**MICROPARTICULATE DRUG DELIVERY SYSTEM- A REVIEW****Bidyut Das and Juti Rani Devi***

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ABSTRACT

Microparticles are small particles of solids or small droplets of liquids surrounded by walls of natural & synthetic polymer films of varying thickness & degree of permeability acting as a release rate controlling substance & have a diameter up to the range of 0.1 μ m-200 μ m. Microparticles are now one of the very widely used technique for drug delivery as it has several advantages like improved bioavailability,

reduced dosage frequency, limited fluctuation during therapeutic range, low toxic effect etc. Several techniques for microparticles preparation are there among those spray drying, hot melt encapsulation, single emulsification, solvent evaporation, ionotropic gelation methods were mainly used, depending up on the type of microparticle to be prepared. Different types of microparticles that have prepared were magnetic, floating, bioadhesive, radioactive, mucoadhesive etc. One major advantage of the microparticulate drug delivery system is that by the use of either natural or synthetic rate controlling polymers it's drug release can be controlled for long period.

KEYWORDS: Microparticles; Microcapsules; Emulsification; Internal gelation; Methods.

INTRODUCTION

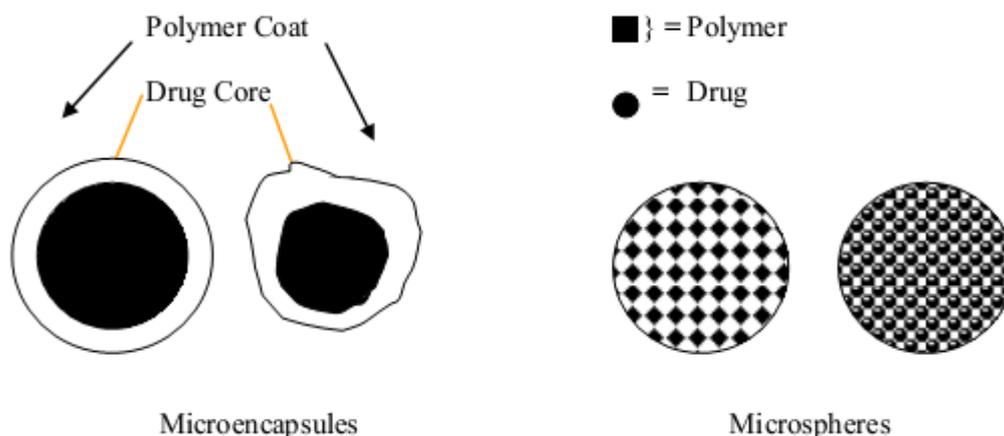
Novel drug delivery systems have several advantages over conventional multi dose therapy. Recent trends indicate that microparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from microparticles depends on a variety of

factors including the carrier used to form the microparticles and the amount of drug contained in them. Consequently, microparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development.^[1]

Between 1940s and 1960s, the concept of microencapsulating technology began as an alternative means of delivering drugs. It continued to evolve for more refined systems, in 1980s polymer membrane technology came to be known at forefront. Further, the process of targeting and site specific delivery with absolute accuracy has been shown to be achieved by attaching bioactive molecules to liposomes, bio-erodible polymers, implants, monoclonal antibodies and various particulate carriers (e.g. Nanoparticles and Microspheres, etc).^{[1],[2]}

The microparticulate delivery systems are considered and accepted as a reliable means to deliver the drug to the target site with specificity and to maintain the desired concentration at the site of interest without untoward effects.^[2]

Micro-particles are the polymeric entities falling in the range of 1-1000 μm . Microparticles covering two types of forms as follows: (1) Microencapsules: micrometric reservoir systems, (2) Microspheres: micrometric matrix systems. Microspheres are matrix systems and essentially spherical in shape, whereas microcapsules may be spherical or non-spherical in shape. Microcapsules are small particles, which contain an active agent or core material surrounded by a coating or shell. Microcapsules, which are smaller than 1 μm , are known as nanocapsules whereas those that have a diameter larger than 1000 μm are known as macrocapsules. The microspheres are spherical in shape.^[2]



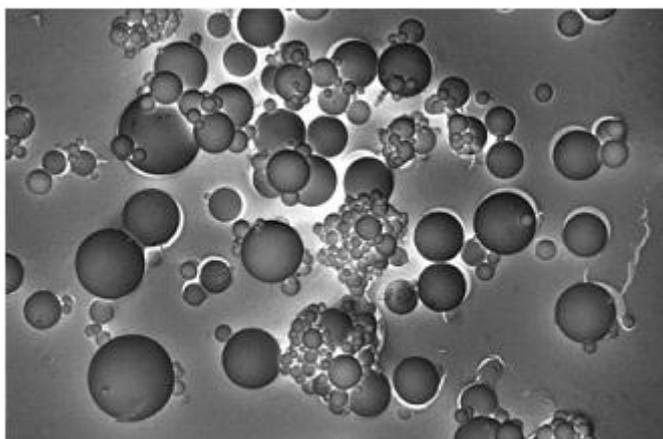


Fig1: Microscopic view of microspheres^[3]

Properties of an ideal microsphere^[3]

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.

Advantages of microparticles^[4]

1. Protection of unstable, sensitive materials from their environments prior to use.
2. Better processibility (improving solubility, dispersibility, flowability).
3. Self-life enhancement by preventing degradative reactions.
4. Masking of odour or taste.
5. They increased the relative bioavailability of drugs.
6. The formulation of microparticles also provides the method of targeting the drug delivery to specific sites.
7. The microparticles hold great potential in reducing the dosage frequency & toxicity of various drugs.
8. They provide the sustained release formulation with lower dose of drug to maintain plasma concentration & improved patient compliance.
9. They also have an advantage of being stored in dry particle or suspension form with little or no loss of activity over an extended storage period.
10. Limiting fluctuation within therapeutic range.

CATEGORIES OF MICROSPHERES

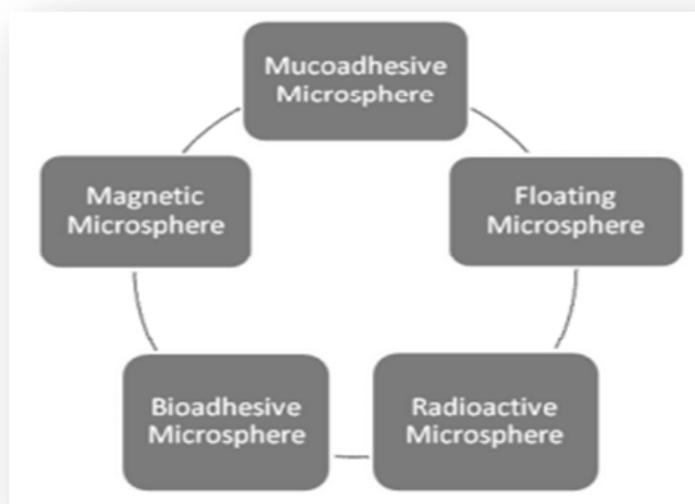


Fig2: Schematics of different categories of microsphere.

Mucoadhesive microspheres

These are of 1-1000mm 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. on the surface of the microspheres.^[5]

As these dosage forms facilitate intimate contact of the formulation with underlying absorption surface thus allows modification of tissue permeability for absorption of macromolecules, such as peptides and proteins. Inclusion of penetration enhancers such as sodium glycocholate, sodium taurocholate and L-lysophosphotidyl choline (LPC) and protease inhibitors in the mucoadhesive dosage forms resulted in the better absorption of peptides and proteins.^[6]

Mucoadhesive dosage forms also prolong residence time of the dosage form at the site of application and absorption to permit once or twice a day dosing.^[6]

Floating microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.^[5]

Radioactive microspheres

They are injected to the arteries that lead to tumor of interest. So all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues.^[6]

Bioadhesive microspheres

Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bioadhesion. Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. 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.^{[6][7]}

Magnetic microspheres

This type of delivery system is very important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. Magnetic microspheres can be filled with drugs or radioactive materials to treat a variety of illnesses. Magnets applied outside the body attract the spheres to the disease site where they deliver therapeutics in a targeted way. The magnets attract the microspheres to the immediate area of the wound site and stop them there. The spheres gradually break down and release growth factors over a period of weeks, allowing blood vessels and damaged tissues to re-grow and repair.^[7]

METHOD OF PREPARATION OF MICROPARTICLES

Following are the various methods for preparing microparticles.

1. Single Emulsification Technique.
2. Double Emulsification Technique.
3. Normal Polymerization Technique.
4. Interfacial Polymerization Technique.
5. Phase Separation Coacervation Technique.
6. Spray Drying and Spray Congealing Technique.
7. Solvent Extraction Method.
8. Solvent Evaporation.
9. Wet Inversion Technique.
10. Complex Coacervation.
11. Hot Melt Microencapsulation.
12. Iontropic gelation technique.

Single Emulsification Technique

Generally, by this technique carriers of natural polymers like proteins and carbohydrates are prepared. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, diacid chloride, tetra phthalate chloride etc. ^[8]

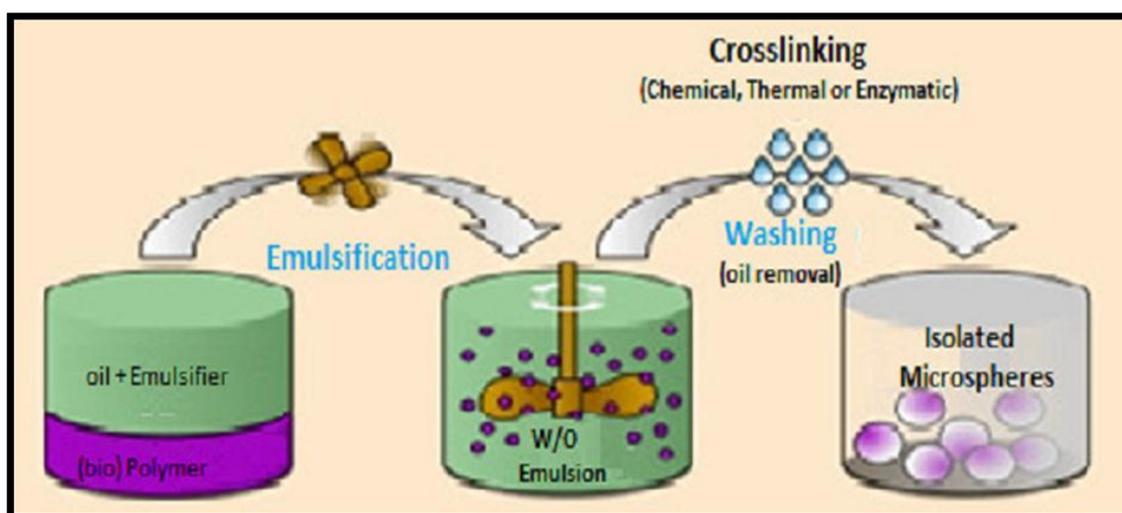


Fig3: Processing steps for microspheres by single emulsion technique

Double Emulsification Technique

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. The method can be used with both the natural as well as synthetic polymers. 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 in formation 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. ^{[9][10]}

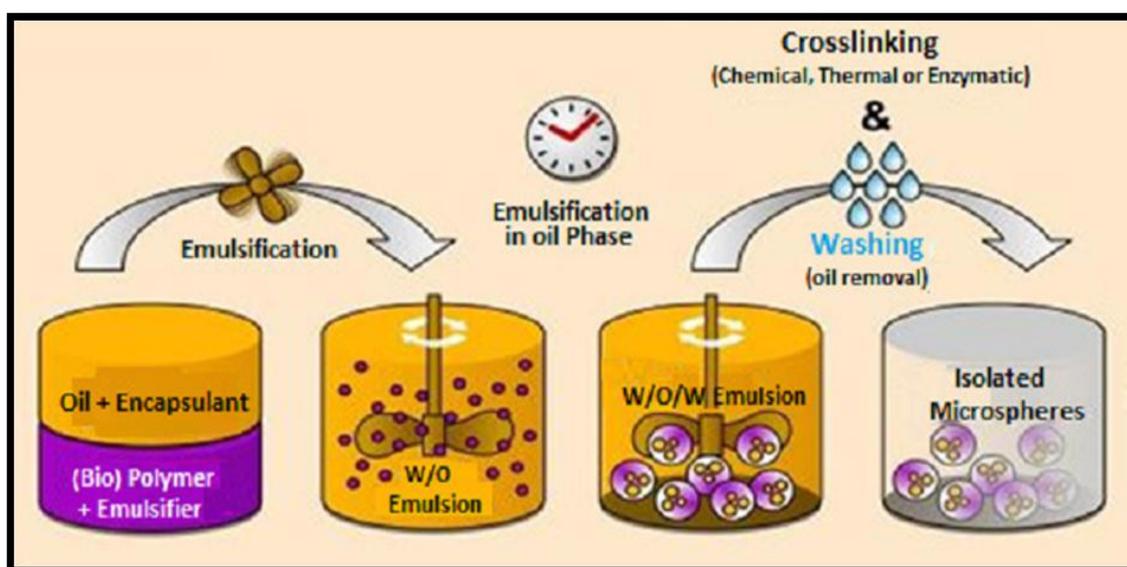


Fig4: Processing scheme for microspheres-preparation by double emulsion technique

Normal Polymerization Technique

This is done using different methods like bulk, suspension, precipitation, emulsion and micellar polymerization processes. Suspension polymerization also called bead polymerization. This is done by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase.

In bulk a mixture of monomers along with the initiator or catalyst is heated to initiate polymerization. Polymer thus obtained can be modulated as microspheres. ^[10]

Interfacial Polymerization Technique

It involves reaction of various monomers at the interface between the 2 immiscible liquid phases to form a film of polymer that essentially envelopes the dispersed phase.^[11]

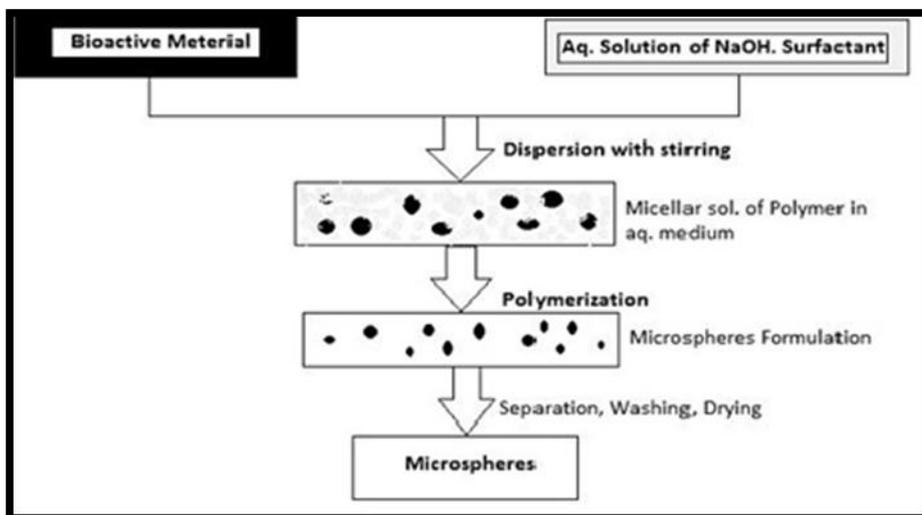


Fig5: Polymerization method.

Phase Separation coacervation Technique

In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer.^{[11][12]}

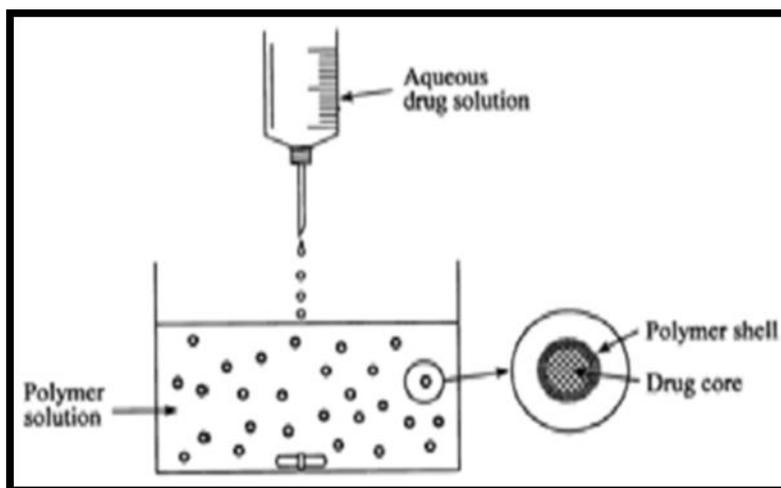


Fig 6: Coacervation phase separation method.

Spray Drying and Spray Congealing Technique

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 μm .

Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. spray drying process is used to encapsulate various penicillins.^[13]

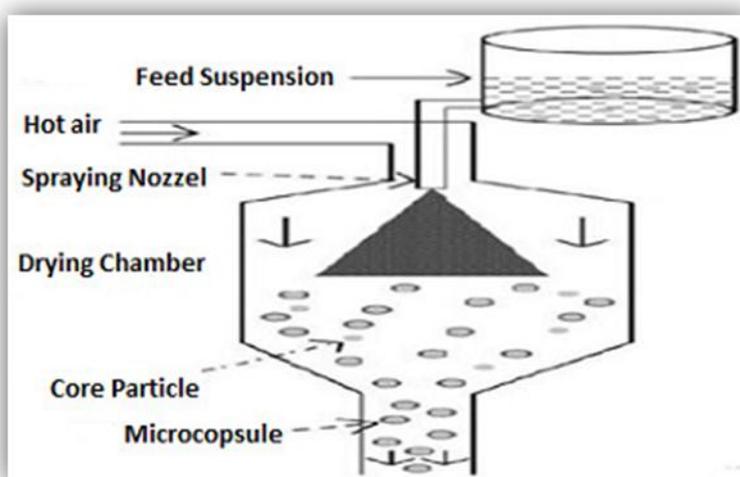


Fig7: Spray drying or spray congealing.

Solvent Extraction Method

It involves the removal of organic phase by extraction of the organic solvent. Here mainly water miscible organic solvents like isopropanol are used, and organic phase is removed by extraction with water. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.^[14]

Solvent Evaporation

The method is carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is dispersed in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix type microcapsules are formed. ^[15]

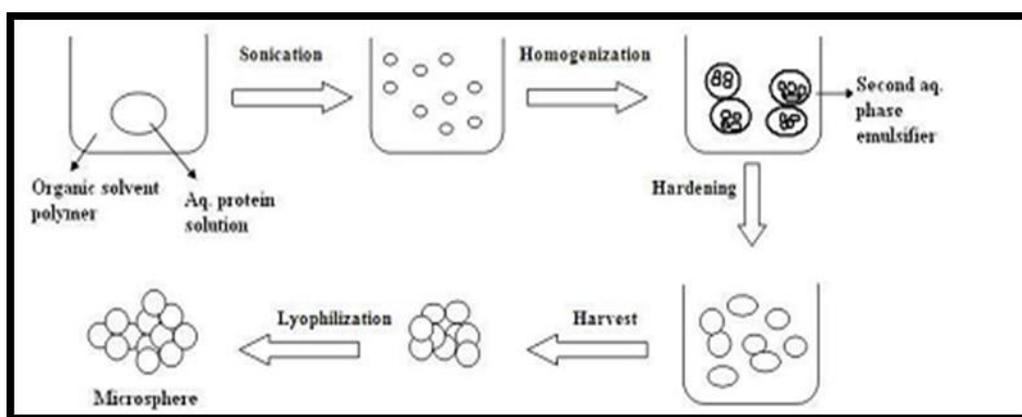


Fig 8: Solvent evaporation method schematically.

Wet Inversion Technique

Chitosan solution in acetic acid was dropped into an aqueous solution of counter ion sodium tripolyphosphate through a nozzle. Microspheres formed were allowed to stand for 1hr and cross linked with 5% ethylene glycol diglycidyl ether. Microspheres were then washed and freeze dried. ^[15]

Complex Coacervation

Chitosan microparticles can also prepare by complex coacervation, Sodium alginate, sodium CMC and sodium polyacrylic acid can be used for complex coacervation with Chitosan to form microspheres. These microparticles are formed by interionic interaction between oppositely charged polymers solutions and KCl & CaCl₂ solutions. The obtained capsules were hardened in the counter ion solution before washing and drying. ^[16]

Hot Melt Microencapsulation

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 μ m. Then the mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5°C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. ^[17]

The Iontropic Gelation Method

The ionotropic gelation method is a very simple and inexpensive. In the ionotropic gelation method polysaccharides (alginate, gellan and pectin) are dissolved in water or in weak acidic medium. These solutions are then added drop wise under constant stirring to the solutions containing other counter ions. Due to the complexation between oppositely charged species polysaccharides undergo ionic gelation and precipitate to form spherical particles (microcapsules or beads). The microcapsules were separated by filtration washed with distilled and dried.

The counter ions used for ionotropic gelation method are calcium chloride, barium chloride, zinc chloride, copper chloride, cobalt chloride, pyrophosphate. Chitosan, sodium alginate, gellan, pectin were some of the recently used polysaccharide. ^{[17][18]}

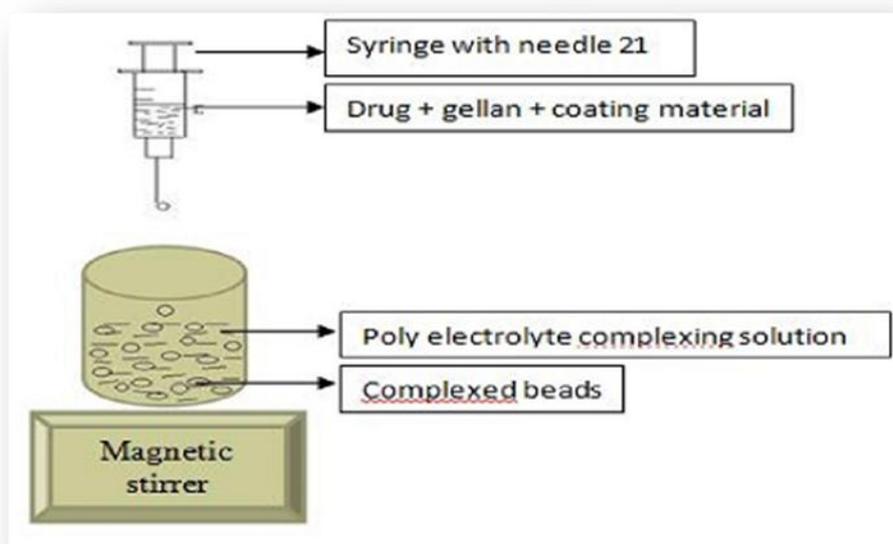


Fig 9: Iontropic gelation method.

POLYMERS USED IN PREPARATION OF MICROPARTICLES

During the preparation of microparticle a number of polymers are used some of they are given in table1.

Table 1: Polymer used for preparation of microparticle^[18]

Coating material	Solvent for coating material	Phasing out solvent (non-solvent)
Acrylonitrile styrene	Methyl ethyl ketone	Polybutadiene
Benzyl cellulose	Trichloroethylene	Propanol
Cellulose nitrate	Methyl ethyl ketone	Polybutadiene
Epoxy resin	Toluene	Polybutadiene
Ethyl cellulose	Methyl ethyl ketone	Polydimethyl siloxane
Natural rubber	Benzene	Methanol
Polyethylene	Xylene	Ethanol
Polymethyl methacrylate	Benzene	Polybutadiene siloxane
Polystyrene	Xylene	Petroleum ether
Polyvinyl acetate	Chloroform	Isopropanol
Polyvinyl formaldehyde	Nitropropane	Polybutadiene
Styrene maleic acid	Ethanol	Isopropyl ether
Vinyl diene chloride acrylonitrile	Methylethyl ketone	Polybutadiene

FACTORS AFFECT IN THE PREPARATION OF MICROPARTICLES^{[18][19]}

Following are different factors which affect in preparation of microparticles.

Stabilizer

The main functions of a stabilizer are to wet the drug particles thoroughly, and to prevent Ostwald's ripening and agglomeration of microparticles in order to yield a physically stable formulation by providing steric or ionic barriers.

- Eg: cellulosics, poloxamers, polysorbates, lecithins and povidones, Lecithin.

Organic solvents

Organic solvents may be required in the formulation of microparticles if they are to be prepared using an emulsion or microemulsion as a template. The acceptability of the organic solvents in the pharmaceutical arena, their toxicity potential and the ease of their removal from the formulation need to be considered when formulating microparticles using emulsions or microemulsion as templates

- Eg: ethanol and isopropanol, and partially water miscible solvents, such as ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate and benzyl alcohol.

Co-surfactants

Co-surfactant can greatly influence the phase behavior.

- Eg: bile salts and dipotassium glycerrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol.

Other additives

Microparticles may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiety.

PROGRESSES IN MICROPARTICULATE DRUG DELIVERY SYSTEMS

❖ **Brahmaiah B, Desu PK, Nama S, et al. 2013**, prepared simvastatin microspheres by orifice-ionotropic gelation method using polymers such as HPMC (K 100 M), carbopol 940P, sodium CMC, guar gum, sodium alginate, ethyl cellulose, methyl cellulose and xanthan gum and it was reported that, one formulation shows extended drug release of 97.11% up to 8 hrs, in phosphate buffer pH 7.0. Surface morphology (SEM) and drug polymer interaction (FTIR) studies were performed, SEM shows smooth elegant appearance and FTIR indicated lack of drug polymer interactions.^[2]

❖ **Vadda AK, Ramana JV, Anand P. 2013**, formulate metoprolol succinate micro beads by ionotropic gelation method using alginate acid, sodium CMC, and calcium chloride as cross linking agent in different ratios and it was found that, beads show maximum drug loading capacity of 77.647-168.823% and encapsulation efficiency of 84.868%, and the formulation shows invitro release up to 6 hrs, as well as the beads shows significant result in different kinetic models like zero order, Higuchi and in Korsmeyer Peppas model.^[4]

❖ **Goudanavar P, Reddy S, Hiremath D, et al. 2013**, prepared esomeprazole loaded gastroretentive microspheres by using ethyl cellulose and different grades of HPMC like HPMC K4M, HPMC K15M using dichloromethane as a solvent, and it was concluded that, the prepared microspheres were found to be free flowing with good buoyancy of 10hrs with a good particle size of $67.24 \pm 4.57 \mu\text{m}$ to 106.35 ± 3.67 . In vitro release profile and diffusion profile show very good controlled release property, and FTIR and DSC studies reveal the absence of drug polymer interaction.^[7]

❖ **Patel H, Patel R, Patel G. 2012**, prepared verapamil hydrochloride microspheres by ionotropic gelation method using polymers like sodium alginate, HPMC, and it was concluded that it showed up to 8 hrs of release in acid buffer pH 1.2 and in phosphate buffer pH 7.2. Surface morphology study shows elegant appearance, and the microspheres shows very good entrapment efficiency.^[10]

❖ **Saleem MA, Muroli YD, Naheed MD. 2012**, prepared valsartan loaded hydrogel beads by ionotropic gelation method using chitosan, sodium alginate and sodium carboxy methyl cellulose. FTIR studies show very good compatibility between drug and the polymer, SEM studies revealed that the beads show spherical or disc shaped with smooth or rough surface. As well as the entrapment efficiency of the prepared beads were found more than 90% and the in vitro study show release up to 10 hr in phosphate buffer pH 6.8.^[12]

❖ **Ramteke KH, Vansola JB, Tailor DJ. 2012**, prepared metformin beads by ionotropic gelation method using Ca⁺², Al⁺³ and it was reported that, Ca⁺² cross linked beads show release upto 8hrs, while Al⁺³ cross linked beads show release upto 10 hrs, and it can be concluded that Al⁺³ is a better cross linking agent than Ca⁺².^[14]

❖ **Manjanna KM, Shivakumar B. 2011**, prepared dexibuprofen micro beads by ionotropic gelation method and it was reported that micro beads shows release up to 6hr in phosphate buffer pH 6.8 and shows release up to 12hr in simulated intestinal fluid in pH 7.4. Moreover, FTIR studies indicated very less drug polymer interactions.^[16]

❖ **Goudanavar PS, Bagali RS, Patil SM. 2010**, prepared diclofenac sodium micro beads by ionotropic gelation method using polymers like sodium alginate, chitosan, pectin and the drug entrapment efficiency was found to be 95%, the release was found also to be more sustained. It can be concluded that increasing calcium chloride concentration decreases the mean diameter of the micro beads.^[20]

CONCLUSION

The microparticles drug delivery system is a physical approach to alter and improve the pharmacokinetic and pharmacodynamics properties of various types of drug molecules. They have been used in vivo to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action with enhanced therapeutic benefit, while minimizing side effect. Various

aspects of microparticle formulations, characterization, effect of their characteristics and their applications in cell specific delivery of drug molecules and therapeutic genes will give the researchers and academicians a better insight of microparticulate drug delivery arena for better management of life threatening diseases.

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