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**Review Article**

# Microsphere: A Modern Approach to Novel Drug Delivery System

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## ABSTRACT

With the advances of our bio medical research, bio-technological improvement and modern genomics, a wide variety of new, more potent and highly specific therapeutics are being created. The aim of the drug delivery system is to provide a therapeutic amount of drug to the proper site of action in the body which should maintain the desired drug concentration. A well-designed controlled drug delivery system can overcome some of problems of conventional therapy and enhance therapeutic efficacy of the given drug, hence it improves bioavailability. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time, hence it is able to maintain a desired concentration of drug. Microspheres are solid approximately spherical particles ranging in size from 1 to 1000 micro meter. It is micrometric matrix system. For the preparation of microspheres synthetic and natural materials are used. These are prepared by methods like Single emulsion, Double emulsion, Polymerization, Phase separation coacervation, Emulsion solvent evaporation and solvent diffusion.

**Keywords:** Conventional therapy, biodegradable polymer microspheres, high bioavailability, micrometric matrix system, biocompatible

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## INTRODUCTION

Several routes may be designed for the delivery of drugs, either locally to a specific site or systemically for distribution to the entire body, Oral route is the most common. The oral route is preferred due to the ease of administration to most patients, as well as the ability to achieve systemic drug distribution. However, oral delivery is not suitable for treatments in which a local drug effect is required and is not easily amenable to fragile drugs, such as proteins, that may be degraded by the digestive system. It is also less bioavailable and less potent.

One of the major obstacles in ensuring therapeutic success of a drug is to ensure its proper bioavailability at the site of action. Of late, multitude of potent drugs have appeared in clinics, most of which are highly lipophilic and hence difficult to deliver efficiently by per oral route [1,2]. Several conventional strategies exist to develop solubility of such poorly water soluble drugs (classed under Biopharmaceutical Classification System as BCS Class II drugs) [3]. However, with such poorly water soluble drugs, most of these strategies do not provide the desired bioavailability improvement when the dose size and cost-effectiveness is considered. In this direction, huge potential exists in the field of colloidal drug delivery systems as a platform technology to act as delivery vehicles for BCS Class II drugs [3].Novel delivery systems have received much attention in contemporary drug delivery research due to their immense potential in targeting, improving solubility, bioavailability and permeability in modulating PK/PD of the drug. Till date several reports have supported the potential of different systems for drug delivery, though a comparative study of their efficacy in improving bioavailability of similar or congener drugs are rare [1]. Therefore, in the proposed research investigation, an attempt will be made to formulate and evaluate Microspheres Drug Delivery [4-6] for solubility & permeability improvement [4,5]. The endeavour will incorporate pharmaceutically acceptable polymers/carriers/ surfactants to study different formulation and processing characteristics of the systems for improvement of its bioavailability along with their comparative study using a model BCS class II drug [6-8].Such a novel delivery system would be useful not only to increase the bioavailability of the drug, but is expected to reduce dose and distribution related toxicity and increase the therapeutic efficacy and stability of the drug and to reduce the time and cost of the formulation development phase.

## FUNCTION OF MICROPHERE DRUG DELIVERY SYSTEM

- Reliable means to deliver the drug to the target site with specificity, if modified, and able to maintain the desired concentration at the site of action without undesired effects.
- Microspheres having specific charges and surface hydrophilicity are found to be important in determining the fate of particles in vivo.
- It is very useful for targeting anti cancerous drug to the specific tumour.
- Biodegradable microspheres can easily control the release of drug by controlling the particle matrix.
- Microsphere also protects the drug from enzymatic and photolytic cleavage.
- It masks the bitter taste by converting liquid to solid form.
- Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal [9].

## POLYMERS USED IN THE FORMUTATION OF MICROSPHERE

Generally bio degradable polymers are used in the formulation of microsphere because Bio degradable carriers which degrade in the body with non-toxic degradation products which do not provide carrier toxicity and are suitable for parenteral applications.

Two types of polymers are used here.

**Natural polymer**: Natural polymers obtained from different sources like carbohydrates proteins and chemically modified Carbohydrates. Albumin is a natural protein. It is considered as a potential carrier of drug or protein . It is broadly used in targeted drug delivery to the tumour cells. Chitosan is a de-acylated product of chitin. The effect of chitosan is suitable of its charge. It forms salts with inorganic and organic salts, but not soluble at neutral and alkaline pH values. Upon dissolution, the polymer gets positively charged as the amino groups of chitosan get protonated. [Shown in **fig No: 1**]

**Synthetic polymers:** These are derived synthetically by various mechanisms. [Shown in **fig No: 2**]

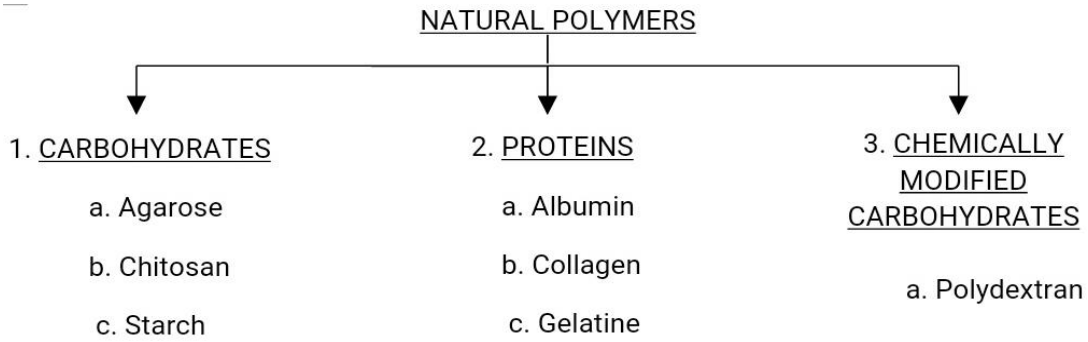


**Fig No 1: Classification of Natural Polymers**

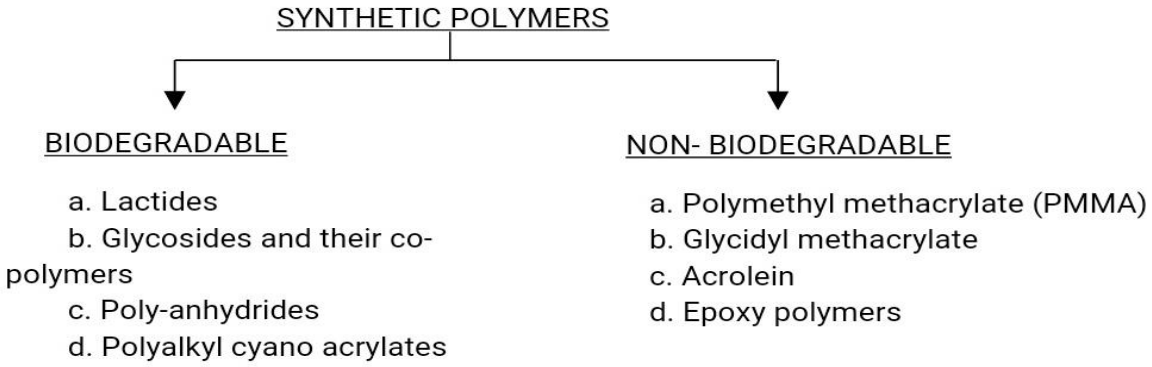


**Fig No 2: Classification Of Synthetic Polymers**

**DRUG RELEASE KINETICS**

There are three mechanism exists which established drug release kinetics through microsphere.

**A. Osmotically driven burst mechanism:** In this mechanism (**Fig. 3**), water diffuse into the core through biodegradable or non-biodegradable coating, creating sufficient pressure that ruptures the membrane.

The following factors are responsible to control the burst effect –

a) The macromolecule/polymer ratio
b) Particle size of the dispersed macromolecule and
c) The particle size of the microspheres.

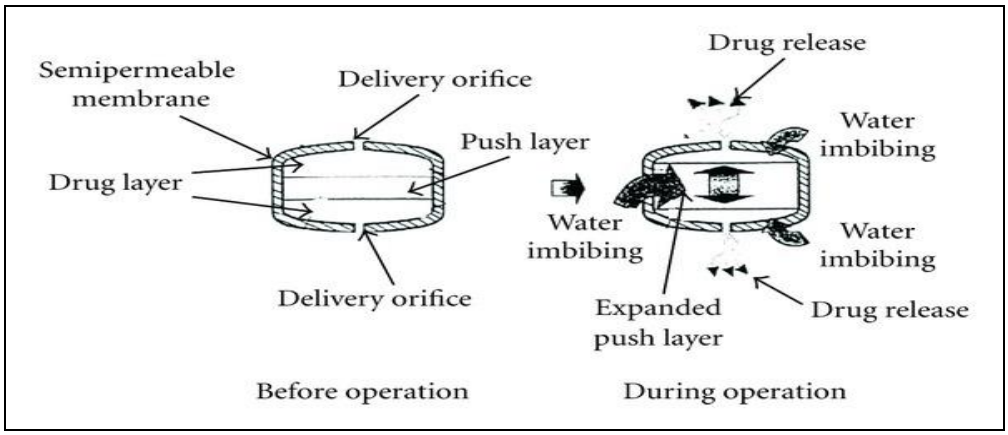


**Fig 3: Drug release by Osmotically driven burst mechanism**

**B. Pore diffusion method:** In this method the penetrating water front continue to diffuse towards the core. The polymer erosion, loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the matrix (**Fig. 4**)

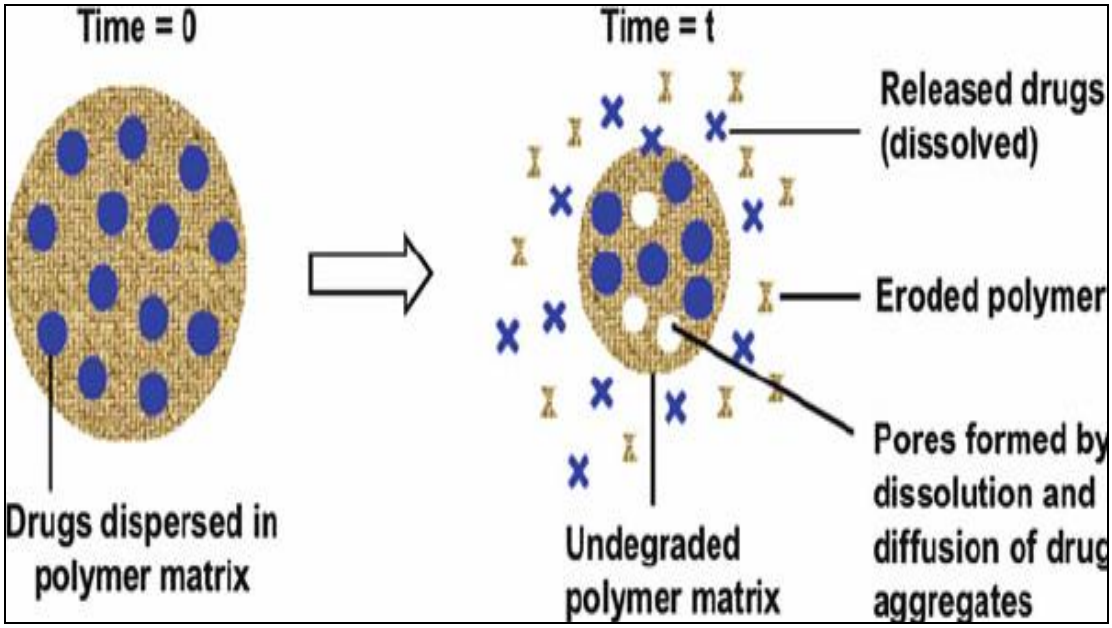


**Fig 4: Drug release by Pore diffusion method**

**C. Degradation of polymer:** Drug release from the non-biodegradable polymers can be known from the geometry of the carrier. The geometry of the carrier, whether it is reservoir type where the drug is present as core, or matrix type in which drug is dispersed throughout the carrier, governs overall release profile of the drug or active ingredients as shown in **fig 5**.

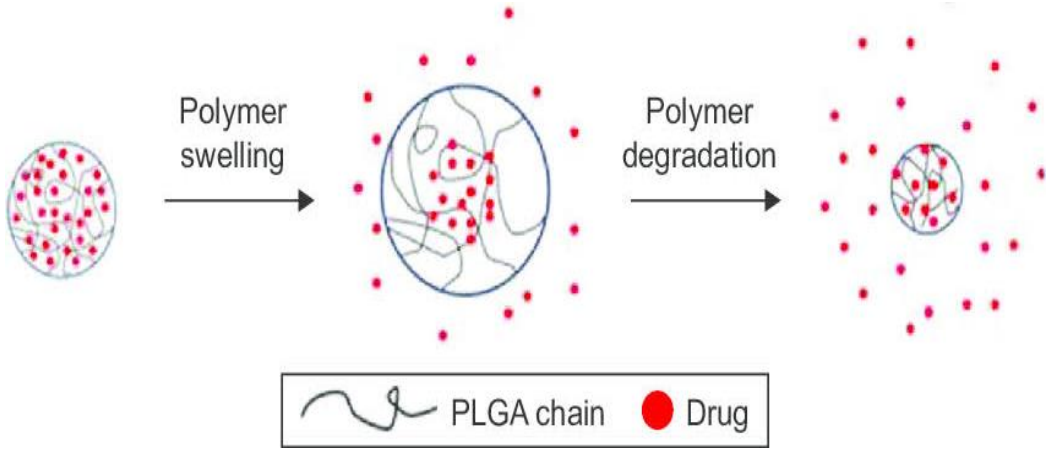


**Fig 5: Drug release by Degradation of polymer**

**CRITERIA FOR IDEAL MICROSPHERE PREPARATION:**

- High concentrations of the drug can be loaded.
- Shelf life stability of the preparation after synthesis is clinically acceptable.
- Particle size and dispersability is checked in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale(controlled release).
- Biocompatibility with a controllable biodegradability.
- It should be susceptible to chemical modification.
- It should able to incorporate proteins/hormones and deliver to the site of action.

**METHODS OF MICROSPHERE PREPARATIONS**

The various methods used in Microsphere preparation are as follows:

1. Single Emulsion Technique
2. Double Emulsion Technique
3. Spray Drying
4. Solvent Evaporation
5. Solvent Extraction
6. Polymerization Technique
    a. Normal Polymerization
    b. Interfacial Polymerization
7. Phase Separation Co-acervation Technique
8. Melt Dispersion Technique
9. Ionic Gelation Method

**Single emulsion technique:** Single emulsion technique (**Fig 6**) is useful for the micro particulate carriers of natural polymers. The natural polymers are generally dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. In then the cross linking of the dispersed globule can be achieved either by means of heat or by using the chemical cross linkers. Glutaraldehyde, formaldehyde, di-acid chloride etc these are some of the chemical cross linkers used in single emulsion technique. Heat denaturation process is not suitable for thermolabile substance. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation, drying. The nature of the surfactants are important for the emulsion phases which may influence the factors such as size, size distribution, surface morphology, loading, drug release, and bio performance of the final multi-particulate product [10].

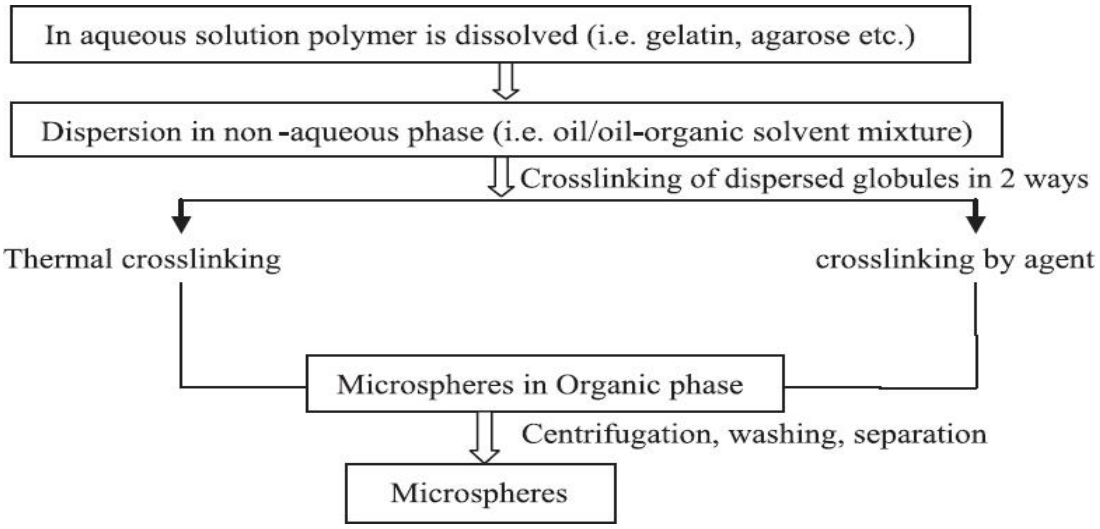


**Fig 6: Microsphere preparation by Single emulsion technique**

**Double emulsion technique:** In this method of microspheres preparation of multiple emulsions or the double emulsion of type w/o/w which is suitable for water soluble drugs, peptides, proteins and the vaccines. Natural and/or synthetic both polymer can used in this technique. At first the aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is further homogenized or sonicated prior to addition to the aqueous solution of the poly vinyl alcohol (PVA).This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction as shown in **fig 7**. Certain hydrophilic drugs like leutinizing releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are incorporated into the microspheres by the method of double emulsion solvent evaporation/ extraction [11].

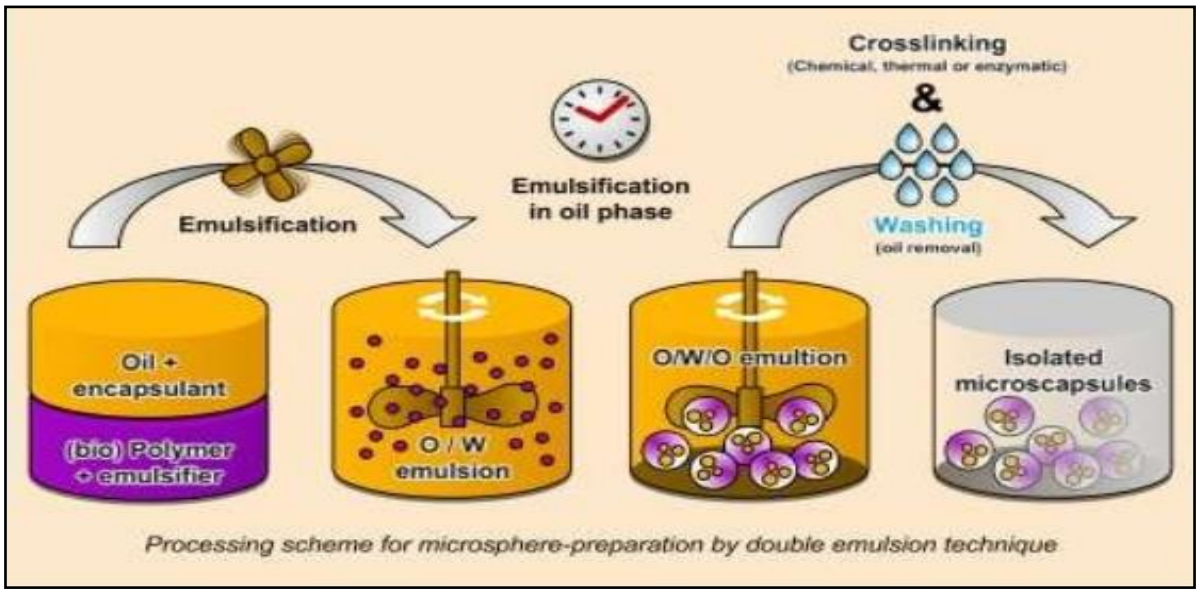


**Fig 7: Microsphere preparation by Double emulsion technique**

**Spray drying:** These methods are based on the drying of the mist of the polymer and drug in the air (**Fig 8**). Two processes such as spray drying and spray congealing are taken considering the removal of the solvent or cooling of the solution. In Spray Drying technique, the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug (solid form) is dispersed in the polymer solution with the help of high-speed homogenization, which 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 1-100µm. Separation of micro particles by hot air of cyclone separator and the traces of solvent is removed with the help of vacuum drying. One of the major advantages of this process is rapid and leads to the formation of porous micro particles.

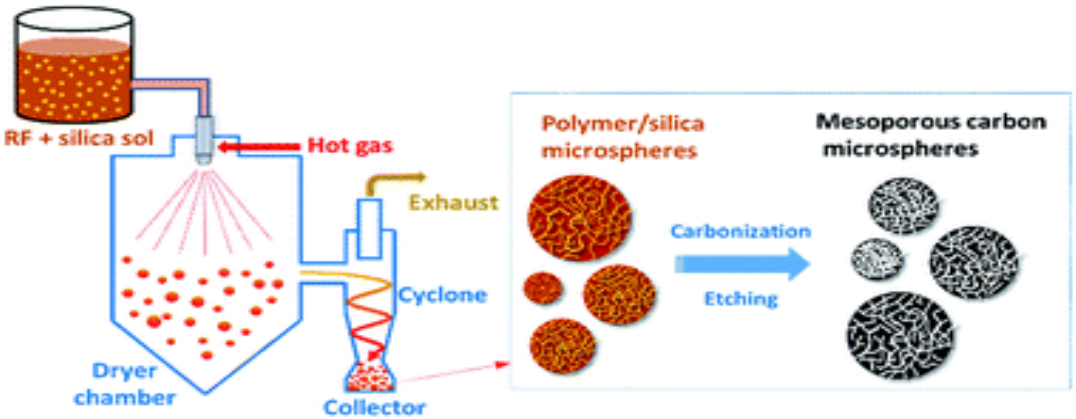


**Fig 8: Microsphere preparation by Spray drying technique**

**Solvent evaporation:** Solvent evaporation method is used for the preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent (**Fig 9**). The method implicates water mixable organic solvents like isopropanol. Organic phase is removed by extraction with water. This procedure reduces the hardening time for the microspheres. One dissimilarity of the process implicates direct inclusion of the drug or protein to polymer organic solution. Solvent evaporation include the development of an emulsion between polymer solution and non-miscible continuous phase even if aqueous (o/w) or non-aqueous. The rate of solvent ejection by extraction method controlled by the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.

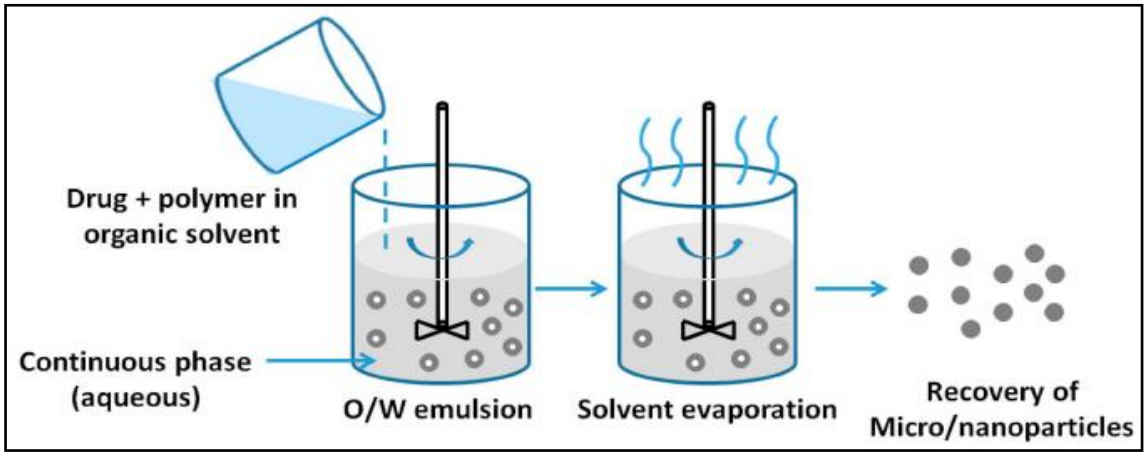


**Fig 9: Microsphere preparation by Solvent evaporation technique**

**Solvent extraction:** Solvent evaporation method is used for the preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent. The method implicates water mixable organic solvents like isopropanol as shown in **fig 10**. Organic phase is removed by extraction with water. This process reduces the hardening time for then microspheres. One dissimilarity of the process implicates direct inclusion of the drug or protein to polymer organic solution. The rate of solvent ejection by extraction method controlled by the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer [11].

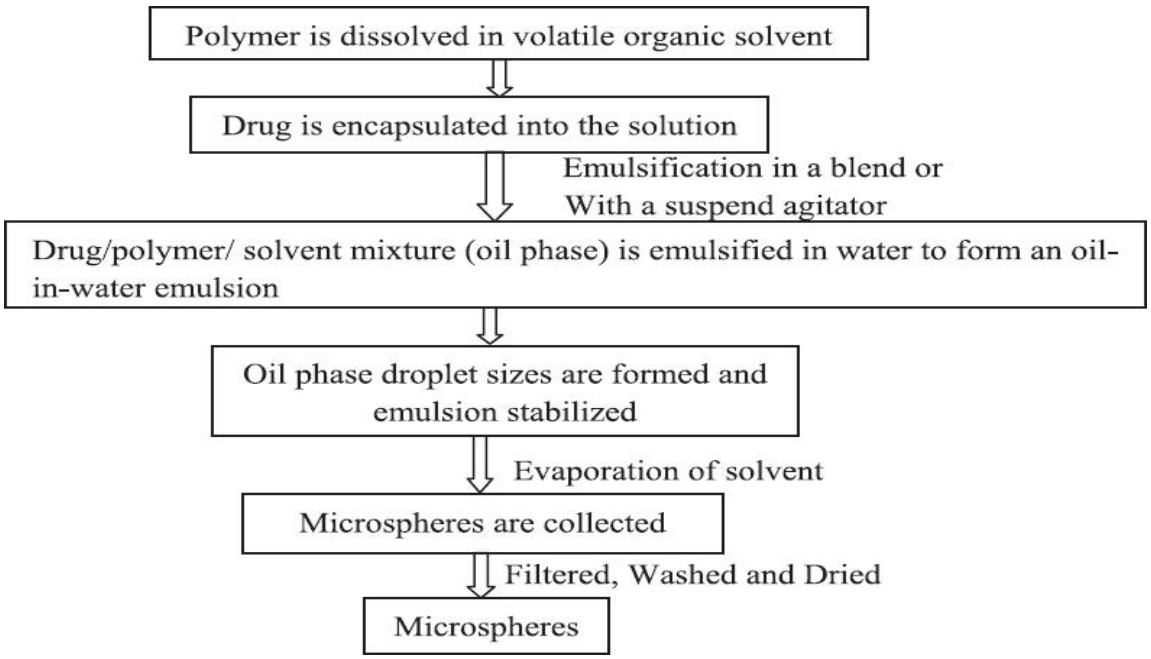


**Fig 10: Microsphere preparation by Solvent extraction**

**Polymerization techniques:** The polymerization method traditionally used for developing the microspheres are mostly classified as:
a. Normal polymerization
b. Interfacial polymerization
Liquid phase is used in both cases.

**a. Normal polymerization:** In bulk polymerization, a monomer or a combination of numeral of monomers together with the catalyst is usually heated to begin polymerization. Polymer, which is to be obtained, may be moulded as microspheres. Drug loading may be finished by inclusion of the drug during the method of polymerization. It is a pure polymer formation technique but it is very difficult to dissipate the heat of reaction which affects the thermolabile active ingredients. Suspension polymerization

is carried out of lower temperature and also refer to as pearl polymerization in which heating the monomer mixture with active drug as droplets dispersion in continuous aqueous phase. Microsphere dimension procured by suspension techniques is less the 100 μm. Emulsion polymerization is dissimilar from the suspension as due to existence of initiator in aqueous phase but is also achieved at low temperature as suspension external phase normally water in last two procedure so through which heat can easily dissipate.

**b. Interfacial polymerization:** Interfacial polymerization essentially proceeds including reaction of different monomers at merge between the two insoluble liquid phases to form a film of polymer that essentially envolves the dispersed phase. In this method two reacting monomers are engaged; one is dissolve in continuous phase while other is disperse in continuous phase (aqueous in nature) all over which the second monomer is emulsified. Two states appear because of solubility of formed polymer in the emulsion globule. That development is monolithic type of conveyor if the polymer is soluble in droplet. Capsular group found if the polymer is insolvable in droplet.

**Phase separation co-acervation technique:** This process is based on the concept of reducing the solubility of the polymer in organic phase to influence the development of polymer rich phase called the coacervates. In this process, the drug particles are diffused in a mixtute of the polymer and an incompatible polymer is attached to the system which produces first polymer to phase separate and engulf the drug particles as shown in **fig 11**. Incorporation of non-solvent produces the solidification of polymer. Poly lactic acid (PLA) microspheres have been produced by this procedure by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment [12].

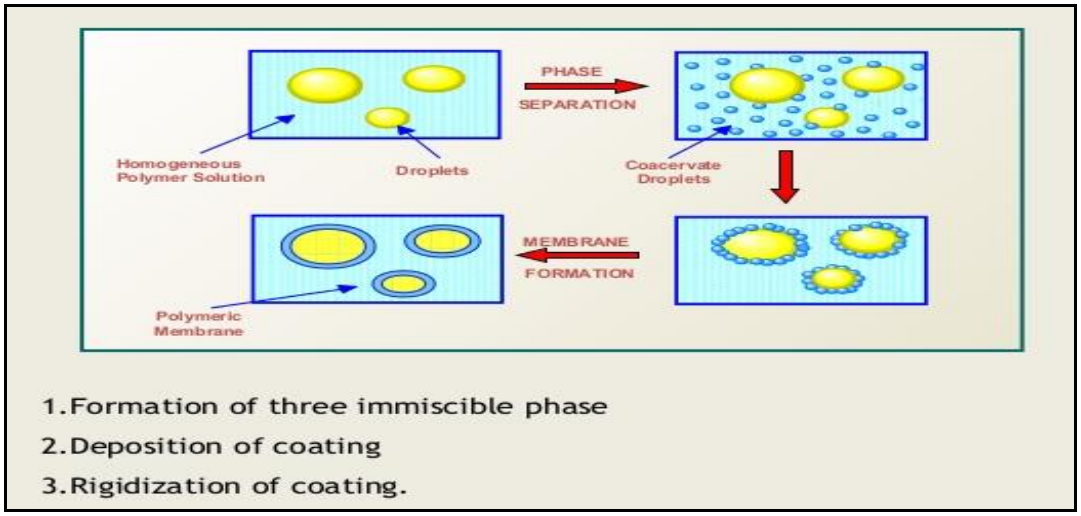


**Fig 11: Microsphere preparation by Phase separation co-acervation technique**

**Melt dispersion technique:** In this technique, the drug is dissolved/ dispersed in the molten lipid/wax like beeswax, spermaceti wax, castor wax, carnauba wax under continuous stirring to form a homogeneous blend. During the emulsion step of microsphere preparation, the temperature is maintained at about 100C above the melting point of lipid/wax. A dispersant solution, previously heated to 50C above the lipid/wax melting point, is added to the melt with constant stirring to form an o/w emulsion. Hardening of the oily internal phase (containing lipoid/wax and drug) and formation of microspheres is accomplished by pouring twice the emulsion volume of ice-cold water into the emulsion [12] (**Fig 12**).

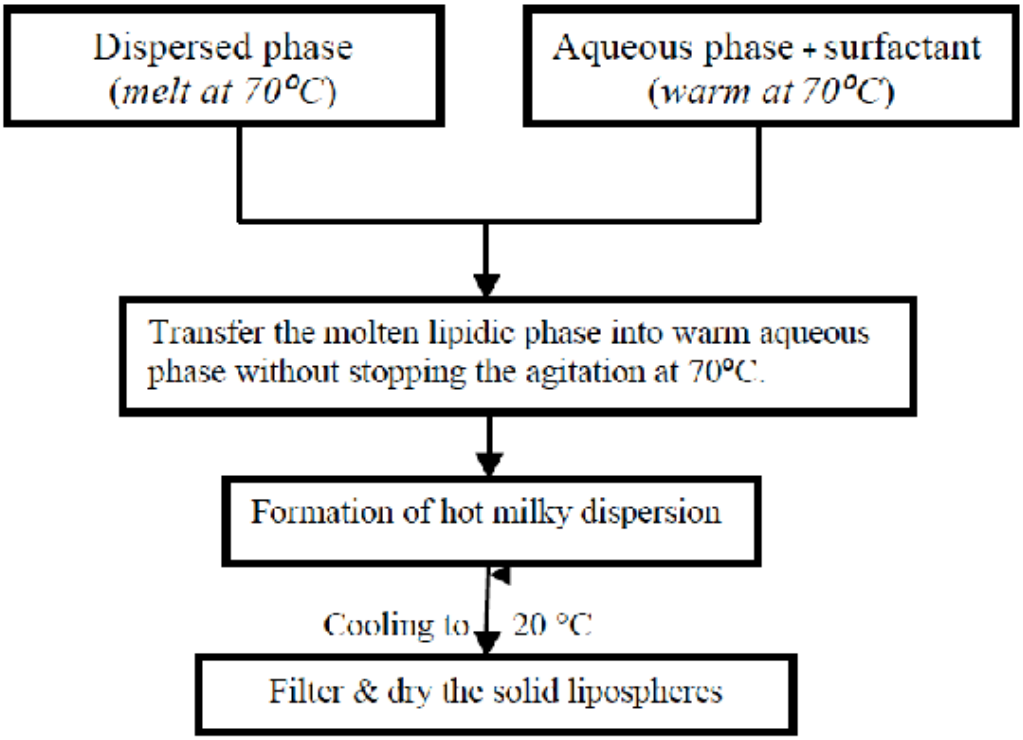


**Fig 12: Microsphere preparation by Melt dispersion technique**

**Ionic gelation method:** Alginate/chitosan particulate system for release of BCS class II drugs was prepared using this technique. Drug and polymers in a particular ratio are dissolved into 2% sodium alginate (controlled release material) to form gel like material. Then this is extruded by 18# syringe and poured in a beaker of $CaCl_2$ (cross linking agent) in which a magnetic stirrer stirs at 50 rpm. The microspheres thus founded were permitted 1 hour for curing in calcium chloride solution then were decanted and washed with petroleum ether and air dried over night at room temperature. [13-15]

## 7. APPLICATION OF MICROSPHERE DRUG DELIVERY SYSTEM

A. Use of microsphere in vaccine delivery
B. Gene delivery
C. Targeted drug delivery
D. Ophthalmic drug delivery system
E. Imaging
F. Monoclonal antibody mediated microsphere targeting
G. Topical porous microsphere
H. Colonic drug delivery
I. Oral drug delivery
J. Nasal drug delivery system
K. Buccal drug delivery system
L. Vaginal drug delivery

### A. Use of Microsphere in Vaccine Delivery:

The condition of a vaccine is preservation against the micro organism or its toxic product. Perfect vaccine must achieve the need of efficacy, safety, convenience in implementation and cost. [16] Several advantages of microsphere drug delivery system in vaccine delivery:

1. Modulation of antigen release
2. Stabilization of antigens
3. Improved antigenicity by adjuvant action
4. Site specific targeting by micro particulate carriers.

Example: Shi *et al*., developed spray dried PLGA microspheres loaded with recombinant tuberculosis (TB) antigen, TB10.4-Ag85B for pulmonary administration against tuberculosis infection. Particles were of 3.3 $\mu$m in size and, hence, were respirable. Outcome has shown intial rupture of antigens followed by a sustained release up to 10 days. Interleukin-2 secretion in a T-lymphocyte investigation due to the microspheres was found to be powerful than antigen solutions.
However, the application of PLGA can be restricted by acid hydrolytic degradation products detrimental to the entrapped protein and loss of immunogenicity on storage. As well as organic solvents used to load the antigen onto the polymer can be undesirable to the antigen. [17]

### B. Gene Delivery:

Gene delivery systems comprise viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems. Viral vectors are beneficial for gene delivery because they are extremely well planned and have a wide range of cell targets. Microspheres could be a helpful

oral gene carrier since its adherent and transport properties in the GI tract. [18]
Mac Laughlin et al showed that plasmid DNA carrying cytomegalo virus promoter sequence and a luciferase reporter gene could be provided in vivo by chitosan and depolymerized chitosan oligomers to reveal a luciferase gene in the intestinal tract. [19]

**C. Targeted Drug Delivery**
Microspheres display a extended residence time at site of application and thus give better therapeutic execution of drugs. Microspheres have been formulated as oral, buccal, ocular, rectal, nasal and vaginal routes for either systemic or local effects. This article presents introduction and the proceed pharmaceutical implementation of bioadhesive microspheres. [20]
Example: Embolotherapy is an important alternative for the treatment of uterine fibroids. In this method the feeding arteries of the fibroids are blocked by localized injection of microparticles. An angiographic catheter is initiated via the femoral artery, through a small opening in the inguinal canal. Microspheres are introduced into the uterine artery that is providing the fibroids. The microspheres subsequently blocks these arteries and induce shrinkage of the fibroid as shown in **fig 13**.

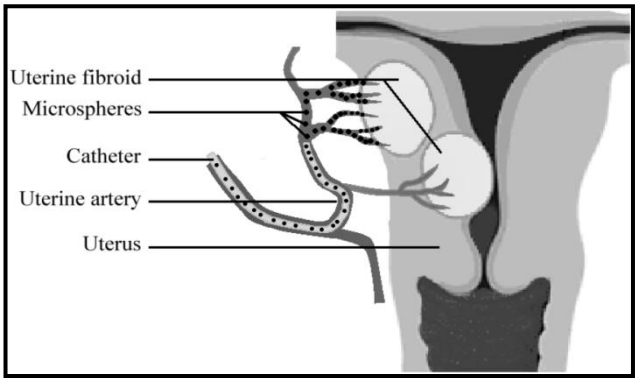


**Fig 13: Mode of action of microspheres in treating Uterine Fibroids**

**D. Ophthalmic Drug Delivery System:**
Polymer exhibits favourable biological behaviour such as bioadhesion, permeability enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Due to their elastic effects, polymer hydro gels provide greater acceptability, with estimation to solid or semisolid formulation, for ophthalmic delivery, like suspensions or ointments.
The micro particulate drug carrier (microspheres) seems a promising means of topical administration of acyclovir to the eye. [21-24]

**E. Imaging:**
The microspheres have been broadly studied and applied for the targeting purposes. Different cells, cell lines, tissues and organs can be imaged by applying radio labelled microspheres. The molecule size range of microspheres is an key factor in determining the imaging of specific sites. The particles introduced intravenously aside 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 microsphere. [25]

**F. Monoclonal Antibody Mediated Microsphere Targetting**
Monoclonal antibodies targeting microspheres are immune microspheres. This targeting method applied to get selective targeting to the particular sites. Monoclonal antibodies are especially specific molecules. This unusual specificity of monoclonal antibodies (Mabs) can be employed to target microspheres loaded bioactive molecules to selected sites. [26]

**G. Topical Porous Microsphere:**
Microsponges are porous microspheres having multiple of conjugated voids of particle size range 5-300 μm. These microsponges having capacity to entangle wide range of active constituent such as emollients, fragrances, essential oils etc, are used as the topical carries system and these porous microspheres with active component can be included into formulations like creams, lotions and powders. Microsponges composed of non collapsible structures with permeable surface through which active constituents are released in a controlled approach. [27-30]

**H. Colonic Drug Delivery:**
Polymer has been applied for the specific transportation of insulin to the colon. The chitosan capsules were overlayed with enteric coating (Hydroxy propyl methyl cellulose phthalate) and consisted, aside from insulin, various additional absorption enhancer and enzyme inhibitor. [31]

**I. Oral Drug Delivery:**
The ability of microspheres containing polymer to form films permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, combined with the reactivity of the primary amine groups, make microspheres more acceptable for oral drug delivery applications. Eg.Chitosan, gelatine. [32]

**J. Nasal Drug Delivery System:**
Polymer based drug delivery systems, like micro-spheres, liposomes and gels have been explained to have good bioresorbable properties and dilate easily when in contact with the nasal mucosa, bioavailability and residence time of the drugs is increasing in the nasal route. Eg.Starch, Dextran, Albumin etc. [33]

**K. Buccal Drug Delivery System:**
Polymer is an excellent polymer to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. Chitosan, Sodium alginate. [34]

**L. Vaginal Drug Delivery:**
Polymer, improved by the introduction of thioglycolic acid to the primary amino groups of the polymer is widely applied for the treatment of mycotic infections of the genitourinary tract. Eg. Chitosan, Gelatin, PLGA. [34]

## CONCLUSION

Microspheres are preferably used in targeted drug delivery because of it's site specificity. It can be modified (as required) to maintain the desired concentration at the site of interest without untoward effects. A microsphere has a drug, placed centrally within the particle, where it is enclosed within a unique polymeric membrane. It can provide us certain applications 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. In future by combining various other strategies, microspheres will find superior place in novel drug delivery.

## REFERENCES


1. Vyas SP, Khar RK. Multiple emulsion, Nanoparticles, In: Targeted and Controlled Drug Delivery.1st ed. New Delhi: CBS Publishers; 2002; 303-80.
2. Goodman and Gilman's. The Pharmacological Basis of Therapeutics, Eds.Hardman Joel G,Limbird Lee E ; 10th ed. New York: MC Graw-Hill Publishing House; 2002; 1972.
3. S. Mohapatra*, S. Sen and S. C. Si. Preparation and Evaluation Of Glipizide Microspheres Using Mucoadhesive Polymers.IJPSR. 2014; 5(1): 189-192.
4. Neelesh K Varde and Daniel W Pack. Microspheres for controlled release drug delivery,ExpertOpinTher. 2004; 4(1): 35-51.
5. A. D'Emanuele, R. Dinarvan. Preparation characterization and drug release from the thermoresponsive microspheres, International journal of pharmaceutics. 24 Mar 2009; 374(1-2): 139-144.
6. Sandeep Singh* and Marina Koland. Preparation And Evaluation Of Glipizide Microspheres Using Hydrophobic Biodegradable Polymerfor Sustained Drug Delivery. 2014; 3(10): 1468-1480.
7. Arora Neha, Khattar Himansh, Parashar Deepa, Arora Nageen, Garg Tarun. Evaluation Of Entrapment Efficiency Of Glipizide Microsphere. IOSR Journal of Pharmacy Mar.-Apr. 2012, Vol. 2(2): 180-181.
8. Jamzad S, Fassihi R. Development of a controlled release low dose class II drug Glipizide. Int J Pharm 2006; 312(1-2): 24-32.
9. Kavita Kunchu, Raje Veera Ashwani, Albumin Microspheres: A Unique system as drug delivery carriers for non steroidal anti-inflammatory drugs. 2010; 5(2): 12.
10. Corrigan L. Owen and Healy Marie Anne.Surfactants in Pharmaceutical Products and Systems "Encyclopedia of Pharmaceutical Technology" 3rd edition; 2003, 1, edited by James Swarbrick Informa healthcare Inc. P.NO- 3590.
11. Agusundaram M, Madhu Sudana Chetty, Microsphere As A Novel Drug Delivery System A Review. International Journal of ChemTech Research. 2009; 1(3): 526-534.
12. Parmar Harshad, Bakliwal, Sunil at al. Different Method Of Evaluation Of Mucoadhesive Microsphere, International Journal of Applied Biology and Pharmaceutical Technology. 2010; 1(3): 1164-1165.

13. Mali D.S., Talele S. G., Mogal R., Chaudhari G., Review on nasal microspheres, Am. J. Pharm Tech Res. 2014; 4(1): 97-111.
14. Pavan Kumar B., Chandiran I. S., Bhavya B., Sindhuri M., Microparticulate drug delivery system: A Review, Indian journal of pharmaceutical science & research, 2011; 1(1): 19-37.
15. CH Saroja, PK Lakshmi, Shyamala Bhaskaran; Recent trends in vaccine delivery systems: A review; International Journal of Pharmaceutical Investigation, 2011; 1(2): 64-74
16. Ketie Saralidze*, Leo H. Koole and Menno L.W. Knetsch; Polymeric Microspheres for Medical Applications; Materials 2010; 3(6): 3537-3564.
17. Kim In-Sook, Kim Sung-Ho. Development of polymeric nanoparticulate drug delivery systems; Evaluation of nanoparticles based on bio tinylated poly(ethylene glycol) with sugar moiety. Int J Pharm 2003; 257: 195-203.
18. Kanav Midha*, Manju Nagpal and Sandeep Arora; Research Article Microspheres: A Recent Update; International Journal of Recent Scientific Research; August, 2015; 6, (8): 5859-5867.
19. Manthorpe M, Cornefert-Jensen F, Hartikka J, Felgner J, Rundell A, Margalith M, Dwarki V. Gene therapy by intramuscular injection of plasmid DNA: studies on firefly luciferase gene expression in mice. Hum. Gene Ther. 1993; 4(4): 419–431.
20. Narender Reddy M, Rehana T, Ramakrishna, Chowdary KPR, Diwan PV. B-Cyclodextrin complex of Celocoxib:Molecular Modeling, Characterization and Discussion Studies. AAPS Pharm Sci 2004; 6(1): 1-9.
21. Haibing HE, Xing Tang, Fude CUI. Pharmacokinetic study of ketoprofen isopropyl ester – loaded lipid microspheres in Rat blood using microdialysis. Biol Pharm Bull 2006; 29(4): 841-45.
22. Boris YS, Chattopadhyay P, Henry HY, Albert HL. Particle size analysis in Pharmaceutics: Principles, method and applications. Pharmaceutical Research 2007; 24(2): 203-27.
23. Ghorab Mamdouh M, Heba M. Abdel-Salam. Effects of Glycerides on the intestinal absorbtion of cyclosporine a using the in-situ mesenteric vein cannulated rat model. Current Drug Delivery 2005; 2(3): 289-94.
24. Kim In-Sook, Kim Sung-Ho. Development of polymeric nanoparticulate drug delivery systems; Evaluation of nanoparticles based on bio tinylated poly(ethylene glycol) with sugar moiety. Int J Pharm 2003; 257: 195-203.
25. Chatttopadhyay Debjit, Galeska Izabela, Bhardwaj Upkar. Controlled release of dexamathazone from microspheres embedded within poly acid containing PVA hydrogels. The AAPS J 2005; 7(1): E.231-40.
26. Junginger HE, Thanou M, Verhoef JC. Chitosan and its derivatives as intestinal absorbtion enhancers.Adv Drug Delivery Rev 2001; 50: 591-99.
27. Mehnert Wolfgang, Madder Karsten. Solid lipid nanoparticles production, characterization and application.Advanced Drug Delivery Rev 2001; 47: 165-96.
28. Yang Xiangliang, Mei Zhinan, Chen Huabing. Solid lipid nanoparticles and microemulsion for topical delivery of triptolide. Euro J Pharm Bio Pharm 2003; 56(2): 189-96.
29. Chi Sang-Cheol, Rhee Yun-Seok. Transdermal delivery of ketoprofen using microemulsion.Int J Pharm 2001; 228(1-2): 161-70.
30. Alonso MJ, Torres D. Design of lipid nanoparticles for the oral delivery of hydrophilic macromolecules. Colloids and Surface B: Biointerfaces 2002; 27: 159-70.
31. Capek I. Preparation of metal nanoparticles in water-in-oil (w/o) microemulsions. Adv Colloid and Inter Sci 2004; 110: 49-74.
32. Labhasetwar Vinod, Panyam Jayanth. Biodegradable nanoprticlesfor drug and gene delivery to cells and tissue. Adv Drug Deliv Rev 2003; 55: 329.
33. Filipovic-GreicJ,Skalko-Basnet N, Jalsenjak I. Mucoadhesive chitosan-coated liposomes;Charecteristics and Stability. J Microencapsulation 2001 Jan-Feb; 18(1): 3-12.
34. JaY.Kim, Young S.Ku. Enhanced absorption of indomethacin after oral or rectal administration of a self-emulsifying system containing indomethacin to rats.Int J Pharm 2000; (194): 81-89.
35. Nasongkla N, Widmann AF, Bruening A, Bema M, Ray D, Bornmann WG, Boothman DA, Gao J. Enhancement of solubility and Bioavailibility of b-lapachonen using cyclodextrin inclusion complexes. Pharmaceutical Research 2003; 20(10): 1626-33.
36. Araya H, Nagao S, Tomita M, Hayashi M. The novel formulation design of self-emulsifying drug delivery systems (SEDDS) type o/w microemulsion I: Enhancing effects on oral bioavailability of poorly water soluble compounds in rats and Beagle Dogas. Drug MetabPharmacokinet. 2005; 20(4): 244-56.