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MICROSPHERES - A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT
The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localized on the targeted site. Hence, surrounding tissues are not affected by the drug. So, carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, niosomes etc which modulates the release and absorption characteristics of the drug. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

KEYWORDS: *Microspheres, controlled release, Types of microspheres, Methods of preparation, characterisation of microspheres, applications.*

INTRODUCTION
Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the health care system. The ideal drug delivery system delivers drug at rate decided by the need of the body throughout the period of treatment and it provides the active entity solely to the site of action. So, carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc which modulates the release and absorption characteristics of the drug.[1] Types of drug delivery system are

- LIPOSOME
- NIOSOME
- NANOPARTICAL
- MICROSPHERE

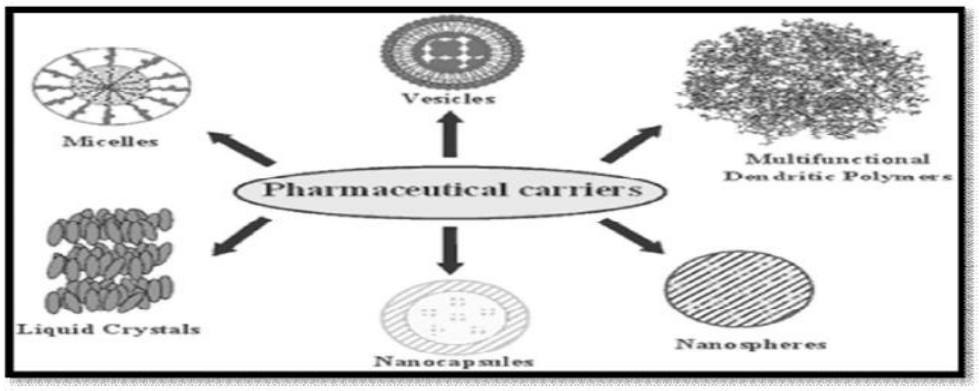

Figure 1. Pharmaceutical carriers

MICROSPHERE

Microspheres are solid spherical particles ranging in size from 1-1000µm. They are spherical free flowing particles consisting of proteins or synthetic polymers. The microspheres are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. There are two types of microspheres

- Microcapsules.
- Micromatrices

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

TYPES OF MICROSHERES

1) Bioadhesive microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bio adhesion. These kinds of microspheres exhibiting it a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.[3]

2) Magnetic microspheres

This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. They are used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system.

Diagnostic microspheres: Can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles super magnetic iron oxides.[4]

3) Floating microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration.[5]

4) Radioactive microspheres

In the release rate from Radio immobilization therapy are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumor of interest. So all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit through gut.[6]

MATERIALS USED

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspheress. These materials include the polymers of natural and synthetic origin and also modified natural substances. Synthetic polymers employed as carrier materials are methyl methacrylate, acrolein, lactide, glycolide and their copolymers, ethylene vinyl acetate copolymer, polyanhydrides, etc. The natural polymers used for the purpose are albumin, gelatin, starch, collagen and carrageenan.

Classification of polymer[8]

A) Synthetic Polymers

Divided into two types-

1) Non-biodegradable - Acrolein, Glycidyl methacrylate, Epoxy polymers, etc.[9,10]

2) Biodegradable - Polyanhydrides, Polyalkyl cyano acryalates Lactides and glycolides and their copolymers.[11]

B) Natural materials

Obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.[12,13]

i) Proteins (albumin, gelatin, collagen)
ii) Carbohydrate (starch, agarose, carrageenan)
iii) Chemically modified carbohydrates

Pre-requisites for ideal micro particulate Carriers[7]

The material utilized for the preparation of micro particulates should ideally fulfill the following prerequisites. Longer duration of action

- Control of content release
- Increase of therapeutic efficiency
- Protection of drug
- Reduction of toxicity
- Biocompatibility
- Sterilizability
- Relative stability
- Water solubility or dispersability
- Bioresorbability
- Target ability

Polymeric microsphere[7]

The various types of polymers are used for preparation of microspheress e.g. Albumin microspheress

- Gelatin microspheress

- Starch microspheress
- Dextran microspheress
- Poly lactide and poly glycolide microspheress
- Polyanhydride microspheress and polyphosphazene microspheress
- Chitosan microspheress
- Polysaccharides or lipid cross linked chitosan microspheress
- Carrageenan microspheress
- Alginate microspheress
- Poly (alkyl cyanoacrylate) microspheress.

ADVANTAGES

Microspheress spread out more uniformly in the GIT, thus avoiding exposure of the mucosa locally to high concentration of drug.

- Microspheress ensure more reproducible drug absorption.
- The risk of dose dumping also seems to be considerably lower than with single unit dosage form.
- Microspheress allow the administration of much smaller doses than are normally required. This reduces local irritation when compared to single unit dosage forms.
- Drug discharge in the stomach may be hindered and local unwanted effects may be reduced or eliminated.
- Microspheress posses many other advantages such as high bioavailability, rapid kinetic of absorption and improvement of patient compliance.
- Microspheress received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour.[13,14]

LIMITATION

Some of the disadvantages were found to be as Follows-

1. The modified release from the formulations.
2. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
3. Differences in the release rate from one dose to another.
4. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
5. Dosage forms of this kind should not be crushed or chewed.[15]

APPLICATIONS

1. Microspheres in vaccine delivery - An ideal vaccine must fulfill the requirement of efficacy, safety, convenience in application and cost. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome 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

2. Targeting using microparticulate carriers

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

3. Monoclonal antibodies mediated microspheres targeting

Monoclonal antibodies targeting microspheres are immune microspheres. This targeting is method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. Mabs can be directly attached to the microspheres by means of covalent coupling. The Mabs can be attached to microspheres by any of the following methods

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

4. Chemoembolisation

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

5. Imaging

The particle size range of microspheres is an important factor in determining the imaging of particular sites using radio labbled microspheres. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintiographic imaging of the tumour masses in lungs using labeled human serum albumin microspheres.

6. Topical porous microspheres

Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5-300µm. These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system.[16]

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, ricin toxoid, 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 marrow purging.
- Used in isolation of antibodies, cell separation and toxin extraction by affinity chromatography.
- Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.[17]

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, interactivity treatment.
- Imaging of liver, spleen, bone marrow, lung and even imaging of thrombus in deep vein thrombosis can be done.[18]

METHODS OF PREPARATION[19]

The choice of the technique mainly depends on the nature of the polymer used, the drug, the intended use, and the duration of therapy. Moreover, the method of preparation and its choice are equivocally determined by some formulation and technology related factors as mentioned below:

1. Single emulsion technique

The micro particulate carriers of natural polymers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, di acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation.

2. Double emulsion technique (Multiple emulsion)

Double emulsion method of microsphere preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w (Fig.1) and is best suited to the water-soluble drugs, peptides, proteins and the vaccines. This method can be usedwith both the natural as well as the synthetic polymers. A number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonist, vaccines, protein/peptidesand conventional molecules are successfully incorporated in to the microspheres using the method of double emulsion solvent evaporation/extraction.

3. Polymerization techniques

The polymerization techniques conventionally used for the preparation ofthe microspheress are mainly classified as:

I. Normal polymerization

II. Interfacial polymerization.

Both are carried out in liquid phase.

3.1. Normal polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheress. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers.

3.2. Interfacial polymerization

Interfacial polymerization essentially precedes involving reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. The monomers present in either phases diffuse rapidly and polymerize rapidly at the interface. Monomer droplet, the formed carrier is of capsular (reservoir) type**.** The interfacial polymerization is not widely used in the preparation of the microspheress because of toxicity associated with the unreacted monomer, high permeability of the film, high degradation of the drug during the polymerization, fragility of microcapsules, non-biodegradability of the microspheress.

5. Spray drying

These methods are based on the drying of the mist of the polymer and drug in the air. congealing respectively. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high- speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheress in a size range 1-100 μm.

Microspheress are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by n vacuum drying. One of the major advantages of the process is feasibility of operation under aseptic conditions. The spray drying process is

used to encapsulatevarious penicillins. Thiamine mononitrate and sulpha ethylthiadizole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous microspheress.

6. Non-aqueous solvent evaporation method

In these methods the polymer is dissolved in an organic solvent such as dichloromethane, chloroform, alcohol or ethyl acetate, either alone or in combination. The drug is either dissolved or dispersed into the polymer solution and this solution containing the drug is emulsified in to a aqueous phase to make oil in water emulsion by using a surfactant or an emulsifying agent. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature or by continuous stirring. Solvent evaporation for preparation of embryonic microspheres under pressure or by continuous stirring, determines the size and morphology of the microspheres. It had been reported that the rapid removal of the solvent from the embryonic microspheres leads to the precipitation at the o/w interface. This leads to the formulation of cavity in the microspheres, making them hollow 15

7. Melt dispersion technique (Congealable disperse phase encapsulation procedures)

In this technique, the drug is dissolved/ dispersed in the molten lipid/wax like bees wax, spermaceti wax, castor wax, carnauba wax under continuous stirring to form a homogeneous blend. During the emulsion step of microsphere preparation the temperature is maintained at about 10 0C above the melting point of lipid/wax. A dispersant solution, previously heated to 5 0C above the lipid/wax melting point, is added to the melt with constant stirring to form an o/w emulsion. Hardening of the oily internal phase (containing lipoid/wax and drug) and formation of microspheres is accomplished by pouring twice the emulsion volume of ice-cold water into the emulsion.

PHYSICOCHEMICAL EVALUATION

Characterization

The characterization of the microparticulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier.[20]

Particle size and shape

The most widely used procedures to visualize microparticles are conventional light microscopy (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 be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of themicrospheres surfaces and after particles are cross-sectioned.[21]

Electron spectroscopy for chemical analysis

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

Attenuated total reflectance Fourier Transform Infrared Spectroscopy

FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The ATRFTIR provides information about the surface composition of the microspheres depending 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 is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of the microsphere carrier is determined.

Isoelectric point

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

Surface carboxylic acid residue

The surface carboxylic acid residue is measured by using radioactive glycine. The radioactive glycine conjugates is prepared by the reaction of C14-glycine ethyl ester hydro chloride with the microspheres. The radioactivity of the conjugate is then measured using liquid scintillation 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 C14-acetic acid conjugate. The carboxylic acid residue is measured through the liquid scintillation counter and hence the amino acid residue can be determined indirectly.

Capture efficiency

The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed

microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated 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 particulate carrier. 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 vitro drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physic-chemically and hydro dynamically defined conditions are necessary, however no standard *in vitro* method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed.[22]

- **Beaker method**

The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using over head stirrer. Volume of the medium used in the literature 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 four compartments. A represents the oral cavity, and initially contained an appropriate concentration of drug in a buffer. The compartment B representing the buccal membrane, contained 1-octanol, and compartment C representing body fluids, contained 0.2 M HCL. The compartment D representing protein binding also contained 1-octanol. Before use, the aqueous phase and 1-octanol were saturated with each other. Samples were withdrawn and returned to compartment A with a syringe.[23]

- **Modified Keshary Chien Cell**

A specialized apparatus was designed in the laboratory. It comprised of a Keshary Chien cell containing distilled water (50ml) at 370 C as dissolution medium. TMDDS (Trans Membrane Drug Delivery System) was placed in a glass tube fitted with a 10# sieve at the bottom which reciprocated in the medium at 30 strokes per min.[24]

- **Dissolution apparatus**

Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using rotating elements, paddle and basket. Dissolution medium used for the study varied from 100- 500 ml and speed of rotation from 50-100 rpm.[25]

- ***In vivo* methods**

Methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrate at the surface. The most widely used methods include *in vivo* studies using animal models, buccal absorption tests, and perfusion chambers for studying drug permeability.

- **Animal models**

Animal models are used mainly for the screening of the series of compounds, investigating the 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 been reported. In general, the procedure involves anesthetizing the animal followed by administration of the dosage form. In case of rats, the oesophagus is ligated to prevent absorption pathways other than oral mucosa. At different time intervals, the blood is withdrawn analyzed.[26]

- **Buccal absorption test**

The buccal absorption test was developed by Beckett & Triggs in 1967. It is a simple and reliable method for measuring the extent of drug loss of the human oral cavity for single and multi component mixtures of drugs. The test has been successfully used to investigate the relative importance of drug structure, contact time, initial drug concentration and Ph of the solution while the drug is held in the oral cavity.[27]

- ***In vitro-In vivo* correlations**

Correlations between in vitro dissolution rates and the rate and extent of availability as determined by blood concentration and or urinary excretion of drug or metabolites are referred to as "*in vitro-in vivo* correlations". Such correlations allow one to develop product specifications 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 of the drug released from different dosage forms and also to estimate the peak plasma concentrations 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 absorbed completely after dissolution, a linear correlation may be obtained by comparing the percent of the drug absorbed to the percent of the drug dissolved. If the rate limiting step in the bioavailability of the drug is the rate of absorption of the drug, a change in the dissolution rate may not be reflected in a change in the rate and the extent of drug absorption from the dosage form.

Dissolution Rate Vs Absorption Rate

The absorption rate is usually more difficult to determine than the absorption time. Since the absorption rate and absorption time of a drug are inversely correlated, the absorption time may be used in correlating the dissolution data to the absorption data. In the analysis of in vitro and in vivo drug correlation, rapid drug absorption may be distinguished from the slower drug absorption by observation of the absorption time for the dosage form. The quicker the absorption of the drug the less is the absorption time required for the absorption of the certain amount of the drug. The time required for the absorption of the same amount of drug 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 be established between the percent of drug dissolved at specified times and the serum drug concentrations 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 drug excreted in the urine. Therefore, a linear relation may be established between the percent of the drug dissolved and the percent of the dose excreted in the urine.

CONCLUSION

The present review article shows that microspheres are better choice of drug delivery system than many other types of drug delivery system. In future by combining various other strategies, 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 diseased organ and tissues in the body.[28]

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