A Comprehensive Review on Microencapsulation Technology

BEENA KUMARI*

Assistant Professor (Pharmaceutics)

IGU, Meerpur, Rewari

HARI KISHAN

Student

IGU, Meerpur, Rewari

JITESH YADAV

Student

IGU, Meerpur, Rewari

ABSTRACT

Microencapsulation is a technology that has shown significant promise in bio therapeutics and other applications. Microencapsulation can be used to achieve a number of objectives. Some goals of microencapsulation include material structuration, protection of the enclosed product, and controlled release of the encapsulated contents. It has been proven useful in the immobilization of drugs, bacterial cells and other biopharmaceutics molecules, as it can provide material structuration, protection of the enclosed product, and controlled release of the encapsulated contents, all of which can ensure efficient and safe therapeutic effects. This paper is a comprehensive review of microencapsulation and its latest developments in the field. It provides a comprehensive overview of the technology and primary goals of microencapsulation and discusses various processes and techniques involved in microencapsulation including

physical, chemical, physicochemical, and other methods involved. It also summarizes various characterization methods of microcapsules and applications of microencapsulation.

Keywords: Microencapsulation, coating material, techniques, applications.

INTRODUCTION

Microencapsulation is a process in which microscopic particles are enclosed in thin coatings of wall material around the particle that may be solids, liquids or even gases.[1,2]

Some of the problems of conventional therapy can be overcome by a well-designed controlled drug delivery system and improve the therapeutic efficacy of a given drug. It becomes necessary to obtain highest therapeutic efficacy deliver the agent to the target tissue in the precise period of time in the optimal amount thereby causing minute toxicity and least side effects. To deliver a therapeutic substance to the target site there are various approaches in a sustained controlled release technique. Microspheres is one such approach is using as carriers for drugs. The proteins or synthetic polymers are free flowing powders which are characteristically microspheres which are biodegradable in nature and ideally having particle size less than 200 μm. In microencapsulation process a continuous film of polymeric material is used by which very tiny droplets or globules or particles of liquid or solid material are surrounded or coated. Microencapsulation includes Bio encapsulation in which biologically active substance is more restricted to the entrapment (from DNA to entire cell or group of cells for example) generally to improve its performance &/or increase its shelf life.[3,4]

Advantages[5-11]

- Not for only controlled release but also for targeting of anticancer drugs to the tumor microcapsules received much attention.

- The microcapsules have demonstrated their potential in targeting drugs to pathogens residing intracellularly by studies on macrophage uptake.
- Microencapsulation have property in enzyme immobilization and microorganism.
- In flavour development and to accelerate ripening enzymes encapsulated in cheeses.
- To improve stability of starter cultures the microorganism encapsulation has been used.
- It is use to enhance flow ability as well as solubility, control hygroscopy, develop texture, processing and less wastage.
- Microcapsulation help to deliver the drug to the target site with specificity.
- Microencapsulation help to protection of drug from u.v, heat, oxidation, acids, or bases.
- Microcapsulation have important in calculating the fate of particle (like size, surface charge, hydrophilicity) in vivo.
- Masking the taste or odours of unpleasant drug.
- For the controlled release of drug, solid biodegradable microcapsules have potential throughout the particle matrix.
- It helps to Improve shelf life property of drug.

Disadvantages of Microspheres[12]

- Reproducibility is less.
- High cost.
- Use to reduce the volatility of drugs.
- In case of toxicity and poisoning recovery of drug is difficult.
- Multiple formulation steps.
- Proportionally higher need for excipients.

- The modified release from the formulations.
- The fate of polymer additives such as plasticizers, stabilizers, antioxidants & fillers.

Rationale for Microencapsulation[13]

- To achieve the prolonged or sustained release of the drug.
- It improves patient compliance to mask the organoleptic properties of many drugs.
- It can be convert the liquid drugs into a free flowing powder.
- Hygroscopic, photosensitive and oxidative drugs can be protected by microencapsulation.
- This technique is also useful to prevent the incompatibility between drugs.
- Microencapsulation technique is useful to prevent the drugs, which are volatile in nature and vaporize at room temperature.
- By microencapsulation technique we can achieve reduction in toxicity and GI irritation.
- Those drug which have the toxicity at lower pH microencapsulation can change their site of absorption.
- Microencapsulation enhance the stability of vitamin A palmitate, as prevents from oxidation.

DIFFERENT TECHNIQUES OF MICROENCAPSULATION

Air Suspension Method

In this method coating material are spraying in the air and dispersion of core material to suspending particles in the air stream within the coating chamber moving air suspend the particles as shown in fig 1.

The coating chamber is designed in a particular way that affect the flow of particle through coating zone of chamber, where moving particles are coated by polymer solution.[10] Depending

upon the required thickness on the core material this cyclic process is repeated several times. The encapsulated product is air dried. Drying rate is directly proportional to temperature. Melting point, solubility, surface area, density, application rate of coating material are various process variable which affect the encapsulation.[14]

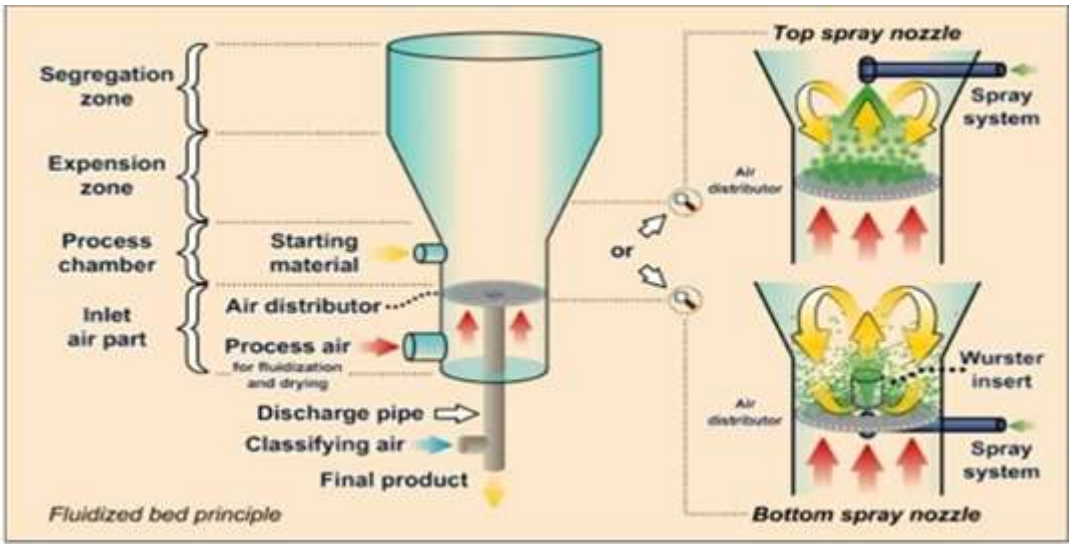


Fig 1: Air suspension method

Coacervation Method

This method involved the core material is dispersed in the solution of coating material. The coating material cannot dissolve or react by core material. The particle size rely upon dispersion parameters such as stirrer shape, viscosity, stirrer speed, surface tension. Particle size ranges between 2µm- 1200µm.[15]

Coacervation Phase Separation

This technique involves three steps as explained in fig 2:

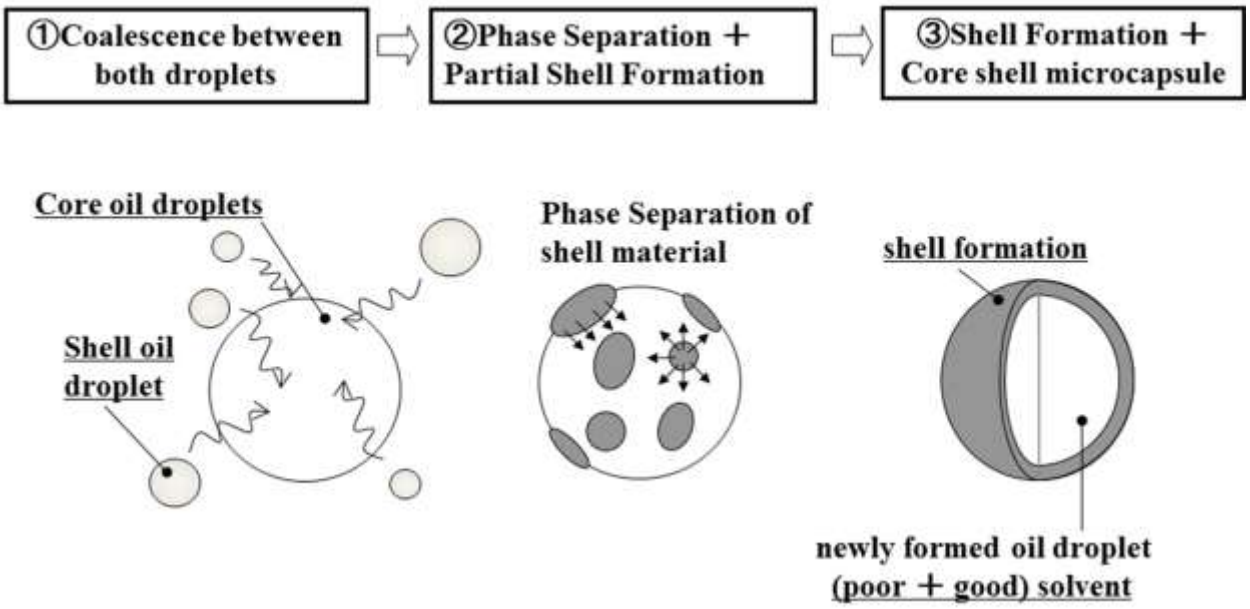


Fig 2: Coacervation phase separation method

Formation of Three Immiscible Phases

Three phases involves liquid solvent phase, core material phase, coating material phase. In this, in the solution of coating polymer the core material is disperse.[15] By one of the methods of phase separation-coacervation the microcapsules are formed i.e by incompatible polymer addition or by polymer-polymer interaction (complex coacervation), change in the temperature of polymer solution or addition of salt, non solvent addition.[16,17]

Deposition of the Coating

In second step, by controlled mixing of coating material and core material in solvent the depositing of the liquid polymer on the core material is obtained.[18] Coating polymer is deposited on the core material When interface formed between the core material and liquid phase/solvent polymer. By deduction in total free energy of system, deposition of coating material is promoted.[14]

Rigidization of Coating

In this step rigidization of coating done by thermal, cross linking or dissolvation techniques, to form a microcapsule. Different type of formulations can be prepared by using coacervation method.[19]

Centrifugal Extrusion

Liquids can be encapsulated, by using rotating extrusion head consist of concentric nozzels. In this method, sheath of wall solution is used for covering of a jet core. As jet goes through the air it breaks, owing to rayleigh instability, into the droplets of core, each one coated with the wall solution as shown in fig 3. The mean diameter of droplets is within 10% range, they come in a narrow ring. 400-2000 micrometer diameter particles are well efficiently formed by this process. Only liquid or slurry are suitably prepared by this process. Microcapsules can be produced at high production rate upto 22.5kg (50lb) by per nozzel per hour per head By using centrifugal extrusion different formulations are prepared.[20]

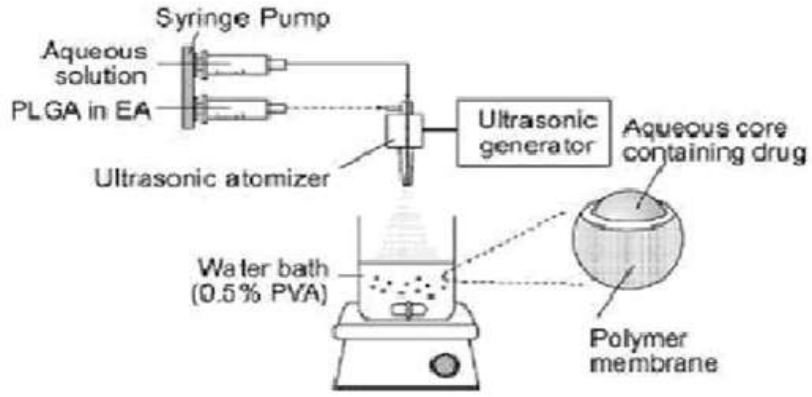


Fig 3: Centrifugal Extrusion Process

Spray Drying and Spray Congealing

These processes are similar in that both involve the liquefied coating substance in which the core material is dispersed and introducing or spraying into core coating mixture, whereby rapid solidification of coating is affected. The basic difference in these two methods is the process through which coating is solidify. In case of spray drying the coating solidification affected by rapid evaporation of solvent in which coating material is dissolved whereas in case of spray congealing method the coating solidification is accomplished by thermally congealing a molten coating material or by introducing the core material into a non solvent as shown in fig 4. Removal of non solvent or solvent from the coated product can be done by sorption extraction or evaporation techniques. Flavors, lipids and cartenoids are the few examples of food ingredients which can be microencapsulated by spray drying. At present researches focused on gums, proteins as well as carbohydrates but a single encapsulating agent cannot hold all ideal wall material properties. The selection of atomiser is one of the most important step in case of spray drying which put momentous effect on size of distribution of final formulation having dried particles.[21] By using spray drying and spray congealing different formulations are prepared.

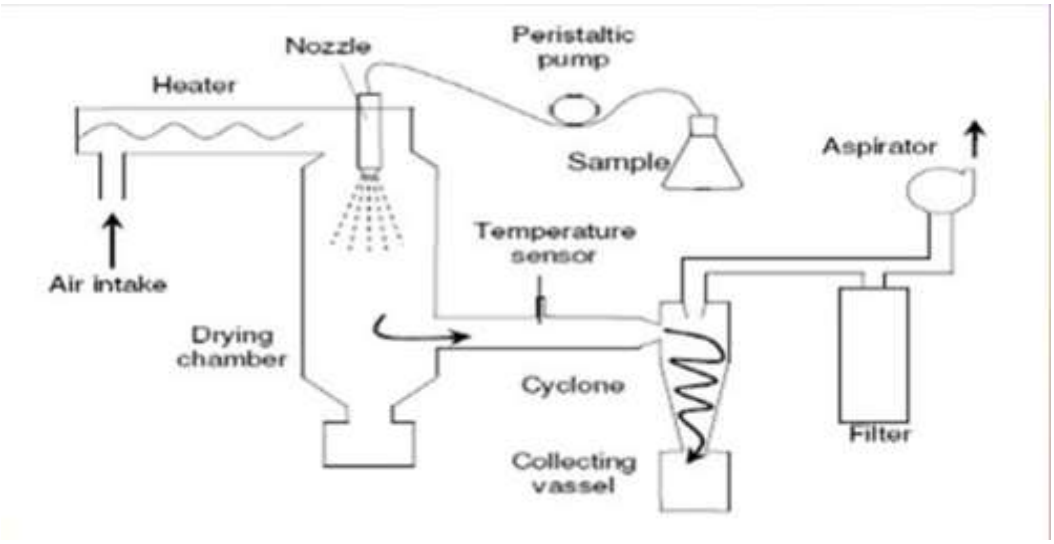


Fig 4: Spray drying and Spray congealing

Pan Coating

This method is widely used in pharmaceutical industry for encapsulate solid particle which have size greater than 600microns as shown in fig 5. It is consider for effective coating and process which is employed for controlled release preparation. On various spherical substrates such as nonpareil sugar seeds with various polymers are coated by medicament. Generally, in coating pan the coating can be applied as a atomized spray or as a solution to desired solid core material. by passing warm air Coating solvent is removed on the coated material.[19-22] This technique is used for preparing different type of formulation.

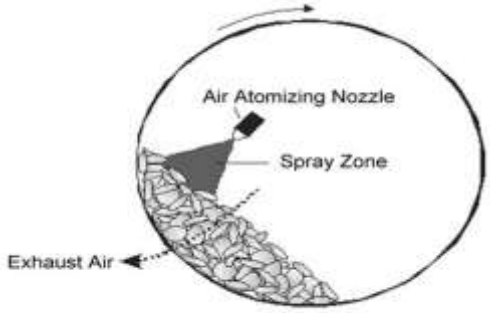


Fig 5: Pan Coating [22].

Solvent Evaporation Technique

By agitation of two immiscible liquids a liquid manufacturing vehicle (o/w) emulsion can be formed in which these techniques can be used. A volatile solvent, which have an immiscible property with liquid manufacturing vehicle phase in which microcapsule coating polymer can be dissolved by this process. After that, dispersion of core material in coating polymer solution. The core and coating material dispersed into liquid manufacturing phase with agitation to obtain

desired size of microcapsules.[23] By using solvent evaporation technique different formulations are prepared. Some advantages are given in fig 6.

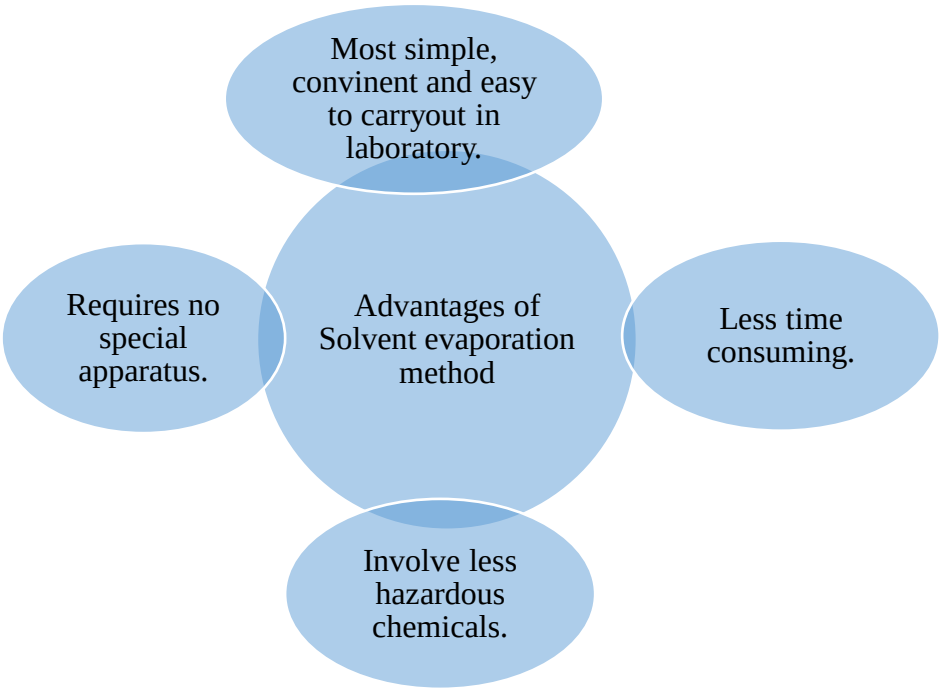


Fig 6: Advantages of solvent evaporation method[23-29]

The aqueous phase of solvent partitioned and in aqueous phase the movement continues by evaporation. Microencapsulation process can be affected by several process variable which include method of forming dispersions, evaporation rate of solvent, temperature cycles and agitation rates. In solvent evaporation technique, two important factors are considered which are choice of vehicle phase and solvent for polymer coating for preparing microcapsules. For core materials, water soluble and water insoluble materials can be used.[29]

Polymerisation

Interfacial polymer

In poly condensation, the two reactants meets at an interface and reacts rapidly. The classical schottenbauman reaction between compound containing acid hydrogen atom and acid chloride, such as amine, polyesters, alcohol, poly urea, polyurethane is the basic of this reaction. Thin walls are formed rapidly at interface under the desired conditions. Poly functional isocyanate is used in emulsified the solution of pesticide and di-acid chloride in water and on aqueous solution containing amine. By the base the acid formation can be controlled during the reaction. At interface of the emulsion droplets condensed polymer walls formed rapidly.[30]

In-situ polymerization

On the particle surface the direct polymerization of a monomer which involves a few microencapsulation process can be carried out. In polyethylene cellulose fibres gets encapsulated and are immersed in dry toluene. Deposition rates are about 0.5 micrometer/minute. Coating thickness ranges upto 0.2-75 micrometer. Coating is uniform over sharp projections.[31]

Matrix Polymer

A core material embedded in the polymeric matrix in most of the processes. Solvent from the matrix material gets evaporated which forms the particles this method is known as spray drying. Matrix is solidified by chemical change. By using polymerisation different formulations are prepared.[30]

CHARACTERIZATION OF MICROCAPSULES

Particle Size and Shape

Conventional light microscopy and scanning electron microscopy (SEM) are the most commonly used methods to visualize microcapsule. The shape and structure of microcapsule can be

analyzed by both of the techniques. Light microscopy provides high resolution than SEM. Investigation of double walled systems and the microsphere surfaces also allowed by it. One of the non destructive visualization technique is Confocal laser scanning microscopy (CLSM), which gives results about structures as well as surface and also reveals about inside particle.[7]

Fourier Transform-Infrared Spectroscopy (FTIR)

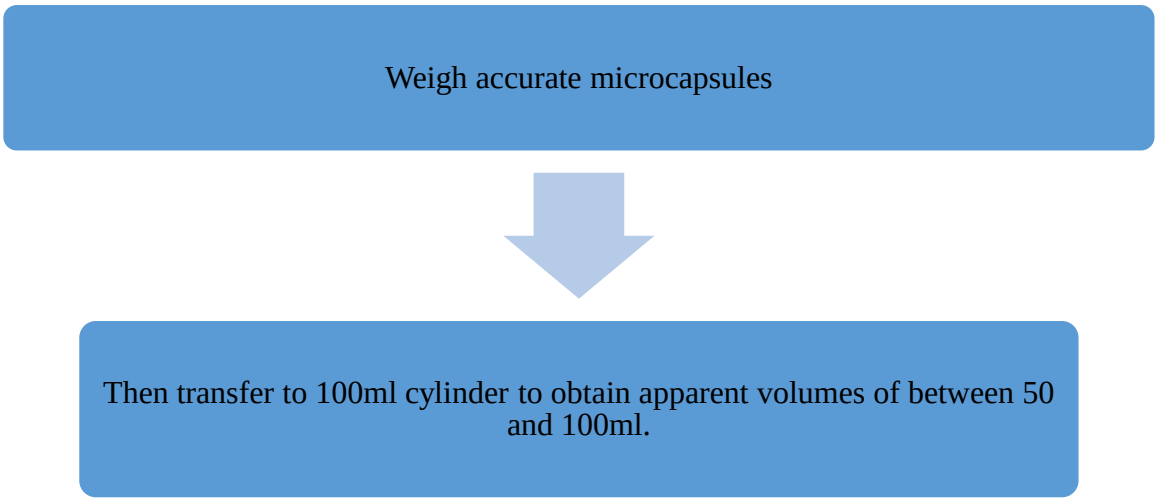
It is used for the analysis of degradation of polymeric matrix of the carrier system and checks the interaction between the polymer and drug system.

Carr's Index and Hausner's Ratio

Fixed funnel and cone method are used for determining the angle of repose. The calculation of bulk density of mixed microcapsules is determine by the hausner's ratio or carr's index, with the help of poured or tapped bulk densities of known weight of sample using measuring cylinder.[31]

Carr’s Index = [Tapped Density-Bulk Density/Tapped Density] ×100 Hausner's ratio (HR)=ρT/ρB where ρT is tapped density and ρB is bulk density [14].

Bulk Density



Bulk Density (ρρ)= [Weight of Microcapsules(g) (M) / Bulk Volume (ml)(V)]

where, M = mass of the powder,

Vo = volume of the powder

Isoelectric Point

To measure electrophoretic mobility of microsphere an apparatus micro electrophoresis is used which can easily calculate isoelectric point. The mobility is related with surface contained charge, ionisable behaviour or ion absorption nature of microcapsules.[7]

Determination of drug Loading, Encapsulation Efficiency and Microcapsule Yield

By extraction of 20mg sample of microcapsules with methanol drug content was determined. Following filtration and dilution with methanol, the resultant concentration was checked by UV spectrophotometry.

%loading = weight of drug/weight of microcapsules

%Encapsulation efficiency= [%Actual drug content/%theoretical drug content] ×100

%Yield=M/ M0 ×100

M = Weight of microcapsules

M0 = Total expected weight of drug and polymer [10,14].

Contact Angle

To determine the wetting property of microcapsule the angle of contact is calculated. The nature of microcapsules in terms of hydrophilicity and hydrophobicity can be easily known by this

method. This is measured by placing a droplet in circular cell mounted above the objective of inverted microscope at solid/air/water surface. It is measured within a minute of decomposition .[7]

***In Vitro* Drug Release Studies**

It can be carried out by USP rotating basket and paddle apparatus in various ph conditions like pH 1.2 and pH 7.4. After particular time intervals the sample should be taken out and is replaced by same medium. By using the plot of amount released function of time the release profile is determined.[32]

APPLICATIONS OF MICROCAPSULES

The application of microencapsulation is numerous.

Medical application[33]

- Over the extended period of time release of proteins, hormones and peptides.
- Gene therapy with DNA plasmids and also delivery of insulin.
- For the treatment of diseases vaccine delivery like hepatitis, influenza, pertusis, ricin.
- Birth control, toxoid, diphtheria.
- Active targeting of tumor cells, antigens, by intra-arterial/ intravenous application and passive targeting of leaky tumor vessels.
- Treatments of leishmaniasis and also tumor targeting with doxorubicin.
- Magnetic microspheres can be used for bone marrow purging and stem cell extraction.
- By affinity chromatography toxin extraction, cell separation and also used in isolation of antibodies.
- Used for the diagnostic tests for infectious diseases like bacterial, viral, and fungal.

Radioactive microsphere's application[34]

- Radioembolisation of liver and spleen tumours can be done.
- Radiosynvectomy of arthiritis joint, local radiotherapy, interactivity treatement can be done.
- Imaging of liver, spleen, bone marrow, lung etc and even imaging of thrombus in deep vein thrombosis can be done.

Various applications are shown in fig 7.

Fig 7: Application of Microcapsules[32-34]

Other applications

- Fluorescent microspheres can be used for membrane based technologies for flow cytomettry, cell biology, microbiology, Fluorescent Linked Immuno-Sorbent Assay.
- Hepatocellular carcinoma can be primary treated by Yttrium 90.

Some more applications are given in table 1.

Table 1: Some Applications of Drugs with their Results

Drugs Category	**Process/Technique**	**Result**	**Ref**
Antimicrobial	Simple & complex co-acervation	Increased compound stability during storage and reduce interation with food components and preventing their inactivation	35
Green tea catechins	Spray drying and freeze drying	Antioxidant activity, safe delivery of polyphenols in food matrices	36
Islet cell	Phase inversion, interfacial ppt., polyelectrolyte	Overcome the need for the immune supression & lack of donor islet cells	37
Vitamin D	Spray drying, liposome nanostructure lipid carrier	Desired functionality & have great potential for fortification of fortificants like vit. D	38
Living cells	Gelatin process (photo cross-	Cancer treatment, drug	39

	linking, thermal & ionic)	delivery, food production, cell culture context	
Probiotics	Spray drying, spray chilling, freeze drying, fluid bed drying	Improve the survival of probiotics during processing, storage and gastrointestinal digestion	40

CONCLUSION

This review article contains around 40 references which summarize the significance of microencapsulation techniques, their methods of preparation, characterization and applications. There is a need to prepare microcapsules in larger quantities and in sufficient quality that is suitable for clinical trials and commercialization due to the widespread interest in various types of drugs. For larger amount of processing fluids and their subsequent recycling the rapid solvent may require. Therefore, combined extraction and evaporation represents a compromise in terms of both time and waste-efficient microsphere production. From a simple immobilization or entrapment microencapsulation technology has been developed to sophisticated and precise micro capsule formation.

REFERENCES

1. Alagusundaram M, Chetty MS, Umashankari C. "Microspheres as a Novel drug delivery system – A review". *Int J Chem Tech*, 2009, 12: 526-534.

2. Allen LV, Popovich NG, Ansel HC. Pharmaceutical Dosage Forms and Drug Delivery Systems. Delhi, India: BI Publication, 2005, 8: 265.

3. Banker GS, Rhodes CT. Modern pharmaceutics. Parma Publication, 2002, 121: 501-527.

4. Bungenburg de Jong, HG. Proc. Acad. Sci, Amsterdam. 1998, 41: 646.

5. Patel P, Piyush R, Modi D. Microencapsulation: Process, techniques and applications. *Int J Universal Pharmacy and Life Sci*, 2012, 2(3): 316-322.

6. Umer H, Nigam H, Tamboli A. Microencapsulation: Process, technique and applications. *Int J Res Pharm Biomed Sci*, 2011, 2(2): 474-481

7. Preet L, Sharma S, Guleri T. Microencapsulation: A new era in novel drug delivery. *Int J Pharm Res Bio Sci*, 2013, 2(2): 456-468.

8. Chanana A, Kataria M, Sharma M, Bilandi A. Microencapsulation: Advancements in applications. *Int Res J Pharm.* 2013, 4(2): 1-5.

9. Sachan K, Singh B, Rao K. Controlled drug delivery through microencapsulation. *Malasian J Pharm Sci*, 2006, 4(1): 65-81

10. Agnihotri N, Mishra R, Goda C, Arora M. Microencapsulation-A novel approach in drug delivery: A review. *Indo Global J Pharm Sci*, 2012, 2(1): 1-20

11. Singh Maninder, Dua JS, Menra Muse, SoniMansi, Prasad DN. Microencapsulation and its Various Aspects: A Review. *Int J of Adv Res*, 2016, 4(6): 2094-2108.

12. Midha K, Nagpal M, Arora S. Microspheres a recent update. *Int J Recent Scientific Res,* 2015, 6: 85860-5861.

13. Mishra KD, Jain KA, Jain PK. Various Technique of Microencapsulation: A Review. *Int Pharm and Chem Sci*, 2013, 2: 2277-85.

14. Mishra D, Jain A, Jain P. A review on various techniques of microencapsulation. *Int J Pharm Clin Sci*, 2013, 2(2): 962-997.

15. Tiwari S, Verma P. Microencapsulation technique by solvent evaporation method. *Int J Pharm Life Sci,* 2011, 2: 998-1005

16 Jadupati M, Tanmay D, Souvik G. Microencapsulation: An indispensable technology for drug delivery system. *Int Res J Pharm*, 2012, 3(4): 8-13

17. Aulten M. The science of dosage form design. Churchill Livingstone. 2nd edition. 2002, 82

18. Remington. The science and practice of pharmacy. Lippincott Williams and Wilkins. 20th edition. 2000, 891

19. Lachman L, Lieberman H, Chapter 13 (Part Three). The theory and practice of industrial pharmacy.Varghese Publishing House. 2009, 412-428

20. Gharsallaoui A, Roudaut G, Chambin O. Applications of spray drying in microencapsulation of food ingredients: An overview. *Food Res Int*, 2007, 40: 1107-1121.

21. Reo M. Microencapsulation by spray drying, Drying technology. *Int J Pharm*, 2007, 16(6): 1195- 1236.

22. Gunjan A, Sharma N, Gupta M. An review of microencapsulation as novel drug delivery. *Asian J Pharm Edu and Res*, 2012, 1(2): 53-66.

23. Venkatesan P, Manavalan R, Valliappan K. Microencapsulation: A vital technique in novel drug delivery system. *J Pharm Sci Res*, 2009, 1(4): 26-35

24. Bhogataj M, Mrhar A, Kristl A, Kozjek F. Eudragit E microspheres containing bacampicillin: preparation by solvent removal methods. *J Microencapsul*, 1991, 8: 401-406

25. Yuksel N, Baykara T. Preparation of polymeric microspheres by the solvent evaporation method using sucrose stearate as a droplet stabilizer. *J Microencapsul*, 1997, 6: 725-733

26. Satturwar PM, Mandaogade PM, Dorle AK. A novel method for preparation of Eudragit RL microcapsules. *J Microencapsul*, 2002, 19: 407-413

27. Kim BK, Hwang SJ, Park JB, Park HJ. Preparation and characterization of drug-loaded polymethacrylate microspheres by an emulsion solvent evaporation method. *J Microencapsul*. 2002, 19: 811-822.

28. Ananad V, Kandarapu R, Garg S. Preparation and evaluation of taste masked orally disintegrating tablets of prednisolone. *Asian J Pharm*, 2007, 2: 227- 238

29. Khamanga SM, Parfitt N, Nyamuzhiwa T, Haridula H, Walker RB. The evaluation of eudragit microcapsules manufactured by solvent evaporation using USP apparatus II. *Dissol Tech*, 2009, 4: 15-22

30. Boh B, Sumiga B. Microencapsulation technology and its applications in building construction materials. *RMZ- Materials and Geoenvironment,* 2008, 55(3): 329-344

31. Dubey R, Shami T, Bhasker K. Microencapsulation technology and applications. *Defence Sci J,* 2009, 59(1): 82-95.

32. Avalani G, Natasha S, Gupta M, Prasad KM, Ritesh V, Mishra SS. Microencapsulation As Novel Drug Delivery: A Review. *Asian J Pharm Edu and Res*, 2012, 2(1): 2278-7496.

33. Brazel SC, Peppas NA. Modeling of drug release from swellable polymers. *Eur J Pharm Biopharm.* 2000, 49: 47–48.

34. Benita S, Donbrow M. Controlled drug delivery through microencapsulation, *J Pharm Sci*, 1982, 71: 205–210.

35. Castro-Rosas J, Ferreira-Grosso CR, Gomez-Aldapa CA, Rangle-Vargas E, Rodriquez-Marin ML, FA Guzman-Ortiz, RN Falfan-Cortes. Recent advances in microencapsulation of natural sources of antimicrobial compounds used in food: A Review. *Food Res Int*, 2017, 102: 575-587

36. Bora AFM, Ma Shaojie, Li Xiaodong, Liu Lu. Application of microencapsulation for the safe delivery of green tea polyphenols in food system: Review and recent advances. *Food Res Int*, 2018, 105:241-249.

37. Omami M, Mc Garrigle, Reddy M, Isa D, Ghani S, Marchese E, Bochenek MA, Longi M, Xing Y, Joshi M, Wang Y, Oberholzer J. Islet microencapsulation: Strategies and clinical status in Diabetes. *Curr Diab Rep*, 2017, 17: 47.

38. Maurya VK, Bashir K, Aggrawal M. Vitamin D microencapsulation and fortification: Trends and technologies. *J of steroid biochemistry and molecular biology,* 2020, 196: 105489.

39. Alkayyali T, Cameron T, Haltti B, Ahmadi A. Microfluidic and cross-linking methods for encapsulating of living cells and bacteria: A Review. *Analytica Chimica Acta*, 2019, 11: 1-21.

40. Liu H, SW Cui, Chen M, Li M, Liang R, Xu F, Zhong F. Protective approaches and mechanisms of microencapsulation to the survival of Probiotic bacteria during processing, storage and gastrointestional digestion: A Review. *Critical Reviews in Food Science and Nutrition*, 2019, 59(17): 2863-78.