OPTIMIZATION AND EVALUATION OF FELODIPINE CO-CRYSTALS EMBEDDED BUCCAL FILM FOR IMPROVING BIOAVAILABILITY

Dissertation submitted to

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Chennai-600 032

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

MASTER IN PHARMACY
IN
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SUBMITTED BY

HEMAVATHY. S (261910007)

Under the guidance of

INDUSTRIAL GUIDE

Dr. MG. DINESH

R&D HEAD,

VOPEC PHARMACEUTICALS Pvt. Ltd.

Chennai- 600037.

INSTITUTIONAL GUIDE

DR. PRIYANKASINHA., M.Pharm., Ph.D.,

Associate Professor,

Department of Pharmaceutics,

C.L.Baid metha college of pharmacy.

DEPARTMENT OF PHARMACEUTICS

C. L. BAID METHA COLLEGE OF PHARMACY

Thoraipakkam, Chennai-97.

OCTOBER 2021

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

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Owned and Managed by Tamilnadu Chemists and Druggists Educational Trust
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Executive Trustee

Dr. Grace Rathnam
Principal

Dr. Grace Rathnam, M.Pharm., Ph.D.,

HOD & Principal,

Department of Pharmaceutics,

THE CERTIFICATE

This is to certify that the dissertation work entitled "**OPTIMIZATION AND EVALUATION OF FELODIPINE CO-CRYSTALS EMBEDDED BUCCAL FILM FOR IMPROVING BIOAVAILABILITY**" submitted to **THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32** in partial fulfilment for the award of the degree of Master of Pharmacy in Pharmaceutics is a bonafide research work done by **HEMAVATHY. S (Reg. No.261910007),** under the guidance of **DR. PRIYANKA SINHA, M.PHARM, Ph.D. Professor**, **Department of Pharmaceutics**, C.L. Baid Metha College of Pharmacy, Chennai-600097, during the academic year 2019-2021.

Dr. Grace Rathnam, M.Pharm., Ph.D.,

Date:

Place: Chennai- 600097.

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

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Place: Chennai -600097

Date:

DR. PRIYANKA SINHA, M.PHARM, Ph.D.

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This is to certify that **S. Hemavathy, Reg number:261910007**. M.Pharm (pharmaceutics) second year student of "**C.L Baid Metha College of Pharmacy, Rajiv Gandhi Salai, Thoraipakkam., Chennai – 600097**" has done Project work in the company under the guidance **of Dr. MG.DINESH., R&D (Head), " VOPEC PHARMACEUTICALS PRIVATE LIMITED**" Located in Mogappair West – Mogappair Industrial Estate, Chennai District, Tamilnadu-600037. INDIA.

The duration of project work was; period from June 2021 to March 2022.

AUTHORIZED SIGNATURE

M. G. Dinesh

Dr. MG.Dinesh., Ph.D.,

R&D (Head)

Vopec Pharmaceuticals Private Limited

Chennai – 600037

Tamilnadu

India

DECLARATION

I HEMAVATHY.S (Reg. No. 261910007) hereby declare that the thesis entitled "**OPTIMIZATION AND EVALUATION OF FELODIPINE CO-CRYSTALS EMBEDDED BUCCAL FILM FOR IMPROVING BIOAVAILABILITY**" has been originally carried out by me under the supervision and guidance of **Dr. PRIYANKA SINHA, M. Pharm., Ph.D.,** Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-97& **Dr. MG. DINESH,** R&D HEAD VOPEC PHARMACEUTICALS Pvt. Ltd. Chennai- 600037 during the academic year 2020-2021. This work has not been submitted in any other degree at any other university and that all the sources I have used or quoted have been indicated and acknowledged by complete reference.

Place: Chennai
Date:

HEMAVATHY.S
Register No: 261910007
Department of Pharmaceutics,
C. L. Baid Metha College of Pharmacy,
Chennai-97.

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LIST OF ABBREVIATIONS

Abbreviation	Expansion
%	Percentage
%w/v	Percentage Weight by Volume
%w/w	Percentage Weight by Weight
^{O}C	Degree Celsius
nm	Nano meter
Fig	Figure
I.m	Intra- muscular
BP	British pharmacopoeia
cm	Centimetre
API	Active Pharmaceutical Ingredient
psi	Pounds per square inch
DSC	Differential scanning calorimetry
PXRD	Powder x-ray diffraction
SEM	Scanning Electron Microscopy
FDA	Food and drug administration
PBS	Phosphate Buffer Solution
mg/ml	Milligram per milliliter
FTIR	Fourier transform infrared
GI	Gastro intestinal
ug/ml	milligram per millilitre
HPMC	Hydroxy propyl methyl cellulose
PVA	Poly Vinyl Alcohol
h/hr	Hour
HCL	Hydrochloric acid
IP	Indian pharmacopoeia
HPC	Hydroxy Propyl Cellulose
Kg/cm^2	Kilogram per square centimetre

L	Litres
mg	Milligram
ml	Millilitre
mins	Minutes
nm	Nanometre
Rpm	Rotation per minute
RH	Relative humidity
F	Formulation
SD	Standard deviation
Sec	Seconds
USP	United states pharmacopoeia
UV	Ultra violet

1. INTRODUCTION

Oral route has been the commonly adopted and most convenient route for drug delivery. Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes, ease of administration as well as traditional belief that by oral administration the drug is well absorbed as the food stuffs that are ingested daily. Pharmaceutical products designed for oral delivery are mostly the immediate release types which are designed for immediate release of drug for rapid absorption. The term drug delivery covers a very broad range of techniques used to get therapeutic agents in to human body. The limitations of the most obvious and trusted drug delivery techniques those of the ingested tablet and of the intravenous/ intramuscular/ subcutaneous injections have been recognized for some time. The former delivers drug in to the blood only through the hepatic system and hence the amount in the blood stream may be much lower than the amount formulated into the tablet. Furthermore, liver damage is the unfortunate side effect of many soluble tableted drug [1].

To overcome some of these limitations, other modes of drug delivery in to the body were investigated. Those are:

1. Trans Dermal Drug Delivery System (through the intact skin)
2. Trans Mucosal Drug Delivery System (through the intact mucosa of the mouth, intestine, rectum, vagina or nose)
3. Trans Ocular Drug Delivery System (through the eye)
4. Trans Alveolar Drug Delivery System (inhalation through the lung tissue)
5. Implantable Drug Delivery System (through the subcutaneous and deeper implants, deliver into surrounding tissue)
6. Injectables (I.M or Subcutaneous)

Of the above modes, Transdermal, Transmucosal, Injectables and Subcutaneous Implants have been found varying degree of commercial acceptance [3].

1.1. TRANSMUCOSAL DRUG DELIVEY SYSTEM

Delivery of drugs through the absorptive mucosa in various easily accessible body cavities, like the Buccal, ocular, nasal, rectal, and vaginal mucosae, has the advantage of bypassing the hepatic-gastrointestinal first pass elimination associated with oral administration. Furthermore, because of the dual biophysical and biochemical nature of these mucosal membranes, drugs with hydrophilic and/or hydrophobic characteristics can be readily absorbed. Different types of transmucosal drug delivery systems are

- ✓ Buccal Drug Delivery System.
- ✓ Ocular Drug Delivery System.
- ✓ Vaginal Drug Delivery System.
- ✓ Rectal Drug Delivery System.
- ✓ Nasal Drug Delivery System.
- ✓ Gastro Intestinal Drug Delivery System.[7]

BUCCAL DRUG DELIVERY SYSTEM

Buccal Drug Delivery The lip, tongue, cheek, soft palate, hard palate, and floor of mouth comprises oral cavity. Oral mucosal layer consist of three layers: outer epithelium, middle basement and inner connective tissues. 100cm total area of the oral cavity consists of about one third of buccal surface of 0.5mm thickness epithelium.25 About 0.5 to 2 litre of saliva runs into oral mucosal surface. PH of salvia varies between 5.5 to 7 depending on its flow rate.[9]

Buccal drug delivery system is defined as the delivery of a medication to the systemic circulation via the buccal mucosa, which is the lining of the cheek. Buccal route is suitable for administration of hydrophilic oligonucleotides and polysaccharides, as well as large unstable proteins. It is used as the mostly desired site for systemic as well as local medication delivery. The buccal mucosa coats the inside of the cheek and to treat systemic and local diseases, a buccal dosage form should be inserted in the mouth between the upper gingiva and the cheek. This system is considered as a possible alternative to drug administration as it has more advantages over peroral routes.

Buccal mucosa avoids enzymatic decomposition in gastrointestinal tract and first pass metabolism of drug as the buccal mucosa are highly vascularized with an abundant

blood supply and is relatively permeable which allows drug to be absorbed directly into the systemic circulation. The buccal cavity has short residence time caused by excessive salivation and swallowing, therefore developing a suitable bio adhesive system is necessary that stick to the buccal mucosa for a prolonged period of time. Bucco-adhesive drug delivery systems are those systems in which the drugs are administered in the oral cavity's buccal mucosa. Buccoadhesive drug delivery system is suitable for drugs having poor permeability and solubility, susceptible to enzymatic decomposition and drug that require sustained effect. The administration of medication using this system is completely safe and easy and the dosage form can be removed any time required in case of emergency. [8]

Characteristics of an Ideal Buccal adhesive System

- Speedy adherence to the buccal mucosa and adequate mechanical strength.
- Medication discharge in a controlled design [10].
- Encourages the rate and degree of medication ingestion.
- Ought to have great patient consistence.
- Ought not upset ordinary capacities, for example, talking, eating and drinking.
- Ought to achieve unidirectional arrival of medication towards the mucosa [11].
- Ought not guide be developed of optional diseases, for example, dental caries.
- Have a wide edge of security both locally and fundamentally.
- Ought to have great protection from the flushing activity of salivation [12].

Advantages of Buccal Drug Delivery System:

- Avoids first pass metabolism and hence offers greater bioavailability.
- Allows drug localization for a prolonged period of time.
- Provides convenience for administration and termination of therapy in case of emergency.
- Can be easily administered to unconscious patient.
- It is possible to obtain significant dose decrease.
- Drugs that are likely to be unstable in acidic or in an alkaline condition of stomach and intestine or drug that are susceptible to enzymatic degradation can be administered.

- Drug absorption takes place by passive diffusion.
- Better patient compliance or acceptance.
- Provides sustained delivery of drug.
- Rapid onset of action.[8]

Disadvantages of Buccal Drug Delivery System:

- Drugs that irritate oral mucosa, have odour and bitter taste, are unpalatable cannot be administered.
- Drugs that are unstable at buccal pH cannot be administered.
- Drugs with a low dosage need can be given.
- Excess salivation may cause swallowing of drug.
- Drugs that are absorbed through passive diffusion can be administered.
- Food and liquid consumption may not be convenient.
- Accidental swallowing of formulation by patients is possible.[8]

Mucoadhesive drug delivery system

Mucoadhesive drug delivery system was now a days a booming field for research interest. These are delivery system, which utilize the property of bioadhesion of certain polymers. Mucoadhesive buccal drug delivery system offer many advantages over conventional system such as ease of administration, be promptly terminated in case of toxicity by removing the dosage from buccal cavity and it was also possible to administer drug 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 system 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
- Should provide the drug release in 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 was possible to realize mucosal (local effect) and trans mucosal

(systemic effect) drug administration. In the first case, the aim was to achieve a site specific release of 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 circulation and there by circumvent the first pass hepatic metabolism, gastric irritation and other problems associated with conventional oral route.

Mucoadhesive drug delivery system interact with the mucus layer covering the mucosal epithelial surface and mucin molecules and increase the residence time of the dosage form at the site of the absorption. Mucoadhesive drug delivery system was a part of controlled delivery system [13].

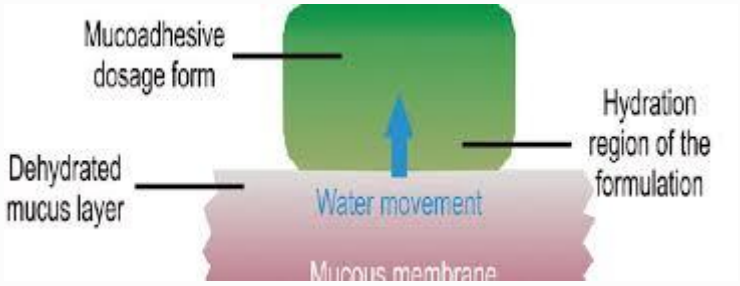


FIG 1: MUCOADHESIVE DOSAGE FORM

Mechanism of mucoadhesion

Basically, mucoadhesion is the phenomenon in which two materials, one which may be artificial substance like polymer for mucoadhesion and other material the mucin layer lining the mucosal tissue are adhered together for prolonged period of time with the aid of interfacial forces. The process of mucoadhesion, generally involves three stages:

Stage 1- wetting and swelling of polymer (contact stage)

Stage 2- interpenetration between the polymer chains and the mucosal membrane

Stage 3- formation of bonds between the entangled chains (consolidation stage) [15]

Contact stage- An intimate bond between the mucoadhesive substance and the mucous membrane take place when they come in contact with each other during this stage.

Consolidation stage- The attachment of mucoadhesive material to the mucous membrane by different physicochemical forces of attraction cause a prolong and deep intimate adhesion and is called as consolidation stage[14].

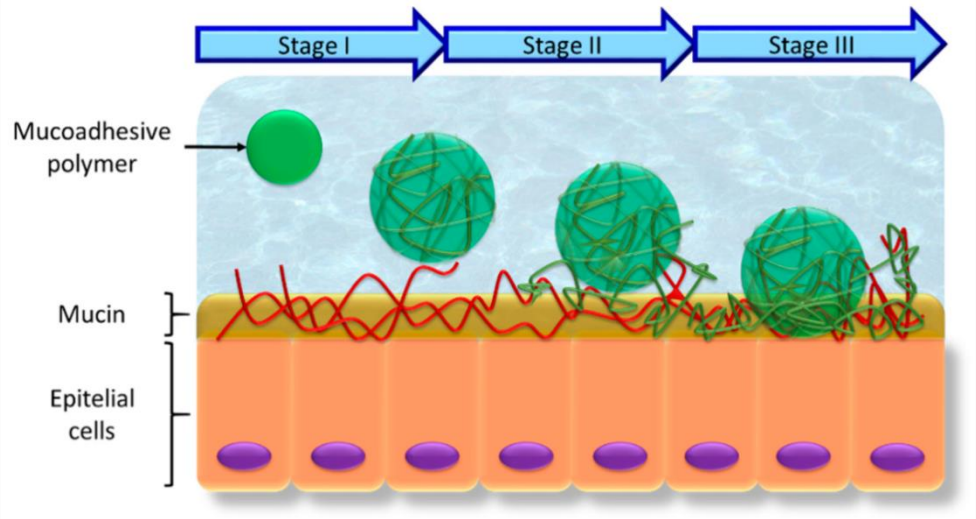


FIG 2: MECHANISM OF MUCOADHESION

THEORIES OF MUCOADHESION

Electronic theory- As the mucoadhesive and biological materials both carry opposite electrical charges, so on coming in contact with each other, transfer of electrons takes place at the interface which results in the formation of double electronic layer. These attractive forces determine the mucoadhesive strength.

Adsorption theory- Initial contact between mucus and mucoadhesive polymer results in the formation of chemical bonds i.e., primary and secondary bonds (covalent and non-covalent).

Wetting theory- The ability of bioadhesive polymer to spread over the biological surface is described in this theory. Here, the angle of contact between the two surfaces is measured. The wettable polymers exhibit optimal adhesion to epithelial surfaces.

Diffusion theory- The penetration of mucin and polymer chains to a suitable depth creates a semi-permanent adhesive bond which is necessary for the components to have good mutual solubility for diffusion to take place.

Fracture theory- The amount of force needed to separate the polymer from the mucus is measured. This theory is based on the measurement of mechanical strength of mucoadhesion.

Mechanical theory- In this theory, adhesion occurs when mucoadhesive liquid fills the irregularities present on a rough surface.

1.2. Oral mucosa:

Buccal cavity was 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 buccinators muscle. The thickness of buccal mucosa was having uneven texture and about 500-800 µm and the buccal epithelium return time at 5-6 days. The non-keratinized stratified squamous epithelium lines the buccal mucosa and having 500-600µ and surface area of about 50.2cm2.

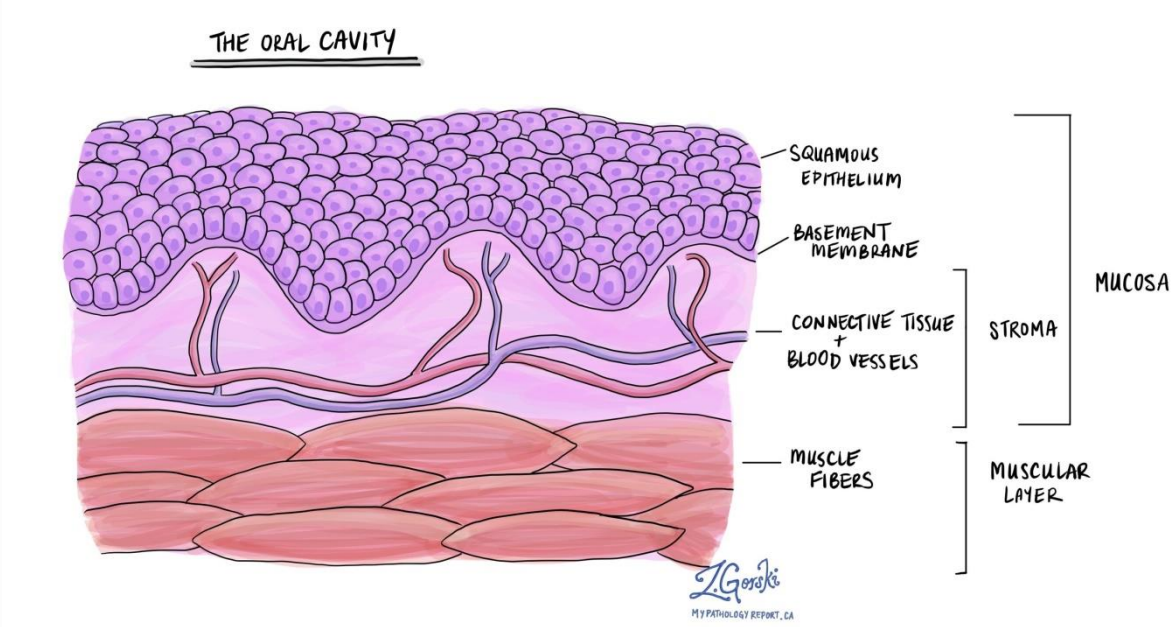


FIG 3: STRUCTURE OF ORAL CAVITY

Structure

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

- Epithelium
- Basement membrane
- Connective tissues

The oral mucosa has three distinctive layers namely the epithelium, connective tissue and basement membrane. The stratified squamous epithelium coated with mucus is found on the outermost layer of oral mucosa. The thickness of epithelium is about 40-50 cell layers thick.

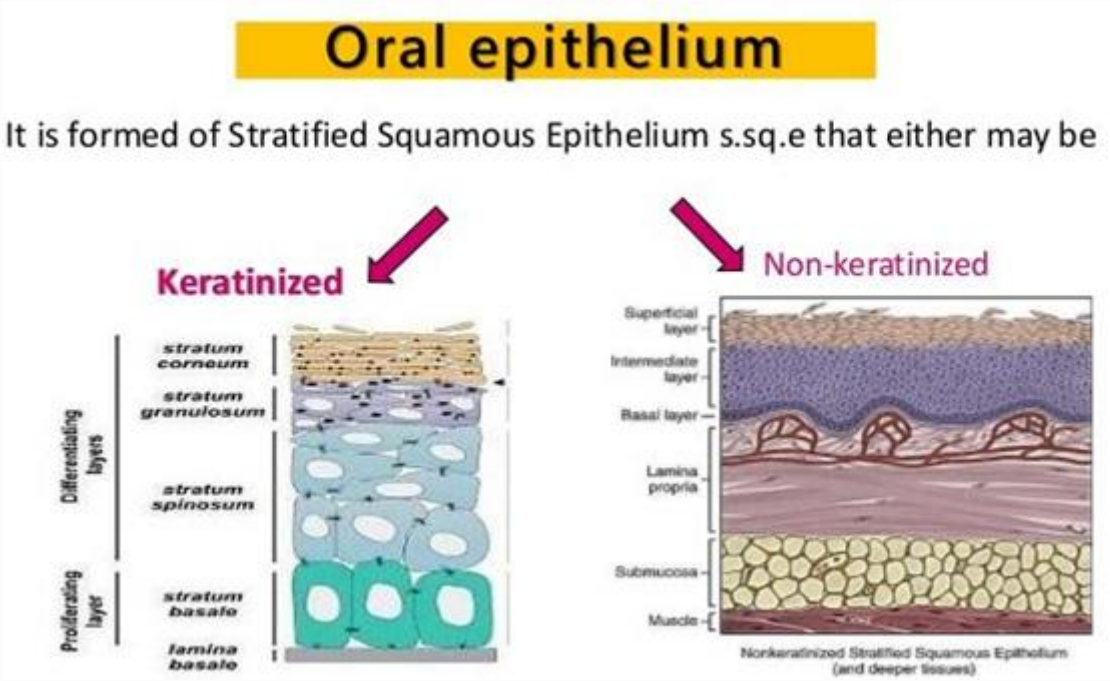


FIG 4: OVERVIEW OF ORAL EPITHELIUM

The basement membrane, lamina propria, and submucosa lie underneath the epithelium. The mucosa of the mouth can be classified into five types based on the different oral cavity areas [17]:

1. The mouth's floor (sublingual region)
2. The mucosa of the buccal cavity (cheeks)

3. The gum (gingiva)

4. The palatal mucosa

5. The lips from the inner side.

The mucosae of buccal, sublingual and soft palate are non-keratinized whereas the mucosae of hard palate and gingivae are keratinized. The non-keratinized epithelia have more permeability than keratinized epithelia. Buccal mucosa permeability is believed to be 4-4000 times higher than skin permeability. Oral mucosa's permeability is in order as sublingual>buccal>palatal which depends mainly on keratinization level and relative thickness. The thickness of buccal mucosa is 500-800mm and the thickness of sublingual region i.e., the ventral tongue, the hard palate, the soft palate, and the gingivae is 100-200mm [8].

1.3. Various buccal bioadhesive dosage forms

Bioadhesive 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 bioadhesive are sodium alginate, carbomers, polycarbophil, HPMC, HPC, gelatin etc.

1. Buccal bioadhesive tablets

Buccal bioadhesive tablet 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 Suscardbuccal (prochlorperazine)

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 di nitrate in the form of unidirectional erodible buccal film is developed and characterized for improving bioavailability.
II. Buccal film of salbutamol sulphate and terbutaline sulphate for treatment of asthma
III. Buccoadhesive film of clindamycin used for pyorrhea treatment

3. **Buccal bioadhesive semisolid dosage form**

Buccal bioadhesive semisolid dosage form consists of finally powdered natural or synthetic polymer dispersed in a polyethylene or in a aqueous solution. Example: arabase

4. **Buccal bioadhesive powder dosage forms**

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

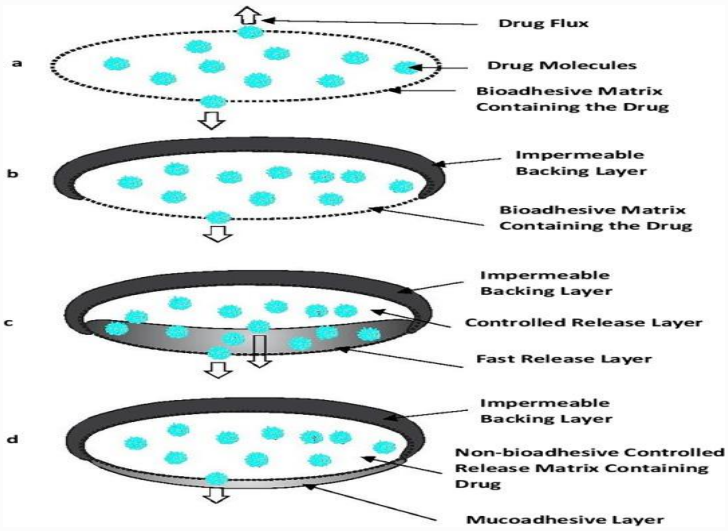


FIG 5: DESIGN OF BUCCAL MUCOADHESIVE DOSAGE FORMS

1.4. Polymer for buccal

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.

Basic components of buccal Mucoadhesive drug delivery system

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 was for rapid release/prolonged release and for local/systemic effect. The selection of suitable drug for the design of buccoadhesive drug delivery system should be based on pharmacokinetic properties
2. **Bioadhesive polymer**- Bioadhesive polymer play a major role in buccoadhesive drug delivery system 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 attachment of bioadhesive devices to the mucus membrane. The material used as backing membrane should be inert and impermeable to the drug and penetration enhancer. Such impermeable membrane on buccal bioadhesive patches prevent the drug loss and offer better patient compliance. The commonly used materials in backing membrane include carbopol, magnesium stearate, HPMC, HPC, CMC, polycarbophil etc.
4. **Penetration enhancer**- penetration enhancer 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, laureth9, sodium fusidate, polmitoylcarnitine, azone, sodium glycocholate, dimethyl formamide etc. [18]

1.5. COCRYSTALS:

Cocrystals are solids crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts. Thus, it is a multiple component crystal modified by intermolecular interaction such as hydrogen bonding, van der Waals force, π-π interactions, and halogen bond between an active pharmaceutical ingredient (drug) and conformer .Cocrystals are multicomponent molecular crystals where all components are at a stoichiometric ratio and comprise of two or more chemically different molecules includes modification of drugs to alter physical properties of a drug, especially a drug's solubility without altering its pharmacology effect[2].

The co-crystallization process is long known; however, recently it is gaining much attention because of its wider application in pharmaceuticals as a newer technique to transform the physicochemical properties of drugs like solubility, stability, bioavailability, thermo stability and many more. The key advantage in co-crystallization is non-modification of pharmacological activity of drug, while their pharmaceutical properties get modified [3].

Solubility is one of the major physicochemical properties which affect the therapeutic efficacy of any drug entity. Among the present new drugs available, approximately 8% possesses high solubility and permeability. Almost 50% of API's face the problem of diminished efficacy due to poor solubility. Hence, solubility and dissolution becomes prime concern in formulation development. Drug polymer complex, emulsification, micronization, salt formation, use of co-solvents are various approaches adopted to overcome the problem of solubility. Many APIs are in the form of molecular crystals. Normally, solubility of the amorphous form is more as compared to crystalline form. Co-crystals are basically molecular complexes resulting from hydrogen bonding between co-former and drug. The physicochemical properties of the drug molecule are modified once it gets converted into co-crystal but its intrinsic activity is preserved. Thus, co-crystals of many class II drugs have shown improved dissolution rate (comparable to amorphous form) and long-term chemical and physical stability [4].

Cocrystals are multicomponent crystals comprising salts, solvates, clathrates, inclusion crystals, and hydrates. In solvates, one component is liquid at room temperature, whereas in cocrystals, both components are solid at room temperature [5].

The major steps involved for supra molecular synthon determination for the preparation of cocrystals are as:

- Identification of important functional groups in the active pharmaceuticals ingredients (API) or moiety.
- Insertion of functional groups in a systemic way in the Cambridge structural database to select and identify most potent coformer.
- Select an appropriate technique for the cocrystal synthesis.
- Perform various crystallization screening processes [6].

FIG 6: MECHANISM OF COCRYSTALS FORMATION

A= Active Pharmaceutical ingredients**,** B = Coformer, AB = Cocrystal

1.6. TECHNIQUES OF COCRYSTAL FORMATION

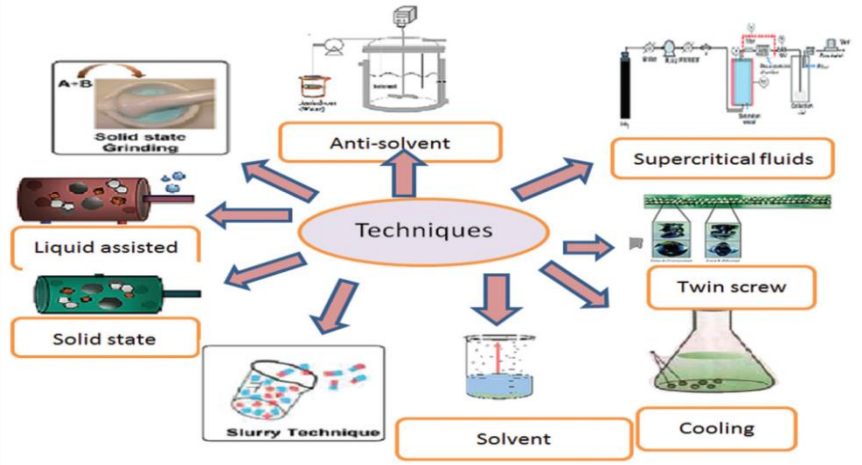


FIG 7: TECHNIQUES OF COCRYSTALS FORMATION

With the advancement in drug development, various methods are being used for the preparation of multicomponent solid forms such as cocrystals, cosolvents, coamorphous, polymorphs, hydrates/salts, and eutectics. Solvent selection, API and coformers are the important parameters for such preparations. The various kinds of methods that are most commonly used are:

Solid-based technique

It generally includes solid phase grinding, melt extrusion, and melts crystallization. In this method, API and coformer are melted and mixed together, resulting in the cocrystal formation in a fixed stoichiometric ratio. It is basically not suitable for thermolabile moiety, but it is easy, scalable, and continuous process.

Grinding method

It is one of the mostly used techniques for the cocrystal formation from the last few years. It is basically of 2 types: (a) dry grinding method and (b) wet grinding method.

Dry grinding method

It is most widely and commonly used technique for cocrystal formation, in which API and coformers are mingled in a stoichiometric proportion using mortar and pestle. This method is simple, easy to perform, ecofriendly, and highly productive but is mechanical and time-consuming. Nowadays, planetary milling systems are also available in a laboratory scale.

Hot melt extrusion method

In this technique, API and coformers are transferred into a fixed controlled temperature system where they are melted and form cocrystals of new moiety. This technique is not suitable for thermolabile drugs because both drug and coformer should be mixed in a molten state. In this method, API and coformer are mixed in their molten state to enhance their surface contact without the use of solution (solvent).

Liquid-based technique

This technique mainly includes: Solvent evaporation, solvent drop grinding, liquid-assisted grinding, solution crystallization, cooling crystallization, supercritical fluids, slurry method, antisolvent method, reaction crystallization method, ultrasound-assisted solution technique, supercritical fluid atomization techniques, and spray drying techniques [26].

1.7. SLOW EVAPORATION OF SOLVENT RESULTS COCRYSTAL FORMATION:

It is also known a solvent evaporation technique, in which a solution (solvent) is made to vaporize slowly. During the process of dissolution, the functional moiety in the API and coformer interchanges with each other to form new hydrogen bonds which is most widely used by many researchers. In this method, both API and coformers are dissolved with a continuous stirring in a boiling solvent until the final volume becomes small. This boiling solution is allowed to cool slowly to form cocrystals in either open air or in hot air oven.

In this technique, solvent dissolving coformers are selected and dissolved, and finally, drug is scattered into it by dispersion homogenizer. The solution is then mixed with a proper solvent for the precipitation of coformer into the drug.

Liquid-assisted grinding method

Liquid-assisted grinding is another commonly used method to form cocrystals. Besides providing faster rate of cocrystal formation than dry grinding, it is more reliable and suitable method as well. It is known to be ecofriendly method for industrial-level production due to less amount of solvent used. The process does not also depend on the temperature, and more importantly, it diminishes the chances of unwanted solvate formation.

Solvent drop grinding

This method involves incorporation of API and coformer with the addition of suitable solvent. The solvent is added in drops with continuous stirring. The solvent used behaves as a catalyst which enhances crystal formation. This technique is also suitable for the synthesis of amorphous cocrystals.

Cooling crystallization method

It is less frequently applied method for the cocrystal formation. It is generally slow and time-consuming process as compared to other techniques, In this, there is an improvement in solubility, dissolution, and micrometric properties than its individual drug.

Ultrasound-assisted solution method

This technique is used for the nanocrystal preparations in which drug and coformers are dissolved in an appropriate vehicle (solvent). Solution is placed in a sonicator to form turbid, and temperature is maintained to prevent fragmentation and degradation. Solution is kept overnight for solvent evaporation and cocrystal formation.

Spray dying method

It is very commonly employed method for the preparation of cocrystals because of its quick, continuous, and single step process. In this technique, solution containing API and coformer is allowed to evaporate over hot air stream. This technique is relevant to scale up and more user friendly.

Slurry method

It is also one of the easiest techniques for the crystallization process where cocrystal formation takes place. The selected drug and coformer are dissolved into a suitable solvent forming a suspension and are finally stirred, filtered, and dried.

Supercritical antisolvent technique

This method is most useful technique for crystal preparation and to prevent the thermal degradation of compound. In this technique, solid sample is dissolved in a suitable solvent (organic or inorganic) which is injected into a supercritical fluid (under high pressure) resulting in a large decrease in solution density forming cocrystals.CO2 (non-polar compound) is the best supercritical fluid applied in the pharmaceutical fields due to its advantages such as non-toxic, non-flammable, economical, and easily available[27].

2. LITERATURE REVIEW

1. Mona Semalty et al., (2008) [19] Mucoadhesive buccal films of glipizide were prepared by solvent casting technique using hydroxyl propyl methylcellulose, sodium carboxy methylcellulose, carbopol-934P and Eudragit RL-100. Prepared films were evaluated for weight, thickness, surface pH, swelling index, in vitro residence time, folding endurance, in vitro release, permeation studies and drug content uniformity. The films exhibited controlled release over more than 6 h. From the study it was concluded that the films containing 5 mg glipizide in 4.9% w/v hydroxyl propyl methylcellulose and 1.5% w/v sodium carboxy methylcellulose exhibited satisfactory swelling, an optimum residence time and promising drug release. The formulation was found to be suitable candidate for the development of buccal films for therapeutic use.

2. **Rajesh Singh Patel et al., (2009)** [20] made a study on preparation and evaluation of mucoadhesive buccal patches for the controlled systemic delivery of Salbutamol sulphate to avoid first pass hepatic metabolism. The developed patches were evaluated for the physicochemical, mechanical and drug release characteristics. The patches showed desired mechanical and physicochemical properties to withstand environment of oral cavity. The in-vitro release study showed that patches could deliver drug to the oral mucosa for a period of 7 h. the patches exhibited adequate stability when tested under accelerated conditions.

3.SandeepSaini et al., (2011) [21] Formulated Fast dissolving film of levocetrizine dihydrochloride were prepared by solvent casting method by using Maltodextrin& HPMC E15 as the main film forming polymers. To decrease the disintegration time, concentration of maltodextrin& HPMC E15 were optimized be using 22 factorial design. Disintegration time, drug release pattern, mouth dissolving time and content uniformity were also evaluated. Compatibility between drug and recipients were studied by means of DSC analysis. Batch F1was found to be the optimized batch as its disintegration was completed within the minimum time as compared to all other batches. The formulation (F1) was also showing sufficient drug release after 5 min. All the 6 formulation was showing approximately 90% drug release after 5min.

4. Zankahanapatel et al., (2020) [22] The mouth dissolving films of Ramosetron Hydrochloride were prepared by using the solvent casting method. Films were formulated using HPMC E5as a film-forming agent, PEG400 as a plasticizer and Aspartame. A 3^2 full factorial design was applied considering the concentration of HPMC E5 (X_1) and concentration of PEG400 (X_2) as independent variables and % cumulative drug release (Y_1) (CDR), disintegration time (Y_2) (DT) and tensile strength (Y_3) (TS) as dependent variables. The prepared films were evaluated for thickness, folding endurance, tensile strength, disintegration time, drug content uniformity and taste masking by E-tongue. The results indicated that factors X_1 and X_2were found to be having a positive effect on DT and TS and negative effects on CDR.

5. Ms. Mital S. Panchal., (2012) [23] The films of Ropinirole Hydrochloride were prepared by using polymers such as pullulan and PEG 400 as plasticizer, by a solvent casting method. Formulation batches were formulated with the help of 32 full factorial designs. The formulated mouth dissolving films were evaluated for physical characteristics such as uniformity of weight, thickness, folding endurance, drug content uniformity, surface pH, percentage elongation, and tensile strength, and gave satisfactory results. The formulations were subjected to disintegration, In-vitro drug release tests and stability study. The FTIR and DSC studies revealed that no physicochemical interaction between excipients and drug. A marked increase in the % drug release was exhibited by mouth dissolving films of Ropinirole Hydrochloride containing pullulan as a polymer at 60 sec., when compared to other polymers films. Mouth dissolving film of Ropinirole Hydrochloride containing pullulan as polymer showed 99.48 ± 0.18 % drug release at 60 sec. Stability studies revealed that optimized formulation was stable. Mouth dissolving films of Ropinirole Hydrochloride can be considered suitable for clinical use in the treatment of parkinson's disease and rest leg syndrome, where a quicker onset of action for a dosage form is desirable along with the convenience of administration.

6. Preetabose et al., (2012) [24] Co-crystallization is one of the most reliable alternative approaches to increase the solubility of poorly water-soluble drugs without affecting their physicochemical properties. Pharmaceutical cocrystals are neutral organic compounds connected to the API preferentially by loosely formed bonds as dipole-dipole interaction. Our present study aims at improving the solubility of an effective oral hypoglycaemic, Glimepiride, a sulphonyl urea class of drug that often lacks water

solubility. In the process of enhancing its solubility, four different co-formers were used as Anthranilic acid, Succinic acid, Salicylic acid, Benzoic acid, and Gallic acid in different stoichiometric ratios like 1:2 and 1:3. The technique opted for the making is slow evaporation and prepare the nanoparticle by using Chitosan and gelatine polymeric matrix with aldehydic oxidized Xanthan gum as crosslinking agent. Initial confirmation was made through melting point determination. Later structure elucidation of co-crystals was carried out by several analytical methods, such as FTIR, X-ray Diffraction. In FTIR spectra, a sharp decrease in the intensity of N-H peak of salicylic acid and succinic acid was observed in 1:2 ratio, which in turn indicates the formation of the hydrogen bond. PXRD indicates crystallinity by the formation of a sharp, high intense peak in drug: salicylic acid in 1:2 ratios. The nanoparticle was evaluated on the basis of size determination, DEE, and in-vitro release study, which gives promising results that release for a prolonged period of time. In the future, in-vivo and other physicochemical properties were evaluated.

7. Vijay kumar et al, (2012) [25] Co-crystallization approach for modification of physicochemical Properties of hydrochloride salt is presented. The objective of this investigation was to study the effect of co-crystallization with different co-crystal formers on physicochemical properties of fluoxetine hydrochloride (FH). FH was screened for co-crystallization with a series of carboxylic acid co-formers by slow evaporation method. Photomicrographs and melting points of crystalline phases were determined. The co-crystals were characterized by FTIR, DSC and PXRD methods. Solubility of co-crystals was determined in water and buffer solutions. Powder and intrinsic dissolution profiles were assessed for co-crystals. Physical mixtures of drug and co-formers were used for comparisons at characterizations and physicochemical properties evaluation stages. Four co-crystals of FH viz. Fluoxetine hydrochloride-maleic acid (FH-MA), Fluoxetine hydrochloride-glutaric acid (FH-GA), Fluoxetine hydrochloride-L-tartaric acid (FH-LTA) and Fluoxetine hydrochloride- DL-tartaric acid (FH-DLTA) were obtained from screening experiments. Physical characterization showed that they have unique crystal morphology, thermal, spectroscopic and X-ray diffraction properties. Solubility and dissolution studies showed that Fluoxetine hydrochloride-maleic acid co-crystal possess high aqueous solubility in distilled water, pH 4.6, 7.0 buffer solutions and dissolution rate in distilled water than that of pure drug. Co-crystal formation approach can be used for ionic API to tailor its physical properties.

8. Sanjay Yadav et al., (2015) [26] Co-crystallization is a new approach of enhancement of solubility, stability, bioavailability and other physicochemical properties. It offers a better optimization of physical and biopharmaceutical properties of drugs. Co-crystal formation involves intermolecular interaction such as Hydrogen bonding, Vander Waals forces and π-π stacking interactions. Robustness of potential intermolecular interaction and hydrogen bonding rules are the important aspects of cocrystallization experiment design. Characterization of co-crystal can be performed by power X-ray diffraction, single crystal X-ray diffraction, infrared spectroscopy, differential scanning calorimetry, scanning electron microscopy, solid state NMR, THz-TDS method. This review covers general consideration of selection of drug for co-crystallization, chemistry of co-crystallization including role of hydrogen bonding in co-crystallization, co-crystal effect on physicochemical properties and characterization of co-crystal using suitable method.

9. Pekamwars. s et al., (2016) [27] Physicochemical characteristics of active pharmaceutical compounds including solubility and flow properties are crucial in the development of drug formulation. The physical form of compound and formulation has potential effect on biopharmaceutical parameters of drug. The crystal engineering approach can be employed for modification of physicochemical properties of the active pharmaceutical ingredients whilst maintaining the intrinsic activity of the drug molecule. This article covers the advantages of co-crystals over salts, solvates (hydrates), solid dispersions and polymorphs, mechanism of formation of co-crystals, methods of preparation of co-crystals and application of co-crystals to modify physicochemical characteristics of active pharmaceutical ingredients along with the case studies.

10. Mona F Arafa et al., (2016) [28] Development of oral disintegrating tablets requires enhancement of drug dissolution and selection of sweetener. Co-crystallization of drugs with inert co-former is an emerging technique for enhancing dissolution rate. The benefit of this technique will become even greater if one of the sweeteners can act as co-crystal co-former to enhance dissolution and mask the taste. Accordingly, the objective of this work was to investigate the efficacy of sucralose as a potential co-crystal co-former for enhancing the dissolution rate of hydrochlorothiazide. This was extended to prepare oral disintegrating tablets. Co-crystallization was achieved after dissolving hydrochlorothiazide with increasing molar ratios of sucralose in the least amount of acetone. The co-crystallization products were characterized using Fourier

transform infrared spectroscopy, differential thermal analysis and powder X-ray diffraction. These measurements indicated that co-crystallization process started at a drug sucralose molar ratio of 1:1 and completed at 1:2. The developed co-crystals exhibited faster drug dissolution compared with the control, with co-crystal containing the drug with sucralose at 1:2 molar ratio being optimum. The later was used to prepare fast disintegrating tablets. These tablets had acceptable physical characteristics and showed fast disintegration with subsequent rapid dissolution. The study introduced sucralose as co-crystal co-former for enhanced dissolution and masking the taste.

11. AnandAmmanage et al., (2020)[29] The aim of the present study was to enhance the solubility of piroxicam (BCS class II drug) using cocrystallization technique and formulate the buccal films of selected co-crystals for improved therapeutic utilization of drug. Co-crystals of drug with various co-formers (molar ratio 1:1) were prepared by solvent evaporation method and were screened for their aqueous solubility and percent drug content. The formation of co-crystals was confirmed by FTIR, DSC and XRD. Piroxicam co-crystals loaded buccal films were prepared and evaluated for in vitro drug release, ex vivo drug permeation while safety of formulation was determined by histopathological study. The co-crystals prepared with different co-formers have proved their potential to improve the solubility of the drug. Co-crystals of piroxicam-sucralose have shown six-folds more solubility than parent drug. FTIR analysis indicated shifting in characteristics peaks of piroxicam. DSC analysis showed an extra exothermic peak and alteration in characteristic endothermic peak. The powder x-ray diffraction pattern exhibited changes in 2θ values of intense peaks. Thus, formation of co-crystal was confirmed. Physical characters of buccal films were found to be within limits. Formulation F6 showed highest mucoadhesive strength (5617 ± 636 dynes /cm2) while formulation F2 showed highest in vitro drug release after 8 h, i.e., 94.557%. The ex vivo drug permeation of F2 was found to be 84.74%. The histopathological study revealed that there was no damage to buccal mucosal tissue and was found to be intact. The piroxicam-sucralose co-crystals based mucoadhesive films of piroxicam could be a better formulation approach with improved solubility, safety, and therapeutic efficacy as compared to conventional tablets.

12. Mounika Reddy et al., (2019)[30] All active pharmaceutical ingredients are having good therapeutic activity and show poor oral bioavailability , because of poor solubility .The present study is to investigate to improve the solubility of Felodipine using different carriers and different methods of preparation of techniques to identify that

which carrier and suitable method of preparation. All formulation is evaluated for hardness, friability, drug content uniformity, and in vitro dissolution studies. Among all the formulations three formulation shows good drug release and the formulation with direct compression method shows good drug release compared to other formulation among all the formulation Poly vinyl pyrrolidone (PVP) with direct compression is considered as ideal formulation from the study.

13. Khalid Akhtar Ansari., (2014) [31] The objective of this research work was to design, develop and optimize the self microemulsifying drug delivery system (SMEDDS) of Felodipine (FL) filled in hard gelatine capsule coated with polymer in order to achieve rapid drug release after a desired time lag in the management of hypertension. Microemulsion is composed of a FL, Lauroglycol FCC, Transcutol P and Cremophor EL. The optimum surfactant to co-surfactant ratio was found to be 2:1. The resultant microemulsions have a particle size in the range of 65-85 nm and zeta potential value of -13.71 mV. FL release was adequately adjusted by using pH independent polymer i.e. ethyl cellulose along with dibutyl phthalate as plasticizer. Influence of formulation variables like viscosity of polymer, type of plasticizer and percent coating weight gain was investigated to characterize the time lag. The developed formulation of FL SMEDDS capsules coated with ethyl cellulose showed time lag of 5-7 h which is desirable for chronotherapeutic application.

14. Usha Kiranmai Gondrala et al., (2015) [32] Felodipine is an antihypertensive drug with poor oral bioavailability due to the first pass metabolism. For improving the oral bioavailability, felodipine loaded solid lipid nanoparticles (SLNs) were developed using trimyristin, tripalmitin and glyceryl monostearate. Poloxamer 188 was used as surfactant. Lipid excipient compatibilities were confirmed by differential scanning calorimetry. SLN dispersions were prepared by hot homogenization of molten lipids and aqueous phase followed by ultrasonication at a temperature, above the melting point. SLNs were characterized for particle size, zeta potential, drug content, entrapment efficiency and crystallinity of lipid and drug. In vitro release studies were performed in 0.1N HCl and phosphate buffer of pH 6.8 using dialysis method. Pharmacokinetics of felodipine-SLNs after oral administration in male Wistar rats was studied. The bioavailability of felodipine was increased by 1.75 fold when compared to that of a felodipine suspension.

15. Sagar Balaso Sangale., (2019) [33] In the present study microspheres containing felodipine were prepared by Solvent evaporation method and characterized by optical microscopy and scanning electron microscopy. The microspheres were analyzed for drug entrapment, bulk density, angle of repose, particle size and In-vitro release pattern. The effect of process variables on microsphere size was studied and based on these preliminary studies, different batches of microspheres were prepared by altering the drug: polymer ratio and cross-linking with calcium evidenced by photomicrographs and scanning electron microscopy. The percent drug entrapment was in the range of 86-88 % and they could sustain drug release over a period of 8 hrs.

16. Mona Hassan Aboul-Einien (2009) [34] Felodipine is a calcium channel antagonist, which is water insoluble and only 15% bioavailable when administered orally. In this study soft gels, with a solubilized-drug core, were used to improve the solubility and consequently the bioavailability of felodipine. Drug solutions were prepared using both cosolvency and micellar solubilization. Methods: The optimum dielectric constant (DEC) for maximum drug solubility was first determined and five cosolvent systems were constructed to fulfill this DEC. Micellar solubilization was achieved by incorporating surfactants of different types (anionic, cationic and non-ionic) in the solvent systems. Softgels were filled with the drug solutions and subjected to in vitro and in vivo studies. Dissolution tests (under sink or non-sink conditions) revealed a correlation between the composition of the softgel core fill liquid and drug dissolution parameters. The incorporation of water in the fill formula as well as the use of ingredients with low hygroscopicity was found to be essential to minimize water migration to the fill liquid during storage. In vivo studies showed rapid and enhanced absorption of felodipine from solubilized core softgels compared with control drug powder filled in hard gelatin capsules. The total amount of drug absorbed over a 24-h period was markedly enhanced (1.6-fold) for softgels compared with control capsules. It was concluded that the formulation of felodipine in soubilized core softgels enhanced the rate and extent of dissolution of this insoluble drug. In addition, the drug absorption was increased leading to improved bioavailability.

3. DRUG PROFILE

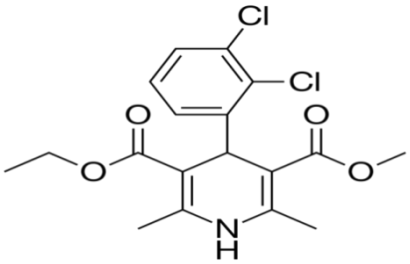
Drug : Felodipine

Synonyms : Plendil, Flodil, Felodipina, Renedil, Feloday, Munobal.,

Chemical IUPAC Name : 5-*O*-ethyl 3-*O*-methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

Molecular Formula : $C_{18}H_{19}CI_2NO_4$

Structure



Molecular Weight : 384.2g/mol

Description : off- white to pale yellow solid

Melting Range : 145°C

Solubility : In-soluble in water but soluble in dichloromethane

Log P value : 3.86

Category : Calcium channel blocker- used to treat hypertension.

Storage : Store, it at room temperature below 30 ℃ away from heat & moisture.

Pharmacokinetic properties:

Absorption

It is completely absorbed from the gastrointestinal tract. It extensively undergoes first-pass metabolism through the portal circulation results in a low systemic bioavailability of 15%

Metabolism

Hepatic metabolism primarily via cytochrome P450 3A4. Six metabolites with no appreciable vasodilatory effects have been identified.

Felodipine

Dehydrofelodipine

Volume of distribution

Felodipine is highly bound (approximately 99%) to plasma proteins and has a volume of distribution is about 10L/kg.

Route of elimination

Although higher concentrations of the metabolites are present in the plasma due to decreased urinary excretion, these are inactive.

Administration

Felodipine is an orally administered drug. It is available in the strengths of 2.5mg, 5mg, and 10mg

Dosing information

Adult: initial 2.5-5mg orally/day; Maintenance: 2.5-10mg orally/day; some recommend up to 20mg/day.

Mechanism of action

- It acts primarily on vascular smooth muscle cells by stabilizing voltage –gate L-type calcium channels in their inactive conformation.
- Normally, L-type of calcium channels admit ca+ & causes depolarization – excitation - contraction coupling through phosphorylation of myosin light chain leads to contraction of vascular smooth muscle result in elevation of BP.
- By inhibiting the influx of ca+ in smooth muscle – cells, felodipine prevents ca+-dependent myocyte contraction & vasoconstriction.

Adverse effects

- headache
- flushing
- dizziness or light-headedness
- weakness
- fast heartbeat
- heartburn
- constipation
- enlargement of gum tissue around teeth

Toxicity

Symptoms of overdose include excessive peripheral vasodilatation with marked hypotension and possibly bradycardia.

Therapeutic uses

- Used to treat high blood pressure.
- Helps to prevent future heart disease, heart attacks, angina and strokes.

4. EXCIPIENTS PROFILE

4.1.HYDROXY PROPYL METHYL CELLULOSE E15

Non-proprietary names:

Hypromellose, Hydroxyl propyl methyl cellulose2208, 2906.

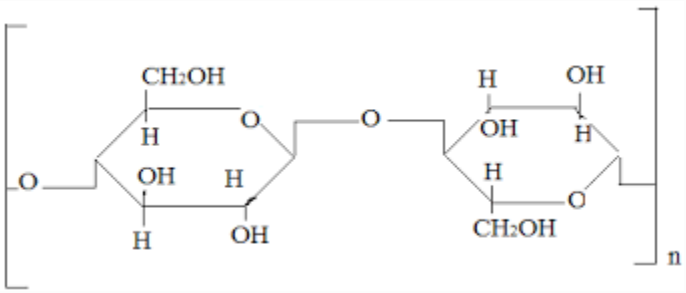
Synonyms:

Methyl hydroxyl propyl cellulose, propylene glycol ether of methyl cellulose, methylcellulose propylene glycol ether.

Description:

An odorless, tasteless, white or creamy white colored fibrous or granular powder.

Structural formula:



Structure of HPMC

Chemical name:

Cellulose, 2-hydroxypropylmethyl ether, cellulose hydroxypropyl methyl ether

Molecular weight:

Approximately 86,000

Functional category:

Coating agent, film former, tablet binder, stabilizing agent, suspending agent, viscosity increasing agent, and emulsion stabilizer.

Density:

- Bulk Density -0.341 g/cm3
- Tapped Density -0.557 g/cm3
- True Density -1.326 g/cm3

Solubility:

Soluble in cold water forming viscous colloidal solution, insoluble in chloroform, alcohol and ether, but soluble in methanol and methylene chloride.

Viscosity:

15 mPas

Stability and storage conditions:

Very stable in dry conditions. Solutions are stable at PH 3.0-11.0. Store in a tight container, in a cool place

Incompatibilities:

Extreme PH conditions, oxidizing materials.

Safety:

Human and animal feeding studies have shown HPMC to be safe.

4.2. SORBITOL

Synonyms

D-Sorbitol, Sorbitol, D-Glucitol, glucitol

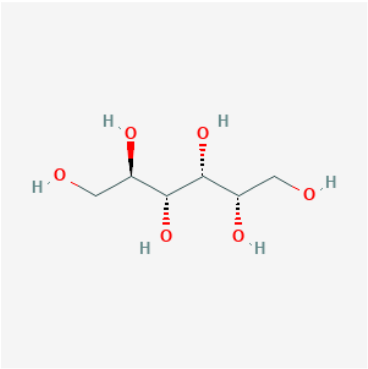
Molecular Formula

C6H14O6

Molecular Weight

182.17 g/mol

Chemical structure



IUPAC Name

(2R,3R,4R,5S)-hexane-1,2,3,4,5,6-hexol

Description

Odourless, white in color and sweet in taste

Boiling point

295 °C at 3.5 mm Hg

Melting point

230 °F

Solubility

Very soluble in water, slightly soluble in ethanol

Density

1.489 g/cu cm 20 °C

Vapor pressure

9.9X10-9 mm Hg at 25 °C (Est)

Functional uses

Bulking Agent; Humectant; Sequestrant; Stabilizer; Sweetener; Texturizer; Thickening agent

4.3. POLY VINYL ALCOHOL

Non proprietary names:

Poly (vinyl acetate), Poly vinyl alcohol.

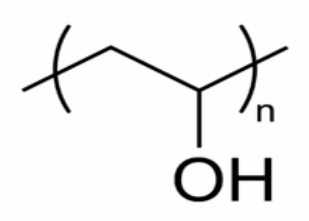
Synonyms:

Poly (Ethanol), Ethanol, Homopolymer, PVA, Polyvinyl, Vinyl,

Description:

Polyvinyl alcohol occurs as an odourless, white to cream-colored granular powder.

Structural formula:



Chemical name:

Poly Vinyl Alcohol

Molecular formula:

CH2CHOH

Molecular weight:

(44.05) n g/mole

Functional category:

Coating agent, lubricant, stabilizing agent, viscosity-increasing agent.

Apparent density:

1.19-1.31 g/cm³

Solubility:

Soluble in cold water, hot water. Insoluble in diethyl ether, acetone, petroleum solvents, aromatic hydrocarbons, esters. Practically insoluble in animal and vegetable oils and chlorinated hydrocarbons.

Melting Point:

Softens at about 200°C (392°F) with decomposition. Decomposition at 2280C.

Safety:

Polyvinyl alcohol is generally considered a nontoxic material. It is non-irritant to the skin and eyes at concentrations up to 10%, concentrations up to 7% are used in cosmetics.

Storage:

Keep container tightly closed. Keep container in a cool, well-ventilated area.

5. AIM AND OBJECTIVE

The aim of the present investigation was to formulate buccal films containing felodipine of dose 5mg with thickness of about 2mm and diameter less than 4mm.

Felodipine is a calcium-channel blocker used in the treatment of hypertension and angina pectoris. Being a dihydropyridine derivative felodipine has the advantage of being more selective as a vasodilator and having fewer cardiac effects than non-dihydropyridine calcium antagonists. This benefit is abolished by the poor bioavailability of the drug, which although being almost completely absorbed from the gastrointestinal tract is only 15% bio-available after oral administration. The poor oral bioavailability of felodipine was attributable to its extensive first-pass metabolism and the very low water solubility of the drug.

The aqueous solubility of a given drug is a very critical factor, affecting drug efficacy and safety as it affects the drug dissolution parameters and the oral bioavailability. The efficacy of a drug can be severely limited by its poor aqueous solubility. The poor aqueous solubility and wet ability of the drug add to the difficulties encountered in drug formulation.

These disadvantages make it an appropriate candidate for the buccal film of felodipine co-crystal. Co-crystals are basically molecular complexes resulting from hydrogen bonding between co-former and drug. The physicochemical properties of the drug molecule are modified once it gets converted into co-crystal but its intrinsic activity is preserved. Thus, co-crystals of many class II drugs have shown improved dissolution rate (comparable to amorphous form) and long-term chemical and physical stability. Buccal films are a novel approach in oral drug delivery systems. Due to the presence of a larger surface area, films provide rapid disintegration and dissolution in the oral cavity. The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing.

6. PLAN OF THE WORK

1. Literature review

2. Preformulation studies

a) Organoleptic properties

b) Solubility test for pure drug

c) Calibration curve of felodipine

d) Incompatibility studies (FTIR)

3. Preparation of felodipine co- crystal

4. Characterization of prepared felodipine co-crystal

a) Morphological study

b) Scanning electron microscope (SEM)

c) Solubility determination

d) IR Spectroscopy

e) Powder X- ray diffraction

5. Optimization of felodipine buccal film.

a) Using 3^2 factorial design experiment.

6. Formulation of felodipine cocrystals embedded buccal film.

7. Evaluation of films

a) Appearance of the film

b) Scanning electron microscopy (SEM)

c) Weight variation

d) Thickness of the film

e) Folding endurance

f) Swelling property

g) Drug content uniformity

h) Surface pH

i) % Moisture loss

j) Mucoadhesive strength

k) Ex-vivo permeation study

l) Drug kinetics study

7. MATERIALS AND METHODS

Table no.1: Materials used in the formulation

SI.NO	Materials	Functional Category	Source
1	Felodipine	Active Pharmaceutical Ingredients (API)	Sai Mirra Inno pharm Pvt Ltd.
2	Sorbitol	Conformer, plasticizer & sweetening agents	Vopec pharmaceuticals Pvt Ltd.
3	HPMC	Buccoadhesive polymer	Vopec pharmaceuticals Pvt Ltd.
4	PVA	Buccoadhesive polymer	Vopec pharmaceuticals Pvt Ltd.
5	Menthol	Flavoring agents	Vopec pharmaceuticals Pvt Ltd.

8. METHODOLOGY

8.1. Pre formulation study

8.1.1 Description of Drug

Physicochemical properties of drugs such as state, color, odour and taste were physically examined and compared with the reported description of drugs.

8.1.2. Solubility of pure drug.

Solubility test were performed as a part of test part of test for purity solubility of the drug was measured by 10mg of drug in a test tube followed by addition of 0.1ml of solvent. Addition of solvent was continued till the sample was dissolved completely. Solubility was recorded in form of the solvent required for solubilization of the drug powder.

8.1.3. Preparation of standard calibration curve

Accurately weighed 10 mg of powdered drug was transferred to 100 ml volumetric flask. To this about 20 ml of phosphate buffer of pH 6.5was added and the contents of the flask were shaken to effect the solution. Finally volume in the flask was made up to the mark by using same solvent. A spectrophotometric method based on the measurement of absorbance at 364 nm in phosphate buffer of pH 6.5 was used in the present study for the estimation of felodipine [39].

8.1.4. Compatibility study:

Fourier transform Infra-red (FT-IR) was the tool for solid state characterization of Pharmaceutical solid. FT-IR Spectroscopy of pure drug, polymers, excipients and physical mixture were carried out on Shimadzu FT-IR 8400S model to investigate any possible interaction between the drug felodipine and the utilized polymers (HPMC, sorbitol). The samples were finely grounded with KBr to prepare the pellets under a hydraulic pressure of 600 psi and a spectrum was scanned in the wavelength range of 4000 and 500 cm-1 using Shimadzu FT-IR spectrophotometer. The compatibility of drug in the formulation was confirmed by comparing FT-IR spectra of pure drug with FTIR of its formulation.

8.2. PREPARATION OF FELODIPINE COCRYSTAL

The co-crystals of felodipine with various co-formers (viz., oxalic acid, L-ascorbic acid and sorbitol) were synthesized by solvent drop grinding method. This method involves incorporation of felodipine and co-former with the addition of ethanol. The ethanol is added in drops-wise with continuous grinding. The ethanol used behaves as a catalyst which enhances crystal formation. Briefly, felodipine and co-formers were taken in 1:1 ratio and mixed completely using mortar & pestle. The obtained product was ground to get a freely flowing powder. The solubility of resulting co-crystals was determined and selected co-former (co-crystal showing highest solubility) was further screened in order to select optimum co-former of felodipine.

Table no 2: Drug with different co-former

COFORMERS	DRUG: COFORMERS
Sorbitol	1:1
L Ascorbic acid	1:1
Oxalic acid	1:1

Table no 3: Drug and coformer (sorbitol) with different ratio

S.NO	Drug and co-former	Ratio
1	Felodipine-sorbitol co-crystals	1:1
2	Felodipine- sorbitol co-crystals	1:1.5
3	Felodipine- sorbitol co-crystals	1: 2

The solubility of formulated co-crystals was determined and the drug with varying co-formers was evaluated for their solubility profiles. From the results the solubility of cocrystals formed with sorbitol showed highest solubility among three coformers, so it was further screened in order to select optimum ratio of drug and coformer. Three ratios of drug: co-former were screened (1:1, 1:1.5, 1:2)

8.3. CHARATERIZATION OF COCRYSTALS

8.3.1. Scanning Electron Microscopy (SEM)

The shape and surface characteristics of felodipine co-crystals was assessed by Scanning Electron Microscopy (SEM)

8.3.2. Saturation solubility determination:

Solubility was determined by dispersing co-crystals corresponding to 100 mg of drug in volumetric flask containing 100 ml of water. The volumetric flask is subjected to agitation using rotary shaker for 24 h. The solution is further diluted suitably with water and analyzed by UV spectroscopically at 364 nm.

8.3.3. IR spectroscopy:

IR spectrum of the drug, co-former, and co-crystals were recorded using FTIR in order to determine predictable interaction between the drug and co-former. The co-crystals were mixed with potassium bromide (K-Br) and then pressed with hydraulic press to form pellets which were further subjected to scanning in between 4000 and 400 cm−1.

8.3.4. Powder X-ray diffraction:

Powder x-ray diffraction is an important tool for prediction of crystalline nature of any substance. This is possible because individual substance shows different diffractogram. Diffractograms of pure drug, co-former and co-crystal were obtained using powder X-ray diffractometer.[4]

8.4. OPTIMIZATION OF FELODIPINE CO-CRYSTALS EMBEDDED BUCCAL FILM

To understand the influence of formulation variables on the quality of formulations with a minimal number of experimental trials and subsequent selection of formulation variables to develop an optimized formulation using established statistical tools for optimization.

Mathematical modelling, evaluation of the ability to fit to the model and response surface modelling were performed with employing Design-Expert® software (Version 11). In a full factorial design, all the factors are studied in all the possible combinations. Hence, 3^2 factorial designs were chosen for the current formulation optimization study.

Design of experiment (DOE)

A two factor and three-level factorial design was used as the experimental design. The independent variables studied were amount of HPMC E15 (X_1) and amount of PVA (X_2). % Drug release at 8hrs, (Y_1)- Mucoadhesive strength (Y_2) were considered as dependent variables which were shown in table- 4

Table 4 : Factors and Factor levels investigated in factorial experimental design

Factors: Formulation Variables	**Levels (mg/film)**		
	-1	**0**	**+1**
HPMC E15	300	600	900
PVA	150	300	450
Response	**Goal**		
Drug release at 8th hour	In Range		
Mucoadhesive strength	Maximize		

Experimental design

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses. Experimental runs were designed by Design Expert 11.0.1 [Stat Ease. Inc.] Software following full factorial method. 3^2

full factorial design was applied for examining two variables (factors) at three levels with a minimum of 9 runs shown in table -4. Totally nine felodipine buccal patch formulations were prepared employing selected combinations of the two factors as per 3^2 Factorial and evaluated to find out the significance of combined effects of the two factor to select the best combination required to achieve the desired felodipine buccal patch.

OPTIMIZATION TABLE FOR BUCCAL FLIM:

Table 5: Optimization table for buccal film

EXPERIMENT	DESIGN FACTORS	
	A:PVA (mg)	B:HPMC (mg)
F1	450	900
F2	300	300
F3	300	600
F4	150	600
F5	450	300
F6	150	300
F7	450	600
F8	150	900
F9	300	900

8.5. PREPARATION OF BUCCAL FILM

Formulation of buccal films:

The films containing felodipine co-crystals were prepared by dissolving 600mg of HPMC- E15, 150mg of PVA and 0.8ml of PEG 400 in 20ml of distilled water with continuous stirring on magnetic stirrer at 800 rpm for 1 hour and then 1ml of menthol is added to the above solution under constant stirring at 1000 rpm at room temperature until a clear viscous polymeric solution was obtained. Then the weighed quantity of felodipine co-crystals were added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform distribution of the drug and then the entrapped air is removed before casting. The quantity of material to be taken is decided on the basis of surface area of the petridish. The resulting solution was then casted on a fabricated glass mould and allowed to dry completely at room temperature to form film. The dried films were carefully separated from the glass mould and cut to produce the desired size required and were stored in double wrapped aluminium foils.

Calculation of drug loading in the film:

The petridish diameter = 9cm

Thus, radius (r) = 4.5cm

surface area of petridish= πr^2

= 3.14 X $(4.5)^2$

= 63.59cm^2

Now, Dose was 5mg in 2 cm X 2 cm= 4cm^2

Thus, 4cm^2 contains 5mg drug.

Since **5 mg of felodipine is equivalent to 12.5 mg of felodipine co-crystal**

So, 63.59cm^2 contains = 187.5 mg of drug

8.6. EVALUATION OF BUCCAL FILM

8.6.1. Appearance of the film

The overall appearance of the patch was checked visually

8.6.2. Scanning Electron Microscopy (SEM)

The shape and surface characteristics of felodipine patch was assessed by scanning electron microscopy (SEM) and size distribution of patch was determined by optical microscopy.

8.6.3. Weight variation

Three films of 2 * 2 cm size were cut randomly, Individually the patch were weighed on electronic balance and the mean weight was calculated [40].

8.6.4. Thickness of patch

The thickness of patch was directly related to drug content uniformity So it was essential to find uniformity in the thickness of the film. It can be measured by calibrated digital vernier Callipers. The thickness was measured at different spots of the patch and average was taken [41].

8.6.5. Folding Endurance

The folding endurance of the patch was used to estimate the mechanical strength of the patch to with stand the folding or the ability to withstand the brittleness. It was measured by repeatedly folding a patch at the same line before it breaks. The folding endurance was the number of times the film was folded without breaking. Higher the folding endurance value greater was the strength of the patch [42].

8.6.6. Swelling property

Simulated solution of saliva was prepared to check the swelling property of the patch. The initial weight of the patch was determined and placed in the pre-weighed stainless steel mesh. The system was dipped in the simulated saliva solution. The increase in the weight of the patch was noted by weighing the system at regular intervals. The degree of swelling was determined by the formula:

$$\text{Degree of swelling} = \frac{[\text{Final weight } (W_t) - \text{Initial weight } (W_0)]}{[\text{Initial weight } (W_0)]}$$

8.6.7. Drug content uniformity:

Drug content uniformity was calculated by taking three film units of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of PH 6.5 phosphate buffer was added and continuously stirred in a magnetic stirrer for 30 minutes. The solutions were filtered, diluted suitably and analyzed at 364nm in a UV spectrophotometer. The average of drug contents of three films was taken as final reading.

8.6.8. Surface pH

Patch was slightly wet with help of water. The pH was measured by bringing the electrode in contact with the surface of the patch. The study was performed on three patches of each formulation and average was taken [45].

8.6.9. Moisture loss

Percent moisture loss is a parameter that determines the hygroscopicity of a film. Usually, this parameter is determined by first finding the initial weight of the film, afterward, putting this film in a desiccator for three days. Desiccator contains calcium carbonate. After three days, strips are taken out and weighed again. Moisture loss is determined by applying the following formula.[46]

$$\% \text{ Moisture loss} = \frac{\text{(Initial weight – Final weight)}}{\text{(Initial weight)}} \times 100$$

8.6.10. In vitro Mucoadhesive strength

The mucoadhesive strength of the mucoadhesive buccal patches was determined at room temperature using the two-arm balance with minor modifications. Fresh sheep buccal mucosa was obtained from a local slaughter house and used for the study within 2 h of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues, and thickness of 2 mm was obtained. The membrane was then washed with distilled water and then with BS pH 6.5 at 37 ◦C. The buccal mucosa was cut into pieces and again washed with PBS pH 6.5. A piece of buccal mucosa was then fixed to the bottom of a smaller beaker with the help of cyano acrylate glue. Two pans of the balance were balanced with a 5 g weight on the right-hand side pan. The buccal patch was then stuck to the lower side of left-hand side pan with help of two way adhesive tape and then was brought in contact with mucosa placed on small beaker by removing

5 g weight from the right pan of the balance. The balance was kept in this position for 5 min and then water was added slowly at 100 drops/min to the right and side pan until the patch detached from the mucosal surface. The excess weight on the pan, i.e. total weight minus 5 g was force required to separate the patch from mucosa. The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength. The experiments were performed in triplicate, and average values were reported [36]

8.6.11. Ex-vivo Permeation study

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 2h of animal sacrifice. The majority of underlying connective tissues 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 500µm. It was then used for permeation study

Permeation study:

The Ex-vivo buccal permeation study was carried out for best optimized formulation. The permeation study of felodipine cocrystal through the excised layer of goat buccal mucosa was performed using Franz diffusion cell ar 37±0.5 oC. Fresh goat buccal mucosa was mounted between the donor and receptor compartments. The buccal patch was placed with the core facing the mucosa, and the compartments were clamped together. The donor compartment was filled with 5ml of phosphate buffer pH 6.8. The receptor compartment was filled with phosphate buffer pH 6.5± 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 at predetermined time intervals and analyzed for drug content by UV spectrophotometer at 364nm [44].

8.6.12. Permeation kinetics [43]

The matrix systems were reported to follow the zero-order permeation rate and the diffusion mechanism for the permeation of the drug. To analyse the mechanism for the permeation and permeation rate kinetics of the dosage form, the data obtained was fitted into, Zero - order, First order, Higuchi matrix and Peppa's model. In this by comparing the r values obtained, the best fit model was selected.

ZERO ORDER KINETICS:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation

$$Q_t = Q_o + K_o t$$

Where Q_t was the amount of drug dissolved in time t, Q_o was the initial amount of drug in the solution and K_o was the zero-order release constant.

First order kinetics:

To study the first order release kinetics the release rate data were fitted to the following equation.

$$\text{Log } Q_t = \log Q_o + k1_t/2.303.$$

Where Qt was the amount of the drug released in time t, Qo was the initial amount of the drug in the solution and K1 was the first order release constant.

Higuchi model:

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation was

$$Q_t = KH\text{-}t^{1/2}$$

Where Qt was the amount of drug released in time t, KH was the Higuchi dissolution constant.

Korsmeyer and Peppa's model:

To study this model the release rate data are fitted to the following equation.

$$M_t/M_\alpha = K.tn$$

Where M_t/M_α was the fraction of drug release, K was the release constant, t was the release time and n were the Diffusional exponent for the drug release that was dependent on the shape of the matrix dosage form

Hixon and Crosswell erosion equation:

$$QO^{1/3} - Qt^{1/3} = K_{HCt}$$

Where,

Qt = Amount of drug released at time t

QO = Initial amount of drug

KHC = Rate constant for Hixson Crowell equation

9. RESULT AND DISCUSSION

9.1. Pre-formulation study:

9.1.1. Description of Drug

The appearance of the felodipine was visually observed. It was found that it was a pale white powder and it complies with the IP.

9.1.2. Solubility

Solubility tests were performed:

S.NO	SOLVENT	SOLUBILITY
1	Water	Poorly Soluble
2	pH 6.5 Buffer	Sparingly Soluble
3	Ethanol	Freely Soluble
4	DMSO & DMF	Highly Soluble

Table 6: Solubility test of pure drug

9.1.3. Calibration Curve of felodipine:

Calibration curve values of felodipine in pH 6.5 phosphate buffer.

Table- 7: calibration curve of felodipine.

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE (nm)
1	0	0
2	10	0.045
3	20	0.082
4	30	0.121
5	40	0.159
6	50	0.198

Calibration curve:

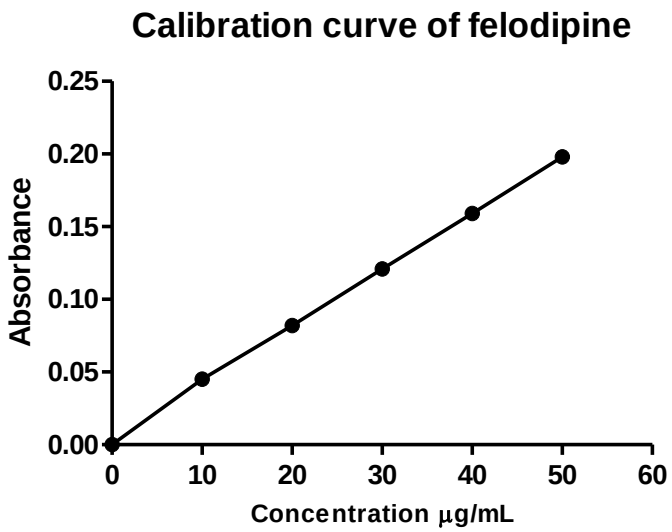


Fig 8: Calibration curve of felodipine in pH 6.5 phosphate buffer at 364nm

9.1.4. Drug polymer compatibility study

Fourier transform Infra-red (FT-IR) was the tool for solid state characterization of Pharmaceutical solid. FT-IR Spectroscopy of pure drug, polymers, excipients and physical mixture were carried out on Shimadzu FT-IR 8400S model to investigate any possible interaction between the drug felodipine and the utilized polymers (HPMC, sorbitol).The samples were finely grounded with KBr to prepare the pellets under a hydraulic pressure of 600 psi and a spectrum was scanned in the wavelength range of 4000 and 500 cm-1 using Shimadzu FT-IR spectrophotometer. The compatibility of drug in the formulation was confirmed by comparing FT-IR spectra of pure drug with FTIR of its formulation.

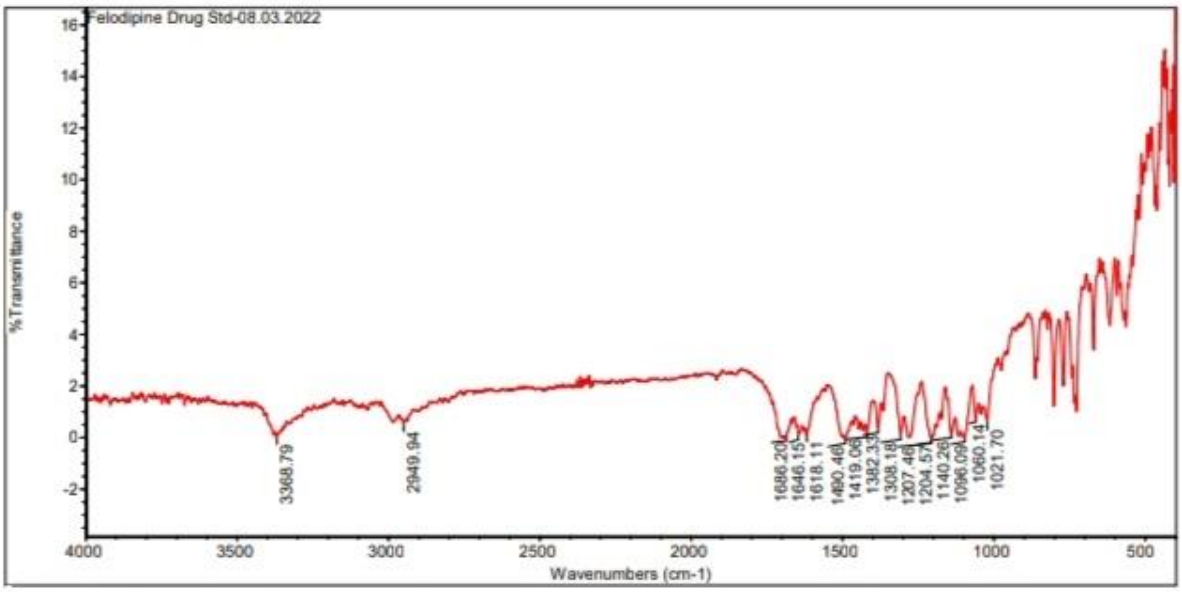


Fig 9: FT-IR SPECTRUM OF DRUG (FELODIPINE)

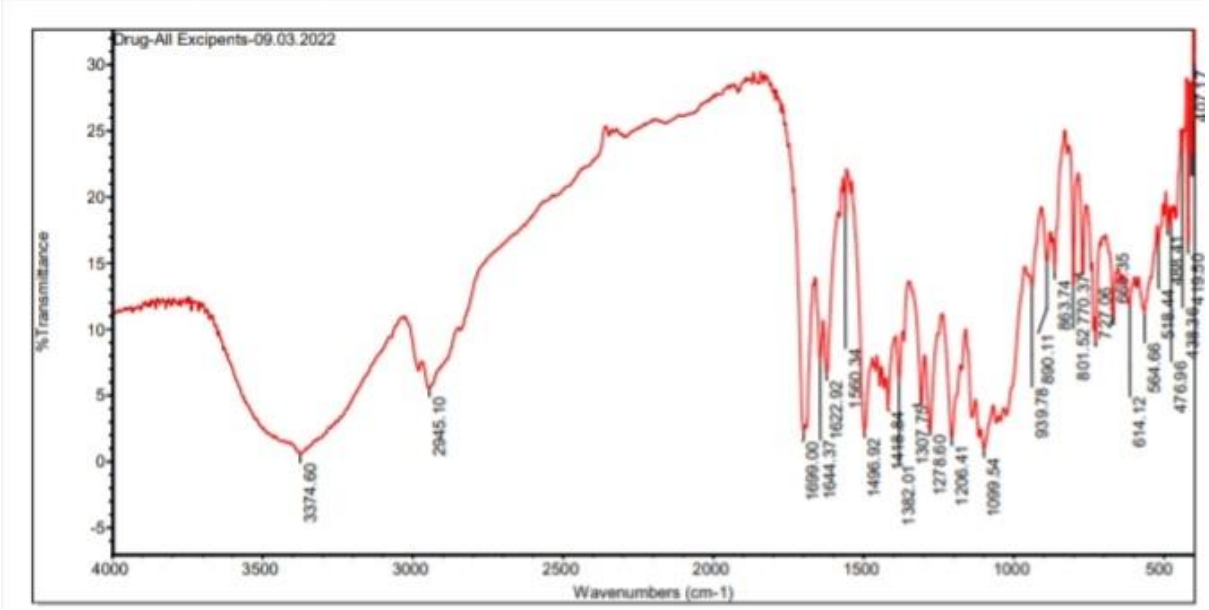


Fig 10: FT-IR SPECTRUM OF (DRUG + ALL EXCIPIENTS)

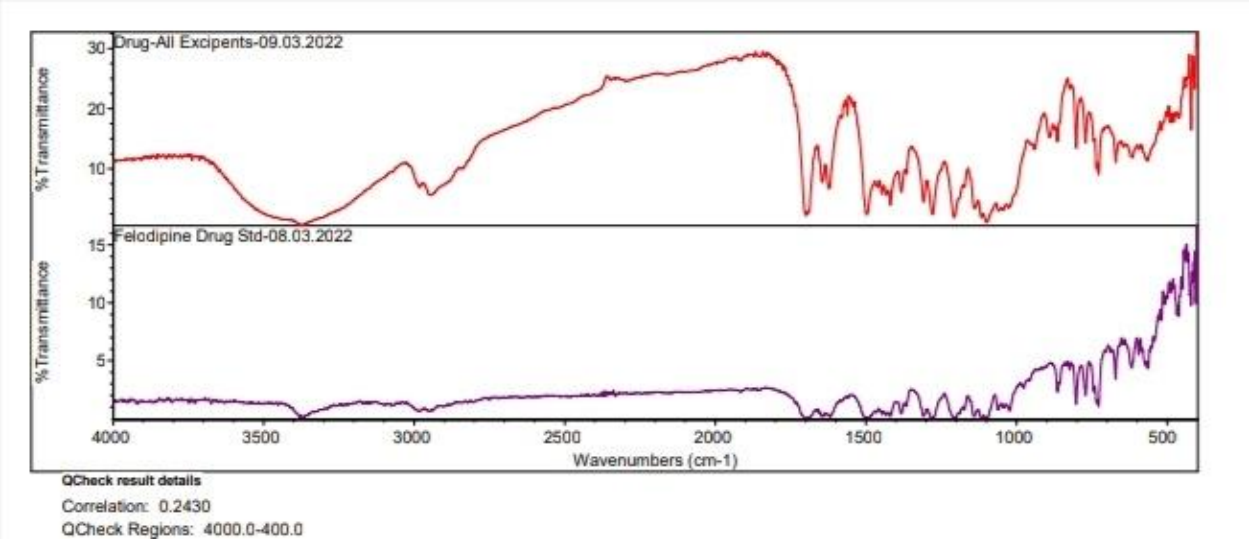


Fig 11: Q- CHECK FOR (DRUG + ALL EXCIPIENTS) & DRUG

9.1.5. CO-CRYSTALS AND POLYMER COMPATIBILITY STUDY:

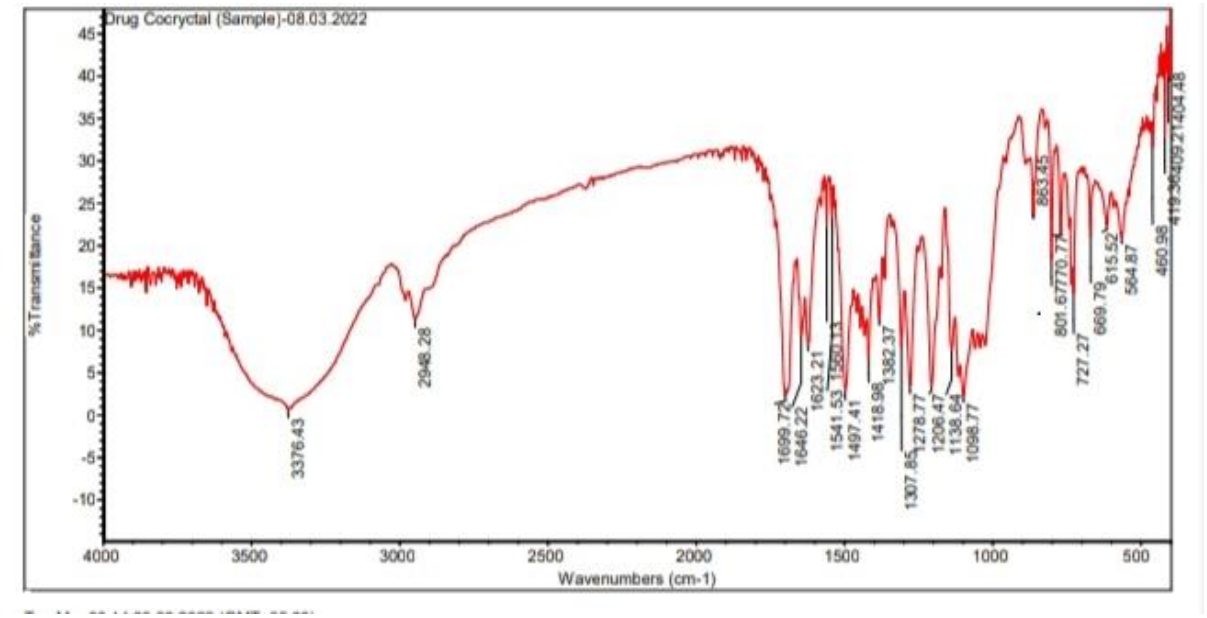


Fig 12: FTIR- SPECTRA OF DRUG COCRYSTAL

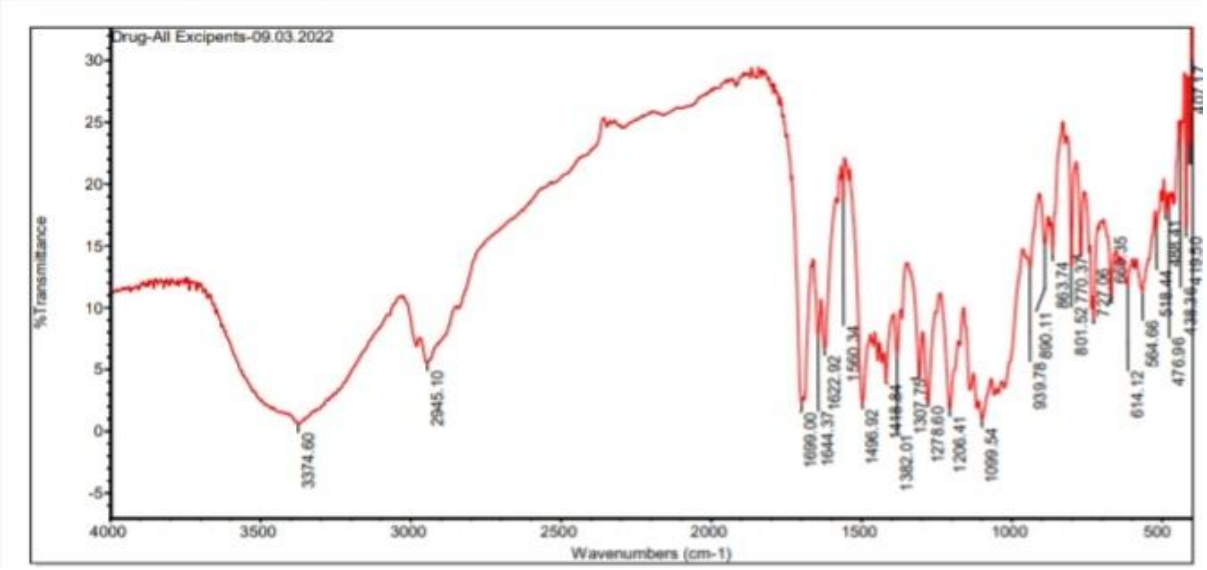


Fig 13: FTIR- SPECTRA OF DRUG COCRYSTAL WITH ALL EXCIPIENTS

INTERPRETATION OF IR- SPECTRA:

Table- 8: Interpretation of IR- spectra

S.NO	PEAKS VALUE	CHARACTERISTIC FUNCTIONAL GROUPS
1	3368.79	O-H Stretching
2	2949.94	C-H Stretching
3	1618.11- 1686.20	C=O Stretching
4	1450- 1600	C= C Stretching
5	1382.33	CH3 C-H bending

Shows the peak values and its corresponding functional group

FT-IR spectroscopy was used to detect the existence of interaction between felodipine and hydrophilic carriers used during preparation of buccal film. The spectrum of felodipine shows characteristic peaks of N-H stretching bond at 3368.79 cm^{-1}. The stretching band peak of 2949.94cm^{-1} was due to stretching between C-H bond. The peak values of 1618.11- 1686.20cm^{-1} was due to stretching between C=O bond of carbonyl group. It was the strong bond lies in this group. The spectrum of peak values 1450- 1600cm^{-1} was due to the C=C stretching and 1382.33 was due to CH_3 C-H bending. All the peaks corresponding to the respective bonds are shown in the table 8.

9.2. CHARACTERIZATION OF COCRYSTALS

9.2.1. Microscopic characterization of co-crystals:

Microscopic characteristics of prepared co-crystals were observed by light microscope.

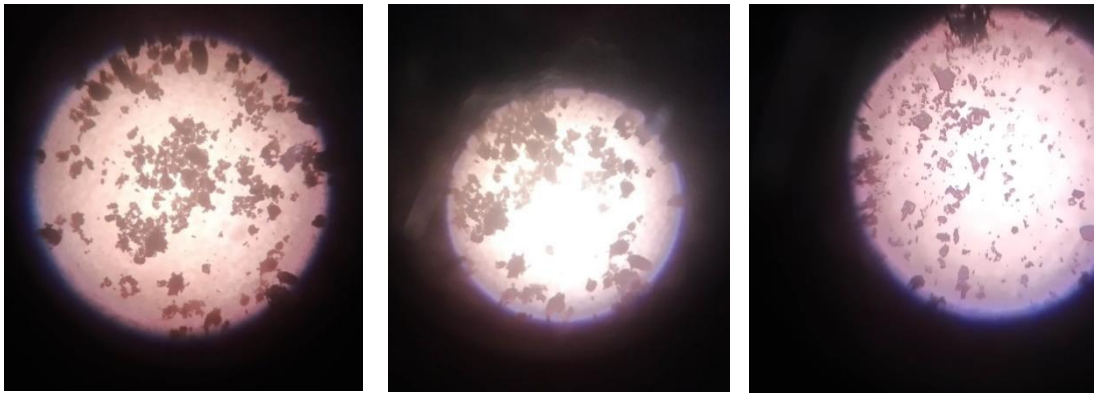


Fig 14: MICROSCOPIC IMAGES OF CO-CRYSTALS

9.2.2. Morphological characteristics of co-crystals

The shape and surface characteristics of felodipine cocrystal was assessed by Scanning Electron Microscopy (SEM)

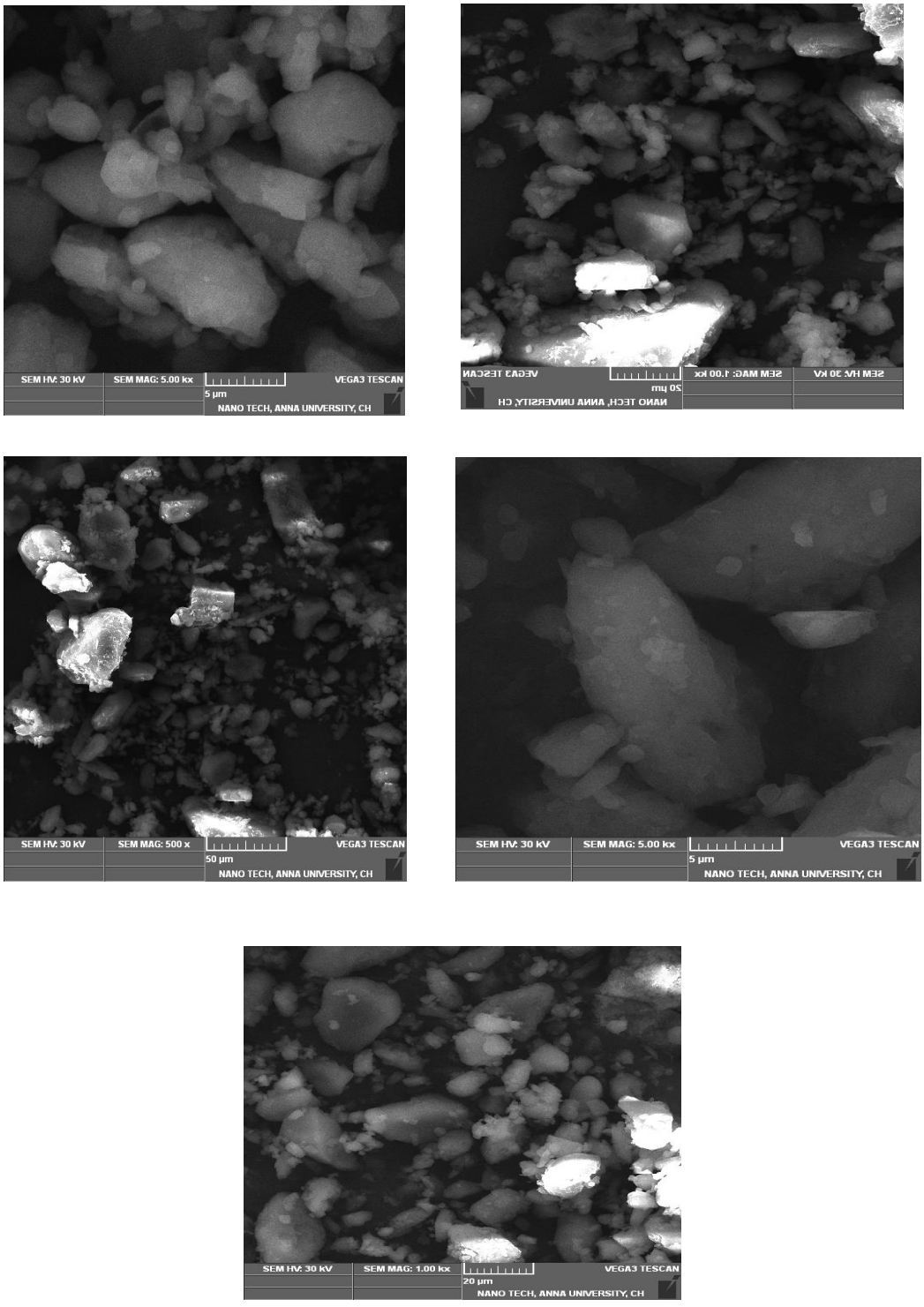


Fig 15: SEM IMAGE OF FELODIPINE COCRYSTALS

9.2.3. Solubility study of co-crystals and pure drug:

S.NO	Drug/ Coformer	Solubility (mg/100 ml)
1	Felodipine	1.97
2	Felodipine-sorbitol co-crystals	3.2
3	Felodipine- L-ascorbic acid co-crystals	2.5
4	Felodipine- oxalic acid co-crystals	2.2

Table 9: Solubility profile of co-crystals and pure drug

The co-crystals prepared with different co-formers have proved their potential to improve the solubility of drug. Co-crystals of felodipine: sorbitol have shown – 2 folds more solubility than parent drug.

9.2.4. IR- Spectroscopy:

The FTIR analysis of the pure drug and felodipine co-crystal was done. IR spectra are as shown in Fig. 16

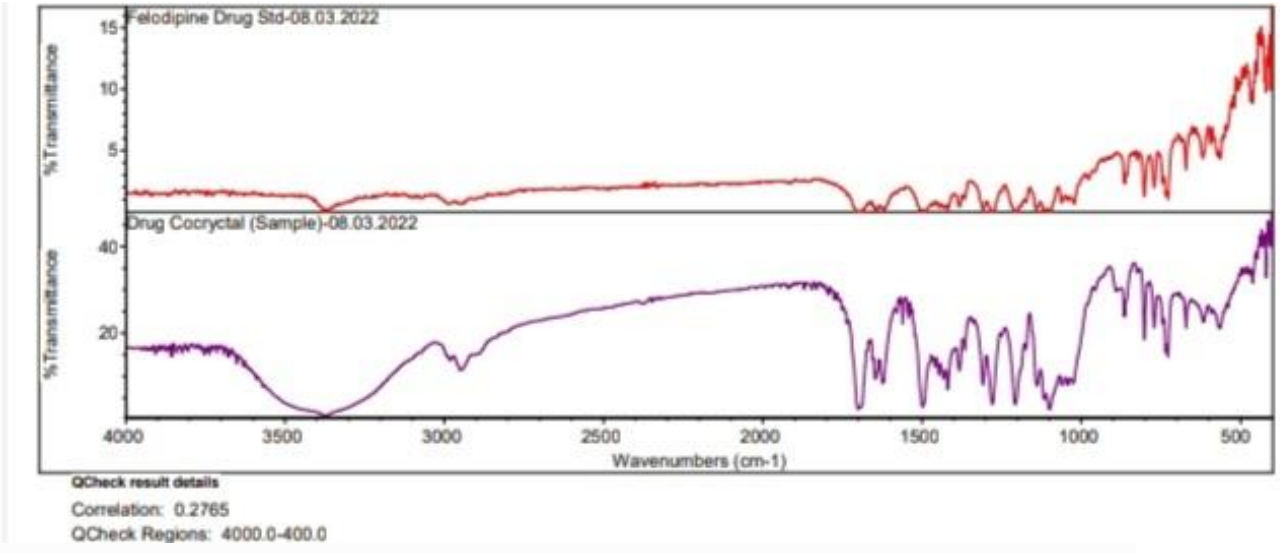


Fig 16: COMPARISON BETWEEN PURE DRUG AND DRUG COCRYSTAL

FT-IR spectroscopy was used to detect the existence of interaction between felodipine and sorbitol coformer used during the preparation of cocrystal. When hydrogen bonding occurs between felodipine and the coformer, a shift in certain peaks, which OH affected by an interaction, can be observed in felodipine spectra. In felodipine, the groups in which hydrogen bonding can occur are the amine group in the ring and the two carbonyl group. When this hydrogen bonding occurs, bond energy at the N-H or C=O bond decrease and peak shift to lower frequencies is observed. This peak shift was most noticeable at the N-H stretch peak at 3376.43cm^{-1}, C-H stretch at 2948.28cm^{-1} and the C=O stretch peak at 1699.72cm^{-1}. These peaks shifting may be the probable group which involved in the bond formation with sorbitol to synthesis co-crystal.

9.2.5. Powder X-ray diffraction (PXRD) study:

PXRD diffractograms for felodipine, sorbitol, and their co-crystal are shown below fig. 17, 18 & 19.

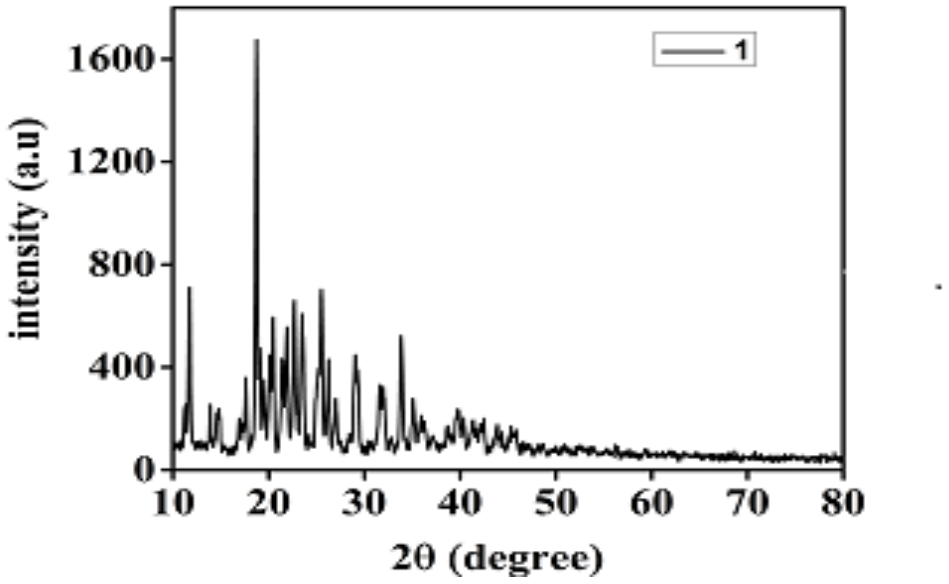


Fig 17: PXRD PATTERNS OF SORBITOL (COFORMER)

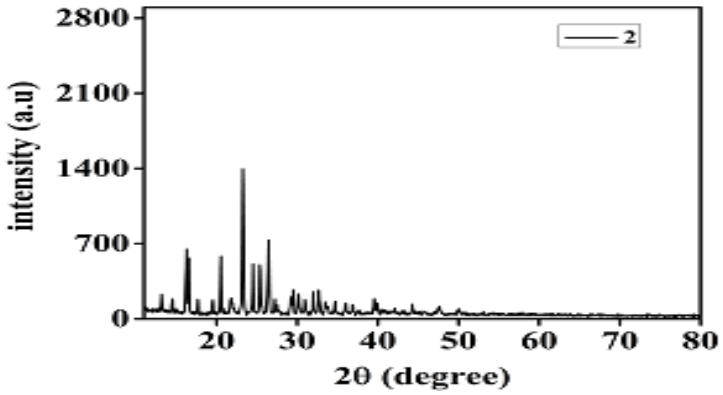


Fig 18: PXRD PATTERNS OF DRUG (FELODIPINE)

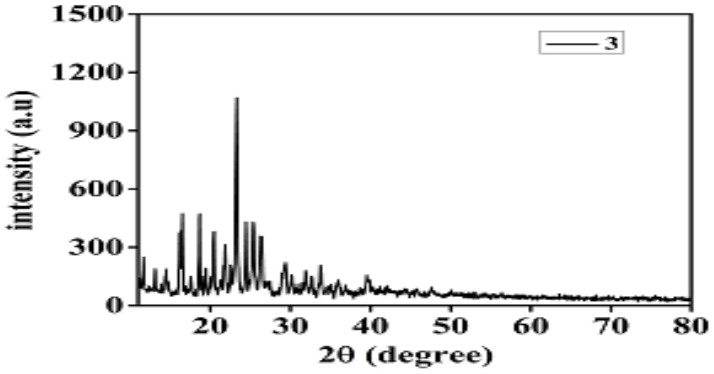


Fig 19: PXRD PATTERNS OF DRUG COCRYSTALS

Though single crystal X-ray diffraction (SXRD) is considered as best technique to analyze the crystal at its atomic level, it is highly difficult to get single crystal suitable for SXRD analysis. Thus PXRD is widely used to confirm the co-crystal formation. Reduction in the peak intensity of the co-crystal was observed as compared to the pure drug and sorbitol. Further, some intense peaks with different angles other than drug specific angles were observed. The PXRD diffractograms for felodipine, sorbitol, and their cocrystal are shown in above Fig.17, 18 & 19. The characteristic peaks of felodipine, sorbitol, & cocrystals were observed at their corresponding 2θ values. The diffractogram of felodipine cocrystal was found to be different from its parent material and more number of peaks was observed. The changes in diffraction pattern and increment in number of peaks were reported as evidence of formation of co-crystals.

9.3. OPTIMIZATION OF FELODIPINE CO-CRYSTALS EMBEDDED BUCCAL FILMS:

The formulations were prepared as 9 sets using two variables following 3^2 factorial designs. Buccal films containing felodipine cocrystals were prepared by solvent evaporation technique. The optimized formulations selected by the design were prepared and the parameters were compared to the expected values. For systematic investigation of the factors, a full factorial design was employed.

On the basis of defined constraints for each independent variable, the Design Expert® 11 automatically generated the optimized formulation. The experiments were performed and the responses were obtained. The data were shown in table -10

Table 10- : Results of independent variable and corresponding dependent variables

	Factor 1	Factor 2	Response 1	Response 2
Trials	PVA	HPMC	% Drug permeation at 8hrs	Mucoadhesive strength
	Mg	Mg	%	G
F1	450	900	68.63	8.4
F2	300	300	92.79	4.8
F3	300	600	87.93	5.6
F4	150	600	88.64	4.3
F5	450	300	84.21	6.5
F6	150	300	96.82	4.5
F7	450	600	82.75	6.8
F8	150	900	73.52	5.3
F9	300	900	65.52	6.2

Drug permeation at 8 hours

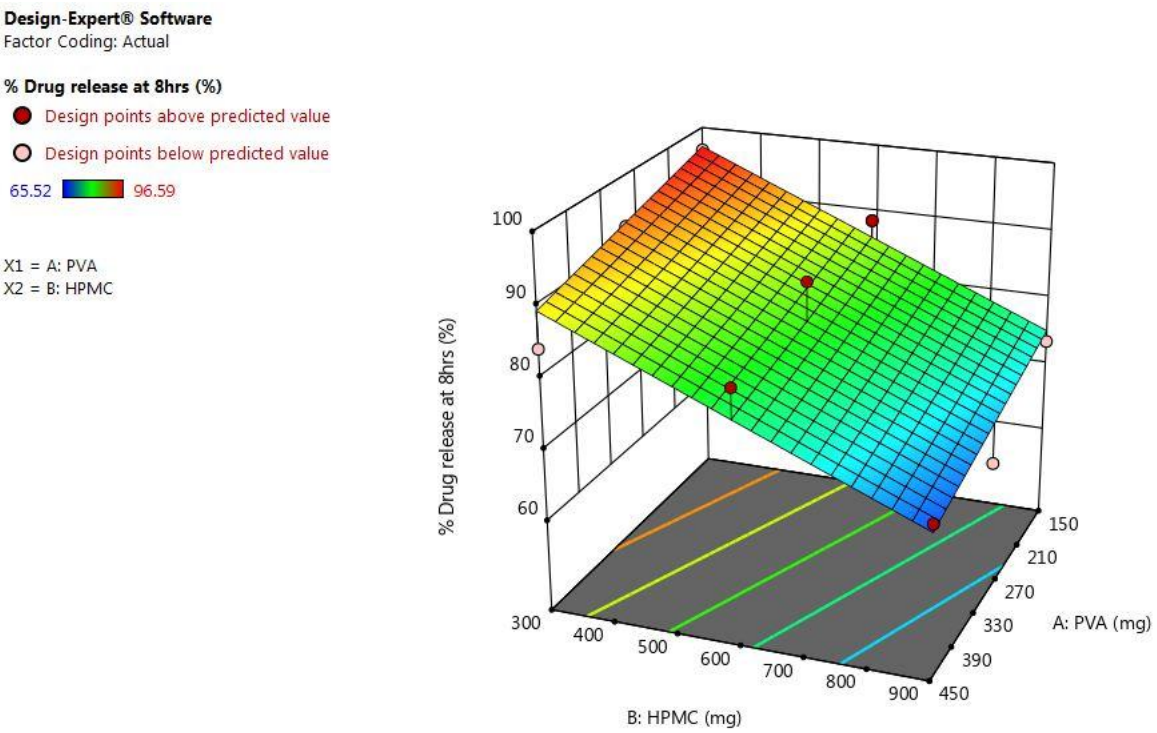


Fig -20: Effect of HPMC E15 and PVA on drug permeation

This 3D surface graph (Fig -20) illustrates that increasing the both polymer concentrations results in decreased drug release. Increasing the HPMC E15 concentration has more release retarding tendency. Thus the formulations containing higher amounts of HPMC E15 has very less drug release at 8^{th} hour.

Mucoadhesive strength

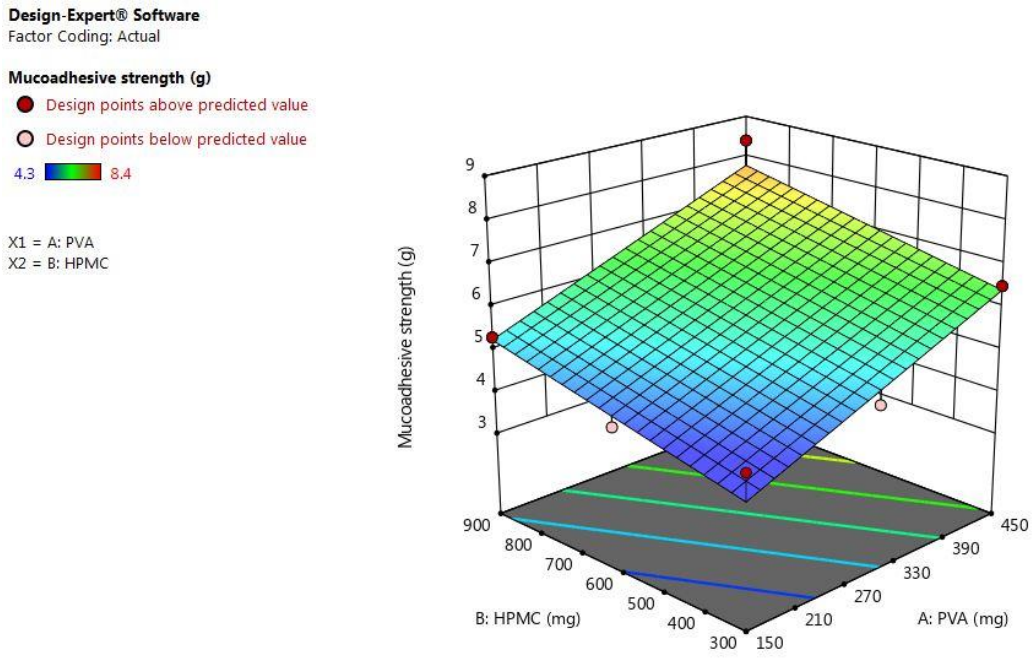


Fig -21: Effect of HPMC E15 and PVA on Mucoadhesive strength

This 3D surface graph (Fig- 21) illustrates that on increasing the concentration of both the polymers results in increasing the mucoadhesive strength. Increasing PVA concentration increases mucoadhesive strength of the films considerably.

9.3.1. ANOVA:

Table –11 represents the statistical parameters such as adjusted R^2, predicted R^2, model P values, adequate precision and % CV. Based on table - 9 the responses time taken for drug release at 8 h and mucoadhesive strength was well fitted to the linear and quadratic model with P value of <0.0500. Table -11 shows adjusted R^2 for Y_1, and Y_2 which is in reasonable agreement with the predicted R^2. Adequate precision measures the signal-to-noise ratio.

A ratio greater than 4 is desirable ratio indicating an adequate signal. This model can be used to navigate the design space. The results show that 90% of response variations in drug release at 8 h and mucoadhesive strength could be described by Factorial design as a function of main composition. So it can be concluded that linear model was suitable model for analysis. The results were shown in table -11.

Table – 11: Response model and statistical parameters obtained from ANOVA

Responses	Adjusted R^2	Predicted R^2	Model P value	Adequate precision	%CV
Drug release at 8 h	0.8259	0.7277	0.0022	11.3974	5.48
Mucoadhesive strength	0.8820	0.7549	0.0007	15.0594	7.70

9.3.2. Point prediction:

The felodipine cocrystals embedded buccal films were formulated and responses were measured. The software generated the optimized formulation and predicted the response based on the constraint. Then batch was formulated based on the suggested formulation and responses were observed. The observed values of responses were compared to the predicted values of the response and % error was calculated to validate the method. The observed value of Y_1 and Y_2 were in a close agreement to the predicted one. By this the validity of optimization procedure was proven. The point prediction has been shown in table -12.

Table –12: Point Prediction of felodipine co-crystals embedded buccal films

Point Prediction	Drug permeation at 8h (%)	Mucoadhesive strength (min)
Predicted	96. 82	8.4
Observed	94.59	6.82
%error	2.30	18.8

% error = (predicted value- observed value)/predicted value x 100

9.4. EVALUATION OF FELODIPINE CO-CRYSTALS EMBEDDED BUCCAL FILMS

9.4.1. Appearance of the film

The overall appearance was found to be clear and transparency was good which Shows that the drug has distributed uniformly.

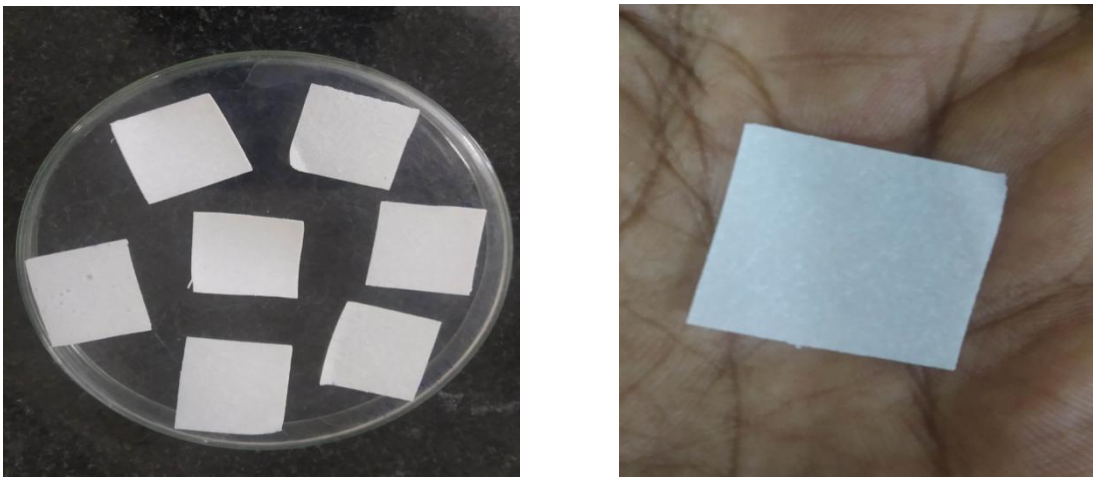


Fig 22: IMAGES OF BUCCAL FILM

9.4.2. Patch morphology

The shape and surface characteristics of felodipine co-crystal embedded buccal film was assessed by Scanning Electron Microscopy (SEM).

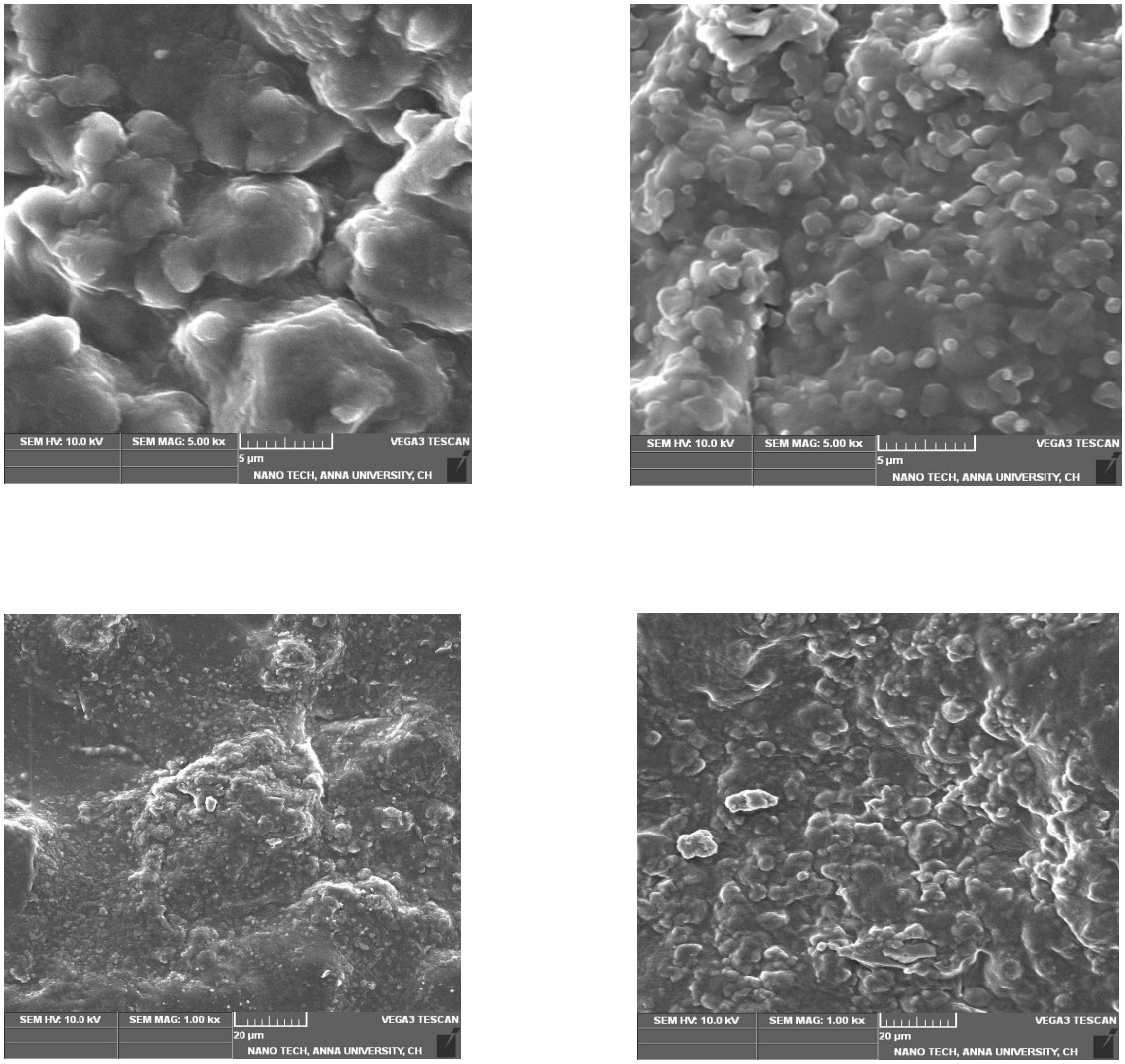


Fig 23: SEM IMAGES OF FELODIPINE COCRYSTALS EMBEDDED BUCCAL FIM

9.4.3. Weight variation:

Three films of 2 * 2 cm size were cut randomly, individually the patch were weighed on electronic balance. The weight ranges from 35.49 to 96.42.

Table 13: Weight variation of the film

FORMULATION	WEIGHT VARIATION
F1	35.49
F2	72.32
F3	53.6
F4	88.24
F5	61.07
F6	43.5
F7	74.81
F8	53.52
F9	96.42

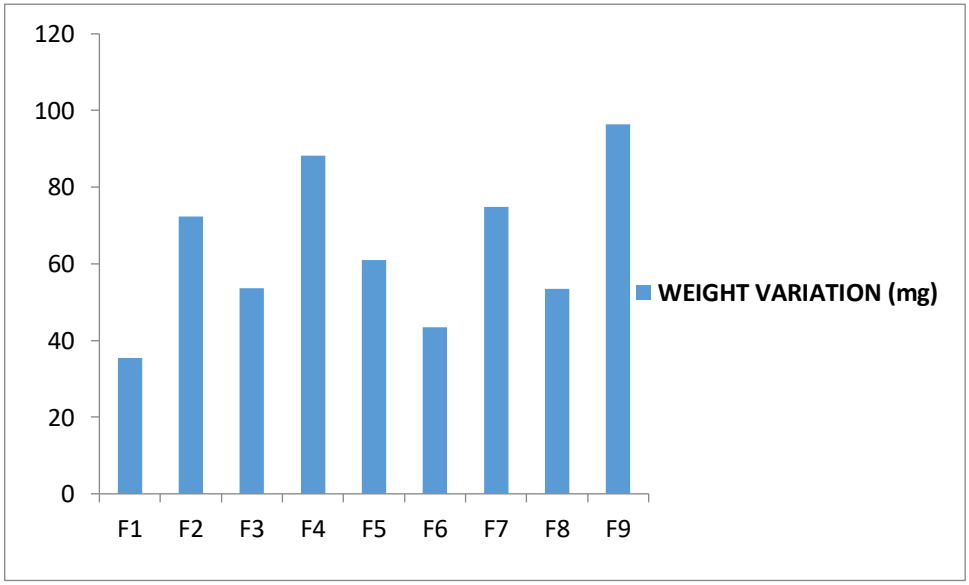


Fig 24: WEIGHT VARIATION OF THE FILM

9.4.4. Thickness of the patch

The thickness of patch was directly related to drug content uniformity So it was essential to find uniformity in the thickness of the film. It can be measured by calibrated digital vernier Calipers. The thickness was measured at different spots of the patch and average was taken. The film thickness ranged from 0.32 to 0.36mm.

Table 14: Thickness of the film

FORMULATION	FILM THICKNESS (mm)
F1	0.33
F2	0.35
F3	0.32
F4	0.34
F5	0.36
F6	0.35
F7	0.35
F8	0.34
F9	0.36

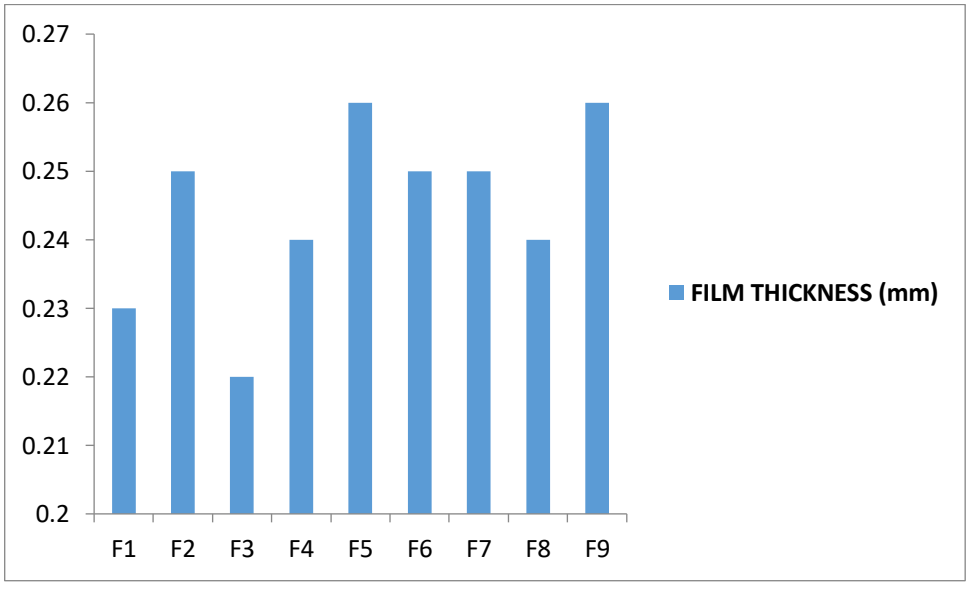


Fig 25: THICKNESS OF THE FILM

9.4.5. Folding endurance

The folding endurance of the patch was used to estimate the mechanical strength of the patch to with stand the folding or the ability to withstand the brittleness. It was measured by repeatedly folding a patch at the same line before it breaks. The folding endurance was the number of times the film was folded without breaking. Higher the folding endurance value greater was the strength of the patch. The highest folding endurance of 318 was achieved by formulation F5

Table 15: Folding endurance of the film

FORMULATION	FOLDING ENDURANCE
F1	314
F2	312
F3	305
F4	310
F5	318
F6	309
F7	305
F8	313
F9	304

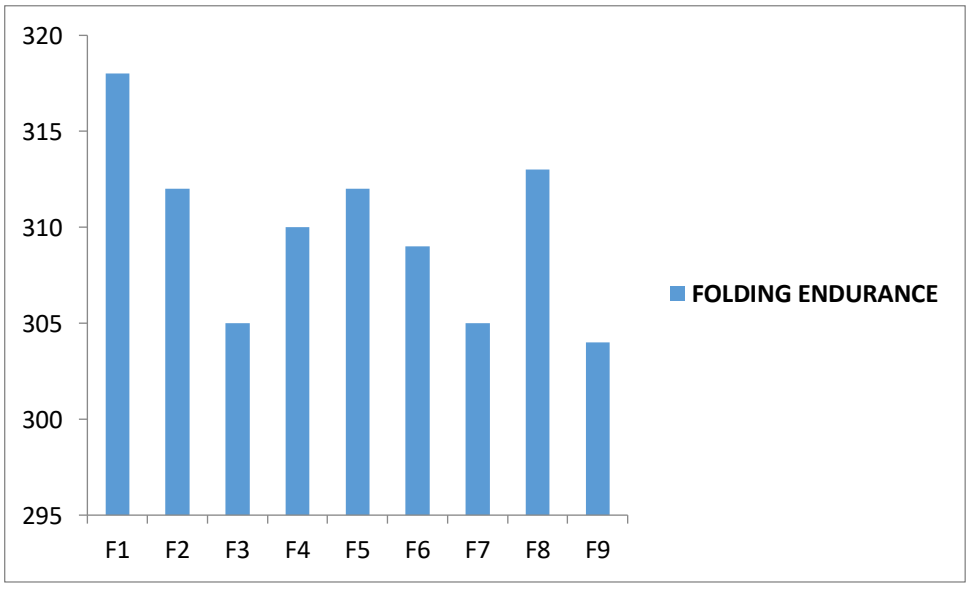


Fig 26: FOLDING ENDURANCE OF THE FILM

9.4.6. Swelling property

Simulated solution of saliva was prepared to check the swelling property of the patch. The initial weight of the patch was determined and placed in the pre-weighed stainless steel mesh. The system was dipped in the simulated saliva solution. The increase in the weight of the patch was noted by weighing the system at regular intervals. The degree of swelling was determined by the formula. The average swelling was found to be 5.62

$$\text{Degree of swelling} = \frac{[\text{final weight(Wt)} - \text{Initial weight(Wo)}]}{[\text{Initial weight(Wo)}]}$$

Table-16: Swelling property of the film

FORMULATION	SWELLING PROPERTY
F1	5.48
F2	4.89
F3	4.50
F4	5.23
F5	4.98
F6	5.62
F7	5.20
F8	5.25
F9	5.28

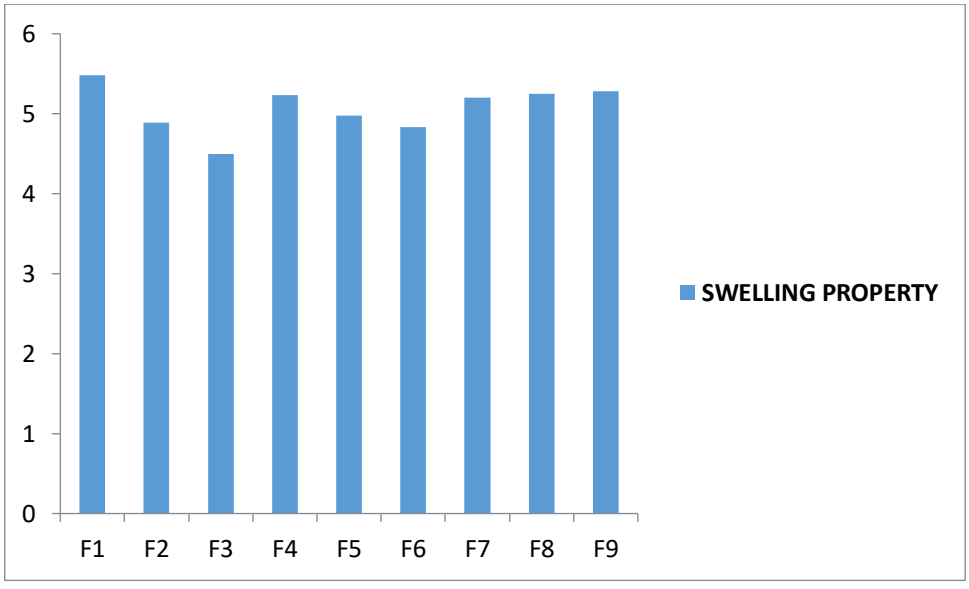


Fig 27: SWELLING PROPERTY OF FILM

9.4.7. Surface pH

Patch was slightly wet with help of water. The pH was measured by bringing the electrode in contact with the surface of the patch. The study was performed on three patch of each formulation and average was taken. The surface pH was ranging from 6.3 -6.6.

Table-17: Surface pH of the film

FORMULATION	SURFACE pH
F1	6.3
F2	6.5
F3	6.4
F4	6.4
F5	6.6
F6	6.4
F7	6.3
F8	6.5
F9	6.4

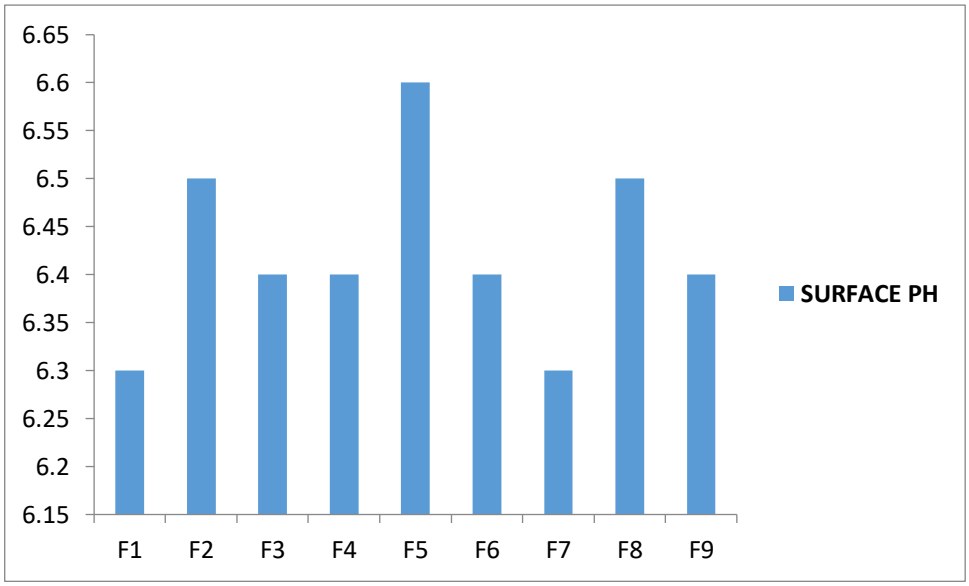


Fig 28: SURFACE pH OF THE FILM

9.4.8. Percent moisture loss

It was done to check the integrity of patch at dry condition and hygroscopicity of patch. Three patch of 2 x 2 cm^2 size were cut out and weighed accurately. Then the patch was rested in a desiccator Containing fused anhydrous calcium carbonate. After 3 days the patches are removed, weighed and percentage weight loss are calculated.

Table 18: % Moisture loss of the film

FORMULATION	% MOISTURE LOSS
F1	1.89
F2	2.14
F3	2.25
F4	1.36
F5	1.56
F6	1.19
F7	2.32
F8	2.21
F9	1.92

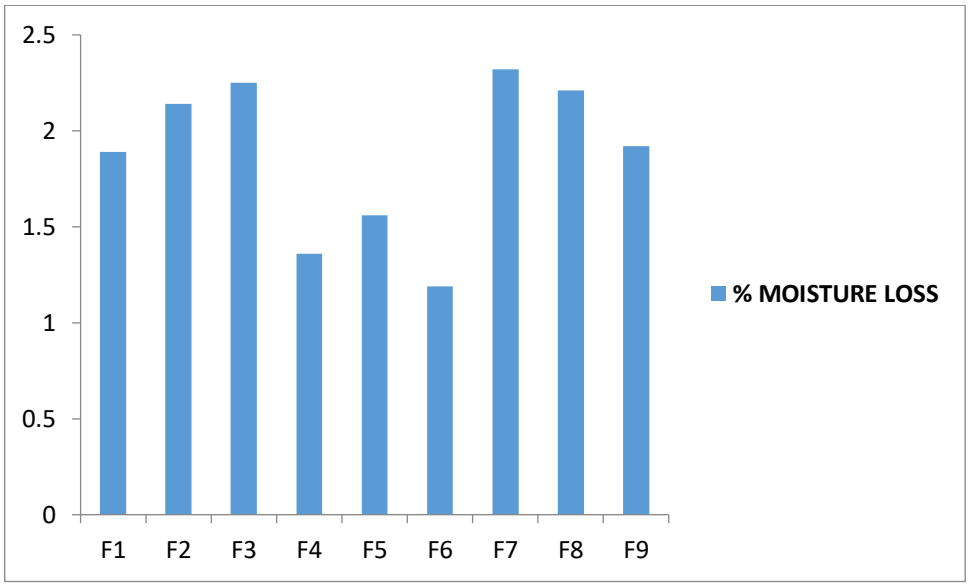


Fig 29: % MOISTURE LOSS OF THE FILM

9.4.9. Mucoadhesive strength

Mucoadhesive strength was an important property to be determined because it ensures the attachment of dosage form and delivery of drug at the site of administration. The direct relationship between the swelling index and adhesion strength has been described by many authors. Formulation F9 and F6 therefore showed highest bioadhesion due to their highest swelling index, thus ensuring adhesion of patch at the site of administration. On applying factorial design, the quadratic model was suggested by software and found to be significant with model p value F" less than 0.0007 for each term was obtained which indicated that every model term was significant.

Table 19: Mucoadhesive strength of film

FORMULATION	MUCOADHESIVE STRENGTH
F1	4.5
F2	4.8
F3	6.5
F4	4.3
F5	5.6
F6	6.8
F7	5.3
F8	6.2
F9	8.4

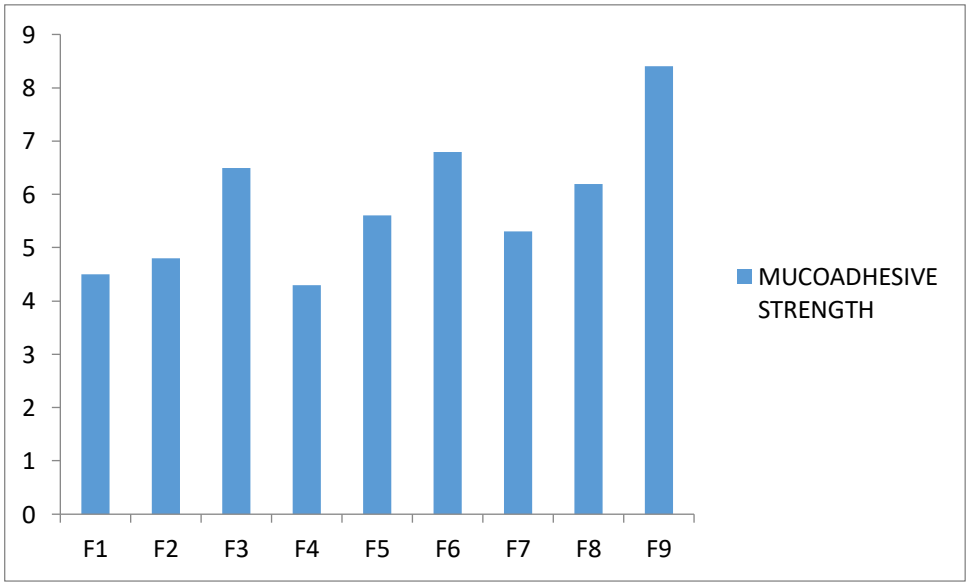


Fig30: Mucoadhesive strength of film

9.4.10. Drug content

All the batches of the film contain 72.82 ± 0.8to 98.16 ±0.3 % of drug which indicate that there is no loss of drug during preparation of the buccal film. All the batches of the film exhibit drug co-crystals content within limit, which is within the desirable range due to the equal distribution of drug in the solution. The results were shown in table -20.

Table 20- : Drug content of the film

FORMULATION	DRUG CONTENT (%) in COCRYSTAL
F1	78.56 ± 0.2
F2	82.51 ± 0.1
F3	98.16 ± 0.3
F4	91.10 ± 0.9
F5	84.62 ± 0.6
F6	73.25 ± 0.9
F7	69.26 ± 0.2
F8	88.54 ± 0.9
F9	72.82 ± 0.8

12.5mg of Felodipine cocrystal is equivalent to 5 mg of felodipine pure drug

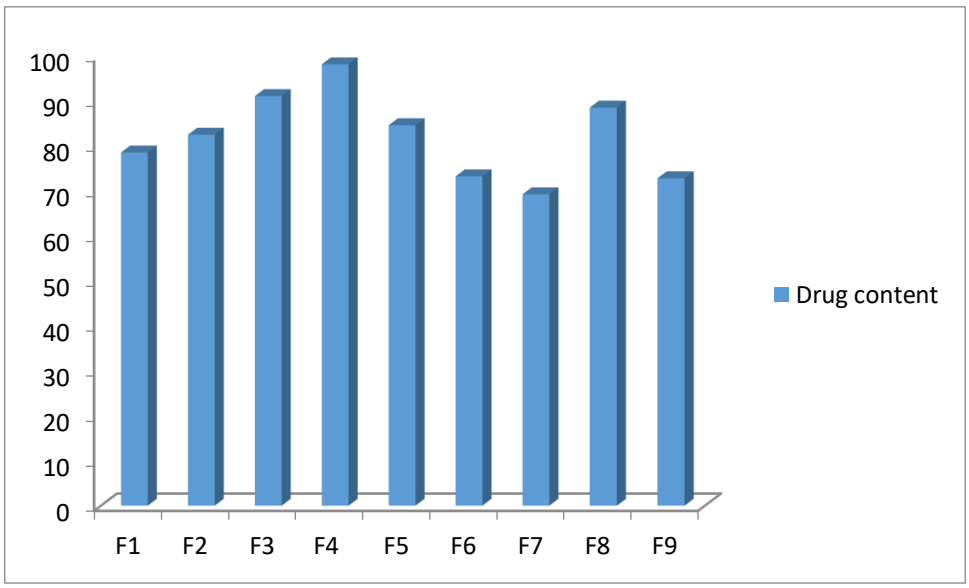


Fig- 31: Drug content of the film

9.4.11. Ex-vivo Permeation study

Ex vivo drug permeation through fresh Goat buccal mucosa using Franz diffusion cell and the results were given in table -21 and Fig -32.

Permeation study parameters

Donor compartment: Phosphate buffer pH 6.5

Receptor compartment: Phosphate buffer pH 6.5

Apparatus: Diffusion cell

Withdrawal time: 8 h with 1 h interval

Volume withdrawn: 5mL

Table 21 -: *Ex vivo* Percentage drug permeation of the films

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	19.96	22.25	22.54	20.14	18.97	11.78	11.85	16.74	20.41
2	35.78	39.46	31.92	37.49	24.96	18.01	26.01	31.32	35.57
3	44.61	45.27	47.23	46.21	41.14	24.36	33.36	45.86	45.83
4	63.19	56.83	53.32	55.32	57.49	31.49	42.17	54.65	56.09
5	78.32	61.44	65.41	60.88	66.03	45.62	57.71	63.52	64.82
6	87.93	74.78	82.9	72.3	81.89	63.9	65.21	74.61	75.63
7		81.75		82.1	88.48	72.86	73.52	79.04	86.12
8				94.59		82.75			

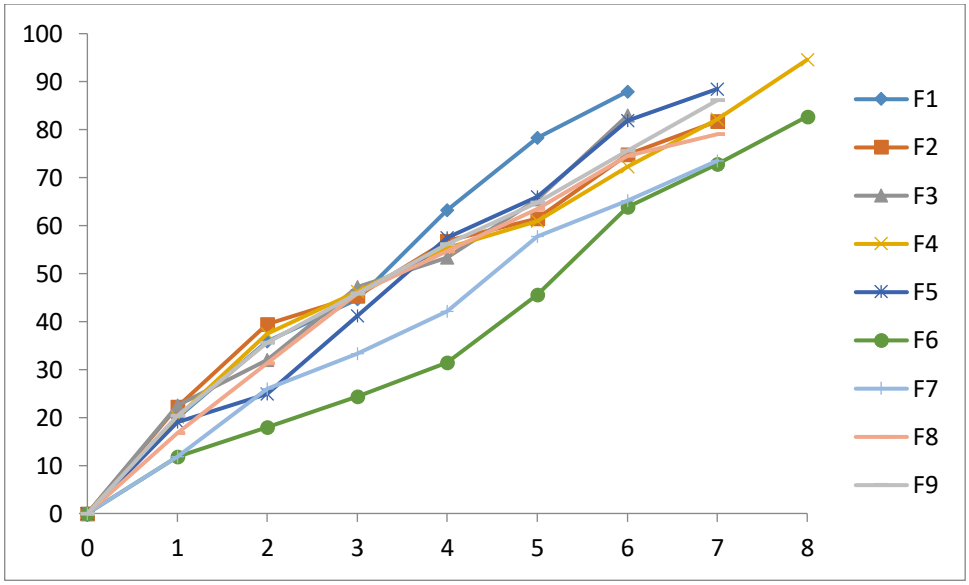


Fig -32: *Ex vivo* drug permeation profile for F1- F9

Table –22: Evaluation of Optimized felodipine cocrystals embedded buccal film

Evaluations	Optimized Formulation results
Weight (mg)	88.24
Thickness (mm)	0.24
Drug content (%)	98.16
Folding endurance	310
Swelling index (%)	5.23
Surface pH	6.4
Percentage moisture loss (%)	1.36
Mucoadhesive strength (gms)	4.3

Table -23: Percentage drug permeation of optimized formulation

Time (hour)	Drug permeation (%)
1	20.14
2	37.49
3	46.21
4	55.32
5	60.88
6	72.3
7	82.1
8	94.59

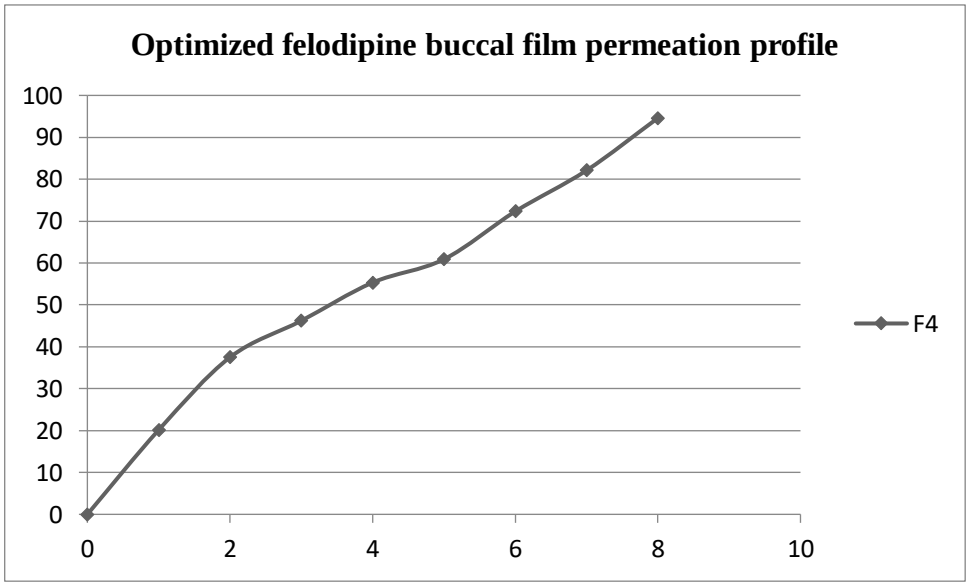


Fig –33: Optimized felodipine buccal film permeation profile

The optimized felodipine buccal film exhibits an 94.59 % permeation at 8 h on goat buccal mucosa, the permeation profile was relatively steady and the amount consistently permeated with duration of time. The results were shown in table -23 and Fig -33.

9.4.12. EX-VIVO DRUG PERMEATION KINETICS OF OPTIMIZED FELODIPINE BUCCAL FILM:

The drug release kinetics for the optimized formulation was calculated and the results obtained are presented in table – 21.

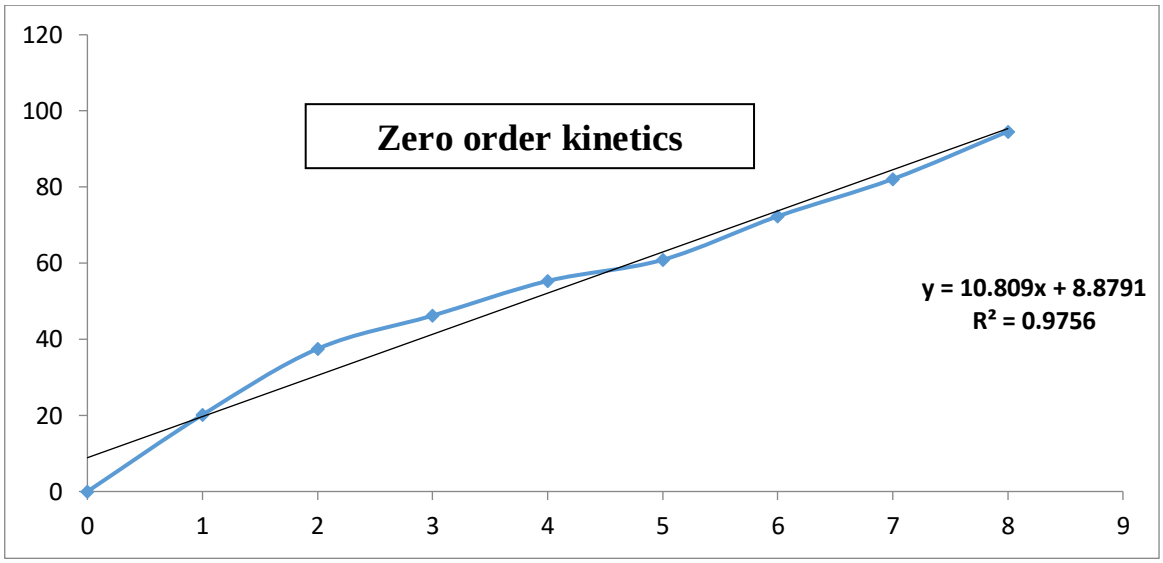


Fig 34: Zero order release for the optimized formulation F4

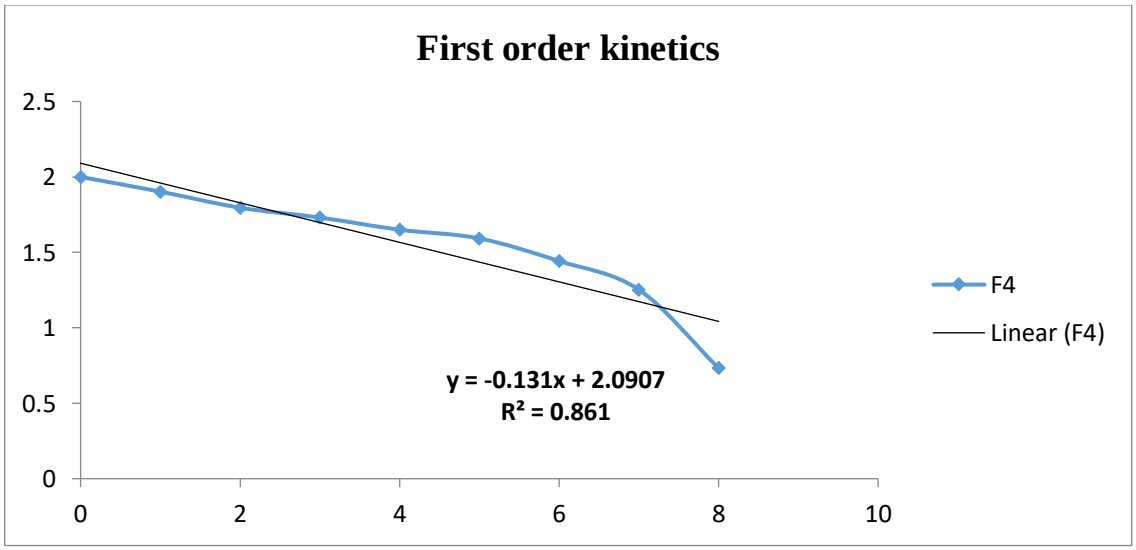


Fig -35: First order release for the optimized formulation F4

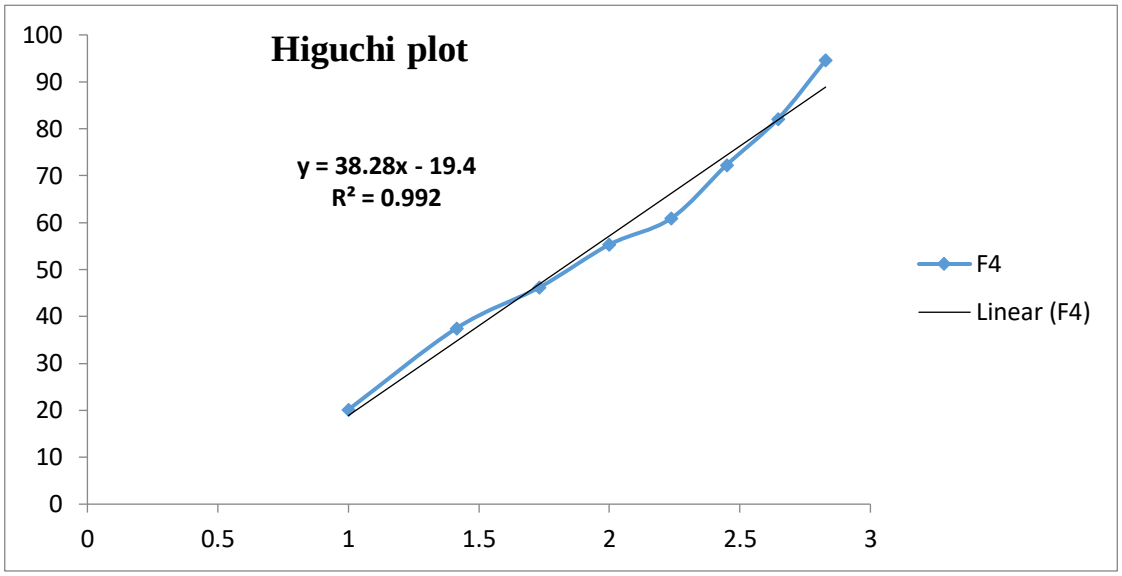


Fig -36: Higuchi plot for the optimized formulation F4

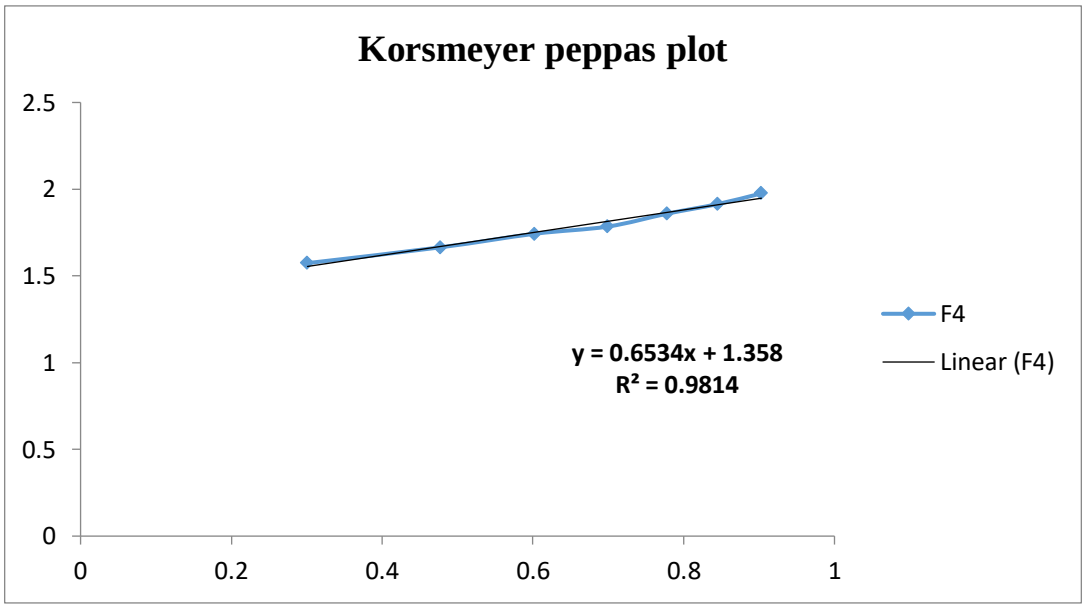


Fig -37: Korsmeyer-peppas model for the optimized formulation

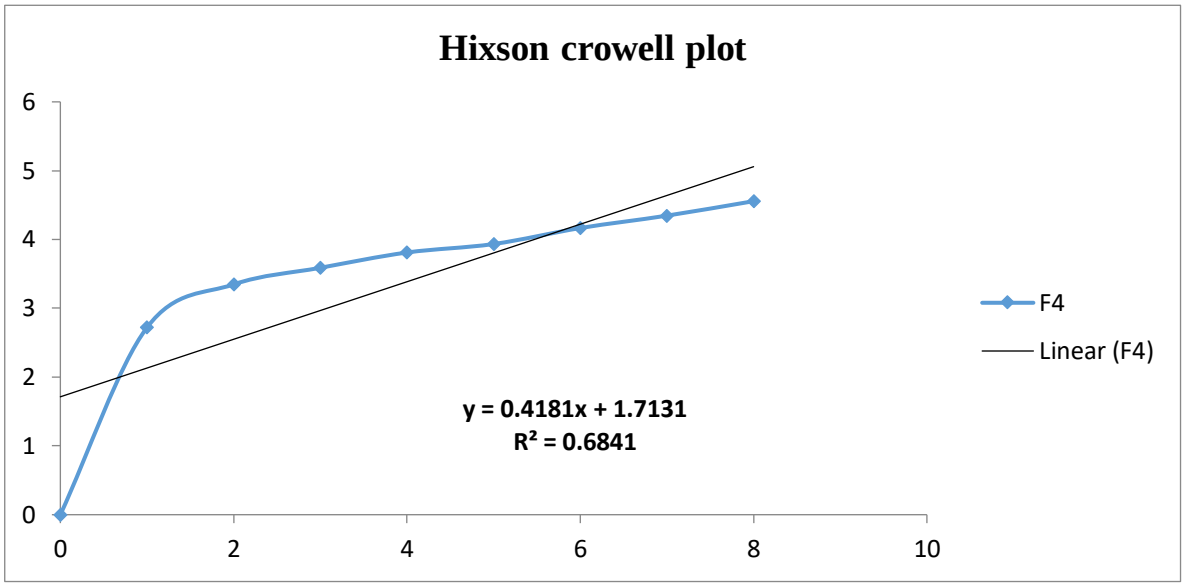


Fig -38: Hixson plot for the optimized formulation F4

Formulation	Zero order R^2	First order R^2	Higuchi R^2	Hixson-Crowell R^2	Korsmeyer-peppas (R^2)	n value
Optimized felodipine cocrystlas buccal film formulation	0.975	0.861	0.992	0.684	0.981	0.653

Table -24: Kinetic modelling of drug permeation

Examination of correlation coefficient (R^2) value indicated that the drug release followed a diffusion-controlled mechanism for the optimized Felodipine buccal film from the R^2 value. To study the drug release kinetics, data obtained from Ex- vivo permeation studies are plotted in various kinetic models. The curve fitting results of the release rate profile of the designed formulation gave an idea on the mechanism of drug release. Based on the "n" value 0.653 for the optimized formulation, the drug release was found to follow Non Fickian transport. This value indicates a coupling of the diffusion and erosion mechanism and indicates that the drug release was controlled by more than one process. Also, the drug release mechanism was best explained by zero order, as the plots showed the highest linearity, as the drug release was best fitted in zero order kinetics, it indicated that the rate of drug release was concentration independent. The kinetics were shown in the following Fig - 34 to 38.

10. CONCLUSION

The preformulation study of felodipine was carried out and it was found that the drug is poorly water soluble. The co-crystals were prepared using three different co-formers sorbitol, ascorbic acid and oxalic acid. The solublity enhancement was observed in combination with sorbitol compared to other co-formers used. The characterization of co crystals was performed like PXRD, FTIR, SEM Analysis. XRD results indicates the amorphous form of the drug.

The co-crystals were embedded within the buccal flim for sustained release of the drug. The buccal film was optimized by Factorial design using HPMC and PVA as independent variables. Two responses were chosen such as Drug permeation and Mucoadhesive strength for optimizing the buccal flim.

Based on desirability value (1.00) the formulation factors were found and observed value is closer to the predicted values. This results reveals that the model is validated.

The morphology of buccal flim was charactarized with SEM analysis. The buccal flim was tested for Thickness, weight variation, Folding Endurance, Drug content, Moisture loss, Surface pH and Swelling studies.

The drug permeation kinetic study was performed in the optimized formulation and the results reveals that the mechanism of drug permeation follows diffusion from higher r^2 value for Higuchi kinetics (r^2 = 0.992) and the n value of peppas model (n=0.653)shows that the mechanism follows Non-Fickian diffusion.

Novel Buccal adhesive cocrystal embedded patch offers innumerable advantages. While the water solubility of the drug is improved by 2 folds so that the permeation efficacy of the drug also improved, aided by increased bioavailability. Buccal patch exerts many advantages like ease of administration and withdrawal, avoiding first pass metabolism, low enzyme activity, enhancement of permeability and high patient compliance.

Hence the novel formulation holds immense opportunities to be explored in terms of different drug candidates.

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