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FORMULATION AND INVITRO EVALUATION OF CARVEDIOL BUCCAL TABLETS

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ABSTRACT

To overcome the disadvantage of extensive first pass effect and low oral bioavailability of carvedilol we designed carvediol buccal tablets by formulation and invitro evaluation of carvediol buccal tablets method so we have proved that carvedilol can certainly be administered through the oral mucosa. Influence of the formulation variables on hardness, drug uniformity, mucoadhesive strength, drug release is evident. Formulation F2 has successfully sustained the release of Carvedilolin buccal cavity, with great mucoadhesive strength. Formulation F2 showed good pre compression and post compression parameters and follows zero order and higuchi kinetics. After the Stability studies the optimized formulation doesn't show any remarkable change in drug release. Based on the all experiment results it can be concluded that hydroxy propyl methyl cellulose and sodium alginate containing buccal formulation would be the suitable candidate for mucoadhesive drug delivery of Carvedilol with sustained release properties for the treatment of hypertension., KBr (potassium bromide) disks compressed under a pressure of 150 lbs. The wave number range is selected between 500 - 3500cm^{-1}. Phosphate buffer pH 6.8, Composition of successful f2 formulation of Carvedilol, Hydroxyl propyll methyl cellulose, Guar gum, Acacia, Sodium alginate, Micro crystalline cellulose, Sodium saccharine, Magnesium stearate is 40,50,0,15,30,166.9,0.6,7.5 respectively in mg., Stability studies were performed at a temperature of 25±2^{0}c and 65±5%RH and 40±2^{0}c and 75±5%RH, over a period of three months (90days) for the optimized buccal tablet, Sufficient number of tablets were packed in amber colored screw capped bottles and kept instability chamber maintained at 40^0±1^{0}C & 75% RH, Results from stability studies indicate that the formulated carvedilol mucoadhesive

tablet are stable for a period of 3 months under 2 different conditions at 25±2^{0}c and 65±5%RH and 40±2^{0}c and 75±5%RH. There were no remarkable changes were observed during the period of storage.

KEYWORDS: Carvediol, ftir, evaluation, formulation, mucoadhesive, buccal.

INTRODUCTION

MUCOADHESIVE DRUG DELIVERY SYSTEMS

These maybe defined as drug delivery systems, which utilize the property of bioadhesion of certain water soluble polymers which become adhesive on hydration and hence can be used for targeting of drug to particular regions of body for extended periods of time. Hence buccal drug delivery systems are generally based on bioadhesive polymers which once hydrated adhere to the buccal mucosa and with stand salivation, tongue movements and swallowing for a significant period of time. The mucoadhesive drug delivery system includes the following.[3]

1. Buccal drug delivery system.
2. Oral delivery system.
3. Vaginal delivery system.
4. Rectal delivery system.
5. Nasal delivery system.
6. Ocular delivery system

BUCCAL DRUG DELIVERY SYSTEM

Drug delivery via membranes of the oral cavity can be subdivided as follows.

- Sublingual delivery, in which the administration of drug via the sublingual mucosa to the systemic circulation.[3]
- Buccal delivery, in which the administration of drug via the buccal mucosa (the lining of cheek) to the systemic circulation via internal jugular vein.[3]
- Local delivery, for the treatment of conditions of the oral cavity, principally ulcers, fungal conditions and periodontal diseases by applications of the bioadhesive system either to the palate, or the cheek.[3]

These oral sites differ from each other, in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for desired period of time. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs

and is convenient, accessible and generally well acceptable, which makes the oral mucosa. Finally the buccal site rather attractive for drug delivery.[3]

- Its ability to recover after local treatment is pronounced and hence allowed a wide range of formulation to be used, e.g., bioadhesive ointment and patches.[3]
- The oral mucosa is accessible, so dosage forms can be administered and even removed from the site of application.[3]
- Since patients are well adapted to the oral administration of drugs in general, patient's acceptance and compliance is expected to be good.[3]
- According to its natural function the oral mucosa is routinely exposed to a multitude of different external compounds and therefore, is supposed to be rather robust and less prone to irreversible irritation or damage by dosage form, it's drug, excipients or additive.

Local delivery of drug to tissue of the oral cavity has a number of applications including the treatment of toothache, periodontal diseases, dental carries, bacterial and fungal infections and aphthous stomatitis.[3]

Overview of the Oral Cavity

The different anatomical regions of the oral cavity and mucosal tissues are shown in Figure no.3. The various target sites for drug delivery and absorption may include the upper and lower lips, gums, hard palate, soft palate, floor of the mouth (sublingual), tongue and buccal mucosal tissue (cheek). The oral mucosal tissues can be divided into two types, namely, keratinized epithelium of the masticatory regions consisting of the gums palatal mucosa and the inner side of the lips and non-keratinized regions consisting of the floor of mouth (sublingual) and the buccal mucosa. The differences between the two types of epithelia are:

- The superficial layer of the non-keratinized layer is rougher when compared to keratinized epithelium and
- The elongated rate processes, which provide the attachment of epithelium to the underlying connective tissue, are deeper and narrower in keratinized epithelium as opposed to non keratinized epithelium.[3]

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of

differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium.[3]

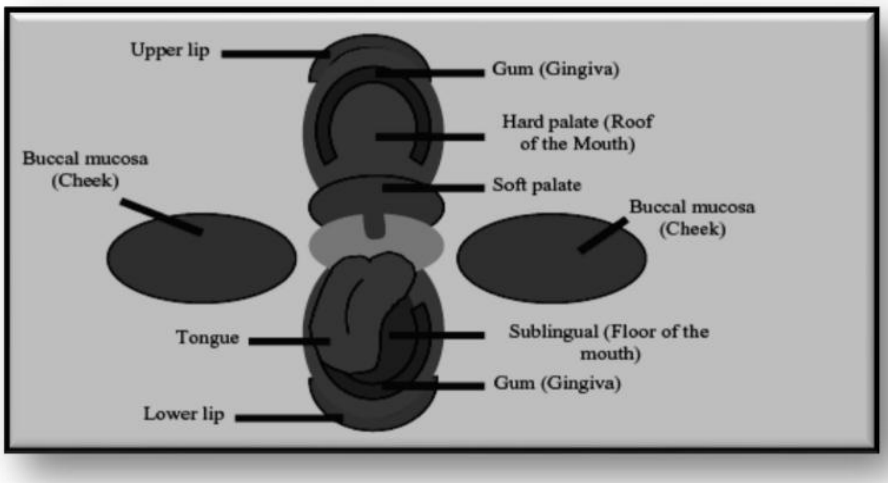

Figure 1: Anatomic regions of oral cavity.

STRUCTUREOFBUCCALMUCOSA

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (Figure 5). Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.

The turnover time for the buccal epithelium has been estimated at 5-6 days and this is probably representative of the oral mucosa as a whole.

The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue and the e measure at about 100-200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosa of areas subject to mechanical stress (the gingivae and hard palate) is keratinized similar to the epidermis. The mucosa of the soft palate, the sublingual and the buccal regions, however, are not keratinized.

The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function.[4]

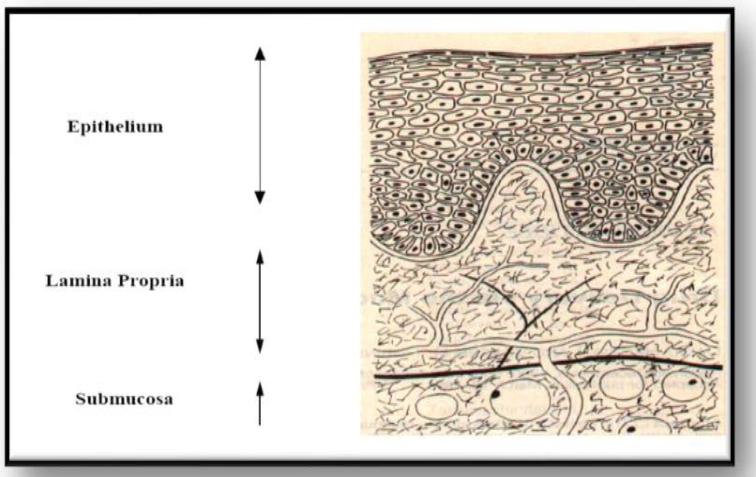

Figure 2: Schematic representation of the structure of oral mucosa.

Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa. In general, the permeability of the oral mucosa decreases in the order of sublingual greater than buccal and buccal greater than palatal region.

This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized and the palatal intermediate in thickness but keratinized.[4]

It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called ‘membrane coating granules’ (MCG). When cells go through differentiation, MCGs start forming and at the apical cell surfaces they fuse with the plasma membrane and their contents are discharged into the intercellular spaces at the upper one third of the epithelium. This barrier exists in the outermost 200μm of the

superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase and lanthanum nitrate.

When applied to the outer surface of the epithelium, these tracers penetrate only through outermost layer or two of cells. When applied to the sub mucosal surface, they permeate up to, but not into, the outermost cell layers of the epithelium. According to these results, it seems apparent that flattened surface cell layers present the main barrier to permeation, while the more isodiametric cell layers are relatively permeable. In both keratinized and non-keratinized epithelia, the limit of penetration coincided with the level where the MCGs could be seen adjacent to the superficial plasma membranes of the epithelial cells. Since the same result was obtained in both keratinized and non-keratinized epithelia, keratinization by itself is not expected to play a significant role in the barrier function.[4]

The components of the MCGs in keratinized and non-keratinized epithelia are different, however. The MCGs of keratinized epithelium are composed of lamellar lipid stacks, whereas the non-keratinized epithelium contains MCGs that are non-lamellar. The MCG lipids of keratinized epithelia include sphingomyelin, glucosylceramides, ceramides, and other non polar lipids, however for non-keratinized epithelia, the major MCG lipid components are cholesterol esters, cholesterol, and glycosphingolipids. Aside from the MCGs, the basement membrane may present some resistance to permeation as well, however the outer epithelium is still considered to be the rate limiting step to mucosal penetration. The structure of the basement membrane is not dense enough to exclude even relatively large molecules.[4]

Environment

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some may be attached to certain regions on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems. Another feature of the environment of the oral cavity is the presence of saliva produced by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals.

It allows for the continuous mineralization of the tooth enamel after eruption and helps in demineralization of the enamel in the early stages of dental caries. Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus and the degree of stimulation. The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the ph. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.[4]

BUCCAL MUCOSA AS A SITE FOR DRUG DELIVERY

There are three different categories of drug delivery within the oral cavity (i.e., sublingual, buccal and local drug delivery). Selecting one over another is mainly based on anatomical and permeability differences that exist among the various oral mucosal sites. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs and is convenient, accessible and generally well accepted. The sublingual route is by far the most widely studied of these routes. Sublingual dosage forms are of two different designs, those composed of rapidly disintegrating tablets and those consisting of soft gelatin capsules filled with liquid drug. Such systems create a very high drug concentration in the sublingual region before they are systemically absorbed across the mucosa.[5]

The buccal mucosa is considerably less permeable than the sublingual area and is generally not able to provide the rapid absorption and good bioavailability as with sublingual administration. Local delivery to tissues of the oral cavity has a number of applications, including the treatment of toothaches, periodontal disease bacterial and fungal infections aphthous and dental stomatitis and in facilitating tooth movement with prostaglandins. Even though the sublingual mucosa is relatively more permeable than the buccal mucosa, it is not suitable for an oral transmucosal delivery system.[5]

The sublingual region lacks an expanse of smooth muscle or immobile mucosa and is constantly washed by a considerable amount of saliva making it difficult for device placement. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action making it appropriate for drugs with short delivery period requirements with infrequent dosing regimen. Due to two important

differences between the sublingual mucosa and the buccal mucosa, the latter is a more preferred route for systemic transmucosal drug delivery.

First difference being in the permeability characteristics of the region, where the buccal mucosa is less permeable and is thus not able to give a rapid onset of absorption (i.e., more suitable for a sustained release formulation). Second being that, the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa which makes it a more desirableregion for retentive systems used for oral transmucosal drug delivery. Thus the buccal mucosa is more fitted for sustained delivery applications, delivery of less permeable molecules and perhaps peptide drugs. Similar to any other mucosal membrane, the buccal mucosa as a site for drug delivery has limitations as well.[5]

BUCCAL ROUTES OF DRUG ABSORPTION

There are two permeation pathways for passive drug transport across the oral mucosa: paracellular and transcellular routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.[6]

Transcellular Pathway

Drug permeation through the epithelial cells involves transport across the apical cell membrane, the intracellular space and the basolateral membrane as shown in Figure no.3. Drug transport through the transcellular pathway, also known as the intracellular pathway, may be by passive transport (diffusion, pH partition) of small molecules or by active transport (facilitated and carrier-mediated diffusion) of ionic and polar compounds and endocytosis and transcytosis of macromolecules.

Drug transport through the transcellular pathway is a complex phenomenon that is dependent on various physicochemical parameters of the drug, including molecular weight, lipophilicity, hydrogen bond potential, charge and conformation. Lipophilic compounds and small hydrophobic molecules predominantly undergo transcellular transport.

Transcellular diffusion is inversely proportional to the amount of membrane coating granules present in the intracellular spaces. Because the cell membrane is lipophilic in nature, hydrophilic drugs will have difficulty permeating the cell membrane due to a low partition coefficient. Passive transport of hydrophilic compounds, including macromolecules such as polypeptides and proteins, can be enhanced by the interaction of the absorption enhancing excipients with both the phospholipids bilayer and the integrated proteins. Some small water-soluble molecules such as amino acids, ions and sugars can be transported through the aqueous pores in the cell membrane.[6]

Para cellular Pathway

Drug permeation through the epithelial cells also involves transport through the lipids or in-between the epithelial cells as shown in Figure no.5. Paracellular pathway (also known as the intercellular pathway) can be of two types:

One is an essentially hydrophobic route, through the lipid bilayer and the other is a hydrophilic route associated with the narrow aqueous regions adjacent to the polar head groups of the lipid bilayer. For compounds transportedthrough the paracellular route, tortuosity and intercellular space are the main hindrances to permeability.

A substance with equal solubility in aqueous and lipid media can permeate by both para and transcellular pathways. However, because the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubility in this environment and thus this route will be preferred by hydrophilic compounds. Para cellular transport is of interest especially in peptide and protein drug delivery because the intercellular space does not contain peptidases.[6]

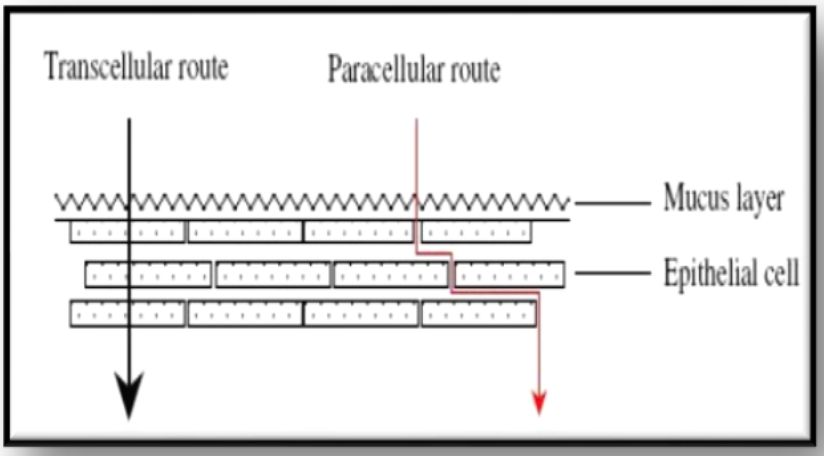

Figure 3: Buccal Routes of Drug Absorption.

ADVANTAGES OF BUCCAL ADHESIVE DRUG DELIVERY SYSTEM

- Ease of administration.[7]
- Drugs, which show poor bioavailability via the oral route, can be administered conveniently.[7]
- Termination of therapy is easily possible.[7]
- Permits localization of drugs to the oral cavity for prolonged period of time.[7]
- It can be administered to unconscious patient.[7]
- Eliminates first pass metabolism thereby offering a greater bioavailability.[7]

DISADVANTAGES OF BUCCAL ADHESIVE DRUG DELIVERY SYSTEM

- Low permeability sometimes results in low flux.[7]
- Total surface area available for absorption is less (~ 170 cm^2).[7]
- Size limitation of dosage form, so more appropriate for drugs with low dose.[7]
- Swallowing of saliva may lead to loss exposure of drug to GI tract.[7]
- Sometimes inconvenient and voluntary removal is possible.[7]

LIMITATIONS OF BUCCAL ADHESIVE DRUG DELIVERY SYSTEM

- Drugs, which irritates the mucosa or have a bitter unpleasant taste or odour cannot administer by this route.[7]
- This route cannot administer drugs, which are unstable at buccalpH.[7]
- Drugs with a large dose cannot be administered.[7]

- By this route we can administer only those drugs, which are absorbed largely by passive diffusion.[7]
- Eating and drinking may become restricted.[7]
- There is a possibility of swallowing the tablet by patient.[7]

STRUCTURE AND DESIGN OF BUCCAL DOSAGE FORM

Adhesive tablets are held between the gum and cheek. These are generally flat, elliptical or capsule shaped. The parotid duct empties into the mouth at a point opposite the crown of the second upper molar, near the spot where buccal tablets are usually placed. This location provides the medium to dissolve the tablets and to provide for release of the medication. Buccal tablets are prepared either by the procedures used for granulation or by direct compression. Formulation contains no disintegrants, so the tablet will dissolve slowly. Flavoring agents and sweeteners are sometimes added to make the tablets more palatable, but this may result in increased flow rate of saliva, important to minimize the swallowing of saliva during the time that the buccal tablet is held in place.

Since buccal tablets are to be held in the mouth for relatively long periods of time, particular care should be taken to see that all the ingredients are finely divided so that the tablets are not gritty or irritating. Buccoadhesive tablet may be monolithic or bilaminated system. The main disadvantages of the monolayer tablet is the multidirectional release of the drug, hence some of the fraction of drug may swallowed.

In order to avoid multidirectional release of the drug a bilaminated system was used. The Bilayered tablet made up of two layers, drug containing core layer and backing layer. The backing layer may be of water insoluble material like Ethyl cellulose or hydrogenated castor oil or may be polymeric coating layer which functioning as a adhesive and backing layer.

A mucoadhesive delivery system with a backing layer on one side can be used for local as well as systemic transmucosal drug delivery. Such a backing layer avoids sticking of the tablet to the finger during application in the oral cavity.[8]

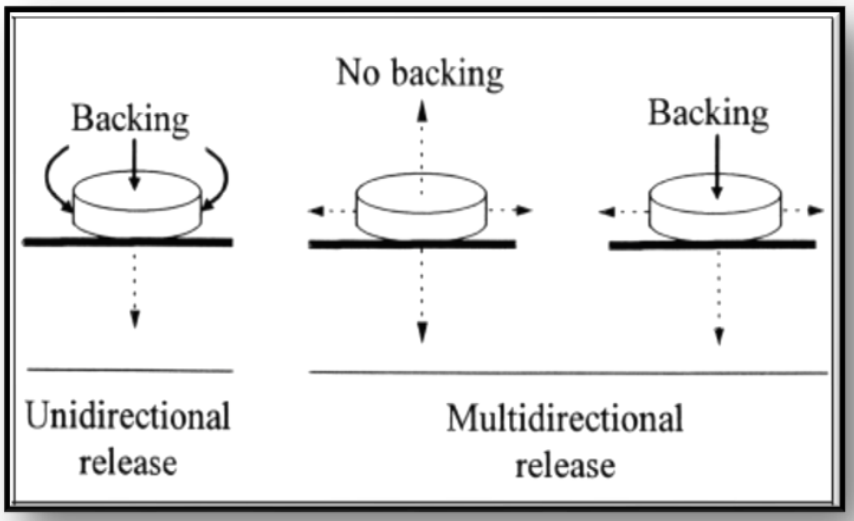

Figure 4: Schematic representation of unidirectional and multi-directional release from buccal tablet.

FACTORS AFFECTING DRUG DELIVERY VIA BUCCAL ROUTE

The rate of absorption of hydrophilic compounds is a function of the molecular size. Smaller molecules (75-100 Daltons) generally exhibit rapid transport across the mucosa, with permeability decreasing as molecular size increases. For hydrophilic macromolecules such as peptides, absorption enhancers have been used to successfully alter the permeability of the buccal epithelium, causing this route to be more suitable for the delivery of larger molecules.[8]

Only the non-ionized forms of molecules have the ability to cross-lipoidal membranes in significant amounts. The more lipid soluble a compound is, the higher its permeability. The permeability for these compounds is direct function of their oil-water partition coefficients.[8]

The partition coefficient is a useful tool to determine the absorption potential of a drug. In general, increasing a drug's polarity by ionization or the addition of hydroxyl, carboxyl or amino groups, will increase the water solubility of any particular drug and cause a decrease in the lipid-water partition coefficient. Conversely, decreasing the polarity of a drug (e.g. adding methyl or methylene groups) results in an increased partition coefficient and decreased water solubility. The partition coefficient is also affected by pH at the site of drug absorption. With increasing pH, the partition coefficient of acidic drugs decreases, while that of basic drugs increases.[8]

The partition coefficient is also an important indicator of drug storage in fat deposits. Obese individuals can store large amounts of lipid-soluble drug in fat stores. These drugs are dissolved in the lipid and are a reservoir of slow release from these fat deposits.[8]

The ionization of a drug is directly related to both its pKa and pH at the mucosal surface. Only the non-ionized form of many weak acids and weak bases exhibit appreciable lipid solubility and thus the ability to cross lipoidal membranes. As a result, maximal absorption of these compounds has been shown to occur at the pH at which they are unionized, with absorbability diminishing as ionization increases.[8]

In short one can say that the lipid solubility of drugs is an important factor in Transmucosal Drug Delivery system. Along with lipid solubility, drugs selected for Transmucosal Drug Delivery system must have physiochemical properties, including size and pKa that facilitate drug movement through the mucosa at a rate capable of producing therapeutic blood concentrations.

The drug must resist, or be protected by salivary and tissue enzymes that could cause inactivation. Additionally, the drug and adhesive materials must not damage the teeth, oral cavity, or surrounding tissues (e.g. by keratinolysis, discoloration and irritation).[8]

FACTORS INFLUENCING BUCCAL ABSORPTION OF DRUGS

As oral mucosa is highly vascular tissue the main factors that influence drug absorption from the mouth are as follows.[9]

Permeability of the oral Mucosa

The lipid membrane of the oral mucosa are resistant to the passage of large molecules, however small unionized molecules tends to cross the membrane with relative easy, other factors associated with this are:

- Mechanism involved in drug absorption across the oral mucosa.[9]
- Membrane storage during buccal absorption of drugs.[9]
- Regional differences in mucosal permeability.[9]
- Permeability barrier of the oral mucosa.[9]

Physiochemical Properties of the Drug[9]

The various physiochemical properties of the drug are of paramount importance as far as drug penetration across the oral mucosa is concerned:

- **Molecular weight:** In general as the molecular weight increase the penetration rate decrease.[9]
- **Degree of ionization:** The absorption of drug depends on unionized form of drug molecule in mouth, so ionization decreases the absorption.[9]
- **Lipid solubility**: - Buccal absorption has been shown to be positively correlated with drug partition coefficient. Drugs with greater lipid solubility (having higher partition coefficient) exhibit higher penetration.[9]
- **Partition coefficient**: - As the partition coefficient of drug increases partitioning of drug through the lipoidal membrane increases as the drug is lipidic in nature.[9]

METHODS TO INCREASE DRUG DELIVERY VIA BUCCAL ROUTE

Absorption enhancers

Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates. These may act by a number of mechanisms, sch as increasing the fluidity of the cell membrane, extracting inters/intracellular lipids, altering cellular proteins or altering surface mucin.[16] The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelleddextrans across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a co-transportmechanism.[10]

Table No. 1 List of Permeation Enhancers.

S. no	Permeation Enhancers	S. no	Permeation Enhancers
1	Aprotinin	12	Cetylpyridinium chloride
2	Benzalkonium chloride	13	Cyclodextrin
3	Cetyltrimethylammonium bromide	14	Glycol
4	Dextran sulfate	15	Lysophosphatidylcholine
5	Lauric acid	16	Phosphatidylcholine
6	Menthol	17	Polysorbate 80
7	Polyoxyethylene	18	Sodium glycocholate
8	Sodium EDTA	19	Sodium lauryl sulfate
9	Sodiumglycodeoxycholate	20	Sodium salicylate
10	Sodium taurocholate	21	Sulfoxides
11	Sodium taurodeoxycholate	22	2,3-Lauryl ether

BIOADHESION

American society of testing and materials has defined—Adhesion as the state in which two surfaces are held together by interfacial forces which may consist of valence forces,

interlocking action or both. Good defined Bio adhesion 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 to adhere to a biological tissue for an extended period of time. In biological systems, four types of bioadhesion can be distinguished.[11]

Adhesion of a normal cell on another cell,

- Adhesion of a cell with a foreign substance,
- Adhesion of a normal cell to a pathological cell,
- Adhesion of an adhesive to a biological substrate.

For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specified biological surface. The biological surface can be epithelial tissue or it can be them mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as Mucoadhesion. Leung and Robinson described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer.[11]

A bioadhesive is defined as a substance that is capable of interacting with biological materials and being retained on the more holding them to get her for extended period of time.

Bioadhesivesareclassifiedintothreetypesbasedonphenomenological observation, rather than on the mechanisms of bioadhesion.[11]

Type I: Bioadhesion is characterized by adhesion occurring between biological objects without involvement of artificial material .E.g.: Cell fusion and Cell aggregation.[11]

Type II: Bioadhesion can be represented by cell adhesion on to culture dishes or adhesion to a variety of substances including metals, woods and other synthetic materials.[11]

Type III: Bioadhesion can be described as adhesion of artificial substances to biological substrates such as adhesion of polymers to skin or other soft tissues.[11]

SIGNIFICANCE

The idea of mucoadhesive was derived from the need to localize drugs at a certain site in body. Extent of drug absorption can be enhanced by increasing the residence time of the drug at the absorption site. E.g. the drug absorption from ocular drug delivery is less than 2 min after the instillation of drug into eye. Since it is removed rapidly by solution drainage, the

ability to extend contact time of an ocular drug delivery system would undoubtedly improve bioavailability of drugs. Even in GI tract, many drugs are absorbed only from the upper part of small intestine. So, Localizing oral drug delivery systems in the stomach or in the duodenum would significantly improve the extent of drug absorption.[12]

Mucoadhesive dosage forms provide intimate contact between dosage form and the absorbing tissue, which may result in high localized drug concentration and hence high drug flux across the absorbing tissue. Furthermore, the intimate contact is likely to increase the total permeability of high molecular weight drugs such as peptides and proteins. By incorporating a permeation enhancer, drug absorption through mucus membrane can be enhanced. Thus bioavailability of the drug increases. Polymers is used to control the release of drug from the formulation. Hence the release of drug from the formulation is sustained.[12]

THEORIES OF MUCOADHESION (BIOADHESION)

For bioadhesion to occur, a succession of phenomena is required. The first stage involves an intimate contact between a bioadhesive and a membrane, either from a good wetting of the bioadhesive surface or from the swelling of the bioadhesive. In second stage, after contact is established, penetration of the bioadhesive in to the crevice of tissue surface or interpenetration of the chains of the bioadhesive with those of the mucus takes place.[13] On a molecular level, mucoadhesion can be explained on the basis of molecular interactions. The interactions between two molecules are composed of attraction and repulsion. Attraction interactions arise from Vander Waal forces, electrostatic attraction, hydrogen bonding and hydrophobic interaction. Repulsive interactions occur because of electrostatic and steric repulsion. For mucoadhesion to occur, the attractive interaction should be larger than non-specific repulsion.[13]

Several theories have been proposed to explain the fundamental mechanisms of adhesion:

1) Electronic Theory: Electron transfer occurs upon contact of an adhesive polymer with a mucus glycol protein network because of difference in the electronic structures. This results in the formation of electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.[13]

2) Absorption Theory: According to the adsorption theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished:

- Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because their strength may result in permanent bonds.
- Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Waal forces, hydrogen bonds and hydrophobic bond.[13]

3) Wetting Theory: Wetting theory is predominantly applicable to liquid bioadhesive systems. It analyses adhesive and contact behavior in terms of the ability of a liquid or a paste to spread over biological system.

The work of adhesion(W_a) is defined as the energy per square centimeter released when an interface is formed and is expressed in terms of surface and interfacial tension(γ). The work of adhesion is given by,

$$(W_a)=\gamma_A+\gamma_B-\gamma_{AB}$$

Where A and B refer to the biological membrane and the bioadhesive formulation respectively. The work of cohesion is given by,

$(W_c)=2\gamma_A$ **or** $2\gamma_B$

Forabioadhesivematerial Bspreadingonabiologicalsubstrate A, thespreading coefficient is given by,

$$S_{B/A}=\gamma_A-\gamma_B+\gamma_{AB}$$

$S_{B/A}$ should be positive for a bioadhesive material to adhere to a biological membrane.[13]

4) Diffusion Theory

According to diffusion theory, the polymer chains and the mucus mix to a sufficient depth to create as semi-permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact.[13]

5) Fracture Theory: Fracture theory attempts to relate the difficulty of separation of two surfaces after adhesion. Fracture theory is equivalent to adhesion strength is expressed by,

$G= (E_\varepsilon/L)^{½}$

Where E is Young‘s modulus of elasticity, ε is fracture energy and L is critical crack length when two surfaces are separated.[13]

FACTORS AFFECTING MUCOADHESION

Bioadhesion power of polymer or polymers is mainly affected by two factors,

POLYMER RELATED FACTORS

- **Molecular Weight:** The interpenetration of polymer molecules is variable for low molecular weight polymers, where as entanglements is favored for high molecular weight polymers.[14]
- **Concentration of Active polymer:** For solid dosage forms such as tablets, the higher the polymer concentration, the stronger is the bioadhesion.[14]
- **Flexibility of polymer:** Flexibility is important for interpenetration and entanglement.[14]
- **Spatial Conformation:** Bioadhesive power also depends upon confirmation of polymers, i.e., helical or linear. The helical conformation may shield many adhesively active groups, primarily responsible for adhesion, which bind strongly in linear conformation in contrast to the polymer of similar molecular weight.[14]

ENVIRONMENTAL-RELATED FACTORS

- **pH:** pH influences the charge on the surface of both mucus and polymers. Mucus will have a different charge, density depending on pH, because of differences in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone.[14]
- **Applied Strength**: To place a solid bioadhesive system, it is necessary to apply a defined strength. Whatever maybe the polymer, the adhesion strength increases with the applied strength or with the duration of its application.[14]
- **Initial Contact time**: The initial contact time between mucoadhesive and the mucus layer determines the extent of swelling and the interpenetration of polymerchains. The mucoadhesive strength increases as the initial contact time increases.[14]
- **Selection of the Model Substrate Surface**: The handling and treatment of biological substrates during the testing of mucoadhesive is an important factor. Physical and biological changes are likely to occur in the mucus gels or tissues under the experimental conditions.[14]
- **Swelling**: The swelling characteristic is related to the polymer itself, and also its environment, inter penetration of chains is easier as polymer chains are detangled and free of interactions.[14]
- **Physiological Variables**: Mucin turnover and disease states of mucus layer are physiological variables.[14]

BIOADHESIVE OR MUCOADHESIVE POLYMERS

Bioadhesive polymers are either water-soluble or water insoluble which forms willable networks joined by cross-linking agents. The polymer should possess optimal polarity to make sure it insufficiently wetted by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.[15]

An ideal polymer for a mucoadhesive drug delivery system should have the following characteristic:

- The polymer and its degradation products should be non-toxic and non-absorbable in the gastrointestinal tract.[15]
- It should be non-irritant to the mucus membrane.[15]
- It should preferably form a strong non-covalent bond with the mucin epithelial cell surfaces.[15]
- It should adhere quickly to moist tissue and should posses some site specificity.[15]
- It should allow easy incorporation of the drug and offer no hindrance to its release.[15]
- The polymer must not decompose on storage or during shelf life of the dosage forms.[15]
- The cost of the polymer should not be too high, so that the prepared dosage form remains competitive.[15]

Table No. 2: Mucoadhesive polymers with their mucoadhesive property[15]

Note: Excellent +++
Fair ++
Poor +

S no	Polymer	Mucoadhesive property
1	carbopol 934	+++
2	carboxy methyl cellulose	+++
3	polycarbophil	+++
4	Traganth	+++
5	Sodium Alginate	+++
6	Hydroxy ethyl cellulose	+++
7	Hydroxy propyl methyl cellulose	+++
8	Gum Karaya	++
9	Guar gum	++
10	Polyvinylpyrrolidone	+
11	Polyethylene glycol	+
12	Hydroxypropyl cellulose	+

MECHANISM OFPERMEATION VIA BUCCAL MUCOSA

There are two routes potentially involved in drug permeation across epithelial membranes. However, several barriers like basal lamina, keratin layer are encountered during the course of Para cellular permeation.[16]

KINETICS

The oral mucosal absorption of drugs could be adequately described by first order rate processes. Several potential barriers to oral mucosal drug absorption have been identified. These include the mucus layer, keratinized layer and inter cellular lipid of epithelium, basement membrane and laminapropria. In addition, the absorptive membrane thickness, blood supply, blood lymph drainage, cell renewal and enzyme contact will all contribute to reducing the rate and amount of drug entering the systemic circulation. Salivary secretions alter the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth. A linear relationship is proposed between salivary secretion and time.

Thus,

$$-dm / dt = KC/ (V_i + V_t)$$

Where m and C are the mass and concentration of drug in mouth at time t, V_i is the volume of solution put into mouth cavity and V_t is salivary secretion rate.[16]

FORMULATIONS OF BUCCAL DOSAGE FORMS

An ideal drug delivery system is that which possess two main properties:

- Spatial placement (Targeting a drug to specific organs/tissues).[17,18]
- Temporal delivery (Controlling the rate of drug delivery to the targeted tissues).[17, 18]

Unfortunately, such ideal systems which fulfill all the necessities are not available till today. This led to development of sustained / controlled release delivery systems. Sustained/ controlled delivery lacks in preventing the drug loss by either hepatic first pass metabolism or pre-systemic elimination like gastric, intestinal or colonal degradation. So several approaches have been tried out to form a suitable dosage form. Oral mucosal drug delivery, one of the physiological approaches was reported to be a method to formulate these drugs into suitable dosage form with good therapeutic effects. Oral mucosal drug delivery of different drugs can be achieved by bioadhesive polymer systems.[17, 18]

With a better understanding of the mechanism of bioadhesion, several bioadhesive dosage forms have be unreported. Because of the presence of a smooth and relatively immobile surface for placement of a bioadhesive dosage form, the buccal region appears to be more suitable for sustained delivery of therapeutic agents using a bioadhesive system. Relevant bioadhesive dosage forms in the buccal cavity include:

- Adhesive Tablets
- Adhesive patches
- Adhesive gels

Adhesive tablets: This is commonly investigated dosage form for buccal route. Tablets are small, flat and oval in shape. Tablets can be applied to different sites in the oral cavity. Unlike conventional tablets, bioadhesive tablets allow drinking and speaking without major discomfort.

Adhesive patches: Bioadhesive Patches may be of simple erodible and non-erodible adhesive discs to laminated systems in the size range of 1-16cm^2. This patch consists of impermeable backing layer, a drug containing reservoir layer, a bioadhesive surface for mucosal attachment. Backing layer controls the direction of drug release by preventing drug loss. These can be designed to provide either unidirectional or bi-directional release of the drug.[17,18]

Adhesive Gels: These are semi solid dosage forms which have the advantage of easy dispersion throughout the oral mucosa. Poor retention of the gels at the site of application has been overcome by using bioadhesive formulation.[17,18]

Table No. 3: Marketed and under clinical trials buccal formulations.

Brand name	Active Pharmaceutical ingredient	Effect	Company
Aphtach®	triamcinolone acetonide	local (mouth)	Teijin Ltd
Laurid	Miconazole	local (mouth and oropharynx)	Bioallaince Pharma (Phase III trials)
Striant SR	Testosterone	systemic	Invaron pharmaceuticals Actient pharmaceuticals
Buccastem	prochlorperazine	systemic	Reckitt Benckiser plc
Estrogen buccal tablets	Estrogen	systemic	Ivax corporation(Phase III trials)

AIM AND OBJECTIVE

AIM: The aim of the present investigation is to develop and characterize sustained release carvediol buccal tablets.

OBJECTIVE

- The buccal route was chosen because of its good accessibility, robustness of the epithelium, facile removal of the dosage form, relatively low enzymatic activity and natural clearance mechanism for elimination of the drug from buccal area, satisfactory patient compliance and avoidance of first pass hepatic metabolism
- The route provides intimate contact between dosage form and absorbing tissue thereby resulting in high drug concentration in a local area and hence high drug flux through the absorbing tissue and drugs showing poor and unpredictable absorption from the stomach and intestine can be administered via the oral mucosa.
- So an attempt has made to formulate Carvedilol as the buccal tablet. As the drug is directed through buccal region, drug reaches into systemic circulation directly.

EXPERIMENTAL SECTION

LIST OF CHEMICALS

The following chemicals are used:

Table 5: List of chemicals.

S.no	Chemicals	Manufacturer
1	Carvedilol	Provided by Chandra labs
2	Hydroxy propyl methyl cellulose	NP chem., Mumbai
3	Acacia	NP chem., Mumbai
4	Sodium alginate	Karnataka fine chem., Bangalore
5	Sodium saccharine	Taj Pharmaceuticals Ltd.,Mumbai
6	Magnesium stearate	Rolex lab, Mumbai
7	Micro crystalline cellulose	NR chem. Mumbai
8	Guar gum	NR chem. Mumbai

LIST OF EQUIPMENTS

The following equipment is used:

Table 6: List of equipments.

Equipments	Manufacturer
Tablet compression machine-16 station	Cad mach Machinery Co. Pvt. Ltd.
Electronic balance	Shimadzu
pH meter	ElicoPvt Ltd. India
Vernier calipers	Pico India ltd
Hardness tester	Pharma test
Fribilator	Thermo lab
UV spectrophotometer	Elico Pvt Ltd. India
FT-IR	Thermo electron corporation(Nicolet IR 200)
USP Dissolution Apparatus	lab India USP XXII

METHODOLOGY

COMPATIBILITY STUDIES

To investigate any possible interactions between the drug and excipients used, the FT-IR spectra of pure drug and its physical mixture with different polymers were carried out using thermo Electron Corporation (Nicolet IR 200 FTIR) spectrophotometer. The samples were prepared as KBr (potassium bromide) disks compressed under a pressure of 150 lbs. The wave number range is selected between 500 - 3500cm^{-1}.

Method: 1 mg of drug is mixed with the 100 mg of Spectroscopic grade of KBr and triturated for uniform mixing. The thin and transparent pellet is prepared by applying 150 lbs pressure. The prepared pellet is exposed to IR beam and spectra are recorded by using FT-IR**.**

CALIBRATION CURVE OF CARVEDILOL

Preparation of Phosphate buffer pH 6.8

Weigh accurately 100 mg of Carvedilol was dissolved in 100 ml of volumetric flask using dissolution medium (phosphate buffer) which gives concentration of 1000 µg/ml. Then 1ml of stock solution was taken and diluted to 100 ml which gives a concentration of 10 µg/ml, from this stock solution subsequent dilutions were made in phosphate buffer ph 6.8 in order to get 2µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, Absorbance of these solutions were measured at λ max 242nm using UV-Visible spectrophotometer and standard curve was plotted. The linearity plot was obtained for the aliquot concentration of 2, 4, 6, 8, 10µg/ml with the absorbance was seen at 242nm.

PRE FORMULATION STUDIES

Pre-formulation can be defined as an investigation of physical and chemical properties of a drug substance alone. The overall objective of pre-formulation studies is to generate information useful to the formulator in developing stable dosage forms.

MICROMERITIC PROPERTIES

Bulk density

Bulk density of powder is determined by pouring sample through a glass funnel into a graduated cylinder. The volumes occupied by the powder are recorded. True density is calculated.

Bulk density = weight of blend (gram) /Bulk volume of the blend (ml)

Tapped density

Tapped density of powder is determined by pouring sample through a glass funnel into a graduated cylinder. The tapped volume occupied by the powder is recorded. Tapped density is calculated.

Tapped density = weight of blend (gram) /tapped volume of the blend (ml)

Angle of repose

Flow ability of powder is determined by calculating angle of repose by fixed height method. A funnel with 10 mm inner diameter of stem is fixed at a height of 2 cm. over the platform. About 10 gm of sample is slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle is drawn around the pile base and the radius of the powder cone is measured. Angle of repose is calculated from the average radius using the following formula.

$$\tan\theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

Where,

θ=Angle of repose

h = Height of the pile

r = Average radius of the heap

Table 7: Relationship belongings angle of repose and powder flow.

S.no	% Compressibility Index	Flow ability
1	5 – 15	Excellent
2	12 – 16	Good
3	18 – 21	Passable
4	23 – 35	Poor
5	33 – 38	Very poor
6	< 40	Very very poor

Carr's Index

It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. A useful empirical guide is given by the Carr's compressibility.

Carr's index = (Tapped Density-bulk density / tapped Density) x100

Table 8: Relationship belongings compressibility index and powder flow.

S no	Angle of repose	Flow property
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	40 &above	Very poor

Hauser's Ratio

This is an indirect index of ease of powder flow. It is calculated by the following formula, Lower.

Hauser's ratio (<1.25) indicates better flow properties than higher ones (>)

Hauser's Ratio = Tapped Density / Bulk Density

FORMULATION OF MUCOADHESIVE TABLETS OF CARVEDILOL

PREPARATION

In this work, direct compression method has been employed to prepare buccal tablet with HPMC and Guar gum as polymers because with the dry granulation and wet granulation the hardness of tablets has increased because of which rate of drug release got decreased. For one tablet accurately weighed 300mg was used in the formulation.

Procedure: All the ingredients were accurately weighed and passed through mesh#60. In order to mix all ingredients thoroughly Drug, polymers, mannitol, micro crystalline cellulose, as part were blended geometrically in mortar and pestle for 10minutes then magnesium stearate were mixed for 1-2 min.

The powder blends of various proportions were evaluated for angle of repose, Carr's compressibility index and compressed into tablets of diameter 9 mm on Cad mach press 16 Station machine. Using stainless steel flat surface dies and punches by maintaining individual tablet weight constant at 300mg.

The Ethyl cellulose was placed on the prepared tablets from as an impermeable backing layer which was aimed to provide unidirectional drug release. The compositions of the prepared formulations areas specified in the table.

Table no 9: Composition of carvedilol buccal tablets.

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carvedilol	40	40	40	40	40	40	40	40	40
Hydroxyl propyll methyl cellulose	30	30	30	--	--	--	15	15	15
Guar gum	--	--	--	30	30	30	15	15	15
Acacia	15	15	15	15	15	15	15	15	15
Sodium alginate	15	30	45	15	30	45	15	30	45
Micro crystalline cellulose	174.4	166.9	151.9	174.4	166.9	151.9	174.4	166.9	151.9
Sodium saccharine	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Magnesium stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total weight	300	300	300	300	300	300	300	300	300

POST COMPRESSION PARAMETERS OF CARVEDIOL BUCCAL TABLETS

Thickness

The thickness of the tablets was measured by vernier calipers. It is expressed in **mm**.

Hardness

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablet was measured by Monsanto hardness tester. The tablets from each batch were used for hardness studies and results are expressed in **Kg/cm^2**.

Weight variation test

Ten tablets were selected at randomly from the lot and weighed individually to check for weight variation.

Friability

It was performed in Roche friabilator where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each revolution. Pre weighted samples of 20 tablets were placed in the Friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that loose less than 0.5 to 1% of their weight are generally considered acceptable.

% Friability= (initial weight-final weight/initial weight) x100

Determination of Drug content

Twenty tablets were taken and triturated well. The quantity equivalent to 40mg of carvedilol was dissolved in 100ml of phosphate buffer pH 6.8 solutions on rotary shaker overnight. The solution was centrifuged and supernatant was collected. The absorbance was measured using UV-Visible spectrophotometer at 242nm.

Microenvironment pH study

The microenvironment pH of the tablets was determined by the method proposed by Battenberg, et al, 1991. The tablets were allowed to swell for 2 hours in 2ml of pH 6.8 phosphate buffer (pH 6.8±0.05) in specially fabricated glass tubes and microenvironment pH was measured by placing the pH electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute.

Swelling Index

The swelling rate of the mucoadhesive tablet was evaluated using 5% w/v Agar gel plate for each formulation 3 tablets were weighed and average weight of 3 tablets was calculated. The tablets were placed with facing gel surface in 7 Petri dishes which were placed in an incubator at 37^0C±0.1. The tablets were removed at time intervals of 1, 4, 6 and 8hours, excess water on the surface was carefully absorbed using filter paper and swollen tablets were weighed. The average weight was determined and then swelling index was calculated using the formula.

Swelling Index = (initial weight-final weight/initial weight) x100

Determination of the Ex Vivo Residence Time

The ex vivo residence time was found using a locally modified USP disintegration apparatus. The disintegration medium was composed of 800 ml pH 6.8 phosphate buffer maintained at 37°C. The sheep buccal tissue was tied with thread to the central stand. The buccal tablet was hydrated with 0.5ml of pH 6.8 phosphate buffer and then the hydrated surface was brought in contact with the mucosal membrane. The tissue was allowed to run in such way that the tablet completely immersed in the buffer solution at the lowest point and was out at the highest point. The time taken for complete erosion or dislodgment of the tablet from the mucosal surface was noted.[53]

Figure 5: Assembly Ex-vivo mucoadhesion time.

In Vitro drug release study

In vitro drug release study of mucoadhesive tablets were performed using standard USP dissolution apparatus type II (lab India USP XXII). The bowls of the dissolution apparatus was filled with 500ml of phosphate buffer pH 6.8 and maintained at a temperature of 37±0.5^{0}C. For each time interval 5ml sample withdrawal and replacement of fresh media at predetermined time interval. The collected samples were filtered through the 0.45µm 59millipore filter. The samples were analyzed for drug content using double beam UV spectrophotometer at 242nm.

Ex-vivo Drug Permeation studies

Invitro permeation of buccal tablets through the excised Sheep buccal mucosal membrane was studied using modified Franz diffusion cell.

Diffusion cell: The diffusion studies were done to get an idea of permeation of drug through barrier from the membrane system. Usually, two types of diffusion cells are used as horizontal and vertical. The Franz and Keshary Chien (K-C) type of diffusion cells are of horizontal type of cells. Diffusion cells generally comprise two compartments, one containing the active component (donor compartment) and the other containing receptor solution (receptor compartment), separated by barrier i.e. Sheep buccal mucosal membrane.

Procedure: The receptor compartment is filled with the 20mL buffer solution of pH 6.8. this is covered with the sheep buccal mucosa. This is followed by the positioning of donor compartment. The tablet is hydrated with the 2ml of buffer and places it in the donor

compartment. Both compartments held tight by clamps. A magnetic bead is used as a stirrer. This diffusion cell is placed on the Magnetic stirrer which is maintained at the temperature of 37^0C.5ml of sample was withdrawn at regular intervals of 1,2,3,4,5,6,7 and 8hrs and replaced with the fresh media. The samples were analyzed for drug content using UV spectrophotometer at 242nm.

Figure 6: Franz diffusion cell for permeation studies.

Drug Release Kinetics

To examine the release mechanism of carvedilol from the prepared buccoadhesive tablets, the results were analyzed according to the following equation:

$$\frac{Mt}{M\infty} = k.t^n$$

Where M_t /M_∞ is the fractional drug released at time t, k is a kinetic constant incorporating structural and geometrical characteristics of drug / polymer system [device] and n is the diffusion exponent that characterizes the mechanism of drug release. It is known that for non-swelling tablets, drug release can generally be expressed by the Fickian diffusion mechanism, for which n=0.5, whereas for most erodible matrices, a zero order release rate kinetics is followed, for which n = 1. For non-fickian release, the n value falls between 0.5 and 1.0 (0.5< n< 0.89) whereas in the case super case II transport n > 0.89.

Data of the in-vitro release was fit in to different equations and kinetic models to explain the release kinetics of carvedilol from buccal tablets. The kinetic models used were zero-order equation (eq.1), first order equation (eq.2), Higuchi equation (eq.3), Korsmeyer-peppas and

equation (eq.4).

Zero Order Kinetics: A zero-order release would be predicted by the equation.

$$A_t=A_0-k_0t \quad \textbf{...1}$$

Where,

A_t=Drug release at time‘t’

A_0=Initial drug concentration

K_0=Zero order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

First Order Kinetics: A first-order release would be predicted by equation,

$$\text{Log } C = \text{Log } C_0 - \frac{K_t}{2.303} \quad \ldots 2$$

Where,

C=Amount of drug remained at time‘t’

C_0=Initial amount of drug

K=first-order rate constant (hr^{-1})

When the data is plotted as log cumulative percent drug remaining versus time yields a straight-line, indicating that the release follows First-order kinetics. The constant ‘K’ can be obtained by multiplying 2.303 with slope values.

Higuchi’s Model: Drug released from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation.

$$Q = \left[\frac{D\varepsilon}{\tau}(2A-\varepsilon C_s)C_s t\right]^{1/2} \quad \ldots 3$$

Where:

Q =Amount of drug released at time‘t’

D =Diffusion coefficient of the drug in the matrix

A =Total amount of drug in unit volume of matrix

Cs =the solubility of the drug in the diffusion medium

ε = Porosity of the matrix

τ = Tortuosity

T = Time (hrs) at which 'Q' amount of drug is released.

Equation (3) maybe simplified if one assumes that D, Cs and A are constant. Then equation (3) becomes:

$Q=Kt^{½}$ (4)

When the data is plotted according to equation (4) i.e., cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

4. Korsmeyer and Peppas Model: The release rates from the controlled release polymeric matrices can be described by the equation proposed by the korsemeyer et al.

$Q = K_1t^n$

Q= percentage of drug released at time't'

K= Constant incorporating structural and geometric characteristics of the tablet

n= Diffusion exponent indicative of the release mechanism.

Stability studies

Stability studies were performed at a temperature of $25±2^0$c and 65±5%RH and $40±2^0$c and 75±5%RH, over a period of three months (90days) for the optimized buccal tablet. Sufficient number of tablets were packed in amber colored screw capped bottles and kept instability chamber maintained at $40^0±1^0$C & 75% RH. Samples were taken at monthly intervals for drug content estimation. At the end of three months period, dissolution test and drug content studies were performed to determine the drug release profiles and drug content.

RESULTS AND DISCUSSION

COMPATIBILITY STUDIES

The FTIR spectroscopy is a useful tool for identifying both organic and inorganic chemicals. It can be utilized to quantify some components of an unknown mixture and can be used to analyze liquids, solids and gases. The FT-IR spectrum did not show presence of any additional peaks for new functional groups indicating no chemical interaction between drug and the used polymers.

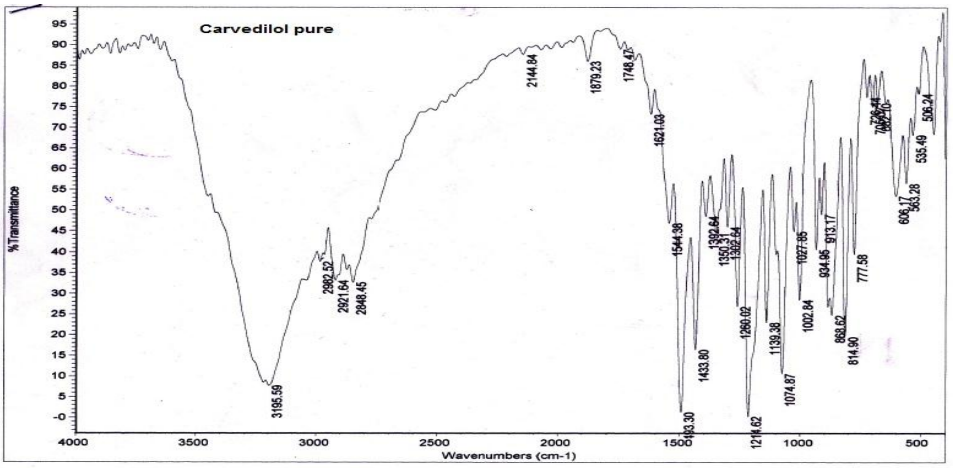

Fig no 7: FTIR Spectra of Carvedilol Pure drug.

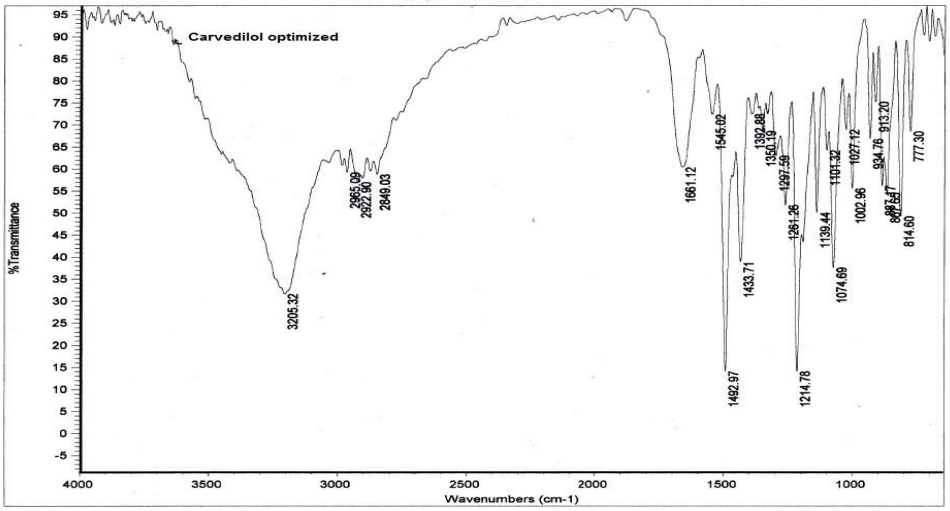

Fig no 8: FTIR Spectra of Carvedilol optimized.

Standard Plot of Carvedilol

The standard graph of Carvedilol has shown good linearity with R^2 values 0.9989 in pH 6.8 buffer, which suggests that it obeys the "Beer-Lambert's law".

Table 10. Standard curve for the estimation of Carvedilol buccal tablets with 6.8 pH Buffer

Conc. (mcg/mL)	Absorbance
0	0
2	0.092
4	0.181
6	0.262
8	0.345
10	0.421

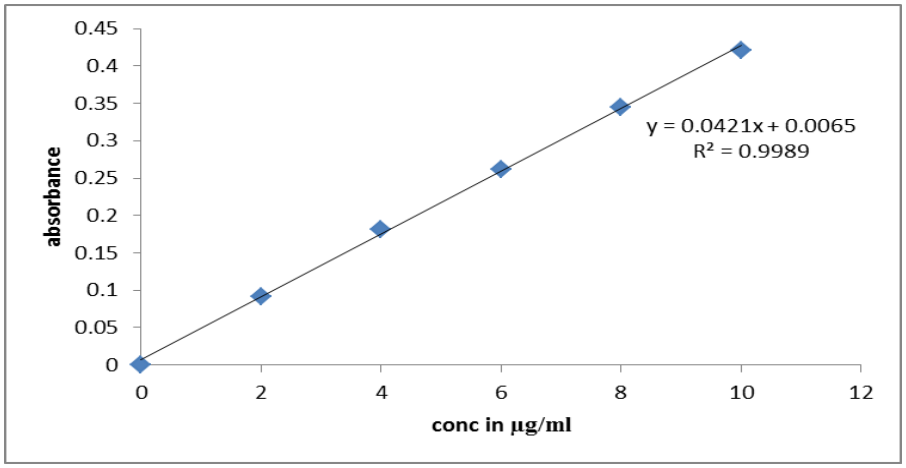

Figure 9: Standard plot of Carvedilol in 6.8 pH buffer.

Pre compression parameters of Blend

The blends for Bucoadhesive tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 30° and Carr's index values were less than 15 for the blend of all the batches indicating excellent to good flow ability and compressibility. Hausner's ratio was less than 1.11 for all the batches indicating excellent flow properties.

Table No. 11 Formulation codes and p^H.

F CODE	Surface pH
F1	6.4
F2	6.6
F3	6.5
F4	6.6
F5	6.5
F6	6.3
F7	6.5
F8	6.4
F9	6.6

Table 12. Physical Properties of Pre-compression Blend.

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio	Flow property
F1	30.25^0	0.342	0.386	11.39896	1.128655	Good
F2	30.43^0	0.358	0.412	13.1068	1.150838	Good
F3	22.87^0	0.326	0.334	2.39521	1.02454	Excellent
F4	22.45^0	0.334	0.348	4.022989	1.041916	Excellent
F5	24.37^0	0.442	0.499	11.42285	1.128959	Excellent
F6	29.41^0	0.321	0.334	3.892216	1.040498	Good
F7	22.88^0	0.326	0.333	2.39531	1.02464	Excellent
F8	30.13^0	0.360	0.414	13.1071	1.1509	Good
F9	24.30^0	0.447	0.500	11.42687	1.1311	Excellent

Physical Evaluation of carvediol buccal tablets

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 298.2±0.83 and 300.8±1.48mg. The hardness of the tablets ranged from 6.34±0.57 to 6.86±0.55 kg/cm^2 and the friability values were less than 0.5% indicating that the carvediol buccal tablets were compact and hard. The thickness of the tablets ranged from 2.52±0.17 to 2.65±0.66 mm. All the formulations satisfied the content of the drug as they contained 98 to 101% of carvedilol and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.

Table 13: Physical Evaluation of carvediol buccal Tablets.

F.Code	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)
F1	6.50 ±0.44	2.52±0.17	300.8±1.48	0.36	98.25±1.37
F2	6.60±0.31	2.57±0.25	299.4±0.54	0.39	99.48±0.80
F3	6.72±0.40	2.54±0.80	298.6±0.41	0.43	99.12±2.47
F4	6.86±0.55	2.50±0.20	298.8±1.64	0.12	100.22±0.88
F5	6.34±0.57	2.65±0.66	300.6±1.14	0.54	100.24±1.25
F6	6.49±0.30	2.63±0.25	298.2±0.83	0.58	99.53±1.87
F7	6.51±0.32	2.57±0.81	298.7±0.46	0.36	99.50±0.60
F8	6.53±0.35	2.58±0.80	298.9±0.64	0.39	99.32±0.87
F9	6.52±0.31	2.57±0.82	298.9±0.44	0.43	99.58±0.60

Microenvironment pH study

Table: Results of Microenvironment pH study

The surface pH of all formulations was found to be within ±1 units of neutral pH. The values are tabulated in the table no. Hence these formulations should not cause any irritation in buccal cavity.

Swelling Index

Table 14: Results of Percent swelling Index.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	20.8	24.6	30.4	14.8	18.3	20.7	20.1	21.3	18.4
4	48.1	51	56.2	30.1	35.3	38.5	46.2	55.2	56.7
6	59.6	63.8	67.5	50.4	54.4	60.6	68.5	76.5	67.9
8	76.45	79.4	85.6	65.8	70.7	74.4	88.3	89.6	85.6

The swelling behavior of a buccal adhesive system is an important properties uniform and prolonged release and effective mucoadhesion. The swelling index study indicated that the

rate of swelling was directly proportional to Sodium alginate and polymer content. Swelling index was calculated with respect to time. The swelling index gives an indication of the relative moisture absorption capacities of polymers and whether the formulations maintain their integrity after moisture absorption. The results of present formulation were tabulated in the table no.

Mucoadhesion time

Table 15: Effects of polymers on mucoadhesion time.

Formulation Code	Mucoadhesion time
F1	6
F2	8
F3	9
F4	5
F5	7
F6	>9
F7	6
F8	7
F9	9

In vivo residence time was determined by using sheep buccal mucosa. The mucoadhesion time is important to know how long the tablet could able to stick to the buccal mucosa. This adhesion time relates to the release rate of drug. The bioadhesive tablet is important for good mucoadhesion. Bioadhesion characteristics are affected by the type and ratios of bioadhesive polymers the results were tabulated in the table no.

In-vitro drug release study

Table 16: In-vitro release of formulation F1-F3.

Time (hrs)	F1	F2	F3
	%DR	%DR	%DR
0	**0**	**0**	**0**
1	17.6	9.8	7.2
2	39.8	17.2	15.0
3	52.31	23.80	20.9
4	70.61	45.6	33.8
5	86.3	60.1	58.0
6	98.2	70.8	65.1
7	--	89.0	79.3
8	--	99.6	86.7

Table No. 17 In vitro drug release profiles of formulations F4 to F6.

Time (hrs)	F4 %DR	F5 %DR	F6 %DR
0	0	**0**	0
1	21.3	20.6	19.8
2	34.9	30.4	25.1
3	48.6	42.6	33.6
4	52.1	54.1	48.2
5	74.8	68.7	56.1
6	98.5	85.9	68.5
7	--	99.6	74.2
8	--	--	90.6

Table No. 18 In vitro drug release profiles of formulations F7 to F9.

Time (hrs)	F7 %DR	F8 %DR	F9 %DR
0	0	**0**	0
1	21.3	20.6	19.8
2	34.9	30.4	25.1
3	48.6	42.6	33.6
4	52.1	54.1	48.2
5	74.8	68.7	56.1
6	97.3	77.4	68.5
7	--	85.9	74.2
8	--	98.6	80.6

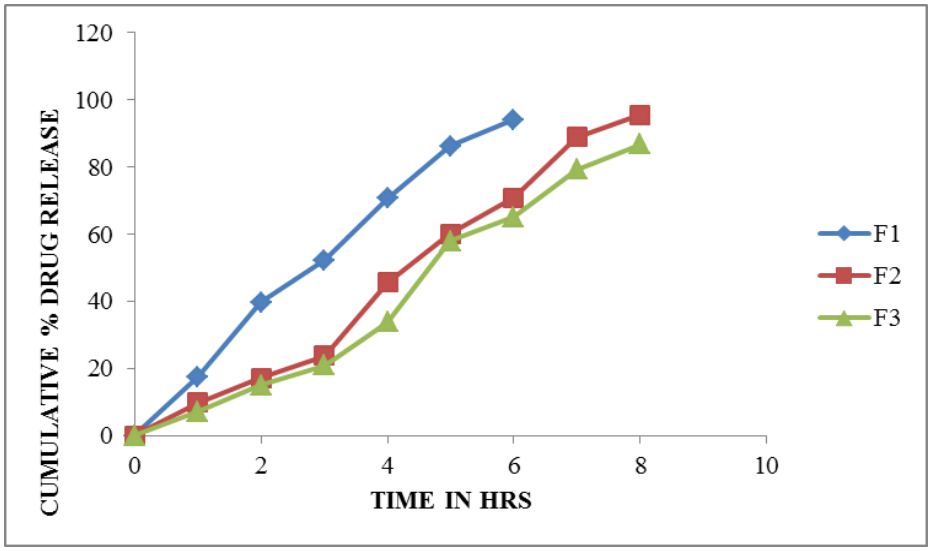

Figure 10: In-Vitro Drug Release for Formulation F1, F2, F3.

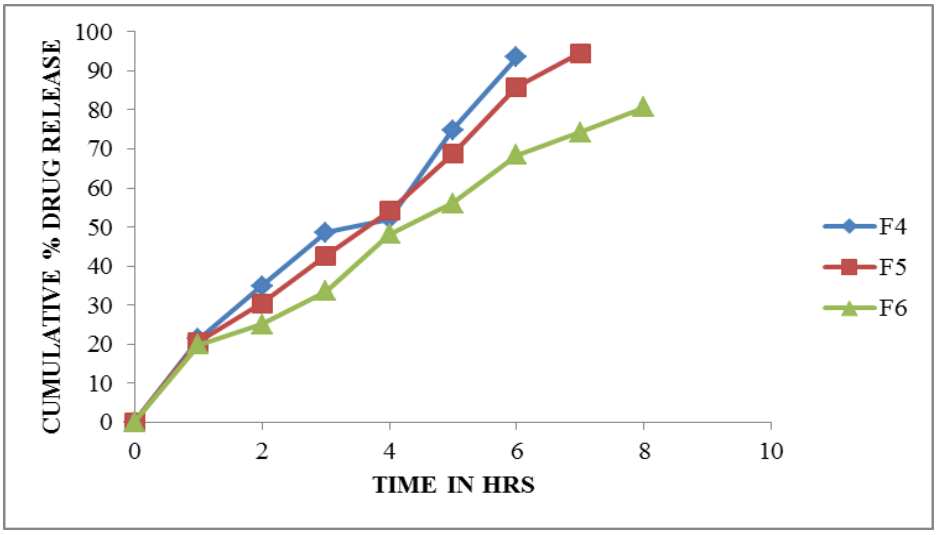

Figure 11: In-Vitro Drug Release for Formulation F4, F5, F6.

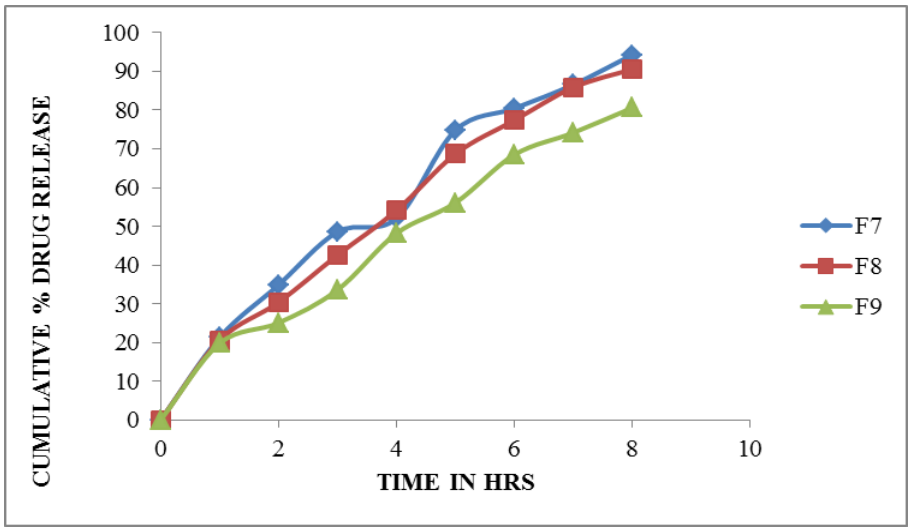

Figure 12: In-Vitro Drug Release for Formulation F7, F8, F9.

In-vitro drug release study

The In-vitro drug release study has been done for various formulations (F1-F9). The different ratios of polymers were used. The results shown that as the proportion of polymers in the formulation increases, cumulative percent drug released was found to be reduced. Among the nine l batches, formulation F_1, F_4 and F_7 have released 98.2%, 98.5% and 97.2% drug release in 6th hr respectively, F2 and F8 formulations shows drug release of 98.6% and 99.6 respectively. Among all F2 and F8 were optimized based on sustained drug release and highest drug release at 98.6% and 99.6 respectively at 8^{th} hr. But mucoadhesion time for F8 formulation was less than 8 hours so F2 was considered as best formulation.

Drug Release Kinetics for Optimized Formula F2

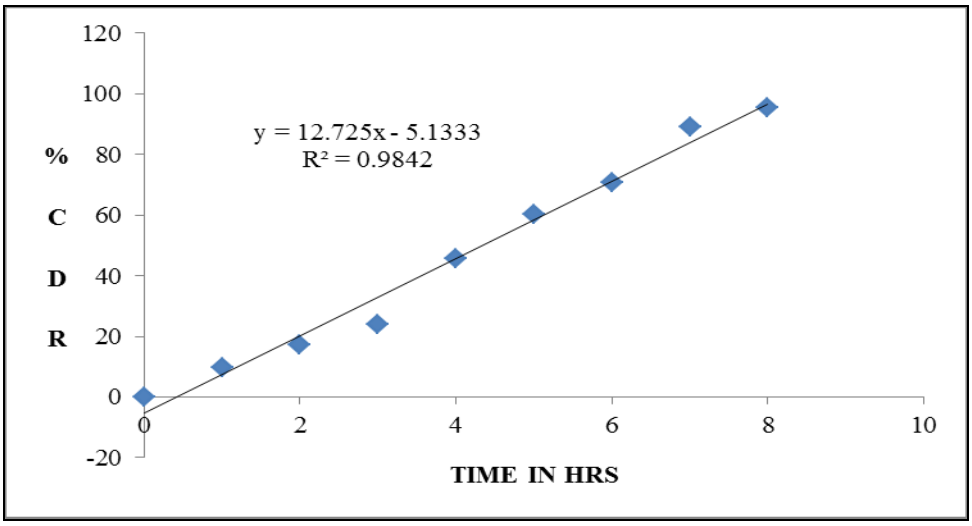

Figure 13: Zero order kinetic plots for formula F2.

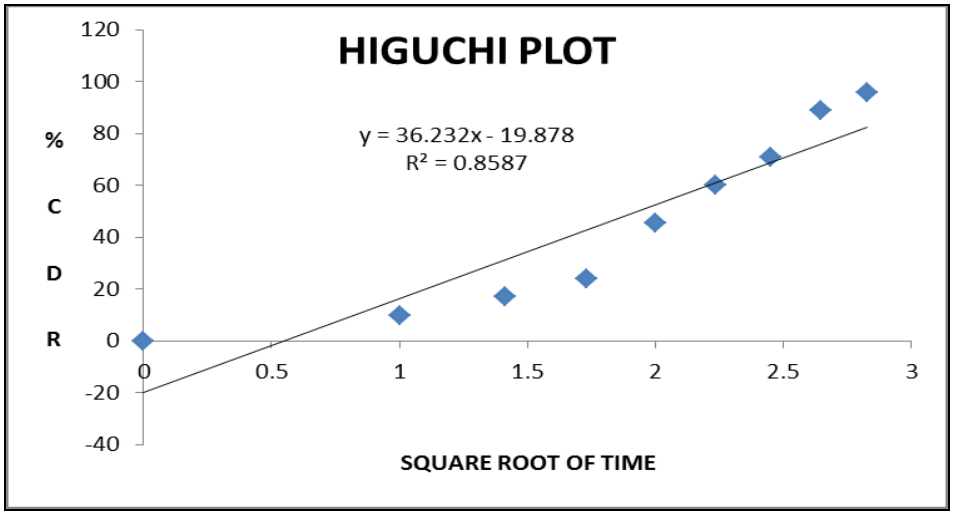

Figure 14: Higuchi kinetic plot for formula F2.

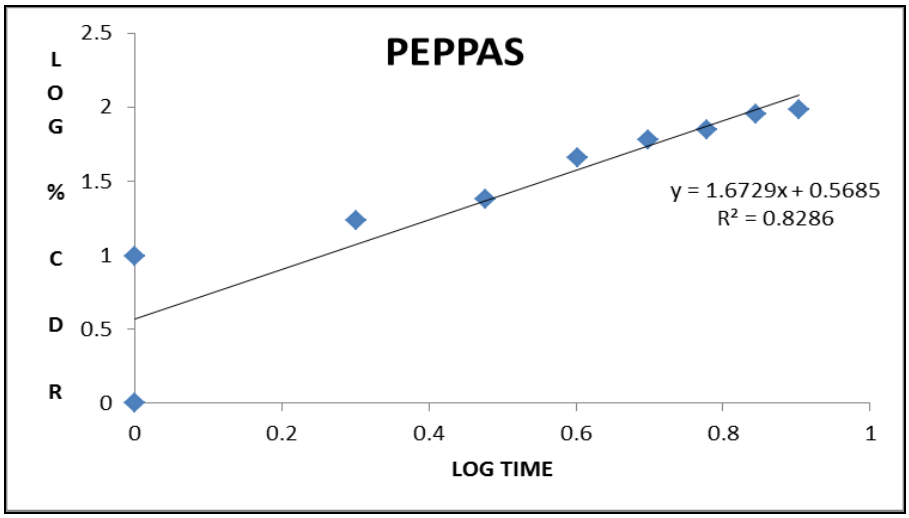

Figure15: Peppas kinetic plot for formula for F2.

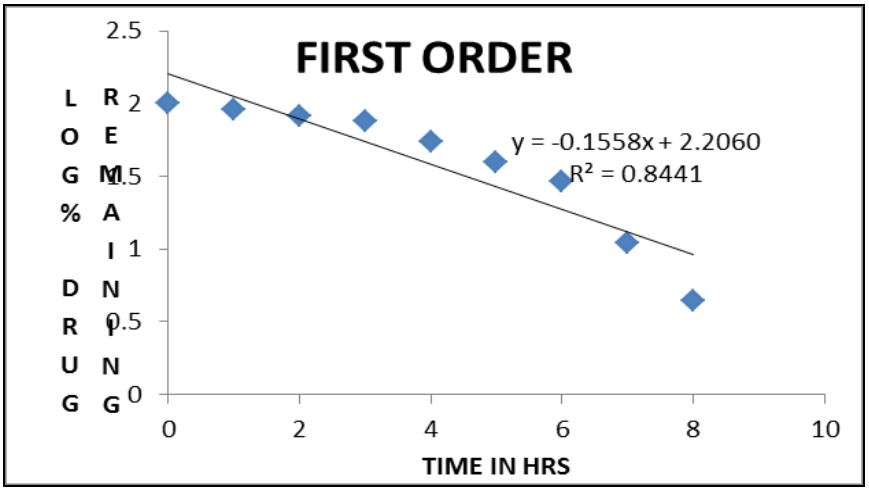

Figure 16: First Order Kinetic plot for Formula F2.

Invitro drug permeation studies for F2.

Table 19: Invitro drug permeation studies for F2.

Time(hrs)	F2
1	9.03
2	13.8
3	26.18
4	35.27
5	44.89
6	58.76
7	70.04
8	84.01

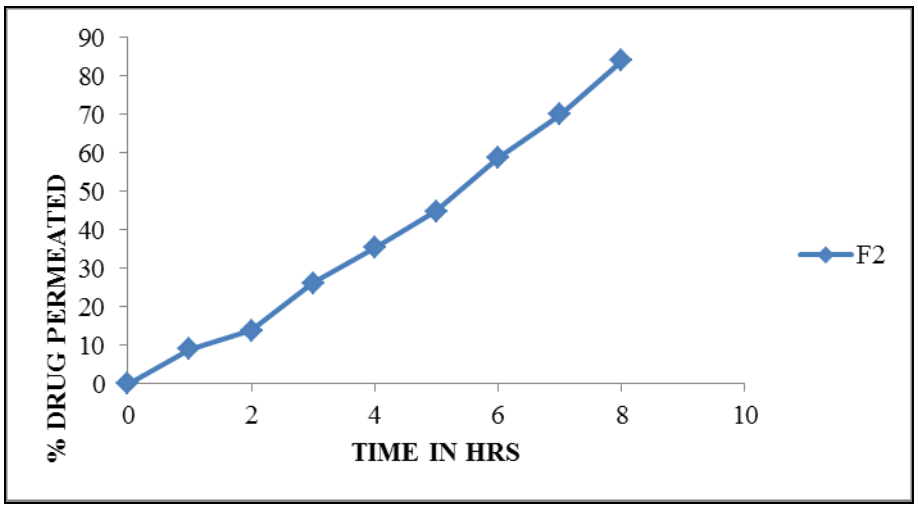

Figure 17: Plot showing permeation studies of formulation F2.

The drug permeation was slow and steady, 84.01% of drug could permeate through the buccal membrane in 8 hours.

Drug release kinetics

In-vitro drug release data of all the buccal tablet formulations was subjected to goodness of fit test by linear regression analysis according to zero order, first order, Higuchi's and Korsmeyer-Peppas models to ascertain the mechanism of drug release.

From the above data, it can be seen the formulation, F2 have displayed zero order release kinetics ('r^2 value of 0.9842). From Peppas data, it is evident that the drug is released by non-Fickian diffusion mechanism. This is because as the proportion of polymers in the matrix increased there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer. Zero-order release from swellable hydrophilic matrices occurs as a result of constant diffusional path lengths.

STABILITY STUDIES

Table 20: Stability studies of Carvedilol mucoadhesive tablet (F2) at room temperature.

Time	Color	Assay		Cumulative % drug release		Surface pH	
		25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH	25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH	25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH
First day	White	99.48	99.48	97.6	98.6	6.6	6.6
30 days	White	99.40	99.30	99.1	97.9	6.6	6.6
60 days	White	99.31	99.2	97.2	97.1	6.6	6.6
90 days	White	98.5	98.0	98	97.8	6.6	6.6

Results from stability studies indicate that the formulated carvedilol mucoadhesive tablet are stable for a period of 3 months under 2 different conditions at 25±2^{0}c and 65±5%RH and 40±2^{0}c and 75±5%RH. There were no remarkable changes were observed during the period of storage.

CONCLUSION

The aim of the study was to explore the drug delivery system of Carvedilol for treatment of antihypertensive. A satisfactory attempt was made to develop buccal drug delivery system of Carvedilol and evaluate it.

From the reproducibility results obtained by the executed experiments it can be concluded that:

Influence of the formulation variables on hardness, drug uniformity, mucoadhesive strength, drug release is evident.

Formulation F2 has successfully sustained the release of Carvedilolin buccal cavity, with great mucoadhesive strength.

Formulation F2 showed good pre compression and post compression parameters and follows zero order and higuchi kinetics.

After the Stability studies the optimized formulation doesn't show any remarkable change in drug release.

Based on the all experiment results it can be concluded that hydroxy propyl methyl cellulose and sodium alginate containing buccal formulation would be the suitable candidate for mucoadhesive drug delivery of Carvedilol with sustained release properties for the treatment of hypertension.

It can be concluded that carvedilol can certainly be administered through the oral mucosa. The designed buccoadhesive tablets can overcome the disadvantage of extensive first pass effect and low oral bioavailability of carvedilol. This increased and predictable availability of carvedilol from designed formulation may result in substantial dose reduction of the dosage form when the drug is administered through oral mucosa so that it will be economical to the patient. Further work is recommended to support its efficacy claims by pharmacokinetic and pharmacodynamic studies in human beings.

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