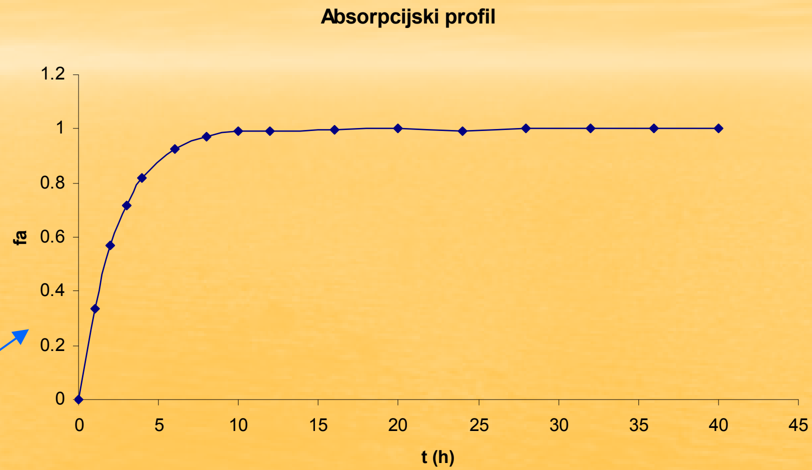
$$U_{gi}^0 = U_A^\infty = F \cdot D$$

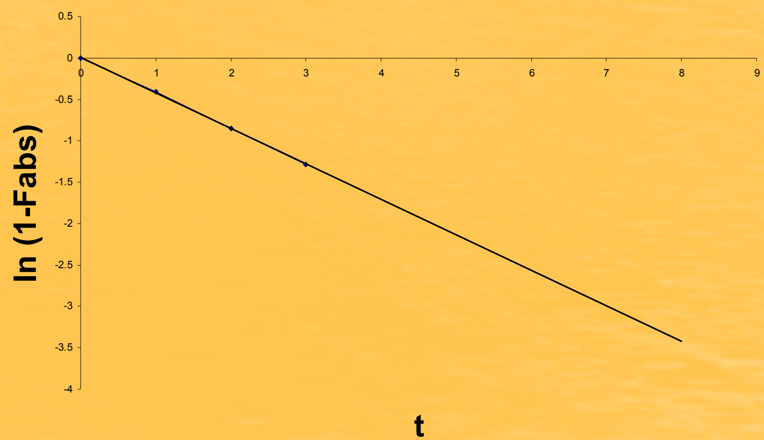
$$U_A^t = U_{gi}^0 - U_{gi}^t \quad \rightarrow \quad U_A^t = U_{gi}^0 - U_{gi}^0 \cdot e^{-k_a \cdot t}$$

$$U_A^t = U_A^\infty \cdot (1 - e^{-k_a \cdot t})$$

$$\boxed{f_a = \frac{U_A^t}{U_A^0} = 1 - e^{-k_a \cdot t}}$$

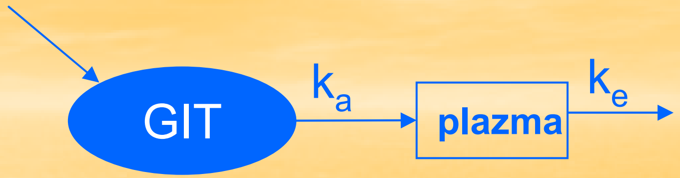
$$1 - f_a = e^{-k_a \cdot t} \quad \rightarrow \quad \boxed{\ln(1 - f_a) = -k_a \cdot t}$$





razpolovna doba absorpcije: $t_{1/2(abs)} = \ln 2 / k_a$

Kinetika absorpcije – 0. red



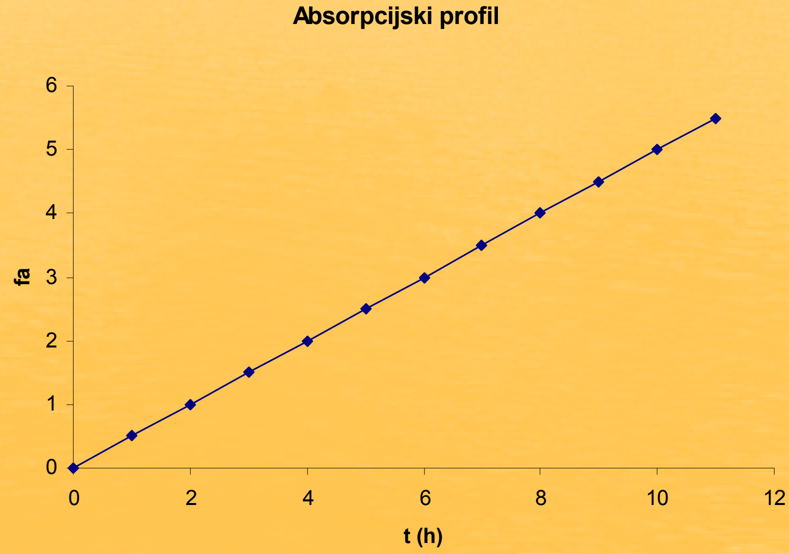
0. red

$$\frac{dU_{gi}}{dt} = -k_0$$

$$U_{gi}^t - U_{gi}^0 = -k_0 \cdot t$$

$$U_A^t = k_0 \cdot t$$

$$\boxed{f_a = \frac{k_0}{U_A^\infty} \cdot t}$$



Postopek

1. v semilogaritemski papir narišemo podatke
2. določimo terminalni naklon β (k_e?)
3. izračunamo površino pod krivuljo AUC_{0-t}, $AUC_{0-\infty}$

   ali hitrost izločanja učinkovine v urin
4. za vsako točko izračunamo f_a po enačbi
5. konstruiramo absorpcijski profil; t.j. $f_a=f(t)$
6. izračunamo k_a iz krivulje $\ln(1-f_a)=f(t)$
7. ugotovimo kinetiko absorpcije

$$f_a = \frac{U_A^t}{U_A^\infty} = \frac{C_p^t + k_e \int_0^t C_p \cdot dt}{k_e \int_0^\infty C_p \cdot dt}$$

t (h)	Cp (mg/l)	ln Cp	AUC 1-2	AUC 0-t	fa	1-fa	ln(1-fa)
0	0		0	0	0	100	4,60517
1	20,4		10,2	10,2	0,333	66,69	4,200055
2	32,9		26,65	36,85	0,567	43,26	3,767228
3	39,1		36	72,85	0,717	28,26	3,341447
4	41,7		40,4	113,25	0,818	18,23	2,903069
6	40,8		82,5	195,75	0,926	7,42	2,004179
8	36,4		77,2	272,95	0,972	2,84	1,043804
10	31,2	3,440418	67,6	340,55	0,991	0,94	
12	25,8	3,250374	57	397,55	0,991	0,91	
16	17,8	2,879198	87,2	484,75	0,995	0,47	
20	12,5	2,525729	60,6	545,35	1,002	-0,24	
24	8	2,079442	41	586,35	0,993	0,7	
28	6	1,791759	28	614,35	1,003	-0,33	
32	3,9	1,360977	19,8	634,15	1,000	0,01	
36	2,7	0,993252	13,2	647,35	1,001	-0,07	
40	1,8	0,587787	9	656,35	1,000	0	
Ke=	0,095		Ka=	0,4447	1.red		
AUC 0-nes	675,2974						

$$f_a = \frac{U_A^t}{U_A^\infty} = \frac{\left(\frac{dU_{eu}}{dt}\right)_t + k_e \cdot U_{eu}^t}{k_e \cdot U_{eu}^\infty}$$

t	Ueut	Ueunes-U	ln (Uen-U	interval	dUeu/dt	fa	100*(1-fa)	ln(1-fa)
0	0	400				0		
1	10	390		0-2	11,50	0,33	67,40	-0,3946
2	23	377		1-3	18,00	0,53	47,13	-0,75227
3	46	354		2-4	23,50	0,73	26,98	-1,31001
4	70	330		2-6	24,00	0,80	19,67	-1,62593
6	119	281		4-8	24,00	0,93	7,42	-2,60062
8	166	234	5,455321	6-10	21,75	0,98	1,56	
10	206	194	5,267858	8-12	19,00	1,01	-1,24	
12	242	158	5,062595	8-16	15,88	1,02	-2,06	
16	293	107	4,672829	12-20	10,38	1,00	-0,41	
20	325	75	4,317488	16-24	7,38	1,01	-0,56	
24	352	48	3,871201	20-28	5,13	1,01	-1,42	
28	366	34	3,526361	24-32	3,25	1,00	-0,01	
32	378	22	3,091042	28-36	2,13	1,00	-0,06	
36	383	17	2,833213	32-40	1,38	0,99	0,65	
40	389	11	2,397895	32-48	1,38	1,01	-0,85	
48	400	0		40-56	0,69	1,02	-1,80	
56	400	0				1,00	0,00	
Ke=	0,0955					Ka=	0,4425	1.red