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# A Review updated on Mucoadhesive

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## *ABSTRACTS*

*The idea of developing Mucoadhesive polymers for drug delivery has been introduced into the pharmaceutical product development for more than 40 years ago and nowadays it has been subjected as a promising strategy to improve the residence time and the specific localization of drug delivery systems on various mucus membranes. Mucoadhesive drug delivery systems based on adhesion to biological surfaces that are covered by mucus. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin are held together for extended periods of time by the help of interfacial forces mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. The Mucoadhesive polymers can be categorized into two broad categories, materials which undergo matrix formation or hydrogel formation by either a water swell able material or a water soluble material. Mucoadhesive drug delivery systems is one of the most important novel drug delivery systems with it various advantages and it has a lot of potential in formulating dosage forms for various chronic diseases. The Mucoadhesive interaction is explained in relation to the structural characteristics of mucosal tissues and the theories and properties of the polymers. The success and degree of mucoadhesion bonding is influenced by various polymer-based properties. In this abstracts for buccal route of administration of Mucoadhesive films are retentive dosage forms and release drug directly into a biological substrate. This review will consider the literature that describes the manufacture and characterization of Mucoadhesive buccal film.*

***Key Words:*** *Mucoadhesive, Drug Delivery System, Labetalol hydrochloride.*

## INTRODUCTION

For the last two decades the research on mucoadhesion has become of interest because of its usefulness in improvising the localized drug delivery, by retaining a formulation at the site of action (e.g. within the gastrointestinal tract) or systemic delivery, by retaining a formulation in intimate contact with the absorption site (e.g. the nasal cavity). Moreover the mucoadhesive materials could also be used as therapeutic agents by coating and protecting damaged tissues (gastric ulcers or lesions of the oral mucosa) or by acting as lubricating agents (in the oral cavity, eye and vagina) [1].

**Mechanisms of mucoadhesion:**

For the occurrence of mucoadhesion, the molecules must involve in bond formation across the interface. The mechanism of bond formation is varied and can be divided into following ways. Ionic bonds-In this the two oppositely charged ions comes together through electrostatic interactions and forms a strong bond (e.g. in a salt crystal). Covalent bonds-this bond forms by sharing the electrons, in pairs, between the bonded atoms in order to fill the orbital's in both.

**Factors affecting mucoadhesion:**

The process of mucoadhesion is complex and many factors influence the mucoadhesion. These most important factors that influence the mucoadhesion process are:

- Optimum Molecular weight
- Flexibility of polymer chains
- Ionizable functional groups in the polymer
- pH of surrounding medium
- Presence of metal ions

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**Theories of adhesion:**

There are six general theories of adhesion, which have been adapted for the investigation of mucoadhesion.

***1) The electronic theory*** indicates the transfer of electrons between the materials and adhering surface because of differences in the electronic structure.

***2) The wetting theory*** is defined by surface and interfacial energies between the adhesive material and mucus membrane and applied mainly to liquid systems.

***3) The adsorption theory*** explains the adhesion on the basis of hydrogen bonding and van der –Waal's forces.

***4) The diffusion theory*** laid down on the basis of the capability of polymeric chains to diffuse across the adhesive interface.

***5) The mechanical theory*** assumes that adhesion arises from an interlocking of a liquid adhesive setting into irregularities on a rough surface.

***6) The fracture theory*** differs a little from the other defined mechanisms in that it relates the adhesive strength to the forces required for the detachment of the two involved surfaces after Adhesion [3, 4].

**Mucoadhesive Microspheres as carriers in Drug Delivery:**

Microspheres are defined as spherical particles having size less than 200µm and made up of polymer matrix in which

therapeutic substance is dispersed throughout the matrix at the molecular or macroscopic level. The rationale of developing mucoadhesive microsphere drug delivery system lies behind the fact that the formulation will be 'held' on a biological surface for localized drug delivery [5].

**Mucoadhesion and microspheres:**

Mucoadhesion or bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are held together for a prolonged time period by means of interfacial forces. In biological systems, bioadhesion can be classified into 3 types.

**Type 1:** Adhesion between two biological phases, for example, platelet aggregation and wound healing.
**Type 2:** Adhesion of a biological phase to an artificial substrate, for example tissue, cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts.
**Type 3:** Adhesion of an artificial substance to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues [6].

Polymers used in the formulation of mucoadhesive microspheres:

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
2. Polymers that adhere through nonspecific, noncovalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
3. Polymers that bind to specific receptor site.

**Methods of preparation of mucoadhesive Microspheres:**

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by micro encapsulation technique. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross linking, drug of cross linking, evaporation time, co-precipitation etc. The various methods of preparations are:-

**Phase separation coacervation technique:**

In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Polylactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. Emulsion cross linking method. In this method drug is dissolved in aqueous gelatin solution which is previously heated for 1 hr at 40 0C.The solution is added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 0C, results in w/o emulsion then further stirring is done for 10 min at 15 0C Thus the produced microspheres are washed respectively three times with acetone and isopropyl alcohol which then airdried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3hrs for cross linking and then treated with 100mL of 10mm glyciene solution containing 0.1%w/v of tween 80 at 37 0C for 10 min to block unreacted glutaraldehyde. Examples for this technique is Gelatin A microspheres [7].

**Solvent Evaporation:**

The processes are carried out in a liquid manufacturing vehicle. Ionic gelation Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique.

**Spray Drying:**

In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, Acetone, etc [8].

**Multiple emulsion polymerization technique:**

***Characterization/ evaluation of mucoadhesive microspheres:***

Interaction study by TLC/ FTIR and IR spectroscopic studies:-The IR spectra of the free drug and the microspheres are recorded. The identical peaks corresponding to the functional groups features confirm that neither the polymer nor the method of preparation has affected the drug stability. Thin layer chromatographic studies:-The drug stability in the prepared microspheres can also be tested by the TLC method. The Rf values of the prepared microspheres can be compared with the Rf value of the pure drug. The values indicate the drug stability. UV-FTTR (Fourier transform infra red):- The drug polymer interaction and also degradation of drug while processing for microencapsulation can be determined by FTIR. In this method the pellets of drug and potassium bromide are prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra are scanned in the wave number range of 4000-600 cm-1. FTIR study is carried on pure drug, physical mixture, formulations and empty microspheres [8]. Particle size distribution of prepared microspheres. The size of the prepared microspheres can be measured by the optical microscopy method.

***Formulation and Evaluation of Mucoadhesive Microspheres of Ciprofloxacin:***

The most desirable and convenient method of drug administration is the oral route due to the ease of administration and patient compliance. One limitation for oral delivery is poor bioavailability and for the drug candidates who show absorption window in the proximal gut and is the major obstacle to the development of controlled release formulation. A number of approaches have been developed to increase the residence time of dug formulation. One of the approaches the formulation of Gastro retentive dosage forms in the form of Mucoadhesive microspheres. Microsphere carrier systems, made from natural polymers are attracting considerable attentions for several years, for sustained drug delivery. Today, those dosage forms which can control the release rates and which are target specific have a great impact in development of novel drug delivery systems. Microspheres are part of such novel delivery systems [9-11].

**Different methods of formulation and evaluation of mucoadhesive microsphere:**

***Preparation of Microspheres by Thermal cross-linking:***

Citric acid, as a cross-linking agent was added to 30 mL of an aqueous acetic acid solution of chitosan (2.5% wt/vol) maintaining a constant molar ratio between chitosan and citric acid (6.90 × 10−3 molchitosan: 1 mol citric acid). The chitosan cross-linker solution was cooled to 0°C and then added to 25mL of corn oil previously maintained at 0°C, with stirring for 2 minutes. This emulsion was then added to175 mL of corn oil maintained at 120°C, and cross-linking was performed in a glass beaker under vigorous stirring (1000 rpm) for 40 minutes. The microspheres obtained were filtered and then washed with diethyl ether, dried, and sieved [11].

***Preparation of Microspheres by Glutaraldehyde cross linking:***

A 2.5% (wt/vol) chitosan solution in aqueous acetic acid was prepared. This dispersed phase was added to continuous phase (125 mL) consisting of light liquid paraffin and heavy liquid paraffin in the ratio of 1:1 containing 0.5% (wt/vol) Span 85 to form a water in oil (w/o) emulsion. Stirring was continued at 2000 rpm using a 3-blade propeller stirrer (Remi Equipments, Mumbai, India). A drop-by-drop solution of a measured quantity (2.5 mL each) of aqueous glutaraldehyde (25% vol/vol) was added at 15, 30, 45, and 60 minutes. Stirring was continued for 2.5 hours and separated by filtration under vacuum and washed, first with petroleum ether (60°C-80°C) and then with distilled water to remove the adhered liquid paraffin and glutaraldehyde, respectively. The microspheres were then finally dried in a vacuum desiccators [12].

***Preparation of microspheres by Tripolyphosphate:***

Chitosan solution of 2.5% wt/vol concentration was prepared. Microspheres were formed by dropping the bubble-free dispersion of chitosan through a disposable syringe (10 mL) onto a gently agitated (magnetic stirrer) 5% or 10% wt/vol TPP solution. Chitosan microspheres were separated after 2 hours by filtration and rinsed with distilled water, then they were air dried [13].

***Preparation of Microspheres by Emulsification and Ionotropic gelation by NaOH:***

Dispersed phase consisting of 40 mL of 2% vol/vol aqueous acetic acid containing 2.5% wt/vol chitosan was added to the continuous phase consisting of hexane (250 mL) and Span 85

(0.5% wt/vol) to form a w/o emulsion. After 20 minutes of mechanical stirring, 15 mL of 1N sodium hydroxide solution was added at the rate of 5 mL per min at 15-minute intervals. Stirring speed of 2200 rpm was continued for 2.5 hours. The microspheres were separated by filtration and subsequently washed with petroleum ether, followed by distilled water and then air dried [13,14].

***Preparation of Ethyl cellulose Microspheres:***

A solution of Ethyl cellulose in acetone was added to liquid paraffin containing emulgent (Span 85) while stirring at a speed of 1500 rpm. The emulsion was stirred for 5 to 6 hours at 25°C to 30°C. Subsequently, a suit able amount of petroleum ether was added to the dispersion, filtered, and dried at ambient temperature. The resultant microspheres were washed with water followed by petroleum ether to remove traces of liquid paraffin. The microspheres were desiccated under vacuum [14].

**Spray Drying:**

In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, Acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100µm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions [15].

**Solvent Evaporation:**

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase.

**Wet Inversion Technique:**

Chitosan solution in acetic acid was dropped in to an aqueous solution of counter ion sodium Tripolyphosphate through a nozzle. Microspheres formed were allowed to stand for 1 hr and cross linked with 5% ethylene glycol diglysidyl ether. Microspheres were then washed and freeze dried. Changing the pH of the coagulation medium could modify the pore structure of CS microspheres.

**Complex Coacervation:**

CS micro particles can also prepare by complex co acervation, Sodium alginate, sodium CMC and sodium polyacrylic acid can be used for complex coacervation with CS to form microspheres. These micro particles are formed by interionic interaction between oppositely charged polymers solutions and KCl & $CaCl_2$ solutions. The obtained capsules were hardened in the counter ion solution before washing and drying.

**Hot Melt Microencapsulation:**

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 µm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5°C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, *e.g.* polyanhydrides. Microspheres with diameter of 1-1000 µm can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only disadvantage of this method is moderate temperature to which the drug is exposed.

**Formulation and Evaluation of Mucoadhesive Bi-layer Buccal Tablets of Labetalol Hydrochloride Using Natural Polymers:**

Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery, but coupling of mucoadhesive properties to tablet has additional advantages, e.g. 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 etc. Mucoadhesive tablets can be tailored to adhere to any mucosal tissue including those found in stomach, thus offering the possibilities of localized as well as systemic controlled release of drugs [16].

**Preparation of mucoadhesive buccal tablets of Labetalol hydrochloride:**

Unidirectional, bi-layered mucoadhesive tablets of Labetalol hydrochloride were prepared by direct compression technique using a flat-faced 13 mm hydraulic press involving two consecutive steps. Initially, a backing layer was made using ethyl cellulose, onto which the drug containing layer were placed and recompressed to get a bilayered tablet. In the formulation of bilayered tablets, labetalol was the drug, sodium alginate and guar gum were used as mucoadhesive polymers, magnesium stearate was used as a lubricant and mannitol was used as diluent. The backing layer was prepared using ethyl cellulose to make the release unidirectional from the tablet. Poly ethylene glycol 6000 was used as permeation enhancer in the formulation [17].

**Evaluation of bi-layered tablets of Labetalol hydrochloride:**

***Weight variation:***

Twenty tablets were randomly selected from each batch weighed individually. The average weight and standard deviation was calculated.

***Thickness:***

3 tablets from each batch of formulation were collected and the thicknesses of the tablets were measured with the help of vernier caliper. The average thickness was calculated.

***Hardness:***

Hardness or tablet crushing strength (fc) is the force required to break a tablet in a diametric Compression was measured using Monsanto tablet hardness tester. The hardness of five tablets in each batch was measured and the average hardness was calculated.

***Friability (F):***

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution.

***Drug content:***

For determination of drug content at least five tablets from each formulation were weighed individually, crushed and diluted to 100 ml with sufficient amount of phosphate buffer of pH 6.8 in a volumetric flask. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 302 nm against blank. Drug content was calculated using standard curve [18].

***In-vitro swelling studies:***

Eight buccal tablets were weighed (W1) and placed separately in Petri dishes with 5ml of phosphate buffer of pH 6.8. At the time interval of 1,2,3,4,5,6,7 and 8hrs, tablets were removed from the petri dish and excess water was removed carefully using filter paper. The swollen tablet were then reweighed (W2) and the percentage hydration was calculated using the following formula.

***Surface pH:***

A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping them in contact with 2 ml of phosphate buffer pH 6.8 in a test tube for 2 hrs. The pH was then noted by bringing the electrode in contact with the surface of the formulation pH and allowing it to equilibrate for 1 min.

***In-vitro mucoadhesion studies:***

Mucoadhesive strength of the buccal tablets was measured on the "Modified Physical Balance method". Max was found to be 302nm. Linearity was observed between the range 10-100µg/ml. The saturation solubility of Labetalol was determined in different solvents. The spectra obtained from IR studies at wavelength 4000cm-1 to 400cm-1. FT-IR reveals that there was no interaction between drug and selected polymers. In the formulations drug has maintained its identity and has not shown any interaction with the polymers. Plain Labetalol hydrochloride

exhibited angle of repose value of 39.71 ± 0.69o indicating poor flow property. It was further supported by high Carr's index (28.89 ± 0.111) and Hausner's ratio (1.40 ± 0.0022). Property of precompression mixture. It exhibited the angle of repose value of 21.32 – 29.100. It was further supported by good Carr's index value of 15.47 - 19.85% and Hausner's ratio of 1.19 - 1.24 for all precompressional mixtures. Hence powder mixture was found suitable for direct compression method [18].

**Development and evaluation of nasal mucoadhesive nanoparticles of an analgesic drug:**

Oral routes are the most preferable route for administration of active ingredients. However certain limitation barred the oral administration especially in case of hydrophilic drugs due to low bioavailability, insufficient intestinal transit time and reliance on paracellular transport (due to tight junction that limits the passage of hydrophilic drugs) [19, 20]. Nasal route had been considerably focused by current researchers as a alternative to target drug molecules directly to brain with help of olfactory neurons providing a loop to enter drug molecules to enter the central nervous system [21]. The only factor that limits the nasal delivery is nasal mucociliary clearance. Drug residence time is drastically affected by this factor by not allowing the drug molecule to get effectively absorbed which completely eradicates the sustainability of drug molecules in nasal drug administration. However this limitation can be overcome by using bioadhesive polymers which will increase the nasal residence time which in turns allows drug to get effectively absorbed by providing a longer contact of drug with nasal mucosa leading to enhanced drug absorption.

***Preparation of TRM loaded Chitosan nanoparticles:***

TRM loaded NPs were prepared using chitosan and TRM in 5 different drugs to polymer ratios. Chitosan solution in aqueous acetic acid (1% w/v) was prepared by continuous magnetic stirring for 24 hrs in order to ensure complete solubilization of chitosan in the aqueous solution. To the prepared chitosan solution, TRM was added under stirring to get the final spray drying solution. 3% Lutrol F68 was added to the above solution as stabilizer. The above solution was kept for homogenization at 25000 rpm for 2 hrs (Polytron PT 1600E). Final resulting solution was spray dried by Buchi 290 spray dryer operating in the closed mode, using the Buchi 295 inert loop and nitrogen as the drying gas with other standard operating conditions (inlet temperature: 110-115 C: Outlet temperature: 80-90 C; Aspirator rate: 45-55% & Feed inlet rate: 0.5 ml/min). Each formulation was carried out in triplicate, n=3.

***Measurement of particle size and zeta potential of prepared nanoparticles:***

Size and zeta potential of TRM loaded NPs were measured by photon correlation spectroscopy (PCS) using Malvern Zetasizer. The particle size analysis was performed at a scattering angle of 90°C at room temperature. The concentration of the particles was adjusted to an appropriate value by pure water filtered through a 0.22 µm membrane. The diameter was averaged from three parallel measurements and expressed as mean±standard deviation.

***Fourier Transform Infrared Radiation Measurements (FT-IR):***

FT-IR analysis was carried out for pure drug and for formuation using KBr pellet method on FTIR spectrophotometer type Shimadzu model 8033, USA in order to ascertain compatibility between drug and polymer used.

***Differential scanning Calorimetry (DSC):***

All dynamic DSC studies were carried out on DuPont thermal analyzer with 2010 DSC module. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10ºC/min heating rate of 10ºC/min.

***Scanning electron microscopic (SEM) study:***

SEM photographs were taken with a scanning electron microscope Model Joel- LV-5600, USA, at the required magnification at room temperature. The photographs were observed to visualize the surface morphology of the TRM loaded NPs.

***X-Ray Powder Diffraction:***

X-ray powder diffraction patterns were recorded at room temperature with a D8 Advance wide-angle diffractometerin the range of 5–40° of 2$\theta$. Tablets for IR analysis were made with KBr and analyzed with an IR Perkin-Elmer model 1420, in the range from 4000 to 600 cm−1.

***Swelling Property:***

Swelling studies were done as procedure adopted by Juan et al & Jain et al with slight modification [22, 23]. Accurately weighed NPs were allowed to swell to their equilibrium in nasal simulated fluid. Weighed amount of NPs was immersed in phosphate buffer (pH 6.6, for 5 min).

**In-vitro mucoadhesion studies:**

Mucoadhesion studies were done in accordance with procedure followed by Sofia P *et al.* [19] with slight modifications. Drug loaded CS NPs were immersed in a 50 mL glass bicker at 37 °C containing a phosphate buffer solution (pH 6.8) for 5 min in such a way that the solution just covered the nanoparticles. Fresh nasal mucosa was obtained from local abattoir which was cut opened and was placed on nanoparticles surface so as to cover all the nanoparticles. Nasal mucosa was removed after 5 min of interval.

**Rheological, mucoadhesive and release properties of Carbopol gels in hydrophilic cosolvents:**

Carbopols, which are very high molecular weight polymers of acrylic acid, have been used mainly in liquid or semi-solid pharmaceutical formulations, such as gels, suspensions and emulsions, as a thickening and viscosity agent, in order to modify the flow characteristics .Recently, they are also used for their mucoadhesive properties and a relevant amount of work has been done on the bioadhesive potential of Carbopol polymers. Formulations include ophthalmic, rectal, buccal, nasal, intestinal, vaginal and topical preparations. In this paper simple dispersions of polymers in different pure cosolvents were compared with the same systems prepared by heating at 70 ◦C, so in order to verify changes in the polymer salvation after heating, and an improvement of the rheological properties giving rise to a gel structure. Samples were also compared with similar systems in water in order to verify the possibility of their use in topical or oral dosage forms instead of the water system. There were no cases in which PEG 400, glycerine and water were mixed in each other.

***Gel preparation:***

Two methods of gel preparation were used with both Carbopol C971 and C974, in order to verify if this could influence the rheological characteristics of the gel. According to the first preparation method, a certain amount of Carbopol was dispersed in water, PEG 400 and glycerine, respectively. The dispersion was homogenised using an Ultraturrax T25 for 5 min at 12500 rpm, degassed under vacuum and then left at rest for one day before being analyzed.

Since preliminary rheological studies of water or PEG 400 Carbopol gels revealed an increased consistency starting from 60 ◦C, in the second preparation method, after a complete dispersion with UltraturraxT25 at the same conditions previously described, the sample was then heated at 70 ◦C and the system was stirred mechanically until a homogeneous and transparent dispersion was formed (30 min). Carbopol concentration in all systems ranged between 0.5 and 4% (w/v). For the release studies, the 0.5% (w/v) of Paracetamol was dissolved in the three different media at room temperature before the addition of the polymer. The final gels contained the 0.5% (w/v) of Paracetamol and the 4% (w/v) of Carbopol. Paracetamol was chosen as the model drug due to its intermediate water solubility (1:70) between an insoluble and a very soluble drug (LVR) of the sample and therefore the consequent choice of the stress value to use in the other oscillation tests.

***Rheological characterization:***

Rheological analyses were performed in triplicate using a stress control rheometer (Stress-Tech, Rheological) equipped with a cone-plate geometry (4/40) operating in the oscillation mode. The gap was 150_m. The following tests then were carried out:

***Drug release studies:***

In vitro drug release tests were carried out on the 4% (w/v) Carbopol gels prepared according to the second method and the 0.5% (w/v) paracetamol was dissolved in the medium during the preparation step. The method used was the USP XXIV apparatus 2 with the use of the Enhancer Cell TM 4 cm 2 sections [24-26]. The height of the Enhancer Cells TM was set to an inner volume of 4ml and gel samples were then placed into them. Therefore, only the upper surface of the gel disk was in contact with the dissolution medium. The dissolution media used were distilled water, phosphate buffer pH 6.8 and HCl 0.1N. Since Carbopolviscosity is sensitive to pH changes, then these three different media were chosen in order to verify if the drug release from the gels was influenced by the external conditions surrounding them. Tests were performed in triplicate for 480 min using an Erweka DT6.

**Development of Satranidazole Mucoadhesive Gel for the Treatment of Periodontitis:**

Periodontitis (pyorrhea) is a plaque-induced chronic inflammatory condition leading to the loss of tooth-supporting structures, namely periodontal ligament and alveolar bone. The current microbiological treatment of Periodontitis is through either the mechanical cleaning of the teeth with systemic antibiotics or a localized delivery system incorporating an antibiotic.

***Preparation of SZ mucoadhesive gel with PL407:***

PL407 possesses a reverse thermal gelling property, and therefore, the gel containing PL407 was prepared by a modification of cold method of was dissolved in 50 ml and SZ in about 25 ml of McIlvaine buffer pH 6.6 separately. The solution of SZ was added to the solution of CB 934P slowly with continuous stirring at 100 rpm. It was then cooled by placing it in an ice bath. Weighed amount of PL407 was then added slowly with continuous stirring (100 rpm) at 5°C temperature. The volume was made up to 100 ml with McIlvaine buffer pH 6.6. The prepared gel was kept for 24 h at room temperature for complete polymer dissolution. The final concentration of SZ in the gel was 0.25% w/v. Different formulations of SZ mucoadhesive gels are given in Table I. The prepared SZ formulations were abbreviated as SC20 (2% SCMC), SC30 (3% SCMC), HPMC30 (3% HPMC), HPMC50 (5% HPMC), HPC50 (5% HPC), HPC150 (15% HPC), HEC20 (2% HEC), HEC30 (3% HEC), and PL300 (30% PL) [27].

**REFERENCES:**


1. Marriott C, Gregory NP. *Mucus physiology and pathology*, in: V. Lanaerts, R. Gurny (Eds.), Bioadhesive Drug Delivery Systems, CRC Press, Florida, **1990**; 1-24.
2. Peppas NA, Sahlin JJ. Hydrogels as mucoadhesive and bioadhesive materials: a review. *Biomaterials,* **1996**; 17: 1553-1561.
3. Ahuja RP, Khar RP, Ali J. Mucoadhesive drug delivery systems, *Drug Dev. Ind. Pharm.,* **1997**; 23: 489-515.
4. Mathiowitz E, Chickering DE. *Definitions, mechanisms and theories of bioadhesion*, in: E. Mathiowitz, D.E. Chickering, C.-M. Lehr (Eds.), Bioadhesive Drug Delivery Systems: Fundamentals, Novel Approaches and Development, Marcel Decker, New York, **1999**; 1-10.
5. Alexander A, Tripathi DK, Verma T, Patel S. Mechanism responsible for mucoadhesion of mucoadhesive drug delivery system. *Int. J. Appl. Biol. Pharm. Tech.,* **2011**; 2(1): 434-445.
6. Shaikh R, Singh TRR, Garland MJ, Donnelly RF. Mucoadhesive Drug Delivery Systems. *J. Pharm. Bioallied. Sci.,* **2011**; 3(1): 89-100.
7. Meena KP, Dangi JS, Samal PK, Namedo KP. Recent advances in microsphere manufacturing technology. *Int. J. Pharm. Tech.,* **2011**; 3(1): 854-855.
8. Moy AC, Mathew ST, Mathapan R, Prasanth VV. Microsphere-An Overview. *Int. J. Pharm. Biomed. Sci.,* **2011**; 2(2): 332-338.
9. Woo BH, Jiang G, De Luca PP. Preparation and characterization of the composite PLGA and poly (acryloyl hydroxymethyl starch) microsphere system for protein delivery. *Pharm. Res.,* **2001**; 18: 1600-1606.
10. Capan Y, Jiang G, Giovagnoli S, De Luca PP. Prepararion and characterization of poly (D,L-lactide-co-glyclide) microspheres for controlled release of human growth hormone. *AAPS Pharm. Sci. Tech*., **2003**; 4: E28.
11. Gogel MC, Amin AF. Formulation optimization of controlled release diclofenac sodium microspheres using factorial design. *J. Control. Relase.,* **1998**; 51: 115-122.
12. Orienti, K. Aiedeh, E. Gianasi, C. Ponti, V. Zecchi. Chitosan indomethacin conjugates: effect of different substituents on the polysaccharide molecule on drug release. *Arch Pharm. (Weinheim),* **1996**; 329: 245-250.
13. B.C. Thanoo, M.C. Sunny, A. Jayakrishnan. Cross-linked chitosan microspheres: preparation and evaluation as a matrix for the controlled release of pharmaceuticals. *J. Pharm. Pharmacol*., **1992**; 44: 283-286.
14. Bodmeier R, Paeratakul O. Spherical agglomerates of water-insoluble drugs. *J. Pharm. Sci*., **1989**; 78: 964-967.
15. Singla AK, Dhawan S. Nifedipine loaded chitosan microspheres prepared by emulsification phaseseparation. *Biotech. Histochem.,* **2003**; 78: 243-254.
16. Rao VR, Devi KP. Swelling controlled release systems: recent developments and application. *Int. J. Pharm.,* **1988**; 48: 1-16.
17. Leitner VM, Guggi D, Bernkop SA. 5th *Central Eur. Symp. Pharm. Tech*, Ljubljana; *Slovenia* **2003**.
18. Andrews GP, Laverty TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. *Eur. J. Pharm. Biopharm.,* **2009**; 71: 505-518.
19. Chein YW. Novel drug delivery systems. 2nd ed. Vol. 50, Marcel Dekker, Inc.; New York, **1992**; 8-9, 139-141, 197-228.
20. Riya D, Asraf KA, Amal K. Bandyopadhyay. Mucoadhesion and Mucoadhesive tablets-a review. *Int. J. Pharm. Sci. Tech.,* **2011**; 6(1): 64-115.
21. Borchard G, Lueben HL, Boer AG, Verhoef JC, Lehr CM, Junginger HE. The potential of mucoadhesive polymers in enhancing intestinal peptide drug absorption. III. Effects of chitosan-glutamate and carbomer on epithelial tight junctions in vitro. *J. Control Rel.,* **1996**; 39: 131–138.
22. Kotze AF, Luessen HL, De Boer AG, Verhoef JC, Junginger HE. Comparison of the effect of different chitosan salts and N-trimethyl chitosan chloride on the permeability of intestinal epithelial cells (Caco-2). *J. Control Rel.,* **1998**; 51(1): 35-46.
23. Wang X, Chi N, Tang X. Preparation of estradiol chitosan nanoparticles for improving nasal absorption and brain targeting. *Eur. J. Pharm. Biopharm.,* **2008**; 70(3): 735-40.
24. Juan JT, Alfredo GA, Santiago TS, Luis G. Spray-dried powders as nasal absorption enhancers of cyanocobalamin. *Bio Pharma. Bull.,* **2001**; 24: 1411-1416.
25. Jain SK, Chourasia MK, Jain AK, Jain RK, Shrivastava AK. Development and characterization of mucoadhesive microspheres bearing salbutamol for nasal delivery. *Drug Deliv.,* **2004**; 11(2): 113-22.
26. Rege, PR, Vilivalam VD, Collins CC. Development in release testing of topical dosage forms: use of the Enhancer Cell TM with automated sampling. *J. Pharm. Biomed. Anal.,* **1998**; 17: 1225–1233.
27. Varshosaz J, Tavakoli N, Saidan S. Development and physical characterization of a periodontal bioadhesive gel of metronidazole. *Drug Delivery,* **2002**; 9: 127-133.


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