

International Journal of Research and Reviews in Pharmacy and Applied science

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A BRIEF REVIEW ON MUCOADHESIVE MICROSPHERES

ABSTRACT:

Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, niosomes etc which modulates the release and absorption characteristics of the drug. Microspheres constitute an important part of novel drug delivery system by virtue of their small size and efficient carrier capacity. Due to their short residence time, bioadhesive characteristics can be coupled to microspheres to develop mucoadhesive microspheres. Mucoadhesive microspheres provide better drug absorption as they get adhere to the mucosal surface and release drug for prolonged time. Mucoadhesive microspheres have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, controlled and sustained release of drug from dosage form and specific targeting of drugs to the absorption site. The present study aims to provide an overview about the mucoadhesive microspheres, their methods of preparation and their evaluation in brief.

KEYWORDS: Mucoadhesive Microspheres, methods of preparation of Mucoadhesive microspheres, Evaluation of Mucoadhesive Microspheres.

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INTRODUCTION:

Recently the novel dosage forms which can control the release rate and target the active drug molecule to a particular site have attained a great formulation interest. Precisely designed controlled drug delivery system can overcome many problems of conventional therapy and enhance the therapeutic efficacy of a given drug. Drug action can be improved by developing new drug delivery system, such as the mucoadhesive microsphere drug delivery system. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to a bioavailability increase and both local and systemic effects.

Tailored mucoadhesive microspheres offers the possibilities of localized as well as controlled release of drugs by adherence to any mucosal tissue present in eye, nasal cavity, urinary, and GI tract¹.

ADVANTAGES OF MUCOADHESIVE MICROSPHERES:

- ✓ Reduces the frequency of daily administration and thereby improve the patient compliance.
- ✓ The use of specific bioadhesive molecules allows for possible targeting of particular sites or tissues, for example the gastrointestinal (GI) tract¹.
- ✓ As a result of adhesion and intimate contact, the formulation stays longer at the delivery site improving API bioavailability using lower API concentrations for disease treatment.
- ✓ Offers an excellent route, for the systemic delivery of drugs with high first-pass metabolism, there by offering a greater bioavailability².
- ✓ Uniform and wide distribution of drug throughout the gastrointestinal tract which improves the drug absorption.
- ✓ Prolonged and sustained release of drug and Maintenance the therapeutic plasma drug concentration.
- ✓ Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of intestine can be administered by this route e.g. buccal, sublingual, vagina³.

DISADVANTAGES OF MUCOADHESIVE MICROSPHERES¹:

- ✓ The release rate may vary from a variety of factors like food and the rate of transit though gut, mucin turnover rate etc.
- ✓ Any loss of integrity in release pattern of the dosage form may lead to potential toxicity.
- ✓ Differences in the release rate can be found from one dose to another.

Ideal Characteristics of mucoadhesive polymer:

1. The polymer and its degradation products should be nontoxic and should be nonabsorbable from the GI tract.
2. It should be nonirritant to the mucus membrane.
3. It should preferably form a strong noncovalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to most tissue and should possess some site specificity.
5. It should allow easy incorporation of the drug and should offer no hindrance to its release.
6. The polymers must not decompose on storage or during the shelf life of the dosage form.
7. The cost of the polymer should not be high so that the prepared dosage form remains competitive⁴.

Mucoadhesive Polymers and their Bioadhesive Property:-**Polymer Bioadhesive property**

CMC Sodium	+++
Carbopol 934	+++
Polycarbophil ⁺⁺⁺	
Tragacanth ⁺⁺⁺	
Poly (acrylic acid/divinyl benzene)	+++
Sodium Alginate	+++
Hydroxy Ethyl Cellulose	+++
HPMC	+++
Gum Karaya ⁺⁺	
Gelatin	++
Guar Gum	++
Thermally Modified Starch	+
Pectin	+
PVP	+
Acacia	+
Psyllium ⁺	
Amberlite-200 resin	+
Hydroxy Propyl Cellulose	+
Chitosan	+

+++ → Excellent ++ → Good + → Poor

MUCOADHESION AND ITS PHENOMENA:

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membranes such as buccal, ocular, rectal, nasal etc can be termed as bioadhesion. The term “bioadhesion” describes materials that bind to biological substrates, such as mucosal membranes. Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration⁵.

Mucus Membranes⁶:

Mucus membranes are the moist surfaces lining walls of various body cavities such as the gastrointestinal and respiratory tracts. Mucus is secreted by the goblet cells. Mucus is present either as a gel layer adherent to the mucosal surface or in suspended form or as a luminal soluble. The major components of all mucus gels are mucin glycoprotein, water, lipids, and inorganic salts. The mucus serves as a protective barrier and for lubrication also.

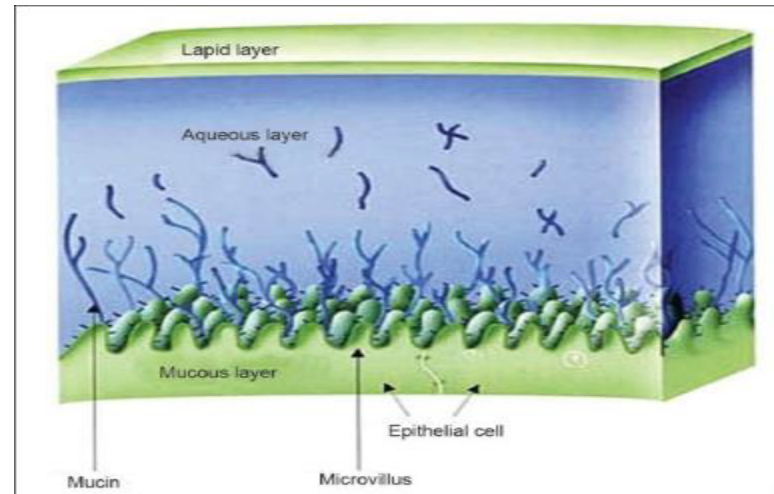


Figure1: Structure of mucous membrane

MECHANISM OF MUCOADHESION⁷:

Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains.

The mechanism of mucoadhesion is as followed:

- The first step is followed by the Intimate contact between a mucoadhesive delivery system and mucosal membrane (where the wetting or swelling phenomenon takes place)
- The second step is finally Penetration of the mucoadhesive delivery system into the tissue or into the surface of the mucous membrane which inturn shows its therapeutic activity.

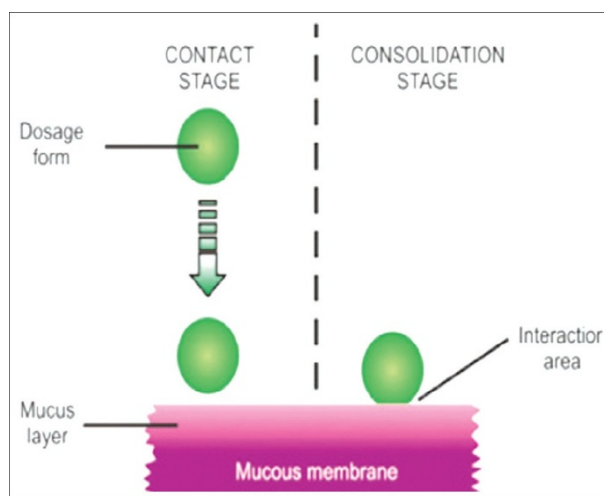


Figure 2: Mechanism of mucoadhesion

THEORIES OF MUCOADHESION⁸:

Different theories are involved in the mucoadhesion which are as follows

1. The electronic theory
2. The wetting theory
3. The adsorption theory
4. The diffusion theory
5. The mechanical theory, and
6. The cohesive theory

1. The Electronic Theory

According to this theory an electrical double layer is formed on the transfer of the electrons among the mucoadhesive and mucosal membrane.

2. The Wetting Theory

This theory is applicable for liquids, postulates that the lower the contact angle of liquid on substrate surface there will be greater affinity for adhesion.

3. The Adsorption Theory

According to this theory the mucoadhesive get adsorbed on the mucosal surface by intermolecular forces, viz. Vander Waal's forces, hydrogen bonding etc.

4. The Diffusion Theory

This theory illustrates the forming of a network structure among the mucoadhesive and the mucosal surface by diffusion of the polymers chains present on the mucoadhesive surface.

5. The Mechanical Theory

Explains the formation of an interlocked structure by the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the mucoadhesive substrate resulting in mucoadhesion.

6. The Cohesive Theory

According to this theory the phenomena of mucoadhesion is mainly due to the intermolecular interactions amongst like-molecules.

METHOD OF PREPARATION OF MUCOADHESIVE MICROSPHERES:

Mucoadhesive microspheres can be prepared by using different techniques like:

1. Complex coacervation
2. Hot melt microencapsulation
3. Single emulsion technique
4. Double emulsion method
5. Solvent evaporation technique
6. Ionotropic gelation
7. Phase inversion method
8. Spray drying

1. Complex Coacervation^{9, 10}

Principle of this method is under suitable conditions when solutions of two hydrophilic colloids were mixed, result into a separation of liquid precipitate. In this method the coating material phase, prepared by dissolving immiscible polymer in a suitable vehicle and the core material is dispersed in a solution of the coating polymer under constant stirring. Microencapsulation was achieved by utilizing one of the methods of phase separation, that is, by changing the temperature of the polymer solution; by changing the pH of the medium, by adding a salt or an incompatible polymer or a non-solvent to the polymer solution; by inducing a polymer polymer interaction. Generally coating is hardened by thermal cross linking or desolvation techniques, to form a self sustaining microsphere.

2. Hot Melt Microencapsulation

Microspheres of polyanhydride copolymer of poly bis(p-carboxyphenoxy) propane anhydride with sebacic acid were firstly prepared by this method¹⁹. In this method the polymer is firstly melted and then the solid drug particles are added to it with continuous mixing. The prepared mixture is then suspended in a non-miscible solvent like silicone oil with stirring and heated at the temperature above the melting point of the polymer with continuous stirring so as to get stabilized emulsion. The formed emulsion is cooled to solidify polymer particles followed by filtration and washing of the microspheres with petroleum ether.

3. Single Emulsion Technique⁷

The microspheres of natural polymers are prepared by single emulsion technique. The polymers and drug are dissolved or dispersed in aqueous medium followed by dispersion in organic medium e.g. oil, results in formation of globules, and then the dispersed globule are cross linked by either of heat or by using the chemical cross-linkers. The chemical cross-linkers used are formaldehyde, glutaraldehyde, diacid chloride etc.

4. Double Emulsion Method

This method is firstly described by Ogawa Y et al. in year 1988, and is the most widely used method of microencapsulation¹¹. In this method an aqueous solution of drug and polymer is added to the organic phase with vigorous stirring to get primary water-in-oil emulsion. This emulsion was then poured to a large volume of water containing an emulsifier like polyvinyl alcohol or polyvinylpyrrolidone, under stirring, to get the multiple emulsions (w/o/w); and stirring was continued until most of the organic solvent evaporates, leaving solid microspheres. The microspheres are then washed and dried.

5. Solvent evaporation technique^{12,13}

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2 % sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs. Aceclofenac microspheres were prepared by this technique.

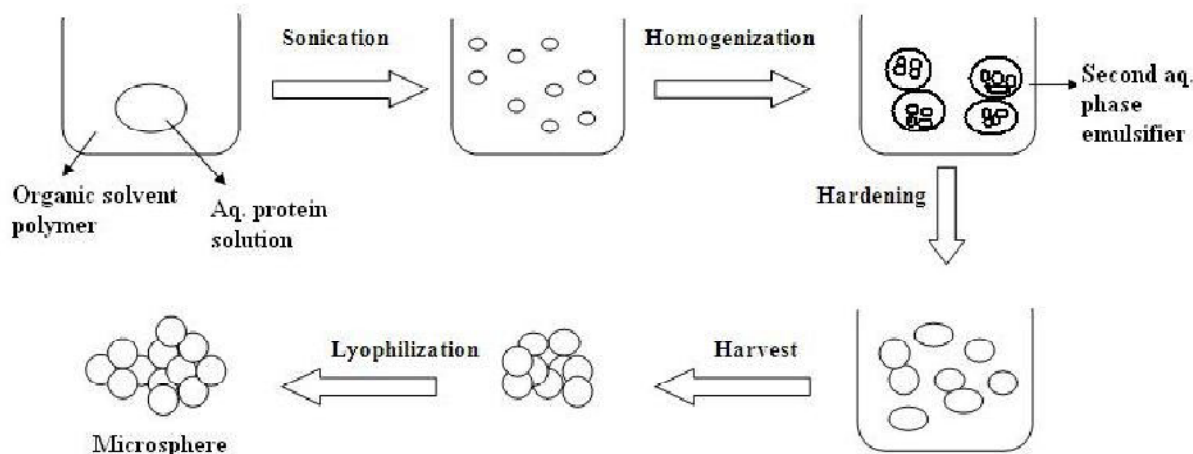


Figure: 3 Solvent evaporation technique

6. Ionotropic Gelation

This method was developed by Lim F and Moss RD¹⁴. Using this method Microspheres are formed by dissolving the gel-type polymers, such as alginate, in an aqueous solution followed by suspending the active ingredient in the mixture and extruding the solution through needle to produce micro droplets which fall into a hardening solution containing calcium chloride under stirring at low speed. Divalent calcium ions present in the hardening solution crosslink the polymer, forming gelled microspheres.

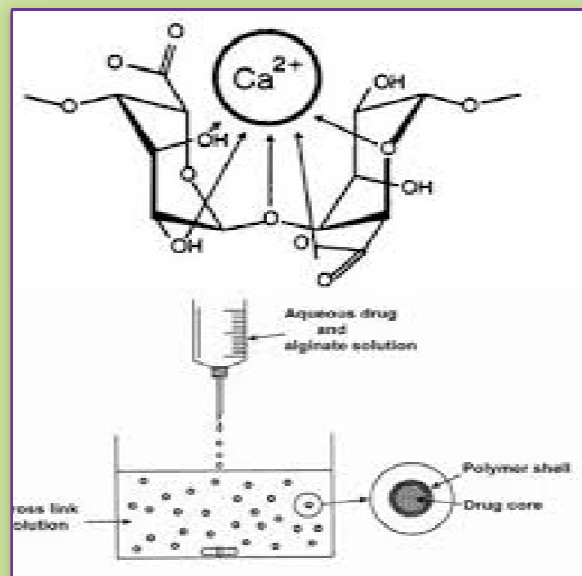


Figure 4: Ionotropic gelation method

7. Phase Inversion Method

The method involves addition of drug into dilute polymeric solution, in methylene chloride; and resultant mixture is poured into an unstirred bath of strong non-solvent, petroleum ether, in a ratio of 1: 100. Microspheres produced are then clarified, washed with petroleum ether and air dried^{15,16}.

8. Spray Drying

This method involves dissolving/dispersing of the drug into the polymer solution which is then spray dried. By this method the size of microspheres can be controlled by manipulating the rate of spraying, feeding rate of polymer drug solution, nozzle size, and the drying temperature¹⁷⁻¹⁹.

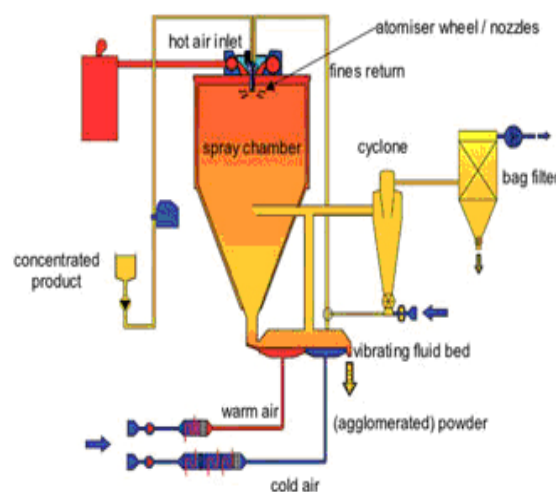


Figure 5: Spray drying

EVALUATION OF MUCOADHESIVE MICROSPHERES:

1. Interaction study by TLC/ FTIR.IR spectroscopic studies:-

The IR spectra of the free drug and the microspheres are recorded. The identical peaks corresponding to the functional groups features confirm that neither the polymer nor the method of preparation has affected the drug stability.

Thin layer chromatographic studies

The drug stability in the prepared microspheres can also be tested by the TLC method. The R_f values of the prepared microspheres can be compared with the R_f value of the pure drug. The values indicate the drug stability.

UV-FTTR (Fourier transform infra red)

The drug polymer interaction and also degradation of drug while processing for microencapsulation can be determined by FTIR. In this method the pellets of drug and potassium bromide are prepared by compressing the powders at 20 psi for 10 min on KBr press and the spectra are scanned in the wave number range of 4000–600 cm⁻¹. FTIR study is carried on pure drug, physical mixture, formulations and empty microspheres²⁰.

2. Particle size distribution of prepared microspheres:-

Carried out using Optical Microscopy

Optical microscopy

This method is used to determine particle size of microspheres by using optical microscope (Meizer OPTIK) The measurement is done under 45x (10x eye piece and 45x objective) and 100 particles are calculated.

3. Surface topography by Scanning Electron Microscopy (SEM):-

SEM of the microspheres shows the surface morphology of the microspheres like their shape and size.

Scanning electron microscopy (SEM)

Surface morphology of microspheres is determined by the method SEM. In this method microspheres are mounted directly on the SEM sample stub with the help of double sided sticking tape and coated with gold film under reduced pressure. Scanning Electron photomicrographs of drug loaded microspheres are taken. A small amount of microspheres is spread on gold stub. Afterwards, the stub containing the sample is placed in the Scanning electron microscopy (SEM). A Scanning electron photomicrograph is taken at an acceleration voltage of 20KV and chamber pressure of 0.6 mm Hg²¹.

4. Entrapment Efficiency:-

The entrapment efficiency of the microspheres or the percent entrapment can be determined by keeping the microspheres into the buffer solution and allowing lysing. The lysate obtained is filtered or centrifuged and then subjected for determination of active constituents as per monograph requirement. The percent entrapment efficiency is calculated using following equation⁷:

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

5. Swelling Index:-

Swelling index illustrates 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 mucoadhesion²². The percent swelling value can be determined using following equation.

$$\text{Percent swelling} = \frac{DT - D_0}{D_0} \times 100$$

Where, D_0 = weight of dried microspheres

DT = weight of swelled microspheres

6. Bulk density:-

The microspheres fabricated are weighed and transferred to a 10-ml glass graduated cylinder. The cylinder is tapped using an autotrap until the microsphere bed volume is stabilized. The bulk density is estimated by the ratio of microsphere weight to the final volume of the tapped microsphere bed.

7. Angle of contact:-

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. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 20°C within a minute of deposition of microspheres²³.

8. In vitro drug release studies:-

In-vitro release studies can be performed according to USP XXII type 2 dissolution apparatus at suitable pH conditions. The temperature should be maintained at $37 \pm 0.5^\circ\text{C}$ and the rotation speed of 100 rpm. Then 5 ml of sample should be withdrawn at various time intervals and replenished with an equal volume of fresh dissolution media. The drug content in the sample can be analyzed spectrophotometrically at specific wavelength (nm)²⁴

9. Ex-Vivo Mucoadhesion Study:-

The mucoadhesive property of the microspheres is evaluated on goat's intestinal mucosa by using phosphate buffer, as per monograph. Weighed microspheres are spread onto wet rinsed tissue specimen and immediately thereafter the slides are hung onto the arm of a USP tablet disintegrating test machine with suitable support at 37°C. The weight of microspheres leached out at different intervals is measured. The % mucoadhesion is calculated by the following equation²⁵:

$$\% \text{Mucoadhesion} = \frac{W_a - W_1}{W_a} * 100$$

Where,

W_a is the weight of microspheres applied

W₁ is the weight of microspheres leached out.

CONCLUSION:

Mucoadhesive microspheres have been proved as a promising tool in delivery of drugs to a particular site in controlled or sustained manner, as they deliver the drug to a particular site for longer duration, the absorption of drug increased and hence, the bioavailability of the drug gets increased. These carrier systems will also increase the residence time of the drug in the gastrointestinal tract. Mucoadhesive drug delivery is a promising area for systemic delivery of orally inefficient drugs as well as an attractive alternative for noninvasive delivery of potent peptide and perhaps protein drug molecules. Therefore, it can be said that in future also mucoadhesive microspheres will play an important role in the development of new pharmaceuticals employing more advanced techniques and materials.

REFERENCES:

1. S. Kataria, A. Middha, P. Sandhu, A. Bilandi and B. Kapoor. Microsphere: A Review. *Int J Res Pharm Chem* 2011; 1(4): 1185-1198
2. Punitha S, Girish Y. Polymers in mucoadhesive buccal drug delivery system. *International Journal of Research and Pharmaceutical Sciences* 2010; 1(2): 170-186.
3. Sachan NK, Bhattacharya A. Basic and Therapeutic Potential of Oral Mucoadhesive Microparticulate Drug Delivery Systems. *International Journal of Pharmaceutical and Clinical Research* 2009; 1: 10-14.
4. Asane GS, Nirmal SA, Rasal KB, Naik AA, Mahadik MS. Polymers for Mucoadhesive drug delivery system. *Drug Development and Industrial Pharmacy* 2011; 34: 1246-1266.
5. Patel J. Bioadhesion is a topic of current interest in the design of controlled or targeted drug delivery system.
6. Boddupalli BM, Zulkar MNK, Nath RA, Banji D. Mucoadhesive drug delivery system: An overview. *J Adv Pharm Tech Res* 2010; 1(4): 381-387.
7. Alagusundaram M, Chetty MS, Umashankari K, Badarinath AV, Lavanya C, Ramkanth S. Microspheres as a novel drug delivery system: A review. *Int J Chem Tech Res* 2009; 1(3): 526-534.
8. Muthukumar M, Dhachinamoorthi D, Chandra KBS, Sriram NA. Review On Polymers Used In Mucoadhesive Drug Delivery System. In. *J Pharm Ind Res* 2011; 1(2) 122-127
9. Zhang L, Liu Y, Wu Z and Chen H. Preparation and characterization of coacervate microcapsules for the delivery of antimicrobial oyster peptides. *Drug Dev Ind Pharm.* 2009; 35(3): 369-278
10. Mathiowitz E, Kreitz MR and Peppas LB. Microencapsulation. In: Mathiowitz E, ed. *Encyclopedia of Controlled Drug Delivery*, Vol. 9. New York: John Wiley & Sons; 1999a: 493-504

11. Bogataj M, Mrhar A and Korosec L. Influence of physicochemical and biological parameters on drug release from microspheres adhered on vesical and intestinal mucosa. *Int J Pharm* 1999; 177(2): 211-220
12. Venkatesan P., Manavalan R., Valliappan K., Preparation and evaluation of sustained release loxoprofen, *J of Basic and Clinical Pharmacy*. 2011; 2(3): 159-162.
13. Lakshmana P.S., Shirwaikar A., Kumar A., Formulation and evaluation of sustained release microspheres of rosin containing aceclofenac, *ArsPhar.*, 2009; 50(2): 51-62.
14. Lim F, Moss RD. Microencapsulation of living cells and tissues. *J Pharm Sci*. 1981; 70(4): 351-354.
15. Chickering DE, Santos CA and Mathiowitz E. Adaptation of a microbalance to measure bioadhesive properties of microspheres. In: Mathiowitz E, Chickering DE, Lehr CM, eds. *Bioadhesive Drug Delivery Systems: Fundamentals, Novel Approaches and Development*. New York: Marcel Dekker; 1999: 131-145.
16. Costa MS and Margarida Cardoso MM. Effect of uniform sized polymeric microspheres prepared by membrane emulsification technique on controlled release of anthracycline anti-cancer drugs. *Desalination* 2006; 200: 498-500.
17. Bodmeier R, Chen HG. Preparation of biodegradable poly(+/-)lactidemicroparticles using a spray-drying technique. *J Pharm Pharmacol*. 1988; 40(11): 754-757
18. B.F. Oliveira de, M.H.A. Santana, M.I. Re, Spray-dried chitosan microspheres crosslinked with d,l-glyceraldehyde as a potential drug delivery system: preparation and characterization. Submitted for presentation at the 14th International Drying Symposium (IDS 2004). Sao Paulo, Brazil, August 2004, B1166-1173
19. Yassin AE, Alanazi FK, El-Badry M, Alsarra IA, Barakat NS, Alanazi FK. Preparation and characterization of spironolactone-loaded geluciremicroparticles using spray-drying technique. *Drug DevInd Pharm*. 2009; 35(3): 297-304.
20. Meena KP, Dangi JS, Samal PK, Namedo KP. Recent advances in microsphere manufacturing technology. *International Journal of Pharmacy and Technology* 2011; 3(1): 854-855.
21. Moy AC, Mathew ST, Mathapan R, Prasanth VV. Microsphere-An Overview. *International Journal of Pharmaceutical and Biomedical Sciences* 2011; 2(2): 332-338.
22. Rajput G, Majmudar F, Patel J, Thakor R, Rajgor NB. Stomach-specific mucoadhesive microsphere as a controlled drug delivery system. *Sys Rev Pharm*. 2010; 1(1): 70-78.
23. Meena KP, Dangi JS, Samal PK, Namedo KP. Recent advances in microsphere manufacturing technology. *International Journal of Pharmacy and Technology* 2011; 3(1): 854-855.
24. Parmar H, 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* 2010; 1(3): 1157-1167.
25. Chakraborty S, Dinda SC, Ch. Patra NC, Khandai M. Fabrication and Characterization of Algino-Carbopol Microparticulate System of Aceclofenac for Oral Sustained Drug Delivery. *Int J Pharm Sci Review Res* 2010; 4(2) 192-199