JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue

JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)

An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A BRIEF REVIEW ON MICROSPHERES IN BUCCAL CAVITY

[1]Diksha sharma*, [2]Anchal Sharma, [3]Anjali, [4]Anjali, [5]Akshay , [6]Akash Chandel

[1,2,3,4,5,6]KC Institute of Pharmaceutical Sciences, Una, H.P, India

ABSTRACT

Hi tech technology supply impressive and resourceful approach for the delivery of drug.It gives conveyance of medication by blend of the medication to the transporter molecule, for example, microspheres, microemulsion, nanoparticles and so on. Microspheres structures a significant piece of this particular medication conveyance framework due to their little size and other valuable properties. Buccal microspheres give predominant medication ingestion as they get where to the buccal surface and arrival of medication for longer timeframe.

Th fundamental focal point of this article is to audit the essential standards of the definition and assessment of microsphere utilized as buccal depression.

KEYWORDS

Bio adhesion, Microspheres, Mucoadhesion, Mucoadhesive polymer.

INTRODUCTION

The word microsphere is explained as a particle with size 1micrometre -1000micrometre. The microsphere is a delegate free streaming powder made of engineered polymer which are biological Ex: clear in nature and having molecule size under 200micrometre.The microsphere delivered from profoundly straightforward glass can proceed as much prime quality optical microcavities or miniature resonators. The progress of these microspheres is limited having give close contact of the medication conveyance framework with engrossing film. The oral course of medication organization amounted to the most appropriate and better method for drug conveyance to fundamental dissemination of the body. albeit oral organization of medication in the ordinary measurement structure has momentary restriction because of their absence of their capacity to forestall and restricted the framework at gastrointestinal lot. Bio bond dose structures may be determined to impede time span and through interfacial power. Bio grip dose structures may be determined to hinder the holding time at the site of use giving a controlled pace of prescription release for expanding restoring yield bio bond drug conveyance framework enjoy three clear benefits when contrasted with traditional dose structure .Firstly bio

attachment framework which is promptly confined in the district applied to a better and increment the bioavailability of medications .furthermore these measurements structure can connect with hidden retention surface bringing about a more prominent ingestion surface fundamental retention surface bringing about a more prominent retention .they can increment home time at the site of use to permit one's or two times every day dosing .microsphere based novel medication conveyance framework might grow the life expectancy of dynamic fixing and stand out enough to be noticed in the focal delivery and target medication to the specific body site of intrigued region without secondary effects and its little claiming to their short home time at adsorption site. So different endeavored have been created to increment bioavailability as well as increment gastric home time in stomach so brought about advancement of bio glue drug conveyance framework which will give on close contact with retaining film this continue towards the utilization of bio cement polymer which can tie to the epithelial surface in stomach which increment drug retention .Bio attachment drug conveyance framework are accessible as patches ,tablet, gels for nasal visual, oral, rectal and skin course for both fundamental and nearby impact. Bio cement microspheres that are keep in the stomach would expand the medication adsorption and diminishing portion recurrence which gives better understanding consistence when contrasted consistence as contrasted and traditional dose structure. (S. Kataria, et al: 2011)

Bio adhesive drug delivery system includes following: -

1. Vaginal delivery system

2. oral delivery system.

3. nasal delivery system.

4.occular delivery system.

5.buccal delivery system.

6.rectal delivery system.

ADVANTAGES

1. Rapid absorption

2. Good bioavailability.

3. Avoiding degradation of gastrointestinal enzymes.

4. Improved patient compliance.

5. Excellent accessibility.

6. Toxicity of drug can be reduced by reducing volume of distribution of drug by targeting.

7. Reduce dosing frequency.

8. Economical.

DISADVANTAGES

1. One of the significant issue in the improvement of oral mucosal conveyance is the absence of good model for invitro screening.

2. Drug which are shaky at target site PH can't be regulated by this course.

3. Drug which bother the oral mucosa have a harsh or disagreeable taste can't be regulated by this course.

4. Fasting and drinking is precluded in this medication conveyance framework.

5. Just medications with little portion prerequisite can be directed by this course.

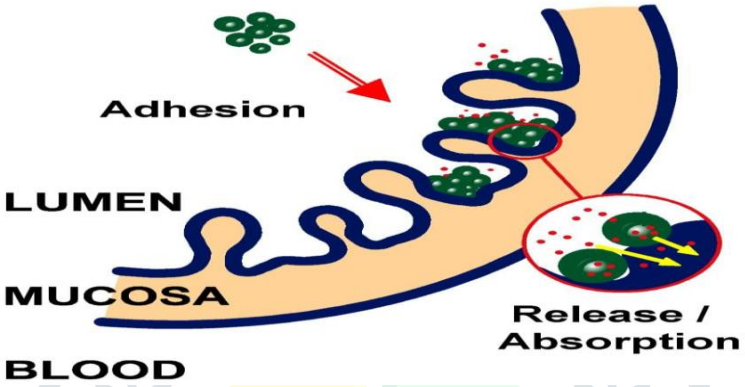
6. These sort of measurements structure can't be squashed or bitten.

7. These medication contained in gulped spit follows the oral course and advantages of buccal course is lost.

8.Costly medication conveyance framework.

BIOADHESION

Bio grip is made sense of as the trade between a mucin surface and engineered or a characteristic polymer Bio bond drug conveyance framework are conveyance framework which utilize the property of muco bond of specific polymer which became connected on hydration and can be utilized for choosing a medication to a particular district of the body for significant stretch of time.



BIOADHESION MEMBRANE

Bio bond layer are the wet surface covering dividers of different body depressions, for example, respiratory plot gastrointestinal parcel bio glue film comprise bodily fluid which is emitted by the flagon cells. bodily fluid is available either a gel layer cement to the mucosal surface or in a suspended structure or as a luminal soluble.the fundamental constituent of all bodily fluid gel are water in natural salts, lipid, glycol protein. The bodily fluid go about as an oil and defensive obstruction.

The different bonds are incorporated for bio attachment happen or the sub-atomic collaboration between the point of interaction and molecule.

HYDROGEN BOND: - Hydrogen bond is seven days connection between the two particles coming about because of an electrostatic fascination between a proton in one atom and an electronegative molecule in an another.

IONIC BONDING: - Ionic holding is sort of holding that includes the electrostatic fascination between oppositely charge particle between two molecules with strongly various electronegativities and is the essential collaboration happening in ionic mixtures.

VANDERWALL BOND: -Vander divider powers somewhat feeble electric powers that draw in nonpartisan particle to each other.

HYDROPHOBIC BOND: -The hydrophobic collaboration remembers the collapsing of the tertiary construction for protein and a particular twofold helical design of DNA. (Lalge M et al: 2014)

LIMITATION

1) Costly medication conveyance framework.

2)Some patient had unsavory inclination.

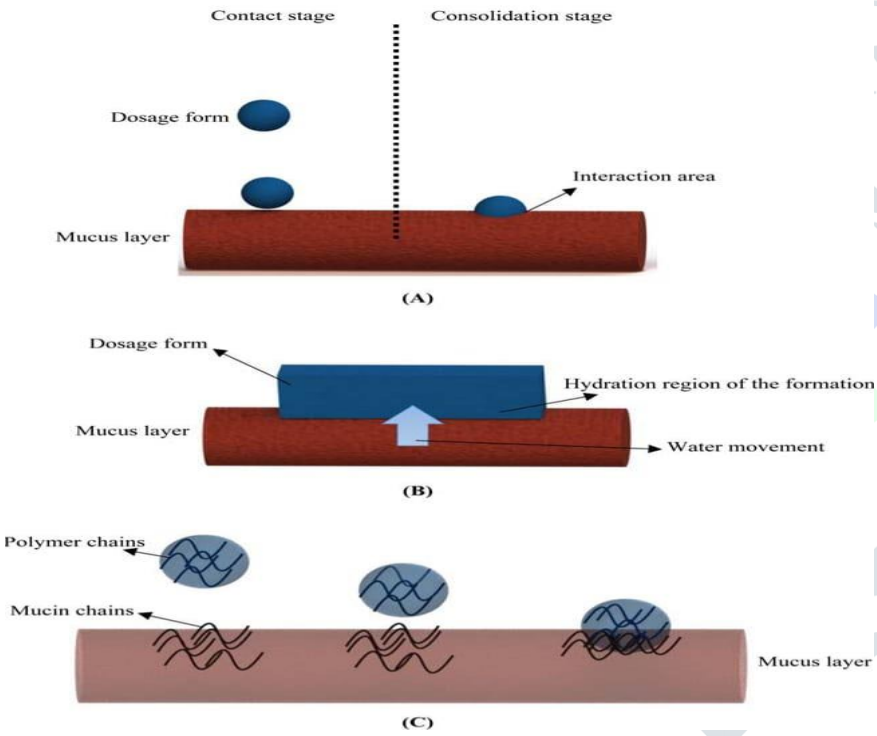
3)Medication controlled orally don't enter the circulation system following section through the buccal hole.

4)If bio glue drug conveyance frameworks are stick firmly in light of the fact that it is unfortunate to apply to much power to eliminate the development after utilize in any case bio cement layer could be harmed.

5)Patient Acceptability in wording to taste

MECHANISM OF BIO ADHESION: -

The component dependable in the development of Muco grip bonds are not completely know, but most examination has portrayed mucoadhesive bond development as a three stage process :-



Stage 1: - wetting and expanding of polymer [the contact stage].

Stage 2: - Interpenetration between the polymer chains and the mucosal layer

Step3: - Formation of compound bonds betweem the snared chains [both known as union stage]

Stage 1: - The wetting and sweeling step happen when the polymer spreads over the outer layer of the natural substrate or mucosal film to foster a close agreement with the substrate. This can be promptly accomplished.

For instance: - by setting a mucoadhesive plan, for example, a tablet or glue inside the oral hole or vagina expanding of polymers happen on the grounds that the parts inside the polymers have a fondness for water.

Stage 2: - The outer layer of mucosal films are made out of high sub-atomic weight polymers known as glycol proteins. In sync 2 of the mucoadhesive bond development, the mucoadhesive polymer chains and the mucosal polymer binds blend and catch to shape semi porous cement bonds. The strength of these bonds relies upon the level of entrance between the two polymer gatherings. To shape solid cement bonds, one polymer bunch should be solvent in the other and both polymer types should be of comparative synthetic construction.

Stage 3: - This progression includes the development of feeble synthetic connections between the ensnared polymer chains. The sort of holding shaped between the chains incorporate essential securities, for example, covalent securities and more fragile optional cooperations and hydrogen securities and Vander dividers connections both essential and auxiliary securities are taken advantage of in the production of mucoadhesive definitions in which solid bonds between polymers are framed. (Mathiowitz, E et a.)

THEORIES OF BIO ADHESION: -

The theories include

1) Electronic theory

2)Adsorption theory

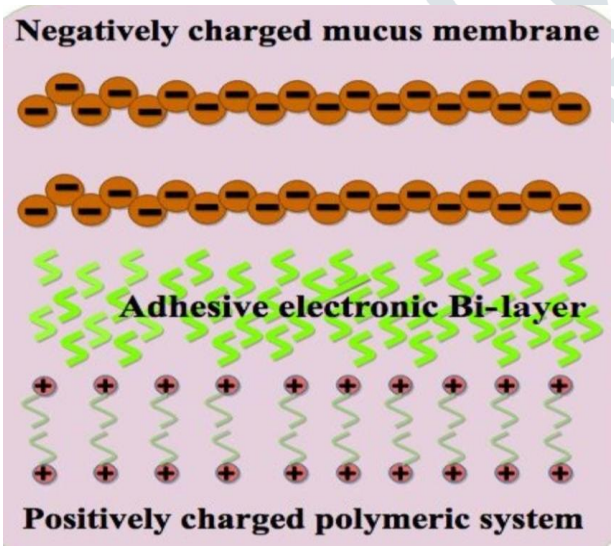
3)The cohesive theory

4)The mechanical theory

5)Fracture theory

1.ELECTRONIC THEORY

Electronic hypothesis is laid out on the conviction that both organic material and bio glue own restricting electrical charge. Consequently when both material come in contact they moves electron prompting the structure of a twofold electronic layer at the connection point where the t he alluring power inside electronic twofold layer decide the bio glue strength. as per the adsorption hypothesis the bio cement gadget stick to the natural film by optional synthetic cooperation, for example, in Vander divider hydrophobic electrostatic power and so on.



2. ADSORPTION THEORY

As per the Adsorption hypothesis the bio glue gadget joined to the bodily fluid by 2 degree synthetic connection, for example, electrolytic fascination or hydrophobic fascination, Vander divider, hydrogen bond and so on For instance: - hydrogen bond are the predominant interfacial power in polymer containing carboxyl gathering. such powers have been viewed as the main in the cement connection process on the grounds that despite the fact that they are separately feeble an extraordinary number of cooperation can bring about an extreme worldwide grip.

3.COHESIVE THEORY: -

The fundamental reason for this cycle the bio bond is basically because of the bury atomic association among like particles.

4. MECHANICAL THEORY: -

Mechanical hypothesis look at grip to be because of the dispersion of fluid glue into the microcracks and administrative present on the bio cement substrate coming about in the bio bond and can be viewed as the main course of the framework .

5.FRACTURE THEORY: -

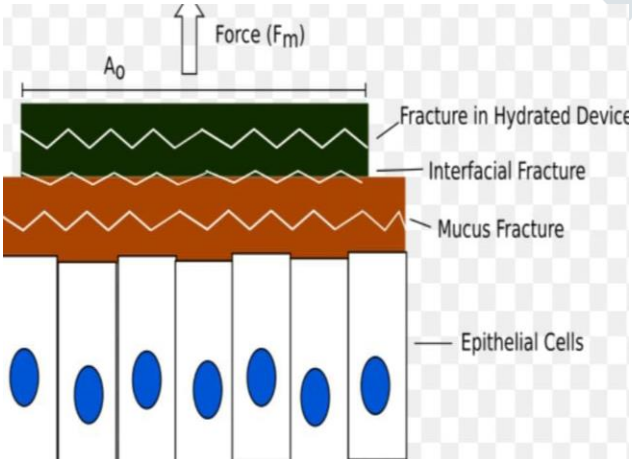
The break hypothesis looks at that is required for the division of two surface after grip. the most extreme power expected to isolate two surfaces after bond. (Patil SB et al: 2006)

Adhesion strength=$(Ee/L)^{1/2}$

E= Young's modulus of elasticity

e= fracture energy

L=critical crack length when two surfaces are separated



FACTOR AFFECTING BIOADHESION

1.Polymer related factor: - Hydrogen holding limit, Molecular weight, convergence of dynamic polymer, presence of utilitarian gathering, adaptability of polymer chains, cross connecting thickness, spatial compliance, change on polymer, Hydrophilicity, Hydration.

2. Physiological factor: - Sickness state and Mucin turn over.

3. Environment related factor: - Introductory contact time, applied strength, expanding and PH of polymer substrate interface.

4. Polymer related factors

1. Molecular weight: - Bio bond is greatest at specific sub-atomic weight. Low sub-atomic Weight: - Interpenetration is more. High sub-atomic Weight: - entrapment is more. Bio cement powers of polymers is increment up to atomic weight 10000, past which there could be no further increase.

2.Conentration of action polymer: - In high fixation: - wound particles of polymer become dissolvable poor and chain accessible for bio bond are less. In low fixation: - bio grip of polymer likewise diminishes.

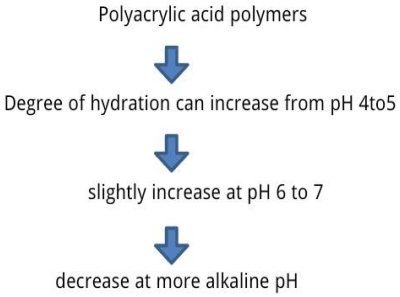
3.Presence of functional group: - Because of immobilization of thiol bunch on polymers like chitosan and polyacrylic corrosive their saturation upgrade, chemical inhibitory and mucoadhesive properties are moved along.

4. Change on Polymer: - mucosal surface is adversely charged.so decidedly charged polymer could work with the mucoadhesive interaction. Chitosan had bio grip because of electrostatic fascination between emphatically charged D-glucosamine buildup of chitosan and adversely charged sialic corrosive deposits.

5. Spatial conformation: -- Close to sub-atomic weight or chain lengths, incomplete compliance of a polymer is likewise significant. Regardless of a high sub-atomic weight 19,50,000 for dextrons. They have cement strength like that of polyethylene glycol (PEG) with a sub-atomic load of 2,00,000. The helical conformity of dextran may protect numerous adhesively dynamic gatherings, fundamentally answerable for grip, dissimilar to PEG polymers, which have a direct compliance. (Sheikh R et al., 2014)

ENVIRONMENTAL FACTORS

1).PH: - PH impacts the charge on the outer layer of both mucusand the polymers. bodily fluid will have an alternate charge thickness relying upon the PH as a result of the distinction in the separation of the practical gatherings on the sugar moiety and amino acids of the polypeptide spine.



2) Applied strength: - To put a strong bio glue framework. Applying a characterized strength is vital. The attachment strength increment with the applied strength or either the span of its application to an ideal level.

3)Initial contact Time: - The underlying contact time between the bio cement and the bodily fluid layer decide the degree of sweeling and the interpenetration of the polymer chains. The bio glue strength increment as the underlying contact time increment.

4)Swelling: - Interpenetration of chains is more straightforward when polymers chains are unrevealed surface of the collaboration When expanding is too extraordinary a reduction in the bio grip happen such peculiarities should not happen too soon, to prompt an adequate season of activity of bio cement framework. (Garg A et al., 2012)

PHYSIOLOGICAL FACTORS: -

1)Mucin Turnover: - the regular turnover of the mucin particle from the bodily fluid layer is significant for somewhere around 2 Reason: - The mucin turnover is supposed to restrict the home season of mucoadhesive measurements structure on the bodily fluid layer and the subsequent explanation is Mucin turnover result in significant measure of solvent mucin atom. these mucin particles interface with mucoadhesive dose structure before they get an opportunity to collaborate with the bodily fluid layer.

2)Disease States: - The physiological properties of the bodily fluid are known to change during illness condition like the normal virus. Gastric ulcers and so on the specific primary changes occurring in bodily fluid under these condition are not yet obviously comprehended. (Sachan NK et al.,2009)

METHODS OF PREPRATION OF BIOADHESIVE MICROSPHERES

There are different strategy to be arranged bio cement microspheres like: -

1) Single emulsion techniques

2)Double emulsion techniques

3)Polymerization

A) Normal polymerization

B) Bulk

C)suspension

D) emulsion

4.phase separation coacervation technique

5.spray drying

6.solvent extraction

7.solution-enhancement dispersion

8.wax coating hot-melt method

METHODS OF PREPARATION OF BIO ADHESIVE MICROSPHERES

1) SINGLE EMULSION TECHNIQUES: - The microparticles contain a natural polymer (those of proteins carbohydrate are make up by single emulsion Technique)

The natural polymers are liquify a terminate in aqueous medium followed by scattering in non-aqueous medium like oil. In the next step the interconnect of dispersed globules is carried out. The interconnect can be obtained either by means of heat or by using the chemical interconnecting agents. The Chemical interconnecting agents used are formaldehyde, acid chloride. Heat denaturation is not suitable for heat sensitive substance chemical Interconnecting suffers a disadvantage of excessive presence of active ingredient to chemicals of added at the time of preparation and then subjected to centrifugation washing separation. The nature of surfactant used to Stabilized emulsion phases can greatly affected the size distribution, surface morphology and bio performance of the final Multi Particulate product.

2). DOUBLE EMULSION TECHNIQUES: - The double emulsion method of microsphere preparation involves the formation of multiple emulsions of the double emulsion of type water in oil and oil in water and is suited for a water soluble drug, proteins peptides and the vaccines. This method can be used with both the natural and synthetic polymers. The aqueous protein solution is dissolved in a lipophilic organic continuous phase. The protein solution may contain a API

The continuous phase is contained of a polymer solution that eventually entrapped of the protein contained in dispersed aqueous phase. The primary emulsion is submitted to the homogenization which results in the formation of double emulsion. The emulsion is subjected to solvent removable or solvent evaporation or by solvent extraction. A number of hydrophilic drugs like luteinizing hormone releasing hormone against vaccines, conventional molecules are successfully encapsulated into the microspheres using the method of double emulsion solvent evaporation and extraction.

3. POLYMERIZATION: - polymerization normal bulk polymerization emulsion polymerization interfacial

A) Bulk polymerization: -Heated to initiate polymerization polymer obtained is Molded/ fragmented monomer /mixture of monomer and initiator.

B) Suspension polymerization: - Microspheres droplets (Vigorous agitation) Monomer or composition of monomers are heated and dispersed in water.

C) Emulsion polymerization: - Polymerization occurs, microsphere are formed and micelles solution of polymer in aqueous medium monomer with aqueous solution of NaOH with initiator and stir it.

4. PHASE SEPARATION COACERVATION TECHNIQUE: - Add a drug for phase separation induce by different means solidified separate wash and dry organic aqueous solution of polymer solution. Polymer reach globules, microspheres present on organic base.

5. SPRAY DRYING: - Polymer dissolved in organic phase (Acetone) solvent evaporation formation of small droplets microspheres atomized in a stream of hot air drug is dispersed in polymer solution under high speed homogenization separated by cyclone separator and traces of solvent is removed by vacuum drying.

6. SOLVENT EXTRACTION: - Microspheres organic phase is removed by extraction with water polymer. In organic solvent drug is dispersed in organic solvent (Water miscible organic solvent like (isopropanol) (Vasr JK et al 2003)

CHARACTERIZATION AND EVALUATION OF MICROSPHERES / DRUG LOADED BUCCAL FILMS

1. Drug content: - A patch of size 1*1 cm^2 was cut and placed in a 10ml volumetric flask. Volume was made up using 6.8pH phosphate buffer. The flask was stirred for 0.5 h, filtered and absorbance of the solution was measured against the corresponding blank solution at λ_{max} 256nm. (Kumria et al., 2013) The test was performed in film F8, F9, F10, F11.

2. Thickness: - The thickness of the films is usually measured well calibrated screw gauze. Measurement of the thickness of the film is essential to ascertain the uniformity of the film thickness as it is directly related to the accuracy of the dose in the film. An optimum thickness is necessary to provide adequate bio adhesion. The thickness of each film is measured at 6 different positions and the average was calculated (Pathak et al., 2013) The test was performed in film F8, F9, F10, F11.

3. Folding endurance: - The flexibility of buccal patches is an important physical characteristic needed for easy application on the site of administration. The flexibility of the buccal patches can be measured quantitatively in terms of folding endurance. Folding endurance of the patches was determined by repeatedly folding one patch at the same place making an angle of 180 till it breaks. The number of times the film patch could be folded at the same place without breaking gave the value of the folding endurance. The test was performed in film F8, F9, F10, F11.

4. Surface pH: - A film with too much acidic or basic pH affects the area of application and causes damage to oral mucosal membrane leading to patient discomfort. In general, the surface pH of the prepared films was measured after allowing it to swell by keeping it in contact with distilled water for a short period 0.5h, at room temperature. It is likely that chemical nature of drug and the excipients influence the pH of the prepared films (Nair et al., 2013) The test was performed in film F8, F9, F10, F11.

5. Mucoadhesive strength: - The apparatus used for bio adhesion testing was assembled in the laboratory. Mucoadhesion strength of film was measured on a modified physical balance using porcine cheek pouch such as model mucosal membrane. The porcine cheek pouch was excised, washed and tied tightly with mucosal side upward using thread over the base of inverted 50ml glass beaker. The beaker suitably weighed was lowered into 500ml beaker which was then filled with isotonic phosphate buffer pH 6.8 kept at 37C such that the buffer reaches the surface of mucosal membrane to keep it moist. This was then kept below left hand side of the balance. The buccal films were then stuck to glass stopper through its backing membrane using an adhesive. The 5gm on right hand side is removed, this cause application of 5gm of pressure on buccal films overlying buccal mucosa. The balance was kept in the same position for 3 minutes and then slowly weights were increased on the right pan till films separate from mucosal membrane. This gives bio adhesive strength in grams. The mean value of 3 trials was taken for each set of formulations. After each measurement the tissue was gently mucoadhesive and thoroughly washed with isotonic phosphate buffer and left for 5 minutes before measuring strength of next film of same formulation to get reproducible multiple results for the formulation. The test was performed in film F8, F9, F10, F11.

Force of adhesion(N) = Mucoadhesive strength * 9.81/1000

Bond Strength N/m^2 = Force of adhesion / surface area

6. Swelling Index: - Films of definite size (1*1 cm^2) were cut and weighed (w1). Film was placed on a weighed stainless steel wire mesh. The wire mesh and the film were immersed in a phosphate buffer saline pH6.8 for predetermined time periods (15,30,45,60 minutes). At these time intervals the wire mesh was withdrawn from the buffer, the films were wiped off using filter paper and weighed. Percent hydration of films was determined using the following equation: - Swelling index= w2-w1/w2*100. The test was performed in film F8, F9, F10, F11.

7. SEM Studies: - All the films selected films were fixed in place by means of a double sided silver electrical tape and gold coated in SCD005 Baltek sputter coater in a neutral environment of argon maintained at a low pressure. SEM images were obtained using a Jeol 457V at intensity of 15KV. The test was performed in film F8, F9, F10, F11.

8. FT-IR of film: - Physiochemical interaction between active pharmaceutical ingredient and polymer was investigated using Fourier Transmission Infra red spectroscopy. Selected buccal films were cut into small pieces and subjected to crushing glass pestle – mortar. The crushed powder was mixed with potassium bromide (1:100) made into a tablet and analyzed by FT-IR spectrophotometer. The test was performed in film F8, F9, F10, F11.

9. In – vitro dissolution: - The film size of 2*1cm^2 was cut and pasted onto the inner side of a beaker containing the dissolution medium (200ml) maintained at 37C . Dissolution medium (Ph 6.8 buffer) stirred at a rate of 50rpm. During the study the temperature of dissolution medium maintained at 37C. the sample were withdrawn at predetermined time intervals and analyzed using double beam UV spectrophotometer. Dissolution was carried out for film F8, F9, F10, F11.

10. Ex- vivo permeation studies: - Ex- vivo permeation studies were carried out using cheek pouch as a permeation barrier on a standard Electro lab Franz's diffusion cell to determined the rate and extent of mucosal permeation of glipizide. The water jacket was maintained at 37C. The receptor compartment was filled with 7ml of phosphate buffer pH 6.8 film of size 1*1cm^2 was cut and weighed. The film was mounted in the donor compartment. The dissolution media was sirred at 50 RPM making use of a magnetic bed. Samples were withdrawn at predetermined time interval from the receptor compartment, suitably diluted and analyzed using UV spectrophotometer at 256nm against a blank. The test was performed in film F8, F9, F10, F11. (Parmar H et al: 2010)

CONCLUSION

It can be concluded that Buccal drug delivery is most promising drug delivery in mucoadhesive system. Range of dosage forms can be incorporated in Buccal drug delivery. But Buccal films are more popular due to simplicity in preparation, drug loading and characterization. First pass metabolism prone drugs can be administered by this non-invasive drug delivery system of Buccal film. It can be concluded that Buccal drug delivery is most promising drug delivery in mucoadhesive system. Range of dosage forms can be incorporated in Buccal drug delivery. But Buccal films are more popular due to simplicity in preparation, drug loading and characterization. First pass metabolism prone drugs can be administered by this non-invasive drug delivery system of Buccal film.

REFERENCES

1. Verma V and Patel MM: Formulation and Evaluation of Mucoadhesive Microspheres Of Antihypertensive Drug. World Journal of Pharmacy and Pharmaceutical Sciences, 2017; 6: 929-950.

2. Kumar S and Nanda A: Formulation Optimization and In-Vitro Evaluation of Gastroretentive Mucoadhesive Microspheres of Furosemide, Research Article. International Journal of Pharmacy and Pharmaceutical Sciences, 2016; 8: 392-398.

3. Parmar H et al: Different method of formulation and evaluation of mucoadhesive microsphere. International Journal of Applied Biology and Pharmaceutical Technology, 2010; 1(3): 1157-1167.

4. Kannan K et al: Formulation and evaluation of sustained release Microspheres of Acetazolamide by solvent evaporation technique. J. Pharm. Sci. & Res., 2009; 1: 36-39.

5. Longer MA and Robinson JR: Remington Pharmaceutical Science. 18th ed. Eastern Pennsylvania: Mack Publishing Company, 1990; 1676-1686.

6. Ahuja A et al: Mucoadhesive drug delivery system. Drug. Dev. Ind. Pharm, 1997; 23(5): 489-515.

7. Vasr JK et al: Bioadhesive Microspheres as a controlled drug delivery system. Int. J.Pharm., 2003; 255: 13-32.

8. Nagpal et al: Evalution parameters of mucoadhesive drug delivery system. International journal of pharmacy & life science, 2016; 5080-5088.

9. Sahoo P.K et al: Formulation and evalution of mucoadhesive microspheres of repaglinide. The pharma innovation-journal, 2014; 3(3): 2014.

10. Tangri P et al : Mucoadhesive drug delivery: mechanism and method of evalution, international journal of pharma and bio sciences, 2011; 2(1): 0975-6299.

11) S. Kataria, et al: Microsphere: A Review. Int. J. Res. Pharm. Chem., 2011; 1(4): 1185-1198.

12. Punitha S and Girish Y: Polymers in mucoadhesive buccal drug delivery system, International Journal of Research and Pharmaceutical Sciences, 2010; 1(2): 170-186.

13. Sachan NK and Bhattacharya A: Basic and Therapeutic Potential of Oral Mucoadhesive Microparticulate Drug Delivery Systems. International Journal of Pharmaceutical and Clinical Research, 2009; 1: 10-14.

14. Sheikh R et al: Mucoadhesive drug delivery system. Journal of pharmacy and bioallied sciences, 2011; 3(1): 89-100.

15. Robinson J.R: Rational of bioadhesion/mucoadhesion. In bioadhesion possibilities and future trends. Gurny R., Junginger HE, Eds, wissenchaftliche verlag cressllschaft, Stuttgar, 1990; 13-28.

16. Ansari V et al: mucoadhesive microspheres for controlled delivery of drugs. Asian journal of pharmaceutical and clinical research, 2015; 8(4): 4-5.

17. Garg A and Upadhyay P: Mucoadhesive microspheres – A short review. Asian J Pharm Clin Res., 2012; 5(3): 24-7.

18. Lalge M et al: mucoadhesive drug delivery system: a review. Critical review in pharmaceutical sciences, 2014; 3(3): 18-19.

19. Garg A and upadhyay P: Mucoadhesive microspheres: a short review.Asian Journal of Pharmaceutical and clinical research, 2012; 5(3): 24-25.

20. Jain N. K: Controlled and Novel Drug Delivery, Mucoadhesive drug delivery. First edition, 1997; 353. 21. P.L. Soo et al: Incorporation and release of hydrophobic probes in biocompatible polycaprolactone-block-poly (ethylene oxide) micelles, implications for drug delivery. Langmuir, 2002; 18.

22. Muthukumaran M et al: Review On Polymers Used In Mucoadhesive Drug Delivery System. Int. J. Pharm. Ind. Res., 2011; 1(2): 122-127.

23. Mathiowitz, E et al : Bioadhesive drug delivery systems: fundamentals, novel approaches, and development, Drugs and the Pharmaceutical Sciences. New York: Marcel Dekker, 1999: 696.

24. Hagerstrom H:Polymer gels as pharmaceutical dosage forms:Rheological Performance and Physicochemical Interactions at the gel-mucus Interface for formulations intended for mucosal drug delivery. Uppsala, 2003: 76 f. [Dissertation for the degree of Doctor of Philosophy in Pharmaceutics. Uppsala University].

25. Peppas N. A. and Salin, J. J: Hydrogels as mucoadhesive and bioadhesive materials: a review. Biomaterials, 1996; 17(11): 1553-1561.

26. Madhav S. et al: Gastroretentivemucoadhesive microsphere: A review. Indo American Journal of Pharmaceutical Research, 2011; 1(6): 483-505.

27. Patil SB et al: Mucoadhesive polymers: Means of improving drug delivery. Pharma Times., 2006; 38: 25-28

28. https://www.slideshare.net/shreeraj9183/bioadhesive-drug-delivery-system