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MICROSPHERES AS DRUG CARRIERS – AN OVERVIEW

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ABSTRACT

Oral modified-release multiple-unit dosage forms have always been more effective therapeutic alternative to conventional or immediate release single-unit dosage forms. Novel drug delivery systems have several advantages over conventional multi dose therapy. Recent trends indicate that micro particulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. Microspheres received much attention not only for prolonged release, but also for targeting of drugs. Micro particulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development. In future microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, genetic materials, and targeted and effective drug delivery. The current aim of this review is to study various aspects of the micro particulates drug delivery system including method of formulation, evaluation & characterization. Microspheres received much attention not only for prolonged release but also for targeting of anticancer drugs to the tumor.

KEYWORDS: Microspheres, Controlled release, Novel Drug Delivery, Therapeutic Efficacy.

1. INTRODUCTION

Microsphere based drug delivery system has received considerable attention in recent years. Microspheres of biodegradable and non biodegradable polymers have been investigated for sustained or controlled release depending upon the final application. The most important characteristic of microspheres is the micro phase separation morphology which endows it with a controlled variability in degradation rate and also drug release.[1] "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1µm to 1000 µm). Microspheres are sometimes starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin, the synthetic polymer include poly lactic acid and polyglycolic acid. The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubility and stabilities, process safety and economic considerations.[2]

2. MICRO PARTICULATE DELIVERY SYSTEMS

The micro particulate delivery systems are intended for oral and topical use.[3]

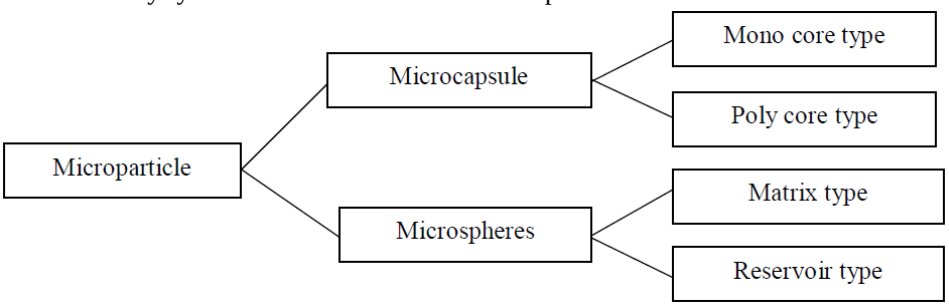

Fig. 1: Classification of Microparticles.

The particles can be coated by a solidified polymeric or proteinic envelope, leading to the formation of microcapsules (Fig. 1). The ultimate objective of micro particulate-delivery systems is to control and extend the release of the active ingredient from the coated particle without attempting to modify the normal bio fate of the active molecules in the body after administration and absorption. The organ distribution and elimination of these molecules will not be modified and will depend only on their physic chemical properties. Thus, the principle of drug targeting is to reduce the total amount of drug administered and the cost of therapy while optimizing itsactivity.

3. MICROSPHERES

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers (Fig. 2) which are biodegradable in nature and ideally having a particle size less than 200 μm[4] and can be injected by 18 or 20 number needle.[5] Drug absorption and side effects due to irritating drugs against the gastrointestinal mucosa is improved because microsphere are made upof small particle size less than 200 μm which are widely distributed throughout the gastrointestinal tract.[6]

3.1 Properties of an Ideal microsphere[7]: described that the preparation of microspheres should satisfy certain criteria:

- The ability to incorporate reasonably high concentrations of the drug
- Stability of the preparation after synthesis with a clinically acceptable shelf life
- Controlled particle size and dispersability in aqueous vehicles for injection
- Biocompatibility with a controlled biodegradability
- Susceptibility to chemical modification
- Control of content release
- Increase therapeutic efficiency
- Reduction of toxicity
- Sterilizability
- Bioreabsorbability

3.2 Advantages[8,9] reported many advantages of microsphere such as:

1. Microspheres provide constant and prolonged therapeutic effect.
2. Masking of odor or bitter taste.
3. Improve physical stability and gastric enzyme stability.
4. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
5. Reduced dosing frequency therefore, improves patient compliance.
6. Reduced toxicity
7. High absorption window with respect to characteristics of drug in GIT
8. Reduced first pass metabolism
9. Enhanced biological half-life
10. Microsphere morphology all owes a controllable variability in degradation and drugrelease.

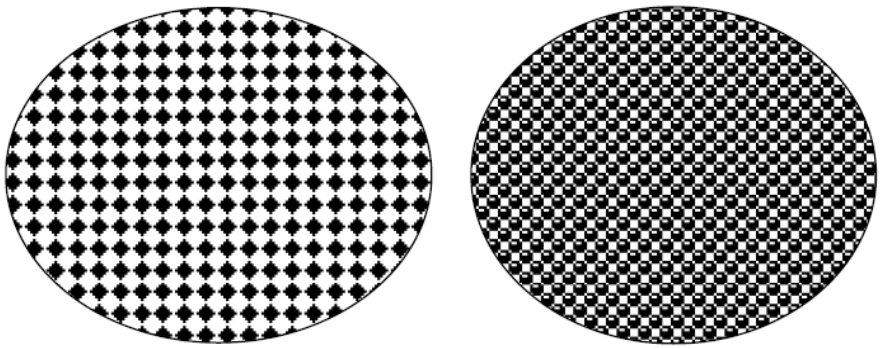

Fig. 2: Structure of microsphere.

3.3 Disadvantage:[10, 11] reported some disadvantages of microsphere:

1. The modified release from the formulations.[12]
2. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.[12]
3. The modified release from the formulation may be due to variety of factors like intrinsic and extrinsic factors, food and the rate of transit through gut.
4. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to dumping of dose, result in failure of therapy and produce potential toxicity.
5. Dosage forms of this kind should not be crushed or chewed.

3.4 Types of microspheres[13, 14, 15]

Microspheres are generally classified into following types (Fig. 3).

3.4.1 Bioadhesive microspheres:[16,17,18] 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 bioadhesion. The term Abioadhesion describes

materials that bind to biological substrates, such as mucosal membranes. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bio adhesion.

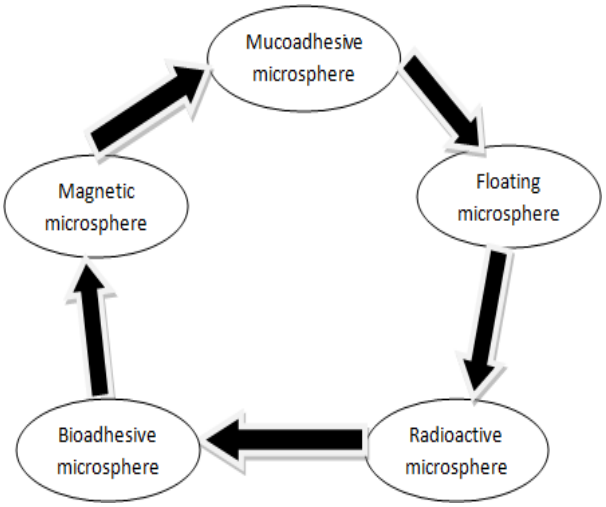

Fig. 3: Types of microspheres.

3.4.2 Magnetic microspheres:[19] in magnetic targeting, a drug or therapeutic radioisotope is bound to a magnetic compound, injected into a patient's blood stream and then stopped with a powerful magnetic field in the target area.[20] Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc.[21] Depending on the type of drug, it is then slowly released from the magnetic microspheres.

3.4.3 Floating microspheres:[22,23] in floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way, it produces prolonged therapeutic effect and therefore reduces dosing frequencies.[24]

Two types of floating microspheres:Effervescent type[25] Non-effervescent type.

3.4.4 Polymeric Microspheres[26]**:** the different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymericmicrospheres.

3.4.5 Radioactive microspheres: Radio emobilization therapy microspheres sized 10-30 nm is of larger than capillaries and gets tapped in first capillary bed when they come across. It differs from drug delivery system, as radioactivity is not released from microspheres but acts from a radioisotope within a typical distance and the different kinds of radioactive microspheres are α, βand γ emitters.[27] It offers new solutions for patients, who need drugs delivered directly to tumors, diabetic ulcers and other disease sites.

3.4.6 Mucoadhesive microspheres: Mucoadhesive microspheres which are of 1-1000 mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it, respectively. Microspheres, in general, have the potential to be used for targeted and controlled release drug delivery but coupling of mucoadhesive properties to microspheres has additional advantages, e.g., efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies etc.

3.4.7 Micellanious

3.4.7.1 Glass microspheres: Glass microspheres are primarily used as filler for weight reduction, retro-reflector for highway safety, additive for cosmetics and adhesives, with limited applications in medical technology.

3.5 Characteristics of microspheres

Table 1: Microsphere property.[28]

S.No.	Property	Consideration
1	Size Diameter	Uniformity/distribution
2	Composition	Density, Refractive Index, Hydrophobicity/hydrophilicity Nonspecific binding Autofluorescence
3	Surface Chemistry	Reactive groups Level of Functionalization charge
4	Special Properties	Visible dye/fluorophore Superparamagnetic

1. Considering traditional diagnostic methods, the test or assay format commonly dictates particle size, such as the use of very small spheres (~0.1- 0.4µm) to ensure satisfactory wicking in lateral flow tests, or the use of larger, cell-sized spheres (~4-10µm) for bead based flow cytometric assays.
2. Common microsphere compositions include polystyrene (PS), poly (methyl methacrylate)

(PMMA), and silica. Polymer beads are generally hydrophobic, and as such, have high protein binding abilities. However, they often require the use of some surfactant (e.g. 0.01-0.1% Tween® 20 or SDS) in the storage buffer to ensure ease of handling. Silica microspheres are inherently hydrophilic and negatively charged. Consequently, aqueous silica suspensions rarely require use of surfactants or other stabilizers. Carboxyl- and amine functionalized silica spheres are available for use in common covalent coating protocols, and plain silica microspheres may be modified using a variety of silanes to generate functional groups or alter surface properties.

3. Microspheres may be coated with capture molecules, such as antibodies, oligonucleotides, peptides, etc. Consideration should also be given to the required stability, development time frame and budget, and the specific biomolecule to be coated. Standard microsphere products support three basic coating strategies: adsorption, covalent coupling, and affinity binding.
4. Many applications in the life sciences demand added properties, such as fluorescence or a visible color, or iron oxide inclusions for magnetic separations. Dye concentrations can be adjusted to produce beads with different intensities to meet special needs, such as QuantumPlex™ for multiplexed flow cytometric assays, or our Dragon Green or Flash Red Intensity Standards, which support imaging applications and associated instrument QC.

3.6 Criteria for microsphere preparation

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by micro encapsulation technique.[29] The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross linking, drug of cross linking, evaporation time, coprecipitation etc.[30] Preparation of microspheres should satisfy certain criteria:

1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.
5. Biocompatibility with a controllable biodegradability and
6. Susceptibility to chemical modification.

3.7 Materials used[31]

Synthetic polymers are divided into two types.

i. Non-biodegradable polymers

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

ii. Biodegradable polymers[32, 33]

- Lactides, Glycolides & their co polymers
- Poly alkyl cyano Acrylates
- Poly anhydrides

Natural polymers obtained from different sources like Proteins, carbohydrates and chemically modified carbohydrates.[34,35]

A] Proteins

- Albumin
- Gelatin
- Collagen

B] Carbohydrates

- Agarose
- Carrageenan
- Chitosan[36]
- Starch

C] Chemically modified carbohydrates

- Poly dextran[37]
- Poly starch.

3.8 Methods of preparation of microspheres

There are different methods for the preparation of microspheres as shown in Fig. 4.

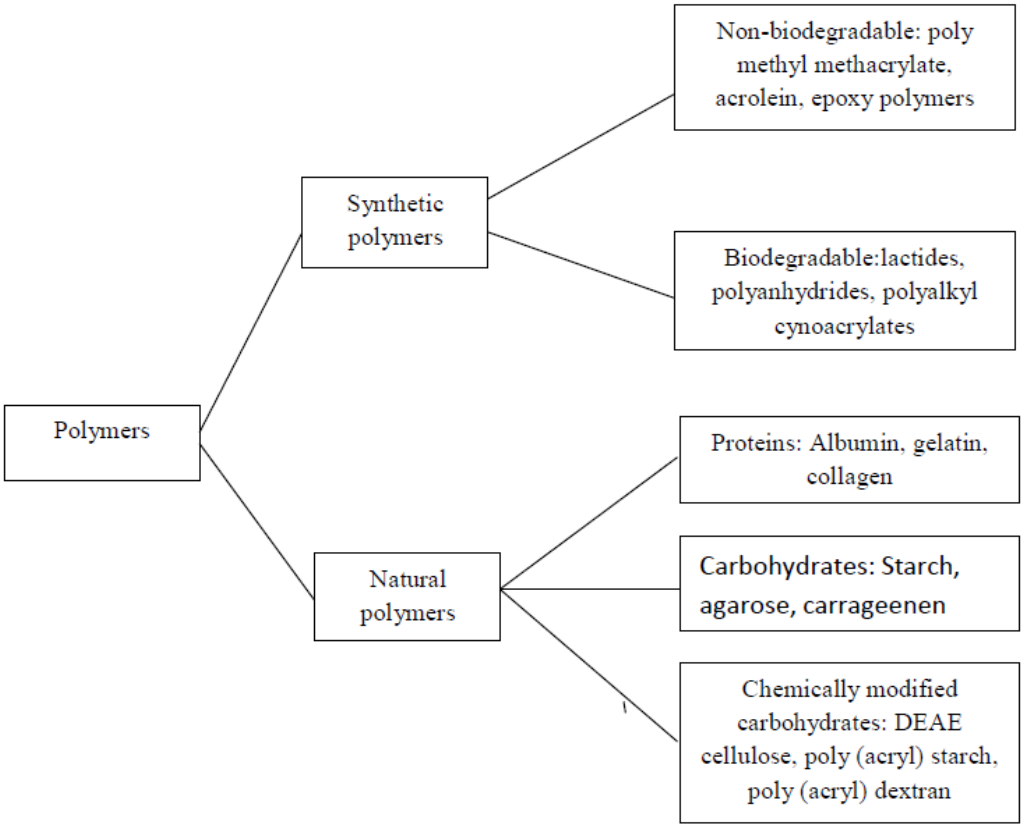

Fig 4: Types of polymers used for the preparations of microspheres.

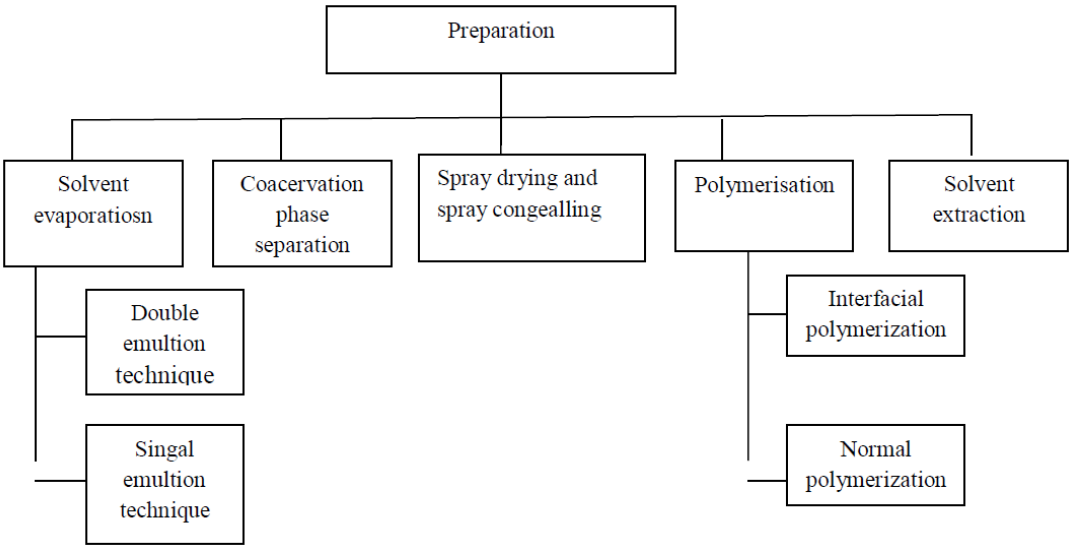

Fig. 5: Method of preparation of microspheres.

3.8.1 Emulsion solvent Evaporation Technique: In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2% sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs.[38]

3.8.1.1 Single emulsion technique: The micro particulate carriers of natural polymers which are proteins and carbohydrates are prepared by single emulsion technique (Fig. 6). The natural polymers are dissolved/dispersed in aqueous medium followed by dispersion in the non-aqueous medium e.g., oil. In the next step, cross linking of the dispersed globule is carried out either by means of heat or by using chemical cross linkers. Cross linking by heat is affected by adding the dispersion to previously heated oil. Heat denaturation is not suitable for the

thermo labile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing andseparation.[39]

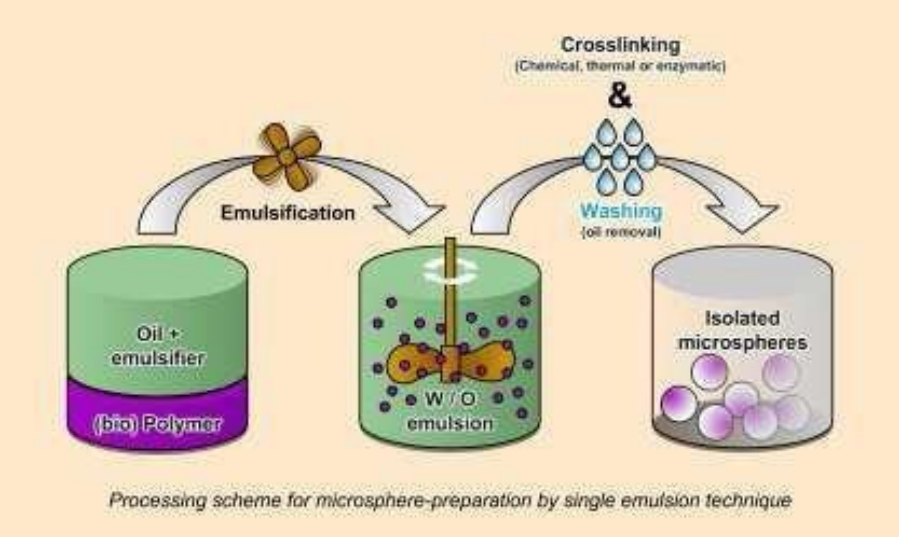

Fig. 6: Microspheres by Single Emulsion Technique.

3.8.1.2 Double emulsion technique[39]: This process consumes formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to the water soluble drugs, peptides, proteins and the vaccines (Fig. 7). The aqueous protein solution is dispersed in a lipophilic organic continuous phase which is generally consisted of polymer solution that eventually encapsulates protein contained in dispersed aqueous phase. The primary emulsion is then subjected to the homogenization before addition to aqueous solution of PVA. This results information of double emulsion which is then subjected to solvent removal by solvent evaporation maintaining the emulsion at reduced pressure or by stirring so that organic phase evaporates out. Examples are hydrophilic drugs like LHRH agonist, vaccines and proteins.

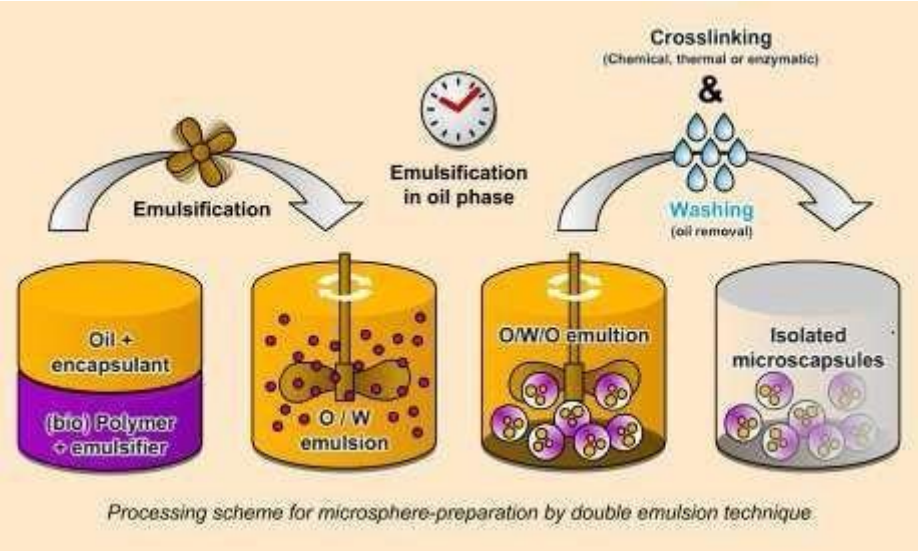

Fig. 7: Microspheres by Double Emulsion Technique.

3.9 Loading of drug

The active components are loaded over the microsphere principally using two methods i.e., during the preparation of the microsphere or after the formation of the microspheres by incubating them with the drug/protein. The entrapment largely depends on the method of preparation and nature of the drug or polymer (monomer, if used). Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives (e.g., cross- linking agent, surfactant stabilizers, etc.) heat of polymerization, agitation intensity, etc.

The drugs and protein can also be incorporated by physical or chemical linkage. The adsorption of the drugs

by proteins depends on the nature of the polymers.[40] The Freundlich model is applied to determine the adsorption of the drugs. The Freundlich equation is:

$$X/M = KC^{p}_{eq}$$

Where, K constant related to the capacity of the adsorbent for the adsorbate and P constant related to the affinity of the adsorbent for the adsorbate.

Although, this equation was first employed empirically, it can be derived with the assumption of a continuously varying heat of adsorption. The Freundlich model unfortunately predicts both infinite adsorptions at infinite concentration and an infinite heat of adsorption at zero coverage.

3.10 METHODS

3.10.1 In Vitro methods

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of in vitro and *in vivo* techniques have been reported. *In vitro* drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physico chemically and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating in vivo conditions has led to development of a number of in vitro release methods for buccal formulations however no standard in vitro method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed.

Beaker method[41,42]: dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using overhead stirrer. Volume of the medium used in the literature for the studies varies from 50-500 mL and the stirrer speed form 60-300 rpm.

Interface diffusion system: This method is developed by Dearden and Tomlinson. It consists of four compartments. The compartment A represents the oral cavity and initially contained an appropriate concentration of drug in a buffer. The compartment B representing the buccal membrane, contained 1-octanol and compartment C representing body fluids, contained 0.2 M HCl. The compartment D representing protein binding also contained 1-octanol. Before use, the aqueous phase and 1-octanol were saturated with each other. Samples were withdrawn and returned to compartment A with a syringe.

Modified Keshary Chien cell[43]: developed a specialized apparatus in the laboratory. It comprised of a Keshary Chien cell containing distilled water (50 mL) at 37°C as dissolution medium. Trans Membrane Drug Delivery System (TMDDS) was placed in a glass tube fitted with a 10 No. sieve at the bottom which reciprocated in the medium at 30 strokes per minute.

Dissolution apparatus: Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using rotating elements, paddle[44] and basket.[45] Dissolution medium used for the study varied from 100-500 mL and speed of rotation from 50-100 rpm.

3.10.2 In Vivo methods

Methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrants at the surface. Some of the earliest and simple studies of mucosal permeability utilized the systemic pharmacological effects produced by drugs after application to the oral mucosa. However, the most widely used methods include *in vivo* studies using animal models, buccal absorption tests and perfusion chambers for studying drug permeability.

Animal models: Animal models are used mainly for the screening of the series of compounds, investigating the mechanisms and usefulness of permeation enhancers or evaluating a set of formulations. A number of animal models have been reported in the literature, very few in vivo animal models are the dogs[46], rats, rabbits[47], cats56, hamsters[48], pigs and sheep[49] etc. In general, the procedure involves anesthetizing the animal followed by administration of the dosage form. In case of rats, the esophagus is ligated to prevent absorption pathways other than oral mucosa. At different time intervals, the blood is withdrawn and analyzed.

Buccal absorption test: The buccal absorption test was developed by Beckett and Trigg's (1967). It is a simple and reliable method for measuring the extent of drug loss of the human oral cavity for single and multi-component mixtures of drugs. The test has been successfully used to investigate the relative importance of drug structure, contact time, initial drug concentration and pH of the solution while the drug is held in the oral cavity.

3.10.3 In Vitro-In Vivo correlations

Correlations between in vitro dissolution rates and the rate and extent of availability as determined by blood concentration and or urinary excretion of drug or metabolites are referred to as "in vitro-*in vivo* correlations". Such correlations allow one to develop product specifications with bioavailability**.**

3.11 Applications

Applications of types of microspheres: New applications for microspheres are discovered every day few are given in Table 2. Some formulations are also presented in Fig. 8.

Table 2: Applications of Types of Microspheres.

Types of microspheres	Applications
Radioactive	Radioembolization of liver and spleen tumors, local radiotherapy, localrestenosis prevention in coronary arteries
Fluorescent	Blood flow determination, reacing, in vivo imaging and calibration ofimaging
Hollow Monodisperse	Used to decrease material density
Ceramic	Calibrate particle sieves and particles counting apparatusPaints and powder coatings
Magnetic	Used for drug targeting, magnetic fluid hyperthermia, improvement indrug release

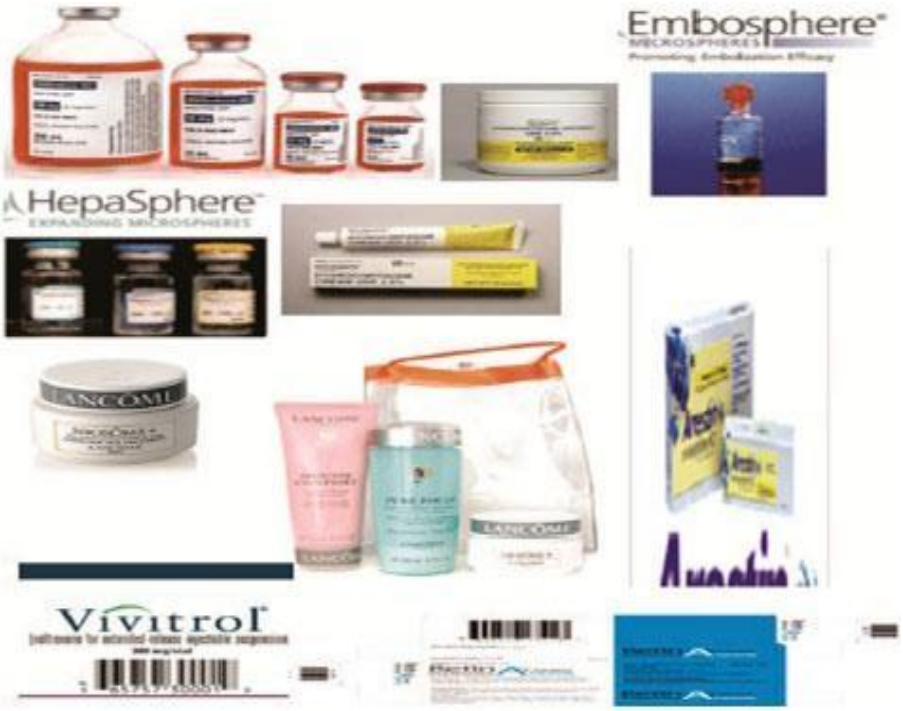

Fig. 8: Marketed formulations.

3.11.1 Microspheres in Vaccine Delivery: The prerequisite of a vaccine is protection against the micro organism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, safety, convenience in application and cost. The aspect of safety and minimization of adverse reaction is a complex issue.[50] The aspect of safety and the degree of the production of antibody responses are closely related to mode of application. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines.[51] The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies sincethey offer specific advantages including:

1. Improved antigen city by adjuvant action
2. Modulation of antigen release
3. Stabilization of antigen.

3.11.2 Targeting using Microparticulate Carriers: The concept of targeting, i.e. site specific drug delivery is a well established dogma, which is gaining full attention. The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors. The ability to leave the pool in reproducible, efficient and specific manner is center to drug action mediated by use of a carrier system. Placement of the particles indiscrete anatomical compartment leads to their retention either because of the physical properties of the environment or biophysical interaction of the particles with the cellular content of the target tissue.

3.11.3 Monoclonal Antibodies Mediated Microspheres Targeting: Monoclonal antibodies targeting microspheres are immune microspheres. This targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites. Mabs can be directly attached to the microspheres by means of covalent coupling. The free aldehyde groups, amino groups or hydroxyl groups on the surface of the microspheres can be linked to the antibodies. The Mabs can be attached to microspheres by any of the following methods

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

3.11.4 Chemoembolisation: Chemoembolisation is an endovascular therapy, which involves theselective arterial embolisation of a tumour together with simultaneous or

subsequent local delivery the chemotherapeutic agent. The theoretical advantage is that such embolisations will not only provide vascular occlusion but will bring about sustained therapeutic levels of chemotherapeutics in the areas of the tumour. Chemoembolisation is an extension of traditional percutaneous embolisation techniques.

3.11.5 Imaging: The microspheres have been extensively studied and used for the targeting purposes. Various cells, cell lines, tissues and organs can be imaged using radio labelled microspheres. The particle size range of microspheres is an important factor in determining the imaging of particular sites. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintiographic imaging of the tumour masses in lungs using labelled human serum albumin microspheres.

3.11.6 Topical Porous Microspheres: Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5-300 µm. These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders. Micro sponges consist of non collapsible structures with porous surface through which active ingredients are released in a controlled manner.[52]

3.11.7 Surface Modified Microspheres: Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution patterns .The adsorption of the poloxamer on the surface of the polystyrene, polyester or poly methyl methacrylate microspheres renders them more hydrophilic and hence decrease their MPS uptake. Protein microspheres covalently modified by PEG derivatives show decreased immunogenicity and clearance. The most studied surface modifiers are:

1. Antibodies and their fragments
2. Proteins
3. Mono-, oligo- and polysaccharides
4. Chelating compounds (EDTA, DTPA or Desferroxamine)
5. Synthetic soluble polymers such modifications are provided surface of microspheres inorder to achieve the targeting to the discrete organs and to avoid rapid clearance from the body.

3.12 Recent advancement in microsphere

3.12.1 Important utilizations of chitosan polymer Cholesterol-lowering effects: The serum cholesterol levels in a control group of mice fed a high fat/high cholesterol diet for 3 weeks increased about 2-fold to 4·3mM and inclusion of any of these fibers at 7·5% of the diet prevented this increase from occurring. The mechanisms underlying the cholesterol lowering effect of cholestyramine were

1) Decreased cholesterol (food) intake,
2) Decreased cholesterol absorption efficiency, and
3) Increased faecal bile acid and cholesterol excretion. The latter effects can be attributed to the high bile acidbinding capacity of cholestyramine.

In contrast, incorporation of chitosan or cellulose in the diet reduced cholesterol (food) intake, but did not affect either intestinal cholesterol absorption or faecal sterol output. The present study provides strong evidence that above all satiation and satiety effects underlie the cholesterollowering.[53]

3.12.2 Increase Stability of Drug: Chitosan polymer is used to increase the stability of the drug in which the drug is complexed with chitosan and make slurry and kneading for 45 minutes until dough mass. This dough mass is pass through sieve no.16 and make a granules is completely stable at different condition.

3.12.3 Orthopaedic Patients: Chitosan is a biopolymer that exhibits osteo conductive, enhanced wound healing and antimicrobial properties which make it attractive for use as a bioactive coating to improve Osseo integration of orthopedic and craniofacial implant devices. It has been proven to be useful in promoting tissue growth in tissue repair and accelerating wound-healing and bone regeneration.

3.12.4 Cosmetics industry: Cosmetic compositions are disclosed for the treatment of hair or skin, characterized by a content of new quaternary chitosan derivatives of the formula. The chitosan derivatives have a good substantial, particularly to hair keratin, and prove to have hair strengthening and hair conditioning characteristics. e.g.; Hair setting lotion, Oxidation Hair- coloring Composition, Hair toning Composition, Skin Cream, Hair treatment Composition, Gel- form.

3.12.5 Dental Medicine: Chitosan have been recognized to accelerate wound healing to attain anaesthetically valid skin surface, and to prevent excess scar formation. In dental medicine, chitosan is also applied as a dressing for oral mucous wound and a tampon following radical treatment of maxillary sinusitis. Furthermore, it is being investigated as an absorbing membrane for periodontal surgery. Chitosan has a variety of biological activities and advertised as a healthy food that is effective for improvement and/or care of various disorders, arthritis, cancer, diabetes, hepatitis, etc.

3.12.6 Chitosan as Permeation Enhancer: It has been reported that chitosan, due to its cationicnature is capable of opening tight junctions in a cell membrane. This property has led to a number of studies to investigate the use of chitosan as a permeation enhancer for hydrophilic drugs that may otherwise have poor oral bioavailability, such as peptides. Because the absorption enhancement is

caused by interactions between the cell membrane and positive charges on the polymer, the phenomenon is pH and concentration dependant. Furthermore increasing the charge density on the polymer would lead to higher permeability.

3.12.7 Chitosan as Mucoadhesive Excipient: Bioadhesivity is often used as an approach to enhance the residence time of a drug in the GI tract, hereby increasing the oral bioavailability. A comparison between chitosan and other commonly used polymeric excipients indicates that the cationic polymer has higher bioadhesivity compared to other natural polymers, such as cellulose, Xantham gum, and starch.

3.12.8 Effect of chitosan: citric acid ratio on drug Release: It has been demonstrated that polymer with appropriate viscosity and expanding property can be used as osmotic agents for therelease of water-insoluble drug. Due to its high molecular weight and a linear unbranched structure, chitosan is completely biodegradable, toxicologically harmless and low cost, and exhibits an excellent gelation characteristic. Hence the potential for chitosan to be used as a polymeric osmotic agent in osmotic pump is obvious.

3.13Future challenges

Future challenges of microspheres look bright particularly in the area of medicinal field because of its wide spectrum of application in molecular biology, e.g. microsphere based genotyping platform is used to detect six single nucleotide polymorphism, yittrium-90 microspheres is used to prevent tumour after liver transplantation and it's advanced way in delivery of vaccines and proteins.

4. CONCLUSION

It has been observed that microspheres are better choice of drug delivery system than many other types of drug delivery system because to it is having the advantage of target specificity and better patient compliance. It is concluded from above that microsphere is the promising candidate for sustained and as a targeted drug delivery in GIT, liver, colon, nasal, pulmonary system and ocular drug delivery etc. Microspheres by ion tropic gelation technique promises to be potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

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