



REVIEW ARTICLE

Mucoadhesive Microspheres as a gastroretentive drug delivery system - A Review

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ABSTRACT

Gastroretentive drug delivery system is a novel drug delivery systems to prolong gastric retention time thereby targeting the drug to the desired site i.e to the upper gastrointestinal tract for local or systemic action thereby improving bioavailability of the drugs. Due to its bioadhesive characteristics and excellent carrier capacity mucoadhesive microsphere promises several advantages as they get adhered to the mucosal surface, releasing the drug for longer duration of time and increasing the drug concentration gradient to the site of action. Mucoadhesive microspheres is an ideal targeting system with high safety profile and have been developed for oral, buccal, nasal, ocular, rectal and vaginal for either systemic or local effects. This review article gives the information about mucoadhesion and theories of mucoadhesion. It also contains a number of available methods of preparation of mucoadhesive microspheres as well as recent gastro-retentive approaches till date.

KEYWORDS

Mucoadhesive Microsphere, GRDDS, Mucoadhesion, Gastroretentive approaches

INTRODUCTION

Oral route is the most desirable and convenient method of drug administration due to ease of administration and patient compliance. Limitation of oral delivery is poor bioavailability and the drug candidates who show absorption window in the proximal gut and it is the major obstacle to the development of controlled release formulation. There are number of approaches that have been developed to increase the residence time of drug formulation.^{1, 2}

Dosage forms that can be retained in the stomach are called Gastro retentive drug delivery system (GRDDs). GRDDSs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site.³

A drug may be defined as a chemical substance, or a combination of substances, administered for the investigation, prevention or treatment of diseases or symptoms, real or imagined.

Advantages of GRDDS⁴⁻⁸

1. Reduced counter-activity of the body.
2. Minimization of fluctuations in drug concentration.
3. Sustained drug delivery/reduced frequency of dosing.
4. Enhanced bioavailability.
5. Targeted therapy for local ailments in the upper GIT.
6. Effective concentration extended time and then minimized the adverse activity in the colon.
7. Enhanced first-pass biotransformation.
8. There is a specific site in drug delivery and improvement in bioavailability and

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therapeutic efficacy of the drugs and possible reduction in dose e.g., Furosemide.

9. Reduced fluctuations of drug concentration.

10. Therapeutic levels are maintained over a prolonged period of time and therefore fluctuation of therapeutic levels get reduced which minimize the risk of resistance e.g., beta-lactam antibiotics (penicillin's and Cephalosporin's).

11. Gastro retentive drug delivery systems minimize the fluctuation of drug. These characteristic are very important for those drugs that are having narrow therapeutic index.

12. Provides sufficient local action and thus minimizes or eliminates the systemic exposure of drugs.

Disadvantages of GRDDS ⁹

1. The drugs which are present in the floating system cause irritation to gastric mucosa.

2. Unsuitable for drugs that is unstable in acidic environment. e.g., Erythromycin.

3. Drugs that absorb equally well through GIT. e.g., Isosorbide dinitrate, Nifedipine.

4. Floating delivery systems required high fluid level in stomach to float.

5. Drugs that absorb selectively in colon. e.g. Corticosteroid.

6. Unsuitable for drugs with limited acid solubility. e.g., Phenytoin.

7. Drugs that irritates or causes gastric lesions on slow release. e.g., Aspirin and NSAID's.

Microspheres constitute an important capacity and these are the carrier linked drug delivery system in which particle size is ranges from 1-1000 μm range in diameter having a core of drug and entirely outer layers of polymer as coating material.¹⁰

They are the spherical free flowing particles consisting of proteins or synthetic polymers which are biodegradable in nature. Microspheres are of two types: microcapsules and micro matrices, which are described as: Microcapsules are the substances which entrapped distinctly surrounded by distinct capsule wall and micro matrices are the substances which entrapped dispersed throughout the matrix. Microspheres are sometimes referred to as micro particles. These can be manufactured by various natural and synthetic materials.^{11,12}

Ideal characteristics of microspheres ^{13,14,15}

- Good control of active reagent release over a wide time scale.
- Susceptibility to chemical modification.
- Biocompatibility with a controllable biodegradability.
- The ability to incorporate reasonably high concentrations of the drug.
- After synthesis stability of preparation with a clinically acceptable shelf life.

Advantages of microspheres ^{16,17}

1. Biodegradable microspheres controlled drug release rates, decreased toxic side effects, and eliminated the repeated inconvenience of injections.
2. Convert liquid to solid form & to mask the bitter taste.
3. Decrease dose and toxicity.
4. Reduce the dosing frequency and thereby improve the patient compliance
5. The drug is protected from enzymatic and photolytic cleavage and therefore found to be wide for drug delivery of protein.
6. The advantage of biodegradable microspheres over large implants of polymer in that they don't required surgical procedures for implantation.

7. The drug utilization of bioavailability is improved and decreased the adverse effects of incidence or intensity.
8. Provide constant drug concentration in blood thereby increasing patent compliance.
9. Protects the GIT from irritant effects of the drug.
10. Microsphere morphology allows a controllable variability in degradation and drug release.
11. Particle size reduction for enhancing solubility of the poorly soluble drug.

Disadvantages of microspheres^{17,18}

1. Change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
2. Reproducibility is less.
3. The fate of polymer matrix and its effect on the environment.
4. The material cost and processing for the controlled release preparation are higher than that of standard formulations.
5. Impact of environment on the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents.
6. Polymer additives such as plasticizers, stabilizers, antioxidants and filler.

The benefits of microspheres are short gastric retention time (GRT) and the unpredictable rapid gastric rate may cause partial drug release in the absorption zone of the patient's body hence, hampering the efficiency of the dosage.^{19, 20}

Types of Microspheres

1. Magnetic microspheres^{21,22}

Magnetic microsphere is a delivery system which is used for localizing the drug to the disease site. In this small amount of magnetically targeted drug replaces large amount of freely circulating drug. Magnetic

carriers receive magnetic responses to a magnetic field from incorporated materials such as dextran, chitosan. The different types of magnetic microspheres are:

Therapeutic magnetic microspheres: deliver chemotherapeutic agent to liver tumour. Drugs that are targeted by this system are proteins and peptides.

Diagnostic microspheres: used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nanosize particles such as supramagnetic iron oxides.

2. Bio-adhesive microspheres^{23,24}

Adhesion can be defined as the sticking of drug to the membrane by using the sticking property of the water soluble polymers. Drug delivery of adhesion device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bio adhesion. Bio-adhesive microspheres shown in (Fig.1) exhibit a prolonged residence time at the site of application and cause intimate contact with the absorption site and produces better therapeutic action.

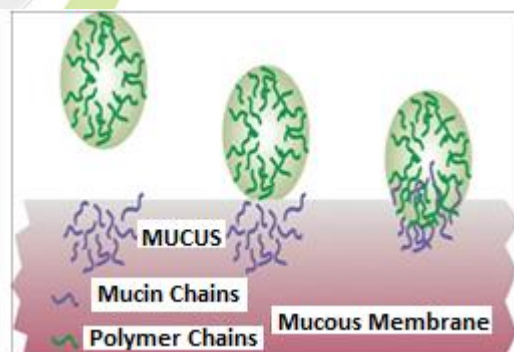


Fig. 1. Bio-adhesive Microspheres

3. Radioactive microspheres^{25,26}

Radioactive microspheres having size range of 10-30 nm are larger than blood capillaries and get trapped when they come across in the first capillary bed. Radioactive microspheres deliver high radiation dose to the targeted areas and do not show any harmful effect to the normal tissues. They are unique from other delivery system because radio activity is not released

from microsphere but acts from within a radioisotope typical distance. Different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

4. Floating microspheres^{27,28}

In floating microsphere (Fig.2) the gastric fluid is greater than the bulk density and remains buoyant in stomach without effecting gastric emptying rate. At desired rate the drug is released slowly, if the system is floating in gastric content it will increase gastric residence and further increases fluctuation in plasma concentration. It can also reduce chances of striking and dose dumping.

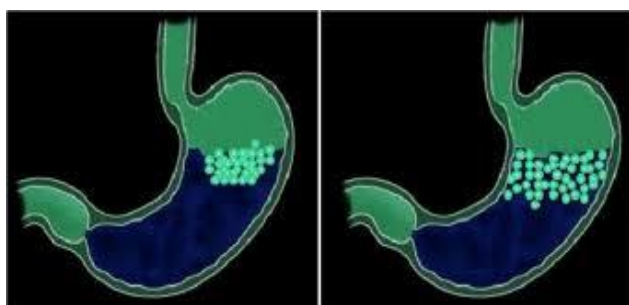


Fig. 2. Floating Microspheres

5. Polymeric microspheres²⁹

Polymeric microspheres are of two types, these are biodegradable polymeric microspheres and Synthetic polymeric microspheres (Fig.3.).



Fig.3. Polymeric Microspheres

6. Biodegradable polymeric microspheres²⁹

Biodegradable polymers increase the residence time when they come in contact with mucous membrane due to its high degree of swelling property with aqueous medium. Release of drug

is controlled by concentration of polymer and the release pattern is in sustained manner. The main disadvantage is that in clinical use the drug loading efficiency of biodegradable microspheres (Fig.4.) is complex and is difficult to control the drug release. They provide wide range of application in microsphere based treatment.

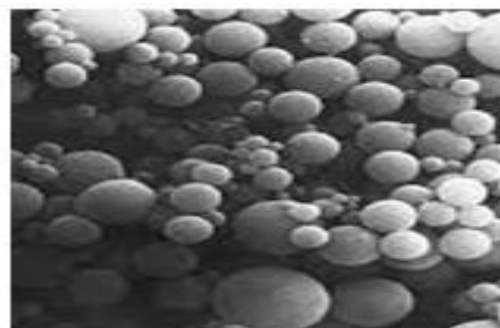


Fig. 4. Biodegradable polymeric microspheres

7. Synthetic polymeric microspheres³⁰

Apart from widely used in clinical application, they are also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. and proved to be safe and biocompatible. The main disadvantage of this types of microspheres is that they tend to migrate away from injection site which will lead to embolism and further organ damage.

METHODS OF MUCOADHESIVE MICROSPHERES

Preparation of microspheres depends on various methods such as particle size, route of administration, duration of drug release. The various methods of preparations are:-

Emulsion cross linking method³¹

In this method previously heated drug dissolved in aqueous gelatin solution for 1 hr. at 40 °C and then solution is added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 °C, results in w/o emulsion then further stirring is done for 10 min at 15 °C. Then the produced microspheres are washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde

saturated toluene solution at room temperature for 3 hr for cross linking and then treated with 100mL of 10mm glycine solution containing 0.1%w/v of tween 80 at 37 °C for 10 min to block unreacted glutaraldehyde.

Phase separation Coacervation technique³²

In this method the polymer solubility is decreased in organic phase to effect the formation of polymer rich phase called the coacervate. The drug particles are dispersed in the polymer solution and addition of incompatible polymer which makes the phase separate which leads to the encapsulation entrapment and the drug particles is engulfed. Polylactic acid (PLA) microspheres are prepared by using butadiene as incompatible polymer. The agglomeration of suspension is avoided by stirring the suspension using a suitable stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates.

Spray Drying³³

In Spray Drying method the dissolving of polymer in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug which is in solid form is dispersed in the polymer solution under high-speed of homogenization. This dispersion is then atomized in a stream of hot air. Formation of atomization of the small droplets or the fine mist from which the solvent evaporated and lead to the formation of the microspheres in a size range 1-100µm. Separation of micro particles from the hot air by the cyclone separator while removing of trace of solvent by vacuum drying. Major advantages of process are feasibility of operation under aseptic conditions. This process is very fast and leads to the formation of porous micro particles.

Ionic gelation³⁴

In aqueous solution of sodium alginate the drug is added to get the complete solution, stirring is continued and the solution is added dropwise containing Ca^{2+} / Al^{3+} . Microspheres that are formed were kept in original solution for 24 hr.

for internal gellification followed by filtration for separation. The complete release of drug is obtained at pH 6.4-7.2 but the drug will not release in acidic PH.

Solvent Evaporation³⁵

This method utilizes liquid manufacture vehicle. The encapsulated coating is dispersed in a volatile liquid which is generally immiscible with liquid manufacturing vehicle. Core material of encapsulation is dispersed in coating polymer solution. The core material is mix vigorously and dispersed in the liquid manufacturing vehicle to obtain microcapsule of desired size. Evaporation of solvent from the core material occurs when the mixture is heated which leads to shrinkage of polymer around the core material.

If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous. The comparison of mucoadhesive microspheres of hyaluronic acid, Chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelatin prepared by complex Coacervation were made.

Multiple emulsion polymerization technique³⁵

In this method formation of (o/w) Primary emulsion (non aqueous drug solution in polymer solution) and then addition of primary emulsion to external oily phase to form o/w/o emulsion followed by either addition of cross linking agent (glutaraldehyde) and evaporation of organic solvent. Poorly aqueous soluble drug is prepared by enhancing its bioavailability. The microspheres were prepared by multiple emulsion technique by making the poorly aqueous soluble drug such as ketorolac.

EVALUATION OF MUCOADHESIVE MICROSPHERES³⁶

Particle size analysis

The Mucoadhesive microspheres are examined by optical microscope. The freshly prepared suspension of microspheres was examined on an optical microscope and size of the microspheres was measured by using a pre-calibrated ocular micrometer and stage micrometer.

Drug entrapment efficiency

The encapsulation efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation:-

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

Theoretical content

Surface topography by Scanning Electron

The shape and surface morphology of the microspheres was studied by using scanning electron microscopy.

Percentage yield

The percentage yield of each batch was calculated on weight basis with respect to the weight of starting material. All experiments were carried out in triplicate. The percent yield of prepared microsphere will be calculated by following formula;

$$\text{Percentage Yield} = \frac{\text{Weight of Microspheres} \times 100}{\text{Weight of Drug} + \text{Weight of Polymer}}$$

Stability studies

By placing the microspheres in screw capped glass container and stored them at following conditions:-

- Ambient humid condition
- Room temperature ($27 \pm 2^\circ\text{C}$)
- Oven temperature ($40 \pm 2^\circ\text{C}$)

- Refrigerator ($5^\circ\text{C} - 80^\circ\text{C}$).

It is carried out for 60 days and the drug content of the microsphere is analyzed.

Drug content estimation

The drug content of prepared microsphere will be calculated by following formula;

$$\text{Drug Content} = \frac{\text{Calculated Drug Content} \times 100}{\text{Total amount of Microspheres}}$$

In vitro drug release kinetics^{37,38}

Analysis of drug release from microspheres was performed with a flexible model that can identify the contribution to overall kinetics, mechanism of drug release and the dissolution data obtained for optimized formulation was treated with the different release kinetic equation. In order to study the exact mechanism of the drug release from microspheres, drug release data was analyzed according to Zero Order, First Order, Higuchi square root, Hixon Crowell, Korsmeyer model. The criteria for selecting the most appropriate model will be chosen on the basis of goodness of fit test.

In-Vitro Mucoadhesion study^{33,40}

A piece of intestinal mucosa (2x2 cm) mounted on to glass slide of (3x1 inch) using elastic bands. Weighed microspheres were spread onto wet rinsed tissue specimen and immediately thereafter the slide was hung onto the arm of a USP tablet disintegrating test apparatus. The disintegration machine containing tissue specimen was adjusted for up and down movement in 6.8 pH Phosphate buffer at 37°C in a beaker. Numbers of microspheres still adhering on to the tissue were weighed at hourly intervals upto 8-10 hr. The weight of microspheres leached out at different intervals is measured. The % mucoadhesion is calculated by the following equation

$$\% \text{ Mucoadhesion} = \frac{\text{Wa} - \text{W1}}{\text{Wa}} \times 100$$

Where, Wa is the weight of microspheres applied W1 is the weight of microspheres leached out.

RECENT ADVANCES ON MUCOADHESIVE MICROSPHERE

S.No.	Author	FORMULATION TYPE	Outcome
1	Badoni. A et al	GASTRO RETENTIVE DRUG DELIVERY SYSTEM	GRDDs offer various potential advantages for drugs with poor bioavailability. ¹⁰
2	Suvarna V et al	MICROSPHERES	The review highlights various types of microspheres, different methods of preparation, its applications and also various parameters to evaluate their efficiency. ¹⁷
3	Sharma and Khan et al	GASTRORETENTIVE DRUG DELIVERY SYSTEM	Gastro retentive drug delivery system have emerged as an efficient means of prolonged retaining ability in the stomach and thereby increase gastric residence time of drugs and also improves bioavailability of drugs. ²⁰
4	Kaurav Hemlata et al	MUCOADHESIVE MICROSPHERES AS CARRIERS	Mucoadhesive microspheres will ensure the maintenance of effective plasma concentration over prolonged period of time by extending the release of drug. ³¹
5	Khobragade Sonali M. et al	MUCOADHESIVE MICROSPHERE OF LOSARTAN POTASSIUM	Katira Gum possesses all requisite qualities required for sustained drug delivery system in the form of mucoadhesive microspheres. ⁴¹
6	Kumar Atul et al	MUCOADHESIVE MICROSPHERES	Derive maximum therapeutic benefits from certain drug substances by prolonging their residence time. ⁴²
7	Sadhana R Shahi et al	MUCOADHESIVE MICROSPHERES OF CAPTOPRIL	Formulation prepared within design space can produce formulation with acceptable in vitro drug release, mucoadhesive strength and size. ⁴³

8	Senthil Adimoolam et al	MUCOADHESIVE MICROSPHERES OF VENLAFAXINE HCL	Increasing the concentration of glutaraldehyde, the mucoadhesiveness decreases and there is no significant effect on time. ⁴⁴
9	Kumari Navita et al	MUCOADHESIVE MICROSPHERES	Reduce drug concentration at the site other than target organ or tissue, delivery of small quantities of potent drugs and protection of labile compounds before and after administration. Microspheres are ideal targeting drug delivery system with high safety profile. ⁴⁵
10	Dhaliwal Sumeet et al	MUCOADHESIVE MICROSPHERES OF ACYCLOVIR	Study revealed that the retention time of acyclovir at its absorption site, i.e. the upper GIT, could be increased by formulating it into microspheres using chitosan, thiolated chitosan, Carbopol 71G or Methocel K15M. ⁴⁶
11	Patel Jayvadan K. et al	MUCOADHESIVE MICROSPHERES OF GLIPIZIDE	The prepared glipizide mucoadhesive microspheres shows sustained action as well as significant hypoglycemic effect ⁴⁷
12	Phanindra B et al	MUCOADHESIVE/ BIOADHESIVE DRUG DELIVERY SYSTEM	The phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for a number of drug candidates ⁴⁸
13	Meneshwari Mohan et al	MUCOADHESIVE MICROSPHERES	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 ⁴⁹

14	Shanthi Priya CH et al	MUCOADHESIVE MICROSPHERES FOR GASTRO-RETENTIVE DELIVERY OF FAMOTIDINE HCL.	Effect of release of famotidine from eight different batches of microspheres was prepared. The drug release prolonged to 17 hr. in optimized formulation. ⁵⁰
15	Sharma Nisha et al	MICROSPHERES AS DRUG CARRIERS FOR CONTROLLED DRUG DELIVERY	Microspheres plays significant role in novel drug delivery particularly in diseased cell sorting, genetic materials, safe, targeting and effective drug delivery. ⁵¹
16	Meng Fan-Yun et al	MUCOADHESIVE MICROPARTICLES FOR GASTRO RETENTIVE DELIVERY	The encapsulation efficiency of the optimized microparticles containing puerarin was increased compared with other agents. ⁵²
17	Sharma Mohit et al	FLOATING MICROSPHERES OF GLIMEPIRIDE	The floating microsphere tablet formulations are needed for glimepiride to prolong its duration of action and to increase its oral bioavailability and to improve patient compliance ⁵³
18	Khan Bashir Arshad et al	MUCOADHESIVE DRUG DELIVERY SYSTEM: NOVEL APPROACHES	The mucoadhesive drug delivery system is a very promising approach for delivering the drugs which have narrow absorption window at the target site to maximize their usefulness. ⁵⁴
19	Kshirsagar R.V. et al	GASTRORETENTIVE MUCOADHESIVE MICROSPHERE	The Mucoadhesive Microsphere should be primarily aimed to achieving more predictable and increased bioavailability of drugs. ⁵⁵
20	Harikarnpakdee S et al	SPRAY DRIED MUCOADHESIVE MICROSPHERES	Spray-dried microspheres of Hydroxy Propyl Methyl Cellulose (H), Chitosan (CS), Carbopol 934 (CP), and CP:H could be prepared to deliver drug through

21	Amin ML et al	FLOATING MUCOADHESIVE MICROSPHERE OF METRONIDAZOLE	Metronidazole mucoadhesive- floating microspheres can be effectively used for sustained drug release to the gastric mucosa in treatment of upper GIT infection. ⁵⁷
22	Naoki Nagahara et al	MUCOADHESIVE MICROSPHERES OF AMOXICILLIN FOR CLEARANCE OF H. PYLORI	A dosage form consisting of mucoadhesive microspheres containing an appropriate antimicrobial agent should be useful for the eradication of H. pylori. ⁵⁸
23	Sockan Ganesh N. et al	MUCOADHESIVE MICROSPHERES OF FLURBIPROFEN AS A MODEL DRUG	Mucoadhesive microspheres loaded with macromolecular bio adhesive polymers can be successfully formulated by emulsification solvent evaporation method shows high entrapment and loading capacity as well as optimum release when prepared with sodium CMC. ⁵⁹

CONCLUSION

Mucoadhesive microspheres will help in maintaining effective plasma concentration over prolonged period of time by extending the release of drug with enhanced bioavailability over longer periods of time and for drug targeting to various sites in the body.

Mucoadhesive drug delivery has a great potential for systemic delivery of orally inefficient drugs as well as striking alternative for noninvasive delivery of numerous drugs molecules in controlled or sustained manner.

Furthermore by combining various other strategies, mucoadhesive microspheres will find the significant place in novel drug delivery.

REFERENCES

1. Hardenia, S. S., Jain, A., Patel, R., & Kaushal, A. (2011). Formulation and evaluation of mucoadhesive microspheres of ciprofloxacin. *Journal of Advanced Pharmacy Education & Research*, 1(4), 214-224.
2. Kumar, A., Jha, S., Rawal, R., Chauhan, P. S., Sheo, D. M. (2013). Mucoadhesive Microspheres for Novel Drug Delivery System: A Review. *Am. J. PharmTech Res.*, 3(4), 195-213.
3. Singh, B. N., & Kim, K. H. (2000). Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *Journal of Controlled release*, 63(3), 235-259.
4. Klausner, E. A., Lavy, E., Friedman, M., & Hoffman, A. (2003). Expandable

- gastroretentive dosage forms. *Journal of controlled release*, 90(2), 143-162.
5. Garg, R., & Gupta, G. D. (2008). Progress in controlled gastroretentive delivery systems. *Tropical Journal of Pharmaceutical Research*, 7(3), 1055-1066.
 6. Hoffman, A., & Stepensky, D. (1999). Pharmacodynamic aspects of modes of drug administration for optimization of drug therapy. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, 16(6).
 7. Hwang, S. J., Park, H., & Park, K. (1998). Gastric retentive drug-delivery systems. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, 15(3).
 8. Guyton, A. C. (1982). Movement of food through the alimentary tract. *human physiology and mechanisms of disease*, London: WB Saunders Co.
 9. Helliwell, M. (1993). The use of bioadhesives in targeted delivery within the gastrointestinal tract. *Advanced drug delivery reviews*, 11(3), 221-251.
 10. Badoni, A. (2012). Review on gastro retentive drug delivery system. *The Pharma Innovation*, 1(8).
 11. Jamini, M., & Rawat, S. (2013). A review on microsphere. *Res. j. pharm. boil. chem. sci*, 4(1), 1223-33.
 12. Patel, N. R., Patel, D. A., Bharadia, P. D., Pandya, V., Modi, D. (2011). Microsphere as a Novel Drug Delivery. *Int. J. Pharm. Life Sci.* 2(8), 992-7.
 13. Singh, C., Purohit, S., Singh, M., Pandey, B. L. (2013). Design and evaluation of Microspheres: A Review. *JDDR*. 2(2), 18-27.
 14. Prasanth, V.V., Moy, A.C., Mathew S. T., Mathapan, R. (2011). Microspheres an Overview, *Int. J. Res. Pharm. Biomed. Sci.*, 2, 3328-3337.
 15. Prasad, B. S. G., Gupta, V. R. M., Devanna, N., & Jayasurya, K. (2014). Microspheres as Drug Delivery System—A Review. *Journal of Global Trends in Pharmaceutical Science*, 5(3), 1961-1972.
 16. Parmar, H., Bakliwal, S., Gujarathi, N., Rane, B., & Pawar, S. (2010). Different methods of formulation and evaluation of mucoadhesive microsphere.
 17. Suvarna, V., & Kadam, N. R. (2015). Microsphere: A Brief Review. *Asian Journal of Biomedical and Pharmaceutical Sciences*, 5(47), 13-19.
 18. Prasad, B. S. G., Gupta, V. R. M., Devanna, N., & Jayasurya, K. (2014). Microspheres as Drug Delivery System—A Review. *Journal of Global Trends in Pharmaceutical Science*, 5(3), 1961-1972.
 19. Kadam, N. R., & Suvarna, V. (2015). Microsphere: A Brief Review. *Asian Journal of Biomedical and Pharmaceutical Sciences*, 5(47), 13.
 20. Sharma, A. R., & Khan, A. (2014). Gastroretentive drug delivery system: an approach to enhance gastric retention for prolonged drug release. *International journal of pharmaceutical sciences and research*, 5(4), 1095.
 21. Thummar, A. V., Kyada, C. R., Kalyanvat, R., & Shreevastva, B. (2013). A review on mucoadhesive microspheres as a novel drug delivery system. *International Journal for Pharmaceutical Research Scholars*, 2(2), 188-200.
 22. Mukherjee, S., & Bandyopadhyay, P. (2012). Magnetic microspheres: a latest approach in novel drug delivery system. *JPSI*, 1(5), 21-25.
 23. FODA, N. GASTRORETENTIVE DRUG DELIVERY SYSTEMS AS A POTENTIAL TOOL FOR ENHANCING THE EFFICACY OF

ANTIBIOTICS: A REVIEW NH FODA AND SM ALI1.

24. Kadam, N. R., & Suvarna, V. (2015). Microsphere: A Brief Review. *Asian Journal of Biomedical and Pharmaceutical Sciences*, 5(47), 13.
25. Kawatra, M., Jain, U., & Ramana, J. (2012). Recent advances in floating microspheres as gastro-retentive drug delivery system: A review. *Int J Recent Adv Pharm Res*, 2(3), 5-23.
26. Batra, D., Kakar, S., Singh, R., Nautiyal, U. (2012). Magnetic Microspheres as a Targeted Drug Delivery System: An Overview. *JDDR*.1(3), 1-17.
27. Dutta, P., Sruti, J., Patra, C. N., & Rao, M. B. (2011). Floating microspheres: recent trends in the development of gastroretentive floating drug delivery system. *International Journal of Pharmaceutical Sciences and Nanotechnology*, 4(1), 1296-1306.
28. Mukund, J. Y., Kantilal, B. R., & Sudhakar, R. N. (2012). Floating microspheres: a review. *Brazilian Journal of Pharmaceutical Sciences*, 48(1), 17-30.
29. Ramteke, K. H., Jadhav, V. B., & Dhole, S. N. (2012). Microspheres: As carriers used for novel drug delivery system. *IOSRPHR*, 2(4), 44-48.
30. Kadam, N. R., & Suvarna, V. (2015). Microsphere: A Brief Review. *Asian Journal of Biomedical and Pharmaceutical Sciences*, 5(47), 13.
31. Kaurav, H., HariKumar, S. L., & Kaur, A. (2012). Mucoadhesive microspheres as carriers in drug delivery: A review. *International Journal of Drug Development and Research*.
32. Saralidze, K., Koole, L.H., Knetsch, M.L. W. (2010). Polymeric Microspheres for Medical Applications. *Materials*. 3, 3537-64.
33. Bansal, H., Kaur, S. P., & Gupta, A. K. (2011). Microspheres: methods of preparation and applications: A comparative study. *Int J Pharm Sci Rev Res*, 10, 69-78.
34. Omkar, T., Alagusundaram, M., Madhu, S. C., Umashankari, K., Attuluri, V., Lavanya, C., & Ramkanth, B. (2009). Microspheres as a novel drug delivery system. *Int J Of Chem Tech and Res*, 3 (1), 526-534.
35. Moy, A. C., Mathew, S. T., Mathapan, R., & Prasanth, V. V. (2011). Microsphere-An Overview. *International Journal of Pharmaceutical and Biomedical Sciences*, 2(2), 332-338.
36. Meena, K. P., Dangi, J. S., Samal, P. K., & Namedo, K. P. (2011). Recent advances in microsphere manufacturing technology. *International journal of pharmacy and technology*, 3(1), 854-855.
37. Rout, P. K., & Nayak, B. S. (2009). Statistical evaluation of losartan microspheres prepared by w/o emulsion method using factorial design and response surface methodology. *Asian Journal of Pharmaceutical and Clinical Research*, 2(4), 1-9.
38. Dash, S., Murthy, P. N., Nath, L., & Chowdhury, P. (2010). Kinetic modeling on drug release from controlled drug delivery systems. *Acta Pol Pharm*, 67(3), 217-23.
39. Garg, A., & Upadhyay, P. (2012). Mucoadhesive microspheres: A short review. *Asian journal of pharmaceutical and clinical research*, 5(3), 24-27.
40. Hardenia, S. S., Jain, A., Patel, R., & Kaushal, A. (2011). Formulation and evaluation of mucoadhesive microspheres of ciprofloxacin. *Journal of Advanced Pharmacy Education & Research*, 1(4), 214-224.
41. Khobragade, S. M., Upadhye, K. P. (2013). Formulation Development and Evaluation of Mucoadhesive Microsphere of Losartan Potassium By Using Natural Polymer. *IJPSR*, 4(11), 4290-4302.

42. Kumar, A., Jha, S., Rawal, R., Chauhan, P.S., Mauryam, S.D. (2013). Mucoadhesive Microspheres for Novel Drug Delivery System: A Review, *Am. J. PharmTech. Res*, 3(4), 2249-3387.
43. Shahi, S. R., Magar, D. R., Ingale, T. B., Mene, H. R. (2015). Formulation and Evaluation of Mucoadhesive Microspheres of Captopril: QbD Approach. *Literati Journal of Pharmaceutical Drug Delivery Technologies*, 1(1), 19-28.
44. SENTHIL, A., BHAI, V., BHAI, T.H.K.R., MEHULKUMAR, D., BHAI, L.T.B., BATTU, B.L. (2011). FORMULATION AND EVALUATION OF MUCOADHESIVE MICROSPHERES OF VENLAFAXINE HCL. *IRJP*, 2(4), 194-199.
45. Kumari, N., Aggarwal, G., & Harikumar, S. L. (2014). MUCOADHESIVE MICROSPHERES: A REVIEW. *Journal of Drug Delivery and Therapeutics*, 4(5), 48-54.
46. Dhaliwal, S., Jain, S., Singh, H. P., Tiwary, A. K. (2008). Mucoadhesive Microspheres for Gastroretentive Delivery of Acyclovir: In Vitro and In Vivo Evaluation. *AAPS Journal*, 10(2), 322-330.
47. Patel, J. K., Patel, R. P., Amin, A. F., & Patel, M. M. (2005). Formulation and evaluation of mucoadhesive glipizide microspheres. *AAPS PharmSciTech*, 6(1), E49-E55.
48. Phanindra, B., Moorthy, B. K., & Muthukumaran, M. (2013). Recent advances in mucoadhesive/bioadhesive drug delivery system: A review.
49. MOHAN, M., & SUJITHA, H. (2014). A Brief Review on Mucoadhesive Microspheres. *IJRRPAS*, 4(1), 975-86.
50. Shanthi, P. CH. (2015). Design and Characterization of Mucoadhesive Microspheres for Gastro-Retentive Delivery of Famotidine Hydrochloride. *J Bioengineer & Biomedical Sci*, 153-155.
51. Patel, U. A., & Shah, H. A. (2016). A REVIEW ON MICROSPHERES AS CONTROLLED DRUG DELIVERY CARRIER. *Pharma Science Monitor*, 7(4).
52. Hou, J. Y., Gao, L. N., Meng, F. Y., & Cui, Y. L. (2014). Mucoadhesive microparticles for gastroretentive delivery: preparation, biodistribution and targeting evaluation. *Marine drugs*, 12(12), 5764-5787.
53. Sharma, M., Bilandi, A., Kataria, M. K. (2015). A Review On Techniques Implemented in Formulation of Floating Microspheres Tablets of Glimepiride. *International Journal of Institutional Pharmacy and Life Sciences*. 5(1), 2249-6807.
54. Khan, A. B., Mahamana, R., & Pal, E. (2014). Review on Mucoadhesive drug delivery system: novel approaches in modern era. *Journal of pharmaceutical science*, 4(4), 128-140.
55. Mule, M. S., & RV, M. K. (2011). Gastroretentive Mucoadhesive Microsphere: A Review. *Indo American Journal of Pharmaceutical Research*, 1(6), 483-505.
56. Harikarnpakdee, S., Lipipun, V., Sutanthavibul, N., & Ritthidej, G. C. (2006). Spray-dried mucoadhesive microspheres: preparation and transport through nasal cell monolayer. *Aaps Pharmscitech*, 7(1), E79-E88.
57. Amin, M. L., Ahmed, T., & Mannan, M. A. (2016). Development of Floating-Mucoadhesive Microsphere for Site Specific Release of Metronidazole. *Advanced Pharmaceutical Bulletin*, 6(2), 195.
58. Nagahara, N., Akiyama, Y., Nakao, M., Tada, M., Kitano, M., & Ogawa, Y. (1998). Mucoadhesive microspheres containing amoxicillin for clearance of Helicobacter pylori. *Antimicrobial agents and chemotherapy*, 42(10), 2492-2494.
59. Laith, A., AL HAMMID, S. N. A., & ALRASOOL, A. A. A. (2014). Formulation and

Evaluation of Flurbiprofen Solid Dispersion. *Int J Pharm Pharm Sci*, 6(Suppl 2), 375-384p.



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