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Magnetic drug targeting. II. Targeted drug transport by magnetic microparticles: factors influencing therapeutic effect

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Summary

The kinetic aspects of magnetically targeted drug transport are considered. The influence of the magnetic drug carrier properties, the transported drug and the target parameters on the biological effect of the drug is discussed. The mathematical model reflecting the mass-transfer processes in a blood flow system is used for the estimation of the influence of these factors on the therapeutic effect of the drug delivered to the target. The character of the effect of drug release parameters, rate of drug released inactivation and the intensity of carrier capture in the liver is shown. Mathematical modelling of magnetically targeted drug kinetics allows possibilities for prognosis of drug effects.

Introduction

During recent years increasing attention has been paid to the development of targeted pharmaceutical preparations containing fine ferromagnetic materials. The delivery of these preparations to the affected area can be achieved using an external magnetic field which being applied to the prescribed region can evoke accumulation of the circulating drug. As a rule, the data published include information on the synthesis of magnetic carriers and the binding of drugs or model compounds with these carriers (Akimoto and Morimoto, 1983; Ibrahim et al., 1983; Kato et al., 1984; Mosbach and Shroder, 1979; Papisov et al., 1985; Torchilin et al., 1985; Widder et al., 1979, 1983). Some information on the influence of a magnetic field on the biodistribution of magnetic microparticles in experimental animals and the behaviour of these particles in model circulatory systems in vitro is also available (Senyei et al., 1978; Widder et al., 1983). Nevertheless, the set of parameters influencing the efficacy of magnetically driven drugs is not limited by such properties of magnetic preparation as particle size, ferromagnetic material and drug content, and biocompatibility of a carrier.

To estimate the influence of magnetic carrier properties and target organ parameters on the efficacy of magnetically driven drug action in more detail, we have used the mathematical apparatus reflecting the regularities of mass transfer processes in the blood circulation system of the living organism. The calculations are performed by taking into account experimental data on dif-

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ferent magnetic particles' biodistribution in experimental animals.

Biodistribution of magnetically sensitive preparations

If the circulation system is considered as a set of individual "targets" (organs or their compartments) included into the total blood flow, then the rate of drug accumulation in the target (as we have shown in our previous report (Papisov et al., 1987)) can be expressed as:

$$\frac{dD_i}{dt} = k_i F_i C \quad (1)$$

where F_i = blood flow through the target, k_i = capture coefficient in the target, D_i = the accumulated dose of the drug and C = drug concentration in the blood:

$$-\frac{dC}{dt} = \frac{1}{V}\sum_i k_i F_i \quad (2)$$

where V = the blood volume. At safe doses of the administered preparation, the accumulation of the drug in the target organ should not affect its functions and the k value can be considered as a constant during the whole experiment or treatment course. In this case it follows from Eqns. 1 and 2:

$$D_i = D_0 \frac{k_i F_i}{V\alpha}(1 - e^{-\alpha t}) \quad (3)$$

$$C = \frac{D_s}{V} = D_0 \cdot \frac{1}{V} \cdot e^{-\alpha t} \quad (4)$$

where

$$\alpha = \frac{1}{V}\sum_i k_i F_i,$$

D_0 = administered dose of the preparation, D_s = the dose of the preparation circulating with the blood at the given moment.

The data available (Akimoto and Morimoto 1983; Widder et al., 1983) point out the high capture of magnetic carriers by liver cells. This phenomenon, in particular, forced the authors (Widder et al., 1983) to use the administration of magnetically driven drug directly into the artery feeding the target organ instead of systemic intravenous administration. Nevertheless, in the case mentioned, the efficacy of drug delivery into the target region was only about 50% in comparison with almost 100% efficacy achieved when drug-containing microspheres (diameter of 20–40 μm), which are mechanically fixed in the target organ vessels, were administered into the feeding artery (Torchilin et al., 1977).

Another way to decrease the liver capture of magnetic particles is the use of carriers providing lower values for the liver. Thus, for example, an attempt was made to incorporate a drug and magnetic particles into red blood cell ghosts (Zimmermann, 1983).

Unfortunately all the literature data on the accumulation of magnetic carriers in different organs provides only the final distribution of a carrier but does not permit consideration of the distribution process in time. To study the kinetics of magnetic carrier distribution in experimental animals we have followed the accumulation of ^{99m}Tc-labelled magnetic particles in different rabbit organs using a gamma-camera (Papisov et al., 1987). The data obtained show the intensive liver capture for all the carriers used. To a lesser extent, carriers are captured by bones, spleen and kidneys. In all cases the curves of the preparation's accumulation in the liver can be described by Eqn. 3 with a high correlation coefficient; k_{liv} values, characterizing the liver accumulation of magnetic particles were 0.3–1.

The results presented by Senyei (1978) give some idea of probable k_{tar} values, which depend, first of all, on magnetic and hydrodynamic properties of the magnetic carrier, external magnetic field parameters and peculiarities of the blood flow in the target. At the same time it should be realized that the values of k_{tar} in in vivo conditions still cannot be satisfactorily predicted and each individual case will most probably require experimental testing.

The influence of k_{tar} and k_{liv} on the carrier accumulation in a target and on the decrease of its

content in blood is illustrated by the data shown in Figs. 1 and 2. The appropriate curves are calculated from Eqn. 3 for the case of the preparation delivery into a single target in the human organism. The ratio between the maximal dose of the preparation delivered to the target and the dose accumulated by the liver is determined by the equation:

$$\frac{D_{tar}}{D_{liv}} = \frac{k_{tar}F_{tar}}{k_{liv}F_{liv}} \qquad (5)$$

The values of k_{liv} obtained from animal experiments vary from 0.3 to 1.0 for the carriers studied. As far as hepatic blood flow constitutes a major fraction of the total blood flow in the body, the value of $k_{liv}F_{liv}$ is high enough. It means that when a drug is administered as fine particles, a large part of the total dose administered should very soon accumulate in the liver. Thus, the question arises about the liver's ability to tolerate large quantities of the drug (especially in case of high toxicity). It is evident that the drug capture by the liver can create serious limitations for the method described, the limitation being maximally expressed in case of small size targets, when $F_{tar} \ll F_{liv}$, and k_{tar} and k_{liv} are comparable.

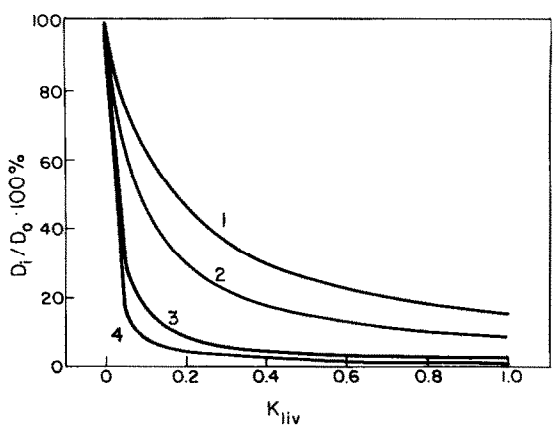

Fig. 1. Efficacy of the carrier capture by the liver (k_{liv}) and by the target on its accumulation in the target. Target parameters: $F = 50$ ml/min; $k_{tar} = 1$ (curve 1); $k_{tar} = 0.5$ (curve 2); $k_{tar} = 0.1$ (curve 3); and $k_{tar} = 0.05$ (curve 4).

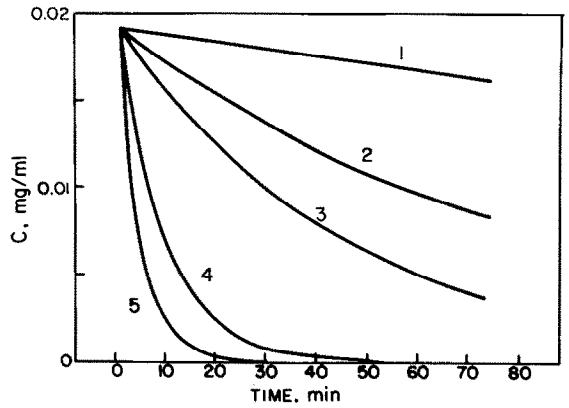

Fig. 2. Efficacy of the carrier capture by the liver (k_{liv}) on the rate of the carrier concentration decrease in the blood. Calculated for the dose 100 mg of a carrier. $k_{liv} = 0.01$ (curve 1); $k_{liv} = 0.05$ (curve 2); $k_{liv} = 0.1$ (curve 3); $k_{liv} = 0.5$ (curve 4); and $k_{liv} = 1.0$ (curve 5).

The efficacy of drugs delivered to the target on magnetic carriers

The drug delivered to the target can act according to the following mechanisms (Fig. 3): (1) the diffusion of the drug from the carrier (which is fixed on the vessel wall by magnetic field) and its subsequent action in a free form; (2) the action of the drug (for example, plasminogen activators) in a bound state; and (3) the penetration of magnetic carrier with a drug from the circulation system of the target into appropriate tissues or its capture by cells (including liver cells and tumor cells) (Spalding et al., 1983; Widder et al., 1983).

In all the cases listed the type and the diameter of blood vessels where carrier particles are fixed by the magnetic field are of great importance. Magnetic particles passing the vascular bed in the region of external field application can easily pass through the vessels where the linear rate of the blood flow is high, but may accumulate in vessels with a lower rate of blood flow (e.g. small arteries or veins, the regions of stenosis or thrombosis in large vessels, branches leading to embolized vessels, etc.). From capillaries magnetic particles will be most probably "squeezed" by blood cells. Thus, particles of magnetic preparation passing the arterial part of the blood flow can, most probably, be accumulated in veins. If the magnetic proper-

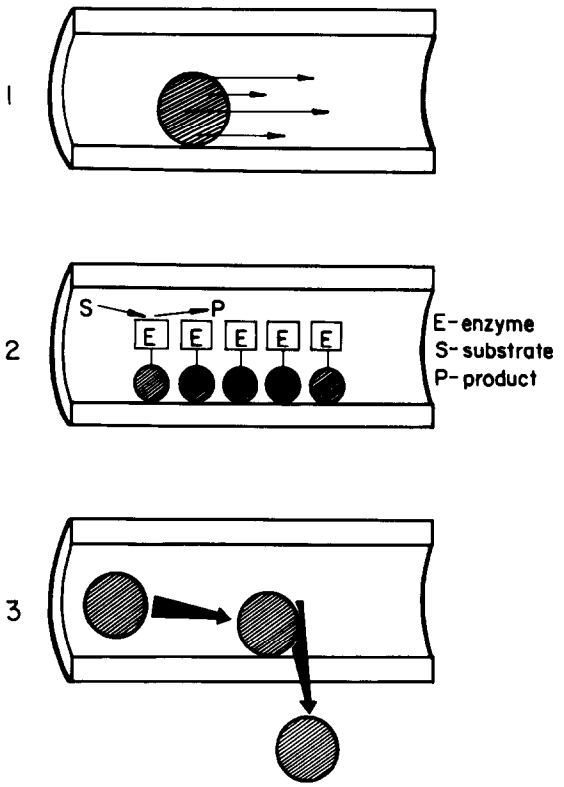

Fig. 3. Possible paths of therapeutic action of targeted drugs after their delivery into the target (see comments in the text).

ties of a carrier are not high enough, or if the external magnetic field is too weak, the accumulation of a magnetic drug can proceed exclusively in veins. This fact can decrease the expected therapeutic effect, because the preparation will be concentrated in the region of target outlet and the active drug will diffuse from the carrier into the systemic blood flow without any effect.

The therapeutic effect is directly conditioned by the dose of the active drug delivered to the target. This dependence is very simple in examples shown in Fig. 3_2 and to a smaller degree, in examples shown in Fig. 3_3. The case shown in Fig. 3_1 seems to be more complicated and is discussed below.

The release of the drug from the carrier and its therapeutic efficacy

The concentration of a free active drug released from the carrier in the target in comparison with its systemic concentration can be considered as a criterion of the drug efficacy. Thus, the parameters characterizing the process of the drug release from the carrier also influence the therapeutic effect. To illustrate this influence let us assume that: (a) the drug release does not depend on the flow rate of the external liquid medium; and (b) the dependence of the release rate on a drug concentration in the carrier is linear (like, for example, in case of the hydrolysis of the drug/carrier chemical bond),

$$\frac{dp}{dt} = ap \tag{6}$$

where p = dimensionless drug concentration in the carrier, mg/mg total weight (we assume that the released drug is substituted for water and the condition $p = \text{const} \cdot p'$ is fulfilled, where p' is a molar drug concentration in the total carrier volume). The quantity of the released drug L_i is connected with a drug dose in the target t_i and with the drug concentration in the carrier with the following equation (from Eqns. 5 and 6):

$$\frac{dL_i}{dt} = D_i ap \tag{7}$$

From condition (a) it follows that the coefficient a does not depend on the location of the carrier (the latter can be fixed on the vessel wall or can circulate in the blood). Thus, from the circulating carrier the drug is released following the same equation

$$\frac{dL_s}{dt} = D_s ap \tag{8}$$

Then, the concentration of a free drug (S) in the systemic blood flow can be expressed (in the case of a drug accumulation in a single target) as:

$$S = \frac{L_s + L_t}{V} - R \tag{9}$$

where R is the quantity of the drug, which is inactivated or removed from the circulation.

In the target vascular bed drug concentration T

should be increased due to its release from the accumulated carrier:

$$T = S + T^{(+)} \tag{10}$$

$T^{(+)}$ is a momentary concentration of a drug in the target and is expressed as a ratio of the drug quantity released from the carrier during the short time period to the blood volume which is pumped through the target during the same time:

$$T^{(+)} = \left(\frac{dL_t}{dt}\right) : \left(\frac{dV_t}{dt}\right); \text{ as } \frac{dV_t}{dt} = F_t \tag{11}$$

$$T = S + \frac{dL_t}{dt} \cdot \frac{1}{F_t}$$

From Eqns. 7–12 it follows that

$$\frac{dL_t}{dt} = D_0 p_0 \frac{a k_t F_t}{V\alpha}(1 - e^{-\alpha t})\, e^{-at} \tag{13}$$

$$L_t = D_0 p_0 \frac{k_t F_t}{V(a+\alpha)}\left(1 - \frac{a+\alpha}{\alpha}e^{-at} + \frac{a}{\alpha}e^{-(a+\alpha)t}\right) \tag{14}$$

$$L_s + L_t = D_0 p_0 \left[\left(1 - \frac{k_{liv} F_{liv}}{V\alpha}\left(1 - \frac{a}{a+\alpha}\right)\right) - \left(1 - \frac{k_{liv} F_{liv}}{V\alpha}\left(1 - \frac{a}{a+\alpha}e^{-\alpha t}\right)\right)e^{-at}\right] \tag{15}$$

In Fig. 4 curves are shown, calculated according to the equations suggested and reflecting the changes of the drug concentration in systemic blood flow and in the blood flow of the target with time.

Assuming (for example) the rate of the drug clearance or inactivation being proportional to its concentration, we have

$$\frac{dR}{dt} = qS \tag{16}$$

where q is a constant of drug inactivation and/or clearance. Eqn. 16 can be used for integration or can be solved relative to R. The solution is too

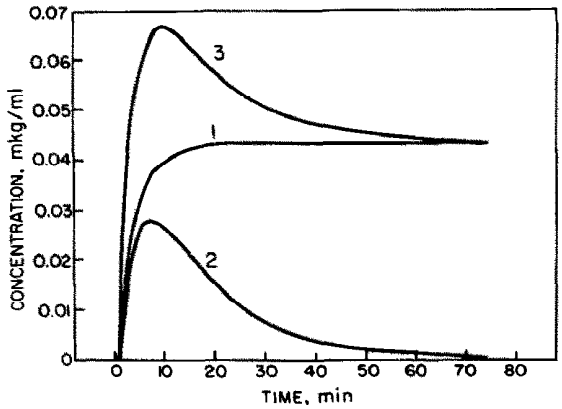

Fig. 4. The concentration of a drug released from the carrier: (1) in the systemic blood flow; (2) proportion of drug released from the carrier accumulated in the target; and (3) summary concentration of a drug in the blood flow of the target. Calculated assuming a preparation dose = 100 mg, time of drug half-release = 10 min, $k_{liv} = 1$, $k_t = 0.5$, $F_t = 50$ ml/min, blood volume = 5200 ml, liver blood flow = 1200 ml/min.

complicated to be presented, but the figures obtained according to the solution and Eqns. 13–16 are easier to understand and to discuss.

The character of the dependence of free drug concentration on different factors as follows from the Eqns. 6–16 is shown in Figs. 5–8. It is necessary to mention that the curves in Figs. 5–8 are not to be considered as a maximal approximation to the real conditions; they just give us an indica-

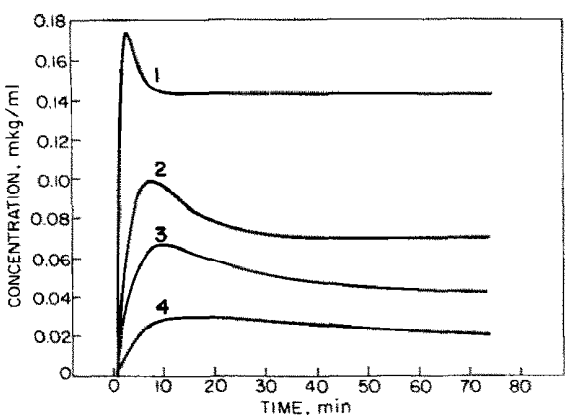

Fig. 5. Dependence of drug concentration profile of the blood flow on the half-time of the drug release. $T = 1$ min (curve 1); $T = 5$ min (curve 2); $T = 10$ min (curve 3); and $T = 30$ min (curve 4).

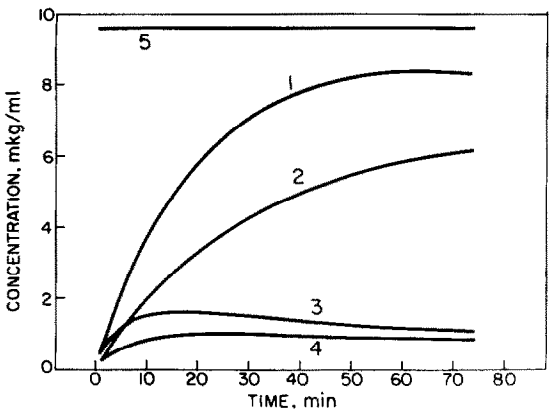

Fig. 6. Dependence of the drug concentration profile of the blood flow of the target (curves 1 and 3) and of the systemic blood flow (curves 2 and 4) on the efficacy of the carrier capture by the liver: $k_{liv} = 0.01$ (curves 1 and 2) and $k_{liv} = 1$ (curves 3 and 4); drug release $T_{1/2} = 30$ min. Curve 5 corresponds to the concentration in the blood flow of a drug administered into the systemic blood flow at the same dose (50 mg) in a free form.

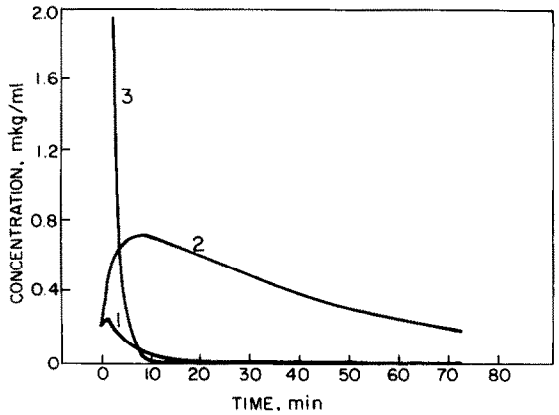

Fig. 8. Increase in the concentration of a drug bound with magnetic carrier in the blood flow of the target (curve 2) in comparison with is systemic concentration (curve 1) and with the concentration of systemically administered free drug at the same dose (curve 3). Half-inactivation time of a free drug is 1 min, and the time of half-release of a drug from a carrier is 10 min; $D_0 = 250$ mg, $P_0 = 0.2$, $k_{liv} = 1.0$, $F_t = 50$ ml/min, blood volume is 5200 ml, liver blood flow is 1200 ml/min.

tion of the principal changes in the efficacy of magnetically targeted drug delivery under the action of different factors.

Fig. 5 demonstrates that both the drug concentration in the blood flow of the target and the average drug concentration in the whole circulation system depend on the rate of the drug release from the carrier. From Fig. 6 it follows that k_{liv} variations influence mainly the absolute drug concentrations in a systemic blood and the blood of a target. Fig. 7 shows the influence of k_{tar} on the drug concentration in the blood flow inside the target and in the whole organism (all the curves in Figs. 5–7 are calculated under the assumption that the drug is not inactivated in the circulation).

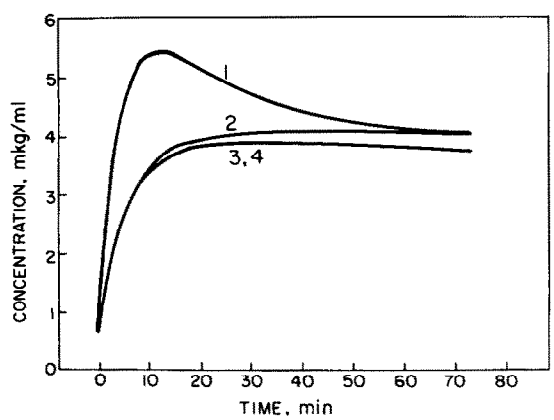

Fig. 7. Efficacy of drug capture by the target on the drug concentration profiles in the systemic blood flow (curves 1 and 3) and in the blood flow of the target (curves 2 and 4). $k_{tar} = 1$ (curves 1 and 2); and $k_{tar} = 0.01$ (curves 3 and 4).

From Figs. 5–7 it can be concluded that the efficacy of magnetic targeting should be very low for the drug possessing a long life-time in the circulation in a free state: (1) drug concentration in the blood flow of the target does not exceed its concentration which can be achieved upon the routine systemic administration of a free drug; (2) the difference between drug concentrations in systemic blood flow and in the blood flow inside the target is very small because the drug which does not accumulate in the target still circulates in the systemic blood flow.

Thus, in the example described we cannot speak about real drug targeting; more exactly we are dealing with some drug redistribution in the circulation. It is also evident that this redistribution cannot lead to the desired "targeting" effect; firstly, the dose of the administered drug cannot be decreased, and secondly, the therapeutic effect

cannot be "concentrated" only in the desired region.

Quite an opposite picture is obtained for the drug which is rapidly inactivated upon its release from the carrier into the blood (assuming that the carrier protects the immobilized drug). In this case drug activity in the systemic blood flow does not increase, but it is maintained at a relatively high level in the blood flow inside the target because of the continuous release from the carrier. As a result the efficacy of drug targeting increases; drug concentration in the target is much higher than in the systemic blood flow than in the case of free drug administration (Fig. 8).

Thus, the principal possibility exists for magnetic targeting of "short-lived" drugs. One can suppose that the approach can be also used to decrease the dose of highly antigenic drugs (primarily, proteins of bacterial origin). The life-time of these drugs in the circulation is very short because of their fast interaction with appropriate immunoglobulins (antibodies). This fact leads to the necessity of the preliminary administration of a "neutralizing" dose of a drug in order to neutralize naturally existing antibodies against this drug (as is done, for example, in case of thrombolytic therapy with the microbial enzyme streptokinase). Targeting of such drugs can permit their application in doses lower than neutralizing dose, because under optimal conditions drug concentration in the target can be high enough to cause a therapeutic effect (Torchilin et al., 1987).

It is also necessary to mention that magnetic drug targeting can be used only for drugs which cause a therapeutic effect even when applied in very small quantities. This is due to the fact that drug concentration in the carrier cannot exceed a specific level – normally P_0 value is lower than 0.2. In the case of a drug acting only at a high concentration one would have to administer large quantities of magnetic carrier, which might cause undesirable side-effects.

Conclusions

When developing systems of magnetic drug targeting, one should take into account not only the size, magnetic properties and biocompatibility of a carrier and the degree of its loading with a drug. Such parameters as rate and kinetics of the drug release from the carrier, drug inactivation rate in the blood and the efficacy of the capture of a preparation by the liver are also of great importance.

Unless carriers are used which are not captured by the liver, then toxicity of a drug used is a more crucial parameter for magnetically driven drugs than for the same drugs used in a free form.

The magnetic delivery of "long-acting" drugs acting in blood is unreasonable because of the insignificant effect which can be achieved.

The use of magnetically driven drugs will be safe with respect to organism overloading with a carrier material only in cases when an active drug can produce a therapeutic effect at low concentrations – several μg/ml of the blood or even lower.

The maximal effect of the magnetic drug targeting and the maximal decrease in the quantity of the drug administered can be expected in case of "short-lived" drugs (with half-inactivation time in the blood being ca. several minutes or less) including proteinic drugs possessing antigenic properties (enzymatic drugs, first of all). Biologically active compounds which at present cannot serve as drugs because of their fast inactivation in the organism can be used for therapy as components of magnetically driven systems.

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