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A Review : Mucoadhesive Drug Delivery System

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Abstract: *Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption. The drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Thus,mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity. In this regard, this review covers the areas of mechanisms and theories of mucoadhesion, factors influencing the mucoadhesive devices and also various mucoadhesive dosage forms*

Keywords: Mucoadhesion, theories mucoadhesive dosage forms

I. INTRODUCTION

Controlled drug delivery system is the one which delivers the drug at a predetermined rate, locally or systemically,for a specified period of time. The basic rationale of a controlled drug delivery system is to optimize the biopharmaceutics, pharmacokinetic and pharmacodynamics properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administrated by most suitable route. These systems are actually controlling the drug concentration in the body, not just the release of the drug from the dosage form, as is the case in a sustained-release system. Another difference between sustained and controlledrelease dosage forms is that the former are basically restricted to oral dosage form whilst controlled release systems are used in a variety of administration routes, including transdermal, oral and vaginal administration.

Mucoadhesive Drug Delivery System:

Mucoadhesive drug delivery systems are delivery systems, which between the mucinlayer and a bioadhesive polymer which could be a natural or synthetic in origin. Mucoadhesion can be defined as the state in which two materials adhere to each other for extended periods of time with the help of interfacial forces and when one of these materials is biological in nature, the phenomenon is known asbioadhesion or the term bioadhesion as the “attachment of a synthetic or to mucus and/or epithelial surface”. In recent years, many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, rectal and vaginal routes for both systemic and local effects. Dosage forms designed for mucoadhesive drug delivery should be small and flexible enough to be acceptable for patients and should not cause irritation. Mucoadhesive drug delivery system having several advantages prolonged residence time enhances absorption, which results in an increase in the therapeutic efficacy of the drug.

Itsenormous blood supply and good blood flow rates cause rapid absorption of the drug. The drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.The relative permeability of mucous membranes ensure or rapid onset of action.increases drug bioavailability by preventing first-pass metabolism. Mucoadhesive formulation reduce fluctuations in plasma drug level.Ease of use valsartan is a class lll drug on the BCS scale.It is an angiotensin receptor blockers that can be used for high blood pressure and heart failure.Mucoadhesive drug delivery systems that take advantage of the bioadhesive properties of specific polymers. Bioadhesiveness is defined as the ability of a material to adhere to a specific area of the body for long period of time for better control of systemic delivery as well as local drug effects.Dosage formulation for mucoadhesive drug delivery must be small and flexible enough to be acceptable to the patient and not cause irritation. Destructive agents may be beneficial because they eliminate the need to retrieve information from the system at the end of the desired dosing intervel. Developing

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sustained-release formulation achieve the goal of slowly releasing the drug over a long period of time,but is not sufficient to achieve sustained therapeutic effects.

Advantages of Mucoadhesive Drug Delivery System

- MDDS offers several advantages over other oral controlled release systems by prolonging drug residence time in the GIT
- Target and localize formulation to specific location.
- Drug flow into absorptive tissue is high
- MDDS server bothsustained release purposes and the presence of formulation at the site of absorption.
- Pain-free administration.
- Accessibility is excellent

Disadvantages Of Mucoadhesive Drug Delivery System

- Patient compliance is difficult to achieve.
- The lack of standardized technique often leads to unclear result.
- Costly drug delivery system.
- Properties like, unpleasant taste,odor,irritability to the mucosa,stability at administrated site possess limitation.

Mucus Membrane:-

Mucus membranes (mucosa) [Fig.1] is the moist surfaces that lines the walls of various body cavities, such as the gastrointestinal and respiratory tracts. They consist of a layer of connective tissue(lamina propria),surmounted by an epithelial layer,the surface of which is usually moistened by the presence of mucus layer.The epithelium may be single layered (e.g. the stomach, small and large intestines and bronchi) or multilayered/multilayered (e.g. in the esophagus, vagina and cornea). The former contain goblet cells which secrete mucus directly onto the epithelial surfaces; the latter contain, or are adjacent to tissues containing, specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus is present either as a gel layer adherent to the mucosal surface or as a luminal soluble or suspended form. The major components of all mucus gels are mucin glycoproteins, lipids, inorganic salts and water, the latter accounting for more than 95% of their weight, making them a highly hydrated system. The major functions of mucus are that of protection and lubrication.

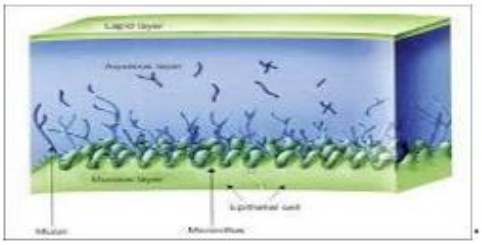

Fig1 mucus membrane structure

Mechanism Of Mucoadhesion

The mechanism responsible in the formation of mucoadhesivebond.The mechanism of mucoadhesion is generally divided into three steps:

Step 1: Wetting and swelling of the polymer(contact stage)

Step 2: Interpenetration between the polymer chains and the mucosal membrane.

Step 3: Formation of bond between the entangled chains(both known as consolidation stage)

The contact phase and integration phase,The first stage is characterized by the contact of the themucus membrane and the mucoadhesive as the composition spreads and swells,thereby initiating deep contact with the mucus layer. In the setting stage, the mucoadhesive materials is activated by the presence of moisture. Moisture plasticizes the system, causing the mucoadhesive molecules to break free and bind toghether through weak van der Waals and hydrogen

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bonds. There are Essentiallytwo theories that explain the consolidation phase: the diffusion theory and the dehydration theory. According to the diffusion theory, the mucoadhesive molecules and the mucus glycoproteins interact with each other through chain interpenetration and secondary bond formation.to achieve this, mucoadhesive device have the ability to promote both chemical and mechanical interaction.For example, molecules with hydrogen bond building groups (–OH, –COOH), an anionic surface charge, high molecular weight, flexible chains and surface-active properties, which help in spreading throughout the mucus layer, can present mucoadhesive properties

Mucoadhesion Theories

Mucoadhesion is a complex process and many theories have been proposed to explain the mechanisms involved. These theories include mechanical blocking,electrostatic,diffusion interpenetration, adsorption,and destructive processes.

1. Wetting theory

The wetting theory applies to liquid systems where a surface has an affinity for spreading over it.these similarities can be found using measurement such as contact angle.The general rule is that the smaller the contact angle, the greaterthe affinity. To ensure sufficient spreading, contact angle must be equal to or close to zero.The spreading coefficient, SAB, can be calculated from the difference between the surface energies γB and γA and the interfacial energy γAB, as given in the equation below. This theory explains the importance of reducting contact angle and surface and interfacial energy to achieve good mucoadhesion.

2. Diffusion theory

Diffusion theory describes the interpenetration of both polymer and mucin chains to a depth sufficient to create a semipermanent adhesive bonds. It is believed that the adhesive strength increases with the degree of penetration of the polymer chains. This rate of penetrationdepends on the diffusion coefficient, flexibility and properties of the mucoadhesive chains,mobility and contact time. According to the literature, the interpenetration depth required to create an effective bioadhesive connection is the range of 0.2-0.5 μm.

3. The electronic theory

This theory explains adhesion that occurs through electron transfer between mucus and the mucoadhesive system due to differences in the electronic structures. Electron transfer between the mucus and the mucoadhesive results in the formation of charged double layer at the interface between the mucus and mucoadhesive. The net result of this process is the formation of attractive forces within double layer.

Factors Affecting Mucoadhesion:-

Molecular weight

The mucoadhesive strength of a polymer increases with molecular weights above 100,000. Direct correlation between the mucoadhesive strength of polyoxyethylene polymers and their molecular weights lies in the range of 200,000–7,000,000.

Flexibility

Mucoadhesion begins with the diffusion of the polymer chains at the interface region. Therefore, it is important that the polymer chains have a significant degree of flexibility to achieve the desired interweaving with the slime. The increased chain interpenetration is due to the increased structural flexibility of the polymer upon inclusion of polyethylene glycol.In general, the mobility and flexibility of polymers can be related to their viscosity and diffusion coefficient, this is because the more flexible the polymer,the greater the diffusion into the mucus.network .Cross-linking densityThe average pore size, the number and average molecular weight of the cross-linked polymers, and the density of cross-linking are three important and inter-related structural parameters of a polymer network. Therefore, it seems reasonable that with increasing density of crosslinking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin.

Hydrogen bonding capacity

Hydrogen bonding is another important factor in polymer mucoadhesion. Desirable polymers should have functional groups capable of forming hydrogen bonds, and polymer flexibility is important to improve this hydrogen bonding

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potential. Polymers such as polyvinylalcohol, hydroxylated methacrylates,polymethacrylic acid,and all their copolymers have excellent hydrogen bonding properties.

Hydration

Hydration is required for a mucoadhesive polymer to expand and create a proper macromolecular mesh of sufficient size,and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and themucus network.

Charge

Some generalizations about the charge of bioadhesive polymers have been made previously, where non-ionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. Strong anionic charge on the polymer is one of the required characteristics for mucoadhesion. Some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium. Additionally some cationic high–molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties.

Concentration

The importance of this factor lies in the development of as Strong adhesive bond with the mucus, and can be explained by the polymer chain length available for penetration into the mucus layer. When the concentration of the polymeric too low, the number of penetrating polymer chains per unit volume of the mucus is small and the interaction between polymer and mucus is unstable. In general, themore concentrated polymer would result in a longer penetrating chain length and better adhesion.

Sites for Mucoadhesive Drug Delivery Systems:

The common sites of application where mucoadhesive polymers have the ability to deliver pharmacologically active agents include oral cavity, eye conjunctiva, vagina,nasal cavity and GIT Each site of mucoadhesion has its own advantages and disadvantages along with the basic property of prolonged residence of dosage form at that particular site. In buccal and sublingual sites, there is an advantage of fast on set along with by passing the first-pass metabolism, but these sites suffer from inconvenience because of taste and in take of food. In GIT, there is a chance for improved amount of absorption because of microvilli, but it has a drawback of acid instability and first-pass effects. Rectal and vaginal sites are the best ones for the local action of the drug but they suffer from inconvenience of administration.

Chitosan as mucoadhesive polymer:-

Chemical Names Chitosan hydrochloride; 2-Amino-2-deoxy-(1,4)-β-D-glucopyranan; deacetylatedchitin;polyD-glucosamine; poly-(1,4-β-D-glucopyranosamine); Poly-β-(1, 4)-2Amino-2-deoxy-Dglucose

Structural Formula and Molecular Weight

Molecular Formula of Chitosan - C56H103N9O39

Molecular Weight of Chitosan - 1526.464 g/mol

Chitosan is a linear polysaccharide composed of randomly distributed β-(1→4)linked D- glucosamine (deacetylation units) and N-acetyl-D-glucosamine (acetylation units).

It is produced by partiallydeacetylating ‘chitin’, a naturalpolysaccharide that makes up the exoskeleton of crustaceans such as crabs and shrimp and the cell walls of fungi.

Chitin is produced by glucosamine with a copolymer of N-acetylglucosamine. During the deacetylation and polymerizationprocess, several steps of chitin form a product called as Chitosan,which generally does not have a clear chemical formula. The individual steps of Ndeacytelation do not account for the nomenclature of chitin and chitosan. This shows that chitosan cannot be composed chemical group and therefore depends on each manufacturer's specifications.

It can be concluded that chitosan is a chitin in a deacytylated state, which forms soluble amine salts. The level at which soluble salts are obtained, has been estimated to be 80-85 %. Therefore, Chitosan could be commercially geared up with the customized molecular weight by 10000 to 1000000 along with varying viscosity and degrees of deacytylation (DAD).

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Functions of Chitosan

- Coating
- film-forming and disintegrating agents
- binder in tablet formulations
- mucoadhesive polymer and viscosity-enhancer

Uses of Chitosan in Pharmaceuticals

- It has often found to use in most of cosmetic applications.
- Recently, many studies have conducted to account its advantages in the pharmaceutical industry.
- various studies have shown positive results for their application in drug delivery systems.
- Its applications includes controlled drug delivery, colonic drug delivery systems. ➢ Chitosan may be processed by numerous methods for its use in drug delivery such as spraydrying, granulation, coacervation and direct compression.

Typical Properties

Chitosan is a cationic polyamine at pH less than 6.5 shows high charge density; and so draw the negatively energized surfaces and chelate with metallic ions. Chitosan is a linear polymer possessing reactive amino and hydroxyl groups, which are basically accessible for chemical reactions and formation of various salts. The characteristics of chitosan molecules are pertain to its polymeric and polyelectrolytes' nature.

Acidity or basicity pH of 4 to 6 in 1% w/v aqueous solution

Density of Chitosan 1.35 To 1.40 gm. /cm3

Glass transformation or transition temperature 203°C.

Water content

Chitosan adsorbs moistness from the natural environment, the volume of adsorbed moisture based on the original moisture content and relative humidity and temperature of the encircling air. **Particle dimensions < 30µm**

Solubility of Chitosan

Chitosan is moderately soluble in water and insolvable in 95 % ethyl alcohol, other natural organic solvents, neutral or alkaline solutions with pH nearly 6.5 or above. It disintegrates easily in the diluted and intense solution of many organic acids and to some amount in mineral inorganic acids (aside from sulfuric and phosphoric acid). The amine sets of Chitosan get protonated on dissolution, leading to a positively charged polysaccharide (RNH+3) and formation of chitosan salts, which are dissolvable in water; the solubility is influenced by the extent of deacetylation.

Viscosity

chitosan in various forms is commercially available. Their higher molecular weight and linear or linear,non-relaxed structure make them attractive viscosity ingredient in acidic environments.It acts as a pseudoplastic material whose viscosity decreases with increasing shear rate.The viscosity of chitosan solutions increases with increasing concentration, decreasing temperature, and increasing degree of deacetylation

Stability and Storage properties

Chitosan is known to be hygroscopic,but is stable at room temperature.It should be stored in a tightly closed container in a cool dry place.For PhEur 2005,the instructions for use state that chitosan should be stored at a temperature between 2 to 8 °C.

Method of Manufacture

Chitosan is industrially produced by chemically processing the exoskeletons of crustaceans,such as crabs and shrimps. The basic manufacturing process involves removing proteins through alkaline treatment and removing minerals such as calcium carbonate and calcium phosphate through acid treatment.Before this processing,The shells were crushed to make them more accessible. The shells are primarily deproteinized by the treatment with an aqueous sodium hydroxide 3-5 % solution. The resultant product was neutralized and calcium was expelle treatment method with aqueous HCL acid 3-5 % solution at room temperature to precipitate chitin. The chitin is dehydrated so that it could be stored being a stable intermediate for deacetylation to chitosan at a later stage

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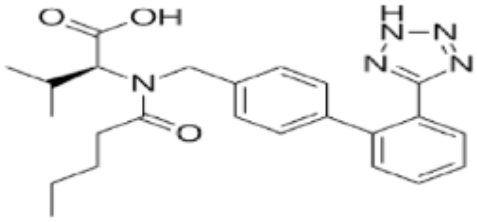
Safety

Chitosan has been extensively analyzed for the application as being an excipient in oral as well as other pharmaceutical products. Chitosan also employed in production of cosmetic formulations. "Often, chitosan is considered as nonirritant and nontoxic materials. It is biodegradable polymer and biocompatible with both healthy and tainted skin.

Valsartan:

Valsartan is a potent orally active non-peptide tetrazole derivative that selectively inhibits the angiotensin II type 1 Receptor which lowers blood pressure and is used in the treatment of hypertension. This product, first developed by Novartis, has a wide market in both developed and the developing countries. It can also be used in combination with other antihypertensive drugs. It is a lipophilic drug with a moderate onset of action compared to other drugs in the same category. This drug is a very good target for generic manufactures.Soluble in the neutral pH range. It belongs to the BCS class III drug and is classified as a drug with low permeability and high solubility. Valsartan is soluble in acetonitrile and methanol. The drug is rapidly absorbed orally, has a limited distribution, and is tightly bound to plasma proteins.Valsartan monotherapy(80 mg initial dose)showed significant efficacy in patients with CHF and renal failure accompanied by hypertension,and adjuvant therapy helped control blood pressure in large group ofhypertension patients who did not respond to β-blockers and ACE inhibitors or diuretics. The importance of aggressive blood pressure control is undisputed, but thetherapeutic focus is now extending to end-organ protection as a treatment goal of equal importance to BP reduction.



Chemical structure of Valsartan

PHARMACOLOGY

Valsartan belongs to the family of angiotensin II type1 receptor (AT1) antagonists and possesses about 20,000 fold greater affinity for it than for the angiotensin II type 2 receptor (AT2).This action exert effects on blood pressure (BP) reduction, as well as decreases vascular smooth muscle contraction, inhibits sympathetic outflow, improves renal function and also leads to reduction in progression of atherosclerosis lesions. Also blockade of AT1 receptor by valsartan leads to increase in local angiotensin II concentration that stimulates the unblocked AT2 receptor.

PHARMACOKINETIC PROFILE:

Absorption

Valsartan is rapidly absorbed orally. After oral administration of Valsartan 80mg capsule and solution formulation in 12 healthy volunteers, maximum plasma concentrations (Cmax) of Valsartan (1.64mg/l and 3.25 mg/l) were respectively reached in ~1-2 h. Plasma levels andthe area under the plasma concentration time curve were not linearly related to dose, indicating a saturable first pass metabolism. According to the AUC values obtained, the bioavailability of capsule was 23% and that of solution was 39%

Distribution

Valsartan has only limited distribution outside the plasma compartment and is extensively bound to the plasma proteins (94- 97%) and hence is only limited distributed outside plasma compartment. Because of the presence of carboxylic groups, Valsartan is soluble in neutral pH range and is mainly present in the ionized form at physiological pH.

Metabolism and Elimination

Valsartan does not require any metabolism in the body to become active. After the oral administration of 80 mg of -radio labelled valsartan only one pharmacologically inactive metabolite was found in plasma nearly about 11%. The primary metabolite was identified as Valery 4-hydroxy Valsartan (M1) accounted for about 9% of the dose and is inactive in hypertension. M1 has about 200 fold lower affinity for the AT1 receptor than valsartan. Valsartan is mainly excreted in faces via biliary excretion and hence it is not recommended for patients with hepatic dysfunction and biliary

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cirrhosis. After the administration of an i.v. dose in healthy volunteers, plasma clearance of Valsartan was found to be ~2 l/h . Renal Clearance was found to be only 30% of the total plasma clearance.

Therapeutic efficacy

The therapeutic efficacy of valsartan has been evaluated in a number of dose ranging and comparative studies in patients with varying degrees of hypertension, diabetes and renal impairment.

II. MATERIALS AND METHODS

Materials: Valsartan was received as a gift sample from Macleods Ltd Gujrat. Chitosan, PVP K30 was purchased from Himedia, Mumbai. Dibasic Calcium Phosphate and Magnesium stearate were purchased from Qualigens Ltd.

Drug-excipient Interaction Study

Infrared spectrophotometer is a useful analytical technique utilized to check the chemical interaction between the drug and other excipients used in the formulation. The sample (1mg) was powdered and mixed with 10mg of dry powdered potassium bromide. The powdered mixture was taken in a sampler and the spectrum was recorded by scanning in the wavelength region of 4000-400cm-1 using IR spectrophotometer. Check was made whether the excipients were compatible or not.

Standard Calibration Curve of Valsartan in Phosphate Buffer pH 6.8 at 252 nm:-

An accurately weighed amount of valsartan (10 mg) was dissolved 100ml 0.1N HCl. From this stock solution, 5, 10, 15, 20 and 25µg/ml concentration of valsartan was prepared respectively. The absorbance of these solutions was measured at 252.20nm (λmax) using phosphate buffer pH 6.8 as a blank.

Sr.No.	Concentration µg/ml	Absorbance
1	5	0.189±0.003
2	10	0.386±0.002
3	15	0.579±0.006
4	20	0.755±0.007
5	25	0.963±0.008

Standard Calibration Curve of Valsartan in Phosphate Buffer pH 6.8 at 252 nm

The Standard Calibration Curve of Valsartan in 0.1N. HCl with a wavelength of 248 nm. Accurately weigh valsartan (10 mg) and dissolve in 100 ml 0.1N HCl. From this mother liquor concentrate. 10, 20, 30, 40 and 50 µm/ml.Valsartan was administered according. The absorbance of these solutions was measured at 248 nm (λmax) using 0.1N as a control.HCL

Standard Calibration Curve of Valsartan in 0.1N HCl at 248 nm

Valsartan (10 mg) was weighed precisely and dissolved in 100 ml 0.1N solution.HCl. From this mother liquor concentrate.10, 20, 30, 40 and 50 µm/ml.Valsartan was administered accordingly. The absorbance of these solutions was measured at 248 nm (λmax) using 0.1N as a control.HCl.

Standard Calibration Curve of Valsartan in 0.1N HCl at 248 nm

Sr.No	Concentration µg/ml	Absorbance
1	10	0.239±0.005
2	20	0.480±0.002
3	30	0.734±0.008
4	40	0.950±0.006
5	50	1.194±0.010

Formulation Composition of Batches by Chitosan in Various Concentration

Formulation composition of batches by Chitosan in Various Concentration

Formulation Code	F1	F2	F3	F4	F5	F6
Valsartan	40	40	40	40	40	40
Chitosan	37.5	38	35	38.8	36.4	38
Mg. Stearate	2.5	2	5	1.2	3.6	2
Total Wt.	80	80	80	80	80	80

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Evaluation of Physicochemical Parameters:-

1. Preformulation Studies

a. Angle of Repose

Angle of repose (θ) was determined by measuring the height (h), radius of the heap (r) of the powder blend. A cut system funnel was fixed to a stand and bottom of the funnel was fixed at a height of 2 cm from the plane. tan θ=h/r

b. Bulk Density

The bulk density of a powder is dependent on particle packing and changes as the powder consolidates. Apparent bulk density (gm/ml) was determined by pouring bulk powder into a graduated cylinder via a large funnel and measuring the volume and weight. Bulk density can be calculated by the following formula Bulk density =Weight of powder/Bulk volume

c. Tapped Density

Tapped density is the bulk density of a powder which has been compacted by tapping or vibration. Tapped density was determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapping apparatus, which is operated for a fixed number of taps (100) or until the powder bed volume has reached a minimum. The tapped density was computed by taking the weight of drug in cylinder and final volume.(19) Tapped density =Weight of powder/Tapped volume

Hausner'scoefficient

Hausner coefficient is an indicator of the ease of powder flow. This is calculated using the following formula: Hausner coefficient=Tapped density of powder/Bulk density of powder

2. Post Compression

Parameters The prepared tablets were evaluated for hardness, friability, uniformity of weight, in-vitro dissolution study, ex-vivo mucoadhesive force and drug content.

a. Weight Variation

Twenty tablets were selected randomly from each batch and weighed individually on electronic balance. The individual weighed is then compared with average weight for the weight variations.

b. Hardness

The strength of tablet is expressed as tensile strength (kg/cm2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester).

c. Friability

Diarrhea tablet Friability was measured using a Roche Fabricator. The device consists of a plastic chamber that is set to rotate at 25 rpm for 4 minutes and drop tablets 6 inches with each rotation.

% friability=initial weight -final weight*100

d. Drug Content

Twenty tablets were weighed and ground into powder using a mortar and pestle. Shake and mix the amount equivalent to 40 mg of valsartan with 100 ml 0.1N.Treat with sodium hydroxide and sonicated for approximately 30 minutes.

III. RESULT AND DISCUSSION

UV Spectroscopy (Determination of λmax) The solutions containing 10 µg/ml and 100µg/ml of valsartan in 0.1 N Sodium Hydroxide were scanned. Wavelength (λmax) was found to be 248 nm.

FTIR- IR spectrum of physical mixture of valsartan, novel polymer, Chitosan (1:1:1).From IR spectra of drug and physical mixture, no significant change in peak pattern was observed. Hence, it was concluded that, absence of drug excipients interaction and drug was compatible with excipients used in the present work.

Data Analysis and Optimization:-

The development and optimization of mucoadhesive valsartan tablets was performed using a central composite design. The quantitative influence of compositional variables on the response was described using Response Surface Methods. Based on the conclusions of the pilot study, the data used to select the concentrations of the independent variables and the placement of the central compounds were developed through specialized software. The experimental values for the response Y1(% Drug Release), Y2(Ex-Vivo Residence Time) and Y3(Ex-VivoMucoadhesive Force) were curve fitted

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in quadratic model. The regression equation for the response fitted in quadratic model was generated. Only statistically significant ($p < 0.05$) coefficients were included in the regression equations

V. CONCLUSION

It may be concluded that the novel natural polymer along with chitosan shows good ex-vivo residence time, ex-vivo bioadhesion force and sustained release properties. Therefore,the isolated polymer can be used as a mucoadhesive.This study provides a novel,inexpensive and biocompatible form of valsartan for the treatment of heart failure. Therefore, the current once-daily formulation of valsartan may improve the patient compliance and reduce costs.

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