A REVIEW ON MICROENCAPSULATION IN ANTI-CANCER THERAPY

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ABSTRACT

The well-known method of encasing or wrapping one material in another, known as microencapsulation, produces capsules with sizes ranging from a few hundred to less than a micron. Microcapsules will be affected by the rate of solvent removal, the concentration of the polymer, the solubility of the organic solvent in water, the solubility of the polymer in solvent, and other parameters. Numerous industries, including the pharmaceutical, agricultural, textile, culinary, printing, and defense sectors, have employed the microencapsulation approach. This technology has led to the introduction of chemical decontaminating fabrics or self-healing composites in the defense sector. This review article summarized materials, release mechanisms, technologies involved in microencapsulation, and also data regarding microencapsulation of anticancer drugs.

Keyword: - *Microencapsulation, Microcapsule, Core material, Coating material, Controlled release.*

1. INTRODUCTION

A well-designed controlled drug delivery system can overcome some of the problems associated with conventional therapy and enhance the therapeutic efficacy of the drug. In order to achieve maximum therapeutic efficacy, it is necessary to deliver the agent to the target tissue in the optimal amount in the right period of time with minimal toxicity and minimal side effects. Various approaches exist for the delivery of a therapeutic substance to the target site in a sustained controlled release manner. One such approach is the use of microspheres as drug carriers. Microspheres are characteristically free-flowing powders consisting of proteins or synthetic polymers that are biodegradable in nature and ideally have a particle size of less than 200 μm. Microencapsulation is a process in which very small droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material. Microencapsulation includes bioencapsulation, which is more limited to the entrapment of a biologically active substance (from DNA to a whole cell or a group of cells, for example) in order to improve its performance and/or its shelf life [1].

Microencapsulation is a means of converting liquids to solids, altering colloidal and surface properties, protecting the environment and controlling the release characteristics or availability of coated materials. Several of these properties can be attained by macro-packaging techniques; however, microencapsulation is unique because of the small size of the coated particles and their subsequent use and adaptation to a wide variety of dosage forms, which is not technically feasible [2].

1.1 Development of Microcapsules:

Core material:

The core material, which is defined as the specific material to be coated, can be liquid or solid. The composition of the core material may be varied, since the liquid core may contain dispersed and/or dissolvable materials. The active constituents, stabilizers, diluents, excipients, and release rate retardants or accelerators of the solid core are considered [2].

The ability to vary the core material composition provides definite flexibility and the utilization of these characteristics often enables the effective design and development of desired microcapsule properties [2].

Coating material:

The selection of appropriate coating material determines the physical and chemical properties of the resultant microcapsules/microspheres. While selecting a polymer, the product requirements, i.e. Stabilization, reduced volatility, release characteristics, environmental conditions, etc. should be taken into account. The polymer must be able to form a film which is cohesive with the core material. It must be chemically compatible and non-reactive with the core material and must provide the desired coating properties, such as strength, flexibility, impermeability, optical properties and stability [1,2].

In general, hydrophilic polymers and hydrophobic polymers (or a combination thereof) are used for microencapsulation. A number of coating materials such as gelatin, polyvinyl alcohol, ethyl cellulose, cellulose acetate phthalate and styrene maleic anhydride have been successfully used. The thickness of the film may vary considerably depending on the surface area of the material to be coated and other physical properties of the system. The microcapsules may consist of a single particle or clusters of particles. After isolation and drying from the liquid production vehicle, the material appears as a free-flowing powder. The powder may be used in compressed tablets, hard gelatin capsules, suspensions and other forms of dosage [1,2].

The coating material must be able to form a film that is cohesive with the core material, chemically compatible and nonreactive with the core material, and provide the desired coating properties such as strength, flexibility, impermeability, optical properties, and stability. The coating materials used in the microencapsulation method may, to some extent, be modified [2].

The selection of a given coating can often be aided by the review of existing literature and the study of free or cast films; however, the practical use of free-film information is often impeded for the following reasons:

- Cast or free films prepared by the usual casting techniques yield films that are considerably thicker than those produced by the microencapsulation of small particles; hence, the results obtained from the cast films may not be extrapolate to the thin microcapsule coatings [2].
- The particular microencapsulation method employed for the deposition of a given coating produces specific and inherent properties that are difficult to simulate with existing film casting methods [2].
- The coating substrate of core material may have a decisive effect on coating properties. Hence, the selection of a particular coating material involves consideration of both classic free-film data and applied results [2].

1.2 Ideal Properties of Coating Material:

- Soluble in an aqueous media or solvent.
- Stabilization of core material.
- It should be pliable, tasteless, stable, economic and should not have high viscosity.
- It should possess sufficient properties such as flexibility, strength, stability.
- It should be chemically compatible with the core and non-reactive.
- It should be capable of forming a film [3].

1.3 List of Coating Materials:

Table -1: List of coating materials [4]

Water soluble resin	Water insoluble resin	Wax & lipid	Enteric resin
PVP, CMC, Methyl cellulose, Polyvinyl acrylate.	Ethyl cellulose, Polyethylene, Polymethacrylates.	Paraffin, Bees wax, Stearic acid.	Shellac, Zein.

1.4 Types of Microcapsules: The microcapsules are divided into three types:

- **Mononuclear/single core:**

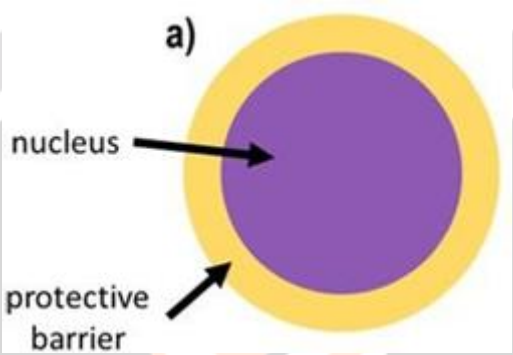

Fig -1: Mononuclear microcapsule [5,6]

- **Polynuclear/multiple core:**

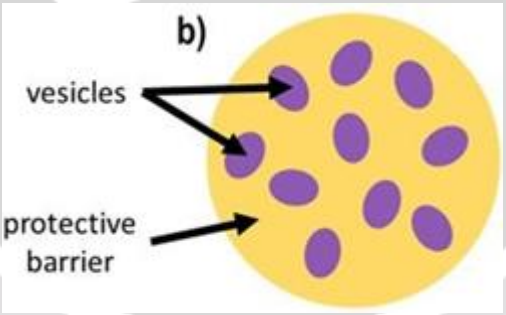

Fig -2: Polynuclear microcapsule [5,6]

- **Matrix type:**

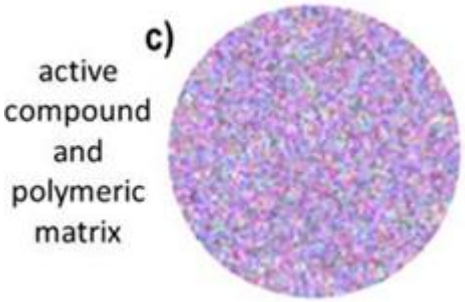

Fig -3: Matrix type microcapsule [5,6]

1.5 Reasons for Microencapsulation in Anticancer:

- It is mainly used to increase the stability, and sustained/prolonged release of the product.
- For converting liquid drugs into a free-flowing powder.
- To reduce the toxicity and GI irritation and many major side effects of the drugs.
- Alteration in site of absorption can be achieved by microencapsulation.
- This technique is mainly used for taste masking and odour of various drugs.
- Reactive substances are protected from the environment by microencapsulation.
- It is helpful to prevent incompatibility between drugs.
- Those drugs, which are volatile in nature, can be protected by microencapsulation.
- The rate of drug release can be controlled by formulating microcapsules [3,7].

1.6 Mechanism of Drug Release from Microcapsules:

A. Diffusion controlled monolithic system:

It is the most common mechanism of drug release from the core material, in which the dissolution fluid penetrates the shell, then the core comes into contact with the dissolution fluid and leaks through interstitial channels or pores. Drug release is dependent upon the:

- The rate of drug dissolution in dissolution fluid.
- Rate of penetration of dissolution fluid to the microcapsules and rate at which the dissolved drug escapes from the microcapsules [5].

The rate kinetics of drug release follows Higuchi equation

Q= [D/J (2A- € CS) CSt] ½

Q = Amount of drug release per unit area of exposed surface in time t.

J = Tortuosity of the capillary system in the wall.

D = Diffusion co-efficient of solute in solution.

A = Total amount of drug per unit volume.

€ = Porosity of the wall of microcapsules.

CS = Solubility of the drug in permeating dissolution fluid [5].

B. Dissolution:

When the coat is soluble in dissolution fluid, the rate of drug release depends upon the dissolution rate of polymer coat. It also depends on its solubility in the dissolution fluid and the thickness of the coating material. The release of the drug takes place by dissolving the coating or melting of the capsule wall [5].

C. Degradation controlled monolithic system:

The drug dissolves in the matrix and is distributed throughout the core. The drug attaches to the matrix and is released upon degradation of the matrix. Diffusion of the drug is slow compared to degradation of matrix [5].

D. Erosion:

The release of the drug by erosion mechanism occurs due to pH or enzymatic hydrolysis of the coating. The release of drugs from microcapsules has become complex. Differences in the physical forms of microcapsules, such as the size, shape, and arrangement of core and coating materials [5].

The physico-chemical properties of the core material, such as solubility, diffusibility, and partition coefficient, as well as the thickness and porosity of the coating materials. The drug release from microcapsules follows zero-order kinetics, i.e., the release rate is constant and a fixed amount of drug is delivered per time period. Monolithic-type microcapsules have t12 dependent release for the first half of the total drug release and then turn down exponentially [5].

2. DIFFERENT MICROENCAPSULATION TECHNIQUES:

Table -2: List of different microencapsulation techniques [5].

Physical	• Air suspension coating • Pan coating • Spray drying • Centrifugal extrusion process
Chemical	• Solvent evaporation method • Interfacial polymerization • In situ polymerization • Matrix polymerization
Physicochemical	• Ionotropic gelation method • Coacervation phase separation

2.1 Physical methods:

a) Air suspension method: -

This method involves spraying the coating material in the air, suspending the particles, and dispersing the core material in the air stream. The particles are suspended in moving air within the coating chamber. The coating chamber is designed in such a way that it affects the particle flow through the coating zone of the chamber, where polymer solution coating material is applied to the moving particles. This cyclic process is repeated several times depending on the thickness of the core material. The encapsulated product is dried in air. Drying rate is directly

proportional to temperature. Variables that affect the process are melting point, solubility, surface area, density, melting point, and application rate of the coating material [3,6].

b) Spray drying: -

In the case of spray drying, coating solidification is affected by rapid evaporation of the solvent in which the coating material is dissolved, whereas in the case of spray congealing, coating solidification is accomplished by thermally congealing a molten coating material or by introducing the core material into a non-solvent [8,9].

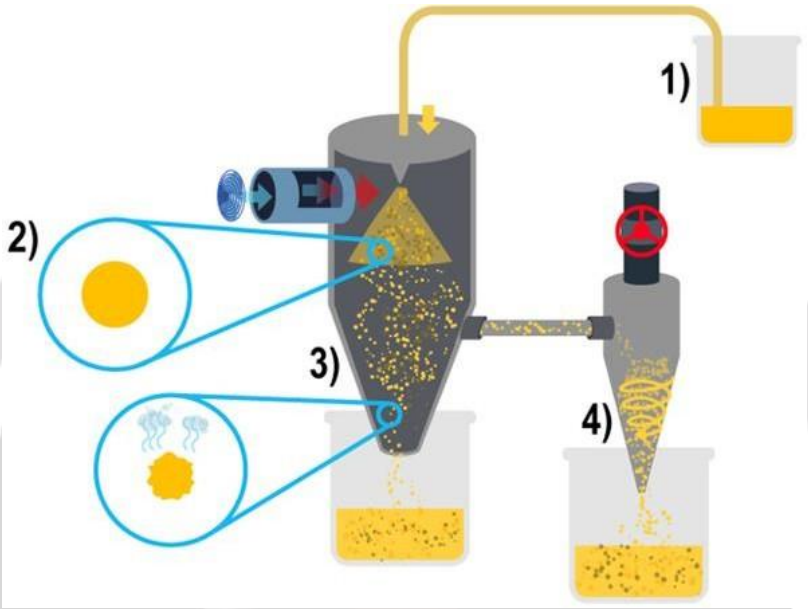

Fig -4: Spray-drying process [6].

Removal of non-solvents or solvents from the coated product can be achieved by sorption extraction or evaporation techniques. Few examples of food ingredients that can be microencapsulated by spray drying include flavors, lipids and carotenoids. A single encapsulating agent cannot hold all ideal wall material properties; therefore, research has focused on gums, proteins and carbohydrates. One of the most important steps in spray drying is the selection of an atomizer that significantly affects the size distribution of the final formulation containing dried particles [10].

c) Pan coating: -

The pan coating method has become widespread in the pharmaceutical industry. Solid particles greater than 600 microns in size are considered as effective coatings, and controlled release preparation processes have been employed. Medicaments are coated with various polymers on various spherical substrates, such as nonpareil sugar seeds. Generally, the coating can be applied as a solution or as an atomized spray to the desired solid core material in the coating pan. The coating solvent can be removed by passing warm air over the coated material [11].

d) Centrifugal extrusion: -

Liquids can be encapsulated using rotating extrusion head containing concentric nozzles. In this method, the jet core is covered by a wall solution sheath. As the jet passes through the air, due to Rayleigh instability, it breaks into the droplets of the core, each of which is coated with the wall solution. The mean diameter of the droplets is within +-

10%, and they form a narrow circle. This process is efficient for forming particles with diameters of 400–2000 micrometers. This process is suitable only for liquids or slurry. The production rate may be high, up to 22.5 kg (50 lb) of microcapsules can be produced per nozzle per hour [12].

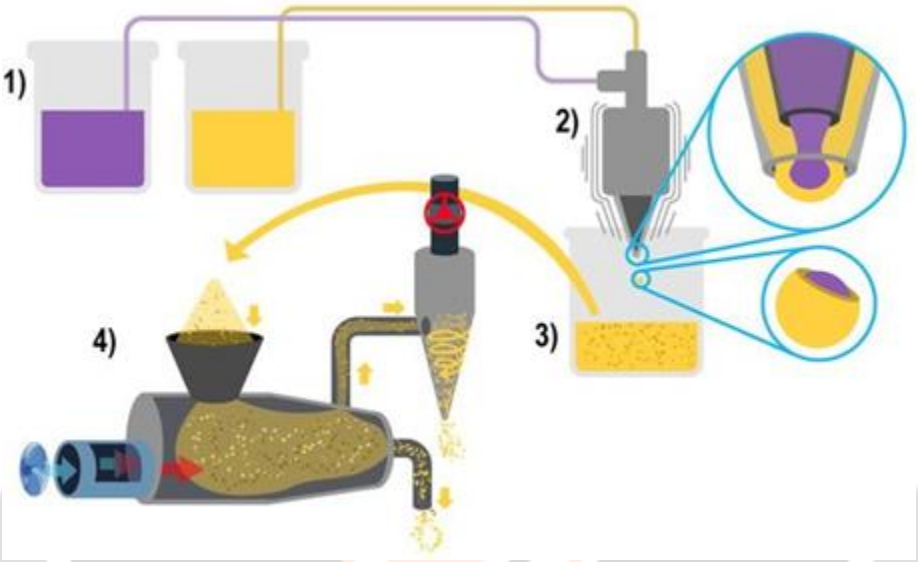

Fig -5: Microcapsule formation by coextrusion [6].

2.2 Chemical methods:

a) Solvent evaporation technique: -

These techniques can be done into liquid manufacturing vehicle (o/w) emulsion which can be formed by agitation of two immiscible liquids. In this process, the microcapsule coating polymer can be dissolved in a volatile solvent that is immiscible with the liquid manufacturing vehicle phase. Subsequently, the core material is dispersed in the

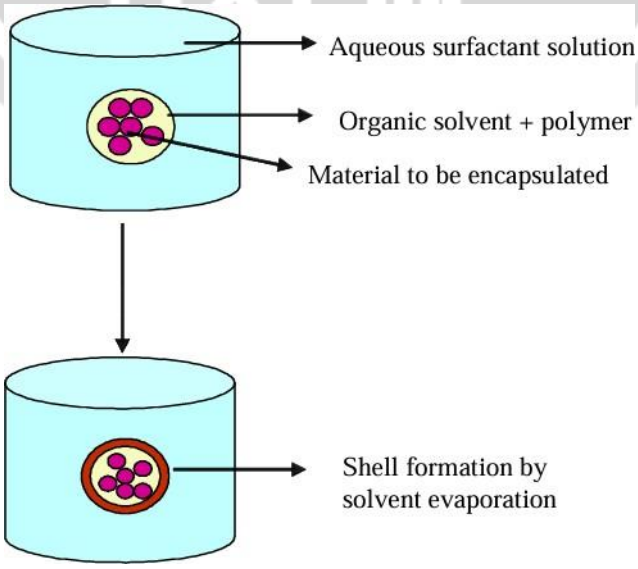

Fig -6: Solvent evaporation process [7].

coating polymer solution. To obtain the desired size of microcapsules, the core and coating material were dispersed into the liquid manufacturing phase with agitation. The agitation continues until the solvent partitions into an aqueous phase and the aqueous phase is removed by evaporation. Several process variables that affect the microencapsulation process include dispersion formation method, solvent evaporation rate, temperature cycles and agitation rates. Two important factors to consider when preparing microcapsules by solvent evaporation technique are the choice of vehicle phase and solvent. Water-soluble and water-insoluble materials can also be used as core materials [13].

b) Interfacial polymerization: -

Here, the two reactants in poly-condensation meet at an interface and react rapidly. The basic of this method involves the classical Schotten–Bauman reaction between amines, polyesters, alcohols, poly urea, and polyurethanes containing acid hydrogen atoms and acid chlorides. Under the desired conditions, thin walls rapidly form at the interface. The solution of pesticide and diacid chloride is emulsified in water, and an aqueous solution containing amine as polyfunctional isocyanate is added. During the reaction, the formation of acid can be controlled by the base. The condensed polymer walls rapidly form at the emulsion droplet interface [7,14].

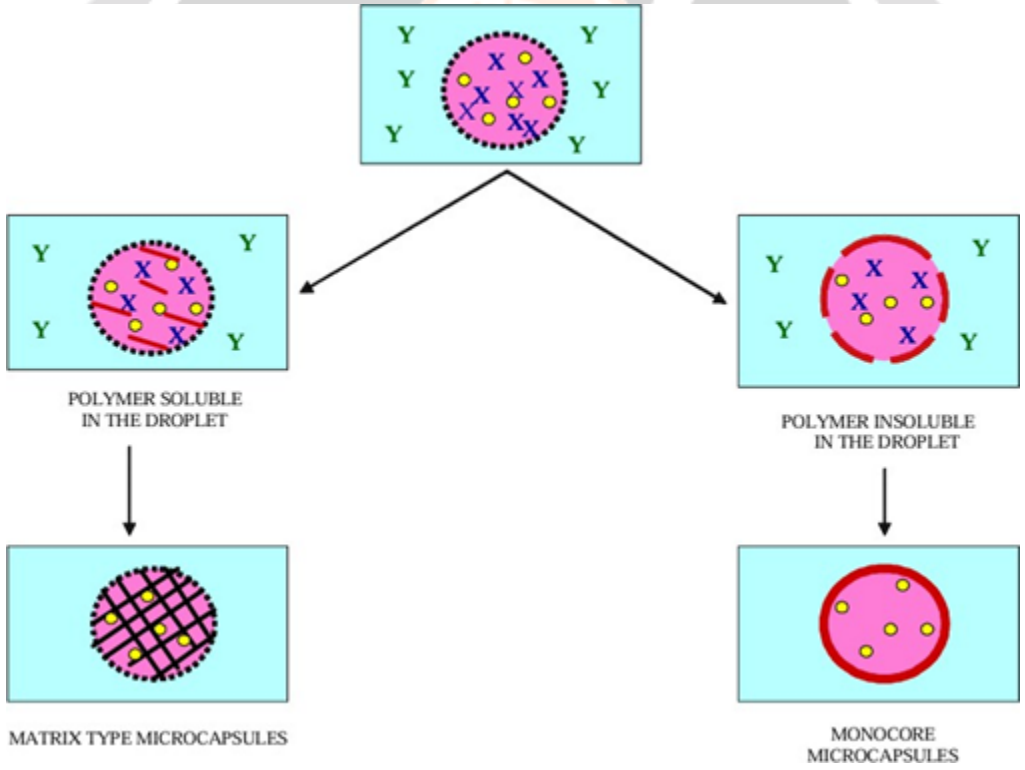

Fig -7: Interfacial polymerization process [7].

c) In-situ polymerization: -

Few microencapsulation processes involving direct monomer polymerization on the particle surface can be carried out. In one process, cellulose fibers are encapsulated in polyethylene while immersed in dry toluene. The deposition rate is approximately 0.5 micrometer/minute. The coating thickness ranges from 0.2 to 75 micrometer. The coating is uniform over sharp projections [15].

d) Matrix polymerization: -

In most of these processes, a core material is embedded in the polymeric matrix. One such method is spray drying, in which particles are formed by evaporation of solvent from the matrix material. Solidification of the matrix occurs by chemical change [16].

2.3 Physicochemical methods:

a) Ionotropic gelation method: -

This method is based on the ability of polyelectrolytes to form hydrogels in the presence of counter ions. Ionotropic gelation occurs when units of uric acid of the chains in the alginate polymer crosslink with multivalent cations. These may include calcium, zinc, iron and aluminum [17].

b) Coacervation/Phase separation: -

Coacervation (or phase separation) is widely employed for the preparation of gelatin and gelatin acacia microcapsules, as well as for a large number of products containing an aqueous surfactant solution, an organic solvent, and a polymer material to be encapsulated by solvent evaporation [6,17].

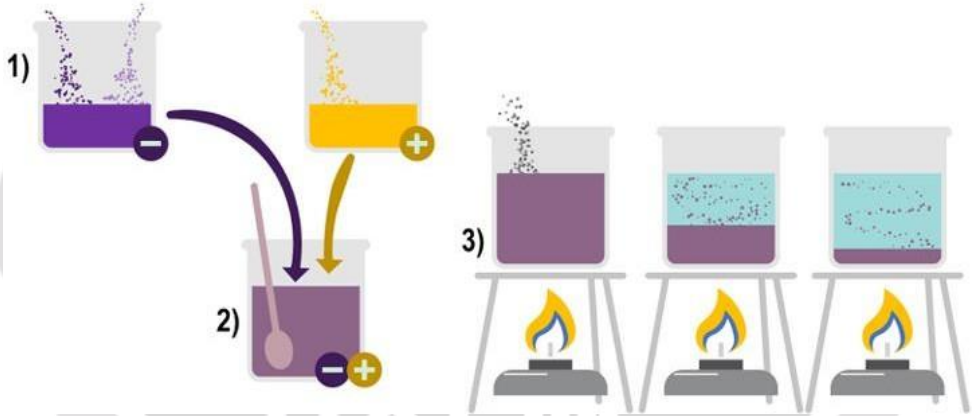

Fig -8: Microencapsulation technique by coacervation [6].

Schematic representation of microencapsulation by solvent evaporation based on cellulose derivatives and synthetic polymers. Phase separation processes can be divided into simple and complex coacervation processes. Simple coacervation involves the use of a single polymer such as gelatin or ethyl cellulose in aqueous or organic media, respectively. Complex coacervation involves two oppositely charged polymeric materials such as gelatin and acacia, both of which are soluble in aqueous media. Coacervation is caused by gradual desolvation of fully solvated polymer molecules in both cases [6,17].

Microencapsulation by coacervation was carried out by preparing an aqueous polymer solution (1–10%) at 40–50°C into which the core material (hydrophobic) was also dispersed. A suitable stabilizer may also be added to the mixture in order to maintain the individuality of the final microcapsules. A suitable desolvating agent (coacervating agent) was gradually introduced into the mixture, which resulted in the formation of partially desolvated polymer molecules on the surface of the core particles and precipitation. The coacervation mixture was cooled to about

520°C, followed by the addition of a crosslinking agent to harden the microcapsule wall formed around the core particles. Gelatin microcapsules loaded with carboquone as well as gelatin acacia microcapsules loaded with sulfamethoxazole have been produced by coacervation [17].

3. APPLICATIONS OF MICROENCAPSULATION:

- Microencapsulation has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat.
- A great degree of protection can be provided by microencapsulation. For ex: Vitamin A, K has been shown to be protected from moisture and oxygen.
- To reduce gastric irritation.
- By microencapsulation liquids are converted to solid powder at low cost and stabilize the shelf life of active ingredients.
- Microencapsulation has proven to be potential for the replacement of therapeutic agents, gene therapy, for treatment of AIDS, tumors, diabetes [18].

4. MICROENCAPSULATED FORMULATIONS:

Table -3: Microencapsulated Formulations [3].

Sr. No.	Drug	Polymer	Method	Purpose	Reference
1.	5-Flurouracil	PEG	Solvent evaporation method	Microspheres	Ganguly et al., 2015
2.	Doxorubicin	Chitosan	Emulsion polymerization	Co-encapsulation	Duan et al., 2012
3.	5-Flurouracil	Guar gum	Emulsion polymerization	Microspheres	Kaushik et al., 2009
4.	Carboplatin	Gelatin	Spray drying	Microspheres	Harsha et al., 2014
5.	Quercetin dihydrate	Eudragit S100	Solvent evaporation method	Mucoadhesive microspheres	RC Jat et al., 2015

5. CONCLUSIONS

The widespread interest in microencapsulated drugs brought forth the need to prepare such particles in larger quantities and in sufficient quality suitable for clinical trials and commercialization. The most frequently described solvent extraction/evaporation- based technology using simple beaker/stirrer setup is inappropriate for producing larger amounts of microspheres in an economic, robust and well controlled manner. Static mixers warrant continuous production and simple scale-up, while the extrusion through porous membranes or micro channels, integrated in small-scaled equipment that is easy to operate and sterilize, additionally offers improved control of the microsphere size distribution as compared to classical mixing processes.

Further, jet excitation is powerful in combining productivity and size control of microspheres. Solvent removal by evaporation may be accelerated using elevated temperatures or reduced pressure. The rapid solvent extraction may require relatively larger amount of processing fluids and their subsequent recycling. Therefore, combined extraction and evaporation represents a compromise in terms of both time and waste-efficient microsphere production. Microencapsulation technology has developed from a simple immobilization or entrapment to sophisticated and precise micro capsule formation.

Microencapsulation in anticancer therapy has emerged as a promising and innovative approach with significant potential for improving the effectiveness and safety of cancer treatments. One key benefit of microencapsulation is the ability to enhance the targeted delivery of anticancer drugs. This targeted delivery helps concentrate the therapeutic payload at the tumor site, improving drug efficacy and reducing side effects on healthy tissues.

Microencapsulation holds great potential in revolutionizing anticancer therapy by providing targeted and controlled drug delivery, enhancing therapeutic efficacy, and minimizing adverse effects. As research in this field progresses, overcoming technical challenges and addressing regulatory considerations will be essential to unlock the full therapeutic benefits of microencapsulation in the fight against cancer.

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