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Product Development Report on Microsphers Loaded with Lamivudine and Curcumin

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Abstract: *Mushroom cultivation offers attractive prospects of profitability converting lignocellulosic residue from agricultural fields, forests, and industry into protein-rich biomass. In the present investigation Soybean straw, cotton straw, and paddy straw were used as basic materials for the production of Pleurotus florida. These straws were mixed with additional supplements such as wheat bran to achieve nitrogen content in the initial material. Because these straws are high in protein and carbohydrates, they supply carbon and nitrogen sources for the growth of Pleurotus florida. The highest stripe length observed was 4.03cm, achieved by paddy straws. It has also been noted that the weight of the stripe increases when it is grown in paddy straws which is 4.26 grams. The maximum dry weight of the strip was observed at 0.26 gm with soybean as a substrate. The average maximum Pileus size and weight observed were 54.25 cm and 15.92 gm respectively and pileus dry weight 0.91gm on cotton. The average total yield of P. florida was 118.26 on cotton. This study concluded that Pleurotus florida can be grown using cotton and paddy straw as a sole substrate.*

Keywords: Pleurotus florida

I. INTRODUCTION

The most preferred method of taking medicine is through the oral route[(1)]. Over a long period of time, oral drug delivery systems (ODDS) provide a consistent, measured, and predictable amount of medication to the target location. The oral routes have received the greatest attention because of their distinct benefits, which include prolonged and controlled distribution, simplicity of administration, practicality for solid formulations, patient compliance, and in the case of vaccinations, enhanced immune response[(2)]. However, many medicines' therapeutic potential is limited by their short circulation half-life and restricted absorption via a specific section of the gut. Due to the natural cycle of the digestive tract, sustained oral administration lasting more than 24 hours is difficult to obtain. One such technique that may be utilised in continuous control release is the use of a microsphere as a drug carrier[(1)] .

Microspheres are free-flowing powders composed of proteins or synthetic biodegradable polymers. Microspheres are defined as a "monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) as a structure composed of continuous phase or off one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. It has particles with a size of (1-1000nm)[(1)]. Microspheres are divided into two types:

MICROSPHRES: also referred as micropaticles.

- **Microcapsules:** Entrapped substance is covered by capsule wall.
- **Micro-matrices**: Entrapped substance is dispersed in the matrix.

The Ideal Properties of Microspheres:

1. Controllable biodegradability with biocompatibility.
2. Higher doses of the medication can be administered to act as a depot.
3. Preparation stability following synthesis with clinically acceptable shelf life.
4. The ability to adjust the discharge rate for a set length of time.
5. Toxicity reduction.

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Microspheres are used in various oral drug delivery systems such as gastro retentive, control, and sustained release drug delivery systems, targeted drug delivery systems as microspheres could provide large surface area and possess an easier estimation of diffusion and mass transfer behaviour [(3)].

Sustained drug delivery by encapsulating the drug inside polymeric carriers has made great progress in last two decades as it can enhance the drug release and decrease adverse effects[(4)].Some of the advantages of using microparticles as sustained release drug delivery systems are an effective protection of the active agent against degradation (e.g., enzymatic) after encapsulation. The possibility to accurately control the release rate of the incorporated drug over periods of hours to months an easy administration (compared to the parenteral controlled release dosage forms such as macro-sized implants). Desired, pre-programmed drug release profiles can be provided which match the therapeutic needs of the patient[(5)] .

Curcumin is a diarylheptanoid belonging to the group of curcuminoids, which are natural phenols responsible for its yellow color. It is potent scavenger of reactive oxygen and nitrogen species such as hydroxyl radicals[(6)]. Curcumin inhibits HBV gene replication via down regulation of cccDNAbound histone acetylation and has the potential to developed as a cccDNA-targeting anti-viral agent for hepatitis B. Lamivudine is a nucleoside reverse transcriptase inhibitor that work by slowing the growth of the virus, thereby decreasing liver damage caused by the virus. Several microencapsulation techniques have been developed for this purpose; however, the appropriateness of such techniques depends on the nature of the drug/polymer.Eudragits are also called as methacrylic acid co-polymers. A combination of Eudragit RS100 (Low water Permeability) and Eudragit RL100 (High water Permeability) in a single matrix was used to sustain the release of drug from microspheres. Both are showing pH independent drug release properties. Eudragit RL100 and Eudragit RS100 are Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) in the ratio of 1:2:0.2 and 1:2:0.1 respectively(7) . The most suitable microencapsulation techniques are emulsion solvent evaporation, phase separation, interfacial polymerization, and spray drying. Of these methods, emulsion solvent evaporation is the method of choice for microencapsulation of water-insoluble drugs using a waterinsoluble polymer(4) . The rationale behind this study was to prepare the microspheres of curcumin and lamivudine encapsulated in EUDRAGIT polymers to control the release of this highly base-soluble drug. EUDRAGIT RS 100 and EUDRAGIT RL 100 are water-insoluble, pH-independent polymers, whereas EUDRAGIT S 100 is a pH-dependent polymer. In addition, the drug-release kinetics for the formulations developed was also evaluated[(7)] .

Advantages[(8)] :

1. Microspheres provide a consistent and long-lasting therapeutic impact
2. Reduces dosage frequency, improving patient compliance.
3. Because of their spherical form and tiny size, they may be injected into the body.
4. Improved medication usage will increase bioavailability and minimise the occurrence or severity of side effects.
5. Controllable diversity in degradation and drug release is enabled by microsphere shape.

Limitations[(9)] :

1. The materials and processing costs of controlled release preparation are significantly greater than those of normal formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants, and fillers.
4. There will be less reproducibility.

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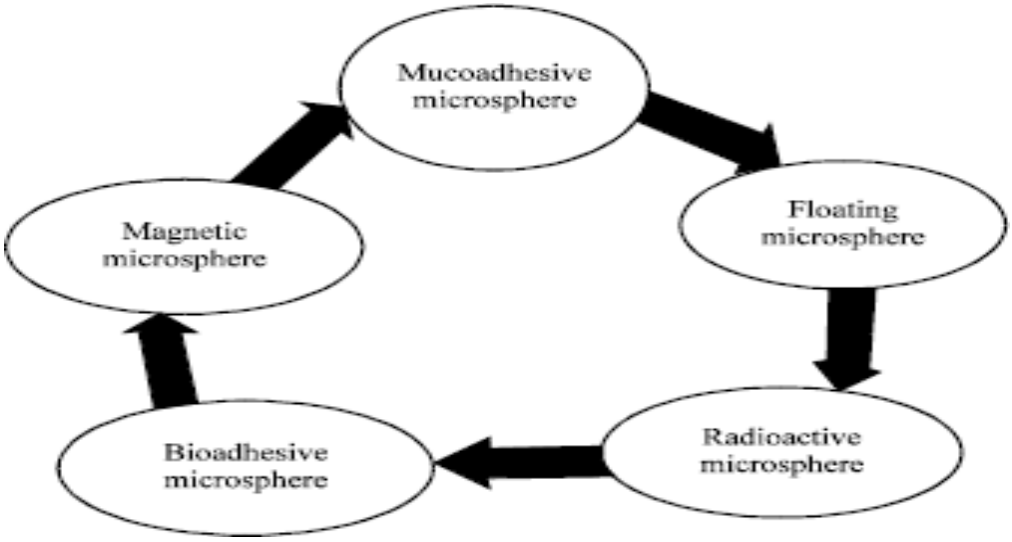
TYPES OF MICROSPHERES

There are various types of microsphere they are as follows:



Bio-Adhesive / Muco-Adhesive Microspheres - Bio adhesion is the method by which a synthetic polymer adheres to a biological membrane. Mucoadhesion occurs when a biological tissue is a mucosal layer. Mucoadhesive microspheres provide a prolonged contact time at the site of application or absorption and aid in aiding intimate contact with the substrate surface where absorption is expected to happen, thereby improving the therapeutic performance of the drug[10] .

Floating Microspheres - The mass density of floating forms is lower in floating types than that of gastric fluid, thus they float in the gastric stomach without changing the rate of gastric emptying [11] . The medicament is delivered at the desired rate slowly, and gastric content is found to float and gastric residency duration rises. Floating microspheres work on a non- effervescent method among the many gastric retention mechanisms. These microspheres are found to be powders that are freeflowing with protein or synthetic polymers. It should be under 300µm in size[11]

Magnetic Microspheres-This sort of delivery mechanism is important because it allows the medicine to be delivered to the site of the sickness. A smaller quantity of magnetically targeted medicines can replace a greater quantity of freely circulating pharmaceuticals[12]. Magnetic carriers receive magnetic responses from integrated materials such as dextran chitosan, which are utilised in magnetic microspheres in response to a magnetic field, and so on. Magnetic microspheres are a viable alternative to standard radiation treatments that employ extremely penetrating radiation that is absorbed throughout the body[13] .

Radioactive Microspheres-Radioembolization treatment is a type of radiation therapy. Microspheres with diameters of 10-30 nm are bigger than the capillary diameters and are tapped in the first capillary bed when they come across. They are injected into the arteries that lead to the tumour of interest, thus radioactive microspheres provide a high radiation dosage to the targeted regions while causing minimal harm to the normal surrounding tissues[14]. It differs from a therapeutic delivery system in that radioactivity is not released from microspheres, but rather acts from inside a radioisotope typical range and from different types of radioactive microspheres such as α emitters, β emitters, γ emitters[15] . Microspheres as a drug delivery system have a lot of potential in terms of achieving the goals of controlled drug delivery and site-specific delivery(15) .

Polymeric Microspheres - Polymeric microspheres are divided into two types: biodegradable polymeric microspheres and synthetic polymeric microspheres[15] . i) Biodegradable Polymeric Microspheres: Starch and other natural polymers are used because they are biodegradable, biocompatible, and bioadhesive. Biodegradable polymers increase the residency time when they come into contact with mucous membranes due to their high degree of swelling in aqueous environments, resulting in gel formation. Microspheres of this sort are utilised in swellable systems[16] .

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Synthetic Polymeric Microspheres:
Synthetic polymeric microspheres are commonly employed in clinical applications as bulking agents, fillers, embolic particles, and drug delivery vehicles, among other things[17] .

Different methods for preparation of microsphere –
There are several other methods too for the preparation of microspheres they are as follows:

Preparation Method:
Solvent Evaporation:

- Single Emulsion Technique
- Double Emulsion Technique

Cocervation Phase separation
Spray Drying And Spray Congealing Polymerization:

- Interfacial Polymerization
- Normal Polymerization

Solvent Extraction
1. Phase Separation Coacervation Technique
The objective of coacervation is to reduce the polymer's solubility in the organic phase in order to impact the formation of the polymer-rich phase known as coacervates. In this technique, drug particles are dispersed in a polymer solution, then an incompatible polymer is introduced to the system, causing the first polymer to phase separate and engulf the drug particles. Butadiene is used as an incompatible polymer in this method to generate polylactic acid (PLA) microspheres[19]

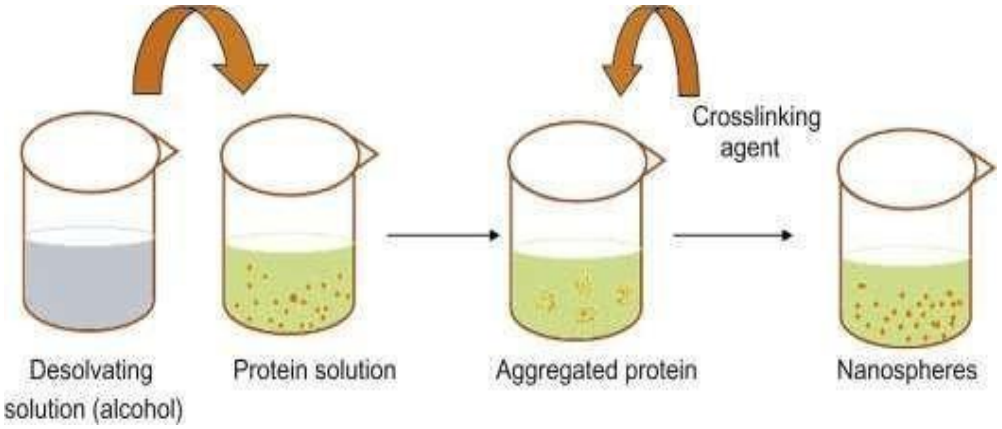

Fig: Coacervation Process

2. Spray Drying and Spray Congealing :
Evaporation is the major process in spray drying, whereas phase inversion from a liquid to a solid is the primary mechanism in spray congealing. Except for the transfer of energy, these processes are quite similar. Spray drying entails three steps: a) Atomization: the process by which a liquid supply is converted into tiny droplets. b) Mixing: this includes passing a hot gas stream between spray droplets, causing liquids to evaporate and dry particles to be left behind.
c) Dry: Dried powder is separated and collected from the gas stream. The polymer is first dissolved in a volatile organic solvent such as dichloromethane, acetone, or a comparable solvent. The solid medication is subsequently disseminated in the polymer solution through high-speed homogenization. This dispersion is subsequently atomized in a stream of hot air, forming minute droplets or a fine mist from which the solvent evaporates instantly, resulting in the production of microspheres. The size range ranges from 1 to 100 nm. The micro-particles are separated utilising hot air via the cyclone separator while vacuum drying removes any residues of solvent[20] .

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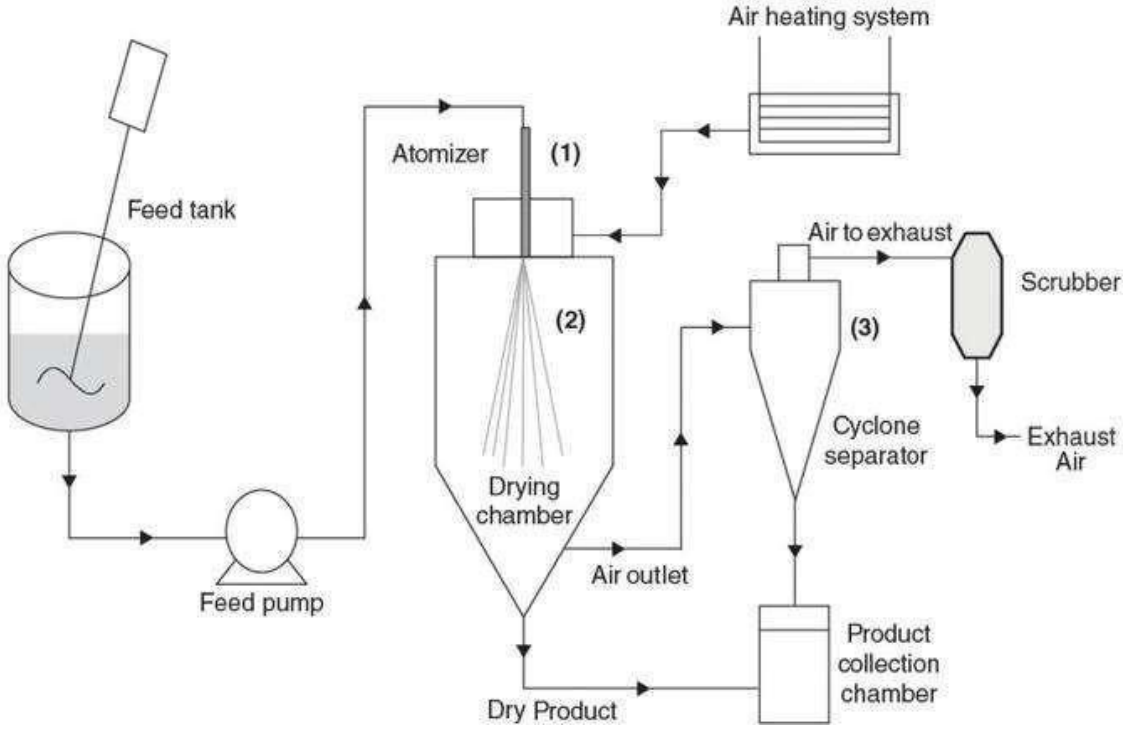

Fig: Spray Dryer

3. Polymerization :

For the preparation of microspheres, there are primarily two procedures.

1. Normal polymerization
2. Interfacial polymerization.

Normal Polymerization:

In bulk polymerization, a monomer or a mixture of the number of monomers along with the initiator or catalyst is usually heated to initiate polymerization. The polymer so obtained may be molded as microspheres. Suspension polymerization is carried out of lower temperature and also refer to as pearl polymerization in which heating the monomer mixture with active drug as droplets dispersion in the continuous aqueous phase. The microsphere size obtained by suspension techniques is less the 100 µm. Emulsion polymerization is differed from the suspension as the due presence of initiator in the aqueous phase but is also carried out at a low temperature in the last two procedures, the external phase is usually water, which allows heat to quickly dissipate[20] .

Normal Polymerization:

- Suspension polymerization
- Emulsion polymerization
- Bulk polymerization

A. Interfacial Polymerization:

The interaction of different monomers at the interface between the two immiscible liquid phases results in the formation of a polymer film that effectively envelops the dispersed phase. In this technique two reacting monomers are employed; one is dissolved in a continuous phase while the other is dispersed in the continuous phase (aqueous) throughout which

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the second monomer is emulsified. Two conditions arise because of the solubility of the formed polymer in the emulsion droplet[18] .

B. Solvent Extraction

The removal of the organic phase by extraction of the organic solvent is included in this technique of microparticle production. As a water-miscible organic solvent, isopropanol can be utilized. The organic phase is removed by extraction with water. This technique can shorten the hardening period of the microsphere. One method includes the direct addition of the drug or protein to a polymer organic solution. The extraction method's rate of solvent removal is affected by water temperature, emulsion volume to water ratio, and polymer solubility profile[22]

II. LITERATURE SURVEY

Satheesh Vilas et al. 2020 to find prolonged or delayed drug release system, exclusively for the treatment of hepatitis-B prepared lamivudine –loaded Eudragit – coated pectin microspheres by emulsion evaporation strategy. The obtained microspheres were then subjected to different characterisation studies.[35]

Kadam N. R. et al., 2015 stated that microspheres are multiparticulate drug delivery systems designed to achieve delayed or controlled drug administration in order to improve bioavailability, stability, and to target the drug to a specific region at a predetermined rate. These delivery systems have a number of advantages over traditional dose forms. Greater efficacy, lower toxicity, improved patient compliance, and convenience are just a few of the benefits.[9]

Thummar, A. V. et al., 2013 described that the goal of this article is to go over the ideas that underpin the development and evaluation of mucoadhesive microspheres, as well as the research that has been done on them. microspheres may be constructed to provide for a longer residence duration at the application or absorption site and to facilitate close contact with the underlying absorption surface, resulting in increased and/or better medication therapeutic effectiveness.[13]

Chitra Singh et al., 2013 stated that a vast range of new, more effective, and specialised medicines are being developed as a result of developments in biotechnology, genomics, and combinational chemistry. Because many of these new medications have difficulties like limited solubility, high potency, and/or poor stability, microspheres are one of the most prevalent types of controlled drug delivery devices, and they have various advantages and come over above barriers.([14]

D. Ridhima et al. 2012 developed multiparticulate gastro retentive drug delivery system of curcumin. The floating drug delivery system of curcumin was prepared by emulsion solvent diffusion method by using ethyl cellulose, HPMC, Eudragit L 100, Eudragit S 100 polymers in varying concentration.[34]

Ankit Vajpayee et al. 2011 formulated curcumin microspheres using calcium chloride. Suitable polymer was identified which is promising in in-vitro mouth-to-colon release profile. The microspheres were prepared by ionic cross-linking method.[31]

H. Bansal et al., 2011 stated a well-designed controlled drug delivery system can address the drawbacks of traditional medication therapy while also improving a medicine's therapeutic efficacy. Because of their spherical shape, microspheres are also referred to as novel/controlled drug delivery systems with particle sizes less than 200 m. Microspheres as a novel medication delivery mechanism are the subject of their review.([19]

Bhabani S Nayak et al. 2009 formulated lamivudine loaded microspheres for oral use to compare sustaining/ controlling efficacy of selected formulation with that of the commercial conventional tablet. The microsphere was prepared by solvent evaporation method and was subjected to various evaluation parameters.[18]

Alagusundaram M. et al. 2009 this article stated that the microspheres are free-flowing powders made up of proteins or synthetic polymers that are biodegradable in nature and have a particle size of less than 200mm. A well-designed controlled drug delivery system can solve some of the drawbacks of traditional therapy while also improving a medicine's therapeutic efficacy. There are several methods for delivering a medicinal chemical to the target region in a regulated and sustained manner. Using microspheres as drug carriers is one such method.[22]

Neelesh k varde et al., 2004 stated that controlled release drug delivery uses drug- encapsulating devices to release therapeutic compounds at a controlled rate over a lengthy period of time, ranging from days to months. These systems have a number of advantages over traditional drug delivery methods, including the ability to customise drug release

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rates, safeguard fragile pharmaceuticals, and improve patient comfort and compliance. Because of their ability to encapsulate a range of medications, biocompatibility, high bioavailability, and prolonged drug release characteristics

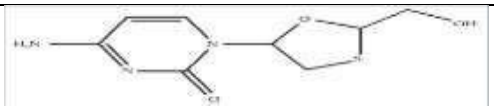
AIM AND OBJECTIVE

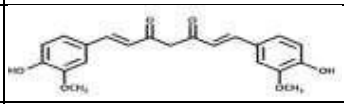
AIM – Product development report microspheres loaded with lamivudine and curcumin.

OBJECTIVES

- To use microspheres in gastro-retentive system to increase gastric tolerance of gastric irritants as an antigen carrier.
- Biodegradable micro-particulate carriers are of significance for oral drug administration to increase bioavailability, improve drug absorption, and target specific organs with less toxicity.
- Microspheres aid in dispersion of water insoluble substance in aqueous media, using microsphere sustained release, controlled release and targeted release is easy to achieve.
- Lamivudine and curcumin is potential drug in treating HBV (hepatitis B virus) their combination gives us more powerful effect in very less dose administration using microsphere as a carrier

DRUG PROFILE:

NAME	LAMIVUDINE
MOLECULAR STRUCTURE	
IUPAC NAME	4-Amino-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one
MOLECULAR FORMULA	C811N2O3S
MOLECULAR WEIGHT	229.25 g/mol
CATEGORY	Antiviral
CAS NUMBER	134678-17-4

NAME	CURCUMIN
MOLECULAR STRUCTURE	
IUPAC NAME	(1E,6E)-1,7-bis (4-hydroxy- 3-methoxyphenyl) -1,6- heptadiene-3,5-dione
MOLECULAR FORMULA	C21H20O6
MOLECULAR WEIGHT	368.38 g/mol
CATEGORY	Anti-inflamentry
CAS NUMBER	458-37-7

PLAN OF WORK :

- Procurement of drug.
- Procurement of excipients.
- Pre-formulation studies.
- Compatibility of drug and excipient.
- Preparation of curcumin and lamivudine loaded microspheres.
- Evaluation and characterization of lamivudine and curcumin loaded microspheres.
- Compilation of work

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EXPECTED OUTCOME:

- Establishment of microspheres as a gold standard for HIV/AIDS treatment.
- Expansion into new markets (Asia, Latin America).
- Development of next-generation microspheres with enhanced efficacy and safety.
- Exploration of microspheres for other infectious diseases (e.g., tuberculosis, malaria).

FUTURE SCOPE:

- Development of microspheres for HIV cure and eradication.
- Investigation of microspheres for other infectious diseases (e.g., tuberculosis, malaria).
- Exploration of gene therapy approaches using microspheres.
- Development of point-of-care diagnostics for HIV/AIDS using microspheres.
- Establishment of microsphere-based vaccine delivery systems

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