FORMULATION AND EVALUATION OF KETOROLAC MUCOADHESIVE BUCCAL TABLETS

A Dissertation submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY
CHENNAI - 600 032

In partial fulfillment of the requirements for the award of the Degree of

MASTER OF PHARMACY
IN
BRANCH-I -> PHARMACEUTICS

Submitted by

GITIKA KUMARI
261710005

Under the guidance of

Dr. GRACE RATHNAM, M.PHARM., Ph.D.,

DEPARTMENT OF PHARMACEUTICS

DEPARTMENT OF PHARMACEUTICS,
C. L. BAID METHA COLLEGE OF PHARMACY,
(AN ISO 9001-2000 CERTIFIED INSTITUTE)
THORAIPAKKAM, CHENNAI – 600 097.

November 2019

Phone : 24960151, 24962592, 24960425
e-mail : clbaidmethacollege@gmail.com
Website : www.clbaidmethacollege.com

C.L. Baid Metha College of Pharmacy
An ISO 9001:2008 approved institution
Jyothi Nagar, Old Mahabalipuram Road,
Thorapakkam, Chennai - 600 097.

Affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai.
Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education, New Delhi

Dr. Grace Rathnam, M.Pharm., Ph.D.,
Principal & HOD,
Department of Pharmaceutics.

THE CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF KETOROLAC MUCOADHESIVE BUCCAL TABELTS"** was submitted to **THE TAMIL NADU Dr. M. G. R. MEDICAL UNIVERSITY, CHENNAI-600032** by **GITIKA KUMARI (Reg. No. 261710005)** under the guidance of **Dr. Grace Rathnam, M.Pharm., Ph.D., Professor, Department of Pharmaceutics** in partial fulfillment of the requirements for the award of the Degree of **MASTER OF PHARMACY** in **PHARMACEUTICS.** The project was carried out at C. L. Baid Metha College of Pharmacy, Chennai-600097 under my supervision in the Department of Pharmaceutics during the academic year 2018-2019.

Dr. Grace Rathnam, M.Pharm., Ph.D.,
Principal & HOD,
Department of Pharmaceutics,
C. L. Baid Metha College of Pharmacy,
Chennai-600097.

Place : Chennai-600097
Date :

DECLARATION

I hereby declare that the dissertation work entitled **"FORMULATION AND EVALUATION OF KETOROLAC MUCOADHESIVE BUCCAL TABELTS"** has been originally carried out by me at C. L. Baid Metha College of Pharmacy Chennai-600097, under the guidance and supervision of **Dr. Grace Rathnam, M.Pharm., Ph.D.,** Professor, Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-600097 during the academic year 2018-2019.

GITIKA KUMARI
[Reg. No: 261710005]
Department of Pharmaceutics,
C. L. Baid Metha College of Pharmacy,
Chennai-600097.

Place : Chennai-600097
Date :

ACKNOWLEDGEMENT

Indeed, it is my great pleasure to express my humble gratitude on the successful completion of my thesis work. I am very thankful to my respective guide Dr. Grace Rathnam, M.Pharm., Ph.D., Professor, Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-600097. I am honored to have worked under her guidance with constant encouragement and support throughout my research work. I am very obliged for the patience with which she guided me at every step of my research work.

I extend thank to store department incharge, Mr. Srinivasan and Mrs. Rajalakshmi library incharge, C. L. Baid Metha College of Pharmacy, Chennai for helping me to utilize lab and library facilities.

I also thank parents and members of my family, who has always supported me as morally as well as economically. At last but not least, gratitude goes to all our faculty members, my friends who directly or indirectly assisted me to complete this project

GITIKA KUMARI

[Reg. No: 261710005]

Department of Pharmaceutics,

C. L. Baid Metha College of Pharmacy,

Chennai-600097.

Place : Chennai-600097

Date : 16/05/2019

CONTENTS

1. INTRODUCTION

"Novel Drug delivery System" (NDDS)[1] refers to the approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects.

Novel drugs are often innovative products that serve previously unmet medical needs or otherwise significantly help to advance patient care and public health. Evolution of an existing drug molecule from a conventional form to a novel delivery system can significantly improve its performance in terms of patient compliance, safety and efficacy. In the form of a Novel Drug Delivery System an existing drug molecule can get a new life.

Conventional drug delivery involves the formulation of the drug into a suitable form, such as a compressed tablet for oral administration or a solution for intravenous administration. These dosage forms have been found to have serious limitations in terms of higher dosage required, lower effectiveness, toxicity and adverse side effects. New drug delivery systems have been developed or are being developed to overcome the limitation of the conventional drug delivery systems to meet the need of the healthcare profession.

1.1 Buccal drug delivery system[2]

Buccal drug delivery is a favorable route compare to parenterals, injectable and adds a several advantages over other routes. The parenteral route offers excellent bioavailability, similarly having poor patient compliance, anaphylaxis, and some other infections. Peroral route possess some inconvenience to patients. Hence for the immediate release of medication and for instant release at desire location in which the drug is absorbed distributer and easily metabolized. This limitation leads to the development of alternative routes of administration. Buccal mucosa has absorptive function and offers many benefits like avoidance of first pass effect, which is a non-invasive route, increase in bioavailability, a rapid action is possible and reduce side effects.

Buccal, sublingual, palatal and gingival regions shows effective drug delivery in oral cavity. Buccal tabets can be administered in the oral cavity as shown in Fig.1. Buccal and sublingual route of drug delivery are most widely in which local and systemic effects are treated. The permeability of oral mucosa denotes the physical nature of the tissues. The permeable part is

sublingual mucosa and buccal mucosa is thinner part and in which there is a high blood flow and surface area; it is a feasible site when a rapid onset of action is desired. For the treatment of acute disorders sublingual route is a preferred one; however its surface washed with saliva which makes formulations in the oral cavity hard in nature.

Fig. 1. Administration of buccal tablet

Buccal drug delivery system[3] is well accepted because it is having several advantages. Buccal areas offer a control release system which is having immobile surface. The buccal layer is tolerate to potential allergens and has capability of preventing damage compare to other mucosal tissues. In treatment of the local or systemic therapies, buccal mucosa favors a useful measure by overcoming drawbacks and as convenient route for the administration. This type of route is well vascularized draining to the heart unswervingly via the internal jugular vein.

In chronic systemic therapies[4] buccal drug delivery acts as potential site and chemical modification due to salivary production and its composition. There is a chance of drug loss at site of absorption in case of the oral route and for some dosage form salivary scavenging is constant with in oral cavity which make difficult for retaining to an extensive duration at the site to enhance the absorption. Bioadhesive polymers have prolonged contact time with the tissues and can notably maintain the performance of several drugs. The controlled drug delivery products have high patient compliance and a low cost with enhanced bioavailability.

The unique environment of the oral cavity offers its potential as a site for drug delivery. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug

administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. Therapeutic agents administered through buccal mucosa enters directly to the systemic circulations and thereby circumvent the first pass hepatic metabolism, gastric irritation and other problems associated with conventional oral route.

1.2 Advantages[5]

1. It is richly vascularised and additional reachable for administration and removal of formulations.
2. Patient accessibility is high.
3. Retentive dosage forms are suitable for administration.
4. Improves bioavailability by eliminating first pass metabolism.
5. Surface of buccal mucosa achieves a fast cellular recovery.
6. Low enzyme activity.
7. Non-invasive method of drug administration.
8. Ability to incorporate permeation enhancer in the formulation.

1.3 Disadvantages[5]

1. Buccal membrane has low permeability.
2. Small surface area (170 cm^2).
3. Continuous secretion of saliva results in following dilution of the drug.
4. Inconvenience route of drug administration when the patient is swallowing or taking.

1.4 Limitations[5]

1. There is a chance of swallowing and the effect of salivary scavenging.
2. Protective characteristics of buccal mucosa.
3. Relatively small absorption area.

1.5 Mucoadhesive drug delivery system[6]

Mucoadhesive drug delivery system is now-a-days a booming field for research interest. These are delivery systems, which utilize the property of bioadhesion of certain

polymers. Mucoadhesive buccal drug delivery systems offer many advantages over conventional systems such as ease of administration, be promptly terminated in case of toxicity by removing the dosage form from buccal cavity and it is also possible to administer drugs to patients who cannot be dosed orally via this route. Recently much attention has been focused on the design and evaluation of buccal drug delivery systems keeping in view their potential for future market. Therefore a buccal drug delivery system needs to be developed and optimized. An ideal buccal adhesive system must have the following properties: should adhere to the site of attachment for few hours, should release the drug in controlled manner and should provide the drug release in a unidirectional way in the mucosa. The unique environment of the oral cavity offers its potential as a site for drug delivery. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. Therapeutic agents administered through buccal mucosa enters directly to the systemic circulations and thereby circumvent the first pass hepatic metabolism, gastric irritation and other problems associated with conventional oral route.

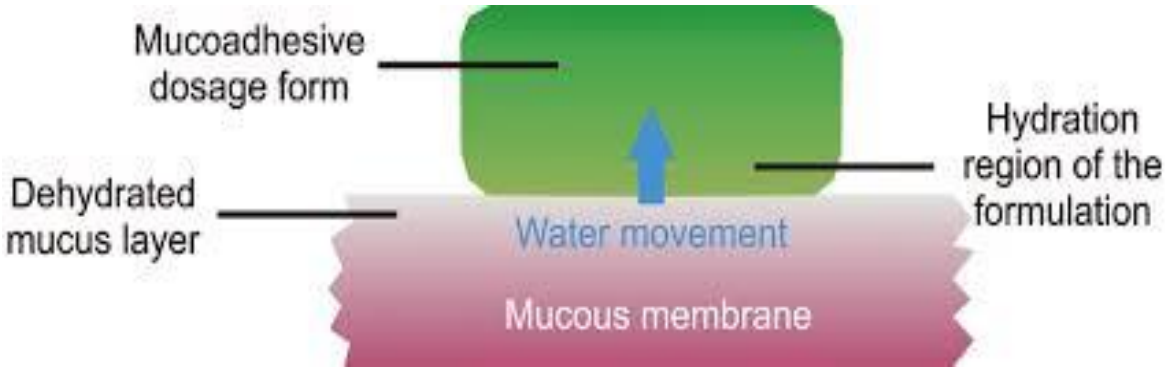


Fig.2. Interaction of mucous membrane with mucoadhesive dosage form

Mucoadhesive drug delivery system interact with the mucus layer covering the mucosal epithelial surface, & mucin molecules & increase the residence time of the dosage form at the site of the absorption as depicted in Fig.2. Mucoadhesive drug delivery system is a part of controlled delivery system.

1.6 Mechanism of mucoadhesion[7]

Several theories have been put forward to explain the mechanism of polymer–mucus interactions that lead to mucoadhesion. To start with, the sequential events that occur during bioadhesion include an intimate contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive as shown in Fig.3. Following this is the penetration of the bioadhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Subsequently low chemical bonds can become operative.

Hydration of the polymer plays a very important role in bioadhesion. There is a critical degree of hydration required for optimum bioadhesion. If there is incomplete hydration, the active adhesion sites are not completely liberated and available for interaction. On the other hand, an excessive amount of water weakens the adhesive bond as a result of an overextension of the hydrogen bonds. During hydration; there is a dissociation of hydrogen bonds of the polymer chains. The polymer–water interaction becomes greater than the polymer-polymer interaction, thereby making the polymer chains available for mucus penetration. Following polymer hydration intermingling between chain segments of the mucoadhesive polymer with the mucus occurs.

The factors critical for this model of mucoadhesion are the diffusion coefficient of the polymer, contact time and contact pressure. The polymer diffusion coefficient is influenced by the molecular mass between cross-links, and is inversely related to the cross-linking density.

Mechanism of mucoadhesion

Stage1- wetting and swelling of polymer (contact stage)

Stage2- interpenetration between the polymers chains and the mucosal membrane

Stage3- formation of bonds between the entangled chains (both known as consolidation stage)

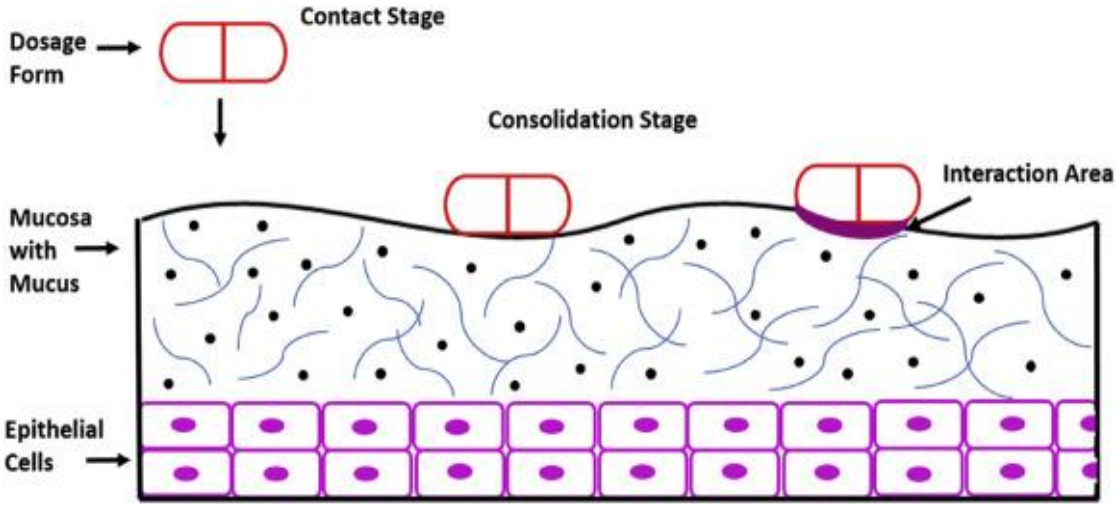


Fig. 3. Mechanism of mucoadhesion

1.7 Theories of mucoadhesion[7]

1. Diffusion Theory: The essence of this theory is that chains of the adhesive and the substrate interpenetrate one another to a sufficient depth to create a semi-permanent adhesive bond. The penetration rate depends on the diffusion coefficient of both interacting polymers, and the diffusion co-efficient is known to depend on molecular weight and cross-linking density. In addition, segment mobility, flexibility of the bioadhesive polymer, mucus glycoprotein, and the expanded nature of both network are important parameters that need to beconsidered.

2. Electronic Theory: The adhesive polymer and mucus typically have different electronic characteristics. When these two surfaces come in contact, a double layer of electrical charge forms at the interface, and then adhesion develops due to the attractive force from electron transfer across the electrical double layer.

3. Adsorption Theory: The adsorption theory of bioadhesion proposes that adhesion of a polymer to a biological tissue results from:

(i) Primary bonds that is somewhat permanent and therefore undesirable in bioadhesion

(ii) Vander Waals, hydrogen, hydrophobic and electrostatic forces, which form secondary chemical bonds.

4. Wetting Theory: Primary application to liquid bioadhesive system, the wetting theory emphasizes the intimate contact between the adhesive and mucus. Thus, a wetting surface is controlled by structural similarity, degree of cross linking of the adhesive polymer, or use of a surfactant. The work of adhesion; expressed in terms of surface and interfacial tension (Y) being defined as energy per cm^2 released when an interface is formed.

According to Dupres equation work of adhesion isgiven by:

$$Wa = Y_A + Y_B - Y_{AB}$$

Where, A & B refer to the biological membranes and the bioadhesive formulation respectively.

The work of cohesion is given by:

$$Wc = 2Y_A \text{ or } Y_B$$

For a bioadhesive material B spreading on a biological substrate, the spreading coefficient is given by:

$$S_{B/A} = Y_A - (Y_B + Y_{AB})$$

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

5. Fracture: Fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by

$$G = (E\varepsilon / L)$$

Where: E=Young's modules of elasticity

ε =Fracture energy

L=Critical crack length when two surfaces are separated

1.8 Bioadhesion[8]

Bio-adhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time. Bio-adhesive polymeric systems have been used since extent in the development of products for various biomedical applications which include denture adhesives and surgical glue.

Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile

environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption. Mucoadhesive controlled-release devices can improve the effectiveness of a drug by maintaining the drug concentration between the effective and toxic levels, inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site. Mucoadhesive characteristics are a factor of both the bioadhesive polymer and the medium in which the polymer will reside. Buccal dosage forms can be of Matrix or Reservoir types. However, this route could become a significant means for the delivery of a range of active agents in the coming years, if the barriers to buccal drug delivery are overcome.

Mucoadhesive polymers are synthetic or natural macromolecules which are capable of attaching to mucosal surfaces. The concept of mucoadhesive polymers has been introduced into the pharmaceutical literature more than 40 years ago and nowadays it has been accepted as a promising strategy to prolong the residence time and to improve the specific localization of drug delivery systems on various membranes.

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract that prohibits oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosas are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug absorption.

1.9 Factors affecting bioadhesion[8]

1. Polymer-Related Factors

i) Polymer molecular weight- The optimum molecular weight for themaximum bioadhesion depends on the type ofpolymers. The bioadhesive forces increaseswith the molecular weight of bioadhesivepolymer.

ii) Molecular flexibility- It is important for interpenetration and enlargement. As water soluble polymers become cross linked, the mobility of the individual polymer chain decreases. As the cross linking density increases, the effective length of chain which can penetrate into the mucus layer decreases even further and mucoadhesive strength is reduced.

iii) Concentration of active polymer- There is an optimum concentration of polymer corresponding to the best bioadhesion. In highly concentrated system, the adhesive strength drops significantly.

iv) Polymer chain length- The polymer molecule must have an adequate length.

2. Environment Related Factors

i) pH- pH was found to have a significant effect of mucoadhesion are observed in studies of polyacrylic polymer cross linked with COOH group. pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different chart density depending on pH because of differences in dissociation of functional groups on the carbohydrate moiety and amino acids of polypeptide backbone.

ii) Hydrogen bonding capacity- Hydrogen bonding is another important factor in mucoadhesion of a polymer. Park and Robinson found that in order for mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds. They have also confirmed that flexibility of the polymer is important to improve this hydrogen bonding potential.

iii) Charge- Some generalizations about the charge of bioadhesive polymers have been made previously, where nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. It has been shown that 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, have shown to possess good adhesive properties.

iv) Hydration (swelling)- 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.

1.10 Mucoadhesive sites in the body[9]

The various sites available for mucoadhesion in the body are :

- Ocular
- Oral – GIT
- Buccal
- Nasal
- Rectal
- Vaginal

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 onset along with bypassing the first-pass metabolism, but these sites suffer from inconvenience because of taste and intake 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. Nasal and ophthalmic routes have another drawback of mucociliary drainage and clearance by tears, respectively, that would clear the dosage form from the site.

1.11 Oral mucosa[9]

Buccal cavity is a component of mouth in which lips and cheeks are anteriorly bounded and teeth, gums bounded posteriorly and medially. The buccal glands are positioned between the mucous membrane and buccinator muscle as shown in Fig. 4. The thickness of buccal mucosa is having uneven texture and about 500-800 μm and buccal epithelium return

time at 5-6 days. The non-keratinised stratified squamous epithelium lines the buccal mucosa and having 500-600μ and surface area of about 50.2 cm^2.

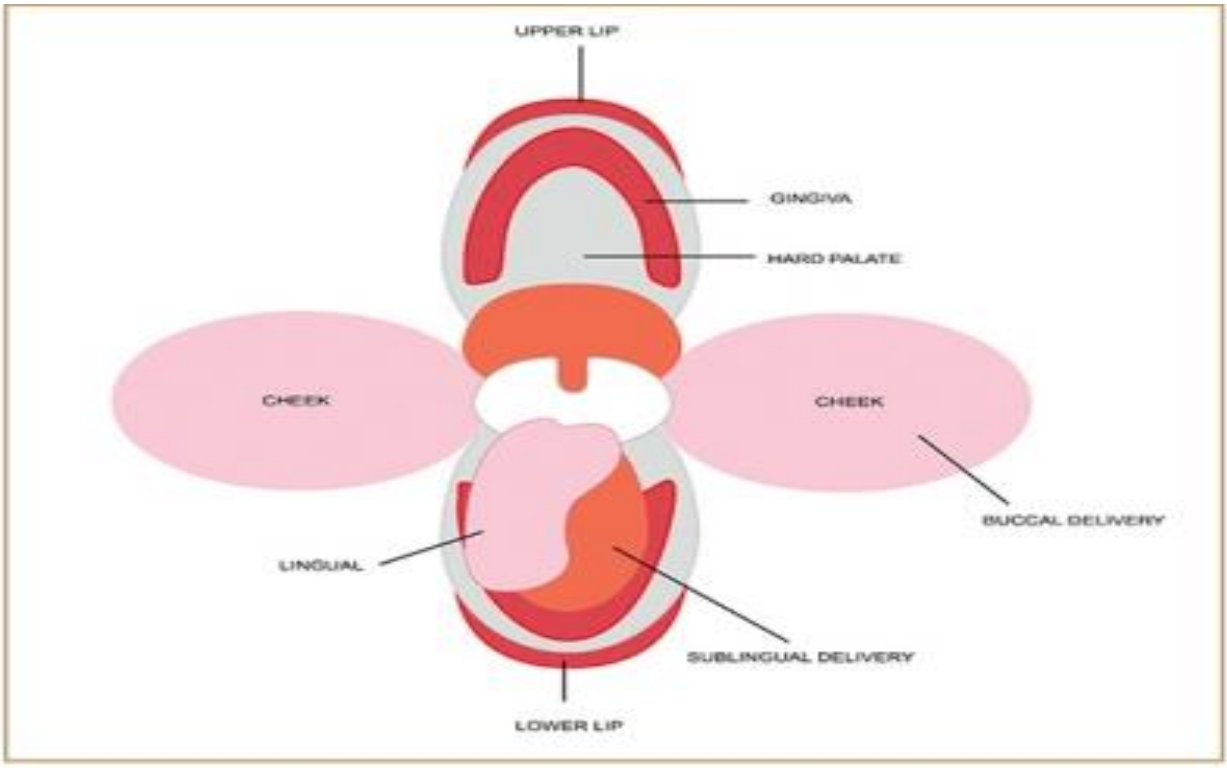


Fig. 4. Sites of buccal drug delivery

1.12 Structure

The oral mucosa consists of three distinctive layers. They are :

- epithelium
- basement membrane
- connective tissues

Buccal cavity is lined with epithelium, supported by basement membrane which is internally supported by connective tissues. In underlying tissues, protective layer is epithelium which is divided into:

(a) Surface which is non-keratinised lining of soft palate, tonguesurface, lips and vestibule.

(b) Hard palate and other non-flexible regions keratinized epithelium present in oral cavity.

The mouth is lined with mucous membrane and among the least known of its functions is its capability of serving as a site for the absorption of drugs. In general, drugs penetrate the mucous membrane by simple diffusion and are carried in the blood, which is richly supplied with the salivary glands and their ducts, into the systemic circulation via the jugular vein. Active transport, pinocytosis and passage through aqueous pores usually play only insignificant roles in moving drugs across the oral mucosa.

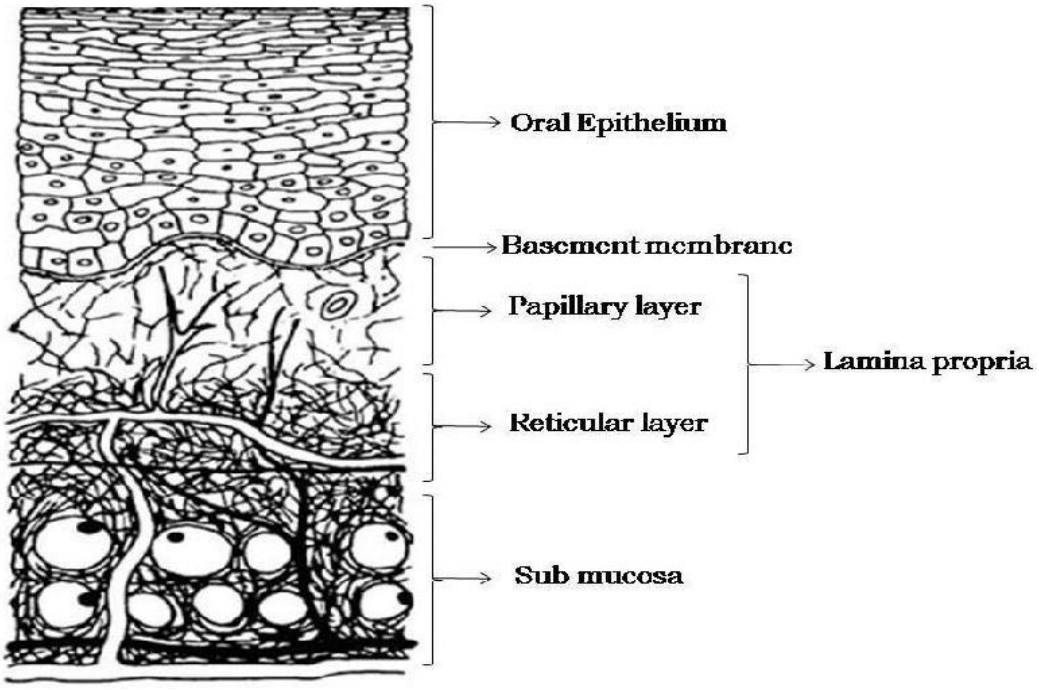


Fig. 5. Cross-section of buccal

The epithelial cells originating from the basal cells mature, change their shape, and increase in size while moving towards the surface. The basement membrane acts as mechanical support for the epithelium and forms a distinctive layer between the connective tissues and the epithelium. The underlying connective tissues provide many of the mechanical properties of oral mucosa. Inner layers called mucosa is covered with viscoelastic fluid. This fluid is secreted by goblet

cells and it composed of water and mucin. Other components include proteins, lipids and mucopolysaccharides,electrolytes.

The non keratinized tissue is a part of buccal epithelium which is penetrated by connective tissues that are tall and conical in form. These tissues, which are also referred to as the lamina propria, consisting collagen fibers, smooth muscles, blood vessels and an underneath film of connective tissues. Lamina propria is followed by the sub mucosa.

The external carotid artery supplies to the oral mucosa. The main sources of blood supply to the lining of the cheek in the buccal cavity are derived from the buccal artery, some terminal branches of the facial artery, the posterior alveolar artery, and the infra orbital artery.[9]

1.13 Buccal Permeation[9]

The oral mucosal epithelium is somewhat leaky and intermediate between that of the epidermis and intestinal mucosa. Buccal mucosal having 4-4000 times greater permeability than skin and different regions having difference in permeability of oral cavity because of its diverse structures and functions of the oral mucosa. The relative thickness and degree of keratinization of the tissues precedes the ranking. Both the sublingual mucosa and buccal mucosa are non-keratinized, however they differ in thickness. The buccal mucosa is thicker than the sublingual mucosa and the palatal mucosa is intermediate in thickness but keratinized. The permeability of the oral mucosa is in the decreasing order sublingual >buccal >palatal.

Within the oral mucosal cavity, delivery of drugs is classified into three categories:

i) Sublingual delivery: Which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.

ii) Buccal delivery: Which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and

iii) Local delivery: Which is drug delivery into the oral cavity.

Owing to the ease of the administration, the oral cavity is an attractive site for the delivery of drugs. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-

specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. The main obstacles that drugs meet when administered via the buccal route derive from the limited absorption area and the barrier properties of the mucosa. The effective physiological removal mechanisms of the oral cavity that take the formulation away from the absorption site are the other obstacles that have to be considered.

The strategies studied to overcome such obstacles include the employment of new materials that, possibly, combine mucoadhesive, enzyme inhibitory and penetration enhancer properties and the design of innovative drug delivery systems which, besides improving patient compliance, favor a more intimate contact of the drug with the absorption mucosa. This presents a brief description of advantages and limitations of buccal drug delivery and the anatomical structure of oral mucosa, mechanisms of drug permeation followed by current formulation design in line with developments in buccal delivery systems and methodology in evaluating buccal formulations.

1.14Permeation enhancers[9]

Permeation enhancers are substances added to pharmaceutical formulation in order to increases the membrane permeation rate or absorption rate of a co-administered drug. They are used to improve bioavailability of drugs with normally poor membrane permeation properties without damaging the membrane and causing toxicity. Enhancer efficacy depends on the physiochemical properties of the drug, administration site, nature of the vehicle and whether enhancer is used alone or in combination.

1.15 Categories and examples of membrane permeation enhancers

- Bile salts: Sodium glycocholate, Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxycholate, Sodium glycodeoxycholate,
- Surfactants : Sodium lauryl sulphate, Polyoxyethylene, Polyoxyethylene-9-Laurylether, Polyoxythylene-20-cetylether, Benzalkonium chloride,
- Fatty acids : Oleic acid, Capric acid, Lauric acid/ propylene glycol, Methyloleate, Lysophosphatidylcholine, Phosphatidylcholi
- Chelators: EDTA, Citricacid, Sodium salicylate, Methoxy salicylates

- Non-surfactants: Unsaturated cyclic ureas

1.16Various buccal bioadhesive dosage forms[10]

Bioadhesives are the substances that are capable of interacting with the biological material and being retained on them or holding them together for extended period of time. Bioadhesive can be used to apply to any mucous or non-mucous membranes and it also increases intimacy and duration of contact of the drug with the absorbing membrane. The commonly used bioadhesives are sodium alginate, carbomers, polycarbophil, HPMC, HPC, gelatin etc.

1. Buccal bioadhesive tablets

Buccal bioadhesive tablets are dry dosage forms that are to be moistened prior to placing in contact with buccal mucosa. Double and multilayered tablets are already formulated using bioadhesive polymers and excipients. The two buccal bioadhesive tablets commercially available buccoadhesive tablets in India are Bucastem (Nitroglycerine) and Suscard buccaP (Prochloroperazine).

2. Buccal bioadhesive patches and films

Buccal bioadhesive patches consists of two poly laminates or multilayered thin film round or oval as consisting of basically of bioadhesive polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bioadhesive films are formulated by incorporating the drug in alcohol solution of bioadhesive polymer.

Example:

i) Isosorbide dinitrate in the form of unidirectional erodible buccal film are developed and characterized for improving bioavailability.

ii) Buccal film of salbutamol sulphate and terbutalin sulphate for the treatment of asthma

iii) Buccoadhesive film of clindamycin used for pyorrhea treatment.

3. Buccal bioadhesive semisolid dosage forms

Buccal bioadhesive semisolid dosage forms consist of finally powdered natural or synthetic polymer dispersed in a polyethylene or in aqueous solution. Example: Arabase.

4. Buccal bioadhesive powder dosage forms

Buccal bioadhesive powder dosage forms are a mixture of bioadhesive polymers and the drug and are sprayed onto the buccal mucosa.

1.17 Buccal Tablets[10]

The buccal tablets are formulated similar to the oral tablets but with the inclusion of a muco-adhesive polymer either of natural origin (tragacanth, guar gum, xanthan gum) or synthetic and semi-synthetic polymers (carboxy methyl cellulose, poly ethylene glycol, polycarbophils, hydroxyl propyl methyl cellulose, poloxamer,poly- acrylic acid- hydroxyl propyl methylcellulose)These polymers when incorporated in a formulation offer varying degrees of muco-adhesion and retention time.

Flat, elliptical or capsule-shaped tablets are usually selected for buccal tablets, since they can be most easily held between the gum and cheek. 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 tablet and to provide for release of the medication. The drugs, usually, presented as candidates for buccal tablets are hormones for hormonal replacement therapy, nicotine for smoking cessation, anti-microbials for the treatment of oral infections and anti-emetics. These are all drug candidates for extended release formulations.

1.18 Types of buccal tablets

The different types of buccal tablets that can be fabricated are as shown in Fig.6.:

a) A simple mono-lithic matrix tablet

b) Matrix tablet with a water impermeable coating – unidirectional drug release

c) Matrix tablet with a backing membrane – unidirectional release

d) A bi-layered tablet with a non-adhesive drug reservoir and a mucoadhesive polymer layer

e) A bi-layered tablet with a non-bioadhesive inert layer and a drug containing bioadhesive layer.

f) A triple layered tablet- central drug containing core, upper backing membrane and a lower bioadhesive layer.

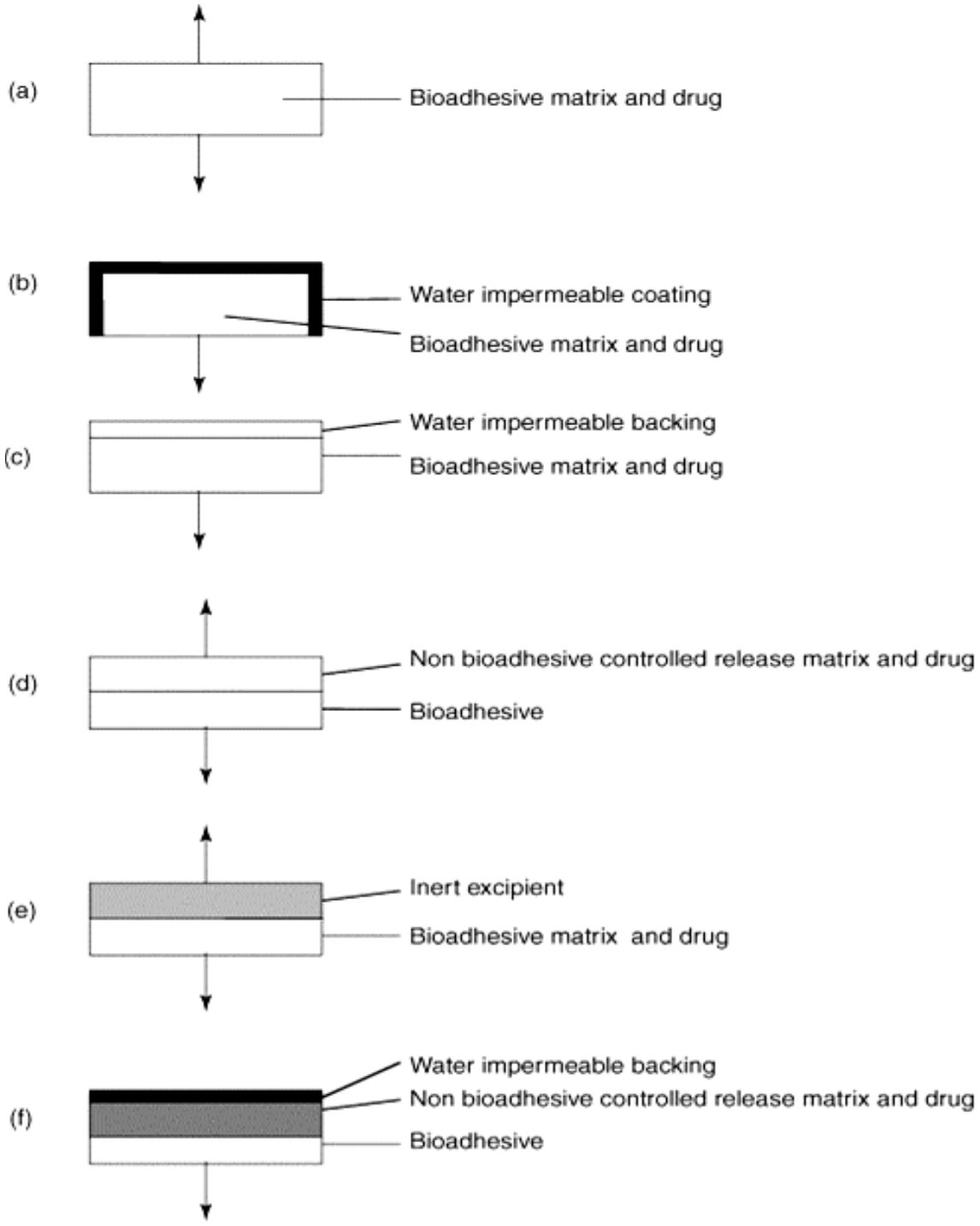


Fig. 6. Schematic representation of different matrix tablets for buccal delivery. (Arrows indicate the direction of drug release.)

1.19 Polymer for buccal[10]

Bioadhesive polymers have properties to get adhered to the biological membrane and hence capable of prolonging the contact time of the drug with a body tissue. The use of bioadhesive polymers can significantly improve the performance of many drugs. This improvement ranges from better treatment of local pathologies to improved bioavailability and controlled release to enhance patient compliance.

1.20 Basic components of buccal mucoadhesive drug delivery system[11]

The basic components of buccal mucoadhesive drug delivery system are-

1. **Drug substance**- Before formulating buccoadhesive drug delivery systems, one has to decide whether the intended, action is for rapid release/prolonged release and for local/systemic effect. The selection of suitable drug for the design of buccoadhesive drug delivery systems should be based on pharmacokinetic properties.
2. **Bioadhesive polymers**- Bioadhesive polymers play a major role in buccoadhesive drug delivery systems of drugs. It should be compatible with the biological membrane. It should form a strong non covalent bond with the mucin/epithelial surface
3. **Backing membrane**- Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. Such impermeable membrane on buccal bioadhesive patches prevents the drug loss and offers better patient compliance. The commonly used materials in backing membrane include carbopol, magnesium stearate, HPMC, HPC, CMC, polycarbophil etc.
4. **Penetration enhancers**- Penetration enhancers are used in buccoadhesive formulations to improve the release of the drug. They aid in the systemic delivery of the drug by allowing the drug to penetrate more readily into the viable tissues. The commonly used penetration enhancers are sodium lauryl sulphate, CPC, polysorbate-80, laureth-9, sodium fusidate, polmitoyl carnitine, azone, sodium glycocholate, dimethyl formamide etc.

1.21 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)[14]

The NSAIDs, sometimes called the aspirin-like drugs, are among the most widely used of all drugs. There are now more than 50 different NSAIDs on the global market. They provide symptomatic relief from pain and swelling in chronic joint disease such as occurs in osteo- and rheumatoid arthritis, and in more acute inflammatory conditions such as sports injuries, fractures, sprains and other soft tissue injuries. They also provide relief from postoperative, dental and menstrual pain, and from the pain of headaches and migraine. As several NSAIDs are available over the counter, they are often taken without prescription for other types of minor aches and pains. There are many different formulations available, including tablets, injections and gels. Virtually all NSAIDs, particularly the 'classic' NSAIDs, can have significant unwanted effects, especially in the elderly. Newer agents have fewer adverse actions

Ketorolac[15] is a well-known non-steroidal anti-inflammatory drug with potent analgesic activity. It is currently administered intramuscularly and orally in multiple divided doses for short-term management of post-operative pain. The drug is administered via the oral route as a conventional tablet (10 mg four times a day) for management of mild to moderate pain. In addition to the limitations in the available routes of administration, the half life of Ketorolac ranges from 4-6 h. Therefore, frequent dosing is required to alleviate pain in postoperative patients due to its short half-life. To avoid an invasive drug delivery technique (i. e. intramuscular injection) and to decreasegastrointestinal side effects produced by the oral tablets, there is a need for an alternative noninvasive mode of delivery for Ketorolac. The new delivery system should also provide sustain in the release of this medication to assist patient compliance and reduce dosing frequency. The buccal mucoadhesive administration may thus represent an alternative route for its delivery.

2. LITERATURE REVIEW

Rupinder Kaur et al.,[15] developed and validated UV spectrophotometric method for the estimation of ketorolac tromethamine in bulk drug. Developed robust, accurate and precise UV spectrophotometric method for determination of ketorolac tromethamine. The developed method was validated as per Internation Conference on Harmonization (ICH) guideines. The spectrometric detection was carried out at an absorption maximum of 322 nm using water as solvent. The method was validated for specificity, linearity, accuracy, precision, robustness and ruggedness.

N.G. Raghavendra Rao et al.,[17] presented an overview on buccal drug delivery systems, advantages as well as limitations of buccoadhesive drug delivery,mucoadhesive polymers, structure and design of buccal dosage form, factors affecting buccal absorption, methods to increase drug delivery via buccal route, bioadhesion, mechanism of bioadhesion, basic components of buccal drug delivery system, manufacturing and evaluation of buccal drug delivery systems.

Marwa Shukr et al.,[18] formulated and evaluated ketorolac tromethamine mucoadhesive buccal tablets by direct compression using bioadhesive polymers such as carbobol 934 with hydroxypropyl methylcellulose K4M and sodium carboxymethyl cellulose. The prepared tablets were characterized by different parameters such as weight uniformity, content uniformity, hardness, swelling index, in vitro drug release studies, ex- vivo residence time and ex- vivo permeation study. The buccal mucoadhesive tablet of ketorolac could be an alternative route to reduce the pronounced gastrointestinal irritations, and reduce dosing frequency to improve patient compliance.

Raja Navamanisubramanian et al.,[19] formulated, evaluated and optimized repaglinide buccal tablets using box-behnken design. Bilayer buccal tablets were prepared by two step direct compression method. Ethyl cellulose was used as backing layer. For optimization, three factors and three eves was employed to evaluate the effects of main, interaction and quadratic terms of independent variables on dependent variables through second order polynomial equation constructed with design expert and to statistically optimize the formulation parameters.

Patel Sweety et. al.,[20] formulated buccal adhesive tablet of ivabradine hydrochloride in the treatment of stable angina pectoris to avoid hepatic first pass metabolism. Buccal adhesive tablet was prepared by direct compression method using poly-carbophil as mucoadhesive polymers and HPMC as sustained release polymer with ethyl cellulose as backing layer. Buccal adhesive was characterized for hardness, thickness, weight variation, drug content, surface pH, mucoadhesive strength, mucoadhesive time, swelling index, in vitro drug release as well as ex vivo drug diffusion.

Hardik Parmar et al.,[21] designed and evaluated a buccal tablet containing Nicorandil as a model drug. Buccal tablet containing anti-diabetic drug (nicorandil), Ethyl cellulose was used as backing membrane and carbopol 934p and hydroxypropyl methyl cellulose K100M was used as bucco adhesive polymer. Aspartame was used as a sweetener. Thickness, hardness, weight variation and drug uniformity were investigated.

Anna Balaji et. al.,[22] formulated and evaluated mucoadhesive buccal tablets of carvedilol using natural polymer (casein). The effect of two independent variables casein and HPMC at three different levels (-1, 0, +1) on independent variabes incuding hardness, cumulative percentage drug reease was studied using 3 full factorial design. FTIR and DSC was done to check any interaction between drug and polymer. All the physicochemical parameters were also studied.

Nisreen hasan et al.,[23]formulated and evaluated a buccal adhesive tablet containing ondansetron hydrochloride (OH). The tablets were prepared using carbopol (CP 934), sodium alginate, sodium carboxymethylcellulose low viscosity (SCMC LV), and hydroxyl propyl methyl cellulose (HPMC 15cps) as mucoadhsive polymers to impart mucoadhesion and ethyl cellulose to act as an impermeable backing layer. The formulations were prepared by direct compression and characterized by different parameters such as weight uniformity, content uniformity, thickness, hardness, swelling index, in vitro drug release studies, mucoadhesive strength, and ex vivo permeation study.

M.Venkataswamy et al.,[24] formulated and evaluated biphasic bilayer buccal tablet containing Ketorolac immediate release layer and Domperidone maleate sustained release layer. FT-IR studies reveal that there were no significant interactions between both the drugs and between the

drugs and their respective excipeints. For achieving immediate result of Ketorolac, Crospovidone and SSG was used to obtain good disintegration activity. The optimized formulations of bilayered tablets prepared by taking Domperidone maleate and Ketorolac as two layers were further evaluated for weight variation, swelling index, ex vivo skin permeation study and drug realease study.

A.P. Sam et al.,[25] evaluated the mucoadhesive property of various film forming and non-film forming polymers using Wilhelmy plate method. The experimental results showed that the mucoadhesive property of the polymers are in the following ranking : CMC > HPMC K100M > HPMCP > Polycarbophil> HPMC K4M > Amylopectin > Eudragit RS 100. The strength of mucoadhesion also depended on the surface area of the polymer submerged in the mucus.

Gazzi Shanker et al.,[27] formulated and evaluated bioadhesive buccal drug delivery of Tizanidine Hydrochloride Tablets, which is extensively metabolized by liver. The tablets were prepared by direct compression using bioadhesive polymers such as hydroxypropyl methylcellulose K4M, sodium carboxymethyl cellulose alone, and a combination of these two polymers. In order to improve permeation of drug, permeation enhancer like beta-cyclodextrin (B-CD), hydroxypropyl beta-cyclodextrin (H-B-CD) and sodium deoxycholate was added to the formulation. The optimized formulation was further evaluated for bioadhesion strength, ex-vivo residence time, swelling studies, surface pH studies, ex-vivo permeation study, stability of buccal tablets and in vivo mucoadhesive performance.

Balamurugan et al.,[28] formulated mucoadhesive buccal tablet of domperidone were fabricated with objective of avoiding first pass metabolism and to improve its bioavailability with reduction in dosing frequency. The mucoadhesive polymers used in the formulations were Carbopol 934P, Methocel K4M, MethocelE15LV and Chitosan. Tablets were prepared by direct compression method using polymer in different ratios. The formulations were characterized for swelling index, in-vitro bioadhesion strength and in-vitro release studies. It was observed that the optimized formulation follows Hixson Crowel release kinetics.

JG Hiremath et al.,[29] prepared the mucoadhesive bilayered tablet of simvastatin for the treatment of hypercholesterolemia, by using the mucoadhesive polymers such as carbopol (CP), hydroxy propyl methyl cellulose (HPMC) and polyvinylpyrrolidone (PVP) in different

concentration. Ethyl cellulose is used in backing layer because of its water impermeable nature. Tablets were prepared by direct compression method. The first layer which adheres to mucosa was obtained by direct compression of mucoadhesive polymers and drug. The second layer containing water impermeable agent was compressed on the first layer. Tablets were subjected for physicochemical characterization tests such as FTIR, DSC, hardness, weight variation, friability, mucoadhesive strength, in vitro drug release study, in vitro drug permeation, and stability in human saliva. The FTIR and DSC analysis of drug, polymers, physical mixture and formulation indicated that the compatibility of drug with excipients.

Binu Raina et al.,[30] formulated, evaluated and optimized fast disintegrating tablets of ketorolac tromethamine. The study aimed to design fast disintegrating tablets (FDT) of ketorolac tromethamine (KT) to reduce gastric side effects of KT by physically associating it with phospholipon 80H (PL) by wet granulation. First preliminary batches were formulated to determine the effect of PL on tablet characteristics and to select best superdisintegrant among sodium starch glycolate and crospovidone. The effect of PL and maltodextrin (MD) concentrations on hardness, disintegration time and % drug release at 4 min was studied for the optimization of FDT. Optimization of FDT was done by employing 32 full factorial design using Design expert 10.1 software.

Khaled M. Hosnyet al.,[31] prepared and evaluated ketorolac tromethamine hydrogel. Ketorolac tromethamine is a non-steroidal anti-inflammatory drug that has two major problems when administered orally; it has severe gastrointestinal side effects as bleeding, peptic ulcer, perforation. Second, it has short half-life (4hr) so require frequent administration. The aim of this study was to overcome these two problems through preparation of this drug as topical hydrogel. Hydroxypropyl, hydroxylpropylmethyl, and sodiumcarboxymethyl were the three cellulosic polymers used as gelling agents, the influence of type and concentration of them on the release of ketorolac was investigated.

VR Sinha, et al.,[32] presented an overview on ketorolac tromethamnine formulations. Detailed study on different formulation of ketorolac drug was studied which included gels, nasal, oral, parenteral, ocular, ointment, transdermal and intra oral. Ketorolac is mostly administered as its tromethamine salt orally, intramuscularly, intravenously and as a topical ophthalmic solution. The frequent occurrence of gastrointestinal disturbances including gastrointestinal bleeding,

perforation and peptic ulceration along with the short mean plasma half-life ($t_{1/2}$ ~ 5.5 h) has prompted for the development of various formulation strategies for the appropriate delivery of KT. The article gives an overview of the main concepts used thus far to design various pharmaceutical dosage forms for the therapeutically effective delivery of the drug candidate through various routes.

Luana Perioli et al.,[33] formulated muco adhesive bilayer tablets for buccal sustained release of flurbiprofen. The bilayered tablets, using mixtures of mucoadhesive polymers and an inorganic matrix (hydrotalcite), for the topical administration of flurbiprofen in the oral cavity. The first layer, responsible for the tablet retention on the mucosa, was prepared by compression of a cellulose derivative and polyacrylic derivative blend. The second layer, responsible for buccal drug delivery, was obtained by compression of a mixture of the same (first layer) mucoadhesive polymers and hydrotalcite containing flurbiprofen. Nonmedicated tablets were evaluated in terms of swelling, mucosal adhesion, and organoleptic characteristics; in vitro and in vivo release studies of flurbiprofen-loaded tablets were performed as well.

Bytul M. Rahmanet al.,[34] developed and evaluated the formulation of Ketorolac Tromethamine tablets and conducted a comparative study with marketed product. The aim of this work was to prepare and evaluate the ketorolac tromethamine tablets with higher dissolution rates and to compare them with marketed product. Direct compression method was adopted for preparation of tablet using different excipients namely; microcrystalline cellulose, spray dried lactose and starch 1500. The effect of excipients on the drug release from prepared tablets was also studied. All the tablet quality control tests were studied.

Shaila Lewis et al.,[35] designed, evaluated and conducted pharmacokinetic study of mucoadhesive buccal tablets of nicotine for smoking cessation. Mucoadhesive tablets for buccal administration of nicotine were prepared as an alternative to the available nicotine dosage forms. Three types of tablets were developed each containing two mucoadhesive components (HPMC, K4M and sodium alginate), (HPMC, K4M and carbopol) (Chitosan and sodium alginate). The tablets were evaluated for release pattern, and mucoadhesive performance. Pharmacokinetic studies were conducted in smokers.

Anup Kumar Royet al.,[36] formulated and studied the mucoadhesive buccal tablets of Valsartan using various suitable bioadhesive polymers such as CP 934, HPMC K4M, and Na CMC. A backing layer of ethyl cellulose was used which was impermeable in nature. Six formulations of Valsartan were prepared by direct compression method. The prepared tablets were characterized by swelling studies, % matrix erosion, surface pH, bioadhesive properties, In-vitro drug dissolution and In-vitro diffusion studies.

Prasanth Vasantha Viswanadhan et al.,[37] formulated and evaluated Buccal tablets of lisinopril were prepared by direct compression method using different hydrophilic polymers such as hydroxypropyl methylcellulose, sodiumcarboxy methylcellulose and Carbopol. All the prepared formulations showed satisfactory mass uniformity, thickness and favourable drug content. The friability of all the formulation was below 1%, which is an indication of good mechanical resistance of tablets. Among all the formulations, F4 showed maximum swelling index and in vitro release. Drug release mechanism was determined by plotting release data to Higuchi and Korsmeyer Peppas model. All the formulations are best fitted to Higuchi model and according to this model the drug releases from theses tablets may be controlled by diffusion. The surface pH of all formulations was found to be almost in neutral pH and no mucosal irritation was expected.

Gore Meghana Milind et al.,[38] formulated and evaluated mucoadhesive buccal tablets of propranolol prepared by wet granulation method using natural polymer like Vigna mungo powder. After the compatibility studies of drug and excipient were performed by FT- IR spectroscopy and DSC, examining the flow properties of the powder blends, it was subjected to compression. The tablets were evaluated for post-compression parameters like weight variation, hardness, thickness, friability, drug content uniformity, surface pH, in-vitro studies like swelling, mucoadhesive strength, residence time and drug release.

Goswami Dhruba Sankar et al.,[39] formulated a mucoadhesive tablet of Famotidine using various combinations of synthetic (HPMC-K4M, SCMC and Sodium alginate) and natural (Tragacanth and Acacia) hydrophilic polymers. The study revealed that the formulation containing HPMC K4M and its combination with tragacanth possessed the greatest mucoadhesive strength.

3. AIM AND OBJECTIVES

The aim of the present investigation was to formulate Ketorolac buccal tablets containing 10 mg, with a thickness of about 2 mm and a diameter less than 4 mm. Ketorolac is a non- steroidal anti-Inflammatory drug (NSAID), prescribed for short term management of post-operative pain. In general, it falls under BCS – class I (high solubility / high permeability) which helps in designing of buccal tablets.

Ketorolac[11] is a non-steroidal anti-inflammatory drug that has two major problems when administered orally; it has severe gastrointestinal side effects as bleeding, peptic ulcer, perforation. The aim of this study was to overcome these problems through preparation of this drug as buccal tablet so that it directly reaches to the systemic circulation avoiding GIT. In this project work, an attempt was made to design efficacious and prolonged release mucoadhesive buccal tablets of ketorolac using various polymers to reduce dosing frequency, decrease gastric irritation and to improve patient compliance.

Ketorolac[12] is currently administered intramuscularly and orally in multiple divided doses for short-term management of post-operative pain. The drug is administered via the oral route as a conventional tablet (10 mg four times a day) for management of mild to moderate pain. In addition to the limitations in the available routes of administration, the half life of KT ranges from 4-6 h. Therefore, frequent dosing is required to alleviate pain in postoperative patients due to its short half-life.

To avoid an invasive drug delivery technique (i. e. intramuscular injection) and to decrease the gastrointestinal side effects produced by the oral tablets, there is a need for an alternative noninvasive mode of delivery for Ketorolac. The new delivery system should also provide sustained release of this medication to assist patient compliance. The buccal mucoadhesive administration may thus represent an alternative route for Ketorolac delivery. In the present investigation, an attempt was made to design efficacious and prolonged release mucoadhesive buccal tablets of Ketorolac using various polymers to reduce dosing frequency, decrease gastric irritation and to improve patient compliance.

Therefore the objective of the formulation includes:

Preparation of various formulations of Ketorolac buccal tablets, using different bioadhesive polymers at varying concentration. Two different polymer combinations (carbopol 934 and PVP K30 as well as carbopol 934 and xanthan gum) are taken according to appropriate ratios. The performance of evaluations on the finished product dosage form of Ketorolac buccal tablets, like weight variation, friability, hardness and thickness are also included in the study. In order to determine the drug release kinetics, the ex vivo drug release data is to be fitted into the various kinetic models.

4. PLAN OF WORK

The present study focused on the formulation of buccal tablets of Ketorolac for use in short-term management of post-operative pain.

4.1 Flow of work

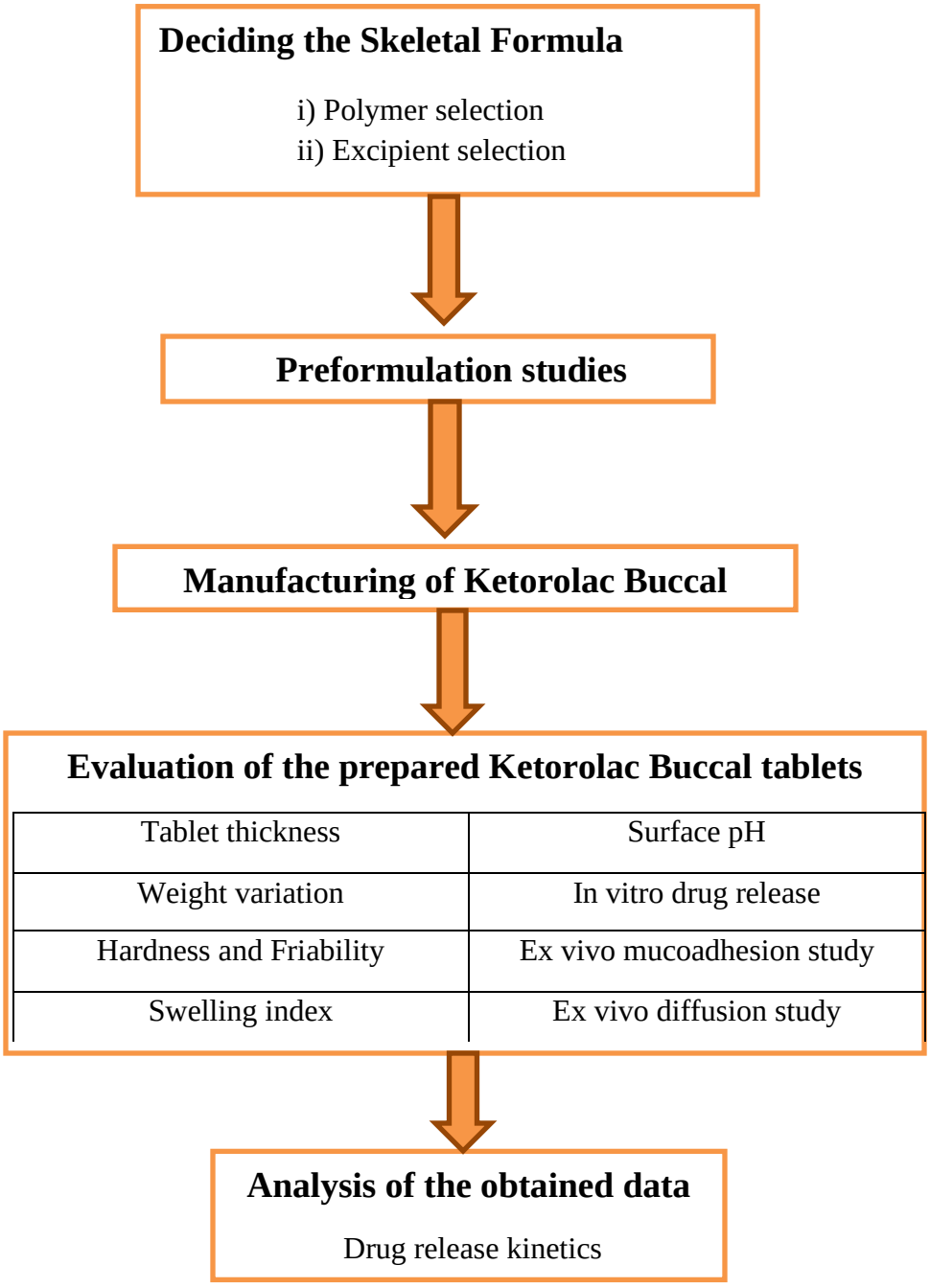


Fig. 7. Schematic representation of plan of work

5. DRUG PROFILE[15]

Name

KETOROLAC

Description

A pyrrolizine carboxylic acid derivative structurally related to indomethacin. It is an NSAID and is used principally for its analgesic activity.

Structure

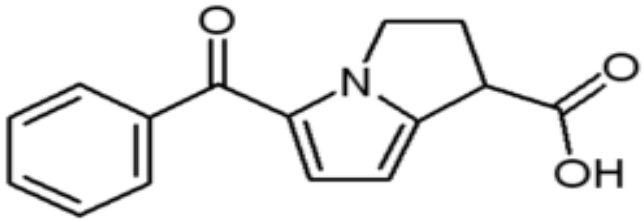


Fig. 8. Structure of Ketorolac

Synonyms

Ketorolac, Ketorolac tromethamine, Ketorolaco(Spanish), Ketorolacum(Latin).

Brand names

Acular, Acular LS, Toradol.

Category

Non-Steroidal Anti-Inflammatory Drug

Chemical Formula

$C_{15}H_{13}NO_3$.

IUPAC Name

5-benzoyl-2, 3-dihydro-1H-pyrrolizine-1-carboxylic acid.

Class

Pyrrolizines

Solubility

Freely soluble in water and methanol, slightly soluble in isopropyl alcohol and insoluble in acetone and dichloromethane.

Mechanism of action:

The primary mechanism of action responsible for Ketorolac's anti-inflammatory, antipyretic and analgesic effects is the inhibition of prostaglandin synthesis by competitive blocking of the enzyme cyclooxygenase (COX). It is considered a first-generation NSAID. It is a non-selective COX inhibitor.

Ketorolac acts by inhibiting both COX-1 and COX-2 enzymes which are normally responsible for converting arachidonic acid to prostaglandins. The COX-1 enzyme is constitutively active and can be found in platelets, gastric mucosa, and vascular endothelium. On the other hand, the COX-2 enzyme is inducible and mediates inflammation, pain and fever.

As a result, inhibition of the COX-1 enzyme is linked to an increased risk of bleeding and risk of gastric ulceration, while the desired anti-inflammatory and analgesic properties are linked to inhibition of the COX-2 enzyme. Therefore, despite its effectiveness in pain management, ketorolac should not be used long-term since this increases the risk of serious adverse effects such as gastrointestinal bleeding, peptic ulcers, and perforations.

Protein binding

99%.

Dose and Administration

Oral

10 mg orally 4 times a day as needed. The maximum daily dose should not exceed 40 mg.

Parenteral:

IM- Patients less than 65 years of age: one dose of 60 mg. Patients who are renally impaired, and/or less than 50 kg : one dose of 30 mg.

IV-Patients less than 65 years of age: one dose of 30 mg. Patients who are renally impaired, and/or less than 50 kg : One dose of 15 mg.

Bioavailability

100% (All routes)

Pharmacokinetics

Absorption

Rapidly and completely absorbed after oral administration.

Metabolism

Primarily hepatic.

Route of elimination

The principal route of elimination of ketorolac and its metabolites is renal (91.4%) and biliary (6.1%).

Half life

2.5 hours for the S-enantiomer compared with 5 hours for the R-enantiomer.

Indication

For the short-term (~5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting.

Contraindications

Ketorolac is contraindicated in those with hypersensitivity, allergies to the medication, cross-sensitivity to other NSAIDs, prior to surgery, history of peptic ulcer disease, gastrointestinal bleeding, alcohol intolerance, renal impairment, cerebrovascular bleeding, nasal polyps, angioedema, and asthma

Adverse effects

Potentially fatal adverse effects include stroke, myocardial infarction, GI bleeding, Stevens-Johnson Syndrome, toxic epidermal necrolysis and anaphylaxis.

Infrequent side effects includeparesthesia, prolonged bleeding time, injection site pain, purpura, sweating, abnormal thinking, increased production of tears, edema, pallor, dry mouth, abnormal taste, urinary frequency, increased liver enzymes, itching and others.

Drug interactions

Drug interactions associated with Ketorolac are similar to those observed with other NSAID's. It interacts with the anti-hypertensive drugs other than Calcium channel blockers by reducing their efficacy.

Probenecid can increase the probability of having an adverse reaction when taken with Ketorolac. Pentoxifylline can increase the risk of bleeding. When aspirin is taken at the same time as Ketorolac, the effectiveness is decreased.

Problematic GI effects are additive and become more likely if potassium supplements, aspirin, other NSAIDs, corticosteroids, or alcohol is taken at the same time.

6. EXCIPIENT PROFILE

6.1 CARBOPOL[16]

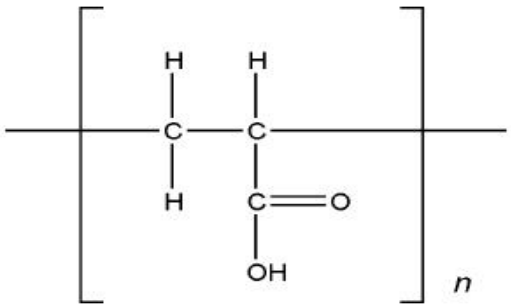
Nonproprietary Names

BP: Carbopols, PhEur: Carbopola, USPNF: Carbopol.

Synonyms

Acritamer, poly acrylic acid polymer, carbopol, carboxy poly methylene, acrylic acid, carboxyvinyl polymer.

Structural formula



Acrylic acid monomer unit in carbopol resins.

Fig. 9. Structure of Carbopol

Molecular Weight

12000-140000Da.

Description

Carbopols are colorless, fluffy, acidic, hygroscopic powders with a slight characteristic odor.

Solubility

It is soluble in water after neutralization in ethanol (95%) and glycerin.

Carbopols merely swell to a remarkable extent but do not dissolve.

Viscosity

Carbopols forms low viscosity colloidal dispersions which are acidic in nature and forms viscous gels when gets neutralized.

Typical properties of Carbopol

Glass transition temperature 100–105ºC

Density (bulk) 1.76–2.08 g/cm3

Density (tapped) 1.4 g/cm3

Specific gravity 1.41

Melting point 260ºC

Functional Category

Bioadhesive, emulsifying and release modifying agent, viscosity promoters, tablet binder and suspending agent.

6.2 POLY VINYL PYRROLIDONE (PVP)[16]

Nonproprietary Names

USP: Povidone, BP: Povidone, JP: Povidone, PhEur: Povidonum

Synonyms

Plasdone, Kollidon, polyvidone, poly vinyl pyrrolidone and 1-vinyl-2 pyrrolidinone polymer

Molecular Weight

2500–30, 00,000g/mol

Description

Povidone exists as a fine, white to creamy white colored, odorless, hygroscopic in nature.

Structural formula

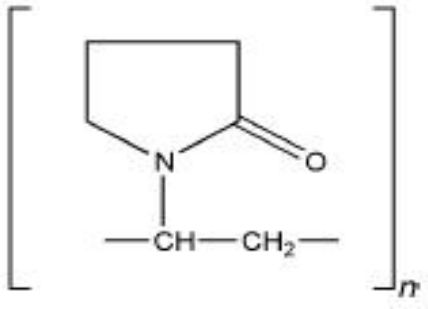


Fig. 10. Structure of PVP

Moisture content

Povidone at low relative humidity absorbs significant amounts of moisture and is very hygroscopic.

Solubility

It is freely soluble in water, methanol, ethanol (95%) and acids.

Viscosity

Both the concentration and the molecular weight of the polymer employed influence the viscosity of aqueous povidone solutions.

Typical properties of PVP

Density (bulk)	1.76–2.08 g/cm3
Density (tapped)	1.4 g/cm3
Density (true)	1.180 g/cm3
Melting point	Softens at 150 ºC.

Functional category

PVP serves as tablet binder, suspending agent, film forming agent, disintegrating agent, dissolution aid.

6.3 ETHYL CELLULOSE (EC)[16]

Non proprietary Names

USPNF: Ethylcellulose, BP: Ethylcellulose, PhEur : Ethylcellulosum

Synonyms

Aqualon; surelease; Aqua coat ECD; Aqualon; E 462; Ethocel;

Structural Formula

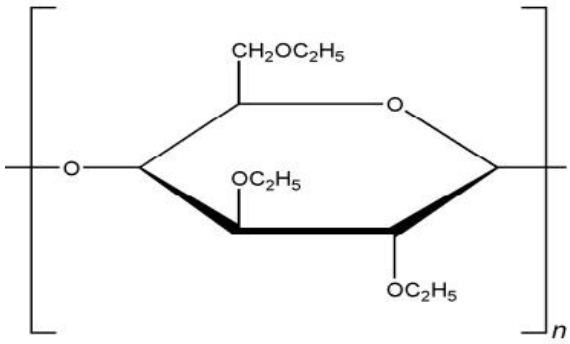


Fig. 11. Structure of EC

Chemical name

Cellulose ethyl ether

Description

White to light tan colored, tasteless and free flowing powder.

Moisture content

During immersion or humid air, EC absorbs very little amount of water and that small amount evaporates readily.

Solubility

It is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol and toluene. It is insoluble in water.

Viscosity

The viscosity of 5% w/v ethyl cellulose dissolved in toluene and ethanol at the ratio of 80:20 were calculated at room temperature and this solution is proportional to concentration of ethyl cellulose.

Typical properties of EC

Glass transition temperature	129-133ºC
Density (bulk)	0.4 g/cm3
Specific gravity	1.12-1.15 g/cm3

Functional category

Used as a tablet binder, tablet filler, viscosity promoters and coating agent.

6.4 MAGNESIUM STEARATE[16]

Non-proprietary Names

BP: Magnesium stearate; JP: Magnesium stearate

PhEur: Magnesiistearas; USPNF: Magnesium stearate

Synonyms

Magnesium octadecanoate, octadecanoic acid magnesium salt and stearic acid magnesium salt.

Chemical Name

Octadecanoic acid magnesium salt

Incompatibilities

It is incompatible with strong oxidizing agents, strong acids, alkalis and iron salts. It cannot be used in products containing aspirin, some vitamins and most alkaloidal salts.

Empirical Formula and Molecular Weight

[CH3 (CH2)16COO]2 Mg ; Mol.Wt. = 591.34 g/mol

Chemical Structure

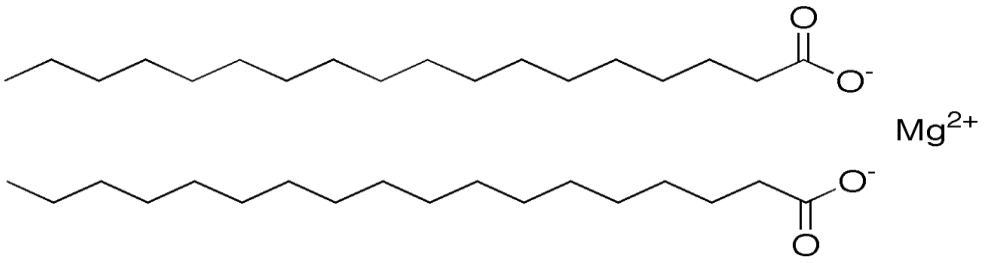


Fig. 12. Structure of magnesium stearate

Physical Properties

Melting point - 117-150˚C

Solubility - It is practically insoluble in ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Functional Category

Tablet and capsule lubricant.

Applications in Pharmaceutical Formulations

It is widely used in cosmetics, foods and pharmaceutical formulations.

It is primarily used as a lubricant in the manufacturing of tablets and capsules, in the concentration of 0.25-5.0%. It is also used in barrier creams.

6.5 TALC[16]

Synonyms

Altalc; hydrous magnesium calcium silicate; hydrous magnesium silicate

Chemical Name

Mussolinite, Agalite, Asbestine, Snowgoose, Steatite

IUPAC name

trimagnesium;dioxido(oxo)silane;hydroxy-oxido-oxosilane

Empirical Formula and Molecular Weight

$Mg_3Si4O10(OH)_2$; Mol.Wt. = 379.27 g/mol

Chemical Structure

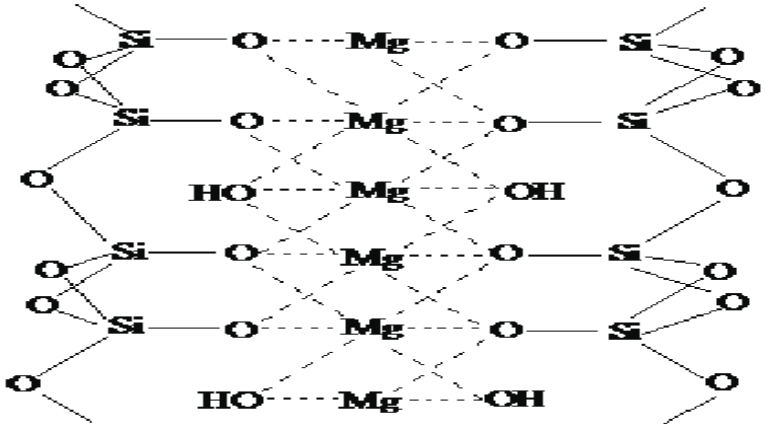


Fig. 13. Structure of talc

Physical Properties

Solubility - Sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol, practically insoluble in octanol, and insoluble in water.

Functional Category

Glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications in Pharmaceutical Formulations

Glident in oral solid dosage form. Used in dissolution retardant in the devlopment of controlled -relase product , in topical preparations used in dusting powder, diluent .

Incompatibilites

Incompatible with quaternary ammonium compounds.

6.6 SODIUM LAURYL SULPHATE[16]

Synonyms

Sodium dodecyl sulfate

Chemical Name

Monododecyl ester sodium salt

Chemical Structure

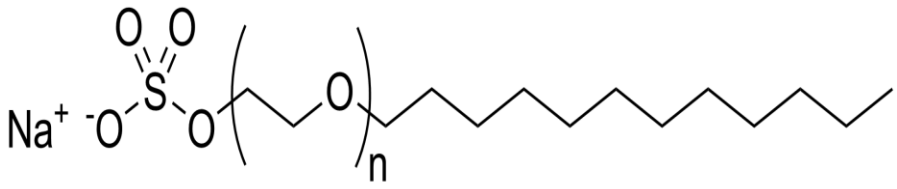


Fig. 14. Structure of sodium lauryl sulphate

Description

SLS occurs as white or cream to pale yellow-coloured crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odour of fatty substances.

Empirical Formula and Molecular Weight

$C_{12}H_{25}O_4S.Na$; Mol.Wt. = 332.43 g/mol

Physical Properties

Meting point- 204°C (399.2°F) - 207° C

Solubility - Solubility in water, g/100ml at 20 °C

Functional Category

Anionic surfactant; emulsifying agent; modified-release agent; penetration enhancer; solubilising agent; tablet and capsule lubricant.

Applications in Pharmaceutical Formulations

Used in pharmaceutical preparations as an emulsifying agent, modified release agent, penetration enhancer, solubilizing agent, tablet and capsule lubricant.

6.7 XANTHAN GUM[16]

Synonyms

Corn sugar gum; Xanthan; Gum xanthan;

Chemical Name

Xanthural

Chemical Structure

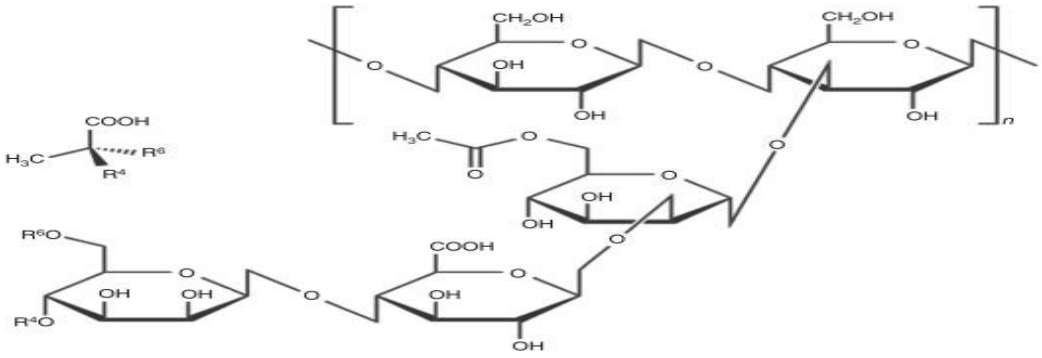


Fig. 15. Structure of xanthan gum

Description

Xanthan gum occurs as a cream to white,odorless, free flowing, fine powder.

Empirical Formula and Molecular Weight

(C35H49O29) n.; Mol.Wt. = 300 kDa to 8 MDa.

Physical Properties

Solubility - practically insoluble in ethanol and ether and soluble in cold or warm water.

Viscosity- 2000 cps (1% aq sol.)

FunctionalCategory

Thickener, Viscosity-increasing agent, Suspending agent, Stabilizer, Emulsifier

Applications in Pharmaceutical Formulations

Used in oral pharmaceutical formulations as suspending and thickening agent.

Incompatibilities

Xanthan gum is anionic compound and usually not compatible with cationic Surfactants.

7.MATERIALS AND METHODS

7.1 Materials

Sl. no.	Materials	Manufacturer	Application
1.	Ketorolac IP	Navakar Biochemical, Gujarat	API
2.	Carbopol grade 934p	Loba Chemicals PrivateLimited, Hyderabad	Buccoadhesive polymer
3.	PVP K30	Merck Limited, Mumbai	Buccoadhesive polymer
4.	Xanthan gum	Fisher Scientific, Mumbai	Buccoadhesive polymer
5.	Sodium lauryl sulphate	Loba Chemicals Private limited, Hyderabad	Penetration enhancer
6.	Magnesium stearate	Merck Limited, Mumbai	Lubricant
7.	Talc	Loba Chemicals Private Limited, Hyderabad	Glidant

7.1.1 Instruments and Equipment

Sl. no.	Instruments/ equipment	Manufacturer
1.	Digital Balance	Infra, India
2.	6 Station Rotary Compression Machine	Accura Punching Machine
3.	Vernier Calipers	Gogna, India
4.	Analytical Digital Balance	Digisun electronics
5.	Hardness Tester	Electrolab, India
6.	Friability Tester	Electrolab, India
7.	Disintegration Apparatus	Electrolab, India
8.	Fourier Transmission infrared radiation (FTIR)	Shimadzu IR-470 (Tokyo, Japan)
8.	Dissolution Apparatus	Panomex Inclusive, India
9.	Franz Diffusion Cell	Orchid Scientifics, India
10.	Magnetic Stirrer / Heating Unit	Remi Electrotechnik Limited Model -C854/4
11.	UV Visible Spectro Photometer	Shimadzu, Japan

7.2 Methodology

7.2.1 Pre-compressional Studies[18]

1. **Calibration curve**

Preparation of stocksolution

Standard stock solution of Ketorolac was prepared by dissolving accurately weighed 10 mg of drug in phosphate buffer pH 6.8 in 100ml volumetric flask to give concentration of 100 µg/ml.

Preparation of standard dilutions

Five 50 ml volumetric flasks were taken. Aliquots of 1 ml, 2ml, 4ml, 6 ml and 8 ml were taken from stock solution and were diluted, made up to the mark to obtain the concentrations as 2 µg/ml, 4 µg/ml, 8 µg/ml, 12 µg/ml and 16 µg/ml respectively. Then it was subjected to UV visible spectrometer at 322 nm. Readings were noted and graph was potted as shown in fig.16.

2. **Drug polymer compatibility study[18]**

To investigate any possible interactions between the drug and the used bioadhesive polymers, infrared spectroscopy was adopted. The IR spectrum of pure drug, polymer as well as physical mixture of drug and polymer was taken, interpreted and compared with each other. The IR spectra was carried out using Shimadzu IR-470 spectrophotometer. The samples were prepared as potassium bromide discs compressed under a pressure of 6 tons. The scanning range was over 4000-400 cm^{-1}

7.2.2 Formulation of mucoadhesive buccal tablets

Ketorolac mucoadhesive tablets were prepared by direct compression method as per the formulations as shown in Table 1. Before direct compression, all the ingredients were shifted through sieve No. 40 and then thoroughly blended in glass mortar and pestle. Blending was carried out separately for core tablet (polymer and drug) and backing layer (ethyl cellulose). The

mixture of core tablet was lubricated with magnesium stearate and talc which was already passed through sieve 60.

At first, the core tablets were compressed by using compression machine with 8 mm punch. Then, one compressed core tablet was placed in die cavity manually. Over it, accurately weighed 50 mg of ethyl cellulose was added to each die cavity. It was then leveled and compressed again to obtain Ketorolac buccal tablets having one sided backing layer of ethyl cellulose. After compression, the tablets were weighed to check that it lies within the range of 100±10 mg.

Table 1. Formulations prepared by direct compression method

Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Core tablet						
Drug(mg)	10	10	10	10	10	10
Carbopol 934 (mg)	18	12	14.5	18	12	14.5
PVP K30 (mg)	18	24	21.5	-	-	-
Xanthan gum (mg)	-	-	-	18	24	21.5
Sodium lauryl sulphate (mg)	2	2	2	2	2	2
Mg stearate (mg)	1	1	1	1	1	1
Talc (mg)	1	1	1	1	1	1
Backing Layer						
Ethyl Cellulose (mg)	50	50	50	50	50	50

7.2.3 Evaluation of the compressed tablets

All the above batches were evaluated for average thickness, average weight and weight variation, hardness, friability, swelling index, surface pH, in vitro drug release, mucoadhesive strength, residence time and in vivo bioavailability studies.

1. Weight variation[20]

20 tablets were collected from each formulation. The tablets were individually weighed from all the selected formulations; the average weight and standard deviation of 20 tablets was calculated.

Table 2. Limits for Tablet Weight Variation

Average weight of tablet	Deviation permitted
80mg or >	±10
80mg-250mg	±7.5
>250 mg	±5

2. Thickness[20]

Thickness of the prepared tablets were measured using Vernier calipers. 20 tablets were collected from each formulation. Then the average thickness and standard deviation of 20 tablets was calculated.

3. Friability[20]

Friability of the tablets was determined by using Roche friabilator. From each batch, 20 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 min. After 4 min the tablets were weighed again. The friability was then calculated using the formula.

$$\text{friability}(\%) = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \text{ x } 100$$

4. Hardness[20]

Monsanto hardness tester was used for this purpose. The hardness of 10 tablets from each batch was measured. Then the average hardness and standard deviation was calculated.

5. In-vitro swelling studies[22]

The swelling rate of mucoadhesive tablets were evaluated using 2% w/v agar gel plate. For each formulation, 10 tablets were weighed and average weight of each 10 tablets were calculated (W_1). Then the tablets were placed with the core facing the gel surface in petridishes which are placed in an incubator at 37±0.1°C. The tablets were removed at time intervals of 1, 2, 3, 4, 5 and 6 hours, excess water on surface was absorbed using filter paper and swollen tablets were weighed. The average weight (W_2) was determined and then swelling index was calculated using this formula

$$\% \text{ Swelling index} = [(W_2 - W_1)/ W_2] \times 100$$

6. Determination of surface pH of tablets[22]

Mucoadhesive tablets from each batch were left to swell for 2 h on surface of agar plate. The surface pH was measured using pH paper placed on core surface of the swollen tablet.

6. In-vitro release studies[25]

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8 ±0.5. The release was performed at 37 ± 0.5°C, with a rotation speed of 50 rpm. The tablet was supposed to release drug from one side only hence one side (backing layer) of tablet was fixed to glass disk with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through filter paper and analyzed by UV spectrophotometer at 322 nm.

7. Ex-vivo mucoadhesion time (wash off test)[28]

The ex-vivo mucoadhesion time was performed after application of the buccal tablet on freshly cut goat buccal mucosa. A segment of fresh goat buccal mucosa (2 cm) was glued to the surface

of glass slide, and a mucoadhesive buccal tablet was wetted with 1 drop of phosphate buffer pH 6.8±0.5 and pasted to the goat buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 100 mL of the phosphate buffer pH 6.8 and was kept at 37 ± 1°C. After 2 minutes, a 50 rpm stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 6 hours. The time for the tablet to detach from the goat buccal mucosa was recorded as the mucoadhesion time.

8. Ex-vivo Permeation Study[31]

Tissue preparation

Buccal mucosa was obtained from freshly sacrificed goat at a local ranch. The mucosa was transported to the laboratory in an isotonic buffer solution (pH 7.4) and used within 2 h of animal sacrifice. The majority of underlying connective tissue was removed with the help of a scalpel blade and then the remaining buccal mucosa was carefully trimmed with surgical scissor to a proximately uniform thickness of about 500 µm. It was then used for permeation study.

Permeation study

The ex-vivo buccal permeation study was carried out for all formulations. The permeation study of ketorolac through the excised layer of goat buccal mucosa was performed using Franz diffusion cell at 37 ± 0.5°C. Fresh goat buccal mucosa was mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa, and the compartments were clamped together. The donor compartment was filled with 5 m1 of phosphate buffer pH 6.8. The receptor compartment was filled with phosphate buffer pH 6.8 ± 0.5 and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. The amount of drug permeated through the buccal mucosa was determined by withdrawing samples (5 ml) at predetermined time intervals and analyzed for drug content by UV spectrophotometer at 322 nm.

9. Release kinetics[35]

In order to examine the release mechanism of drug from the tablets, the in-vitro drug release data of best buccoadhesive tablet formulation of Ketorolac was subjected to following release models

- Zero order equation

The zero order release kinetics can be obtained by plotting cumulative % drug released (vs) time (hours). It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$C = K_o t$……**Equation 1**

Where, K_o = Zero order constant in conc. / time

t = Time in hours

- First order equation

The graph was plotted as log % cumulative drug remaining (vs) time in hours.

Log C = log Co + Kt/2.303 ……...**Equation 2**

Where,

Co = Initial drug concentration

K = First order constant

t = Time in hours.

- Higuchi Kinetics

The graph was plotted as % cumulative drug remaining (vs) square root of time.

$Q = Kt^{½}$……..**Equation 3**

Where,

K = Constant reflecting design variable system (Differential rate constant)

t = Time in hours.

The drug release rate is inversely proportional to the square root of time.

- Korsmeyer – Peppas equation

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released (vs) log time.

$M_t/M_\alpha = Kt^n$……..**Equation 4**

Where,

M_t/M_α= Fraction of drug released at time t

t = Release time

K = Kinetics constant (Incorporating structural and geometric characteristics of the formulation)

n = Diffusional exponent indicative of the mechanism of drug release.

Table 3. Release mechanisms based on n-value

Release mechanisms	**n-value**
Fickian diffusion	n<0.5
Non-Fickian transport	0.45<n<0.89
Case II transport	n=0.89
Super case II transport	n>0.89

The n value obtained is used to characterize different release mechanisms for cylindrical shaped matrices.

- Hixson and Crowell erosion equation

$Q_o^{1/3} - Q_t^{1/3} = K_{HC}t$……..**Equation 5**

Where,

Qt = Amount of drug released at time t

Qo = Initial amount of drug

K_{HC} = Rate constant for Hixson Crowell equation

8. RESULT AND DISCUSSION

8.1 Results

8.1.1 Pre-compressional Evaluations

8.1.1.1 Calibration curve

The calibration curve of drug obeyed Beer Lambert's law in the concentration range of 0-16 µg/ml (R^2 = 0.9994) at 322nm and the result is shown in table 4 and plot is shown in fig. 16.

Table 4. Calibration curve of Ketorolac in pH 6.8

Sl. No.	Concentration (µg/ml)	Absorbance at 322 nm
1	2	0.087
2	4	0.16
3	8	0.299
4	10	0.45
5	12	0.591

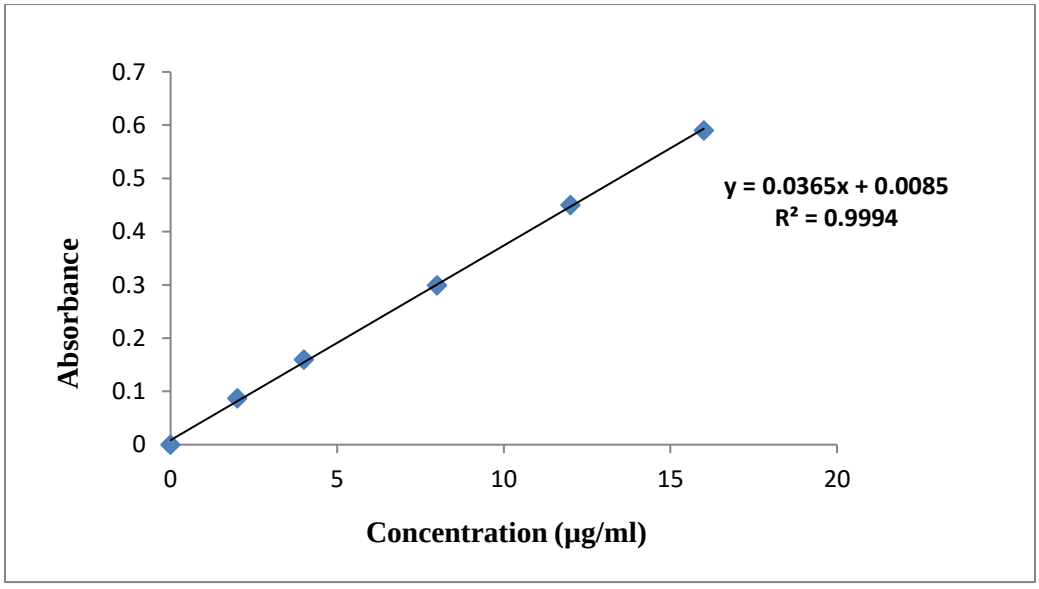


Fig. 16.Standard calibration curve of Ketorolac in Phosphate buffer pH 6.8

8.1.1.2 Compatibility study by FTIR

Fig. 17 presents the results obtained from FT-IR spectroscopy analysis. The spectrum of Ketorolac shows characteristic peaks of C-H stretching band at 3,058 cm^{-1}, strong C=O stretching band at 1,644 cm^{-1}, strong N-O stretching band at 1,533 cm^{-1}, C-N stretching of the oxazole ring at 1,350 cm−1, strong C-F stretching at 1,130 cm^{-1}, and weak C-N stretch of tertiary amine at piperidine ring at 1,192 cm^{-1}. The spectrum of PVP K30 gives broad -OH stretching of carboxylic acid at 3,400–2,800 cm^{-1}, C=O stretching of carbonyl group at 1,699 cm^{-1}, and C-OH asymmetric stretching band at 1,166 cm^{-1}. The spectrum of xanthan gum displays distinct peaks of -OH stretching centered around 3,200 cm^{-1}, asymmetric and symmetric -COO- stretching at 1,613 $cm^{-1}$and 1,417 cm^{-1}, respectively, and C-O stretching at 1,025 cm^{-1}. All the peaks corresponding to the respective bonds are shown in table 5.

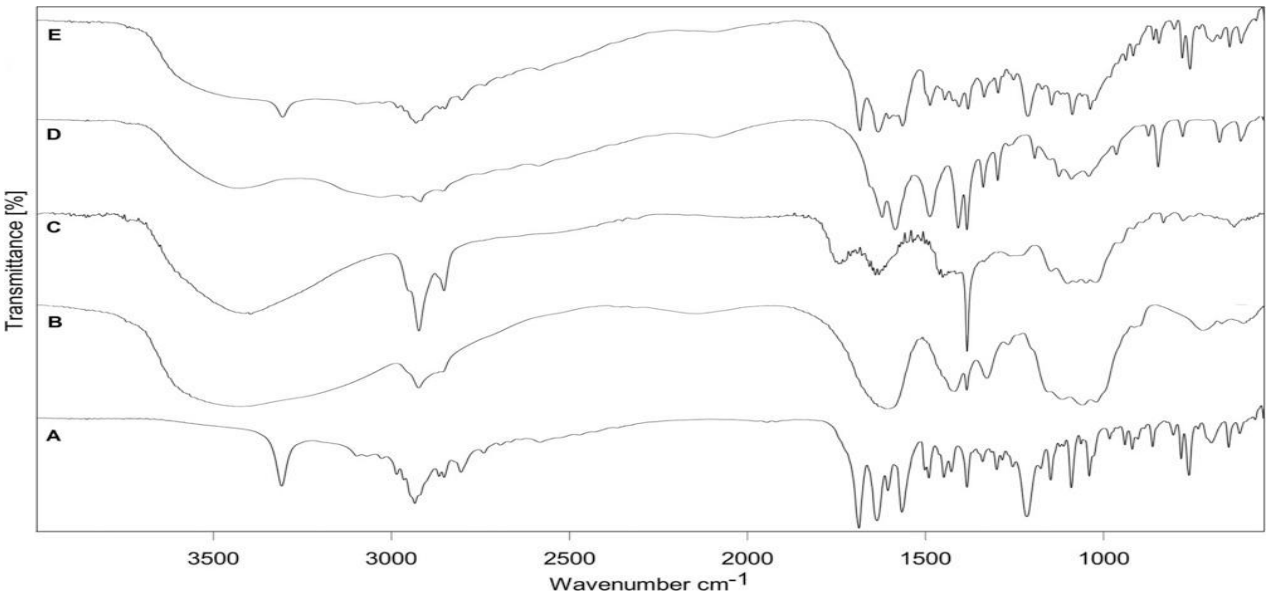


Fig. 17. FTIR spectra of (A)-Ketorolac ; (B)- PVP K30; (C)- Xanthan gum; (D)- physical mixture of Ketorolac, carbopol and PVP 30; (E)- physical mixture of Ketorolac, carbopol and xanthan gum

Table 5. Peaks obtained for various chemical bonds.

Characteristic functional group	Peaks
-OH stretching	3,200 cm^{-1}
-COO- stretching	1,417 cm^{-1}
-COO- stretching	1,613 cm^{-1}
C-O stretching	1,025 cm^{-1}
C=O stretching	1,699 cm^{-1}
C-F stretching	1,025 cm^{-1}
C-N stretch	1,192 cm^{-1}

8.1.2 Ketorolac - Buccal Tablet Evaluations

8.1.2.1 Uniformity of Weight:

The results for the uniformity of weight are tabulated in table 6.

Table 6. Uniformity of Weight

Sl. No.	Formulation code	Weight uniformity (mg)
1.	F1	101.3 ± 3.62
2.	F2	99.2 ± 3.32
3.	F3	98.9 ± 1.91
4.	F4	97.3 ± 2.16
5.	F5	102.1 ± 3.02
6.	F6	101.2 ± 2.81

8.1.2.2 Thickness of the Ketorolac buccal tablet

The results for the thickness of the Ketorolac buccal tablets are tabulated in table 7.

Table 7. Average thickness of the Ketorolac buccal tablets

Sl. No.	Formulation code	Thickness (mm)
1.	F1	2.98 ± 0.091
2.	F2	2.60 ± 0.067
3.	F3	2.081 ± 0.08
4.	F4	2.77 ± 0.051
5.	F5	2.75 ± 0.023
6.	F6	2.80 ± 0.053

8.1.2.3 Hardness of the Ketorolac buccal tablets

The results for the hardness of the Ketorolac buccal tablets are tabulated in Table 8.

Table 8. Average hardness of the Ketorolac buccal tablets

Sl. No.	Formulation code	Avg.hardness (kg/cm^2)
1.	F1	3.24 ± 0.23
2.	F2	3.86 ± 0.18
3.	F3	3.63 ± 0.52
4.	F4	4.02 ± 0.09
5.	F5	3.52 ± 0.55
6.	F6	3.90 ± 0.11

8.1.2.4 Friability of the Ketorolac buccal tablets

The results for the friability test for the Ketorolac buccal tablets are tabulated in table 9.

Table 9. % Friability of the Ketorolac buccal tablets

Sl. No.	Formulation code	Friability (%)
1.	F1	0.164±0.36
2.	F2	0.025±0.21
3.	F3	0.127±0.85
4.	F4	0.478±0.09
5.	F5	0.031±0.11
6.	F6	0.52±0.10

8.1.2.5 Surface pH

The results for the surface pH of the Ketorolac buccal tablets are tabulated in table 10.

Table 10.Surface pH of the Ketorolac buccal tablets

Sl. No.	Formulation code	Surface pH
1	F1	6.78 ± 0.05
2	F2	6.88 ± 0.10
3	F3	7.01 ± 0.02
4	F4	6.90 ± 0.05
5	F5	6.83 ± 0.01
6	F6	6.99 ± 0.21

8.1.2.6 Swelling Index

The swelling index of the various buccal formulations are tabulated in Table 11. The extent of swelling is represented in Fig. 19.

Table 11. Swelling index (%) of the Ketorolac buccal tablets

Formulation code	Time (h)					
	1	2	3	4	5	6
F1	5.55±1.11	9.72±0.77	15.01±0.67	19.63±1.12	23.33±0.45	26.2±0.31
F2	11.28±1.09	19.71±0.87	27.91±0.99	36.21±1.33	44.83±0.96	51.37±0.14
F3	7.99±0.91	12.18±0.99	18.77±1.12	21.31±0.63	26.66±1.19	33.81±1.23
F4	7.01±0.87	11.51±0.78	16.73±0.99	19.94±0.76	24.94±0.67	29.21±1.121
F5	12.06±0.75	22.41±1.22	31.79±1.11	39.51±0.54	47.01±0.79	53.42±0.51
F6	8.67±0.91	13.12±2.01	19.91±1.23	25..18±1.45	34.61±0.61	47.95±0.66

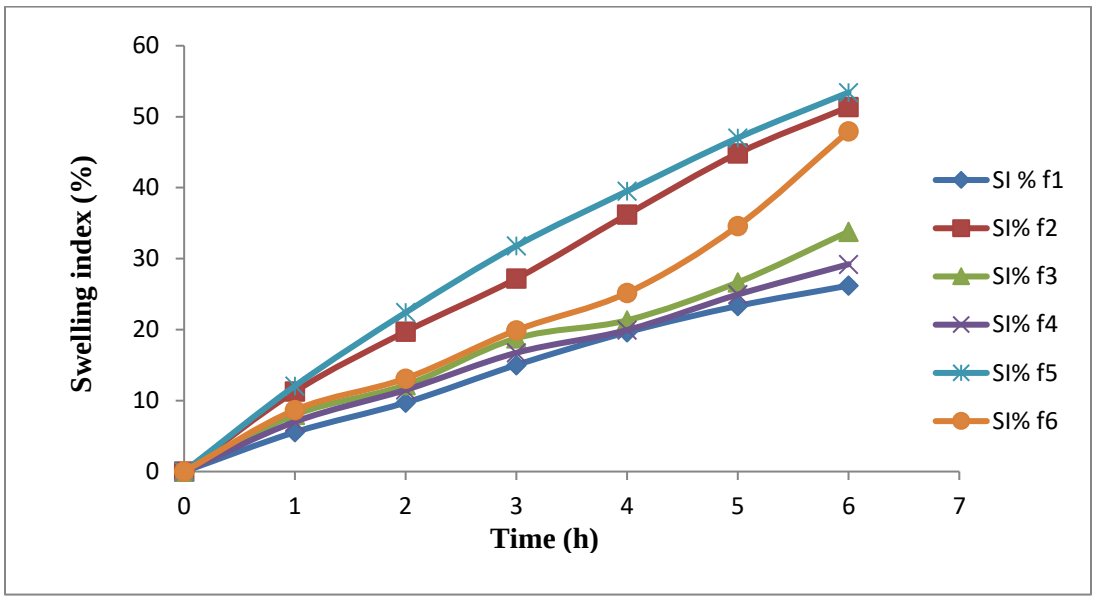


Fig. 18. Swelling index(%) for all formulations

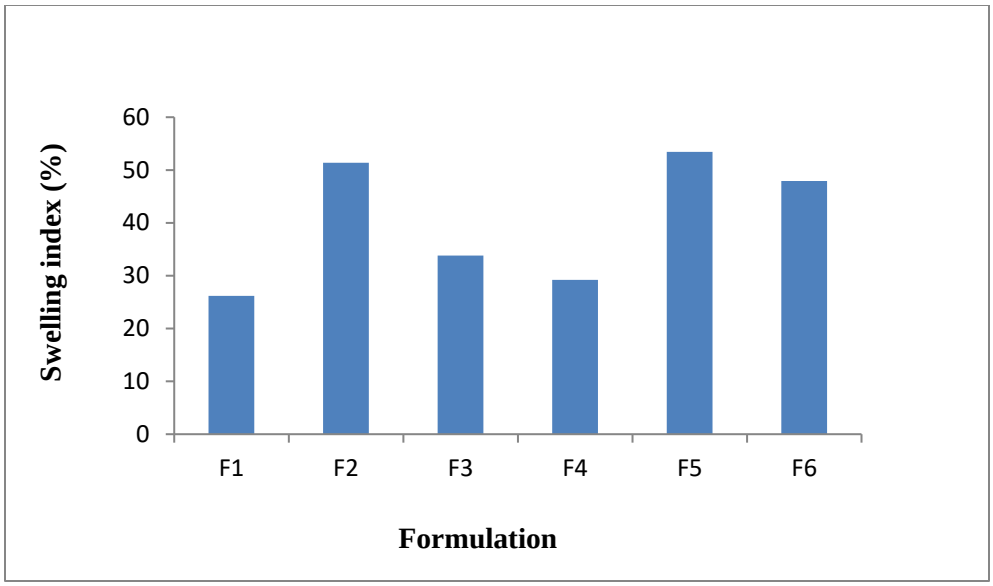


Fig. 19. Extent of swelling in all formulation

8.1.2.7 Mucoadhesive time (Wash-off test)

The data from the Wash off test are tabulated in table 12.

Table 12. Time duration of attachment of the Ketorolac buccal tablets

Sl. No.	Formulation code	Mucoadhesive time
1.	F1	> 6 h
2.	F2	5 h 38 min
3.	F3	5 h 49 min
4.	F4	> 6h
5.	F5	5 h 31 min
6.	F6	5 h 45 min

8.1.2.8In vitro drug release study

The data obtained from the in vitro drug release study are representedin table 13 for formulations F1, F2, F3 and in table 14 for formulation F4,F5,F6.

The in-vitro dissolution profile for the various Ketorolac buccal tablet formulations is given below in Fig. 20 for formulation F1, F2 ,F3 and in Fig. 21 for formulations F4, F5, F6**.**

Table 13. Cumulative percentage in-vitro drug release of Ketorolac buccal tablet formulations F1,F2,F3

Time (min)	F1	F2	F3
15	10.11±0.77	15.51±0.54	11.39±0.66
45	23.32±0.56	26.79±0.34	21.88±0.15
60	30.62±0.65	41.57±1.22	36.63±2.02
120	40.01±0.97	62.91±1.34	55.15±1.01
180	51.23±0.78	76.98±0.17	67.29±0.81
240	66.61±0.51	83.62±0.19	70.31±0.14
300	74.41±0.18	93.11±0.99	74.05±0.22
360	78.32±0.88	98.25±0.23	83.50± 0.12

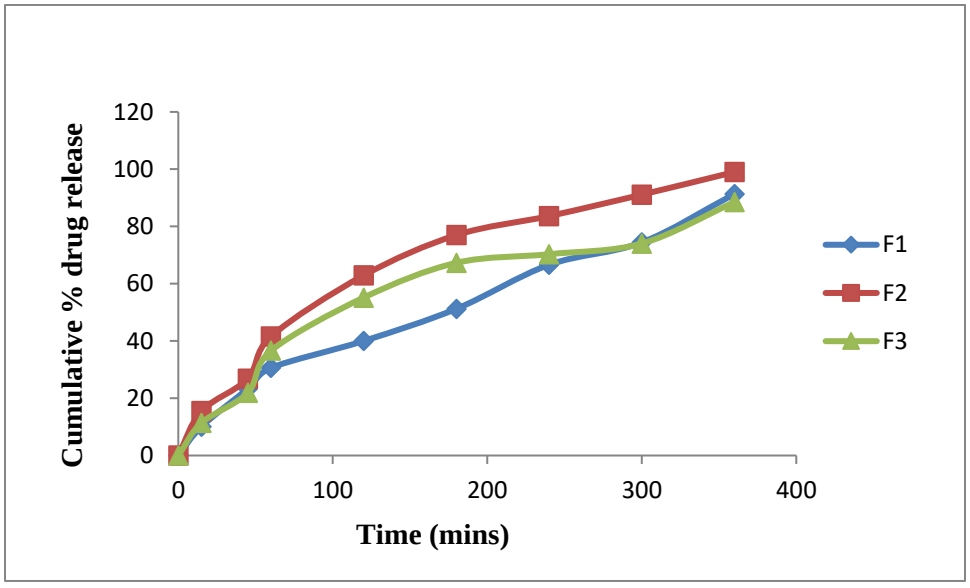


Fig. 20. In vitro dissolution profiles of Ketorolac buccal tablet formulations F1 ,F2, F3

Table 14.Cumulative percentage in-vitro drug release of Ketorolac buccal tablet formulations F4,F5,F6

Time (min)	F4	F5	F6
15	15.77±1.22	14.38±1.34	12.41±0.79
45	23.12±1.34	29.11±1.77	25.62±0.56
60	41.23±0.36	55.31±0.99	46.97±1.11
120	52.79±1.91	74.92±2.01	61.66±1.04
180	61.44±0.87	80.96±1.31	75.32±0.67
240	72.52±0.48	91.73±0.22	77.81±1.22
300	77.92±0.53	93.41±1.23	81.33±0.33
360	81.34±0.65	96.54±0.88	87.32±1.04

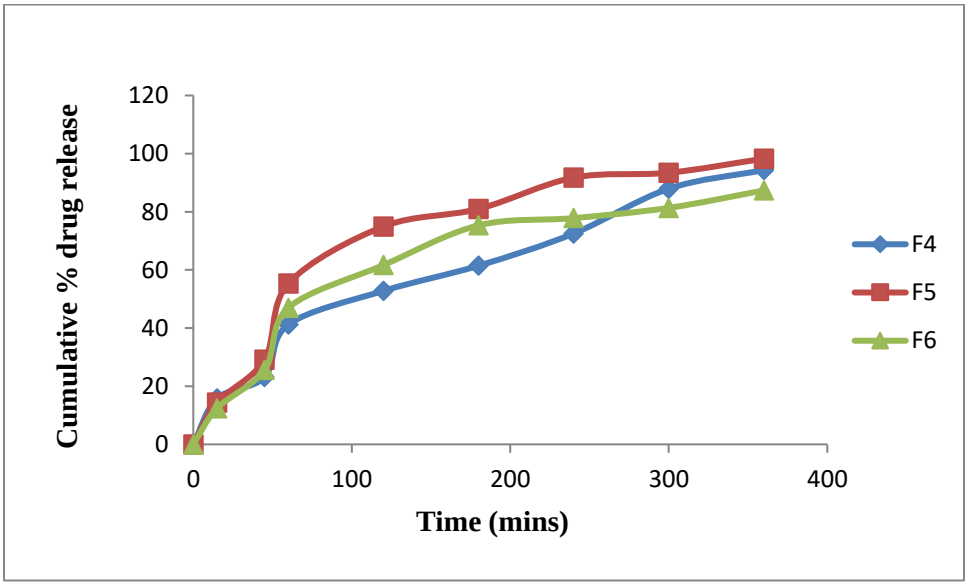


Fig. 21. In vitro dissolution profiles of Ketorolac buccal tablet formulations F4, F5, F6

8.1.2.9Ex vivo drug permeation study

The drug permeation data for the various Ketorolac buccal tablet formulations is given below in table15 for formulation F1, F2, F3 and in table 16 for formulations F4, F5, F6.

The ex vivo drug permeation profile for the various Ketorolac buccal tablet formulations is given below in Fig. 22 for formulation F1, F2, F3 and in Fig. 23 for formulations F4,F5,F6**.**

Table 15. Cumulative percentage drug permeation for Ketorolac buccal tablet formulations F1, F2, F3

Time (min)	F1	F2	F3
15	8.93±1.28	11.2±1.22	7.32±1.24
45	20.13±1.45	25.42±0.56	21.01±0.63
60	29.86±1.71	31.3±0.34	30.51±1.05
120	36.23±2.04	49.71±2.01	40.13±1.12
180	47.51±2.11	66.32±1.73	56.91±0.89
240	56.31±0.66	79.52±0.77	60.91±0.67
300	68.92±0.79	83.08±0.225	79.70±0.35
360	72.63±0.71	96.63±0.23	83.55±0.78

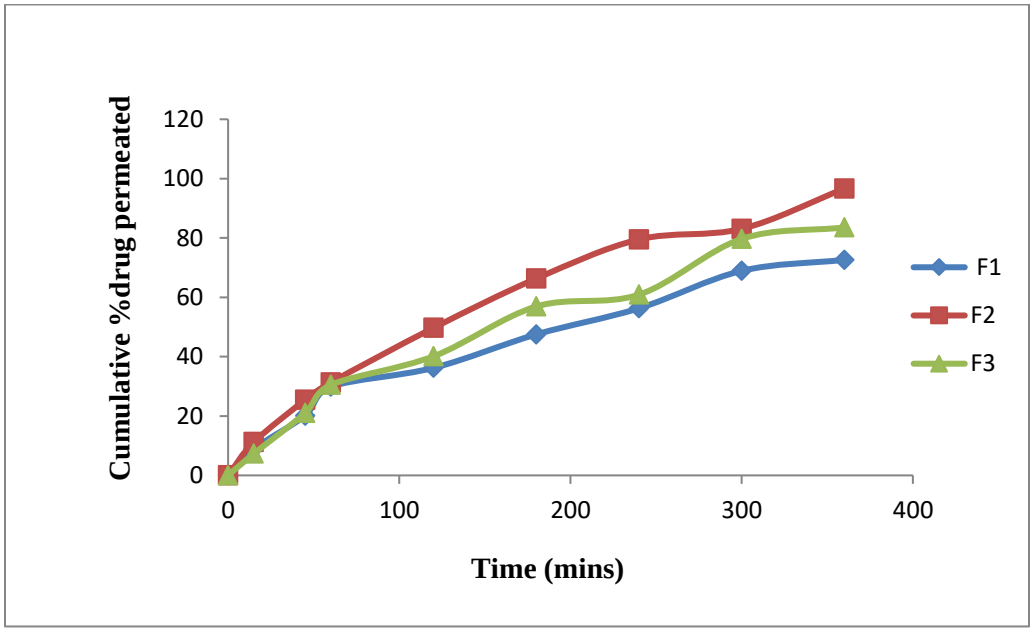


Fig. 22. Ex-vivo diffusion profile of Ketorolac buccal tablet formulations F1, F2, F3

Table 16.Cumulative percentagedrug permeation for Ketorolac buccal tablet formulations F4, F5,F6

Time (min)	F4	F5	F6
15	9.58±0.64	12.81±1.55	9.77±0.89
45	16.8±1.33	28.52±1.79	17.12±0.78
60	19.35±1.92	36.71±0.89	21.33±1.76
120	28.3±0.91	59.21±0.86	39.82±1.54
180	47.17±0.75	71.39±0.78	53.27±1.03
240	59.5±0.47	82.4±1.27	61.8±1.07
300	70.23±0.59	89.51±1.11	74.59±0.74
360	79.54±1.63	95.81±0.36	81.03±0.97

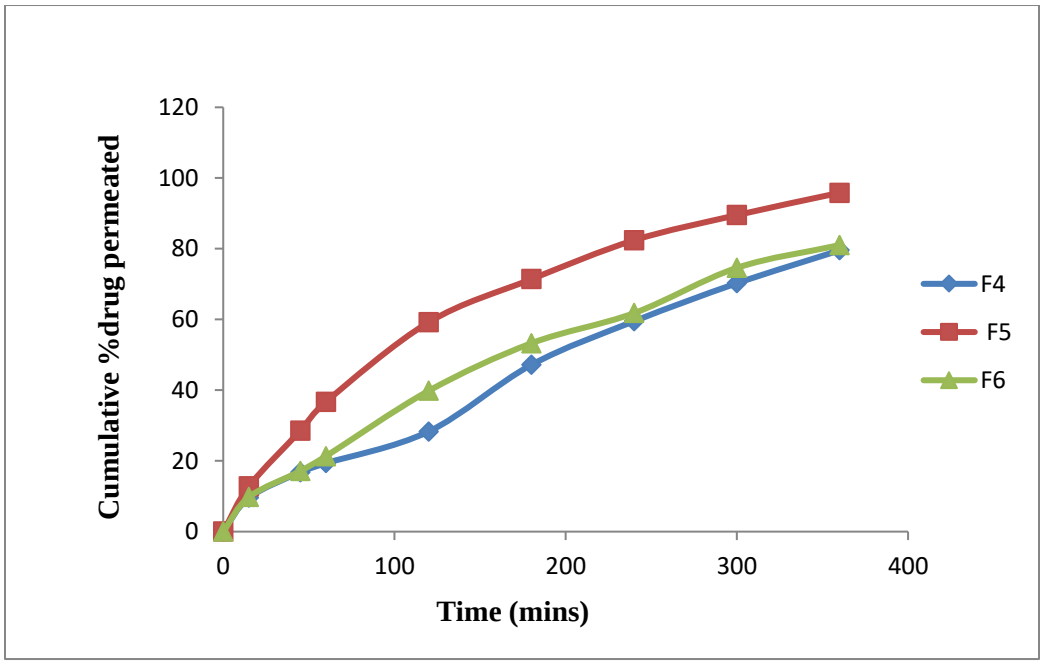


Fig. 23. Ex-vivo diffusion profile of Ketorolac buccal tablet formulations F4,F5,F6

8.1.2.10 Drug release kinetics for the buccal tablet formulations

Out of all the prepared formulation, F2 was selected as optimized formulation as it gave the best results for cumulative percentage drug release.

The drug release kinetics for the optimized formulation (F2) was calculated and the results obtained are represented in table 17. The zero order profile, first order profile, Higuchi profile and Korsmeyer-Peppas plot is represented in Fig. 24, 25, 26 and 27 respectively.

Table 17. Release kinetics and mechanisms of Ketorolac buccal tablet of optimized formulation (F2)

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Hixon-Crowell (R^2)	Korsmeyer-Peppas		Possible drug release mechanism
					(R^2)	N	
F1	0.9908	0.911	0.9835	0.799	0.9465	0.6798	Non-Fickian transport

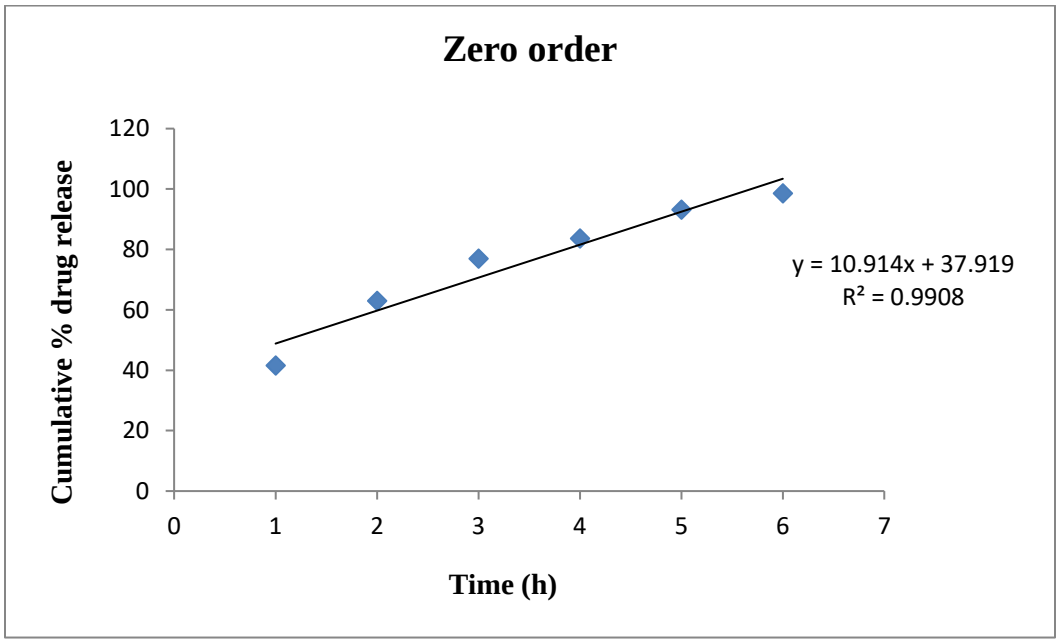


Fig. 24. Zero order profile for optimized formulation F2

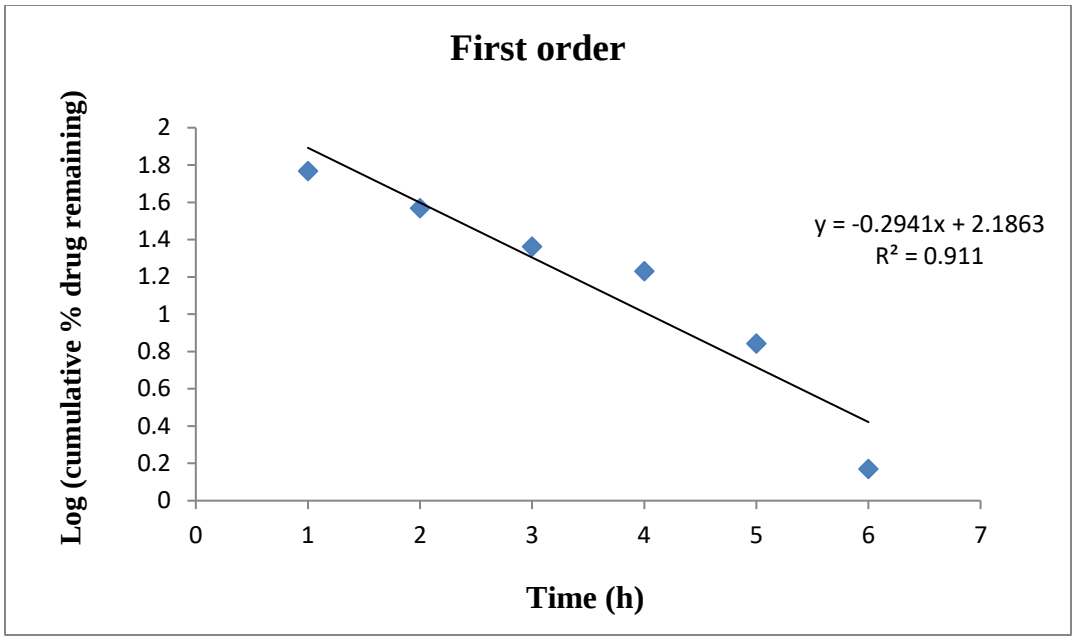


Fig. 25. First order profile for optimized formulation F2

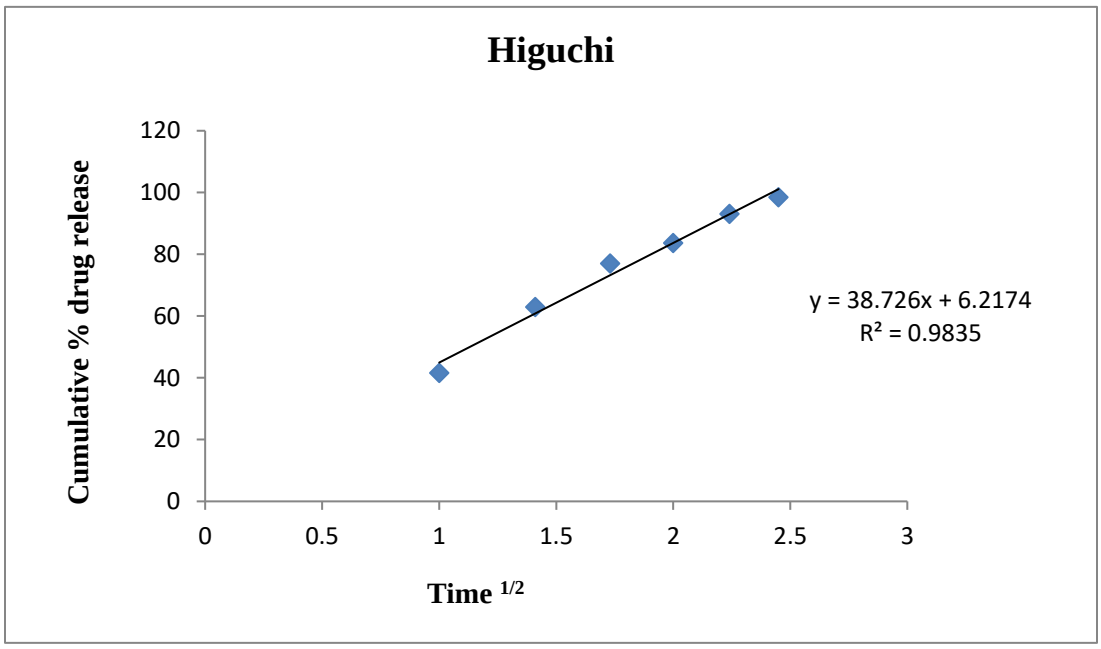


Fig. 26. Higuchi profile for optimized formulation F2

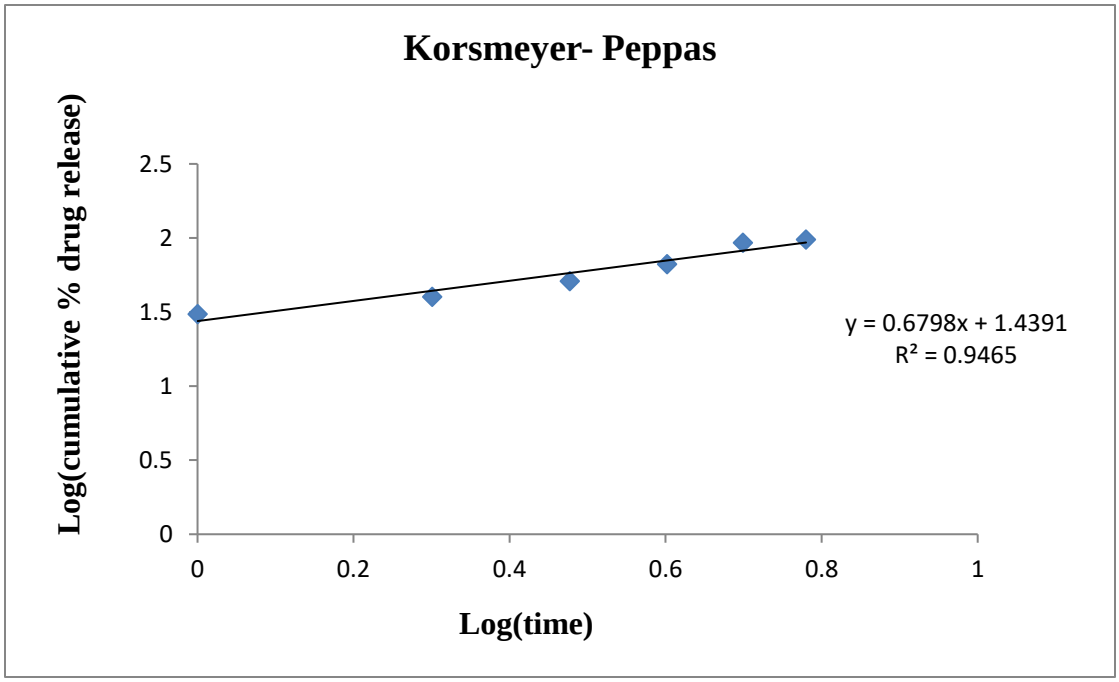


Fig. 27. Korsmeyer- Peppas profile for optimized formulation F2

7.2 DISCUSSION

Precompressional formulation parameters

The standard calibration of pure drug proved that Ketorolac supplied was of pharmacopoeia standards.

From the obtained FTIR peaks it can be concluded that the physical mixture of the drug Ketorolacdoes not show any major interactions with formulation excipients.

Weight variation

Values of weight variation are found to be within the permissible limits of conventional oral tablets stated in the I.P.

Weights of the tablets varied between 97.3-102.1mg with deviation in the range of 1.91-3.62

The extreme variation could have been the result of mishandling of the tablet weights during punching process.

Thickness

The average thickness of Ketorolac buccal tablets is found to be quite uniform with minimum variation.

The thickness of various tablet preparation were observed in the range of 2.60mm to 2.98mm with standard deviation in the range 0.023 to 0.091.

The thickness of the tablet and hence its total weight must be appropriate in order to obtain good mucoadhesion, as the mucoadhesive property is also dependent on the geometry of the dosage form.

Hardness and friability

The hardness of the prepared Ketorolac buccal tablet lies in the range of 3.24 to 4.02 g/cm^2 with the standard deviation in the range of 0.09 to 0.55.

Also the friability lies in the range of 0.025% to 0.520%

Friability is not more than 1% for any formulation.

The hardness of Ketorolac buccal tablets is low, but the friability data suggests that the tablets are quite robust enough to withstand the normal handing.

Surface pH

The surface pH of all the tablets is within the range of 6.58 to 7.01 which is close to neutral pH.

There is negligible or no change in the surface pH of the tablets.

Hence, no irritation to the buccal cavity is assumed.

Swelling Index

The result of swelling study reveals that the swelling index of all the tablets increases with time because the polymer gradually absorbs water due to hydrophilicity of the polymer.

Appropriate swelling behavior of mucoadhesive buccal system is essential for uniform and prolonged drug release and effective mucoadhesion.

The swelling index after 6 h. is in the range from 16.92 to 41.37% for formulation containing carbopol 943 with PVP 30, while for buccal tablets containing carbopol 934 with xanthan gum, it was in the range from 19.21-43.42%.

The swelling index is directly proportional to the concentration of second polymer (i.e. PVP 30 or xanthan gum) and inversely proportional to carbopol.

The formulation containing higher levels of the second polymers (PVP K30 and Xanthan gum) displays the highest swelling index.

The reason for this is, they are of lower viscosity grade and hence the water penetration into the tablet matrix is facilitated by them or in other words, they are having a faster rate of water uptake.

In vitro drug release

All the formulation shows good release (i.e.>85%)

For formulation F1, F2, F3 (containing carbopol and PVP 30) the drug release is found in the range of 78.23±0.7% to 98.25±1.2%

On the other hand formulation F4, F5, F6 (containing carbopol and xanthan gum) the drug release is found in the range of 81.34±1.5% to 96.54±0.2%

It can be concluded that an increase in carbopol content delays the drug release from the tablets.

Also the formulation which showed highest swelling index also exhibit high extent of drug release.

This may be due to the fact that the higher amount of water uptake by the polymers may lead to considerable swelling of polymer matrix, allowing the drug to diffuse out at a faster rate.

Ex-vivo drug permeation study

For formulation F1, F2, F3 (containing carbopol and PVP 30) the cumulative percentage drug diffusion is found in the range of 72.63±2.1% to 96.63±1.4%.

Whereas formulations F4, F5, F6 (containing carbopol and xanthan gum) the drug release is found in the range of 79.54±1.8% to 95.81±0.6%.

From the data obtained from diffusion study, it can be concluded that higher level of carbopol retards the release from buccal tablet.

Whereas formulation containing higher level of second polymer (PVP K30 and Xanthan gum) showed a higher extent of drug diffusion.

Ex- vivo muco adhesion time

The ex-vivo mucoadhesion time for the prepared buccal tablets varies from 5 h to more than 6 h.

The difference between the values of the ex-vivo mucoadhesion time for buccal tablets can be attributed to the combination of the various amounts of the polymer which affect the mucoadhesion.

Moreover, PVP K30 and xanthan gum owing to its solubility in water and the observed high swelling rate and extent, resulted in lower mucoadhesion time.

Whereas, tablets containing high proportion of carbopol, mucoadhesion time is found to be increased.

Drug release kinetics

Examination of the correlation coefficient (R^2) value indicated that the drug permeation followed a diffusion-controlled mechanism for the buccal tablet of bestformulation (F2)as the R^2 value for zero order plot (0.9908) was higher in comparison to the first-order (0.911),Higuchi plot (0.9835), Korsmeyer Peppas plot (0.9465) and HixsonCrowell plot (0.799) kinetic models, as shown in Table 23. The drug release is independent of concentration. Also, the n value of Korsmeyer-Peppas lies within $0.45<n<0.89$, which indicates that it undergoes anomalous diffusion or non-fickian diffusion.

9. SUMMARY

In the present work, an attempt was made to design efficacious and prolonged release mucoadhesive buccal tablets of Ketorolac using various polymers to reduce dosing frequency, decrease gastric irritation and to improve patient compliance.

Two polymer combinations (carbopol 943 and PVP K30 as well as carbopol and xanthan gum) were taken at varying proportions. The buccal tablets were tested for weight uniformity, thickness, friability and hardness. Tablets were then evaluated for their swelling index, in vitro drug release, mucoadhesion time (wash-off time) and ex vivo drug permeation.

The kinetics and mechanism of the drug permeation through the excised buccal tissue of goat from the buccal tablets were also characterized. The data collected were then analyzed using software to determine the effects of each parameter. The effects of the various parameters involved were then interpreted.

The best polymer composite was selected from the various ratios of the polymers. The best polymer ratio was found to be Carbopol 934 and PVP K30 in the ratio 1:2. The mucoadhesive strength of buccal tablets increases as the concentration of secondary polymer increases. The above polymer composite had shown satisfactory results in the parameters such as thickness, hardness, drug content, swelling index, mucoadhesive time, in-vitro dissolution and in-vitro diffusion. The satisfactory formulation shows a zero order drug release profile depending on the regression value and shown a satisfactory dissolution profile. Slow, controlled and maximum release of Ketorolac over a period of 6 h was obtained from buccal tablets F2 formulation containing Carbopol 934 and PVP K30.

Further work is to be carried out in order to determine its efficacy and safety by long term pharmacokinetic and pharmacodynamic studies in human beings.

10. CONCLUSION

The oral cavity and its highly permeable mucosal tissues have been taken advantage for decades as a site of absorption for delivery of drugs to the systemic circulation. So the formulations which target the oral cavity through buccal mucosa are of considerable interest to improve the bioavailability and reduce the frequency of administration of APIs.

Drugs administered through the buccal route have a rapid onset of action and leads to improved bioavailability of drugs. The buccal route can bypass the first-pass metabolism, bypass contact of the drugs with the gastrointestinal fluids and paves way for easy access to the membrane sites so that the delivery system can be applied, localized and removed easily. Furthermore, there is good potential for prolonged delivery through the mucosal membrane within the oral mucosal cavity.

Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. Adhesions of these drug delivery systems to mucosal membranes lead to an increased drug concentration gradient at the absorption site and therefore improve bioavailability of systemically delivered drugs.

The research work highlights the development and evaluation of novel buccal drug delivery system of Ketorolac so that the non-invasive administration of injection as well as gastrointestinal side effects of the drug (when administered orally) can be avoided.

At the current global scenario, scientists are finding ways to develop buccal adhesive systems through various approaches to improve the bioavailability of drugs used orally by manipulation of the formulation strategies like inclusion of pH modifiers, enzyme inhibitors as well as permeation enhances.

11. REFERENCE

1. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharmaceut Sci, 1998; 1(4): 15-30.
2. Radha Bhati, Raja K Nagrajan. A detailed review on oral mucosal drug delivery system. Int J Pharm Sci Res. 2012; 3(3): 659-681.
3. https://en.wikipedia.org/wiki/Buccal_administration (last accessed on May 8, 2019)
4. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A clinical perspective on mucoadhesive buccal drug delivery systems. J Biomed Res. 2014;28(2):81–97.
5. Shaikh R, TRR Singh, Garland MJ, Woolfson AD, Donnell RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci. 2011; 3(1): 89–100.
6. RoyS, Pal K, Anis A, Pramanik K, Prabhakar B, Polymers in mucoadhesive drug delivery system: a brief note, Des. Monomers Polym. 2009; 3(12): 483–489.
7. Sudhakar Y, Kuotsu K, Bandyopadhyay AK, Buccal bioadhesive drug delivery: a promising option for orally less efficient drugs. J Control Release. 2006; 11(9): 15–40.
8. Lieberman HA, Lachman, Schwartz B. Pharmaceutical Dosage forms: Tablets Volume 1. 2nd ed. New York: Marcel Dekker; 1989.
9. Parth S Patel, Ashish M Parmar, Nilang S Doshi, Hardik V Patel, Raxit R Patel. Buccal drug delivery system: a review. Int J Drug Dev Res. 2013; 5(3): 35-48.
10. Patil SB, Murthy RSR, Mahajan HS, Wagh RD, Gattani SG. Mucoadhesive polymers: means of improving drug delivery. Pharma Times. 2006; 38(4): 25-28.
11. https://www.ncbi.nlm.nih.gov/pubmed/1494990 (last accessed on May 9, 2019)
12. Burak Celik. Risperidone mucoadhesive buccal tablets: formulation design, optimization and evaluation. Drug Des Devel Ther. 2019; 11(3): 3355-3365.
13. https://www.drugs.com/pro/ketorolac.html (last accessed on Oct 8, 2019)
14. https://en.wikipedia.org/wiki/Ketorolac (last accessed on Oct 7, 2019)
15. Rupinder Kaur, Sukhdev Singh, Aaliya Hasan, Sunny Jalhan, Upendra K Jain. Development and evaluation of UV spectrophotometric method for the estimation of ketorolac tromethamine in bulk drug. World J Pharm Pharm Sci. 2016; 5(4): 1792-1799.

16. Rowe RC, Sheskey PJ, Weller PJ. Handbook of pharmaceutical excipients. 5th ed. UK. Pharmaceutical press. 2003; 298, 430, 617, 821.
17. Raghavendra N Rao, Shravani B, Mettu Srianth Reddy. Overview on buccal drug delivery systems: J Pharm Sci Res. 2013; 5(4): 80-88.
18. Marwa Shukar, Amal Abdel Reheem. Development and evaluation of ketorolac mucoadhesive buccal tablets; Int J Pharm Pharm Sci. 2014; 6(8): 294- 298.
19. Raja Navamanisubramanian, Raghunandan Nerella, Chamundeeswari Duraipandian, Shanmuganathan Seetharaman. Quality by design approach for optimization of repaglinide buccal tablets using box behnken design. Future Journal of Pharmaceutical Sciences. 2018; 4(2): 265-272.
20. Patel Sweety, Anuradha Patel, Sachin Narkhede. Formulation evaluation and optimization of buccal tablets of ivabradine hydrochloride. J PharmSciBioScientific Res. 2016; 6(3): 329-337.
21. Hardik Parmar, Biswajit Biswal, Jyotiranjan Nayak. Design development and evaluation of buccal tablet containing nicorandil. Asian J Pharm Clin Res. 2015; 8(2): 102- 106.
22. Anna Balaji, Vadepalli, Radhika, Vishnuvardhan Goud.Formulation and evaluation of mucoadhesive buccal tablets by using natural polymer. Int J Pharma Sci Res. 2014; 5(3): 4699- 4708.
23. Nisreen Hasan, Khar RK, Javed Ali. Development and evaluation of buccal bioadhesive tablet of an anti-emetic agent ondansetron. AAPS PharmSciTech 2009; 10(4): 1085-1093.
24. Venkataswamy M, Santhoshini M, Priyanka JP, Prathyusha. Preparation and evaluation of biphasic bilayered buccal tablet containing ketorolac immediate release layer and domperidone maleate sustained release layer. World J Pharm Res. 2018; 7(11): 905-945.
25. Rahamatullah Shaikh, Thakur Raghu Raj Singh, Ryan F Donelly.Mucoadhesive drug delivery systems. J Pharm Bioallied Sci. 2011; 3(1): 89- 100.
26. Perioli L, Ambrogi V, Rubini D, Giovagnoli S, Ricci M, Blasi P, et al. Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease. J Control Release. 2004; 95(11): 521-533.

27. Gazzi Shankar, Chegonda K Kumar, Prabhakar Reddy.Formulation and evaluation of bioadhesive buccal drug delivery of tizanidine hydrochloride tablets.AAPS PharmSciTech. 2009; 10(2): 530–539.
28. Balamurugan Mohan, Saravana VS, Ganesh P, Senthil SP, Hemalatha PV, Sudhir V Pandya.Development and in-vitro evaluation of mucoadhesive buccal tablets of domperidone. Res J Pharm Tech. 2008; 1(4): 377-380.
29. Hiremath JG, Sarfaraz MD, Hiremath D, Sarudkar SA. Preparation and physicochemical characterization of simvastatin loaded mucoadhesive bilayered tablet. Indian Journal of Novel Drug Delivery. 2009; 1(1)**:** 18-24
30. Binu Raina, Abhimanyu Sharma, Prabhjot Singh Bajwa. Formulation, evaluation and optimization of fast disintegrating tablet of ketorolac tromethamine. Int J Pharm Investig. 2017; 48(6): 233-246.
31. Khaleed M Hosny, Ravda Zaki, Ahmed Khamies Mohamed, Ahmed Abdelbary. Preparation, characterization and in vivo evaluation of ketorolac tromethamine in situ ocular hydro gel. Indian J Drug Dev. 2011; 3(3): 315-330.
32. Sinha VR, Kumar RV, Singh G. Ketorolac tromethamine formulation: an overview. Expert Opin Drug Deliv. 2009; 6(9): 961-975.
33. Luana Perioli, Valeria Ambrogi, Stefano Givagnoli, Maurizio Ricci. Mucoadhesive bilayer tablet for buccal sustained release of flurbiprofen. AAPS PharmSciTech. 2007; 8(3): E20-E27.
34. Bytul M Rahman, Mukhlesur M Rahman, Maruf Ahmed, Ranjan K Barman, Robiul Islam. Development, evaluation and formulation of ketorolac tromethamine tablet and a comparative study with marketed products.Res J Medicine Med Sci. 2007; 2(2): 102-105.
35. Shaila Lewis, Subramanian G, Pandey S, Udupa N. Design, evaluation and pharmacokinetic study of mucoadhesive buccaltablet of nicotine for smoking cessation.
36. Anup K Roy, Vinod SM, Syed Jalaluddin Basha, Rabiul Haque, Roopa Kark. Formulation and evaluation of mucoadhesive buccal tablets of valsartan. Int J Drug Dev Res. 2013; 5(4): 145-155.
37. Prasantha Vasantha Viswanadhan, Anand Padole, Abin Abraham, Sam Thomarayil Mathew.Buccaltablets of lisinopril by direct compression method for buccal drug delivery. Int Res J Pharm. 2012; 2(2): 30-38.

38. Gore Meghna Milind, Gurav Yogesh, Adhikrao Yadav. Int J Pharm Sci Res. Formulation and evaluation of mucoadhesive buccal tablets of propanolol using natural polymer. 2017; 6(2): 2905-2913.
39. Goswami Druba Shankar, Goyal Sandeep, Goyal Deepak, Sharma Rini, Mehta Naveen, Puja Kumari, et. al. Formulation and evaluation of mucoadhesive tablets of famotidine. J Pharm Biomed Sci. 2011; 12(6): 279-280.