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Journal of Current Pharma Research 5 (3), 2015, 1505-1512.

Journal of Current Pharma Research

http://www.jcpronline.in

Original Article

Mucoadhesive Microsphere as a Drug Delivery System: A Review.

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Received 10 May 2015; received in revised form 21 June 2015; accepted 22June 2015

Available online 28 June 2015

Abstract

The present study deals with the mucoadhesive microsphere which constitutes an important part of novel drug delivery system by virtue of their small size and efficient carrier capacity. In recent years the multiparticulate drug-delivery systems are used in the oral delivery of drugs. One of the approaches toward this goal is to develop the mucoadhesive microspheres so as to increase the gastric retention time. Such systems have more advantages over the single-unit dosage forms. The development of mucoadhesive microspheres involves different solvent evaporation techniques to create the hollow inner core. 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 of various aspects of mucoadhesive microsphere

Keywords: Microsphere, Mucoadhesion, Controlled drug delivery system, Bioavailability.

Introduction

Oral administration is the most convenient and predominant route for drug delivery. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. Gastric emptying is a complex process, which is highly variable and makes in vivo performance of the drug-delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the gastric retention time of the drug-delivery systems . The mucoadhesive drug-delivery systems are useful in such applications. In recent years the multiparticulate drug-delivery systems are used in the oral delivery of drugs.

One of the approaches toward this goal is to develop the mucoadhesive microspheres so as to increase the gastric retention time. Such systems have more advantages over the single-unit dosage forms. [1]

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm (1 mm)). Microspheres are sometimes referred to as microparticles. In addition, some related terms are used as well. For example, "microbeads" and "beads" are used alternatively. Sphere and spherical particles are also employed for a large size and rigid morphology. They are made from polymeric, waxy, or other protective materials such as starches, gums, proteins, fats and waxes ad used as drug carrier matrices for drug delivery. Mucoadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach. Thus, they improve the prolongation of gastric retention.Various polymers used in

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bioadhesive formulations include NaCMC, sodium alginate, chitosan H.P.M.C.etc. . [2,3.]

Importance of Microspheres in the Body

Micro-particulate carrier systems can be administered through different routes such as intravenous, oral, ocular, intramuscular, etc. Each route has its own biological significance, limitation and pharmaceutical feasibility. The microspheres are intended to be administered to achieve desired activity of either sustained action or targeting or both through different routes. Different mechanism of uptake, transport and fate of translocated particles has been proposed.

Mucoadhesive Microsphere

Mucoadhesive drug delivery systems are the systems which utilize the property of mucoadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time. The term mucoadhesion is used. The mucosal layer lines a number of regions of the body including the nose, gastrointestinal tract, urogenital tract, the airways, the ear and eye. However, the success of microspheres is limited due to their short residence time at absorption site [6]. It would, therefore, be advantageous to have means for providing an intimate contact of the microspheres with absorbing membranes. It can be achieved by. In the case of polymer attached to mucin layer of a mucosal tissue, associate mucoadhesion characteristics to microspheres and developing mucoadhesive [4,5.]

Mechanism of Bioadhesion: [6, 7.]

For Bioadhesion to occur, three stages are involved.

Stage-1: An intimate contact between a Bioadhesive and a membrane either from a good wetting of the Bioadhesive and a membrane or from the swelling of bioadhesive.

Stage-2: Penetration of the bio-adhesive into the service of the tissue takes place.

Stage-3: Inter penetration of the chains of the bioadhesive with mucous takes place. Low chemical bounds can then settle.

The mucoadhesive drug delivery system may include the following

1. Buccal delivery system.
2. Sublingual Delivery system.
3. Gastrointestinal delivery system.
4. Vaginal delivery system.
5. Rectal delivery system.
6. Nasal delivery system.
7. Ocular delivery system

Methods which are employed for the preparation of microspheres are :- [18.]

- Single emulsion technique.
- Double emulsion technique.
- Polymerization techniques
- Normal polymerization: Bulk polymerization, suspension polymerization, emulsion polymerization, miceller polymerization, and precipitation polymerization.
- Interfacial polymerization.
- Phase separation technique.
- Spray drying and spray congealing.
- Solvent evaporation.

Advantages of Mucoadhesive Microspheres in Drug Delivery: [16, 17.]

1. Mucoadhesive microspheres have advantages like efficient absorption and improved bioavailability of the drugs due to a high surface to volume ratio, much more intimate contact with the mucus membrane
2. Prolongs the residence time of the dosage form at the site of absorption or action.
3. A localization of drug action of the delivery system at a given target site
4. A direct contact with intestinal cells that the first step before particle absorption.
5. Better patient compliance- ease of drug administration.
6. Drugs which are unstable in the acidic environment or destroyed by enzymatic or alkaline environment of intestine can be administered by this route. E.g. Buccal, sublingual, vaginal
7. Increased safety margin of high potency API due to better control of plasma levels.

8. Maximum utilization of drug enabling reduction in total amount of drug administered.
9. The use of specific bioadhesive molecules allows for possible targeting of particular sites or tissues, for example the gastrointestinal (GI) tract.
10. Increased residence time combined with controlled API release may lead to lower administration frequency and cost reductions.

Disadvantages of Mucoadhesive Drug Delivery Systems:

1. Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property
2. One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.
3. Patient acceptability in terms to taste, irritancy and mouth feel is to be checked.
4. The mucus on the walls of the stomach is in a state of constant renewal, resulting in Unpredictable adherence.
5. In all the above systems the physical integrity of the system is very important and primary requirement for the success of these systems.

Pharmacokinetic Aspects [9-13].

1. Absorption window-validation that the drug is within the category of narrows absorption window agents:

In general, appropriate candidates for CR-GRDD are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GI tract. In the case of absorption by active transporters that are capacity limited, the efficacy of the transport activity may increase following sustained presentation of the drug to the transporting enzymes in comparison to non CR mode of administration.

2. Enhanced bioavailability:

Once it has been ascertained that the compound in question is defined as narrow absorption window, the possibility of improving bioavailability by continuous administration of the compound to the specific site should be tested. For example, certain bisphosphonates, including alendronate, are absorbed directly from the stomach. However, the magnitude of this pathway remains modest even in the case where the prolonged gastric retention of the bisphosphonate rats is produced by experimental/surgical means. On the other hand, the bioavailability of riboflavin and levodopa CRGRDD is significantly enhanced in comparison to administration of non-GRDD CR polymeric formulations. It may be concluded that several different processes, related to absorption and transit of the drug in the gastrointestinal tract, act concomitantly and influence the magnitude of drug absorption. Therefore, in vivo studies are necessary to determine the release profile of the drug from the dosage form that will provide enhanced bioavailability.

3. Enhanced first pass biotransformation:

In a similar fashion to increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

4. Reduced frequency of dosing:

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDD may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

6. Targeted therapy for local ailments in the upper GI tract:

The prolonged and sustained administration of the drug from the GRDD to the stomach may be advantageous for local therapy in the stomach and the small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while the systemic concentrations, following drug absorption and distribution, are minimal.

PHARMACODYNAMIC ASPECTS

1. Reduced fluctuations of drug concentration:

Continuous input of the drug following CR-GRDD administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent

adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugswith a narrow therapeutic index.

2. Improved selectivity in receptor activation:

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

3. Reduced counter-activity of the body:

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

4. Extended time over critical (effective) concentration:

For certain drugs that have non-concentration dependent pharmacodynamics, such as betalactam antibiotics, the clinical response is not associated with peak concentration, but rather, with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

5. Minimized adverse activity at the colon:

Retention of the drug in the GRDD at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDD formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to development of microorganism's resistance. In most cases, due complexity of pharmacokinetic and pharmacodynamic parameters, in vivo studies are required to establish the optimal dosage form for a specific drug.

Polymer used in Mucoadhesive drug delivery systems [19].

Hydrophillic polymers

These swell when in contact with water and adhere to the mucus membrane. These are further classified according to their charge Contains carboxylic group and possess excellent mucoadhesive properties. These are pvp (poly vinyl pyrrolidine) Mc (methyl cellulose) Scmc (sodium carboxy metyhyl cellulose) Hpc (hydroxyl propyl cellulose)

Hydrogels

Anionic polymers - carbopol, polyacrylates

Cationic polymers - chitosan

Neural/ non ionic polymers - eudragit analogues

They can also be classified as,

Synthetic polymers- cellulose derivatives, carbopols, etc.

Natural polymers- tragacanth, pecyin, gelatin sodium alginate

Applications in Drug Delivery System [15].

Pharmaceutical applications in drug delivery system

1. Ophthalmic Drug Delivery

Polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Due to their elastic properties, polymer hydro gels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments.

2. Gene delivery

.polymer could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. MacLaughlin et al showed that plasmid DNA containing cytomegalo virus promoter sequence and a luciferase reporter gene could be delivered in vivo by chitosan and depolymerized chitosan oligomers to express a luciferase gene in the intestinal tract.

3. Oral drug delivery

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

polymer a unique polymer for oral drug delivery applications.

4. Nasal drug delivery

The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. Polymer based drug delivery systems, such as microspheres, have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route.

5. Buccal drug delivery

Polymer is an excellent polymer to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. chitosan, with or without anionic cross linking polymers (polycarbophil, sodium alginate, gellan gum) has promising potential for use in controlled delivery in the oral cavity.

6.Peroral drug delivery

As polymer and most of its derivatives has a mucoadhesive property, a presystemic metabolism of peptides can be strongly reduced leading to a strongly improved bioavailability of many per orally given peptide drugs, such as insulin, calcitonin, and buserelin. Unmodified chitosan has a permeation-enhancing effect for peptide drugs.

7. Vaginal drug delivery

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

8. Transdermal drug delivery

Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Chitosan-alginate polyelectrolyte complex has been prepared in-situ in beads and microspheres for potential applications in packaging, controlled release systems and wound dressings. Polymer gel beads are a promising biocompatible and biodegradable vehicle

9. Colonic drug delivery

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

Limitations Of Mucoadhesive drug deliver system-

- It required high level of
- Drugs which create solubility and stability problems in gastric fluids, & drugs that are irritant to the gastric mucosa not suitable for mucoadhesive drug delivery.
- Drugs, which under go higher first pass metabolism, not a better candidates for mucoadhesive drug delivery.

Evaluation Parameters[20 - 22.]

1. Physicochemical Evaluation

The characterization of the microparticulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier.

2. Particle size and shape

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microparticles. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to

the LM. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems. Conflocal fluorescence microscopy is used for the structure characterization of multiple walled microspheres. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size, shape and morphology of the microspheres.

3. Electron spectroscopy for chemical analysis:

The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of the atomic composition of the surface. The spectra obtained using ECSA can be used to determine the surface degradation of the biodegradable microspheres.

4. Attenuated total reflectance Fourier Transfom- Infrared Spectroscopy:

FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATRFTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

5. Density determination:

The density of the microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of the microsphere carrier is determined.

6. Isoelectric point:

The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity at different Ph values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be determined. The electrophoretic mobility can be related to surface contained charge, ionisable behavior or ion absorption, nature of the microspheres.

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 200C within a minute of deposition of microspheres.

8. In vitro methods

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of in vitro and in vivo techniques have been reported. In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physico chemically and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating in vivo conditions has led to development of a number of in vitro release methods for buccal formulations; however no standard in vitro method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed. The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using over head stirrer. Volume of the medium used in the literature for the

studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.

9. In vivo methods

Methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrate at the surface. Some of the earliest and simple studies of mucosal permeability utilized the systemic pharmacological effects produced by drugs after application to the oral mucosa. However the most widely used methods include in vivo studies using animal models, buccal absorption tests, and perfusion chambers for studying drug permeability.

10. In vitro-In vivo correlations

Correlations between in vitro dissolution rates and the rate and extent of availability as determined by blood concentration and or urinary excretion of drug or metabolites are referred to as “in vitro-in vivo correlations”. Such correlations allow one to develop product specifications with bioavailability. Amount of drug available for absorption is less for poorly formulated dosage form than from a well formulated dosage form the drug dissolved. If the rate limiting step in the bioavailability of the drug is the rate of absorption of the drug, a change in the dissolution rate may not be reflected in a change in the rate and the extent of drug absorption from the dosage form.

11. Swelling Index

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. To ensure the complete equilibrium, exactly weighed amount of microspheres were allowed to swell in given buffer. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using microbalance. The hydrogel microspheres then dried in an oven at 60° for 5 h until there was no change in the dried mass of sample.

The swelling index of the microsphere was calculated by using the formula Swelling

Index = (mass of swollen microspheres – mass of dry microspheres/mass of dried microspheres) 1

Conclusion

The phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for a number of drug candidates. The various advantages of the oral mucoadhesive drug delivery systems like prolongation of the residence time of the drug which in turn increases the absorption of the drug are important factors in the oral bioavailability of many drugs. Mucoadhesive microspheres offer a promising carrier system for many pharmaceutical components and can be modified to adhere to any mucosal tissue including those found in eye, nasal cavity, rectal, urinary and oral mucosal delivery, thus providing the potential for localized as well as systemic controlled release of drugs. The various advantages of mucoadhesive micro spheres can be used not only for controlled release but also for enhancing bioavailability of many drugs by prolongation of the residence time of the drug which in turn increases the absorption of the drug, for targeted delivery of drugs to various sites in the body Mucoadhesive delivery system is a promising area for continued research with the aim of achieving controlled release with enhanced bioavailability and for drug targeting to specific sites in the body

References

1. Nayak Amit, Maji Ruma, Das Biswarup. Gastroretentive drug delivery systems: a review on gastroretentive drug delivery systems, 3 (2010.
2. V.V. Prasanth, Akash Chakraborthy Moy, Sam T Mathew, Rinku Mathapan. Microspheres an Overview International Journal of Research in Pharmaceutical and Biomedical Sciences, 2,2 (2011) 332-338.
3. Sellappan VelmuruganA, Mohamed Ashraf Ali. A Mucoadhesive Microspheres-A Promising Carrier in Drug Delivery: A Review, Int. J. Drug Dev. & Res., 5,3 (2013) 49-66
4. Harshad Parmar, Sunil Bakliwal, Nayan Gujarathi, Bhushan Rane, Sunil Pawar. Different methods of formulation and evaluation of

Mucoadhesive microsphere, 3 (2010) 3.

5. Nikalje Anna Pratima, Shailee Tiwari, Smrutigandha Kamble Mucoadhesive: As Oral Controlled Gastroretentive Drug Delivery System, IJRPS, 2, 3 (2012) 32-59.

6. Sheu M, Chen R, Ho. Hsiu, Yu C. Development of swelling/floating gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for Losartan and its clinical relevance in healthy volunteers with CYP2C9 polymorphism. European Journal of Pharmaceutical Sciences, 39 (2010) 82–89.

7. K Vinod, Vasa Santhosh, S Anbuazaghan, Banji David, et al. Approaches for gastrotentive drug delivery systems International Journal of Applied Biology and Pharmaceutical Technology, 1,2 (2010) 589-601.

8. M. Chavanpatil, P. Jain, S. Chaudhari, R. Shear, P. Vavia. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. International Journal of Pharmaceutics, 316 (200) 686–92.

9. A. Hoffman, D. Stepensky, E. Lavy, S. Klausner, Michael Friedman. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. Int. J. Pharma., 277 (2004)1 41–153.

10. Pranshu Tangri, N.V. Satheesh Madhav. Oral Mucoadhesive Drug Delivery Systems: A Review. International Journal of Biopharmaceutics, 2,1 (2011) 36-46.

11. Microsphere: A Review Kataria Sahil, Middha Akanksha, Sandhu Premjeet, Ajay Bilandi and Bhawana Kapoor IJRPC 2011, 1(4)

12. G.S. Asane. Mucoadhesive gastro intestinal drug delivery system: an overview. 5, 6 (2007).

13. Sudhakar Yajaman, Ketousetuo Kuotsu. Buccal bioadhesive drug delivery. Journal of Controlled Release 2006; 114: 15–40.

14. S. Singh, J. Singh. Preparation of floating microsphere for oral controlled drug delivery, The Indian pharmacist, 5, 53 (2006) 61-70.

15. Vjera Grabovac , Davide Guggi , Andreas Bernkop-Schnu¨Comparison of the mucoadhesive properties of various polymer Advanced Drug Delivery Reviews 57 (2005) 1713–1723

16. 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., 3, 1 (2011).

17. Santosh Shep, Sham Dodiya, Sandeep Lahoti, Rahul Mayee. Swelling System: A Novel Approach Towards Gastroretentive Drug Delivery System, Indo Global Journal of Pharmaceutical Sciences, 1, 3 (2011) 234-242.

18. Hemlata Kaurav, S. L. Amanpreet Kaur Mucoadhesive Microspheres as carriers in Drug Delivery: a Review HariKumar and Int. J. Drug Dev. & Res., 4,2 (2012) 21-34.