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Review on Novel Drug Delivery System of Microsphere: Type, Material, Method of Preparation and Evaluation

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ABSTRACT

The Non ideal pharmaceutical, pharmacokinetic, and therapeutic properties often combine to reduce the effectiveness of certain compounds. For the vectoring of such compounds to target areas, liposomes, nanoparticles, and microspheres have been suggested. Microsphere are spherical in shape so, therapeutic efficacy of microspheres containing drug depends upon their characteristics that can be altered in required terms by altering materials, , methods, polymers or techniques of microsphere.

Microspheres are characteristically free flowing powders having particle size ranging from 1-1000 µm consisting of natural or synthetic polymers. Microspheres are used in drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and action at the specific site to predetermined rate.

Microsphere can be manufactured by various type of material natural, and synthetic in microsphere. Microspheres are various types like Bioadhesive microspheres, Magnetic microspheres, Floating microspheres, radioactive microspheres, Polymeric microspheres, Biodegradable polymeric microspheres, Synthetic polymeric microspheres. microspheres and are prepared by methods like Spray Drying, Solvent Evaporation, Single emulsion technique, Double emulsion technique, Phase separation coacervation technique, Spray drying and spray congealing, Solvent extraction, Quassi emulsion solvent diffusion. Microspheres have wide range of applications and their evaluation parameter.

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INTRODUCTION

A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug.

To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects [1]

There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs.

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]

ADVANTAGES OF MICROSPHERES [3,4,5,6]

1. They provide protection before after administration for unstable drug.
2. They reduced concentration of drug at site other than the tissue or the target organ.
3. Decrease dose and toxicity.
4. Particle size reduction for enhancing solubility of poorly soluble drugs.
5. Microspheres provide constant and prolonged therapeutic effect.
6. Reduces the dosing frequency and thereby improve the patient compliance.
7. They could be injected into the body due to the spherical shape and smaller size.
8. Better drug utilization will improve the bioavailability and reduce side effect.
9. Taste and odour masking.
10. Conversion of oils and other liquids to solids for easy of handling.
11. Protection of drugs against the environment (moisture, light etc.).

12. Improvement of flow of powders.
13. Aid or helps in the dispersion of water-insoluble substances in aqueous media.

Disadvantage of microsphere [7]

1. The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard 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. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents [7].

Materials

Microspheres used usually are polymers. They are classified into two types:

- Synthetic Polymers
- Natural polymers

Synthetic polymers are divided into two types.

A. Non-biodegradable polymers

Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers

B. Biodegradable polymers

Lactides, Glycolides & their co polymers, Poly alkyl cyanoacrylates, Poly anhydrides.

C. Natural polymers

Obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins:

Albumin, Gelatin, Collagen

Carbohydrates:

Agarose, Carrageenan, Chitosan,

Starch Chemically modified carbohydrates:

Poly dextran, Poly starch

TYPES OF MICROSPHERES

A. Bio adhesive 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 exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

B. 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. The different types are therapeutic magnetic microspheres and diagnostic microspheres [8,9]

1. **Therapeutic magnetic microspheres** It is used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.
2. **Diagnostic microspheres** It 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 supramagnetic iron oxides.

C. 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. More over it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.[10]

D. Radioactive microspheres

Radio immobilization therapy microspheres sized 10-30 nm is of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery sys-tem, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres.

E. Polymeric microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.

1. 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 the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release [11].

2. 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 kinds of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage [12] . as radio activity is not released from microspheres but acts from within a

radioisotope typical distance and the different kinds of radioactive microspheres' are a emitters, ß emitters, g emitters.[13]

Method of Preparation: [14,15,16]

Method of Preparation							
Spray drying	Solvent evaporation	Single Emulsion technique	Double Emulsion technique	Phase separation Coacervation technique	Spray Drying And spray congealing	Solvent extraction	Quassi Emulsion Solvent diffusion

1. Spray Drying

In Spray Drying technique, firstly the entire polymer are dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. and then the drug in the solid form is dispersed in the polymer solution with 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 microspheres in a size range 1-100µm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of this process is feasibility of operation under aseptic conditions.

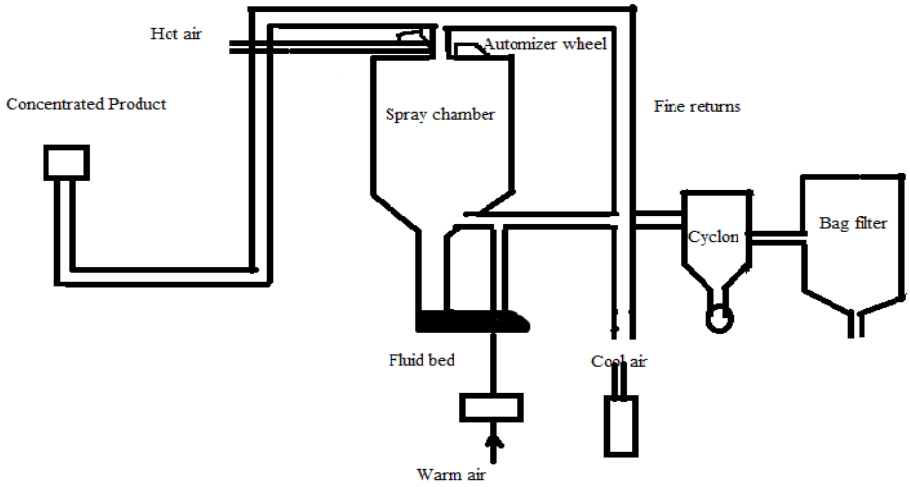

Fig.1 Spray drying technique

2. Solvent Evaporation:

This process are carried out in vehicles in this the two phases aqueous and organic phase that process called as emulsification i.e. o/w type emulsion after this the solvent evaporate and remains raw nanospheres of microspheres.

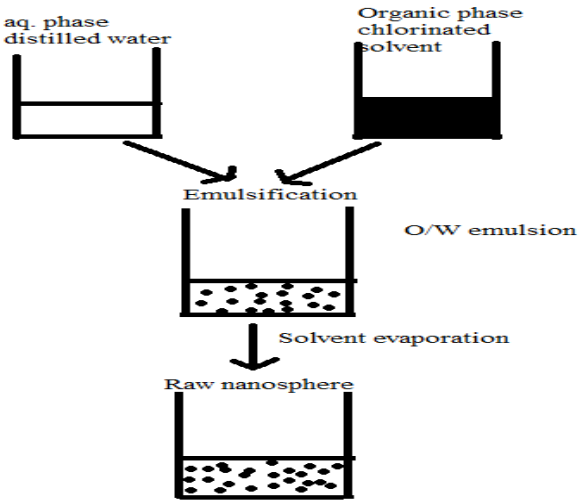

Fig. 2 Solvent evaporation

3. Single emulsion technique:

In this technique aqueous solution of polymer are dispersed in organic phase oil/chloroform with continuous stirring this process called as sonification. After this microsphere can be prepared by two ways, first heat denaturation and chemical cross linking and centrifuge the product and washing or finally separation to produce microspheres.

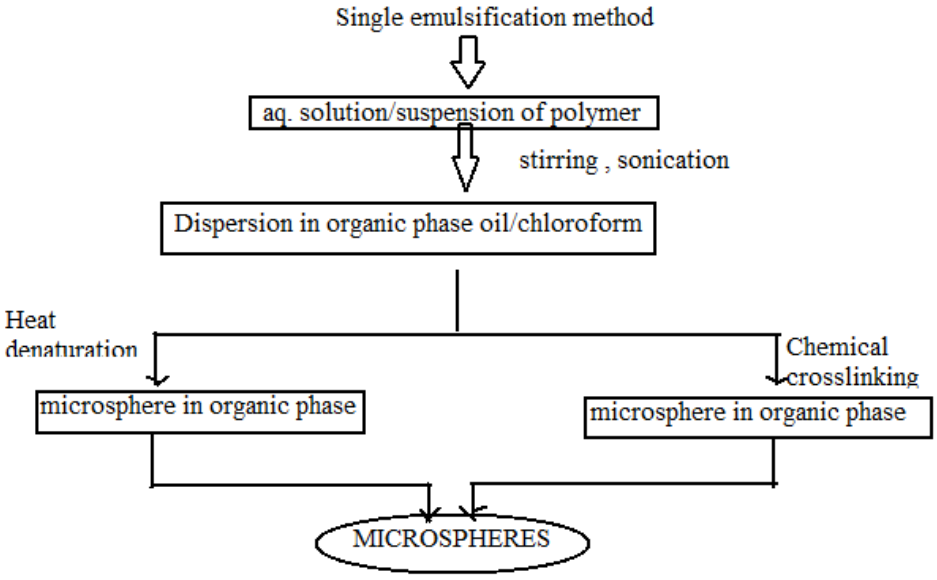

Fig.3 Single emulsion techniques

4. Double emulsion technique:

In this method aqueous solution of polymer and drug are dispersed in organic phase which produce first emulsion after addition of aq. Solution of PVA and make multi emulsion in solution separation, washing and drying to produce microspheres.

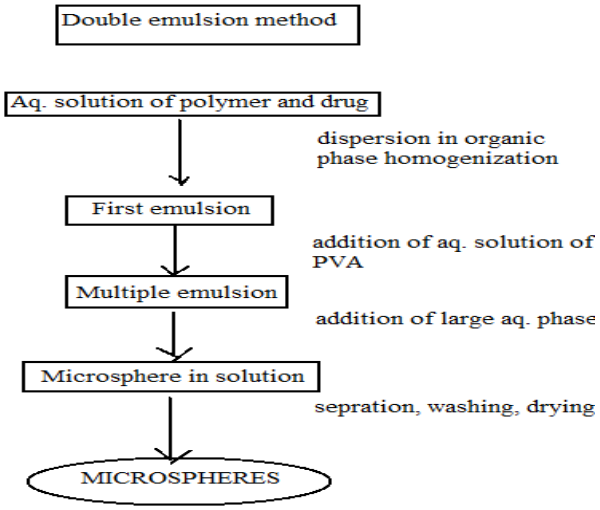

Fig.4 Double emulsion technique

5. Phase separation coacervation technique:

In this technique aqueous/organic solution of drug dissolved in polymer solution that forms polymer rich globules or droplets and Harding in aqueous/organic phase, separation, of microspheres washing and then drying to pure form of microspheres.

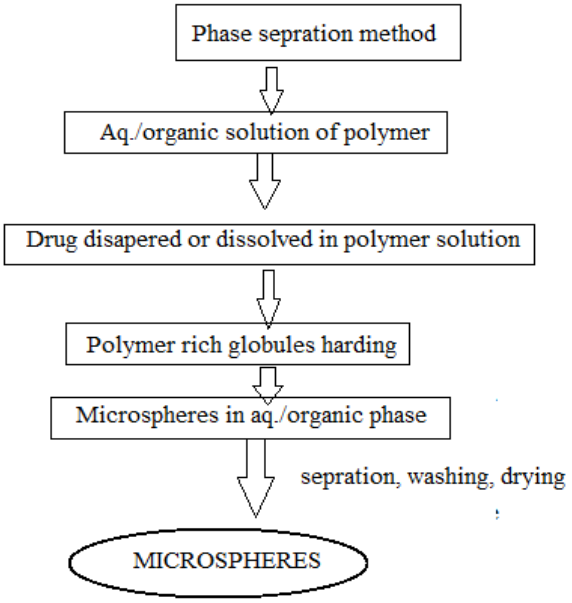

Fig. 5 Phase separation coacervation technique

6. Spray drying and spray congealing:

Polymer dissolved in suitable volatile organic solvent such as acetone, chloroform, etc. dissolved in polymer solution under high speed homogenization atomized in stream of hot air and this lead to formation of small droplets and then solidifying and form of minute particles.

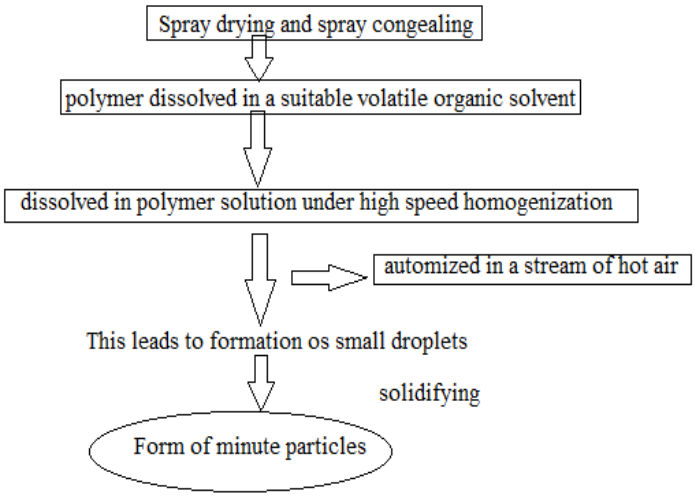

Fig.6 Spray drying and spray congealing

7. Solvent extraction:

In the solvent extraction polymer and drug must be soluble in organic solvent which forms a solution that called aq. Phase and extract this solution with water missible organic solvent to produce microsphere in aqueous media

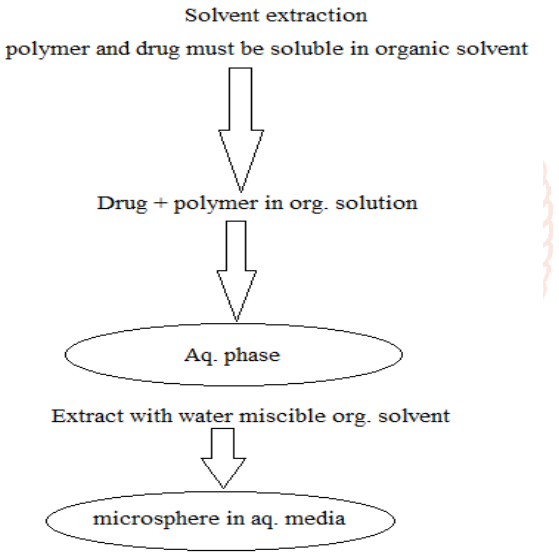

Fig.7 Solvent extraction technique

8. Quassi emulsion solvent diffusion:

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be manufactured by a quasi emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase consists of drug, ethanol and polymer. The concentration of polymer is in order to enhance plasticity. At first, the internal phase is manufactured at 60.C and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40o C.

Evaluation of microsphere:

1. **Particle size and shape**
2. The most widely used procedures to visualize micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM).
3. **Electron spectroscopy for chemical analysis:**
4. The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA)[15].
5. **Density determination:** The density of the microspheres can be measured by using a multi volume pycnometer [16].
6. **Isoelectric point:** The micro electrophoresis is used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined [17].
7. **Angle of contact:** The angle of contact is measured to determine the wetting property of a micro particulate carrier [18].

8. **In vitro methods:** Release studies for different type of microspheres are carried out by using different suitable dissolution media, mostly by rotating paddle apparatus (USP / BP) [19].
9. **Drug entrapment efficiency:** Drug entrapment efficiency can be calculated using following equation, % Entrapment = Actual content/Theoretical content x 100.
10. **Swelling index:** The swelling index of the microsphere was calculated by using the formula, Swelling index= (mass of swollen microspheres - mass of dry microspheres/mass of dried microspheres) [20].

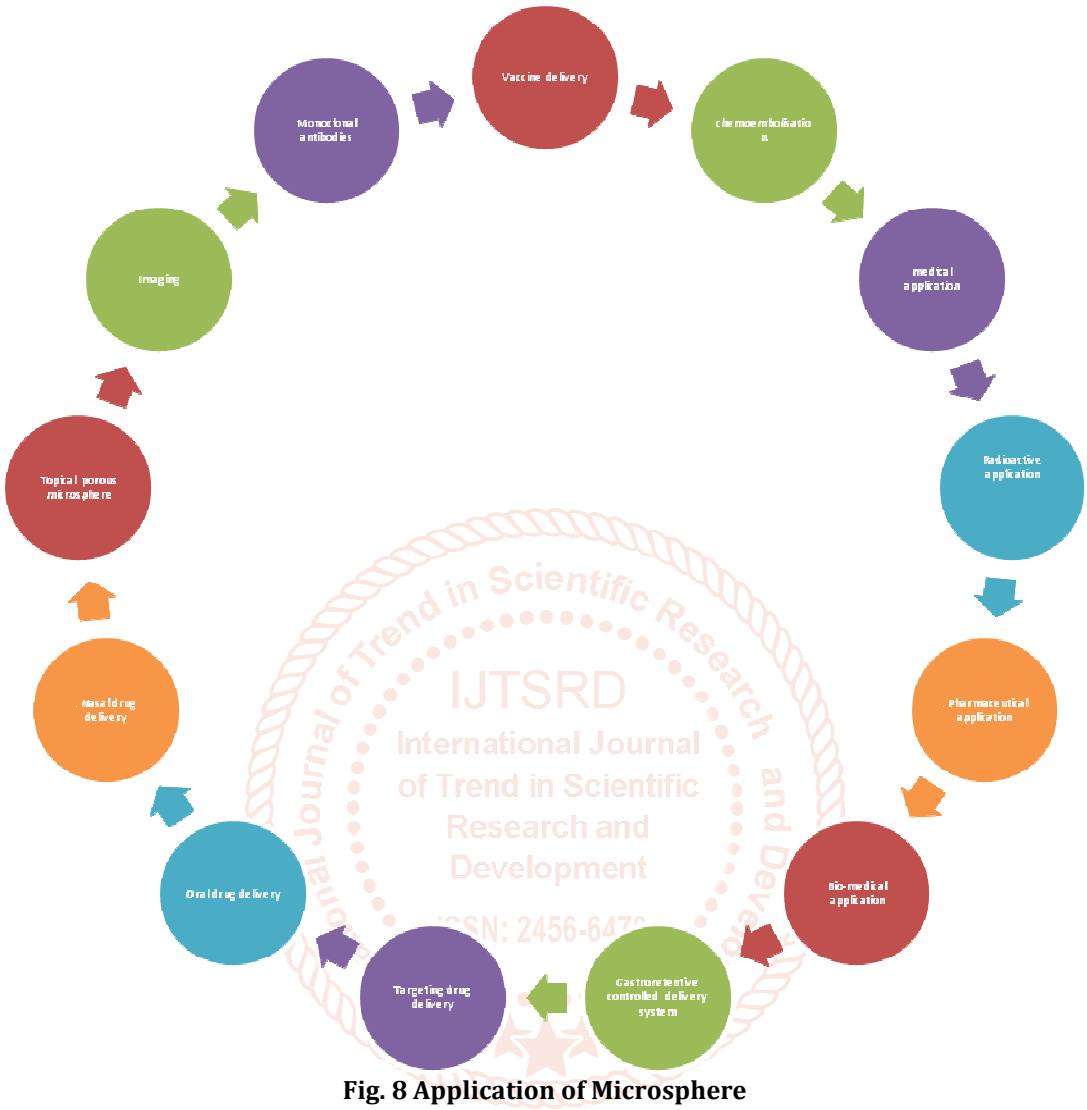

Fig. 8 Application of Microsphere

Conclusion:

Microsphere can be manufactured by various type of material such as polymers, and microspheres. Microspheres are various types like Bioadhesive microspheres, Magnetic microspheres, Floating microspheres, radioactive microspheres, Polymeric microspheres, Biodegradable polymeric microspheres, Synthetic polymeric microspheres their method of preparation, evaluation and application of microscope.

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