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MAGNETICALLY TARGETED MICROSPHERES: A REVIEW

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SUMMARY

The site specific delivery of chemotherapeutic agents allows maximum concentration of an agent at a desired body site. This area specific drug delivery decreases the unwanted systemic distribution and decreases toxicity of the administered drug due to small doses.

Magnetic microspheres, which contain ultrafine magnetic particles, are selectively localized in the target by applying a magnetic field which immobilizes the microsphere. In the targeting experiments, there is a 6 to 10 fold higher concentration of carrier at the target site.

The procedures for preparing magnetic microspheres, magnetic slabs, and magnetic hemispheres are discussed. The craracteristics of the magnetic field like magnetic field strength, magnetic field orientation and the frequency of oscillation that influence the degree of modulation are also given with examples.

The factors that are critical in controlling the release rates of the magnetically targeted systems are stated and the possible mechanism of release is described.

These carrier systems are beneficial in 4 categories of drugs like standard drugs, biomodulators, biophysical and diagnostic agents. Examples of these drugs are also stated.

In this review the advantages and limitations of the magnetically modulated drug delivery systems are discussed with emphasis on the future applications.

Key words: *Magnetically targeted microspheres, slab, hemispheres, properties, formulation, release profiles, ad-*

MANYETİK OLARAK HEDEFLENDİRİLEN MİKROKÜRELER : DERLEME

ÖZET

Manyetik partiküller içeren mikroküreler manyetik alan uygulaması sonucunda hedef organda toplanabilirler. Bu hedeflendirme istenilen bölgede 6-10 kez daha

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fazla birikmeye neden olur.

Manyetik mikroküreler, slabler ve yarıkürelerin hazırlama yöntemleri açıklanmıştır. Hedeflenmeyi etkileyen manyetik alan gücü, manyetik alan oryantasyonu ve salınım frekansı gibi manyetik alan karakteristikleri örneklerle açıklanmıştır.

Manyetik hedeflenen sistemlerde salım hızını kontrol eden faktörler sıralanmış ve olası salım mekanizmaları verilmiştir.

Manyetik olarak hedeflendirilen standart ilaçlara, biyomodülatörlere, biyofiziksel ve diagnostik ajanlara örnek verilmiş ve gelecekteki uygulamaları üzerinde durulmuştur.

INTRODUCTION

Microspheres are homogenous, spherical, monolytic new drug delivery systems which are used to target the active substances to certain desired parts of the body(1). Magnetic targeting of the microspheres are developed to overcome the two major problems being the RE clearance and target site speciffi-city(2). These microspheres contain ultrafine magnetic particles. These magnetic micropheres are selectively localized in the target by applying a magnetic field which immobilizes the microsphere.

The site specific delivery of chemotherapeutic agents allows for maximum concentration of an agent at a desired body site, thus permitting the use of much smaller doses than are normally required with systemic administratior

Area specific tdrug delivery decreases the unwanted systemic distribution of drugs, eradicates localized diseases and decreases toxicity of the administrated agent due to small doses.

This review discusses the properties, formulation, release characteristics, toxicity, advantages and limitations of the magnetically modulated systems with emphases on their future application.

PROPERTIES :

Drug bearing magnetically responsive albumin microspheres offer many advantages for achieving high local concentrations of chemotherapeutic agents at a desired target site. The desired properties of this targeting system can be summarized as follows(3).

* Its small size should permit penetration to the capillary level of circulation at its target site.
* Should have the ability to carry a wide variety of chemotherapeutic agents.
* The release rate of the active drug from the carrier at the target site should be controllable and predictable.
* The released drug should retain its original biological activity.
* Should have the ability to preferentially localize at a desired target ste.
* Its circulatory half-life should be adequate to achieve acess to the target site
* Should be biodegradable.
* Should show minimal antigenicity, pyrogenicity and non-thrombogeni

city.

* Should have long shelf-life with convenient storage requirements.
* Magnetically guided carriers should have predictable magnetic responsiveness.

DRUG TARGETING

Why do we try to target drugs? The reasons for targetting drugs can be summarized as given by Tomlinson et al (4) (TABLE 1).

Table 1. Reasons for targetting drugs.

Pharmaceutical
- Drug instability in conventional formulations
- Solubility

Biopharmaceutical
- Low absorption
- High membrane binding
- Biological instability

Pharmacokinetic/Pharmacodynamic
- Short half-life
- Large volume of distribution
- Low specificity

Clinical
- Low therapeutic index
- Anatomical and/or cellular barriers

Commercial
- Drug presentation

MAGNETIC TARGETING

Magnetic drug targeting is a highly efficient method of site specific delivery. Before formulation the following four question must be asked (5).

1. Is this drug so dangerous or labiel that your cannot allow it to circulate freely in the blood stream?
2. Is the agent so expensive that you cannot afford to waste 99.9 % of it?
3. Must you actieve a selective, regional effect to meet your therapeutic objective?
4. Do you require an alternative formulation of an essential agent to continue treatment in patients whose systemic therapy must be temporarily discontinued due to life threatening toxicity directed at selected organs?

The use of a magnetic field of appropriate strength and gradient accomplishes three functions in the targetting of this carrier (3). First, it restricts the circulating microspheres and the drug to the area of tumor thus permitting the use of significantly smaller quantities of drug. Secondly, by using the appropriate magnetic field, microspheres are selectively retained at the capillary bed level of the target area. A defined magnetic force over an arterial route will permit the passa-

ge of microspheres flowing at the higher arterial velocity but will retain them when they reach the capillary velocity. Finally, by retarding the microspheres at the site of infusion, their accumulation at RES is avoided. Significantly higher concentration of carrier is localized to the target site than found in the RES organs.

In magnetic targeting there is a 6 to 10 fold higher concentration of carrier at the target site than in the liver or spleen (3). After an initial 30 minutes of appiled magnetic field, the microspheres remain at the site of localization for up to three weeks with good blood flow. Two processes are involved at the retention (3). Microspheres wedge into capillary gap junctions, and some are transported to the basement membrane. Drug is released at a controllable rate depending on the extent of matrix stabilization.

Advantages and Limitations of Magnetic Targeting:

Magnetic targeting has the following advantages (5):

* Crossing microvascular barriers independent of endothelial status,
* Protecting drug, blood cells, and endothelium during transit,
* Delivering up to 60 % of the injected dose to target tissues,
* Making drug available in a controlled fashion within the tissue.
* This reduces circulating concentrations of free drug by a factor of 100 or more,
* Minimizes damage to normal tissue cells,
* Allows effective treatment or regionalized disease at 0.1 of the free drug se or less.

These advantages are achieved at significant cost (5):

* Magnetic targeting is an expensive, technical approach limited to univer sities and research centers,
* It requires special microspheres and magnets,
* It demands new methods for monitoring of drug levels in target tissues,
* Tissue localization of microspheres results in long term depositing of magnetite.

COMPOSITION OF MAGNETICALLY MODULATED SYSTEMS

A polymeric system that is capable of delivering drugs at increased rate on demand consist of active drug, polymeric matrix, magnetic beads (ferrofluids)

and cross-linking agent (6-9).

Matrix Material

A variety of biodegradable materials have been used including Human Serum Albumin (HSA) (2-4, 10-12), cellulose (23-24), polyethyleneimine (PEI) (25-26), gelation (19,29,30) agarose (31), alganate (32), starch (33,34). Albumin is chosen as the matrix since it conforms to most of the properties required of matrix materials. The size range can be readily controlled. They are biodegradable and have minimal toxicity. Any water soluble agent less than 100 MW may be readily encapsulated.

The amount of matrix material to be used will usually be within the range from 5 to 60 parts by weight of the matrix material per 100 parts of water. With albumin and similar matrix materials preferred portions are from 20 to 30 parts per 100 parts of H_2O(10).

Magnetic Beads:

A ferrofluid is a stable colloidal suspension of magnetic particles (F_3O_4) in a carrier fluid (35). The particles are sufficiently small (Approx.100 A^O) in diameter) and coated with a surfactant to avoid agglomeration or fall out when a strong magnetic field gradient is applied. In the absence of an external magnetic field, the nagnetic moments of individual particles are distributed and the fluid has no net magnetization. The particles used as nagnetic beads are either magnetic steel beads composed principally of iron (79 %), chromium (17 %), carbon (19 %), manganese (19 %), and silicone (1 %) or small samarium cobalt magnets (6).

The preferred amount of magnetic material is from 10-150 parts by weight per 100 parts of the matrix material (10) (FIGURE 1).

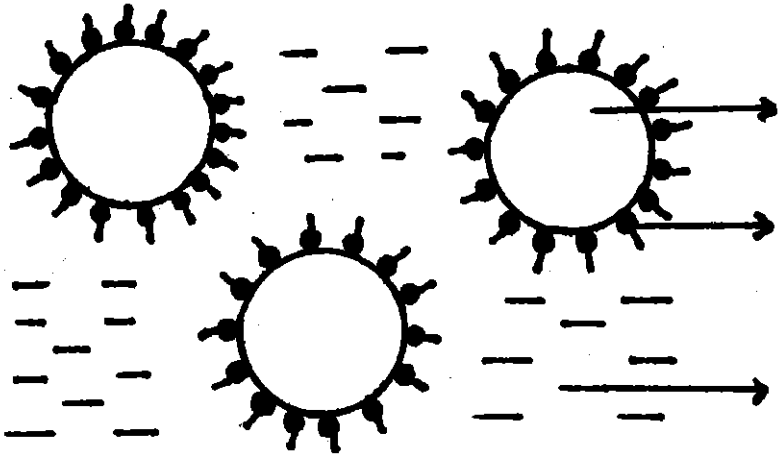

Figure 1. Schematic diagram of ferrofluids (35).

Active Drug :

These include the delivery of insulin, antiarrhythmics, B-blockers, birth control agents, anticancerogens, immunosupressive and antienflammatory agent.

The amount of the therapeutic agent can vary over a wide range depending on the purpose for which the microspheres are to be used (10). In general, for water soluble chemotherapeutic agents, from 1 to 20 parts by weight of the agents can be ancorporated per 100 parts by weight of the matrix material.

FORMULATION OF MAGNETICALLY RESPONSIVE SYSTEMS

These systems could be divided into three groups as:

* microspheres
* slabs
* hemispheres

Formulation of Microspheres :

The method of preparing microspheres is adopted and modified from the studies of Scheffel et al (36) and Widder et al (21). The procedure is shown in Figu re 2.

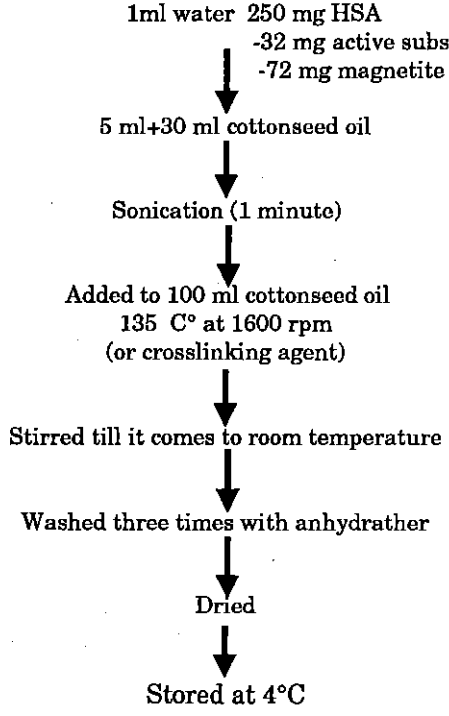

Figure 2. Procedure for preparation of magnetic sustained releaserospheres (10)

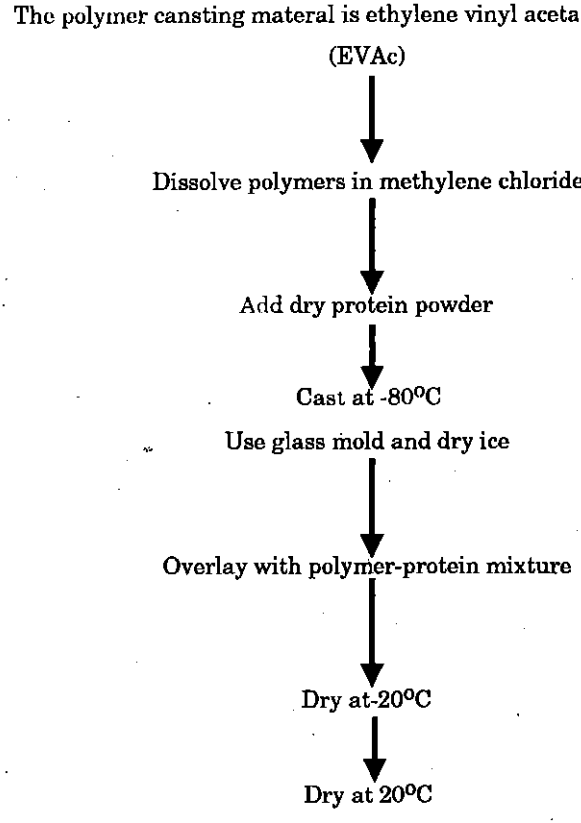

Figure 3 : Procedure for preparation of magnetic sustained release slabs (7, 37).

Formulation of Slabs :

The procedure for preparing the magnetic sustained release slabs is modified from the earlier method for preparing non-magnetic sustained release implants (7). The procedure for preparation is shown in Figure 3. The polymer casting material is ethylene vinyl acetate copolymer (EVAc).

Formulation of Hemispheres :

The procedure for preparing the hemispheric magnetic sytems consists of four stages (8):

* Casting

* Drying
* Coating
* Opening a cavity

The procedure is shown schematically in Figure 4.

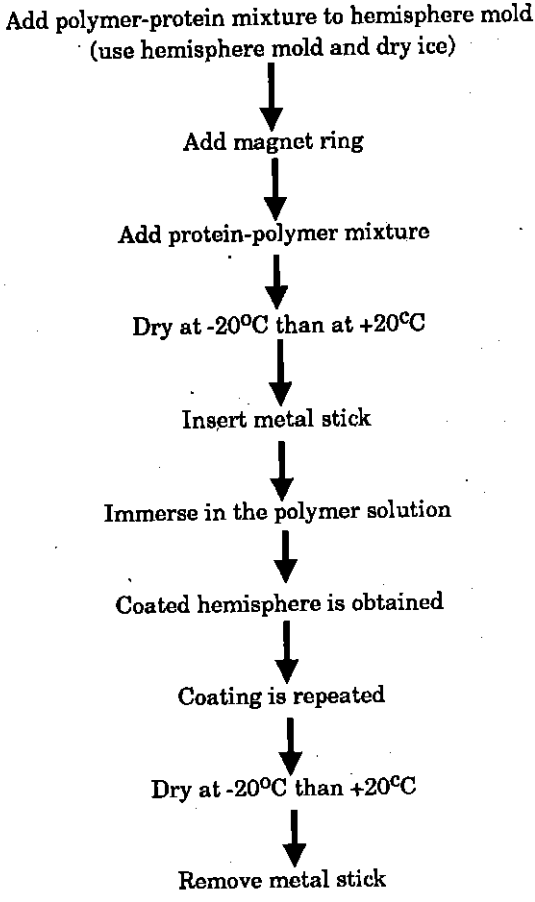

Figure 4. The procedure for preparing magnetic hemispheres (8,37)

MECHANISM OF RELEASE

In systems, where the drug is incorporated into a polymeric material, the rate of drug release is determined by the properties of the systems and is only weakly dependent on environmental factors such as pH and inter-patient variations (6). The factors that are critical in controlling the release rates are the characterictics of the magnetic field and the properties of polymers.

Polymer Properties :

The mechanical properties like the modulus elasticity of the polymer a effect the extent of magnetic enhancement (TABLE 2) (6).

Table 2. Moduls of elasticity of EVAc copolymers (6).

Vinyl Acetate Content (%)	Modulus of Elasticity (psi)
16	4480
30	970
40	430
50	110

Characteristics of the Magnetic Field :

Magnetic field strength, magnetic field orientation, and the frequency of oscillation are the characteristics of the magnetic field that influence the degree of modulation (38). These effects are summarized as follows:

Magnetic Field Strength : The amplitude of the magnetic field is varied by increasing the external magnetic and polymer matrix. The ratio of the release rates when the magnetic field is on as compared to when it was off for samples exposed to fields of 870, 1300, and 1800 G is illustrated in FIGURE 5 (38).

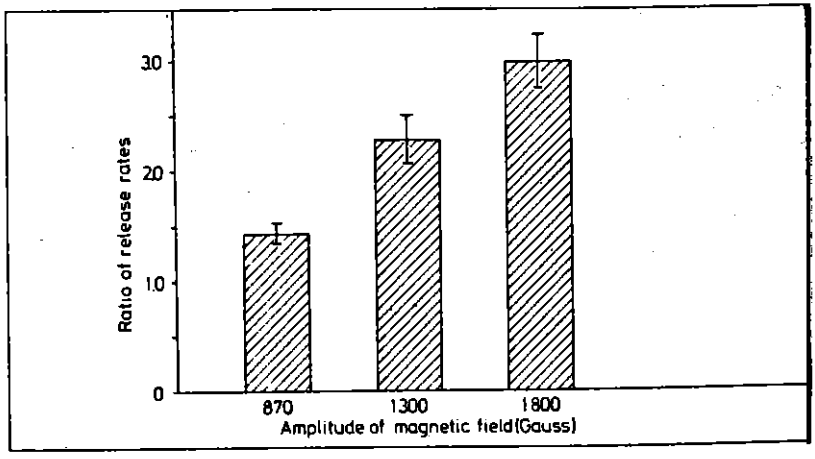

Figure 5: Ratio of release rate for identical polymer matrices subjected to magnetic fields of 870, 1300 and 1800 (9).

Magnetic Field Frequency : When the frequency of the applied field is varied from 5-11 Hz a wide difference in release rates is observed. In all cases an 1800G field is used. FIGURE 6 shows that as the frequency increases the amount of modulation rises in a linear fashion.

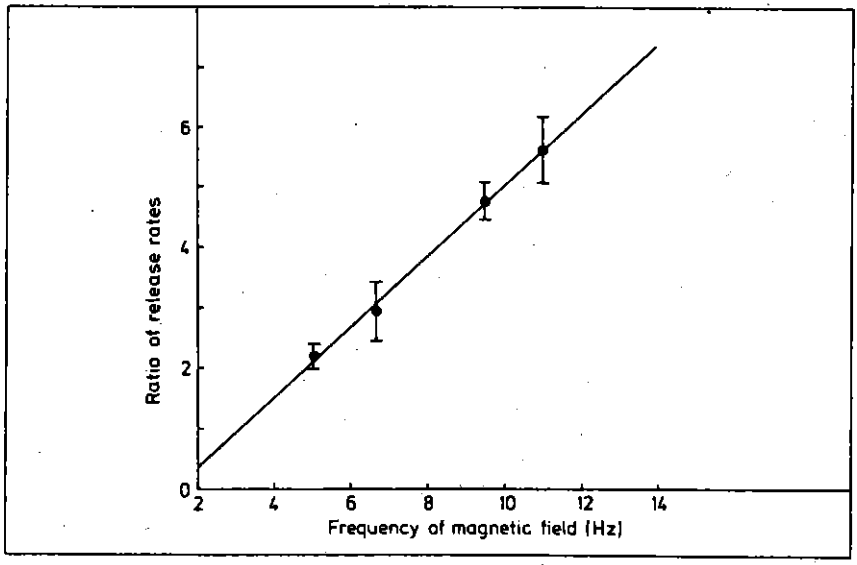

Figure 6: The average ratio of the release rates during field applied and field absent (9).

Embedded Magnet Strength : In this experiment, a series of polymer matrices embedded with a single paramagnetic sphere is compared to ones made with a single high-strength SmCo magnet. An 1800 G field oscillating at 4 Hz is used to test 10 samples. The ratio of release rates during the field exposed times to the field absent times is significantly greater for systems with the higher strength magnets (FIGURE 7) (38).

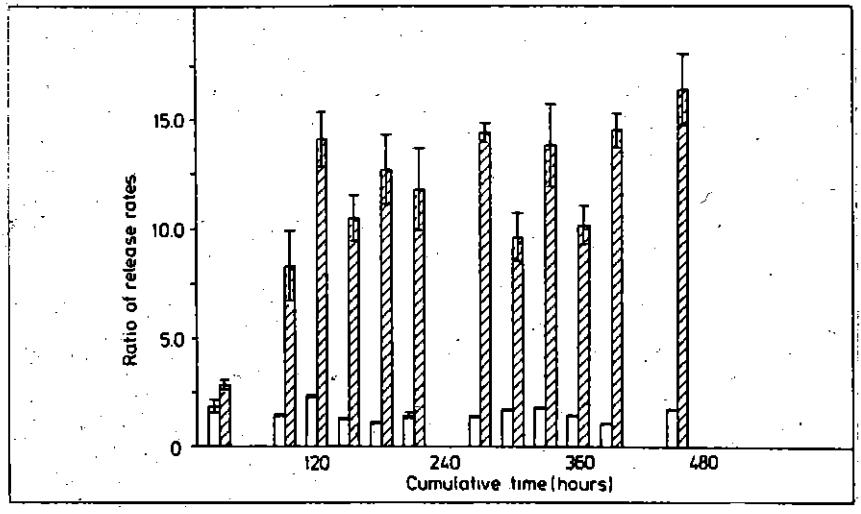

Figure 7: Ratio of release rates from matrices embedded with paramagnetic spheres (clear bars) and 1100 Gauss magnets (hatched bars) (12).

Embedded Magnet Orientation : 10 samples are used each with a single 1100 G magnet embedded to study magnet orientation (38). The magnet is embedded perpendicular and parellel to the applied field. The ratio of release rates is illustrated in FIGURE 8. The average release rate ratio in the parellel case is

2.14 while the gabs with magnetic cylinders oriented 90^0 to that achieved a ratio of 2.4. A5-8 fold difference is observed (38).

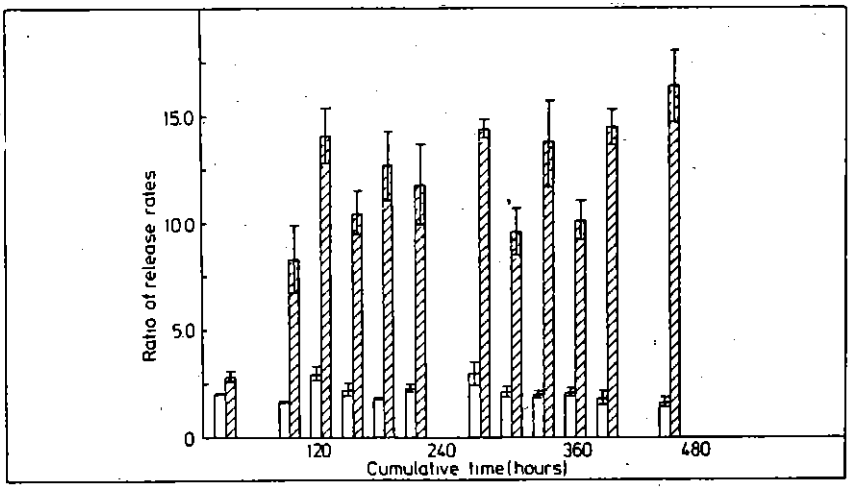

Figure 8: Ratio of release rates from matrices embedded with magnetic cylinders oriented with pole vectors perpendicular to (clear bars) and parellel to (hatched bars) to applied magnetic field (12).

Release rates are controlled by an oscillating external magnetic field which is generated by a device that rotates permanent magnets beneath the vials (9,37) (FIGURE 9 and 10). Byplacing small plastic cages containing animals on the top

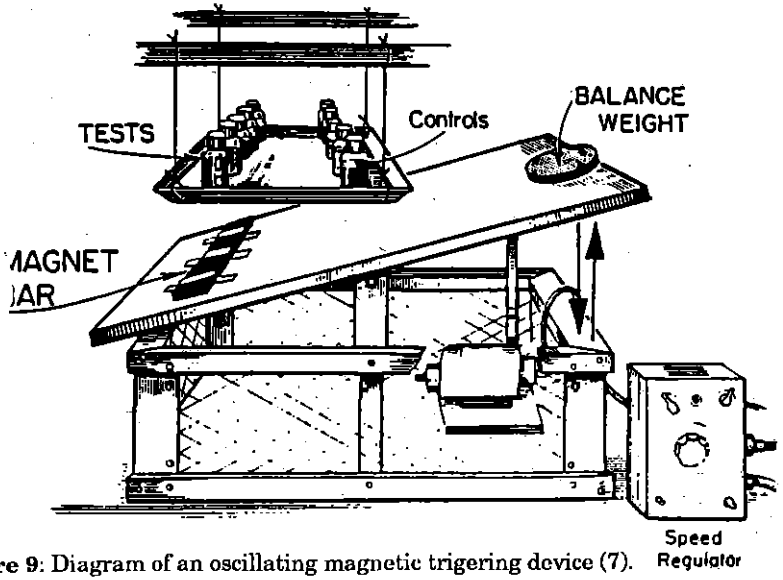

Figure 9: Diagram of an oscillating magnetic trigering device (7).

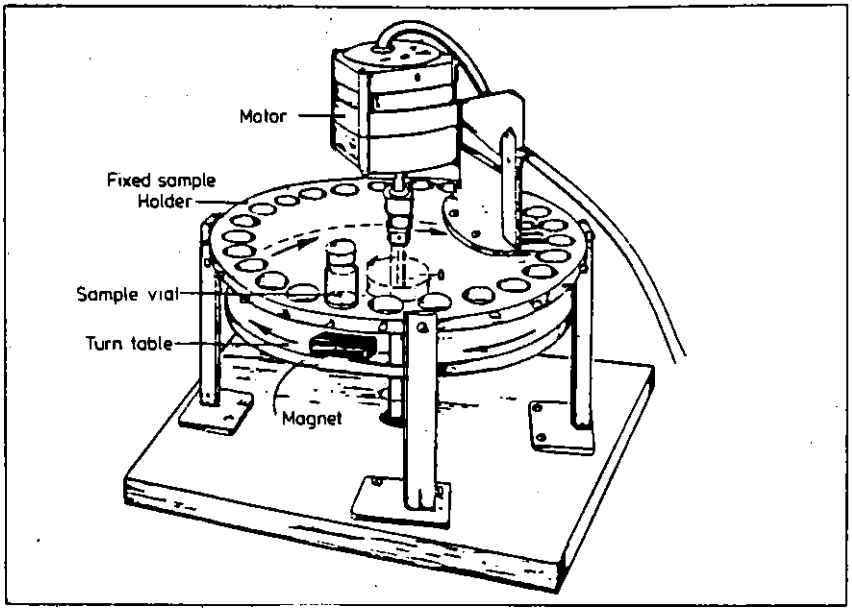

Figure 10: Trigering device for magnetic polymers (9).

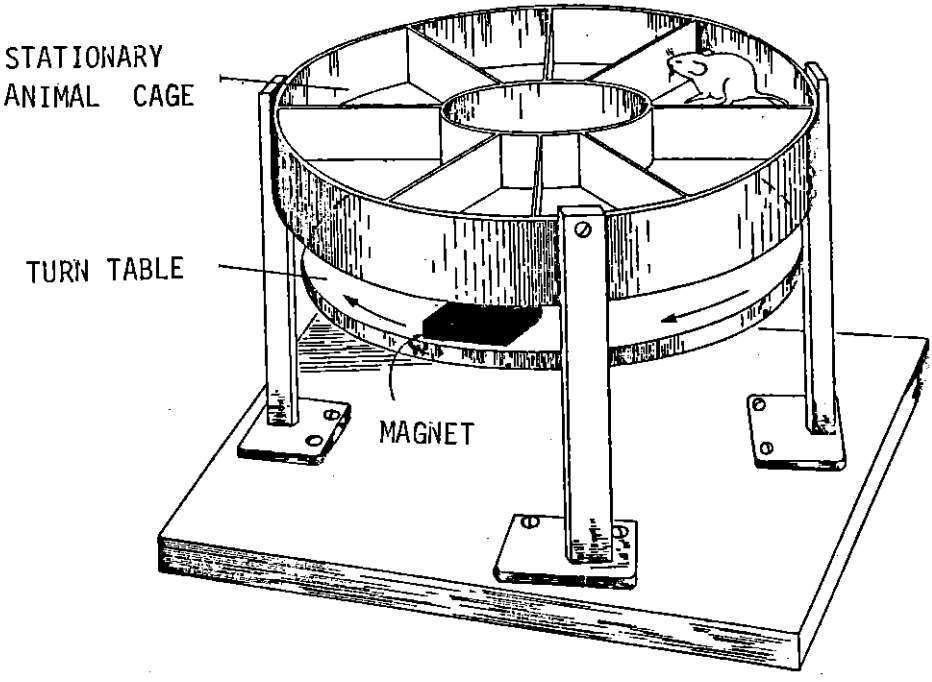

Figure 11: Magnetic triggering device for in vivo animal experiments (46).

disc, it can also be used for in vivo studies (46) (FIGURE 11). Magnets can release up to 30 times more drug when exposed to the magnetic field and release rates returned to normal when the magnetic field is diiscontinued (FIGURE 12).

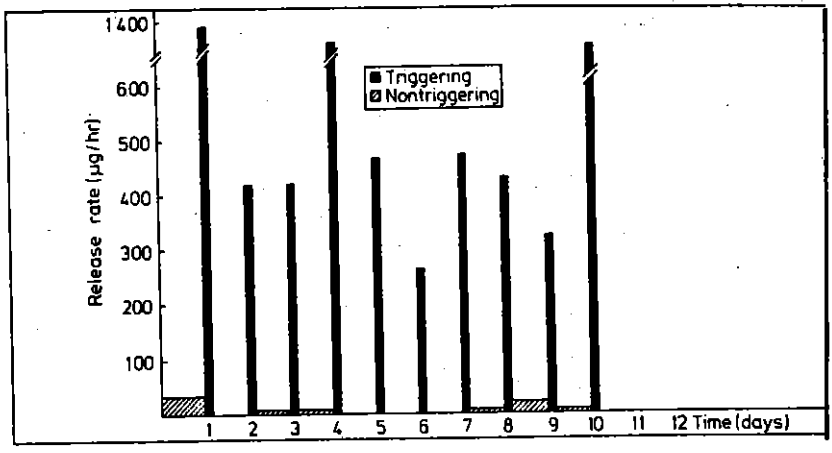

Figure 12: Release rate during the magnetic modulation period (full bars); and non-triggered period (clear bars) (37).

One possibility in release mechanism is that the magnetic field increases release rates because the beards compress and expand the matrix pores, thereby "squeezing" out more drug (6).

Mc Carthy et al (6) proposed a model for the enhanced release and suggested that the major effects stems from the alternate compression and expansion of the pores, causing the fluid to flow. They developed a mathematical model, based on ideal axial diffusion in a cylinder with pulsed flow. This describes the increase release rate with increasing frequency.

Video recordings of the polymer matrix surface show that the beads actually move within the matrix in responce to the external magnetic field and move adjacent material containing polymer and drug with it "squeezing" out the dissolved drug through the pores. A schematic representation of this process is shown in (FIGURE 13) (6).

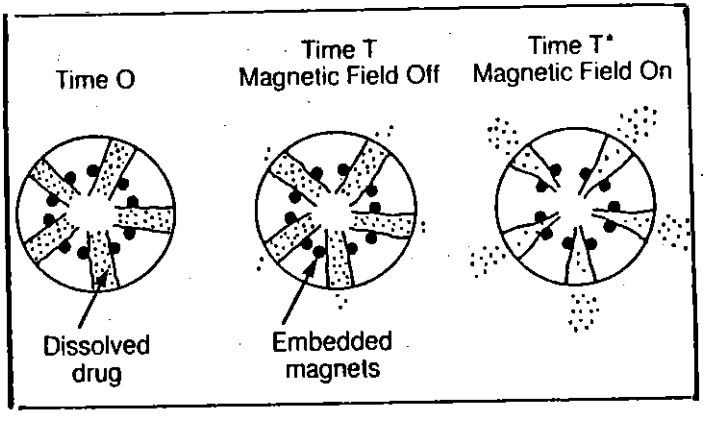

Figure 13: Schematic presentation of the release process in responce to the external magnetic field (6).

APPLICATION

Regardless of the mechanism of action, this carrier system will prove beneficial in a varifety of diseases (6). These include the delivery of antineoplastic drugs for cancer chemotherapy, insulin for patients with diabetus mellitus, antiarrhytmics for patients with heart rhythm disorders and nitrates for patients with angina pectoris, as well as selective β-blockade, birth control general hormone replacement, and immunization. Magnetically localised drugs may also be useful in the treatment of pulmonary embolism and thrombophlebitis. The inclusion of anti-inflammatory and immunosupressive agents into microspheres which are localized to severe inflammatory processes such as chronic arthritic joints or kidney transplants may prove beneficial.

Magnetically targeted systems fall into 4 categories with respect to the type of agents targeted. These are Standart Drugs, Biomodulators, Biophysical and Diagnostic Agents (5).

A- Standard Drugs:

Since the fundamental problem in cancer chemotherapy is the supply of drug in lethal concentrations to cell in a solid tumor, antineoplastic drugs like, doxorubicin HCl (2,5,13-16,39-42), amphotericin B (5), vindecin sulphate (43), and BCNU (44) are magnetically targeted. Examples of these will be stated in the following pages.

Doxorubicin HCl (Adriamycin), is chosen as a prototype drug. It has demonstrated activity against a broad range of tumors and also has direct activity at a tumor site. It is the first agent chosen for magnetic targeting because it is active against a wide variety of human solid tumors. But its efficacy is compromised by a major, organ directed side effect or irreversible, dose dependent cardiomyopathy (5).

In vivo kinetics of low-dose doxorubicin (0.05 mg/kg), entrapped in a carrier and magnetically targeted are characterized in a rat tail. 1 % of the free intravenous dose targeted magnetically yielded approximately twice the local doxorubicin concentration at a preselected target site with no detectable systemic distribution (FIGURE 14) (39).

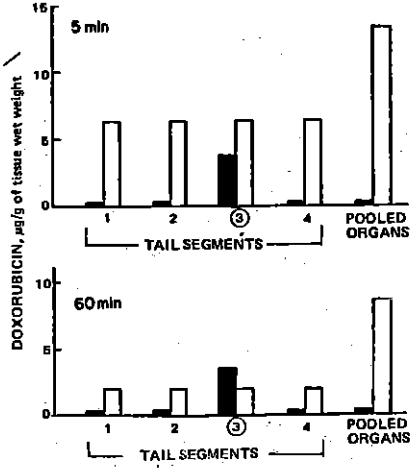

Figure 14: Doxorubicin tissue concentration (39). Free doxorubicin (clear bars); magnetic microspheres (full bars).

	Untreated control	Adriamycin		Placebo microspheres with magnet	Microspheres bearing 0.5 mg/kg adriamycin		Microspheres bearing 2.5 mg/kg adriamycin
		5 mg/kg intraarterially	0.5 mg/kg intraarterially		No magnet	With magnet	With magnet
Initial tumour size (mm^2)	423	496	459	254	502	413	226
Final tumour size (mm^2)	932	859	701	594	1,076	38	22
Deaths (%)	90	100	100	100	100	0	0
Regressions (%)	0	0	0	0	0	100	100
Total remissions (%)	0	0	0	0	0	75	80
Metastases (%)	100	100	100	100	100	0	0

TABLE 3

Effect of magnetic microspheres containing adriamycin on Yoshida sarcoma-bearing rats (2)

Magnetically responsive albumin microspheres containing doxorubicin and magnetite are selectively targeted to Yoshida sarcoma tumors in rats. Marked tumor regression is observed in three rats. 9 out of 12 animals treated with a single dose in the experimental group, exhibited total remission of the tumor. Significant increases in tumor size with wide spread metastases occurred in all control groups and most rats died (16). In another study by Widder et all (21) magnetic albumin microspheres are targeted to subcutaneous solid Yoshida sarcoma tumors in Holtzman rats. Animals are killed at 10, 30, 60 min and 24 and 72 hrs. after microsphere administration. Microspheres are still observed within tumor cells as late as 72 hrs. after administration.

The influence of magnetic albumin microspheres on the disposition of Doxorubicin is evaluated. Doxorubicin concentrations are monitored in multiple rat tissues for 48 hr after arterial administration (13).

Widder et al (2) has chosen Yoshida rat sarcoma for its known sensitivity to Doxorubicin. Animals received 0.5 mg/kg or 5 mg/kg Doxorubicin on days 1,5, and 9 post innoculation of the tumor. Animals are assessed for tumor size, weight change and life span. The results of single dose therapy within magnetically responsive microspheres are presented in TABLE 3 (2). The tumor size increased markedly in all the animals treated with free Doxorubicin. There is a significiant (83 %) decrease in tumor size in animals receiving Doxorubicin containing microspheres with the magnet placed adjacent to the tumor.

Sugibayashi et al (42) compared the antitumor effects of intravenously administered Doxorubicin entrapped magnetically localized bovine serum albumin micropheres and free doxorubicinon AH 7974 lung matesthases in rats. The mean survival times of the group treated with magnetically localized drug bearing microspheres were significantly longer than either the control group or the group treated with free Doxorubicin.

Although magnetic adriamycin spheres have reached an advanced stage of animal testing, they have not yet progressed to human trials.

Videsine sulphate bearing magnetic microsheres at a dose level of 0.5-2.5 mg/kg are infused to the ventral caudal artery. Of the 20 animals receiving magnetically localized vindesine 85 % had total remission of the tumor (43). In contrast, animals receiving free vindesine exhibited tumor growth, with widespread metastases.

In the brain tumor laboratories, major efforts have been directed towards the use of magnetically responsive microspheres for brain tumors. Using radioactively labelled microspheres it has been proven that the spheres can be concentrated in the brain 100 fold compared to spheres studied without a magnetic field.

BCNU is an antineoplastic agent used for brain tumors (44). They are located in the animal and human brain as magnetic beads or slabs. The life span of the animals and human treated with magnetic BCNU is extended. And this treatment is used in nearly 30 hospitals in USA (44).

Amphotericin B produces severe side effects. The major one is nephrotoxicity, requires occasional interruption of systemic therapy. Magnetically targeted albumin micropheres of Amphotericin B accumulated in the brain. This reduced

the severe side effects in the kidneys (5).

Insulin is another active substance targeted magnetically. Saslawski et al (32) describes a new formulation for triggered delivery of insulin which consisted of magnetic particles disperselied, the release rate of insulin was about 50 times higher than in the absence of magnetic field.

Kost et al (45,46) implanted polymer matrices containing insulin and magnets in diabetic rats for 51 days. When the diabetic rats are exposed to an oscillating magnetic field, the blood glucose levels are lovered by nearly 30 % (FIGURE 15).

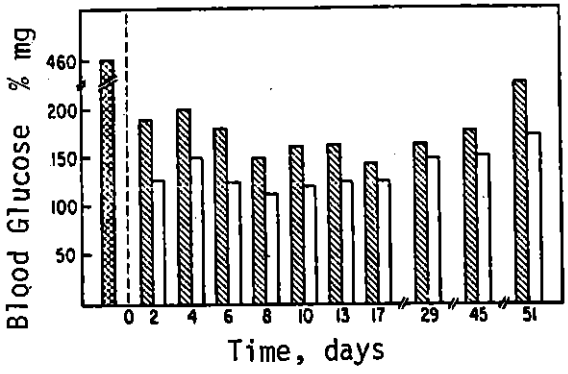

Figure 15: Result of triggering experiment on a rat with implant containing magnet and insulin (46). Before triggering (hatched bars), after triggering (clear bars).

B- Biomodulators :

There are two major classes of agents, indirect and direct (5). Indirect immunomodulators such as interferons (α, β,γ), interleukins *(1-4)*, white cell activato peptides. Due to the lability, toxicity and unfavorable biodistribution, direct acting ones require microencapsulation, site-specific targeting and controlled release in target tissues. This provcides a strong rational for the continued development of magnetic drug targeting (47-50).

C- Biophysical Agents :

Hyperthermia is an important adjuvant technique for treating cancer. In small primary tumors, magnetic micropheres can accentuate heating. This is based on the capacity of magnetic materials to couple with oscillating external magnetic fields and generate heat (5).

D- Diagnostic Agents :

In situations where a high dose in required for adequate sensitivity (MR Images) and in cases where systemic toxicity is high (fluorodeoxyglucose) ferromagnetic spheres can provide highly selective targeting (5).

A super paramagnetic MR Contrast Agent is synthesized by incorporat150-250 A^0 particles of magnetite in HSA microspheres. MAM will have a clinical application in detecting hepatic and splenic lesions (22)

TOXICITY

Very little information is available on the toxicity of these magnetic beads- The Fe_3O_4 in these microspheres is in particulate form and not immediately available to the ionic pool. The quantity of magnetite necessary to localize therapeutic concentrations of microspheres to a 500 gram tumor mass would be less than the normal adult daily intake of iron. Furthermore human experimental studies of lung clearance function utilizing inhaled Fe_3O_4 particles showed minimal adverse efffects including no significant inflammation or fibrosis (6). Magnetically controlled implant does not cause inflammation in vivo. This is confirmed by the lack of edema, cellular infiltrate or neovascularization as judged by histological examination in rabbits (6).

CONCLUSIONS AND FUTURE APPLICATIONS

In conclusion, magnetically responsive microspheres offer a new approach in accomplishing the goal of drug targeting. Based on the targeting capabilities and release characteristics of the available drug carriers, it appears that magnetically responsive small albumin microspheres represent an optimal prototype system for the area specific delivery of anti-tumor agents (2). Its protracted residence within a tumor affords long term sustained therapy. In addition, the carrier exhibits minimal toxicity at doses required for the therapy of large doses (2). Magnetically responsive microspheres can be held in a higly vascularized tissue such as the brain. This gives promise of the future use of this method in brain tumors.

Since the rates can be increased or decreased by changing the frequency or intensity of the externally applied magnetic field, a triggering device could be programmed to be activated near meal time or the patient could activate the device manually at desired times (6). With the implanted glucose detector release rates from the magnetically triggered device could be adjusted automatically and that the release of insulin will be response to physiological needs (6).

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