



Microspheres as a Promising Mucoadhesive Drug Delivery System-Review

Swapna. S^{*1}, Dr. Anna Balaji¹, Dr. M.S Uma Shankar¹, A.Vijendar²

¹Department of Pharmaceutics, Trinity College of Pharmaceutical Sciences, Karimnagar, Andhra Pradesh, India.

²Department of Pharmaceutics, Sree Datha Institute of Pharmacy, Ibrahimpatnam, Hyderabad, Andhra Pradesh, India.

*Corresponding author's E-mail: swapnasiri13@gmail.com

Accepted on: 23-07-2013; Finalized on: 30-11-2013.

ABSTRACT

Microspheres constitute an important part of novel drug delivery system (NDDS) by virtue of their small size and efficient carrier capacity. Microspheres are the carrier linked drug delivery system in which particle size ranges from 1-1000 μm range in diameter having a core of drug and entirely outer layers of polymer as coating material. Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesion while considering drug delivery is having several merits, because of the ideal physicochemical characters of the mucosal membrane. Due to their short residence time, bioadhesive characteristics can be coupled to microspheres to develop mucoadhesive microspheres. Various sites for mucoadhesive drug delivery system are ocular, nasal, buccal cavity; GIT, vaginal, rectal and several specific dosage forms have been reported. Factors affecting mucoadhesion are molecular weight, flexibility of polymer chain, pH. Several synthetic and natural polymers are identified as suitable candidates for mucoadhesive formulation. The aim of this article is to review the principles under laying the development, preparation methods, applications and evaluation of mucoadhesive microspheres.

Keywords: Carrier-linked, Microspheres, Mucoadhesion, Mucoadhesive polymers, Site-specific.

INTRODUCTION

The oral route of drug administration is the most commodious and preferred means of drug delivery to systemic circulation of body. However the drugs which are administered through oral route in the form of conventional dosage have limitations of their inability to limit and localize the system at gastro-intestinal tract. Microencapsulation is one of the approaches to enhance the oral bioavailability. Due to their small size and efficient carrier characteristics, microspheres constitute an important part of particulate novel drug delivery system. The successes of microspheres are limited due to their short residence time at the site of absorption and it can be subdued by for providing an intimate contact of the drug delivery system with the absorbing membrane. This can be accomplished by coupling bioadhesion characteristics to microspheres and developing "mucoadhesive microspheres".

Mucoadhesive microspheres include micro particles of 1-1000 μm range in diameter which comprises of entire mucoadhesive polymer or having an outer coating of it. Bioavailability of the drugs are enhanced due to their high surface to volume ratio which provides an intimate contact with the mucus layer, resulting in controlled and sustained release of drug from dosage form and specific targeting of drugs to the absorption site.¹

The rationale of developing mucoadhesive microspheres are that the formulation will be confined on a biological surface for localized drug delivery and the drug will be released close to the site of action with a consequent enhancement of bioavailability.²

Advantages of mucoadhesive microspheres:^{3,4}

1. Increased prolonged time of drug at the absorption site results in enhanced bioavailability of the drug due to adhesion and intimate contact.
2. Use of specific bioadhesive polymers results in targeting of sites or tissues.
3. It offers an excellent route for systemic delivery of drugs with high first-pass metabolism thereby offering greater bioavailability.
4. Maintenance of therapeutic plasma drug concentration.

Mucoadhesion

Bioadhesion is defined as a phenomenon in which materials are held for a longer period of time to the mucus membrane by means of interfacial forces. In biological systems, bioadhesion can be classified into 3 types.

1. Type 1, adhesion between two biological phases, for example, platelet aggregation and wound healing.
2. Type 2, adhesion of a biological phase to an artificial substrate, for example tissue, cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts.
3. Type 3, adhesion of an artificial substance to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues



Mechanism of mucoadhesion⁵

Mechanism of bioadhesion can be described in two successive steps of formulation:

1. Wetting and Contact stage- Wetting and swelling of polymer to permit intimate contact with biological tissue (Figure 1).
2. Consolidation stage- Interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin chains.

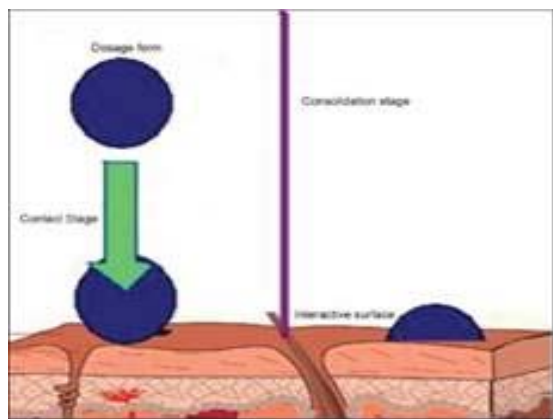


Figure 1: Mechanism of Mucoadhesion

Theories of Mucoadhesion⁶

Different theories of mucoadhesion include electronic, wetting, adsorption, diffusion, mechanical and fracture theories.

Electronic theory

Electronic theory include transfer of electrons across the adhesive interface and adhering surface which results in formation of the electrical double layer at the interface and a series of attractive forces responsible for maintaining contact between the two layers.

Wetting theory

Wetting theory describes the ability of bioadhesive polymer to spread and develop intimate contact with the mucous membrane. Spreading coefficient of polymer must be positive and Contact angle between polymer and cells must be near to zero.

Adsorption theory

According to the Adsorption theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the chemical structures at the two surfaces.

Interpenetration theory or Diffusion theory

Diffusion theory describes the entanglements of the polymer chains in to mucus network and reaches a sufficient depth within the opposite matrix to allow formation of a semi permanent bond. The exact depth needed for good bioadhesive bonds is estimated to be in the range of 0.2–0.5 μm .

Mechanical theory

Adhesion arises from an interlocking of liquid adhesive into irregularities on the rough surface which provide an increased surface area available for interaction.

Fracture theory

This theory relates to the force necessary to separate to surfaces to the adhesive bond strength and it is often used to calculate fracture strength of adhesive bonds.

Formulation Factors Affecting Mucoadhesion⁷⁻⁹

Factors affecting mucoadhesion include:

- I. Polymer related factors
- II. Environmental related factors
- III. Physiological factors

I. Polymer related factors

Hydrophilicity

Bioadhesive polymers possess numerous hydrophilic functional groups which allow hydrogen bonding with the substrate, swelling in aqueous media, thereby allowing maximal exposure of potential anchor sites.

Molecular weight

The molecular weight should be optimum for the maximum mucoadhesion. Low-molecular-weight polymers favor the interpenetration of polymer molecules whereas physical entanglements are favored at higher molecular weights.

Cross-linking density

Cross-link density is inversely proportional to the degree of swelling. Lower the cross-link density, higher the flexibility and hydration rate; larger the surface area of polymer, better the mucoadhesion.

Chain flexibility

Chain flexibility is critical for interpenetration and entanglement of mucoadhesive polymers. Highly cross-linked such as water-soluble polymers decrease the mobility of individual polymer chains and reduces bioadhesive strength.

II. Environmental factors

p^H

pH can influence the charge on the surface of mucus as well as of certain ionisable mucoadhesive polymers. If the local p^H is above the p^K_a of the polymer, it will be largely ionized; if the pH is below the p^K_a of the polymer, it will be largely unionized.

Initial Contact time

Initial Contact time determines the extent of swelling and interpenetration of the mucoadhesive polymer chains. Moreover, mucoadhesive strength increases as the initial contact time increases.

III. Physiological factors

Mucin turnover

The residence time of mucoadhesive depends on whether the polymer is soluble or insoluble in water and the associated turnover rate of mucin. Mucoadhesion decreases with increase mucin turnover.

Polymer characteristics that are required to obtain adhesion:^{10, 11}

1. Sufficient quantities of hydrogen-bonding chemical groups (-OH and -COOH).
2. Anionic surface charges.
3. High molecular weight of mucin strands with flexible polymer chains and/or interpenetration of mucin strands into a porous polymer substrate.

Sites for Mucoadhesive Drug Delivery Systems

Buccal cavity

At this site, first-pass metabolism is avoided, and the non-keratinized epithelium is relatively permeable to drugs. Due to the short residence time, it is selected as one of the most suitable areas for the development of bioadhesive devices that adhere to the buccal mucosa and remain in place for a considerable period of time.

Nasal cavity¹²

Ease of access, avoidance of first-pass metabolism and a relatively permeable and well-vascularised membrane, contribute to make the nasal cavity an attractive site for drug delivery.

Gastrointestinal tract¹³

The gastrointestinal tract has been the subject of intense study for the use of bioadhesive formulations to improve drug bioavailability.

Eye

One major problem for drug administration to the eye is rapid loss of the drug and or vehicle as a result of tear flow, and so it is a target for prolonging the residence time by bioadhesion.

Polymers used in Mucoadhesive Drug Delivery System

Mucoadhesive polymers are water-soluble and water insoluble polymers, which include:

a) Hydrophilic polymers

These polymers swell when come in contact with water and eventually undergo complete dissolution. Systems coated with these polymers show high mucoadhesion (Table 1).

Examples: Hydroxy propyl methyl cellulose, Sodium carboxy methyl cellulose.

b) Hydrogels¹⁴

These are three-dimensionally cross-linked polymer chains which have the ability to hold water within its porous structure. The water holding capacity of the hydrogels is mainly due to the presence of hydrophilic functional groups.

Examples: Polycarbophil, Carbopol, Polyox.

c) Co-polymers/Interpolymer complex

A block copolymer is formed when the reaction is carried out in a stepwise manner, leading to a structure with long sequences or blocks of one monomer alternating with long of the other.

d) Thiolated polymers (Thiomers)¹⁵

These are hydrophilic macromolecules exhibiting free thiol groups on the polymeric backbone.

Examples Cationic thiomers: Chitosan–cysteine.

Anionic thiomers: Poly (acrylic acid)–cysteine.

Table 1: List of Mucoadhesive polymers¹⁶

Criteria	Category	Examples
Source	Natural/semi-synthetic	Chitosan, Agarose, Various gums (guar gum, Xanthan gum, Gellan, Pectin)
	Synthetic	Cellulose derivatives like HPC, HPMC; Polyacrylic based polymers
Aqueous solubility	Water-soluble polymers	Carbopol, HPMC, HPC.
	Water-insoluble polymer	Chitosan, Ethyl cellulose.
Charge	Cationic	Aminodextran, Chitosan
	Anionic	Carboxyl methyl cellulose (CMC), Polyacrylic acid (PAA), Sodium alginate, Xanthan gum.
	Non-ionic	HPC, Polyvinyl alcohol, Polyvinyl Pyrrolidone.

HPMC- Hydroxy propyl methyl cellulose, HPC- Hydroxy propyl cellulose.

Methods of Preparation

Different types of methods are employed for the preparation of the microspheres. These include

1. Emulsion cross-linking method
2. Solvent evaporation
3. Spray drying
4. Phase separation coacervation technique
5. Orifice-ionic gelation method
6. Hot melt microencapsulation

Emulsion cross-linking method¹⁷

Natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in the non-aqueous medium i.e., oil. In the second step, cross-linking of the



dispersed globule is carried out either by means of heat or by using the chemical cross-linking agents like glutaraldehyde, formaldehyde. Heat denaturation is not suitable for the thermolabile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation.

Solvent Evaporation¹⁸

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution (Figure 2). With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for polymer of the core material, polymer shrinks around the core.

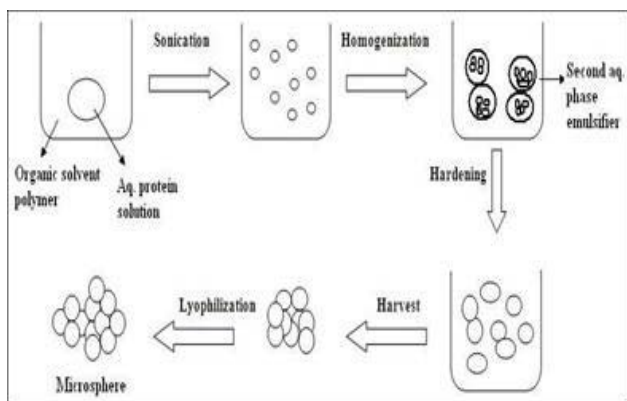


Figure 2: Solvent evaporation method for preparation of microspheres

Spray Drying¹⁹

In Spray Drying, the polymer is first dissolved in a suitable volatile organic solvent. The drug is dispersed in the polymer solution under high-speed homogenization (Figure 3). This dispersion is then atomized in a stream of hot air, leads to the formation of the small droplets from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100 µm.

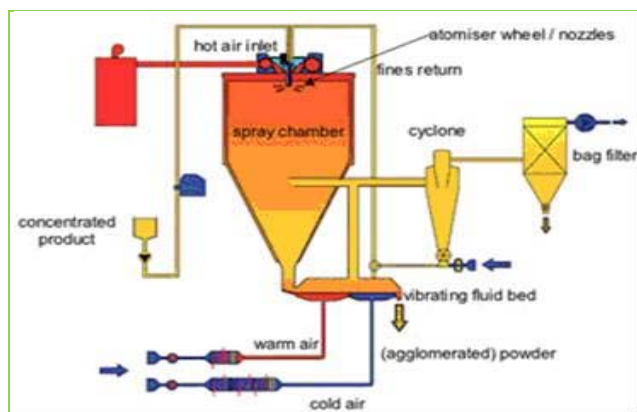


Figure 3: Spray drying method for preparation of microspheres

Phase separation coacervation technique²⁰

In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer.

Orifice-Ionic Gelation Method^{21, 22}

Polymer is dispersed in purified water to form a homogeneous polymer mixture. Drug is added to the polymer matrix and mixed thoroughly to form a smooth viscous dispersion which is then sprayed into calcium chloride solution by continuous stirring. Produced droplets are retained in the calcium chloride solution for 15 minutes to complete the curing reaction and to produce rigid spherical microspheres. The resulting microspheres are collected by decantation, and the product is washed repeatedly with purified water and then dried at 45°C for 12 hrs.

Hot Melt Microencapsulation²³

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

Evaluation of Mucoadhesive Microspheres

Particle size and shape

The particle size of the prepared microspheres can be measured by the optical microscopy method using a calibrated stage micrometer for randomly selected samples of all the formulations.

Entrapment Efficiency

The percent entrapment efficiency can be determined by allowing washed microspheres to lyse. The percent encapsulation efficiency is calculated using following equation.

$$\% \text{ Entrapment} = \frac{\text{Actual content} \times 100}{\text{Theoretical content}}$$

Swelling Index²⁵

Swelling index illustrate the ability of the mucoadhesive microspheres to get swelled at the absorbing surface by absorbing fluids available at the site of absorption, which is a primary requirement for initiation of mucoadhesion.

Angle of contact²⁶

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of

hydrophilicity or hydrophobicity. Contact angle is measured at 20° within a minute of deposition of microspheres.

In-vitro drug release studies²⁷

An *in-vitro* release profile reveals fundamental information on the structure (e.g., porosity) and behavior of the formulation on a molecular level, possible interactions between drug and polymer, and their influence on the rate and mechanism of drug release and model release data.

Ex-vivo mucoadhesion test²⁸

The *ex-vivo* mucoadhesion tests are important in the development of a controlled release bioadhesive system because they contribute to studies of permeation, release, compatibility, mechanical and physical stability, superficial interaction between formulation and mucous membrane and strength of the bioadhesive bond. These tests can simulate a number of administration routes including oral, buccal, periodontal, nasal, gastrointestinal, vaginal and rectal.

Surface topography by Scanning Electron Microscopy (SEM)²⁹

SEM uses a focused beam of high-energy electrons to generate a variety of signals at the surface of solid specimens. The signals that derive from electron sample interactions reveal information about the sample including external morphology (texture), chemical composition, and crystalline structure and orientation of materials making up the sample.

Zeta Potential Measurement³⁰

The surface charge can be determined by relating measured electrophoretic mobility into zeta potential with in-built software based on the Helmholtz–Smoluchowski equation. Zeta potential is an indicator of particle surface charge, which can be used to predict and control the adhesive strength, stability, and the mechanisms of mucoadhesion.

Drug polymer interaction (FTIR) study³¹

IR spectroscopy can be performed by Fourier transformed infrared spectrophotometer. The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned.

Applications of Microspheres⁴²

1. Microspheres in vaccine delivery for treatment of diseases like hepatitis, influenza, and pertussis.
2. Microspheres act as potential carriers for targeting to various organs.
3. Monoclonal antibodies mediated microspheres targeting.
4. Scintigraphic imaging of the tumors masses in lungs using labeled human serum albumin microspheres.
5. Used for radio synvectomy of arthritis joint, local radiotherapy, interactivity treatment.

Table 2: List of currently available Commercial bioadhesive drug formulations²⁴

Brand name	Company	Bioadhesive polymer	Pharmaceutical Form
Buccastem	Reckitt Benckiser	Xanthum gum and locust bean gum	Buccal tablet
Corlan Pellets	EllTech	Acacia gum	Oromucosal pellets
Suscard	Forest	HPMC	Buccal tablet
Gaviscon Liquid	Reckitt Benckiser	Sodium alginate	Oral liquid
Corsodyl gel	Glaxo Smith Kline	HPMC	Oromucosal gel
Nyogel	Novartis	Carbomer and PVA	Eye gel
Crinone	Serono	Carbomer	Vaginal gel

HPMC- Hydroxy propyl methyl cellulose, PVA-Polyvinyl acetate

Table 3: List of various mucoadhesive microspheres formulations

Drug	Category	Polymer	References
Glipizide	Anti-diabetic	Xyloglucan	32
Gliclazide	Anti-diabetic	Chitosan	33
Raloxifene HCl	Anti-resorptives	HPMC	34
Gentamicin sulphate	Aminoglycosidal antibiotic	HPMC, SCMC	35
Famotidine	H2-receptor antagonist	SCMC	36

HPMC- Hydroxy propyl methyl cellulose, SCMC-Sodium Carboxymethyl cellulose

Table 4: List of various patents on microspheres

Patent No.	Contents	References
US0171260A1 (2013)	Invention relates to the preparation of silk fibroin microspheres using lipid vesicles as templates to efficiently load therapeutic agents in active form for controlled release.	37
US0244198A1(2012)	This invention relates to biodegradable microspheres of hydrolysed starch with endogenous, charged ligands attached to it and also relates to use of the microspheres in hemostasis, wound healing, vascular embolisation.	38
US0247663A1(2010)	The invention relates to the production of microspheres using thermally induced phase separation, especially microspheres for use in tissue engineering.	39
US0160246A1 (2010)	The present invention relates to the use of microspheres for the treatment of a brain tumour, in which the microspheres comprise a water-insoluble polymer and a cationically charged chemotherapeutic agent.	40
US0141021A1 (2006)	The invention relates polymeric microsphere comprises a first polymer, a layer formed on the surface of the first polymer, and a second polymer formed on the layer. The invention also provides a method for preparing the polymeric microsphere by an aqueous-two-phase emulsion process.	41

CONCLUSION

Mucoadhesive microspheres offer unique carrier system for many pharmaceuticals and can be tailored to adhere to any mucosal tissue. Mucoadhesive drug delivery system shows promising future in enhancing the bioavailability and specific needs by utilizing the physiochemical characters of both the dosage form and the mucosal lining. Improvements in bioadhesive based drug delivery and, in particular, the delivery of novel, highly-effective and mucosa compatible polymer, are creating new commercial and clinical opportunities for delivering narrow absorption window drugs at the target sites to maximise their usefulness. With the influx of a large number of new drug molecules from drug discovery, mucoadhesive drug delivery will play an even more important role in delivering these molecules.

REFERENCES

- Harshad P, Bakliwal S, Gujarathi N, Rane B, Pawar S, Different method of Formulation and evaluation of mucoadhesive microsphere, International Journal of Applied Biology and Pharmaceutical Technology, 1(3), 2010, 1157-1167.
- Alexander A, Ajazuddin, Tripathi DK, Verma T, Maurya J, Patel S, Mechanism responsible for mucoadhesion of mucoadhesive drug delivery system: A Review. International Journal of Applied Biology and Pharmaceutical Technology, 2(1), 2011, 434-445.
- Gavin PA, Lavery TP, Jones DS, Mucoadhesive Polymeric Platforms for Controlled Drug Delivery, European Journal of Pharmaceutics and Biopharmaceutics, 71(3), 2009, 505-518.
- S. Kataria, Middha A, Bilandi A, Kapoor B, Microsphere: A Review, Int J Res Pharm Chem, 1(4), 2011, 1185-1198.
- Garg A, Upadhyay P, Mucoadhesive Microspheres: A Short Review, Asian Journal of Pharmaceutical and Clinical Research, 5 (3), 2012, 24-27.
- Smart JD, The basics and underlying mechanisms of mucoadhesion, Adv Drug Del Rev, 57 (11), 2005, 1556-1568.
- Muthukumar M, Dhachinamoorthi D, Sriram N, Chandra sekhar KB, Review on Polymers Used in Mucoadhesive Drug Delivery System, In. J Pharm & Ind. Res, 1 (2), 2011, 122-127.
- Chen JL, Cyr. G.N., Composition producing adhesion through hydration, in mainly R.S., ed., Adhesion in biological system. New York; Academic Press, 163-181.
- Ch'ng HS, Park H, Kelly P, Robinson JR, Bioadhesive polymers as platform for oral controlled drug delivery II: Synthesis and evaluation of some swelling water insoluble bioadhesive polymers, J Pharm Sci, 74 (4), 1985, 399-405.
- Hans E. Janginger, Janet A, Hoogstraate and Coos Verhoef J, "Recent advances in buccal drug delivery and absorption *invitro* and *invivo* studies" Journal of controlled release, 62, 1999, 149-59.
- Dr. Bhaskar Jasti, Xiaoling Li, Gary Cleary, "Recent advances in Mucoadhesive drug delivery systems" Pharmatech, 2003, 194-196.
- Coos Verhoef J, Merkus FWHM, Schipper G. M, The Nasal Mucociliary Clearance: Relevance to Nasal Drug Delivery, Pharmaceutical Research, 8 (7), 1991, 807-814.
- Woodley J, Bioadhesion: New Possibilities for Drug Administration, Clin Pharmacokinet, 40 (2), 2001, 77-84.
- Zhao Y, Kang J, Tan TW, Salt, pH and temperature responsive semi-interpenetrating polymer network hydrogel based on poly (aspartic acid) and poly (acrylic acid). Polymer, 47 (22), 2006, 7702-7710.
- Bernkop - Schnurch A, Thiomers, A new generation of mucoadhesive polymers. Adv Drug Deliv Rev, 58 (11), 2005, 1569-1582.
- Savage DC, Microbial ecology of the gastrointestinal tract, Annu. Rev. Microbiol., 31, 1977, 107- 133.



17. Alagusundaram M, Chetty MS, Umashankari K, Lavanya C, Ramkanth S, Microspheres as a novel drug delivery system: A review, *Int J Chem Tech Res*, 1 (3), 2009, 526-534.
18. Shashank Tiwari, Prerana Verma, Microencapsulation technique by solvent evaporation method (Study of effect of process variables), *International Journal of Pharmacy & Life Sciences*, 2 (8), 2011, 998-1005.
19. Bodmeier R, Chen HG, Preparation of biodegradable poly (+/-) lactide microparticles using a spray-drying technique, *J Pharm Pharmacol.*, 40 (11), 1988, 754-757.
20. Meena JS, Samal PK, Kedar Prasad, Namdeo KP, Recent advances in microsphere manufacturing technology, *International Journal of Pharmacy and Technology*, 3(1), 2011, 854-855.
21. Moy AC, Mathew ST, Mathapan R, Prasanth VV, Microsphere - An Overview. *International Journal of Pharmaceutical and Biomedical Sciences*, 2(2), 2011, 332-338.
22. Lim F, Moss RD, Microencapsulation of living cells and tissues, *J Pharm Sci*, 70 (4), 1981, 351-354.
23. Mathiowitz E, Kline D, Langer R, Polyanhydride microspheres as drug carriers I. Hot-melt microencapsulation, *J Control Release*, 5(1), 1987, 13-22.
24. Batchelor H, Novel bioadhesive formulation in drug delivery; *The Drug Delivery Company Report*, 2004, 16-19.
25. Rajput G, Majmudar F, Patel, Thakor R, Rajgor NB, Stomach-specific mucoadhesive microsphere as a controlled drug delivery system. *Sys Rev Pharm.*, 1(1), 2010, 70-78.
26. Meena KP, Dangi JS, Samal PK, Namedo KP, Recent advances in microsphere manufacturing technology, *International Journal of Pharmacy and Technology*, 3(1), 2011, 854-855.
27. Susan S. D'Souza, Patrick P. DeLuca. Methods to Assess in Vitro Drug Release from Injectable Polymeric Particulate Systems, *Pharmaceutical Research*, 23 (3), 2006, 460-465.
28. Vinod KR, Rohit Reddy T, Sandhya S, David B, Venkatram B, Critical Review on Mucoadhesive Drug Delivery Systems, *Hygeia.J.D.Med*, 4 (1), 2012, 7-28.
29. Goldstein J, D E. Newbury, D C. Joy, C E. Lyman, P Echlin, E Lifshin, L Sawyer, and J R. Michael, *Scanning electron microscopy and X-ray microanalysis*, 3rd edition, 2003, 689.
30. Bogataj M, Vovk T, Kerec M, Dimnik A, Grabnar I, Mrhar A, The correlation between zeta potential and mucoadhesion strength on pig vesical mucosa, *Biol Pharm Bull*, 26(5) , 2003, 743-746.
31. Meena KP, Dangi JS, Samal PK, Namedo KP, Recent advances in microsphere manufacturing technology, *International Journal of Pharmacy and Technology*, 3 (1), 2011, 854-855.
32. Mangesh R, Kalpesh P, Ashwini R, Formulation Optimization and evaluation of mucoadhesive microspheres of Xyloglucan, *Int. J. Pharm. Health Sci*, 1(1), 23-31.
33. Senthil A, Thakkar Hardik R, Ravikumar, Narayanaswamy V.B, Chitosan Loaded Mucoadhesive Microspheres of Glioclazide: In vitro and In vivo Evaluation: *RJPS*, 1 (2), 2011, 163-171.
34. Ram K. Jha, Sanjay Tiwari, Brahmeshwar Mishra, Bioadhesive Microspheres for Bioavailability Enhancement of Raloxifene Hydrochloride: Formulation and Pharmacokinetic Evaluation: *AAPS Pharm Sci Tech*, 12(2), 2011, 650-657.
35. Canan Hasçiçek, Nursin Gönül, Nevin Erk, Mucoadhesive microspheres containing gentamicin sulfate for nasal administration: preparation and in vitro characterization: *Il Farmaco*, 58(1), 2003, 11–16.
36. Rajeshwar Kamal Kant Arya, Ripudam Singh, Vijay Juyal, Mucoadhesive Microspheres of Famotidine: Preparation, Characterization and *In-vitro* Evaluation: *International Journal of Engineering Science and Technology*, 2(6), 2010, 1575-1580.
37. Kaplan; David L, Wang, Xiaoqin, inventors; Trustees of Tufts College, assignee. Silk Microspheres for Encapsulation and Controlled Release, US Patent 0171260A1, 2013 July 4.
38. Malmsjo, Malin, Thordarson, Eddie, Apell, Sten Peter, Fyhr, Peter, inventors; Magle ab, assignee. Microspheres of Hydrolysed Starch with Endogenous, Charged Ligands, US Patent 0244198A1, 2012 Sept 27.
39. Day, Richard Michael, Blaker, Jonny, inventors; King's College London, assignee. Microspheres, US Patent 0247663A1, 2010 Sept 30.
40. Lewis, Andrew Lennard, Tang, Yiqing, Stratford, Peter William, inventors; Biocompatibles UK Limited, assignee. Microspheres for treatment of brain tumors, US Patent 0160246A1, 2010 July 24.
41. Wang, Ae-June, Lin, Yi-Fong, Jian, Chi-Heng, Liu, Shin-Jr, inventors; Industrial Technology Research, assignee. Polymeric *microspheres* and method for preparing the same, US Patent 0141021A1, 2006 June 29.
42. Shun Por Li, Kowalski CR, Feld KM and Wayne M, Recent Advances in Microencapsulation Technology and Equipment, *Drug Delivery Ind. Pharm*, 14 (2-3), 1988, 353-376.

Source of Support: Nil, Conflict of Interest: None.

