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AN OVERREVIEW ON MICROSPHERES PREPARATION AND EVALUATION METHODS

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ABSTRACT

The concept of targeted drug delivery is designed for attempting toconcentrate the drug inthe target tissues of interest while reducing the relativeconcentration of the medication in the remaining tissues i.e., other than target tissues, so that the drugis localized on the targeted site. Hence, other/surrounding tissues are notaffected by the drug. So, carrier technology offers an intelligent approachfor drug delivery systems by coupling the drug into carrier particles such asmicrospheres, nanoparticles, liposomes, niosomes etc., which modulatesthe release and absorption characteristics of the drugs. Microspheres arecharacteristically free flowing powders consisting of proteins or syntheticpolymers which are biodegradable in nature and ideally having a particlesize less than 200 µm. It is the reliable means to deliver the drug to thetarget site with specificity, if modified and to maintain the desiredconcentration at the site of interest without untoward effects.Microspheres received much attention not only for prolonged release, butalso for targeting of anticancer drugs to the tumour. In future by combining various otherstrategies, microspheres will find the central place in novel drug delivery systems, particularly indiseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in-vivo* delivery and supplements as miniature versions of diseased organ and tissues in thebody.

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INTRODUCTION

Drug delivery systems (DDS) that can precisely control the release rates or target drugs to aspecific body site have had an enormous impact on the health care system. The ideal drugdelivery system delivers drug at rate decided by the need of the body throughout the period oftreatment and it provides the active entity solely to the site of action. So, carrier technologyoffers an intelligent approach for drug delivery by coupling the drug to a carrier particle suchas microspheres, nanoparticles, liposomes, etc., which modulates the release and absorptioncharacteristics of the drug.[1]

Types of drug delivery system are;Liposome, Niosome, Nanopartical and Microsphere.

MICROSPHERE:

Microspheres are solid spherical particles ranging in size from 1 – 1000µm. They are sphericalfree flowing particles consisting of proteins or synthetic polymers. The microspheres are freeflowing powders consisting of proteins or synthetic polymers, which are biodegradable innature. There are 2 - types of microspheres; Microcapsules and Micromatrices.

Microcapsules are those in which entrapped substance is distinctly surrounded by distinctcapsule wall and micromatrices in which entrapped substance is dispersing throughout themicrospheres matrix. Solid biodegradable microspheres incorporating a drug dispersed ordissolved through particle matrix have the potential for the controlled release of drug. Theyare made up of polymeric, waxy or other protective materials, that is, biodegradablesynthetic polymers and modified natural products.[2]

TYPES OF MICROSPHERES:

Bioadhesive microspheres –

Adhesion can be defined as sticking of drug to the membrane by using the sticking propertyof the water soluble polymers. Adhesion of drug delivery device to the mucosal membranesuch as buccal, ocular, rectal, nasal etc., can be termed as bioadhesion. The term "bioadhesion"describes materials that bind to biological substrates', such as mucosal members. Adhesion ofbioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating anintimate and prolonged contact at the site of administration. This prolonged residence timecan result in enhanced absorption and in combination with a controlled release of drug alsoimproved patient compliance by reducing the frequency of administration. Carrier technologyoffers an intelligent approach for drug delivery by coupling the drug to a carrier particle suchas microspheres, nanospheres, liposomes, nanoparticles, etc., which modulates the releaseand absorption of the drug. Microspheres constitute an important part of these particulatedrug delivery systems by virtue of their small size and efficient carrier capacity.[3]

Magnetic microspheres:

This kind of delivery system is very much important which localises the drug to the diseasesite. In this larger amount of freely circulating drug can be replaced by smaller amount ofmagnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic fieldfrom incorporated materials that are used for magnetic microspheres are chitosan, dextranetc.,[4] The different type are Therapeutic magnetic microspheres are used to deliverchemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targetedthrough this system.[5]

Magnetic drug transport technique is based on the fact that the drug can be eitherencapsulated into a magnetic microsphere or conjugated on the surface of the microsphere.The accumulation of the carrier at the target site allow them to deliver the drug locally.[7]

Diagnostic microspheres:[6]

Floating microspheres:

In floating types the bulk density is less than the gastric fluid and so remains buoyant instomach without affecting gastric emptying rate. The drug is released slowly at the desiredrate, if the system is floating on gastric content, increases gastric residence and fluctuation inplasma concentration. It also reduces chances of striking and dose dumping and producesprolonged therapeutic effect.

Example; Drug (ketoprofen) given through this form.[8]

Radioactive microspheres:

Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries andgets tapped in 1st capillary bed when they come across. They are injected to the arteries thatlead to tumour of interest. So these radioactive microspheres deliver high radiation dose tothe targeted areas without damaging the normal surrounding tissues. It differs from drugdelivery system, as radio activity is not released from microspheres but acts from within aradioisotope typical distance and the different kinds of radioactive microspheres are α -emitters, β - emitters, γ - emitters.[9]

Mucoadhesive microspheres:

Mucoadhesive microspheres which are of 1 – 1000mm in diameter and consisting eitherentirely of a mucoadhesive polymer or having an outer coating of it and coupling ofmucoadhesive properties to microspheres has additional advantages, eg;efficient absorptionand enhanced bioavailability of the drugs due to a high surface to volume ratio, a much moreintimate contact with the mucus layer, specific targeting of drug to the absorption siteachieved by anchoring plant lectins, bacterial adhesions and antibodies, etc., on the surface ofthe microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosaltissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thusoffering the possibilities of localized as well as systemic controlled release of drugs.[1]

Polymeric microspheres:
The different types of polymeric microspheres can be classified as:

Biodegradable polymeric microspheres:
Natural polymers such as starch are used with the concept that they are biodegradable,biocompatible and also bioadhesive in nature. Biodegradable polymers prolongs theresidence time when contact with mucous membrane due to its high degree of swellingproperty with aqueous medium , results gel formation. The rate and extent of drug release iscontrolled by concentration of polymer and the release pattern in a sustained manner. Themain drawback is, in clinical use drug loading efficiency of biodegradable microspheres iscomplex and is difficult to control the drug release.[10]

Synthetic polymeric microspheres:
The interest of synthetic polymeric microspheres are widely used in clinical application,moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc., and proved to be safe and biocompatible. But the main disadvantage of these kind ofmicrospheres, are tend to migrate away from injection site and lead to potential risk,embolism and further organ damage.[11]

Materials and methods:
Microspheres used usually are polymers. They are classified into 2 - types:Synthetic Polymers and Natural polymers.

Synthetic polymers are divided into 2 – types;
i)Non-biodegradable polymers –
Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers.

ii)Biodegradable polymers –
Lactides, Glycolides& their co polymers, Poly alkyl cyanoacrylates, Poly anhydrides.
Natural polymers obtained from different sources like proteins, carbohydrates and chemicallymodified carbohydrates.

Proteins:
Albumin, Gelatin, Collagen.

Carbohydrates:
Agarose, Carrageenan, Chitosan, Starch.

Chemically modified carbohydrates:
Poly dextran**,** Poly starch.[12]

METHODS OF PREPERATION: Preparation of microspheres should satisfy certain criteria;
1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersibility in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.
5. Biocompatibility with a controllable biodegradability and
6. Susceptibility to chemical modification.

Emulsion solvent evaporation technique:
In this technique the drug is dissolved in polymer which was previously dissolved inchloroform and the resulting solution is added to aqueous phase containing 0.2 % sodium ofPVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug andpolymer (eudragit) was transformed into fine droplet which solidified into rigid microspheresby solvent evaporation and then collected by filtration and washed with demineralised waterand desiccated at room temperature for 24 hrs. Aceclofenac microspheres were prepared bythis technique.[11]

Emulsion cross linking method:
In this method drug was dissolved in aqueous gelation solution which was previously heatedfor 1 hr at 40^{o}C. The solution was added drop wise to liquid paraffin while stirring themixture at 1500 rpm for 10 min at 35^{o}C, results in w/o emulsion then further stirring is donefor 10 min at 15^{o}C. Thus the produced microspheres were washed respectively three timeswith acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueousglutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking andthen was treated with 100mL of 10mm glyciene solution containing 0.1%w/v of tween 80 at37^{o}C for 10 min to block unreacted glutaraldehyde.[13]Examples for this technique is GelatinA microspheres.

Coacervation method:

i. Coacervation thermal change:

Performed by weighed amount of ethylcellulose was dissolvedin cyclohexane with vigorous stirring at 80^{o}C by heating. Then the drug was finely pulverized and added with vigorous stirring on the above solution and phase separation was done byreducing temperature and using ice bath. Then above product was washed twice withcyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individualmicrocapsule.

ii. Coacervation non - solvent addition:

Developed by weighed amount of ethylcellulose wasdissolved in toluene containing propylisobutylene in closed beaker with magnetic stirring for6 hr at 500 rpm and the drug is dispersed in it and stirring is continued for 15mins. Thenphase separation is done by petroleum benzoin[14]times with continuous stirring. After that themicrocapsules were washed with n-hexane and air dried for 2 hr and then in oven at 50^{o}C for4 hr.

Spray drying technique:

This was used to prepare polymeric blended microsphere loaded with ketoprofen drug. Itinvolves dispersing the core material into liquefied coating material and then spraying themixture in the environment for solidification of coating followed by rapid evaporation ofsolvent. Organic solution of poly (epsilon caprolactone) (PCL) and cellulose acetate butyrate(CAB), in different weight ratios and ketoprofen were prepared and sprayed in differentexperimental condition achieving drug loaded microspheres. This is rapid but may loosecrystalinity due to fast drying process.[15]

Emulsion-solvent diffusion technique:

In order to improve the residence time in colon floating microparticles of ketoprofen wereprepared using emulsion solvent diffusion technique. The drug polymer mixture wasdissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was addeddrop wise to sodium lauryl sulphate (SLS) solution. The solution was stirred with propellertype agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microsphereswere washed and dried in a dessicator at room temperature. The following microparticleswere sieved and collected.[15]

Multiple emulsion method:

Oral controlled release drug delivery of indomethacin was prepared by this technique. In thebeginning powder drug was dispersed in solution (methyl cellulose) followed byemulsification in ethyl cellulose solution in ethyl acetate. The primary emulsion was then reemulsified in aqueous medium. Under optimized condition discrete microspheres wereformed during this phase.[15]

Ionic gelation:

Alginate/chitosan particulate system for diclofenac sodium release was prepared using thistechnique. 25% (w/v) of diclofenac sodium was added to 1.2% (w/v) aqueous solution ofsodium alginate. In order to get the complete solution stirring is continued and after that itwas added drop wise to a solution containing Ca^{2+} /Al^{3+} and chitosan solution in acetic acid.Microspheres which were formed were kept in original solution for 24 hr for internalgellification followed by filteration for separation. The complete release was obtained at pH6.4-7.2 but the drug did not release in acidic pH.[15]

Hydroxyl appetite (HAP) microspheres in sphere morphology:

This was used to prepare microspheres with peculiar spheres in sphere morphologymicrospheres were prepared by o/w emulsion followed by solvent evaporation. At 1sto/wemulsion was prepared by dispersing the organic phase (Diclofenac sodium containing 5%w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organicphase was dispersed in the form of tiny droplets which were surrounded by surfactantmolecules this prevented the droplets from co-solvencing and helped them to stay individualdroplets .While stirring the DCM was slowly evaporated and the droplets solidify individualto become microspheres.[16]

PHYSICOCHEMICAL EVALUATION:

Characterization:

The characterization of the microparticulate carrier is an important phenomenon, which helpsto design a suitable carrier for the proteins, drug or antigen delivery. These microsphereshave different microstructures. These microstructures determine the release and the stabilityof the carrier.[22]

Particle size and shape:

The most widely used procedures to visualize microparticles are conventional lightmicroscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microparticles. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can bevisualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned.[17]

Electron spectroscopy for chemical analysis:

The surface chemistry, atomic composition of surface and surface degradation ofbiodegradable microspheres can be determined using the electron spectroscopy for chemicalanalysis (ESCA).

Attenuated total reflectance Fourier Transform Infrared Spectroscopy:

FTIR is used to determine the degradation of the polymeric matrix of the carrier system. Thesurface of the microspheres is investigated measuring alternated total reflectance (ATR). TheATRFTIR provides information about the surface composition of the microspheresdepending upon manufacturing procedures and conditions.

Density determination:

The density of the microspheres can be measured by using a multi volume pychnometer.Accurately weighed sample in a cup is placed into the multi volume pychnometer. Helium isintroduced at a constant pressure in the chamber and allowed to expand. This expansionresults in a decrease in pressure within the chamber.2 - Consecutive readings of reductionin pressure at different initial pressure are noted. From 2 - pressure readings the volume andhence the density of the microsphere carrier is determined.

Isoelectric point:

The micro electrophoresis is an apparatus used to measure the electrophoretic mobility ofmicrospheres from which the isoelectric point can be determined. The electrophoreticmobility can be related to surface contained charge, ionisable behaviour or ion absorptionnature of the microspheres.

Surface carboxylic acid residue:

The surface carboxylic acid residue is measured by using radioactive glycine. The radioactiveglycine conjugates is prepared by the reaction of C^{14}-glycine ethyl ester hydro chloride with the microspheres. The radioactivity of the conjugate is then measured using liquidscintillation counter. Thus the carboxylic acid residue can be compared and correlated.

Surface amino acid residue:

Surface associated amino acid residue is determined by the radioactive C^{14}-acetic acidconjugate.The carboxylic acid residue is measured through the liquid scintillation counter and hence theamino acid residue can be determined indirectly.

Capture efficiency:

The capture efficiency of the microspheres or the percent entrapment can be determined byallowing washed microspheres to lyse. The lysate is then subjected to the determination ofactive constituents as per monograph requirement. The percent encapsulation efficiency iscalculated using following equation:

% Entrapment = Actual content/Theoretical content x 100

Angle of contact:

The angle of contact is measured to determine the wetting property of a micro particulatecarrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity.The angle of contact is measured at the solid/air/water interface.

Drug release

In vitro methods –

In vitrodrug release studies have been employed as a quality control procedure inpharmaceutical production, in product development etc., Sensitive and reproducible releasedata derived from physic-chemically and hydro dynamically defined conditions arenecessary, however no standard in vitromethod has yet been developed. Different workershave used apparatus of varying designs and under varying conditions, depending on the shapeand application of the dosage form developed.[18]

Beaker method –

The dosage form in this method is made to adhere at the bottom of the beaker containing themedium and stirred uniformly using overhead stirrer. Volume of the medium used in theliterature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.

Interface diffusion system –

This method is developed by Dearden & Tomlinson. It consists of 4 - compartments. Arepresents the oral cavity and initially contained an appropriate concentration of drug in abuffer. The compartment B representing the buccal membrane, contained 1-octanol andcompartment C representing body fluids, contained 0.2 M HCL.The compartment Drepresenting protein binding also contained 1-octanol. Before use, the aqueous phase and 1-octanol were saturated with each other. Samples were withdrawn and returned tocompartment A with a syringe.[19]

Modified Keshary Chien Cell:

A specialized apparatus was designed in the laboratory. It comprised of a Keshary Chien cellcontaining distilled water (50ml) at 370 C as dissolution medium. TMDDS (Trans MembraneDrug Delivery System) was placed in a glass tube fitted with a 10# sieve at the bottom whichreciprocated in the medium at 30 strokes per min.[20]

Dissolution apparatus:

Standard USP or BP dissolution apparatus have been used to study in-vitrorelease profilesusing rotating elements, paddle and basket. Dissolution medium used for the study variedfrom 100- 500 ml and speed of rotation from 50- 100 rpm.[21]

***In vivo* methods:**

Methods for studying the permeability of intact mucosa comprise of techniques that exploitthe biological response of the organism locally or systemically and those that involve directlocal measurement of uptake or accumulation of penetrate at the surface. The most widelyused methods include in-vivostudies using animal models, buccal absorption tests andperfusion chambers for studying drug permeability.

Animal models:

Animal models are used mainly for the screening of the series of compounds, investigatingthe mechanisms and usefulness of permeation enhancers or evaluating a set of formulations.Animal models such as the dog, rats, rabbits, cat, hamster, pigs and sheep have beenreported. In general, the procedure involves anesthetizing the animal followed byadministration of the dosage form. In case of rats, the oesophagus is ligated to preventabsorption pathways other than oral mucosa. At different time intervals, the blood iswithdrawn analyzed.[22]

Buccal absorption test:

The buccal absorption test was developed by Beckett & Triggs in 1967. It is a simple andreliable method for measuring the extent of drug loss of the human oral cavity for single andmulti-component mixtures of drugs. The test has been successfully used to investigate therelative importance of drug structure, contact time, initial drug concentration and pH of thesolution while the drug is held in the oral cavity.[23]

***In*-vitro and In-vivocorrelations:**

Correlations between in-vitro dissolution rates and the rate and extent of availability asdetermined by blood concentration and or urinary excretion of drug or metabolites arereferred to as "*in-vitro-in vivo* correlations". Such correlations allow one to develop productspecifications with bioavailability.

Percent of Drug Dissolved *In-Vitro* Vs Peak Plasma Concentration:

One of the ways of checking the in-vitro and in-vivo correlation is to measure the percent ofthe drug released from different dosage forms and also to estimate the peak plasmaconcentrations achieved by them and then to check the correlation between them.

Percent of Drug Dissolved Vs Percent of Drug Absorbed:

If the dissolution rate is the limiting step in the absorption of the drug, and is absorbedcompletely after dissolution, a linear correlation may be obtained by comparing the percent ofthe drug absorbed to the percent of the drug dissolved. If the rate limiting step in thebioavailability of the drug is the rate of absorption of the drug, a change in the dissolutionrate may not be reflected in a change in the rate and the extent of drug absorption from thedosage form.

Dissolution Rate Vs Absorption Rate:

The absorption rate is usually more difficult to determine than the absorption time. Since theabsorption rate and absorption time of a drug are inversely correlated, the absorption timemay be used in correlating the dissolution data to the absorption data. In the analysis of invitro and in vivo drug correlation, rapid drug absorption may be distinguished from theslower drug absorption by observation of the absorption time for the dosage form. Thequicker the absorption of the drug the less is the absorption time required for the absorptionof the certain amount of the drug. The time required for the absorption of the same amount ofdrug from the dosage form is correlated.

Percent of Drug Dissolved Vs Serum Drug Concentration:

For drugs whose absorption from GIT is dissolution rate limited, a linear correlation may beestablished between the percent of drug dissolved at specified times and the serum drugconcentrations at corresponding times.

Percent of Drug Dissolved Vs Percent of the Dose Excreted in urine:

The percent of a drug dissolved and the percent of drug absorbed are linearly correlated.There exists a correlation between the amount of drug in body and the amount of drugexcreted in the urine. Therefore, a linear relation may be established between the percent ofthe drug dissolved and the percent of the dose excreted in the urine.[24]

Advantages:

1. Reliable means to deliver the drug to the target site with specificity, if modified and tomaintain the desired concentration at the site of interest without untoward effects.
2. Solid biodegradable microspheres have the potential throughout the particle matrix forthe controlled release of drug.
3. Microspheres received much attention not only for prolonged release, but also fortargeting of anticancer drugs to the tumour.[25]
4. The size, surface charge and surface hydrophilicity of microspheres have been found tobe important in determining the fate of particles in-vivo.
5. Studies on the macrophage uptake of microspheres have demonstrated their potential intargeting drugs to pathogens residing intracellularly.
6. Blood flow determination: This study has been carried out using radiolabelledmicrospheres.

APPLICATIONS:

Microspheres in vaccine delivery -

An ideal vaccine must fulfill the requirement of efficacy, safety, convenience in applicationand cost. Biodegradable delivery systems for vaccines that are given by parenteral route mayovercome the shortcoming of the conventional vaccines. The interest in parenteral(subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

1. Improved antigenicity by adjuvant action
2. Modulation of antigen release
3. Stabilization of antigen.

Targeting using microparticulate carriers –

The concept of targeting, i.e., site specific drug delivery is a well-established dogma, which isgaining full attention. The therapeutic efficacy of the drug relies on its access and specificinteraction with its candidate receptors. The ability to leave the pool in reproducible, efficientand specific manner is center to drug action mediated by use of a carrier system.

Monoclonal antibodies mediated microspheres targeting –

Monoclonal antibodies targeting microspheres are immune microspheres. This targeting ismethod used to achieve selective targeting to the specific sites. Monoclonal antibodies areextremely specific molecules. Mabs can be directly attached to the microspheres by means ofcovalent coupling. The Mabs can be attached to microspheres by any of the followingmethods;

1.Nonspecific adsorption and Specific adsorption
2. Direct coupling and
3. Coupling via reagents.

4. Chemoembolisation –

Chemoembolisation is an endovascular therapy, which involves the selective arterialembolisation of a tumour together with simultaneous or subsequent local delivery thechemotherapeutic agent.

5. Imaging –

The particle size range of microspheres is an important factor in determining the imaging ofparticular sites using radio labbled microspheres. The particles injected intravenously apartfrom the portal vein will become entrapped in the capillary bed of the lungs. Thisphenomenon is exploited for the scintiographic imaging of the tumour masses in lungs usinglabeled human serum albumin microspheres.

6. Topical porous microspheres –

Microsponges are porous microspheres having myriad of interconnected voids of particle sizerange 5 – 300µm. These microsponges having capacity to entrap wide range of activeingredients such as emollients, fragrances, essential oils etc., are used as the topical carriessystem.[26]

7. Medical application;

- Release of proteins, hormones and peptides over extended period of time.
- Gene therapy with DNA plasmids and also delivery of insulin.
- Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricintoxoid, diphtheria, birth control.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens,by intra-arterial/intravenous application.
- Tumour targeting with doxorubicin and also
- Treatments of leishmaniasis.
- Magnetic microspheres can be used for stem cell extraction and bone marrowpurging.
- Used in isolation of antibodies, cell separation and toxin extraction by affinitychromatography.
- Used for various diagnostic tests for infectious diseases like bacterial, viral andfungal.[27]

8. Radioactive microsphere's application:[4]

- Can be used for radio embolisation of liver and spleen tumours.
- Used for radio synvectomy of arthiritis joint, local radiotherapy, interactivitytreatment.
- Imaging of liver, spleen, bone marrow, lung and even imaging of thrombus in deepvein thrombosis can be done.

CONCLUSION

The present review article shows that microspheres are better choice of drug delivery systemthan many other types of drug delivery system. In future by combining various otherstrategies, microspheres will find the central and significant place in novel drug delivery,particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted,specific and effective *in vivo* delivery and supplements as miniature versions of diseasedorgan and tissues in the body.

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