WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 4, 480-495. Review Article ISSN 2277– 7105

A REVIEW ON FORMULATION AND EVALUATION OF COLONAL PATCHES

***Botla Sirisha, Rayidi Priyanka and Dr. K. Abbulu**

Department of Pharmaceutics, CMR College of Pharmacy, Kandlakoya, Medchal Road, Hyderabad, Telangana, India.

Article Received on
07 Feb. 2020,

Revised on 28 Feb. 2020,
Accepted on 19 March 2020,

DOI: 10.20959/wjpr20204-17102

***Corresponding Author**
Botla Sirisha
Department of Pharmaceutics, CMR College of Pharmacy, Kandlakoya, Medchal Road, Hyderabad, Telangana, India.

ABSTRACT

The main aim of this study was to Formulate and evaluate colonal patches based colon targeted systems of Abiraterone acetate using different Mucoadhesive polymers such as carbopol934P, HPMC K100M, NaCMC containing the drug Abiraterone acetate were prepared using solvent casting method. The polymers like ethyl cellulose, Hpmck100m, xanthum gum in different combinations for effective delivery of drug to the colon**.** The prepared hydrogel plug with this polymer was plugged to the capsule body containing the formaldehyde coating The formaldehyde coated capsules were prepared to decrease the solubility of gelatin where cross linking of the amino group in gelatin group with aldehyde group. In vitro drug release studies were performed in 0.1N HCl for 2 h followed by in pH 6.8 phosphate buffer for 3 h, finally in pH 7.4 phosphate buffer for 6-12 h. The dissolution data demonstrated that the rate of drug release decreased by the formaldehyde treatment and hydrogel plug till the delivery of the drug to the colon. The colonal patches were studied for various physic chemical properties. The weight uniformity is 242.00±1.0 to 250.30±1.60mg. The thickness is 0.43±0.031 to 0.49±0.037mm. The folding endurance is 163±2.0 to 195±4.0sec. The surface pH is 6.2±0.15 to 7.4±0.30.The swelling index is 70.12 to 81.71%. The Mucoadhesive strength is 204±29.53 to 251±24.61.The Mucoadhesive time is 204±29.53 to 250±24.27. The drug content is 90.21 to 99.96%. The moisture uptake and moisture content is 0.3±0.01 to 1.68±0.02 and 0.32±2 to 0.54±4. The release was sustained in colonal patches prepared with carbopol and sodium alginate. capsule were evaluated and confirmed that 8 hrs formaldehyde treatment was sufficient.100mg hydrogel plug was optimized Hardness and thickness of the plug controlled lag time.

KEYWORDS: Pulsatile drug delivery system, Hydrogel plug, Formaldehyde treatment, colonal drug delivery.

INTRODUCTION

Colon it is a part of large intestine which forms the major part of large intestine. It start from cecum and last to sigmoid Colon. The length for large intestine is 1.5m and diameter 6.5cm.Colon contains the following the cecum, ascending Colon, hepatic feluxure, transverse Colon, splenic flexure, descending Colon, sigmoid Colon. Cecum of about 6cm was connected to ileum with ascending Colon to the ileocecal valve.Lenght of 8cm twisted coiled tube of appendix or vermiform appendix is connected to the caecum. Caecum opens through the ascending colon passes to the transverse Colon then to the abdomen then to the descending Colon. Two layers namely the outer longitudinal layer and inner circular layer are distributed in smooth muscles of Colon.

Colon reabsorbs the excess water from the digested food. It stores feces and allows elimination. It is the site where colonic micro flora grows. Colon can deliver the drug both locally and systemically. Targeting of drug to the Colon through oral route can be achieved by ease of administration and with better patient compliance. Colon delivery of drugs is formulated to prevent the release and the drug is not absorbed in the stomach and small intestine at last releases the drug in the colon. Drugs that targeted to the Colon are useful for treatment of colonic diseases is Colon cancer, inflammatory bowel disease, ulcerative colitis, irritative bowel syndrome.

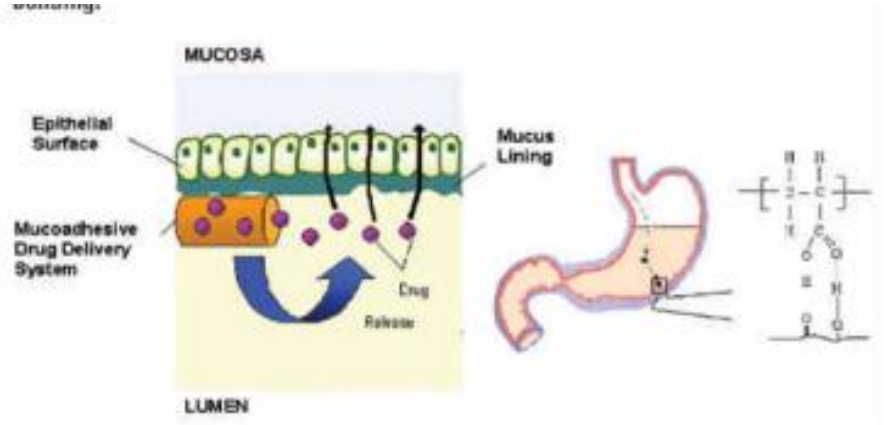
MUCOADHESIVE SYSTEMS

Mucoadhesion is a topic of current interest in the design of drug delivery systems. The Mucoadhesive drug delivery system prolong the residence time of the dosage form at the site of absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved and / or better therapeutic performance of the drug. Mucoadhesive patch systems provide bioadhesion, drug protection and unidirectional release. This combination of function could improve the overall oral bioavailability.

Mucoadhesion is defined as attractive interactions at the interface between a pharmaceutical dosage form and a mucosal membrane. Various administration routes, such as ocular, nasal, buccal and gingival, gastrointestinal (oral), vaginal and rectal, make Mucoadhesive drug

delivery systems attractive and flexible in dosage form development. The advantages associated with the use of Mucoadhesive in drug delivery include increased dosage form residence time, improved drug bioavailability, and reduced administration frequency, simplified administration of a dosage form and termination of a therapy as well as the possibility of targeting particular body sites and tissues.

According to Good defined bioadhesion as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces. It is also defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time.



In case of mucoadhesion, the biological tissue is the mucous membrane. For mucoadhesion to occur, a succession of phenomena is required.

MUCOADHESION STAGES

1) An intimate contact between a bioadhesive and a membrane.
2) Penetration of the Bioadhesive into the crevice of the tissue surface.
3) Mechanical interlocking between mucin and polymer.

TYPES OF MUCOADHESION IN BIOLOGICAL SYSTEMS, FOUR TYPES OF MUCOADHESION CAN BE DISTINGUISHED

1) Adhesion of a normal cell on another normal cell.
2) Adhesion of a cell with a foreign substance.
3) Adhesion of a normal cell to a pathological cell.
4) Adhesion of an adhesive to a biological substrate.

MUCOADHESIVE POLYMERS

Mucoadhesive polymers are water-soluble and water-insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. Mucoadhesive polymers that adhere to the musin-epithelial surface can be conveniently divided into three broad classes.

1) Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.

2) Polymers that adhere through nonspecific, non-covalent interactions are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).

3) Polymers that bind to specific receptor site on tile self surface.

EXAMPLES OF SOME MUCOADHESIVE POLYMER

Natural /Semi-synthetic Na alginate, Agarose, Chitosan, Pectin, Tragacanth, Gelatin, Xanthum gum, Carragenan, Starch Synthetic Poly vinyl alcohol, Polyamides, Polycarbonates, Poly alkaline glycols, Poly vinyl ethers, Esters and halides, Poly meth acrylic acid, PMMA, Methyl cellulose, Ethyl cellulose, HPC, HPMC Methyl cellulose, Sod. CMC Biocompatible Esters of haluronic acid, polyvinyl acetate, Ethylene glycol. Biodegradable Poly (lactides), Poly (lactide-coglycolides), Poly caprolactones, Poly alkyl cyanoacrylates. Poly orthoesters, Poly(glycolides), Poly phosphoesters, Poly anhydrides, Poly phosphazenes, Chitosan, Poly ethylene oxide.

RECENT ADVANCEMENT IN MUCOADHESIVE POLYMERS

Recently, a novel promising strategy to imp-rove mucoadhesion has been introduced into the pharmaceutical literature. The most commonly bridging structure in biological systems, the disulfide bond, is thereby utilized to improve adhesion of polymeric carrier systems to mucosal membranes.

Thiolated polymers, designated as thiomers, are believed to interact with cysteine-rich sub domains of mucus glycol- proteins forming disulfide bonds between the mucoadhesive polymer and the mucus layer.

APPROACHES TO GASTRO-INTESTINAL DRUG DELIVERY SYSTEM

TWO TYPES OF APPROACHES ARE MAINLY USED

GASTRORETENTIVE DRUG DELIVERY SYSTEMS

a. Mucoadhesive Tablets.

b. Mucoadhesive micro/nanoparticles.

INTESTINAL DRUG DELIVERY SYSTEM

a) MUCOADHESIVE PATCH

1) GASTRO RETENTIVE DRUG DELIVERY SYSTEM

These are the systems which can remain in gastric region for several hours and significantly prolongs the gastric residence time of drug. After oral administration, such a delivery system would be retained in stomach. It releases the drug there in a controlled & prolonged manner, so that the drug could be supplied continuously to absorption site in GIT.

A) TABLETS

Mucoadhesive tablet have potential to be used for controlled release drug delivery but coupling of Mucoadhesive properties to tablet has additional advantages. Mucoadhesive tablet can be tailored to adhere to any mucosal tissue found in GIT, thus offering the possibilities of localized as well as systemic controlled release of drug.

B) MICRO AND/OR NANOPARTICLES

Despite the limited loading capacity of drug, Bioadhesive micro-and /or nanoparticles have been widely investigated for three major features.

1. Immobilization of particles on the mucosal surface by adhesion after modification of surface properties via Bioadhesive polymers.
2. Very large specific surface between the dosage forms and the oral mucosa.
3. Sustained release of entrapped drug, leading to higher absorption.

2) INTESTINAL DRUG DELIVERY SYSTEM

These are the systems which can remain in Intestinal region for several hours and prolongs the intestinal transit time. Prolonged transit improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to proximal small intestines.

a) MUCOADHESIVE PATCHES

One of the proposed approaches for inducing greater levels of absorption and stability at the intestinal epithelium is the use of a multilayered patch system. Patches comprise layers of thin, flexible membranes: an impermeable backing; a drug reservoir; a rate-controlling membrane; and an adhesive. When the patch is applied, the drug flows through the skin into the bloodstream at a rate regulated by the membrane that is preprogrammed to keep the drug at an effective level from a technological standpoint, these protective, rate- controlling and adhesive properties are also ideal for oral dosage forms intended for delivery to the intestinal mucosa.

A) GASTRO INTESTINAL-MUCOADHESIVE PATCH SYSTEM

This system consists of four layers

(i)A backing layer made of a water insoluble polymer to protect protein drugs from enzymatic hydrolysis.

(ii)A surface layer made of a polymer sensitive to intestinal pH.

(iii) A drug-carrying middle layer.

(iv) An adhesive layer between the middle and surface layers to generate a high concentration gradient between the patch and intestinal enterocytes.

The pH-sensitive surface layer was prepared using one of three polymers:- hydroxypropylmethylcellulose (HP-55), Eudragit L100 or Eudragit S100 (Rohm). The Mucoadhesive layer, an aqueous solution of carboxyvinyl polymer [Carbopol}and polyethylene glycol 400, was spread uni- formly on the surface of the pH-sensitive layer and then attached to the middle layer. The four-layered film was cut into smaller pieces (0.5 mm in diameter for rat studies and 3.0 mm in diameter for dog studies) and treated with micro pulverized stearic acid and magnesium silicate to cover the edges of the films to prevent patch agglutination.

B) DRUG-IN-ADHESIVE PATCH

This was designed mainly to increase the loading dose. The reworked patch system consisted of three layers.

i) A backing layer of ethyl cellulose.

ii) An enteric polymer membrane of HP-55.

iii) A new drug-carrying layer, based on Carbopol, loaded with 30 mg of fluorescein or fluorescein-dextran as a model drug.

Eaimtrakarn et al 40-41 redesigned the intestinal patch with an increased loading space and without the adhesive layer. The three-layer preparation was heat sealed and cut into patches 3 mm in diameter. As a reference, the patches were compared with a compressed tablet of 30 mg of fluorescein or fluorescein-dextran mixed with microcrystalline cellulose. In vitro dissolution tests performed in pH 7.4 phosphate buffers at 37°Cshowed that 50% dissolution of fluorescein from the patch preparation was more than two times slower than from the tablet preparation.

The three layered oral patch preparation was also evaluated in human volunteers using caffeine as a model drug. This preparation consisted of an ethyl cellulose backing layer, a layer of Eudragit L100 and a Carbopol based drug-carrying layer loaded with caffeine (50 mg). The three-layered preparation was heat-sealed, punched into patches 3 mm in diameter and administered in a batch of 120 by enteric encapsulation.

C) MICROSPHERE PATCH

An alternative patch system similarly consists of three layers.

(i) A Mucoadhesive layer.

(ii) A layer of drug-loaded microspheres partially immersed in the Mucoadhesive layer.

(iii) An impermeable membrane encompassing the microspheres.

This patch is prepared by cross-linked bovine serum albumin microspheres having diameter 10-30 µm and loaded with one of three model drugs [sulforhodamine B, phenol red or fluorescein isothiocyanate (FITC)-dextran]. The microspheres were spread uniformly and partially pressed into a 5 µm? thick Mucoadhesive layer made of Carbopol and pectin, which was then covered with an ethyl cellulose layer. After drying, the three-layered film was cut into smaller squares and circles.

D) INSULIN PATCH FOR ORAL DELIVERY

A bilayered intestinal patch was designed for the oral delivery of insulin43. These patches were fabricated using a Mucoadhesive matrix of Carbopol, pectin and sodium CMC and loaded with bovine insulin (0.25–2.50 U/mg) as a model drug. This mixture was compressed under 0.5– 4.0 tons using a hydraulic press and cut into disks with a diameter of 2–8 mm and a thickness of 400µm.Three sides of the patch were coated with a solution of ethyl cellulose in acetone. The acetone was evaporated to obtain a 50µm thick ethyl- cellulose backing

(Figure 7). The efficacy of the intestinal patch was evaluated in terms of insulin-induced hypoglycemia in rats, patch adhesion and insulin release.

E) GATED HYDROGELS PATCH

Drug delivery system that provides controlled release using a bilayered self folding pH sensitive hydrogel gate. The main device consisted of two parts- a poly (hydroxyl methaacrylate) (HEMA) based drug reservoir with targeting function and a hydrogel gate. A hydrogel drug entrapping matrix was prepared by free radical photo polymerization at room temperature. Drug release from the device was controlled by the pH dependent swelling properties of the bilayered gate. In pH 3.0 medium, (MAA-g-EG) and (HEMA) hydrogels showed similar response, thus the gate remained closed and stable. When the pH of the medium was increased to pH 7.3, swelling of the (MAA-g-EG) increased significantly. Whereas the swelling of the (HEMA) layer remained constant.

F) MICROPATCHES

The small particles of <5µm have an increases adherence in the whole gut, they are more likely to induce a localized inflammatory response followed by phagocytosis by macrophages. Particles of larger size are taken up less effectively by macrophages, therefore micro patches were fabricated that were large enough (50-200µm) to prevent endocytosis. They were designed to be small enough to travel between intestinal villi, thereby increasing the large absorptive surface area. The processes for fabricating micro patches in the three different substrates (silicon oxide, porous silicon and poly (methyl methaacrylate) PMMA have been developed based on standard microelectromechanical systems techniques, including photolithography, etching and thin film deposition.

G) COLONAL PATCHES

The proposed study is to formulate a colonal patch which contains adhesion property. these design contained layers that are useful in delivery of drug to the colon. The layers contain Mucoadhesive materials adhered to the mucosal surface where the patch gets adhered to the mucosal surface in the colon. The drug get loaded in the Mucoadhesive layer uniformly and spread in the patch. It contains a backing membrane where the colonal patch is administered the patch get adhered to the mucous membrane of the large intestine and the drug get slowly adhered to the Mucoadhesive layer of the patch where unidirectional release takes place. The backing layer which controls the drug delivery in large intestine and also used in minimizing the drug release from the patch. The unidirectional release of the drug can be achieved by

using Mucoadhesive polymers where the drug release takes place in the sustained release. These unidirectional releases enhance absorption efficiency and increases local concentration. The colonal patches which adhered to the Mucoadhesive layer contains extended transit time in the large intestine where the sustained release takes place. The colonal patch which is millimeter in size are encapsulated in capsule body and delivered to the large intestine.

Abiraterone acetate as a tablet was formulated into the patch where the formulation of the drug Abiraterone acetate was of tablet and this formulation contain Abiraterone acetate as a active pharmaceutical ingredient and is combined with the polymers in order to formulated a patch where the patch is folded and kept in the capsule body and the capsule body is coated with the formaldehyde coating and it also contains a Hydrogel plug which helps in delivery of the drug to the colon upon contact with the water the Hydrogel plug swells and releases the patch at the large intestine and the patch is released and adheres to the mucous layer for the treatment of Colon cancer. Abiraterone acetate works by androgen deprive therapy Abiraterone acetate inhibits the enzymes that is expressed in testicular, adrenal and prostatic tumor tissue and requires parts of the body androgen production process and the amount if androgens produced becomes diverse where the blocked of androgen production at the three sites that is testes, adrenal gland and the tumor. Abiraterone acetate is used in formulation of the patch in order to reduce the tumor by selectively inhibiting the action of enzymes C17,20lyase and 17hydroxylase on cytochrome P450 when administered as a patch.

METHOD OF PREPARING COLONAL PATCHS

- **Casting and drying**

(a) Solvent casting

(b) Semi-solid casting.

- **Extrusion**

(a) Hot melt extrusion

(b) Solid dispersion extrusion

- **Rolling method**

(a) Casting and Drying

a) SOLVENT- CASTING METHOD

The oral film is mostly prepared by using the solvent-extraction method, in which water soluble ingredients are dissolved to form a clear viscous solution. The active pharmaceutical ingredient and other agents are dissolved in small amount of solution and combine with bulk. This mixture is then added into aqueous solution. Remove entrapped air and resulting solution is casted as PATCHES and then dried which is then cut into pieces of the desired sizes.

b) SEMI-SOLID CASTING

First of all, a solution of water soluble patches forming polymer is prepared in semi solid casting method. Then resulting solution is added to insoluble polymer like cellulose acetate butyrate, cellulose acetate phthalate etc., prepared in sodium or ammonium hydroxide. Then add accurate amount of plasticizer to get gel mass. Finally cast gel mass into patches by using heat controlled drums. The thickness of the patch is about 0.015-0.05.

EXTRUSION

a) HOT-MELT EXTRUSION

In hot melt extrusion method, the initial mass is formed with the help of carriers. To form initial mass, the drug is mixed with carriers and a solid mass is obtained and dried. Then dried granular material is introduced into the extruder. The extruder is divided into four zones having following degrees of temperature: 800 (zone 1), 1150 (zone 2), 1000 (zone 3), and 650°C (zone 4). The speed of extruder screw speed should be set at 15 rpm in order to process the granules inside the barrel of extruder for approximately 3-4 min so that mass should be properly melted. The extrudate (T = 650°C) obtained is then pressed into a cylindrical calendar in order to obtain a film. There are certain benefits of hot melt extrusion: Fewer operation units, minimum product wastage, possibility to scale up, an anhydrous process, absence of organic solvents, include shorter temperature and shorter residence time of the drug carrier mix, and better content uniformity.

b) SOLID DISPERSION EXTRUSION

Method involves the solid dispersion of drug incorporated in melted polymer solution so that drug can be loaded. The drug is dissolved in suitable liquid solvent and obtained solution is added to the melt of suitable polymer, obtainable below 70°C without removing the liquid solvent to obtain the solid dispersion. Finally the obtained solid dispersions are shaped into films by means of dyes.

ROLLING METHOD

In rolling method, both the drug solution and film forming polymer solution are mixed thoroughly and the resultant solution or suspension is subjected to the roller. The solution or suspension should have specific rheological consideration. The film is dried on rollers and cut into desired shapes and sizes.

PREPARATION OF COLONAL PATCHES

Colonal patches were prepared by Solvent casting method the polymer was taken in a ratio of 1:1 and are dissolver first in the 10ml of water and kept aside for swelling of the polymer solution. Then the drug of about 75gm was taken and to it 9Ml of ethanol was added in order to dissolve the drug to the polymer solution after 10min the drug solution was added and kept on magnetic stirring at 50rpm for 30-40min after which casted on petriplates and kept for drying at 40^{o} c in oven and after drying they are removed and cutter into desired size of patch that is 4x4mm patches and are stored in desiccators.

The calculation of the drug loaded in the patch;-
Diameter of the petriplates=6.5cm
Radius of the petriplates=r2 =6.5x6.5=3.25cm
Area of the plate=22/7xr2=35.9
Dose of Abiraterone acetate=125mg where cut into 4x4=16mm
Number of patches casted=area of the plate/area of the
=35.9/16=2 patches.

Abiraterone acetate as a tablet was formulated into the patch where the formulation of the drug Abiraterone acetate was of tablet and this formulation contain Abiraterone acetate as a active pharmaceutical ingredient and is combined with the polymers in order to formulated a patch where the patch is folded and kept in the capsule body and the capsule body is coated with the formaldehyde coating and it also contains a Hydrogel plug which helps in delivery of the drug to the colon upon contact with the water the Hydrogel plug swells and releases the patch at the large intestine and the patch is released and adheres to the mucous layer for the treatment of Colon cancer. Abiraterone acetate works by androgen deprive therapy Abiraterone acetate inhibits the enzymes that is expressed in testicular, adrenal and prostatic tumor tissue and requires parts of the body androgen production process and the amount if androgens produced becomes diverse where the blocked of androgen production at the three sites that is testes, adrenal gland and the tumor. Abiraterone acetate is used in formulation of

the patch in order to reduce the tumor by selectively inhibiting the action of enzymes C17, 20lyase and 17hydroxylase on cytochrome P450 when administered as a patch.

EVALUATIONS OF COLONAL PATCHES

WEIGHT UNIFORMITY OF THE PATCH

1cm2 patches of ten was taken and are weighed individually for all the ten patches and the average was calculated.

THICKNESS OF THE PATCH

Screw gauge was used to measure the thickness of each patch. The patches were taken and by using screw gauge at five positions the patch thickness was measured. To this average was calculated.

FOLDING ENDURANCE

By repeated folding of the patch at the same place of one patch and the time taken for the patch to fold up to the point where the patch was broken on repeated folding was considered. The test was done on the 5 patches where the number of times the patch could be folded gives the value of folding endurance.

SURFACE PH

It is used to determine the possibilities of any side effects due to the change in the pH. Both the environment of acidic or basic may cause irritation in the large intestine.

The patch was taken and placed in Petri plates moistened with the 0.5ml distilled water and room temperature and leaved for 30s. The pH was determined by placing the electrodes in contact with the patch surface and pH was determined using pH meter.

SWELLING INDEX

It is one of the important factors in swelling of the Mucoadhesive polymers. The patch of size 3x3mm was taken and weighed on a placing the patch on the cover slip and was weighed. Then the patch was placed in the buffer solution of pH 6.8 after 5min the cover slip from the buffer was removed and weighed till 30min. sweeling of the patch is due to the absorption of buffer to the patch. The difference in the weight gives the weight increased due to absorption of the buffer to the swelling of patch.

Swelling index=at time t the weight of the patch-at time 0 the weight of the patch/weight of the patch at time t.

DRUG CONTENT

The drug content was determined by dissolving the colonal patch in 100ml of the 6.8 phosphate buffer solution for about 12hr and then it is sonicated for about 30min. t hen the solution was filtered through Whatman filter paper and measured spectrophotometrically by UV-Visible spectrophotometer at 274nm with the blank. And the calibration cure was determined.

MOISTURE CONTENT

Desiccators containing anhydrous calcium chloride was taken and the Colonal patches was weighed and kept in it. The patch was taken out after 3dys.then the MC was determined by:-

MC=WEIGHT TAKEN INITIALLY-WEIGHT TAKEN FINALLY/WEIGHT TAKEN INITIALLYX100.

MOISTURE ABSORPTION

At 76% and 86% relative humidity the Colonal patches was weighed and placed in desiccators of 100ml saturated solution of aluminum chloride. The Colonal patches was taken out after 3dys and weighed.

MOISTURE ABSORPTION=final weight-initial weight/initialweightx100.

MUCOADHESIVE STRENGTH

To check the residential time of the Colonal patches at the site of attachment was determined. The porciline buccal mucosa was taken and was measured using the physical balance. The Colonal patches was attached at the bottom of the pan with the help of the glue or plaster and the other side of the pan the weights were placed one after the other and the time of the detachment of the patch from the pan was measured as a Mucoadhesive strength of the Colonal patches.

CONCLUSION

In conclusion, different Mucoadhesive polymers such as Carbopol and sodium alginate along with the drug shows god physiological properties and good dissolution study. The polymers such as ethyl cellulose, HPMC K100M both hydrophobic and hydrophilic polymers prepared as a hydrogel plug can be successfully employed in order to regulate water penetration into

capsule content and drug release prior to complete erosion of plug material. The formaldehyde coating to the capsule body helps in reaching the patch for colon targeting. Which possess poor oral bioavailability, self regulated release, mucoadhesion, drug protection, unidirectional release and cell specific targeting provides additional smart characteristics to this innovative therapeutic platform. The formulation were prepared and succeeded in targeting to colon. Combination of polymer can be successfully employed for better results. The prepared formulations can be successfully commercialized after establishing the safety and efficacy studies for in-vivo after healthy human volunteers.

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