APPLICATION OF MICROSPHERES IN PHARMACEUTICAL INDUSTRY

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Abstract

Microspheres are small, round particles commonly made from biodegradable and biocompatible polymers having the scale starting from 1 to 1000μm and incorporating tablets and different bioactive inside their core. They provide numerous benefits which includes covering and shielding the encapsulated tablets from the tough surroundings of the gastrointestinal tract, sustained and controlled drug release, progressed stability, and bioavailability, site-particular focused on of the energetic healing moieties, etc. The tablets encapsulated withinside the microspheres may be focused both through their localization to precise sites of the body (for, e.g., in lungs), to a collection of cells (for, e.g., in cancer cells), or to an intracellular region (for, e.g., withinside the lysosomes). Plumbagin-loaded albumin microspheres had been additionally organized so that you can growth its healing ability and decrease the toxicity. The organized microspheres had been investigated for his or her antitumor and antifertility activities and it exhibited useful antitumor and antifertility activities in assessment to niosomes as a manage group. Microsphere (MS), which can be emulsion cells or stable particles dispersed in a non-stop segment, had been applied in numerous industries consisting of foods, cosmetics and prescription drugs etc. Emulsions are dispersed multiphase structures which include or greater nearly at the same time insoluble liquids, with the dispersed section present withinside the form of droplets in a non-stop segment. Microsphere has specific packages in pharmaceutical industry, Drug transport system, specific microspheres application & Novel software of microsphere.

Keywords Microsphere, Drug transport system, microparticulate carriers, monoclonocal antibodies (Mabs) and polymer

Introduction

Microspheres are the materials or compounds which having loose flowing property (powders). Microspheres are which include proteins or artificial polymers which can be biodegradable in nature and preferably having a particle length from 1-1000μm. Microspheres also are referred to as as microparticals. Microsphere may be synthetic through diverse form of fabric consisting of glass, polymers, and ceramic microspheres. Micro sphere are kinds microcapsules and micrometrics, which can be defined as, micro-tablets are the ones wherein entrapped substance is particularly surrounded through wonderful tablet wall. And micrometrics wherein entrapped substance is dispersed during the matrix. Microsphere performs an crucial position to enhance bioavailability of traditional tablets and minimizing facet effect. They are utilized in specific packages, their use relies upon on their fabric and particle length utilized in construction. Due to current upgrades in high-satisfactory and functionality, microspheres are actually broadly utilized in clinical diagnostics as reagents of diagnostic devices, injectable biomaterial, tissue filler and drug transport vehicles. Microspheres also are used as tracers and undertaking debris. Colored microspheres are generally utilized in checking out of filtration media and systems, vial and container

cleansing evaluations, waft tracing and fluid mechanics, centrifugation and sedimentation processes, pharmaceutical production and infection manage. Fluorescent microspheres are advocated for packages consisting of microcirculation and organic research, imaging and waft cytometry, which require using particles that emit exclusive colorations whilst illuminated through ultraviolet (UV) mild and provide extra sensitivity for statement the usage of microscopes, lasers and different analytical devices.Applications of microspheres as injectable biomaterial has become more and more popular over the last few decades due to recent developments that have improved quality and functionality. In order to be suitable for clinical or in vivo use, microspheres must be biocompatible, safe and stable, display desired functionality inside patients, and demonstrate desired and predictable degradation properties. These parameters are determined by the raw materials used to manufacture microspheres. Surface treatment of microspheres can also be used to achieve specific functionality and the desired response within surrounding tissue.

Application Of Microspheres In Pharmaceutical Industry

- For Taste and odour masking
- To delay the volatilisation
- For Separation of incompatible substances
- For Improvement of flow properties of powders
- To Increase the stability of the drug against the external conditions
- For Safe handling of toxic substances
- To Improve the solubility of water insoluble substances by incorporating dispersion of such material in aqueous media
- To reduce the dose dumping potential compared to large implantable devices.
- For conversion of oils and other liquids to solids for ease of handling

Applications Of Microsphere In Drug Delivery System

Pharmaceutical applications in drug delivery system

- **Ophthalmic Drug Delivery**

Polymer exhibits favorable biological behavior 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 properties, polymer hydro gels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments, ophthalmic chitosan gels improve adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow. In addition, its penetration enhancement has more targeted effect and allows lower doses of the drugs. In contrast, polymer based colloidal system were found to work as transmucosal drug carriers, either facilitating the transport of drugs to the inner eye (chitosan-coated colloidal system containing indomethacin) or their accumulation into the corneal/conjunctival epithelia (chitosan nanoparticulate containing cyclosporine). The micro particulate drug carrier (micro

spheres) seems a promising means of topical administration of acyclovir to the eye. The duration of efficacy of the ofloxacin was increased by using high MW (1930 kd) chitosan

- **Gene delivery**

Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems. Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets. However, when used in vivo they cause immune responses and oncogenic effects. To overcome the limitations of viral vectors, non-viral delivery systems are considered for gene therapy. Non-viral delivery system has advantages such as ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale reproducible production. Polymer has been used as a carrier of DNA for gene delivery applications. Also, polymer could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. MacLaughlin et al showed that plasmid DNA containing cytomegalo virus promoter sequence and a luciferase reporter gene could be delivered in vivo by chitosan and depolymerized chitosan oligomers to express a luciferase gene in the intestinal tract.

- **Intratumoral and local drug delivery**

Intratumoral and local drug delivery strategies have gained momentum recently as a promising modality in cancer therapy. In order to deliver paclitaxel at the tumor site in therapeutically relevant concentration, polymer films were fabricated. Paclitaxel could be loaded at 31% (w/w) in films, which were translucent and flexible. Polymer films containing paclitaxels were obtained by casting method with high loading efficiencies and the chemical integrity of molecule was unaltered during preparation according to study.

The microspheres for Ocular delivery

Most of the applications of the drug loaded ophthalmic delivery systems are for the glaucoma therapy especially the cholinergic agonists like the pilocarpine. From the very short time (1 to 3 minutes) the short elimation half-life of the aqueous eye drops can be extended to prolonged time (15-20 minutes) using the microspheres which have the biodegradable properties. For eg- Polyalkylcyanoacrylate

The microspheres for DNA Delivery

For the transfer of plasmid DNA the microspheres have been recently used as the delivery vehicle which leads to improve the transfer of the plasmid DNA & their stability in the bio-environment. In 1998, Truong-Le and co-workers developed the novel system for the gene delivery based on the use of DNA-gelatin nanoparticles/microspheres formed by the salt induced complex coacervation of the gelatin and plasmid DNA.

- **Oral drug delivery**

The potential of polymer films containing diazepam as an oral drug delivery was investigated in rabbits. The results indicated that a film composed of a 1:0.5 drug-polymer mixture might be an effective dosage form that is equivalent to the commercial tablet dosage forms. The ability of polymer to form films may permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make polymer a unique polymer for oral drug delivery applications.

- **Nasal drug delivery**

The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. Polymer based drug delivery systems, such as microspheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Various polymer salts such as chitosan lactate, chitosan aspartate, chitosan glutamate and chitosan hydrochloride are good candidates for nasal sustained release of vancomycin hydrochloride. Nasal administration of Diphtheria Toxoid incorporated into chitosan microparticles results in a protective systemic and local immune response against Diphteria Toxoid with enhanced IgG production. Nasal formulations have induced significant serum IgG responses similar to secretory IgA levels, which are superior to parenteral administration of the vaccine. Nasal absorption of insulin after administration into polymer powder were found to be the most effective formulation for nasal drug delivery of insulin in sheep compared to chitosan nanoparticles and chitosan solution.

- **Buccal drug delivery**

Polymer is an excellent polymer to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. Buccal tablets based on chitosan microspheres containing

chlorhexidine diacetate gives prolonged release of the drug in the buccal cavity improving the antimicrobial activity of the drug. Polymer microparticles with no drug incorporated have antimicrobial activity due to the polymer. The buccal bilayered devices (bilaminated films, palavered tablets) using a mixture of drugs (nifedipine and propranolol hydrochloride) and chitosan, with or without anionic crosslinking polymers (polycarbophil, sodium alginate, gellan gum) has promising potential for use in controlled delivery in the oral cavity.

- **Gastrointestinal drug delivery:**

Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug prednisolone. Floating hollow microcapsules of melatonin showed gastroretentive controlled-release delivery system. Release of the drug from these microcapsules is greatly retarded with release lasting for 1.75 to 6.7 hours in simulated gastric fluid. Most of the mucoadhesive microcapsules are retained in the stomach for more than 10 hours e.g., Metoclopramide and glipizide loaded chitosan microspheres

- **Peroral drug delivery**

As polymer and most of its derivatives has a mucoadhesive property, a presystemic metabolism of peptides can be strongly reduced leading to a strongly improved bioavailability of many perorally given peptide drugs, such as insulin, calcitonin, and buserelin. Unmodified chitosan has a permeation-enhancing effect for peptide drugs. A protective effect for polymerembedded peptides towards degradation by intestinal peptidases can be achieved by the immobilization of enzyme inhibitors on the polymer. The mucoadhesive property of polymer gel can be enhanced by threefold to sevenfold by admixing chitosanglyceryl mono-oleate. Drug release from the gel followed a matrix

diffusion controlled mechanism. Nifedipine embedded in a chitosan matrix in the form of beads have prolonged release of drug compared to granules.

- **Vaginal drug delivery**

Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer, embeds clotrimazole, an imidazole derivative, is widely used for the treatment of mycotic infections of the genitourinary tract. By introducing thiol groups, the mucoadhesive properties of the polymer are strongly improved and this is found to increase the residence time of the vaginal mucosa tissue (26 times longer than the corresponding unmodified polymer), guaranteeing a controller drug release in the treatment of mycotic infections. Vaginal tablets of polymer containing metronidazole and acriflavine have showed adequate release and good adhesion properties.

- **Transdermal drug delivery**

Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Chitosan-alginate polyelectrolyte complex has been prepared in-situ in beads and microspheres for potential applications in packaging, controlled release systems and wound dressings. Polymer gel beads are a promising biocompatible and biodegradable vehicle for treatment of local inflammation for drugs like prednisolone which showed sustained release action improving therapeutic efficacy. The rate of drug release was found to be dependent on the type of membrane used. A combination of chitosan membrane and chitosan hydrogel containing lidocaine hydrochloride, a local anesthetic, is a good transparent system for controlled drug delivery and release kinetics.

1.Surface Modified Microspheres:

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

- Antibodies and their fragments
- Proteins
- Mono-, oligo- and polysaccharides
- Chelating compounds (EDTA, DTPA or Desferroxamine)
- Synthetic soluble polymers Such modifications are provided surface of microspheres in order to achieve the targeting to the discrete organs and to avoid rapid clearance from the body.

2. Topical Porous Microspheres:

Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5- 300μm. These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc. are used as the topical carries system further, these porous microspheres with active

ingredients can be incorporated into formulations such as creams, lotions and powders. Microsponges consist of non collapsible structures with porous surface through which active ingredients are released in a controlled manner.

- **Colonic drug delivery**

Polymer has been used for the specific delivery of insulin to the colon. The chitosan capsules were coated with enteric coating (Hydroxy propyl methyl cellulose phthalate) and contained, apart from insulin, various additional absorption enhancer and enzyme inhibitor. It was found that capsules specifically disintegrated in the colonic region. It was suggested that this disintegration was due to either the lower pH in the ascending colon as compared to the terminal ileum or to the presence bacterial enzyme, which can degrade the polymer.

- **Multiparticulate delivery system**

H.Steckel and F. Mindermann-Nogly have prepared chitosan pellets using the extrusion/spheronization technology. Microcrystalline cellulose was used as additive in concentrations range from 0-70 %. The powder mixture was extruded using water and dilutes acetic acid in different powder to liquid ratios. The study showed that chitosan pellets with a maximum of 50 % (m/m) could be produced with demineralized water as granulating fluid. The mass fraction of chitosan within in the pallets could be increased to 100% by using dilute acetic acid for the granulation step.Other potential applications include

- Conversion of oil and other liquids to solids for ease of handling
- Taste and odor masking
- To delay the volatilization
- Safe handling of toxic sybstances

Microspheres in Vaccine Delivery:

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

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

Novel Applications Of Microsphere

Monoclonal antibodies mediated microspheres targeting

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

1. Non specific adsorption

2. Specific adsorption

3. Direct coupling

4. Coupling with reagents

Targeting by using microparticulate carriers

The concept of targeting, i.e. site specific drug delivery is a well established dogma, which is gaining full attention. The therapeutic efficacy of the drug depends on its access and specific interaction with its candidate receptors. Placement of the particles indiscrete anatomical compartment leads to their retention either due to the physical properties of the environment or biophysical interaction of the particles with the cellular content of the target tissue. Microspheres in vaccine deliver. The prerequisite of a vaccine is protection against microorganism or its toxic product. An ideal vaccine must fulfil the requirement of efficacy, convenience in application and cost. The aspect of safety and minimization of side effect is a complex issue. Biodegradable delivery systems for vaccines that are given by i.v. route may overcome the shortcoming of the conventional vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies because they offer specific advantages including:

1. Modulation of antigen release

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Topical porous microspheres These microsponges are having capacity to entrap wide range of active ingredients such as emollients, fragrances, volatile oils etc., are used as the topical carries system furthermore, these porous microspheres with active medicaments can be incorporated into formulations such as creams, lotions and powders. .

Surface modified microspheres

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The adjuvant effect for vaccines

In several studies on the substances or the oral administration an adjuvant effect of the nanoparticles/microspheres with either matrix entrapped or the surface adsorbed vaccines have been demonstrated. The Kreuter and co-workers observed that the poly methyl methacrylate microspheres containing the influenza antigen induced significant antibody response. The oral delivery of the antigens with the microspheres may be an elegant means of producing an increase response of Ig A [Immunoglobin A] antibody.

The microspheres in chemotherapy

One of the most promising application of the microspheres are possible to use as the carriers for the antitumor agents. The enhanced endocytic activity & the leaky vasculature administrated microspheres. By coating with the soluble polyoxyethylene the stealth microspheres are prepared. For the cancer chemotherapy the accumulation of the non-stealth microspheres in RES [Reticulo Endothelial System] may also be exploited.

2. Targeting using Microparticulate Carriers:

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3. Chemoembolisation:

Chemoembolisation is an endovascular therapy, which involves the selective arterial embolisation of a tumour together with simultaneous or subsequent local delivery the chemotherapeutic agent. The theoretical advantage is that such embolisations will not only provide vascular occlusion but will bring about sustained therapeutic levels of chemotherapeutics in the areas of the tumour. Chemoembolisation is an extension of traditional percutaneous embolisation techniques.

4. Imaging:

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

Application Of Different Microsphere

S.No.	Type of microspheres	Applications
1.	Bioadhesive microspheres	Buccal, oral, ocular, nasal, colonic drug delivery Nasal - Gentamicin, Insulin[19] , GI - Glipizide[20] Colonic - Insulin[21], Ocular - Methyl prednisolone[22]
2.	Magnetic microspheres	Used in DNA analysis, cell isolation, protein purification and targetting drugs to tumour sites(Doxorubicin)[4][7]
3.	Floating microspheres	Carriers for drugs like antiviral, antifungal and antibiotic agents(so called absorption windows), non-steroidal anti inflammatory drugs, Prednisolone, Lansoprazole[4][8][23]
4.	Radioactive microspheres	For diagnostic purpose - Diagnostic radioembolization: ^{99m}Tc-macroaggregated human serum albumin (MAA)[24] , Thrombus imaging in deep vein thrombosis: ^{99}mTc-sulfur colloid[25] For therapeutic purpose - Radioembolization of liver and spleen tumours: ^{90}Y- microspheres [26], Local radiotherapy: ^{212}Pb-sulfur colloid [26].
5.	Polymeric microspheres	Vaccine delivery: Hepatitis, Influenza, Pertussis, Diptheria toxoid[4][10] ,Oral drug delivery of easily degraded drugs: Gene therapy with DNA plasmids; delivery of insulin, LHRH Controlled drug delivery after local application: Release of proteins, hormones and peptides over extended times

Other Application of Microspheres

Category	Drug	Use	Method	Result
NSAID	Acelofenac25	anti-inflammatory	By dissolving drug in polymer	Controlled release and minimize local side effect
Antibiotic	Amoxicillin26 Gentamicin27	for helicobacter pylori infection eliminating infection	Crosslinking double emulsion technique	Slow release rate Controlled release
Antiinflammatory	Indomethacin28 Diclofennac29 Ketoprofen30	Anti-inflammatory …….. ……..	Co-matrix method Coacevation phase separation Multiple emulsion o/w/o	Decrease in release rate Suppress the release rate Modulate drug release
Cardiac agent	Nifedipine31,32 Propanolol31,32 Dilitazam33	Calcium channel blockers ……. Calcium channel blockers	Encapsulation Emulsification coacevation technique Controlled coacevation technique	More drug entrapment efficiency Enhance drug encapsulation efficiency Retard drug release
Steroidal	Progesterone34	Steroid	Crosslinking	Maintain plasma drug concentration
Antidiabatic agent	Insulin35	Antihyperglycemic	…..	Improve systemic absorption
Diuretics	Furosemide36	Diuretic	Crosslinking	Reduce affect of external variables
Anticancer	Fluoroucil37 Cisplatin38 Mitoxantrone Oxantrazol	For targeted delivery to treat cerebral tumors Antitumors activity Antitumor anticancer	Dry-in-oil w/o emulsion system crosslinking technique combined emulsion	Slow down of release rate of drug Reduse release rate Minimize drug toxicity & minimize therapeutic efficacy Enhance the delivery of drug in brain 100 times

Evaluation Parameters Of Microsphere

1. Particle size and shape: The most widely used procedures to visualize micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM).

2. Electron spectroscopy for chemical analysis: The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA) [19].

3. Density determination: The density of the microspheres can be measured by using a multi volume pycnometer.

4. Isoelectric point: The micro electrophoresis is used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined.

5. Angle of contact: The angle of contact is measured to determine the wetting property of a micro particulate carrier.

6. In vitro methods: Release studies for different type of microspheres are carried out by using different suitable dissolution media, mostly by rotating paddle apparatus (USP / BP).

7. Drug entrapment efficiency: Drug entrapment efficiency can be calculated using following equation, % Entrapment = Actual content/Theoretical content x 100.

8. Swelling index: The swelling index of the microsphere was calculated by using the formula, Swelling index= (mass of swollen microspheres - mass of dry microspheres/mass of dried microspheres) [19].

Conclusion

The concept of microsphere drug delivery systems offers certain advantages over the conventional drug delivery systems such as controlled and sustained delivery improved the stability, reduced the dose frequency, dissolution rate & bioavailability the microspheres drug delivery system is the most popular drug delivery system. As well as microspheres also allow drug targeting to various systems such as gastrointestinal, ocular, IM route, transdermal, intranasal, oral and IV route. Novel technologies like magnetic microspheres, immune-microspheres offer great advantages and uses than conventional technologies. By combining various other strategies, in future the microspheres will find the significant & central place in the novel drug delivery particularly in the diagnostics, diseased cell sorting, gene & genetic materials, targeted, safe, effective & specific in vitro delivery & supplements as the miniature versions of the diseased tissues & organ in the body. Therefore, microsphere are offers great affinity to the preparation to make them efficient and enhance the therapeutic effect.

Reference

[1]. *Bhalerao S.S., Lalla J.K., Rane M.S., "Study of processing parameters influencing the properties of diltiazem hydrochloride", J. Microencap. 2001;18: Page no.- 299-307.*
[2]. *Bhalerao S.S., Lalla J.K., Rane M.S., "A study of electrokinetic and stability property of suspension of diltiazem hydrochloride microcapsule", Indian Drugs 2001;38: Page no.- 464-467.*
[3]. *Chowdary K.P., Ramesh K.V., "Studies on microencapsulation of diltiazem", J. Pharm. Sci. 1993;55: Page no.- 52-54.*
[4]. *Reddy M.N., Shriwaikar A.A. Rosin, "a polymer for microencapsulation of diltiazem hydrochloride for sustained release by emulsion-solvent evaporation technique", Indian J. Pharm. Sci. 2000;62: Page no.- 308-310.*
[5]. *Saravanan M., Dhanraj M.D., Sridhar S.K., Ramachandran S., Sam S.K., Rao S.G.,*

"Preparation, characterization and in vitro release kinetics of ibuprofen polystyrene microspheres", Indian J. Pharm. Sci. 2004;66: Page no.- 287-292.
[6]. *Pandey V.P., Manavalan R., Sundarrajan T., Ganesh K.S., 'Formulation and release characteristics of sustained release diltiazem hydrochloride tablets", Indian J. Pharm. Sci. 2003; 65: Page no.- 44-48.*
[7]. *Ishikawa T., Watanabe Y., Takayama K., Endo H., Matsumoto M., "Effect of hydroxypropylmethylcellulose (HPMC) on the release profiles and bioavailability of a poorly water-soluble drug from tablets prepared using macrogol and HPMC", Int. J. Pharm. 2000;202: Page no.- 173-178.*
[8]. *Higuchi T., "Mechanism of sustained-action medication -theoretical analysis of rate of release of solid drugs dispersed in solid matrices", J. Pharm. Sci. 1963;52: Page no.- 1145-1149.*
[9]. *Wagner J.G., "Interpretation of percent dissolved-time plots derived from in vitro testing of conventional tablets and capsules", J. Pharm. Sci. 1969;58: Page no.- 1253-1257.*
[10]. *S. Freiberg and X. X. Zhu, "International Journal of Pharmaceutics", Volume 282, Issues 1-2, 10 September 2004, Page no.- 1-18.*
11. *M. A. Bayomi, S. A. Al-Suwayeh, A. M. El-Helw and A. F. Mesnad, Pharmaceutica Acta Helvetiae, Volume 73, Issue 4, December 1998, Page no.- 187-192.*
[12]. *Jin-Chul Kim, Dae Ho Kim, Min Chul Kwon, Hae Gon Chung, Seung-Jun Lee, Jong-Duk Kim, Hyeon Yong Lee, "Journal of Dispersion Science and Technology", Volume 27, Issue 2, April 2006, Page no.- 165-169.*
[13]. *Amita Bagal, Ravi Dahiya, Vance Tsai, Peter A. Adamson, "Archives of Facial Plastic Surgery", Jul/Aug 2007, Vol 9, No. 4, Page no.- 275-280.*
[14]. *Kumaresh S. Soppimath, Anandrao R. Kulkarni, Walter E. Rudzinski, Tejraj M. Aminabhavi, Drug Metabolism Reviews, Volume 33, Issue 2, April 2001, Page no.- 149-160.*
[15]. *T. Hekmatara, G. Regdon, P. Sipos, I. Er?s and K. Pintye- Hódi, "Journal of Thermal Analysis and Calorimetry", Volume 86, No.- 2, November 2006, Page no.- 287-290.*
[16]. *M.N. Reddy and A .A. Shirwalkar, "Indian Journal of Pharmaceutical Sciences", April 2000, Volume 62, Issue 4, Page no.- 308-310.*
[17]. *Reza Arshadya, "Journal of Controlled Release", Volume 14, Issue 2, October 1990, Page no.- 111-131.*
[18]. *Costas Kaparissides, Sofia Alexandridou, Katerina Kotti and Sotira Chaitidou, "A Zojono journal of Nanotechnology Online, Recent Advances in Novel Drug Delivery Systems", July, 2005, Page no.- 121-131.*
[19]. *Lidia Elfstrand , Ann-Charlotte Eliasson, Monica Jönsson , Mats Reslow, Marie Wahlgren, Starch–Stärke, Jun 2006, Volume 58, Issue 8, Page no.- 381-390.*