WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 9, 273-287. Review Article ISSN 2277– 7105

ORAL MUCOADHESIVE MULTIPARTICULATE DRUG DELIVERY SYSTEM: A OVERVIEW

Navya N.* and Dr. V. Chandrakala

Department of Pharmaceutics, East Point College of Pharmacy, Bidarahalli, Bengaluru 49, Karnataka, India.

Article Received on
04 May 2022,

Revised on 24 May 2022,
Accepted on 14 June 2022,

DOI: 10.20959/wjpr20229-24618

***Corresponding Author**
Navya N.
Department of Pharmaceutics, East Point College of Pharmacy, Bidarahalli, Bengaluru 49, Karnataka, India.

ABSTRACT

Revolutions in pharmaceutical s are undertaking for designing more modern drug remedies to remove lethal diseases. Master plan for such improvements usually swing with keys and goals of minimal detrimental outcomes and powerful treatement. Latest go with the flow in pharmaceutical era specify that mucoadhesive drug transporting device is specially relevent than oral manipulate launch to gather nearby systemic transfer of medicine in GIT for prolonged programming language time of a predetermined rate. the drug launch from mucoadhesive multiparticulates is contingent on few sorts of elements made from provider want to provide the multiparticles and amount of medicine drug comprise in them. Mucoadhersive drug delivery systems interacts with the mucus layer covering the mucosal epithelial surface and mucin molecules thereby increasing the residence time of the dosage form at the time of absorption. The process of mucoadhesion includes a polymeric drug delivery system is a complex one that involves processes such as wetting, adsorption and interpretation of polymer chains.

KEYWORDS: Multiparticulate, Oral, Mucoadhesion.

INTRODUCTION

Multi-particulate drug shipping structures are particularly oral dosage bureaucracy along with a multiplicity of small discrete devices, every showing a few favoured characteristics. In those structures, the dosage of the drug materials is split on a plurality of subunit, generally along with heaps of round debris. To supply the encouraged overall dose, those subunits are stuffed right into a sachet and encapsulated or compressed right into a pill. Multiparticulates

are discrete debris that make up a multiple-unit device. They offer many benefits over unmarried-unit structures due to their small length. Multiparticulates are much less depending on gastric empty ting, ensuing in much less inter and intra-problem variability in gastrointestinal transit time. There are many motives for formulating a drug as a multiparticulate device for example, to facilitate disintegration withinside the stomach, or to offer a convenient, speedy disintegrating pill that dissolves in water earlier than swallowing which could useful resource compliance in older sufferers and children.[1]

Advantages of Multiparticulate Mucoadhesive Oral Drug Delivery

- Prolonged and sustained launch of drug.
- Conservation of healing plasma drug concentration.
- Lower management frequency with multiplied house time with managed API launch.
- Good affected person compliance because of much less common drug management.
- Improving solubility, dispersibility and flowability.

Overview of the oral Mucosa

Structure: The oral mucosa is constructed from squamous stratified (layered) epithelium, basement membrane, the lamina propria and submucosa. It additionally includes many sensory receptors which include the flavor receptors of the tongue. The epithelium of the buccal mucosa is set 40-50 mobileular layers thick, even as that of the sublingual epithelium includes relatively fewer.[5]

Permeability: The oral mucosa in widespread is relatively leaky epithelia intermediate among that of the dermis and intestinal mucosa. It is predicted that the permeability of the buccal mucosa is 4-4000 instances more than that of the skin. In widespread, the permeabilities of the oral mucosae lower withinside the order of sublingual more than buccal and buccal more than palatal. This rank order is primarily based totally at the relative thickness and diploma of keratinization of those tissues, with the sublingual mucosa being notably skinny and non-keratinized, the buccal thicker and palatal intermediate in thickness however keratinized.[5]

Environment: The cells of the oral epithelia are surrounded through an intercellular floor substance, mucus, the precept additives of that are complexes made from proteins and carbohydrates. These complexes can be freed from affiliation or a few perhaps connected to sure areas at the mobileular surfaces. This matrix can also additionally truely play a function

in mobileular-mobilCular adhesion, in addition to appearing as a lubricant, permitting cells to transport relative to at least one another.[5]

Composition of Mucus Layer: Mucus is a translucent and viscid secretion which bureaucracy a skinny, contentious gel, imply thickness of this deposit varies from approximately 50-450 Î¼m in human beings secreted through the globed cells lining the epithelia. It has the subsequent widespread composition.[5]

Functions of Mucus Layer

1. **Protective:** ensuing mainly from its hydrophobicity.[6]
2. **Barrier:** The function of the mucus layer as a barrier in tissue absorption of the medicine and have an impact on the bioavailability.[6]
3. **Adhesion:** Mucus has robust adhesion properties.[6]
4. **Lubrication:** It is to hold the mucus from the goblet molecular is essential to catch up on the elimination of the mucus layer because of digestion, bacterial degradation and solubilisation of mucin molecules.[6]

Role of Saliva

Saliva consists of 99% water and is complicated fluid containing natural and inorganic material. Secretion of saliva is maximum in the course of running hours.

1. Defencing liquid for all substances of the oral cavity.
2. Continuous mineralization/demineralization of the enamel.
3. Moisten the oral cavity.[1]

Mechanism of drug release from multi-particulates

The mechanism of drug launch from multiparticulates may be arise withinside the following ways:

Diffusion: On touch with aqueous fluids withinside the gastrointestinal tract (GIT), water diffuses into the indoors of the particle. Drug dissolution takes place and the drug answers diffuse throughout the discharge coat to the outdoors.

Erosion: Some coatings may be designed to erode regularly with time, thereby liberating the drug contained withinside the particle.

Osmosis: In permitting water to go into below the proper circumstances, an osmotic strain may be constructed up withinside the indoors of the particle. The drug is pressured out of the particle into the outdoors thru the coating.[6]

Designs of Various Multiparticulate Structures

Integration of a triumphing drug into a singular drug shipping device can substantially development its implementation in phrases of effectiveness, safety and superior compliance of affected person. Upon the define of a singular drug shipping device, normally an present drug molecule is capable of get a singular lifestyles, because of that it complements its marketplace really well worth in addition to competitiveness. Consequently, it additionally expands the patent lifestyles of the ensuing molecule.

Diffucaps: In this type of class of multiparticulate device the profiles of drugs are finally superior through casing a energetic drug upon a impartial middle as an example spheres of sugar, crystals, or granules which in route being accompanied through the implementation of a fee scheming, capable membrane that is powerful. The substances wished for coating both can be water-soluble or insoluble, touchy to pH, which in flip problem to the desires of individual. Generally, diffucaps beads having a minute in length, very almost round diameter length of one mm, that are packed right into a tablet so that you can generate the closing dosage form. Beads of contradictory launch profiles of drugs also can be eagerly united in a solitary or unmarried tablet giving expanded ranges of manipulate over launch profiles. Diffucaps beads of various remedy are united to make appropriate solitary dosage devices for remedies of combination or mixture remedies.[4]

Minitabs: The Eurand minitabs era is specific in that it gives the benefits of a pill blended with the ones of a multiparticulate drug form. Eurand MINITABS are tiny (2mm x 2mm) pills containing gel- forming excipients that manipulate drug launch fee. Additional membranes can be introduced to similarly manipulate launch fee. The small length of Eurand minitabs method that they may be stuffed into drugs as a very last dosage form . mixture merchandise may be advanced to permit for 2 or greater launch profiles inside a unmarried tablet. Eurand minitabs provide excessive drug loading, the cappotential to pleasant music launch fees for focused shipping and content material uniformity for greater correct dosing. Eurand Minitabs provide excessive drug loading, a extensive variety of launch fee designs, and pleasant tuning of those launch fees. The drugs may be opened and the contents used as a "sprinkle" system.[4]

Pelletised pill: Pelletised pill (Peltab) device makes use of polymer-lined drug pellets or drug crystals, that are compressed into pills. In order to offer a managed launch, a water insoluble polymer is used to coat discrete drug pellets or crystals, which then can face up to the motion of fluids withinside the GIT. This era carries a robust polymer coating allowing the lined pellets to be compressed into pills without vast breakage.[4]

Flashtab: Flashtab era is a quick dissolving/disintegrating oral pill system. It is a mixture of flavor masked multiparticulate energetic drug materials with particular excipients compressed into pills. A disintegrating agent and a swelling agent are utilized in mixture with lined drug debris on this system to provide a pill that disintegrates withinside the mouth in much less than one minute. These oro-dispersible pills disperse unexpectedly earlier than the affected person swallow them.[4]

InnoHerb: This era is used coating the pellets internal of the tablet, InnoHerb Phytogranules. The multiparticulate is made of many micropellets or small beads containing energetic natural compounds. The unique coating for every plant extract incorporates pinnacle pleasant standardised dried extracts which assures efficacy and protection of the semi- permeable membrane, improves stability, masks taste/odor and offers gastro-safety in addition to sell managed launch of actives, most useful availability and higher absorption.[4]

Macrocap: Macrocap composed of on the spot launch beads organized with the aid of using numerous strategies consisting of spheronization, pelletization, extrusion etc, or by way of answers layering or overspreading powders upon seeds of nonpareil. Specifically, the polymers of launch modulating be sprayed at the beads by way of numerous coating strategies. The beads that are gone through coating are completed to tablet cells of difficult gelatin. Due to right diffusion associated with both osmosis or bioerosion thru the membrane of floor that effects into the powerful launch of drugs. The launch phenomenon may be both relies upon pH or its activation.[4]

Orbexa: Orbexa era is a particular form of multiparticulate machine that helps loading of big medicament which is only suitable for merchandise which want granulation. This tool brings out beads which are on top of things of length in addition to density by way of miscellaneous strategies consisting of granulation, extrusion and spheronization etc. This method is best one in every of its kind, that precise and consists of superior drug loading than others. Some of the high deserves encompass enzyme sensitivity and flexibility.[4]

Clinical fame of mucoadhesive multiparticulate machine

The predefined goal approximately bioadhesion and small particulates performs a difficult and sizable venture for the medical assessment factor of view. A bioadhesive polymer, consisting of chitosan having houses related to as an adjuvant, has tested correctly. Its assessment become finished in pretty a number of medical researches, and additionally withinside the case of starch microparticles. Only a few research consisting of chitosan structures were tested in human volunteers. In spite of recurrent research related to chitosan primarily based totally vaccination withinside the mucous layer in animal designs. For immunization functions of intranasal therapy, chitosan become correctly applied to attain higher comments of antibodies adjoining to some of proteins, influenza, antigens associated with diphtheria, in addition to meningococcal conjugates (group-C type) withinside the case of medical trials studies. Presently, for the protection, efficacy and safety of novo virus Ligocyte Pharmaceuticals Inc. used the ChiSys meant for vaccine containing intranasal powder. In- intensity medical trial studies discovered approximately the vaccines that elicit an immunological reaction and commonly capable of be tolerated in human volunteers. It has been discovered out that, whilst medical research associated with any diphtheria toxin, for exampleCRM197 that's a non-poisonous mutant, can show off the responses of serum antibody with the aid of using mutual mixture with chitosan. This method has happened after a hit immunization of intranasal therapy. This idea is genuinely equal to the topic of proactive immunity. In the prevailing scenario, rather than infants, about all of the medical studies of intra nasal course is efficaciously achieved with the aid of using the usage of healthful person volunteers. By blending the protocols of immunization thru numerous routes, systematic immunological impact may be generated primarily based totally on a preclinical factor of view.[4]

Factors Affecting Mucoadhesion

Mucoadhesion can be stricken by some of factors, consisting of hydrophilicity, molecular weight, move linking, swelling, pH and the awareness of the energetic polymer.

Hydrophillicity: Bioadhesive polymer operated infinite hydrophilic useful organizations, particularly hydroxyl and carboxyl. These organizations permit hydrogen bonding with the substrate, swelling in aqueous media thereby permitting maximal publicity of ability anchor sites. In addition, swollen polymers have the most distance among their chains main to extended chain flexibility and green penetration of the substrate.[13]

Molecular Weight: The interpenetration of polymer molecules is favoured with the aid of using low molecular weight polymers, while entanglements are favoured at excessive molecular weights. The most useful molecular weight for the most mucoadhesion relies upon at the form of polymer, with bio adhesive forces growing with a molecular weight of the polymer.[13]

Cross Linking and Swelling: The decrease the move hyperlink density, the better the power and hydration rate, the bigger the floor place of the polymer, the higher the mucoadhesion. Cross hyperlink density is inversely proportional to the diploma of swelling.[13]

Spatial Conformation: Apart from molecular weight or chain length, spatial conformation of polymer is likewise important. Despite a excessive molecular weight of 19,500,000 for dextrans, they've adhesive electricity much like that of polyethylene glycol (PEG), with a molecular weight of 200,000. The helical conformation of dextran can also additionally defend many adhesively energetic organizations, basically answerable for adhesion, not like PEG polymers, that have a linear conformation.[13]

PH: The pH on the bio adhesive to the substrate interface can have an effect on the adhesion of bio adhesives utilized in drug transport are polyanions owning ionizable organizations. Many bio adhesives utilized in drug transport are polyanions owning carboxylic acid functionalities. If the neighbourhood pH is above the pK of the polymer, it will likely be in large part ionized; if the pH is underneath the pK of the polymer it will likely be in large part unionized.[13]

Concentration Of Active Polymer: There is the perfect awareness of polymer similar to the great mucoadhesion. In surprisingly focused structures, past the most useful awareness the adhesive electricity drops significantly. In focused answers, the coiled molecules come to be solvent terrible and the chains to be had for interpenetration aren't numerous. this end result appears to be of hobby best for greater or much less liquid mucoadhesive formulations.[13]

Drug/Excipient Concentration: Blanco Fuente et al studied and discovered out adhesion extended whilst water restricted withinside the machine because of an growth withinside the elasticity, because of the complicated formation among drug and polymer. While the presence of big portions of water, the complicated brought on out, main to a mild lower withinside the adhesive character.[13]

Polymers Used In Formulating Mucoadhesive Drug Delivery System

Mucoadhesive polymers are water-soluble and water insoluble polymers, that are swellable networks, jointed with the aid of using move-linking agents. These polymers own most useful polarity to ensure that they allow enough wetting with the aid of using the mucus and most useful fluidity that allows the mutual adsorption and interpenetration of polymer and mucus to take place.[21]

Hydrophilic polymers: The polymers inside this class are soluble in water. Matrices advanced with those polymers swell whilst placed into an aqueous media with next dissolution of the matrix. The polyelectrolytes make bigger extra mucoadhesive assets whilst as compared with impartial polymers. Anionic polyelectrolytes, e.g. poly (acrylic acid) and carboxymethyl cellulose were appreciably used for designing mucoadhesive transport structures because of their capacity to show off sturdy hydrogen bonding with the mucin gift withinside the mucosal layer. Chitosan presents an extraordinary instance of cationic polyelectrolyte, which has been appreciably used for growing mucoadhesive polymer because of its correct biocompatibility and biodegradable houses.[21]

Hydrogels: Hydrogels may be described as three-dimensionally crosslinked polymer chains that have the capacity to keep water inside its porous structure. The water conserving potential of the hydrogels is specifically because of the presence of hydrophilic useful organizations like hydroxyl, amino and carboxyl organizations. Hydrogels organized with the aid of using the condensation response of poly (acrylic acid) and sucrose indicated an growth withinside the mucoadhesive assets.[21]

Thiolated polymers: The presence of loose thiol organizations withinside the polymeric skeleton allows withinside the formation of disulphide bonds with that of the cysteine-wealthy sub-domain names found in mucin that can drastically enhance the mucoadhesive houses of the polymers e.g. poly (acrylic acid) and chitosan). Various thiolated polymers en compass chitosan-iminothiolane, poly(acrylicacid)cysteine, poly (acrylic acid)homocysteine, chitosan-thioglycolicacid,chitosan-thioethylamidine, alginate-cysteine,poly(methacrylic acid) cysteine and sodiumcarboxymethylcellulose cysteine.[21]

Lectin-primarily based totally polymers: Lectins are proteins that have capacity to reversibly bind with precise sugar carbohydrate residues and are discovered in each animal and plant kingdom. The precise affinity of lectins in the direction of sugar or carbohydrate

residues presents them with precise cyto-adhesive assets and is being explored to broaden focused transport structures. Lectins extracted from legumes were broadly explored for focused transport structures.[21]

Table 1:[46] Patent Filed on Mucoadhesive Drug Delivery.

SL.NO	PATENT NO.	DRUG USED
1	CN201110142359	Ketoprofen
2	CN201110313846	Paclitaxel
3	CN201210025085	5-Fluorouracil
4	US08455091	Ganciclovir
5	EP19980924438	Cimetidine
6	EP20070808011	Risperidone
7	CA2217462	Cyclosporin
8	CA2579533	Irinotecan
9	DE1999609777	Levonorgesterel
10	DE1994632867	Doxorubicin

Table 2:[4] Current patents filed on mucoadhesive drug delivery.

SL NO	PATENT NO	TYPE OF DELIVERY SYSTEMS
1	WO/2003/086297	Tablets
2	US20110028431	Tablets
3	WO/2006/069911	Gels
4	US20100100064	Ostomy appliences
5	US20140056949	Gels,paste and lozenges
6	US8529939	Wafer,tablet,sheet and cylinders
7	WO/2013/188979	Ointments,creams,pastes and gels
8	US20150174076	Wafers
9	US20090098203	Mouth rinse or tablet
10	US20100144618	Ointments,cream and gels

CONCLUSION

Oral multiparticulate mucoadhesive drug delivery provide greater adaptability and flexibility to the clinicians or which take part in product growth commanding novel devices to improve the efficiency of treatment. The thought of utilizing bioadhesive resources in connection with surfaces of the mucosal layer, as a technique to progress the effectiveness of therapeutic medications that has been of immense curiosity in the reproducible drug availability.

ACKNOWLEDGEMENT

The authors are greatefully acknowledge the east point college of pharmacy for support and institutional support.

REFERENCES

1. Bhatt DA, Pethe AM. Mucoadhesive drug shipping structures: an assessment. J Pharm Res, 2010; 3: 1743-47.
2. Sayani AP, Chien YW. Systemic shipping of peptides and proteins throughout absorptive mucosae. Critical evaluations in healing drug provider structures, 1996; 13(1-2): 85-184.
3. Alur HH, Johnston TP, Mitra AK. Encyclopedia of Pharmaceutical Technology, in: J. Superbrick, J.C. Boylan (Eds.), Peptides and Proteins: Buccal Absorption, Marcel Dekker Inc., New York, 2001; 20: 193218.
4. Someshwar Komati, Suryakanta Swain, Muddana Eswara Bhanoji Rao, Bikash Ranjan Jena, Vishali Dasi mucoadhesive multiparticulate drug delivery systems: an extensive review of patents, 2019; 9(4): 521-538.
5. Senel S, Kremer M, Katalin N, Squier C. Delivery of bioactive peptides and proteins throughout oral (buccal) mucosa. Current Pharmaceutical Biotechnology, 2001 Jun 1; 2(2): 175-86.
6. Gandhi PA, Patel MR, Patel KR, Patel NM. A evaluation article on mucoadhesive buccal drug shipping gadget. International Journal of Pharmaceutical Research and Development, 2011 Jul; 3(5): 159-73.
7. Phanindra B, Moorthy BK, Muthukumaran M. Recent advances in mucoadhesive/bioadhesive drug shipping gadget: A evaluation. International Journal of Pharma Medicine and Biological Sciences, 2013; 2(1): 68-84.
8. Rao NR, Shravani B, Reddy MS. Overview on buccal drug shipping structures. Journal of Pharmaceutical Sciences and Research, 2013 Apr 1; 5(4): 80.
9. Duchene D, Touchard F, Peppas NA. Pharmaceutical and scientific factors of bioadhesive structures for drug management. Drug improvement and business pharmacy, 1988 Jan 1; 14(2-3): 283-318.
10. Mujorruya R, Dhamande K, Wankhede UR, Dhamande K. A evaluation on look at of buccal drug shipping gadget: Innovative System Design and Engineering.
11. Patel VF, Liu F, Brown MB. Advances in oral transmucosal drug shipping. Journal of managed launch, 2011 Jul 30; 153(2): 106-16.
12. Satyabrata B, Ellaiah P, Choudhury R, Murthy KV, Bibhutibhusan P, Kumar MS. Design and assessment of methotrexate buccal mucoadhesive patches. Int J Pharm Biomed Sci., 2010; 1(2): 31-6.

13. Patil BS, Tate SS, Kulkarni U, RC H WG. Development and in-vitro assessment of mucoadhesive buccal drugs of Tizanidine hydrochloride the usage of herbal polymer xanthan gum. Int J Pharm Sci., 2011; 8(2): 140-6.
14. Gandhi RB, Robinson JR. Bioadhesion in drug shipping. Indian Journal of Pharmaceutical Sciences, 1988 May 1; 50(3): 145.
15. Edsman K, HaÌˆgerstroÌˆm H. Pharmaceutical packages of mucoadhesion for the non oral routes. Journal of pharmacy and pharmacology, 2005 Jan; 57(1): 3-22.
16. Steward A, Bayley DL, Howes C. The impact of enhancers at the buccal absorption of hybrid (BDBB) -interferon. International magazine of pharmaceutics, 1994 Apr 11; 104(2): 145-9.
17. Vaughan DF. Pharmacokinetics of albuterol and butorphanol administered intravenously and thru a buccal patch (Doctoral dissertation, Texas A&M University).
18. Wise DL. Handbook of pharmaceutical managed launch technology. CRC Press, 2000 Aug 24.
19. Indian Journal of Pharmaceutical Science, July-Aug, 2004; 66(4): 371-536: 556-562.
20. Repka MA, Repka SL, McGinity JW, inventors; Mcginity James W., assignee. Bioadhesive hot-soften extruded movie for topical and mucosal adhesion packages and drug shipping and method for guidance thereof. United States patent US 6,375,963, 2002 Apr 23.
21. Anujkumar V, Naveen P, KumudPadhee M, Neeta S. Formulation improvement & assessment of carvedilol bioerodible buccal mucoadhesive patches. Pharmacie Globale. Int J Comprehensive Pharm, 2011; 3(7): 1-5.
22. Miller NS, Johnston TP. The use of mucoadhesive polymers in buccal drug shipping, Advanced Drug Delivery Reviews, 2005; 57: 166691.
23. Vishnu MP, Bhupendra GP, Madhabhai MP. Design and in vitro characterization of eudragit containing mucoadhesive buccal patches. Int J PharmTech Res, 2009; 1(3): 7839.
24. Ching HS. Bioadhesive polymers as systems for oral managed drug shipping II: Synthesis and assessment of a few swelling, water- insoluble bioadhesive polymers. J Pharm Sci., 1985; 74(4): 399405.
25. Coutel EA, Maitani Y, Veillard M, Machida Y, Nagai T. Combined consequences of pH, cosolvent and penetration enhancers at the in vitro buccal absorption of propranolol via excised hamster cheek pouch. Int J Pharm, 1992; 84: 117-28.

26. Patel R, Shardul N, Patel J, Baria A. assessment on buccal mucoadhesive films. Arch Pharm Sci & Res, 2009; 1(2): 212-7.
27. B.F. Oliveira de, M.H.A. Santana, M.I. Re, Spray-dried chitosan microspheres crosslinked with d,l-glyceraldehyde as a capability drug shipping gadget: guidance and characterization. Submitted for presentation on the 14th International Drying Symposium (IDS 2004). Sao Paulo, Brazil, August 2004.
28. Yassin AE, Alanazi FK, El-Badry M, Alsarra IA, Barakat NS, Alanazi FK. Preparation and characterization of spironolactone-loaded gelucire microparticles the usage of spray-drying technique. Drug Dev Ind Pharm, 2009; 35(3): 297-304.
29. Mathiowitz E, Chickering D, Jacob JS, Santos C. Bioadhesive drug shipping structures. In: Mathiowitz E, ed. Encyclopedia of Controlled Drug Delivery, Vol. 9. New York: John Willey & Sons, 1999b; 9-44.
30. Peppas NA, Buri PA. Surface, interfacial and molecular factors of polymer bioadhesion on tender tissues. J Control Rel, 1985; 2: 257-275.
31. Vyas TK, Babbar AK, Sharma RK, Singh S, Misra A. Intranasal mucoadhesive microemulsions of clonazepam: initial research on mind targeting. J Pharm Sci., 2006; 95(3).
32. Bogataj M, Vovk T, Kerec M, Dimnik A, Grabnar I, Mrhar A. The correlation among zeta capability and mucoadhesion energy on pig vesical mucosa. Biol Pharm Bull.
33. Rajput G, Majmudar F, Patel J, Thakor R, Rajgor NB. Stomach- unique mucoadhesive microsphere as a managed drug shipping gadget. Sys Rev Pharm, 2010; 1(1): 70-78.
34. Sonani NG, Hiremath SP, Dasankoppa FS, Jamakandi VG and Sreenivas SA. Design and assessment of gastroretentive mucoadhesive cephalexin drugs. Pharm Dev Technol, 2010; 15(2): 178-183.
35. 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.
36. Microsphere: A Review Kataria Sahil, Middha Akanksha, Sandhu Premjeet, Ajay Bilandi and Bhawana Kapoor IJRPC, 2011; 1(4).
37. G.S. Asane. Mucoadhesive gastro intestinal drug shipping gadget: an assessment, 2007; 5: 6.
38. Sudhakar Yajaman, Ketousetuo Kuotsu. Buccal bioadhesive drug shipping. Journal of Controlled Release, 2006; 114: 1540.

39. S. Singh, J. Singh. Preparation of floating microsphere for oral managed drug shipping, The Indian pharmacist, 2006; 5(53): 61-70.
40. Vjera Grabovac, Davide Guggi, Andreas Bernkop-Schnu Comparison of the mucoadhesive homes of numerous polymer Advanced Drug Delivery Reviews, 2005; 57: 1713 1723.
41. Suresh Fartyal, Sajal Kumar Jha, Manvendra Singh Karchuli, Rohit Gupta, Ankit Vajpayee. Formulation and Evaluation of Floating Microspheres of Boswellic acid. Int.J. Pharm. Tech Res., 2011; 3(1).
42. Santosh Shep, Sham Dodiya, Sandeep Lahoti, Rahul Mayee. Swelling System: A Novel Approach Towards Gastroretentive Drug Delivery System, Indo Global Journal of Pharmaceutical Sciences, 2011; 1(3): 234-242.
43. Nikalje Anna Pratima, Shailee Tiwari, Smrutigandha Kamble Mucoadhesive: As Oral Controlled Gastroretentive Drug Delivery System, IJRPS, 2012; 2(3) 32-59.
44. Sheu M, Chen R, Ho. Hsiu, Yu C. Development of swelling/floating gastroretentive drug shipping gadget primarily based totally on a mixture of hydroxyethyl cellulose and sodium carboxymethyl cellulose for Losartan and its scientific relevance in healthful volunteers with CYP2C9 polymorphism. European Journal of Pharmaceutical Sciences, 2010; (39): 8289.
45. K Vinod, Vasa Santhosh, S Anbuazaghan, Banji David, et al. Approaches for gastrotentive drug shipping structures International Journal of Applied Biology and Pharmaceutical Technology, 2010; 1(2): 589-601.
46. M. Chavanpatil, P. Jain, S. Chaudhari, R. Shear, P. Vavia. Novel sustained launch, swellable and bioadhesive gastroretentive drug shipping gadget for ofloxacin. International Journal of Pharmaceutics, 2009; 316: 68692.
47. Hoffman, D. Stepensky, E. Lavy, S. Klausner, Michael Friedman. Pharmacokinetic and pharmacodynamic factors of gastroretentive dosage paperwork. Int. J. Pharma., 2004; 277(1): 4153.
48. Nayak Amit, Maji Ruma, Das Biswarup. Gastroretentive drug shipping structures: evaluation on gastroretentive drug shipping structures, 2010; 3.
49. V.V. Prasanth, Akash Chakraborthy Moy, Sam T Mathew, Rinku Mathapan. Microspheres an Overview International Journal of Research in Pharmaceutical and Biomedical Sciences, 2011; 2(2) 332-338.

50. Sellappan VelmuruganA, Mohamed Ashraf Ali. A Mucoadhesive Microspheres-A PromisingCarrier in Drug Delivery: A Review, Int. J. Drug Dev. & Res., 2013; 5(3): 49-66.
51. Tripathi KD. Essential of scientific pharmacology. fifth Edn, JayPee Brothers scientific publishers (P) Ltd New Delhi, 2003; 245-248.
52. Complete Metformin Hydrochloride statistics, drug statistics online, and www.drug_com.mht.
53. Yellanki Shiva Kumar, Deb Sambit Kumar, Goranti Sharada, Nerella Naveen Kumar. Formulation Development of Mucoadhesive Microcapsules of Metformin HCL Using Natural and Synthetic Polymers and In vitro Characterization. Int J Pharm, 2010; 2(2): 321-329.
54. Kalyankar TM, Nalanda T. Rangan, Mubeena khan, Avinash Hosmani and Arvind Sonwane. Formulation and Evaluation of Mucoadhesive Pioglitazone HCL Microspheres. IJPWR, 2010; 1.
55. Najmuddin M, Ahmed A, Shelar S, Patel V, Khan T. Floating Microspheres of Ketoprofen, system and assessmentâ€. Int J Pharm and pharmaceutical sciences, 2010; 2(12): 83-87.
56. Kakkar AP. Characterization of Ibuprofen Loaded Microcapsules Prepared through Ionotropic Gelation. Ind. J. Pharm. Sci, 1995; 57(2): 56-60.
57. Manna A, Ghosh I, Goswami N, Ghosh LK, Gupta BK. Design and Evaluation of an Oral Controlled Release Microparticulate Drug Delivery System of Nimesulide through Ionotropic Gelation Technique and Statistical Optimization through Factorial Analysis. J Sci Ind. Res, 1999; 58(9): 717-722.
58. Yadav KS, Satish CS, Shivkumar HG. Preparation and assessment of chitosan-Poly (Acrylic acid) Hydrogels as Stomach unique shipping for amoxicillin and Metronidazole. Indian J. Pharm. Sci, 2007; 69: 91-95.
59. Note for steerage on balance trying out. Stability trying out of recent drug materials and merchandise, 2003. [Cited 2008 Dec 02], Available from URL, http,//www.tga.gov.
60. Rouge N, Buri P, Doelker E. Drug absorption webweb sites withinside the gastrointestinal tract and Dosage paperwork for webweb page unique shipping. Int J Pharm, 1996; 136: 117-139.
61. Thomas Wai-Yip Lee and Joseph R. Robinson. Controlled / Release Drug-Delivery Systems 'Remington's Pharmaceutical Sciences', twentieth Edn, Vol 1, Mack Publishing Company, 2000; 903-929.

62. Woo B, Jiang G, Jo Y, DeLuca P. Preparation and characterization of composite PLGA and Poly (acryloyl hydroxyl methyl starch) microsphere gadget for protein drug shipping. Pharm Res, 2001; 18: 1600-1606.
63. Capan Y, Jiang G, Giovagnoli S, DeLuca PP. Preparation and characterization of poly (D, L-lactide-co-glycolide) microsphere for managed launch of human boom hormone. AAPS Pharm Sci Tech, 2003; 4: E28.
64. Gohel MC, Amin AF. Formulation optimization of managed launch diclofenac sodium microspheres the usage of factorial design. J Control Release, 1998; 51: 115-122.
65. Vasr JK, Tambwekar K, Garg S. Bioadhesive microspheres as a managed drug shipping gadget. Int J Pharm, 2003; 255: 13-32.
66. Ikeda K, Murata K, Kobayashi M, Noda K. Enhancement of bioavailabity of dopamine thru nasal direction in beagle dogs. Chem Pharm Bull (Tokyo), 1992; 40: 2155-2158.
67. Nagai T, Nishimoto Y, Nambu N, Suzuki Y, Sekine K. Powder dosage shape of insulin for nasal management. J Control Release, 1984; 1: 15-22.
68. Ilium L, Farraj NF, Critechley H, Davis SS. Nasal management of gentamicin the usage of a Novel microsphere shipping gadget. Int J Pharm, 1988; 46: 261-265.
69. Schaefer MJ, Singh J. Effect of isopropyl myristic acid ester at the bodily traits and in vitro launch of etoposide from PLGA microspheres. AAPS PharmSciTech, 2000; 1: E32.
70. Rao SB, Sharma CP. Use of chitosan as biomaterial, research on its protection and haemostatic Potential. J Biomed Mater Res, 1997; 34: 21-28.
71. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. In vitro assessment of mucoadhesive homes of chitosan and a few different herbal polymer. Int J Pharm, 1992; 78: 43-48.
72. Henriksen I, Green KL, Smart JD, Smistad G, Karlsen J. Bioadhesion of hydrated Chitosans, an in vitro and in vivo look at. Int J Pharm, 1996; 145: 231-240.
73. Chowdary KPR, Rao YS. Design and in vitro and in vivo assessment of mucoadhesive Microcapsules of glipizide for oral managed launch, a technical note. AAPS PharmSciTech, 2003; 4: E39.
74. Yellanki shiva kumar, Deb sambit kumar, Goranti sharada, Nerella Naveen kumar. Formulation Development of Mucoadhesive Microcapsules of Metformin HCL Using Natural and Synthetic Polymers and In vitro Characterization. Int J Pharm, 2010; 2(2): 321-329.
75. Imam ME, Hornof M, Valenta C, Reznicek G, Bernkop-Schnurch A, Evidence for the interpenetration of mucoadhesive polymers into the mucous gel layer, STP Pharma. Sci., 2003; 13: 171176.