IJMPR 2020, 4(5), 207-214

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

MICROSPHERES AS CONTROLLED & SUSTAINED ADVANCED DRUG DELIVERY SYSTEM

Patel Parita N.[1]*, Dr. Chainesh Shah[2] and Dr. Umesh Upadhyay[3]

[1]VIIth Semester B-Pharm, Sigma Institute of Pharmacy, Bakrol, Ajwa, Vadodara - 390019 (Gujarat, India).
[2]Associate Professor, Sigma Institute of Pharmacy, Bakrol, Ajwa, Vadodara - 390019 (Gujarat, India).
[3]Principal, Sigma Institute of Pharmacy, Bakrol, Ajwa, Vadodara - 390019 (Gujarat, India).

Received on: 21/09/2020
Revised on: 11/10/2020
Accepted on: 31/10/2020

***Corresponding Author**
Patel Parita N.
VIIth Semester B-Pharm, Sigma Institute of Pharmacy, Bakrol, Ajwa, Vadodara - 390019 (Gujarat, India).

ABSTRACT

Microspheres are naturally free flowing powders having molecule size going from 1-1000 µm comprising of proteins or polymers. Commercially available in wide variety of materials, including ceramics, glass, polymer & metals. Microspheres are spherical microparticles. In general microspheres are solid or hollow & do not have fluid inside, as opposed to microcapsules. There are different methodologies in conveying remedial substance to objective site in sustained controlled delivery style. Very much planned controlled medication conveyance framework can conquer issues of show drug treatment and gives better restorative adequacy of medication. It is dependable way to convey medication to objective site with explicitness, whenever altered, and to keep up ideal fixation at site of intrigue. Besides microspheres are of micron size so they can undoubtedly find way into different hair like beds which are likewise having micron size. Microspheres got lot of consideration for delayed delivery, yet in addition for focusing of anticancer medications. There are different branches of medication like malignancy, pneumonic, cardiology, radiology, gynaecology, and oncology and so on, various medications are utilized and they are conveyed by different sorts of medication conveyance framework. Among them microspheric drug conveyance framework has increased tremendous consideration. Motivation behind audit is to gather different kinds of microspheres, various techniques to readiness, its applications and furthermore different boundaries to assess their proficiency.

KEYWORDS: Microsphere, types of microsphere, advantage, disadvantage, method of preparation, evaluation & application.

INTRODUCTION

Microspheres are spherical free flowing particles consisting of proteins or synthetic polymers which are biodegradable in nature & ideally having particle size less than 200µm. There are two type of microspheres – microcapsules & micromatrices, which are described as, Microcapsules are those in which entrapped substance is dispersed throughout matrix. Microspheres are sometimes referred to as microparticles. Microsphere can be manufactured from various natural & synthetic materials. Microspheres play important role to improve bioavailability of conventional drugs & minimizing side effects. Controlled oral drug administration does not usually provide rate controlled release or target specificity. Microparticulate (Microsphere/Microcapsule) drug delivery system are considered & accepted as reliable one to deliver drug to target site of interest without untoward effects.

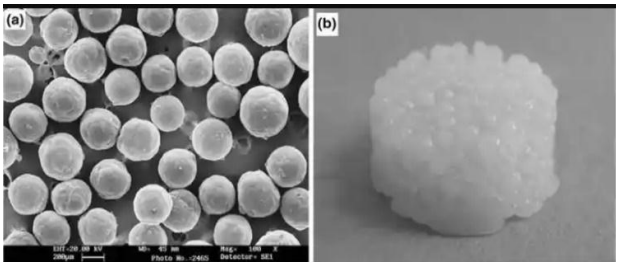

Figure 1: Microspheres.

TYPES OF MICROSPHERES

Microspheres can be manufactured from various natural & synthetic materials.

1. Glass microspheres

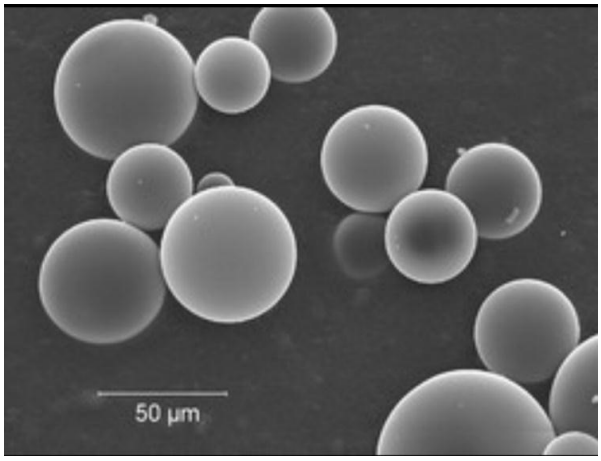

Figure 2: Glass microspheres.

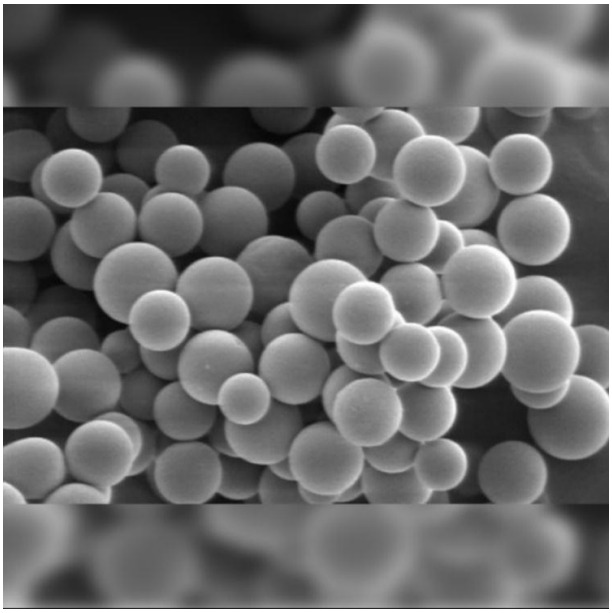

Figure 3: Hollow glass microspheres.

2. Polymer microspheres
3. Metal microspheres
4. Ceramic microspheres

Solid & hollow microspheres are typically used as additives to lower the density of a material.

TYPES OF POLYMER

Microspheres used usually are polymers.
They are classified into 2 types:

1. Synthetic Polymers
2. Natural polymers

1. Synthetic polymers are divided into two types.

(A) Non-biodegradable polymers

Examples: Poly methyl methacrylate acrolein (PMMA), Glycidyl methacrylate, Epoxy polymers

(B) Biodegradable polymers

Example: Lactides and Glycolides and their copolymers, Poly alkyl cyano acrylates, Polyanhydrides and Poly-ε-caprolactone (PCL)

2. Natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Gelatin[1], and Collagen
Carbohydrates: Agarose, Carrageenan, Chitosan, Starch
Chemically modified carbohydrates: Poly dextran, Poly starch.

The microsphere in drug industry has been considered since 1960s for their after applications:

- Masking of taste and scent.
- Delay of volatilization
- Safe if there should be occurrence of poisonous substances.
- Flow of powder is improve
- Sustained-release, controlled-release, directed drug can create
- Reduced portion unloading
- Best for inconsistent materials
- Provide security to drug against climate and so forth

Ideal microparticulate carriers

Material utilized for preparation of microspheres should have following properties.[2]

- Longer duration of action
- Provide protection of drug
- Sterilizability
- Water solubility
- Toxicity
- Water dispersability
- Relative stability
- Bioresorbability

IDEAL CHARACTRISTICS[3,4]

Ideal Characteristics of Microspheres

1. Ability to control release rate for predefined timeframe
2. Higher groupings of medication can be given fill in as warehouse.
3. Stability of planning after amalgamation with clinically satisfactory shelf life.
4. Controlled molecule size and scattering of medication in fluid dissolvable for parenteral.
5. Biocompatibility with controllable biodegradability.

ADVANTAGE

1. Constant helpful concentration for delayed timeframe.
2. Improved tolerance consistence because of decrease in dosing recurrence.
3. Ability to be infused into body in view of their spherical shape and more modest size.
4. Improved bioavailability and diminish results.
5. Controllable inconstancy in corruption and medication release.
6. Size decrease prompts increment in surface region which can upgrade solvency of inadequately dissolvable medication.
7. Provide consistent medication concentration in blood which can build patent consistence,

8. Decrease portion and poisonousness.
9. Coating of medication with polymers helps drug from enzymatic cleavage henceforth discovered to be best for drug conveyance.
10. Less dosing recurrence prompts better patient consistence.
11. Better medication use will improve bioavailability and lessen rate or force of antagonistic impacts.
12. Protects GIT from aggravation impacts of medication.
13. Convert fluid to strong structure and to cover severe taste.
14. Reliable intends to convey medication to target site with particularity, whenever adjusted, and to keep up wanted concentration at site of enthusiasm without untoward impacts.
15. Reduce reactivity of center according to outside climate.
16. Biodegradable microspheres have advantage over huge polymer embeds in that they don't need surgeries for implantation and evacuation.
17. Controlled release conveyance biodegradable microspheres are utilized to control drug release rates subsequently diminishing harmful results, and killing bother of rehashed infusions [5,6,7,8].

DISADVANTAGE

1. The expenses of materials and handling of controlled release readiness are generously higher than those of standard definitions.
2. The destiny of polymer matrix and its impact on climate.
3. The destiny of polymer added substances, for example, plasticizers, stabilizers, cancer prevention agents and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, dissolvable expansion, and dissipation/disturbance may impact soundness of core particles to be epitomized.
6. The ecological effect of debasement results of polymer matrix created in light of warmth, hydrolysis, oxidation, sun based radiation or organic operators.[3]

METHODS OF PREPARATION

Planning of microspheres ought to fulfill certain standards:

- The capacity to fuse sensibly high concentrations of medication.
- Stability of arrangement after blend with clinically adequate shelf life.
- Controlled molecule size and dispersability in watery vehicles for infusion.
- Release of dynamic reagent with great power over wide time scale.
- Biocompatibility with controllable biodegradability and
- Susceptibility to substance alteration.

The decision of method relies on nature of polymer also nature of medication and term of treatment [2]. Most significant physical substance factors that might be controlled in microsphere make are:-

- The molecule size necessity
- Molecular weight of polymer
- Polymer to sedate proportion
- No soundness issue
- Final item ought to be non-harmful.
- Total mass of medication and polymer
- Reproducibility
- Controlled molecule size and dispersability in watery vehicles for infusion
- Release of dynamic reagent with great power over wide time scale

Techniques for microsphere preparation

1. Single emulsion techniques
2. Double emulsion techniques
3. Polymerization

A. Normal polymerization

- ❖ Bulk
- ❖ Suspension
- ❖ Emulsion

B. Inter-facial polymerization

4. Phase separation coacervation technique
5. Spray drying
6. Emulsion solvent evaporation tech.
7. Solution-enhancement dispersion method
8. Wax coating Hot-melt method

1. Single emulsion technique

There are a few Proteins and sugars, which are set up by this method. In which characteristic polymers are disintegrated in watery medium and followed by scattering in oil stage for example non-fluid medium. That is initial phase in Next advance cross linking is done by 2 techniques

- Cross linking by heat: by including scattering into warmed oil, however it is inadmissible for thermolabile medications.
- Chemical cross linking operators: - by utilizing specialists for example formaldehyde, di corrosive chloride, and glutaraldehyde and so on however it is having disservice of unreasonable presentation of dynamic fixing to synthetic compounds whenever included a season of arrangement and afterward exposed to centrifugation, washing and detachment. Chitosan arrangement (in acidic corrosive) by adding to Liquid paraffin containing surfactant coming about development of w/o emulsion. Metformin hydrochloride microsphere are plan by utilizing gluteraldehyde 25% arrangement as cross linking operator.[9]

2. Double emulsion technique

It is development of numerous emulsions for example W/O/W is planning by pouring essential w/o emulsion into watery arrangement of poly vinyl liquor. This w/o/w emulsion put t steady mixing for 30 min. gradually add some water to emulsion over time of 30 min. gather

Microcapsules by filtration and dry under vacuum. It is most appropriate to water solvent medications, peptides, proteins and antibodies. Common just as engineered polymer can use for this strategy. Watery protein arrangement is scattered in lipophilic natural nonstop stage. This protein arrangement may contain dynamic constituents. Scatter in oil/natural stage homogenization/energetic for example arrangement of first emulsion then expansion to watery arrangement of PVA (Poly Vinyl Alcohol) for example different emulsion framed now by expansion to enormous watery stage denaturation/solidifying after this detachment, washings' and drying and assortment of microspheres genistein chitosan microsphere were set up by o/w/o numerous emulsion strategy by Wu and Li (2002).[10]

3. Polymerization techniques

Basically two procedures are utilizing for readiness of microsphere are named:

a) Normal polymerization

In mass polymerization, monomer or combination of number of monomers alongside initiator or impetus is typically warmed to start polymerization. Polymer so acquired might be formed as microspheres. Medication stacking might be finished by including drug during cycle of polymerization. It is unadulterated polymer development procedure however it is exceptionally hard to disperse warmth of response which influences thermo labile dynamic fixings. Suspension polymerization is completed of lower temperature and furthermore allude to as pearl polymerization in which warming monomer blend with dynamic medication as beads scattering in constant fluid stage. Microsphere size acquired by suspension procedures is less 100 µm. Emulsion polymerization is vary from suspension as due presence of initiator in watery eliminate but at the same time is conveyed at low temperature as suspension outside stage regularly water in last two strategies so through which warmth can undoubtedly disperse arrangement of higher polymer at quicker rate is conceivable by these methods however relationship of polymer with un responded monomer and different added substances can happen.[2]

b) Interfacial polymerization

It includes response of different monomers at interface between two immiscible fluid stages to shape film of polymer that basically encompasses scattered stage. In this procedure two responding monomers are utilized; one is break down in ceaseless stage while other is scatter in nonstop stage (fluid in nature) all through which second monomer is emulsified. Two conditions emerge due to solvency of framed polymer in emulsion bead. That is arrangement is solid kind of transporter if polymer is solvent in bead. Capsular sort framed if polymer is insoluble in bead.[2,9]

4. Spray drying and spray congealing

Idea of spray drying method (fig 1) contingent on expulsion of dissolvable or cooling of arrangement two cycles are spray drying and spray hardening. Dissipation is essential system in spray drying, though in spray congealing it is that of stage reversal from fluid to strong. The two cycles are comparative, aside from energy stream.[2] Spray drying is most generally utilized modern cycle including molecule development and drying. Thusly, spray drying is ideal cycle where finished result must conform to exact quality norms with respect to molecule size circulation, lingering dampness content, mass thickness, and molecule shape.

Principle:[11-13] Three stages associated with spray drying

1. Atomization: of fluid feed change into fine beads.
2. Mixing: it includes passing of hot gas stream through spray beads which bring about dissipation of fluids and abandoning dried particles.
3. Dry: Dried powder is isolated from gas stream and gathered.

In this method polymer is first disintegrated in appropriate unstable natural dissolvable, for example, dichloromethane, $(CH_3)_2CO$, and so on drug in strong structure is then scattered in polymer arrangement under rapid homogenization. This scattering is then atomized in stream of hot air, this structure little beads or fine fog, from which dissolvable vanishes quickly driving development of microspheres. Size reach is 1-100 µm. By utilizing hot air separate of Microparticle by methods for typhoon separator while hints of dissolvable are eliminated by vacuum drying. Favourable circumstances of cycle are practicality of activity. This strategy is exceptionally helpful to embody different penicillin's. Thiamine mononitrate and sulpha ethylthiadizole are embodied in combination of mono-and diglycerides of stearic corrosive and palmitic corrosive utilizing spray hardening. Exceptionally fast dissolvable vanishing, anyway prompts development of permeable microparticles.[2]

The sprays are creates by either revolving (wheel) or spout atomizers. Dissipation of dampness from beads and development of dry particles continue under controlled temperature and wind stream conditions.

The microsphere size is controlled by pace of spraying, spout size, temperature (in drying and gathering chambers.) and feed pace of polymer drug arrangement. Nature of item is improved by expansion plasticizer spray stream rate should kept steady around 6ml/min.[14]

Spray drying strategy is likewise helpful for planning chitosan microsphere[10], In 1999 He et.al. Utilized formaldehyde as crosslinking and furthermore detailed novel technique in which cimetidine and famotidine were ensnared in microspheres arranged by spray drying of numerous emulsion (o/w/o or w/o/w). They found that release of medications from microspheres by this novel technique was altogether sustained when contrasted with those readied by traditional spray drying or o/w emulsion strategy. In 1994 Giunchedi et al. was utilized spray

drying utilized for arrangement of PCL microspheres of ketoprofen.[14] He utilized natural arrangement of medication and two polymers, cellulose acetic acid derivation butyrate and PCL was made in combination of dichloromethane and chloroform (1:1). Arranged arrangement was sprayed through spout in spray drier under various exploratory conditions. Strong microspheres were gathered into definite base vessel spray drier.[15]

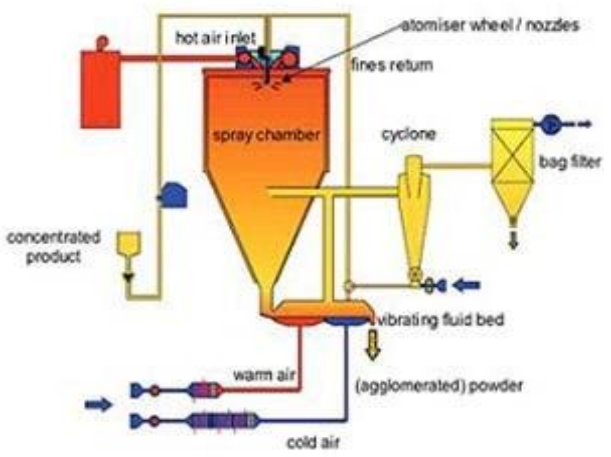

Figure 4: Spray drying method for preparation of microspheres.

Advantages and disadvantages

Spray drying is very useful for pulmonary drug delivery as well as for oral dosages form and it is remarkable versatility of technology, and wide range of product can be obtained by this technique. It is very flexible and reproducible method that, why number of industries use this technique for drying operation. It can be designed to virtually any capacity required easily. Can be used with both heat-resistant and heat sensitive products. Powder quality remains constant during dryer. Particles which produced uniform in size and frequently hollow thus reduce bulk density of product. But there are some drawbacks in technique; equipment is very bulky and expensive. Overall thermal efficiency is low, as large volumes of heated air pass through chamber without contacting particle.[11,16]

5. Wax Coating and Hot Melt

In this method polymer is scatter in appropriate scattering medium and gradually cooled to frame microspheres. Polymers which having low liquefying point manufactured into microspheres by this strategy without any problem.[14] For coating and coring of molecule wax is use generally. In which exemplify drug by scattering in shed wax. Wax suspension is scattered by rapid blending into cold answer for instance fluid paraffin. Unsettle blend for 60 minutes. At that point emptied outside stage and suspended microspheres gather from dissolvable. Also, permit drying it in air. It is economic strategy as correlation with others and medication release is quicker. Generally Carnauba wax and beeswax can be utilized as coating materials and these can be blended so as to accomplish wanted attributes.[17]

6. Emulsion Solvent Evaporation Technique:

In this strategy drug is broken down in polymer which was recently disintegrated in chloroform and coming about arrangement is added to watery stage containing 0 .2 % sodium of PVP as emulsifying operator. Above blend was fomented at 500 rpm at that point medication and polymer (eudragit) was changed into fine bead which set into inflexible microspheres by dissolvable vanishing and afterward gathered by filtration and washed with demineralised water and dried up at room temperature for 24 hrs.[18]

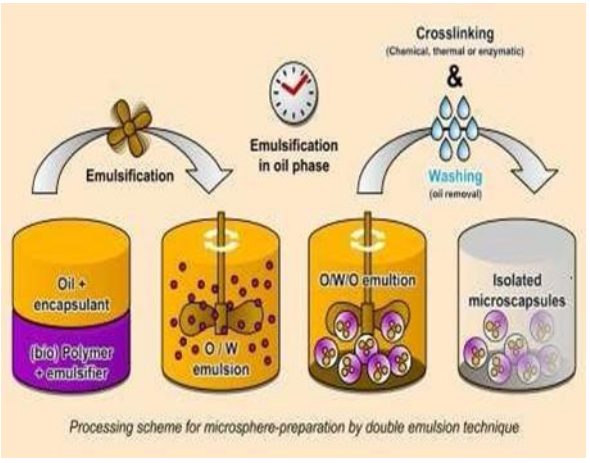

Figure 5: Microspheres by Double Emulsion Technique.

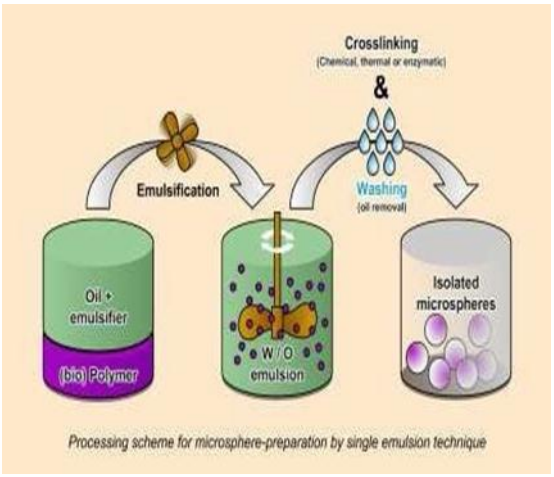

Figure 6: Microspheres by Single Emulsion Technique.

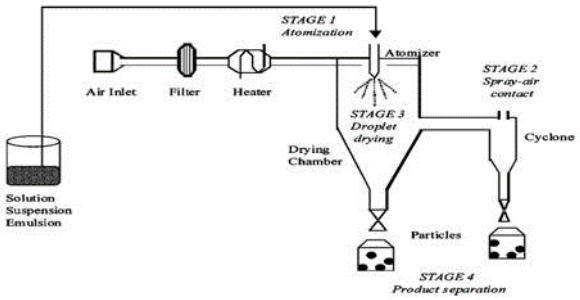

Figure 7: Microspheres by Spraying Drying Technique.

7. Phase separation coacervation technique

It is straightforward separation of micromolecular arrangement into two immiscible fluid phase. In this cycle, polymer is solubilized to for arrangement. This cycle is intended for getting ready store type framework for example exemplify water solvent medications for example peptides, proteins and so forth [2]. Guideline of coacervation is diminishing solvency of polymer in natural phase to influence arrangement of polymer rich phase called coacervates. In this technique, arrangement of scattering of medication particles in arrangement of polymer and contradictory polymer is added to framework which makes first polymer to phase isolate and immerse drug particles. Matrix types arrangements can likewise be set up by this cycle for hydrophilic medication for example steroids, Addition of non-dissolvable outcomes in cementing of polymer. Poly lactic corrosive (PLA) microspheres have been set up by this strategy by utilizing butadiene as inconsistent polymer.

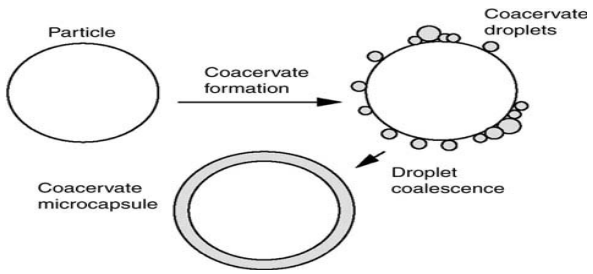

Figure 8: Schematic diagram of formation of coacervate around core material.

Be that as it may, this strategy isn't reasonable for natural solvents and glutaraldehyde which are harmful in nature. Berthold et al. (1996a) arranged prednisolone sodium phosphate stacked chitosan microspheres utilizing sodium sulphate as precipitant. Expansion of sodium sulphate to arrangement of chitosan in acidic corrosive brought about diminished dissolvability of chitosan, prompting precipitation of chitosan as ineffectively solvent subsidiary.[19]

8. Solvent extraction

In this strategy readiness of microparticles, includes evacuation of natural phase by extraction of natural solvent. Isopropanol can be utilized as water miscible natural solvents. By extraction with water, Organic phase is eliminated. Solidifying season of microsphere can be decline by this technique. One variety of cycle includes direct expansion of medication or protein to polymer natural arrangement. Pace of solvent evacuation by extraction technique relies upon temperature of water, proportion of emulsion volume to water and dissolvability profile of polymer.[2,20]

9. Emulsification method

Multiple emulsions may also be formed[21] for instance; warmed watery medication arrangement can be scattered in liquid wax to shape water-in-oil emulsion, which is emulsified in warmed outer fluid phase to frame water-in-oil-in-water emulsion. Framework is cooled and microcapsules gathered. For profoundly fluid dissolvable medications, non - aqueous phase can be utilized to forestall loss of medication to outside phase. Another option is to quickly diminish temperature when essential emulsion is set in outside watery phase.

Evaluation of Microspheres

1. Particle size & shape

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) & scanning electron microscopy (SEM).

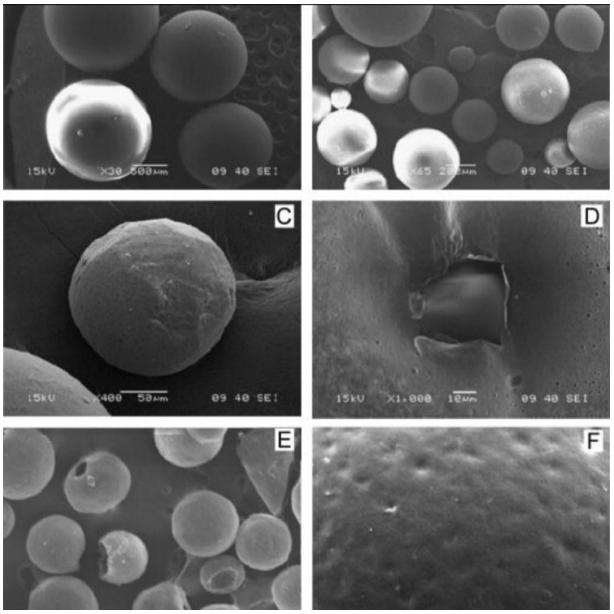

Figure 9: Scanning Electron Microscopy(SEM) of solid microspheres.

2. Particle size analyzer

Microsphere (50 mg) was suspended in distilled water (5mL) to prevent microsphere aggregation, above suspension is sonicated in water bath and particle size was expressed as volume mean diameter in micrometre.

3. Optical microscopy

This method was used to determine particle size by using optical microscope (Meizer OPTIK) measurement was done under 450x (10x eye piece and 45x objective) and100 particles were calculated.

4. Degradation behavior
The surface chemistry of microspheres can be determined using electron spectroscopy for chemical analysis (ESCA).

5. Angle of repose
The powder mass was allowed to flow through funnel orifice kept vertically to plain paper kept on horizontal surface, giving heap angle of powder on paper. Angle of repose was calculated by following equation.
tan θ = h/r
Where h & r are height band radius of powder cone.

6. Bulk density
Bulk density was obtained by dividing mass of powder by bulk volume in cm^3. It was calculated by using equation.

Bulk density = mass of microspheres / bulk volume

7. Tapped density
It is ratio of total mass of powder to tapped volume of powder. It is expressed in g/ml and is given by

Tapped density = mass of microspheres/Tapped volume

8. Drug entrapment efficiency
It is percentage of drug that is successfully entrapped with in microspheres. Drug entrapment efficiency can be calculated using following equation,

%Entrapment = Actual content / Theoretical content x 100

9. Swelling index
It is conducted in phosphate buffer of pH 6.8. Their diameter is measured periodically by using laser particle size distribution analyser until they were decreased by erosion & dissolution.

Swelling index = (mass of swollen microspheres – mass of dry microspheres/mass of dried microspheres) 100

10. In vitro methods
Release studies for different type of microspheres are carried out by using phosphate buffer pH 7.4, mostly by rotating paddle apparatus. Agitated with 100 rpm, samples were collected at specific time intervals & replaced by same amount & analysed.

11. Adhesion property
Freshly cut piece of pig intestine is used, clean and wash it with isotonic saline solution. Accurate weight of microspheres was placed on mucosal surface, phosphate buffer of pH 6.8 is warmed at 37~c was peristaltically pumped at rate of 5 ml/min over tissue. Duration of complete washing of microspheres from pig intestine was recorded.

Pharmaceutical Application
a. Vaccine delivery
b. Monoclonal antibodies
c. Imaging
d. Topical porous microsphere
e. Nasal drug delivery
f. Oral drug delivery
g. Targeting drug delivery
h. Gastro retentive controlled delivery system
i. Bio-medical application
j. Pharmaceutical application

Future Challenges
Future challenges of microspheres look brilliant especially in region of restorative field on account of its wide range of utilization in atomic science, e.g.: microsphere based genotyping stage is utilized to identify six single nucleotide polymorphism, yittrium-90 microspheres is utilized to forestall tumour after liver transplantation and it's serious path in conveyance of antibodies and proteins.

This statement is signed by all the authors to indicate agreement that the above information is true and correct.

Author's name (typed)	Author's signature	Date
Parita Patel	Parita Patel	27/10/2020
Dr. Chainesh Shah	Chainesh Shah	27/10/2020
Dr. Umesh Upadhyay	Umesh Upadhyay	27/10/2020

CONCULSION

It has been seen that microspheres are better decision of medication delivery framework since it is having preferred position of target explicitness and better patient consistence. Number of techniques have been concocted to plan microspheres of wanted size shape and surface. Contrast with other Novel medication conveyance framework, Microspheres have better decision for drug conveyance framework, especially in sick cell arranging, symptomatic of quality, directed and successful in-vivo conveyance. So in include; microspheres will have significant task to carry out in headway of clinical field.

Conflicts of Interest Statement

Manuscript title: Microspheres as controlled & sustained advanced drug delivery system.

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing

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Author names
Parita Patel - VIIth Semester B-Pharm, Sigma Institute of Pharmacy, Bakrol, Ajwa, Vadodara – 390019 (Gujarat, India).

Dr. Chainesh Shah - Associate Professor, Sigma Institute of Pharmacy, Bakrol, Ajwa, Vadodara - 390019 (Gujarat, India).

Dr. Umesh Upadhyay - Principal, Sigma Institute of Pharmacy, Bakrol, Ajwa, Vadodara - 390019 (Gujarat, India).

The authors whose names are listed immediately below report the following details of affiliation or involvement in an organization or entity with a financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Please specify the nature of the conflict on a separate sheet of paper if the space below is inadequate.

Author names
Parita Patel - VIIth Semester B-Pharm, Sigma Institute of Pharmacy, Bakrol, Ajwa, Vadodara - 390019 (Gujarat, India).

Dr. Chainesh Shah - Associate Professor, Sigma Institute of Pharmacy, Bakrol, Ajwa, Vadodara - 390019 (Gujarat, India).

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