II. REVIEW OF LITERATURE

MICROSPHERES - A REVIEW [Siepmann, J. et al., (2006)]

Microspheres are controlled drug delivery systems of polymeric devices in the size range < 250 microns thus they can be administered using standard needles in a suspended form by reconstituting with suitable vehicle. The drug delivery rate can controlled or sustained depends on composition of the microparticle matrix. Polymers used in the synthesis of microparticles are biodegradable, biocompatible and nontoxic so that the longevity of residence at the site of injection to deliver the drug release in a continuous manner thus reducing adverse reactions of polymer and drug. Thus the drug delivery is controlled to a particular area and avoiding circulation throughout the body as in conventional dosage forms.

Advantages of microparticles:

(i) The possibility to avoid the firstpass act by im or sc injection;

(ii) easily administered via standard needles (in compare to other controlled release parenteral dosage forms, for example macrosized implants);

(iii) The chance to directly administer the drug into the target site

(iv) The ability to reach target sites, which are restricted for the entry of drug (e.g., the tumour tissue, the central nervous system); and

(v) Since polymers are biodegradable and biocompatible surgical removal of empty debris are not required.

SOURCES OF MICROPARTICLES

Biodegradable polymer particles (e.g., microcapsules, microparticles, and nanoparticles) are greatly useful since they can be delivered to different areas \textit{in vivo} using a syringe needle. Almost all the drugs, despite of their water solubility and molecular weights, can be incorporated into the biodegradable microspheres using different fabricating methods. Different types of biodegradable polymers used in microparticle synthesis include polyesters poly(ortho esters), polyphosphazenes, polyanhydrides and polysaccharides.
Some of the widely used biodegradable polymers:

1) Synthetic Polymers
   i. polyesters
   ii. poly(ortho-esters)
   iii. Polyadhydrides
   iv. Polyphosphazenes

2) Natural Polymers
   i. Chitosan
   ii. Hyaluronic acid
   iii. Alginic acid

TYPES OF MICROPARTICLES

The microparticles have been classified as a function of

i. The mode of application (for example: Magnetic microspheres, Bioadhesive microspheres, Floating microspheres) or

ii. The method of preparation (for example: Emulsion-solvent evaporation, Phase separation, Spray drying)

Magnetic microspheres

Magnetic drug delivery system delivers the drug to the disease site [C.Nithya shanthi et al (2010), Hafelie, U. O. (2004)]. Magnetic microspheres reduce the larger amount of free drug in systemic circulation to a smaller amount of magnetically targeted drug; thereby drug toxicity, dosage regimen etc. can be reduced [Hafeli, U. et al (1997)]. Therefore first pass metabolism and gastrointestinal tract degradation are avoided. Magnetic microspheres receive magnetic
responses to an external magnetic field from encapsulated materials that are used in magnetic microspheres are iron oxide. Magnetic microparticles find its application in bone marrow purging and stem cell extraction. They are of two types:

I. Therapeutic magnetic microspheres: for example: they are used to target anticancer agents to tumour without causing damage to the normal tissue [Hafeli, U. O. (2001)]. Small molecules like proteins, peptides, DNA plasmids, antigens are encapsulated into the polymeric matrix with the loss of bioactivity and maintaining it during preparation of the delivery device.

II. Diagnostic microsphere: finds widely used applications such as magnetic resonance imaging contrast enhancement, drug delivery, detoxification of biological fluids, immunoassay, hyperthermia, liver metastases, cell separation, and in tissue repair, etc, with the help of superparamagnetic iron oxides particles encapsulated with diagnostic agents [Vonod Labhasetwar. et al (2005)].

**Bioadhesive microspheres**

Bioadhesive drug delivery devices stick to the mucosal membrane with the help of adhesion property of the hydrophilic polymers. Bioadhesion is a property of adhesion of a drug delivery device to the mucosal membranes like buccal, ocular, nasal, rectal etc. Bioadhesive microspheres resides for longer time at the application site and produces strong contact with the absorption site moreover produces controlled delivery of drugs.

**Floating microspheres**

Mechanism behind the floating system is buoyancy of the microspheres i.e., the bulk density is less than the gastric fluid and helps floating in stomach without disturbing gastric emptying rate. Controlled release rate is achieved when the system floats on gastric content thereby increases gastric residence time. Chances of striking and dose dumping are reduced by floating microspheres. This system produces prolonged therapeutic effect in a controlled manner and therefore simplifies dosage regimen [Shagufta Khan et al (2012)].
Radioactive microspheres

Radioactive microsphere is most beneficial in radioembolization of liver and spleen cancers. Radioactive microspheres are designed for local radiotherapy, radiosynvectomy of arthritis joint, interactivity treatment. Imaging of organs like spleen, liver, lung, bone marrow etc and even deep vein thrombosis can be made. Radio emobilisation treatment uses microparticles ranged between 10-30 nm are of larger than capillaries and gets trapped in capillary bed during their passage when administered to the arteries that go to tumour site. All these above reasons make therapeutic radioactive microspheres to deliver high radiation dose to the targeted sites without affecting the underlying normal tissues. Radioactive microspheres encompass highly radioactive material causes ionizing radiation to kill cancerous cells and shrink tumours. A therapeutic radioactive microsphere differs from drug delivery system; as radio activity is released by radioisotope within a typical distance and not by microspheres. The different kinds of radio emission microparticles are α (alpha) emitters, β (beta) emitters, γ (gamma) emitters [Urs Hafeli (2002)].

Microspheres in Chemoembolization

Chemoembolization treats patients with diseased liver and even its origination in the liver or spreaded to liver from other organs or tissues. Anti-neoplastic agents in microspheres along with embolic agents are injected into the veins separately which supply tumour cells. Embolic agents act by trapping the microsphere in the cancerous tumour [Chemoembolization. (2013)].

Polymeric microparticles [Shagufta Khan et al (2012)]

There are two types of polymeric microparticles and they are as follows

1. Natural polymeric microparticles and

2. Synthetic polymeric microparticles

1. Natural polymeric microparticles

Biodegradable polymers such as cellulose, chitosan, hyaluronic acid, alginic acid and proteins are used in drug delivery devices since they are biodegradable, biocompatible.
Natural polymers possess prolonged residence time upon contact with mucous membrane owing to its high intake of water and swelling character resulting in gel structure. Concentration of polymer in the microparticles controls the rate and extent of drug delivery from the device and the release pattern in a controlled and sustained manner. Advantage of natural polymers is broad range of application in particulate delivery systems.


Now a day, synthetic polymeric microparticles are being extensively practiced in clinical use; in addition they are used as drug delivery systems, fillers, bulking agent, embolic particles, etc and showed to be biodegradable, biocompatible, nontoxic and safe. The main disadvantage of synthetic polymeric particles, are they have the tendency to accumulate away from injection site, causes embolism and potential risk to organ damage.

MICROPARTICLE PREPARATION [Park, K. (2005)]

The considered suitable encapsulation process must meet the following requirements during the preparation of microparticles using biodegradable polymers.

i. The chemical stability and efficacy of the encapsulated drugs should be protected during manufacturing process.

ii. The yield and the entrapment efficiency of the microspheres should be sufficiently higher for large scale production.

iii. The formed microparticles must be in the size range i.e., < 250 µm to facilitate administration using the syringe needle through the parenteral route.

iv. The drug release profile should be reproducible with no significant change in the initial burst release.

v. The method intended should produce non-aggregated, free-flowing microspheres, this allows us to formulate uniform distribution of the microparticles.
There are different techniques by which microencapsulation of drugs are made such as the emulsion-solvent evaporation/extraction technique, spray drying method, phase separation-coacervation technique, interfacial deposition method, and in situ polymerization technique. The method selection depends on the physicochemical properties of the polymer and the drug, the site of action, and the duration of the treatment.

**SPECIFIC TECHNIQUES OF PREPARATION FOR MICROPARTICLES**

The methodology for microparticles research has been evolved rapidly during the last few decades as a response to the need to prepare well defined microparticles for specific applications. Different methods of preparation of microparticles are:

- Emulsion-solvent evaporation/extraction methods (o/w, w/o, w/o/w)
- Phase separation (non solvent addition and solvent partitioning)
- Spray drying

**FACTORS AFFECTING PARTICLE SIZE, ENTRAPAMENT EFFICIENCY AND RELEASE CHARACTERISTICS** [Kevin, K. K et al (2006)]

The drug release is strongly influenced by a various parameters including the drug content, the nature of polymer, the physical state of the drug, the molecular weight of polymer, the density of crosslinking the copolymer concentration, the type of any excipients included in the microparticles preparation, and the microsphere size.

1) **Drug content**

The amount of drug that present in the microparticle determines the release kinetics of the drugs from the matrix devices; the release proportionately increases with increase in drug content in the microparticles.

2) **Nature of polymer**

The nature of polymer present in microparticles and the type of polymer erosion clearly determine the drug delivery rate. Polymers are generally classified into two types: surface-
erosion and bulk-erosion. In bulk-eroding polymers, the matrix degrades by diffusion of water molecules. While, in surface-leaching polymers, water repelling monomers resist penetration of water molecules therefore degradation takes place from the surface of the particle.

iii) Physical state of the drug

The physical state of a drug affects the drug release kinetics from a dosage form. The presence of the drug inside the microparticles may vary from molecular dispersion to well defined crystalline structures.

iv) Molecular weight of polymer

Molecular weight of polymer plays a major role in polymer degradation as well as drug delivery rates. This indicates that, higher the molecular weight lower the diffusivity and decreased drug delivery rate. In addition, drug delivery takes place by diffusion through water filled pore. The decrease in delivery rates reported for small molecules such as drugs, and macromolecules with increasing molecular weight of polymer.

v) Density of crosslinking

The crosslinking density plays a major role on the release kinetics of drugs from the microparticles. It was observed from the results that drug delivery rates become slower when microparticles preparation utilizes polymer at higher concentration and polymer with higher molecular weight and/or a lower drug concentration [Subbiah, G. et al (2007)].

vi) Copolymer concentration

The concentration of co-monomer presence in copolymers have a strong effect on release rates. Normally, the release rate increases with increasing the concentration of polymer that degrades faster. Likewise, when polymer erosion controls the drug delivery, release rate is usually increased by higher concentration of more soluble and/or the smaller monomer.
vii) Type of excipients

To maintain stability of the drug a range of excipients might be included to microparticle preparations during manufacture and/or release. Decreased delivery rate may be due to interaction with the excipients and forming chelation, complexation, polymerization, isomerisation, racemisation etc.

viii) Microparticle size

Largely, the rate of drug release will be strongly influenced by microparticles size. The surface area-to-volume ratio of the particle increases when size decreases. Therefore, drug diffusion and the release rate will increase with declining particle size. In addition, the smaller the radius of the microparticle the higher the water penetration.

**INVIVO BEHAVIOUR OF MICROPARTICLES** [Daniel, S. K. et al (2006)]

Microparticles easily settle in almost all tissues after injection and they have the ability to survive and degrade slowly for more than 8 weeks e.g., peritoneum of mice with size < 250 µm particles. At the same time nanoparticles of the same polymer exhibits complete clearance from the site of application.

**Crossing Barriers**

Microparticles face difficulty to cross biological barriers, as they are administered to the desired site of target. While, nanoparticles are able to diffuse across the barriers of their smaller in size. Disease or deliberate disruption of barrier improves the ability to diffuse barriers. As instances, the tumours cells are leakier than normal, and the osmotic disruption loosens the blood-brain barrier.

**Entering Cells**

Endocytosis enables the particles to cross cells; they are of two types phagocytosis and pinocytosis. “Cell eating” (phagocytosis) is a means of eating up particles < 10 microns in diameter. Phagocytic cell types, for example the neutrophils, macrophages, dendritic cells. “Cell drinking” (pinocytotic) engulfing of particles by all cell types, and engulfs sub-micron particles.
in solution. Therefore, polymeric micropaticles can only be administered into cells which perform phagocytic mechanism, while polymeric nanoparticles can be administered to all cells.

**Tissue Reaction**

Particle size determines whether they are phagocytosed or not, and whether to stay at the site of injection. Some particles initiate an acute inflammation, bringing neutrophils and macrophages at the site of injection. 1–2 weeks later, chronic inflammatory response brings lymphocytes and macrophages, due to the presence of polymeric particulate mater. Giant foreign body cells engulf larger particles individually. Big sized foreign body cells are collections of smaller particles, surrounding off of a large area.

**CHARACTERIZATION OF MICROPARTICLES**

i. **Particle size and morphology:** [Bhagwat, D, A. et al (2009)]

Particle size and surface morphology were analyzed by using scanning electron microscopy (SEM). In this scanning electron microscope sample stub is used to mount microparticles with the help of double sided adhesive tape which is covered with gold film under low pressure.

ii. **Entrapment efficiency:** [Subbiah, G. et al (2007)]

Drug loaded microspheres were powdered and then dissolved in distilled water with the help of ultrasonic sonicator and filtered then assayed. Entrapment efficiency is expressed as (amount entrapped/ Total amount added) x 100.

iii. **In-vitro release rate:** [Arul, B. et al (2003)]

Release of drug can be determined by microparticular suspension in a buffer at definite temperature (37 °C) determining the drug content of medium by assayed at a particular wavelength in (UV) ultraviolet region using UV spectphotometer.
iv. **Thermal analysis:** [Alfred Martin, (2011)]

Thermal analysis is performed to know the undesirable change of state of drug and excipients. The change may be physical, chemical or therapeutic, and these changes may be either intentional or unintentional. The study can be done by using-

- Differential Scanning Calorimetry (DSC)
- Thermo Gravimetric Analysis (TGA)
- Differential Thermometric Analysis (DTA)
- Thermo Mechanical Analysis (TMA)

Accurately weighed quantity of the sample was on alumina pan and heated at constant rate of 10 °C/min under nitrogen atmosphere at a flow rate of 40 ml/min.

v. **Fourier-Transform Infra Red (FT-IR):** [David, G. W. (1999)]

FT-IR detects chemical interaction between drug-drug, drug-polymer drug-excipients and also degradation of drug, polymer, excipients and additives during the process of microencapsulation can be determined by FT-IR spectrum.

vi. **Stability studies:** [Alfred Martin, (2008b)]

Stability studies determine the shelf life of drug products by subjecting the formulations to long-term, intermediate and short term thermal studies. The stability study is divided into thermal and nonisothermal. Formulations are placed in a screw capped container in which they are formulated and stored them in a stability chamber; samples are assayed at regular intervals as per ICH guidelines.
PNEUMONIA - A REVIEW

Pneumonia is inflammation of the lungs that is caused by different types of bacteria, viruses and fungi. There are two types of pneumonia namely [Wardlia, T. M. et al (2006)]

1. Community-acquired pneumonia

2. Hospital acquired pneumonia

Community-acquired pneumonia found in individuals outside the hospital or Health care facility (rehabilitation facility). UNICEF estimates every year pneumonia causes death in children 1 in 5 under-five deaths globally: more than 20 lakhs children.

Hospital acquired pneumonia affects persons in nursing home or rehabilitation facility.


Pneumonia is caused by a numerous pathogens, including bacteria, viruses and fungi.

- Streptococcus pneumoniae – most common pneumococcus cause pneumonia in children;
- Haemophilus influenza type b (Hib) – the next most likely to cause bacterial pneumonia;
- Pneumocystis jiroveci is the most common cause of pneumonia in immunosuppressive patients and infants;
- Respiratory syncytial virus, are also common cause of viral pneumonia.

Transmission

Pneumonia can be transmitted in number of modes. The causative organisms that are generally found in an infant’s nose or throat, if inhaled can transmit a disease to the lungs. They may also transmit through air-borne, who expectorate cocci in droplet nuclei as they cough, sneeze or talk.
**Clinical Presentation** [Limper A. H. (2011)]

UNICEF/WHO estimated viral and bacterial pneumonia children death accounts for over 2 million. The most common clinical manifestation of pneumonia is:

- Cough (with greenish or yellow mucous, or even bloody mucous) [Neiderman, M. (2009)]
- Fever - mild or high
- Shortness of breath – during work, climbing stairs
- Wheezing – in viral pneumonia
- Unconsciousness
- Hypothermia
- Convulsions

Other symptoms are:

- Confusion
- Headache
- Sweating and clammy skin
- Loss of appetite, fatigue
- Chest pain during deep breathe or cough
- Leukonychia, or white nail syndrome

**TREATMENT** [Harrisons (2008)]

During treatment normally patient’s gets improve before 2 weeks. Geriatric or chronic patients might require longer therapy. [Neiderman, M. (2009)]

Patients who may be subjected to have serious pneumonia are:

- Elderly patients
- Individuals with immuno suppressive disorder
- Individuals with other, chronic health complications for example cirrhosis of the liver or diabetes

In all these above situations, pneumonia causes death, if condition worsens.

In some patients rarely, more complicated conditions may arise, including;
• Life-threatening changes in the respiration that requires a breathing machine
• Pleural effusion (Fluid surround the lung)
• Lung abscesses

**WHO response** [Wardlia, T. M. *et al* (2006)]

Integrated Global action plan (GAPPD) was initiated in 2013 by WHO and UNICEF for pneumonia and diarrhoea. The objective is to speed up pneumonia control with an addition of protect, prevent, and treat pneumonia in infants with measures to:

- **protect** infants from pneumonia – promoting breastfeeding and supplementary feeding;
- **prevent** – vaccinations, hand washing using soap, reducing household air pollutants, HIV preventive measure and prophylactics like cotrimoxazole for HIV-patients and children nearby;
- **treat** – confirming every infected child is under right kind of care – that is from a community based health worker, or in a rehabilitation facility if the condition is severe – and availability of antibiotics and oxygen.

**ARTICLES SURVEY – A REVIEW**

**Baxter Healthcare Corporation (2014)** emphasized following intramuscular administration of a unit 500 mg or 1 g dose of cefotaxime injection to normal volunteers, mean peak serum concentrations were attained within 30 minutes (11.7 and 20.5) mcg/mL respectively. About 60% of the given dose was excreted from urine during the first 6 hours following the start of the infusion. Approximately 20-36% of an IV dose of cefotaxime is excreted by the kidney as unchanged cefotaxime and 15-25% as the desacetyl derivative. The desacetyl metabolites also contribute to the bactericidal activity. Two other metabolites account for about 20-25%. They lack bactericidal activity. The maximum adult dosage should not exceed 12 grams/day.

**Yiqi Huang *et al* (2014)** determined the effect of release of cefotaxime sodium from modified starch-g-polylactic acid and the release increased with raise in pH of buffer.
Aphios Corporation USPC424499 (2013) invented the nature of dosage form, method of preparation of micro particulates consisting proteins or derivatives enclosed in polysaccharides or derivatives and applications of the formulation in animals and humans to produce immunization.

Le Shin Chang USPC424499 (2013) invented the processes of encapsulation of growth factor in a polysaccharide micro-particle.

Murugesh, S. et al (2013) reported the nature of grafting and cross linking of Chitosan-acryl amide and polyethylene glycol to extend the release of Cefotaxime from hydro gels based delivery system.

David W. Grainger et al., (2012) reviewed that hard tissue disorders and diseases are the main causes of physical disability. He indicate that novel drug delivery devices for combination device applications intra-operatively, efficiently undergoing drug therapies on implanted hard tissue fixation devices.

Govind Asane et al., (2012) fabricated gastro retentive sustained release microparticles containing hydroxy propyl methyl cellulose derivative and chitosan as retardant material. The study demonstrates that the drug release from the formulation was found to be extended. It indicates that the increase in concentration of both the polymers shown to sustain the release of active ingredient.

Shagufta Khan et al., (2012) stated microspheres take much consideration in the area of prolonged release, and also for targeting of anticancer drugs.

Stefania racovita et al., (2012) determined the absorption kinetics and equilibrium of cefotaxime sodium salt on chitosan-polybetaine complexes. This study carried out as a preformulation study in the development of oral drug delivery system.

Bhatt et al., (2011) studied that the processing variables effect in preparation and growth of biodegradable microparticles. The principal method of encapsulation is by emulsion solvent evaporation technique involves two principal steps, the growth of stable droplets of the drug-containing polymer organic solution and the subsequent removal of solvent from the droplets.

Itai Cohen et al., (2011) fabricated microparticles using selective withdrawal of one solvent so that coating of small particles with polymer films takes place. By using a single tube he determined that 10,000 particles can be generated per hour.

Prasanth V.V et al., (2011) emphasized different types of microspheres bioadhesive microspheres, magnetic microspheres, floating microspheres, radioactive microspheres, and polymeric microspheres further divided into biodegradable polymeric microspheres, and synthetic polymeric microspheres.

Vijaya Ramesh et al., (2011) used different polymers for the development of microparticles for controlled release of antibiotic drug. Microspheres were prepared by emulsion solvent evaporation technique. Attempts are also made to increase the entrapment efficiency by changing experimental variables.

Shekhar, K et al., (2011) investigated the release of cefotaxime sodium from microparticles using ethylcellulose as retardant polymer.

Adrian Raiche USPC528354 (2010) invented the processes of manufacturing microparticles by emulsification method using solvent and salt in a continuous medium.


Jaromir Hubalek et al., (2010) determine the possibility of magnetic nanoparticles for drug delivery and drug therapy is to carry the active drug to the specific site of action and thereby treat it knowingly, without affecting other areas on the body. Increasing the magnetic property is beneficial to facilitate modification in drug delivery designs. He listed most commonly used as
source of magnetization materials and some others. It is evident that only maghemite and magnetite suitable for biouse.

Ketie Saralidze et al., (2010) fabricated polymeric microspheres for range of applications in therapeutics. The components of the microparticles changes with the site of application and therefore different materials has been utilized to produce microparticles. Alteration of the surface with constituents of the extra-cellular matrix, would prompt adhesion of cells, and therefore, stronger fixing of the microparticles at the injection site.

Khan et al., (2010) determined the floating behavior of microparticles using low-viscosity hydroxypropyl methylcellulose. He concluded that using analytical techniques the coacervation non solvent addition is a preferable technique for preparing floating microparticles using low-viscosity polymer.

Ye M. et al., (2010) shown that biodegradable microparticles can be applied in long-term protein delivery. The conventional way of delivering a protein drug needs daily, sometimes multiple, injections to achieve its therapeutic effectiveness. To perfect patient compliance and ease, sustained release dosage forms have been developed. This section examines the properties of protein-loaded microparticles, in specific, protein loading and release characteristics from polymeric microparticles.

A. Dalmoro et al., (2009) referred enteric microparticles for controlled and made drug delivery applications through different ways of microencapsulation (namely single emulsions: water in oil-W/O; oil in water-O/W; or double emulsions: water-in oil-in water-W/O/W) and their impact on final properties of the product. Microcapsules or microspheres can be designed to progressively release active ingredients. A coating may also be given to open in specific areas of body “smart polymers” which are perfect candidates for advancing self regulated delivery systems.

Alagusundaram M. et al., (2009) described microspheres are typical free flowing powders enclosing proteins or synthetic polymers which are biodegradable in nature. It is the safe means to bring the drug to the target site with definite, if transformed, and to maintain the desired concentration at the site of interest without unfavorable effects.
Anderson D. G. *et al.*, (2009) developed microparticles for controlled drug delivery using a microfluidic flow-focusing device. He formulated biodegradable drug-loaded microparticles by uniting the formation of droplets in a microfluidic flow-focusing producer with rapid evaporation of solvent from the droplets.

Maria Letizia Manca., (2009) developed chitosan microspheres by precipitation method containing rifampicin. He concluded that the PLGA polymer is superior that chitosan, for the formation of microparticles.

Naikwade S. *et al.*, (2009) studied the pulmonary delivery of budesonide microparticles formulation and *in vitro* determination by spray drying. Prepared Microparticles were spherical in shape and they are characterized by smooth surface with low-density particles. Formulations shown extended *in vitro* drug release for hours thus use of microparticles possibility offers sustained release profile along with increase delivery of drug to the pulmonary tract.

Ravi Kumar Reddy J. *et al.*, (2009) investigated the delayed release microparticles prepared from different polymers by emulsion-solvent evaporation method and examined the physico-chemical characters. The mechanism of drug release was set up to be erosion as it was caused by \((1-Mt/M)^{1/3}\) versus time plots. Relative drug release study allow that the formulated product have more sustained effect than the marketed product.

Roy S. *et al.*, (2009) prepared mefenamic acid microspear by cross linking chitosan with gluteraldehyde. The *in vitro* release pattern was found to follow zero order release as the dissolution exponent come nearer to 1.

Sree Harsha *et al.*, (2009) demonstrated the possibility of site-specific targeting albumin microsperes to deliver drug to the organ without affecting other areas of the body. Following intravenous administration the drug concentration of microparticles group in organ of mice after 15 min when compared to that of controlled.

Vasiliu S. *et al.*, (2009) designed microparticles based on acrylic ion exchange resin as delivery system. Resin microparticles were prepared by suspension polymerization technique and then core-shell microparticles are prepared by immersing into polysaccharides aqueous solutions containing cefotaxime.
**Beata Chertok et al., (2008)** determine the possibility of magnetically controlled nanoparticles for the delivery of drugs to brain cancer using iron oxide. *In vivo* study of magnetic targeting reveals that the nanoparticle gets accumulated in cancers of rats was identified with images of MRI.

**Lu et al., (2008)** formulated microparticles with an ability to enter ovarian carcinoma using PLG polymers. These microparticles were prepared by solvent evaporation method. The present study provided several findings that may be applied to improving intraperitoneal therapy.

**Parthiban, K. (2008)** determined the *invitro* release of niosomes by diffusion model using dialysis membrane tide to open cylinder inserted into a medium containing buffer.

**Ajay Kumar Gupta et al., (2007)** determine the magnetic nanoparticles ability to deliver drugs, proteins and antibodies to cell, tissue or tumors. He also reviewed magnetic particles applications for early diagnosis of chronic diseases such as cancer, atherosclerosis and diabetes.

**Daniel S. Kohane., (2006)** studied that generally, microparticles have the inability to cross most biological barriers, and they should be delivered directly to the site of action. Micro- and nanoparticles for drug delivery has become the tool in area of research and, growth, in clinical practice, food, cosmetics and other industries.

**Siepmann, J. et al., (2006)** envisaged that microparticles offer an effectual defence of the encapsulated active agent against degradation, (ii) the chance to precise control the release rate of the incorporated drug above periods of hours to months, and (iii) an easy administration.

**Kevin et al., (2006)** emphasized that controlled release drug delivery systems are being evolved to address many of the difficulties connect with conventional methods of administration. Controlled release drug delivery utilize devices—such as polymer-based disks, rods, pellets, or microparticles—that incorporate drug and release it at controlled rates for comparatively long periods of time.

**Rouholamini najafabadi et al., (2006)** studied the cause of subtle lactose as an excipient on aerosolization of cefotaxime as dry powder formulations. He determined the deposition profile of a drug, cefotaxime, using coarse and fine carriers.
Ajay Kumar Gupta et al., (2005) reported that micro and micromolecules such as, enzymes, proteins, antibodies, or nucleotides and drugs can be targeted to the specific site to an organ, tissue, or tumour by binding these substances to polymeric magnetic nanoparticles under the influence of an external magnetic field.

Desai et al., (2005) demonstrated drug release that when the amount of polymer increased in microparticles. The highly important variable use to be the crystallinity of the drug, volume of polymer solution added, and molecular weight of polymer, significantly changes particle morphology and release rate.

Kinam Park et al., (2005) evidenced that the drug delivery has grow increasingly significant mainly due to the awareness of the problems associated with a variety of old and new drugs. Of the numerous polymeric drug delivery systems, biodegradable polymers have been used broadly as drug delivery systems because of their biocompatibility and biodegradability.

Vinod Labhasetwar et al., (2005) developed iron oxide nanoparticles which is capable of sustained and controlled intracellular delivery of anticancer agents. He also emphasized that the formulation may be used as a delivery device for systemic administration of hydrophobic drugs while at the same time permitting magnetic targeting and/or imaging.

Sathesh Kumar S. et al., (2004) formulated and carried out physico-chemical evaluation of polystyrene nanoparticles containing sodium salt of cefotaxime. Preparation was made by emulsion polymerization and the graphical representation indicates that the release of the drug from the nanoparticles followed zero order kinetics.

V. R. Sinha et al., (2004) reviewed the possibility of using biodegradable and biocompatible natural polymer with improved dissolution and serves as a carrier for hydrophobic drugs. The author also considered the factors that affect the incorporation efficiency and release of drugs from chitosan microparticles.

Yeo, Y. et al., (2004) revealed initial burst is ordinarily unwanted because the drug released in this time is not accessible for prolonged release, and, more significantly, it can effect in toxic side effects. In order to inhibit the initial burst and gain effective control over the release rate, it is needful to realize possible causes of the initial release and relevant formulation variables.
Arul, B. et al (2003) determined the *invitro* release of microspheres by diffusion model using dialysis bag suspended in a medium containing buffer.

Pascal Le Corre et al., (2002) formulated bupivacaine incorporated microparticles using spray-drying method and reported that the prepared microparticles were able to control the release of the drug. He reported that the release pattern shows a zero-order absorption profile for 24 hrs.

Jong eun lee et al., (2001) studied the preparation and evaluation of microparticles formulated from natural polymer hyaluronan. In this study the quality of hyaluronan as a carrier system for sulfadiazine was evaluated and their physiochemical properties were decided.

M Tuncay et al., (2000) fabricated microparticles for parenteral delivery of diclofenac sodium and the release rate is controlled by poly (lactide-co-glycolide) polymers. The designed drug delivery systems were formulated for intra-articular administration in patients with severe inflammatory disease.

Dubernet C et al., (1999) compared two ethylcellulose forms as raw material and microsphere using thermal analysis study. Ethylcellulose microspheres were prepared by the emulsion solvent evaporation procedure. Author had determined that the major physicochemical properties of the polymer remain unchanged.

M Guyot et al., (1998) optimized the effect of nifedipine/ ethylcellulose/ hydroxypropyl cellulose viscosity, or ethylcellulose/hydroxypropylmethylcellulose viscosity on the physical properties of microparticles like particle size, drug content and release kinetics.

Dabbagh M.A. et al., (1996) determined the release rate of anti-hypertensive drug, from matrices containing ethylcellulose can be transformed using smaller particle sizes and a lower viscosity grade of cellulose polymers. Cellulose appeared to alleviate the penetration of water into the wafers consist of HPMC: ethylcellulose.

R. J. Ko et al., (1991) investigated the nature of cefotaxime and its metabolite in patients with chronic parenchymal liver disease. Toxicity is indicated in patients chronic liver abnormalities due to high therapeutic index of the drug, and dosing adjustment may not be required.
Ulf, D. et al., (2007) determined the possibility of Superparamagnetic iron oxide nanoparticles as a promising tool to diagnose the tumours identified by MRI scanning.