INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Research Article

Formulation And Evaluation Of Mucoadhesive Buccal Tablet Of Favipiravir

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ARTICLE INFO

Received: 10 Aug 2024
Accepted: 14 Aug 2024
Published: 25 Aug 2024

Keywords:
Favipiravir, Mucoadhesive Buccal Tablet, Direct Compression, Mucoadhesion, Swelling Index.

DOI:
10.5281/zenodo.13371490

ABSTRACT

This research work investigates the formulation and evaluation of mucoadhesive buccal tablets containing Favipiravir, an antiviral medication with proven efficacy against various RNA viruses, including influenza and certain strains of coronaviruses. The objective of this study is to develop a novel drug delivery system that enhances the bioavailability and therapeutic efficacy of Favipiravir through buccal administration, thereby addressing the limitations associated with conventional oral dosage forms. The formulation development phase involves the selection of suitable mucoadhesive polymers such as Carbopol 934, sodium carboxy methyl cellulose and other excipients to optimize the mechanical properties, drug release kinetics, and adhesive characteristics of the buccal tablets. The mucoadhesive buccal tablet of Favipiravir was formulated by using direct compression method by using different polymer. The developed formulations may offer advantages such as improved patient compliance, reduced systemic side effects, and rapid onset of action, making them promising candidates for the treatment of respiratory viral infections and other diseases requiring localized drug delivery via the buccal route.

INTRODUCTION

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

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

increase in bioavailability, a rapid action is possible and reduce side effects. Buccal and sublingual route of drug delivery are most widely in which local and systemic effects are treated. The permeability of oral mucosa denotes the physical nature of the tissues. Buccal tablet can be administered in the oral cavity as shown in the figure.

Advantages :

It is richly vascularised and additional reachable for administration and removal of formulations.

- Patient accessibility is high.
- Retentive dosage forms are
- suitable for administration.
- Improves bioavailability by eliminating first pass metabolism.
- Surface of buccal mucosa achieves a fast cellular recovery.
- Low enzyme activity.
- Non-invasive method of drug administration.
- Ability to incorporate permeation enhancer in the formulation .

Disadvantages :

- Buccal membrane has low permeability.
- Small surface area (170 cm2).
- Continuous secretion of saliva results in following dilution of the drug.
- Inconvenience route of drug administration when the patient is swallowing or taking.

Mucoadhesive drug delivery system :

Mucoadhesive buccal drug delivery systems offer many advantages over conventional systems such as ease of administration, be promptly terminated in case of toxicity by removing the dosage form from buccal cavity and it is also possible to administer drugs to patients who cannot be dosed orally via this route. Mucoadhesive drug delivery system interact with the mucus layer covering the mucosal epithelial surface, & mucin molecules & increase the residence time of the dosage form at the site of the absorption as depicted in Figure.

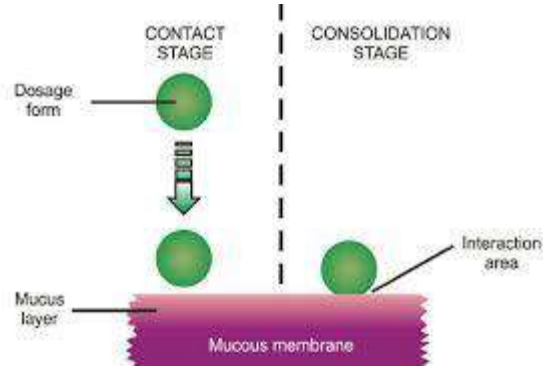


Figure no 1 :Interaction of mucus membrane with mucoadhesive dosage form

MECHANISM OF MUCOADHESION :

Stage1-

wetting and swelling of polymer (contact stage)

Stage2-

interpenetration between the polymers chains and the mucosal membrane

Stage3-

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

Buccal bioadhesive tablets

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

Polymer used in buccal drug delivery system :

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 :

Drug substance-

Before formulating buccoadhesive drug delivery systems, one has to decide whether the intended, action is for rapid release/prolonged release and for local/systemic effect. The selection of suitable drug for the design of buccoadhesive drug delivery systems should be based on pharmacokinetic properties.

Bioadhesive polymers-

Bioadhesive polymers play a major role in buccoadhesive drug delivery systems of drugs. It should be compatible with the biological membrane. It should form a strong non covalent bond with the mucin/epithelial surface.

Backing membrane-

Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. Such impermeable membrane on buccal bioadhesive patches prevents the drug loss and offers better patient compliance. The commonly used materials in backing membrane include Carbopol, magnesium stearate, HPMC, HPC, CMC, polycarbophil etc.

Penetration enhancers-

Penetration enhancers are used in buccoadhesive formulations to improve the release of the drug. They aid in the systemic delivery of the drug by allowing the drug to penetrate more readily into the viable tissues. The commonly used penetration enhancers are sodium lauryl sulphate, CPC, polysorbate-80, laureth-9, sodium fusidate, polmitoyl carnitine, azone, sodium glycocholate, dimethyl formamide etc.

REVIEW OF LITERATURE :

Ritu Singh, Kanchan Thakur, et.al :

In the development of mucoadhesive tablet of antifungal drug Posaconazole to treat oral thrush locally β-cyclodextrin used as hydrophilic matrix to improve the solubility. Posaconazole is poorly water soluble drug hence β-Cyclodextrin was used to improve the solubility and bioavailability of drug, simultaneously enhances the erosion rate of tablet. Which increases the drug release and permeation through buccal mucosa. The formation of inclusion complex of Posaconazole with β-Cyclodextrin was confirmed by phase solubility studies. Co-precipitation method was used to prepare inclusion complex of Posaconazole with β-cyclodextrin. The inclusion complex was characterized for compatibility studies. The results of compatibility studies reveal the successful complexation between Posaconazole and β-cyclodextrin. Mucoadhesive tablets of Posaconazole were prepared by direct compression method using altered concentrations of HPMC K4, Carbopol 934P and Maltose as polymers and Chitosan Polymer also used to enhance solubility. From the results concluded increase amount of polymers decreases the drug release at controlled rate. Formulation F6 was proved to most promising with the drug release time of 8hours 98.96%. Formulation F6 was subjected to stability testing at 45℃ & 75% RH and there is no significant change Observed. The outcome of the projected work is to designed mucoadhesive tablet of Posaconazole for controlled release in buccal mucosa.

Yahdiana Harahap, Roesytas Fitria Noer, et. al

Favipiravir and remdesivir are drugs to treat COVID-19. This study aims to find an optimum and validated method for simultaneous analysis of favipiravir and remdesivir in Volumetric Absorptive Micro sampling (VAMS) by Ultra High-Performance Liquid Chromatography–Tandem Mass Spectrophotometry. The use of VAMS can be an advantage because the volume of

blood is small and the sample preparation process is simple. Sample preparation was done by precipitation of protein using 500 µl of methanol. Analysis was carried out by ultra high-performance liquid chromatography–tandem mass spectrophotometry with ESI+ and MRM with m/z 157.9 > 112.92 for favipiravir, 603.09 > 200.005 for remdesivir, and at m/z 225.968 > 151.991 for acyclovir as the internal standard. The separation was carried out using an Acquity UPLC BEH C18 column (100 × 2.1 mm; 1.7 m), 0.2% formic acid— acetonitrile (50:50), flow rate was 0.15 mL/min, and column temperature was 50°C.

Dasari Nirmala, Vaddi Harika, Muvvala Sudhakar, et.al :

The aim of present study was to formulation and evaluation of Mucoadhesive buccal tablets of Risperidone. Mucoadhesive buccal tablets of Risperidone were prepared by direct compression method using polymers such as Karaya gum, tamarind gum, Carbopol, and Sodium carboxy methyl cellulose. The Buccal tablets were evaluated for various physical, drug content uniformity, in-vitro drug release and drug-excipient interactions (FT-IR). FT-IR spectroscopic studies indicated that there were no drug-excipient interactions. The formulation F9 (containing 30mg of Carbopol) were found to be best formulation, which showed maximum drug release within 8 h. These formulations have showed good bioadhesion strength .

Dr. Bharat.V. Jain, Miss. Kiran Jijabrao Patil, Dr. Sandip.R. Pawar, et. al. :

Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules increase the duration of the dosage form at the position in any bio adhesive systems for the reason that mucosal layer lines number of the body with the gastric tract, the urogenital tract, vaginal tract, the eye, ear, and nose. The mucoadhesive layer tablets containing of dual various forms of drug particles and that they display on set of actions on their specific sites. This analysis defines the structure of mucosal layer, mechanism of action of mucoadhesion, and planning of tablets and evaluation parameters of tablet.

M. S. Kalshetti, Sagar G. Adlinge, et al :

HPLC method has been developed and validated for the quantification of Favipiravir in tablet formulation The chromatographic separation was achieved by using Luna® Phenomenex C8(150x4.6 mm,5µm) with the mobile phase comprising of water and methanol in the ratio of 95:5v/v. The flow rate was 1ml/min and the separated Favipiravir was detected at 229 nm. The retention time of Favipiravir was 4.3 minutes. The linearity data showed good linear relationship (r2= 0.9997) within the concentration range of 10-50 µg/ml. The method was successfully validated in accordance to the ICH guidelines and method was found to be sensitive, accurate, precise, and reproducible.

Sachin Kushwaha, Vivek Gupta, et. al :

Naratriptan completely absorbed following oral administration. The mean oral absolute bioavailability of the tablet is about 60%. This clearly indicates that Naratriptan have first pass metabolism problem. The aim of present work to formulate and characterize buccal mucoadhesive tablets of Naratriptan. Buccal tablets of Naratriptan using HPMC K4, Carbopol 934 and Na Alginate prepared by direct compression method were found to be good without chipping, capping and sticking. The drug content was uniform in all the formulations of tablets prepared. Low values of standard deviations indicate uniform distribution of drugs within the matrices. The drug polymer ration influenced the release of drug from the formulations. An increase in polymer decreased the drug release. Formulation F4 with drug polymer (HPMC K4, Carbopol and Na Alginate) has shown promising results as per USP test II requirements.

Dr Nethaji Ramalingam, Neema K Ramesh, Vandana Govindan, et.al:

Pantoprazole sodium (PAS) is a proton pump inhibitor, with an anti-ulcer activity. Due to the short elimination half-life and poor bioavailability, it's rapidly degrades in gastro intestinal tract (GIT). An objective of work, to formulate mucoadhesive tablets for prolongation of drug release and preventing GI degradation. PAS tablets formulated using different concentration of HPMC and Xanthan gum by wet granulation technique and evaluated characterizations. Prepared granules were subjected to the pre-compression and post-compression evaluations, and there is no significant variation of tablets. PAS 3 showed better ex-vivo mucoadhesive strength (31.44±1.06g), and force (3.08±0.072N), highest invitro mucoadhesion time (476±0.596 min) and good swelling index (82.07%). PAS 3 had proven 79.48% drug release at end of dissolution studies and the mechanism of drug release kinetics was analyzed.

AIM, OBJECTIVES AND NEED OF RESEARCH WORK :

AIM:

To Develop & Evaluate the Mucoadhesive Buccal tablets formulation of Favipiravir by using different polymers with the help direct compression technique.

OBJECTIVES:

1. To conduct the detail literature survey related to proposed research
2. To select the suitable ingredients for the proposed sustained release formulation of Favipiravir
3. To develop Mucoadhesive Buccal tablets formulation of Favipiravir using direct compression technique
4. 4)To evaluate the formulated of Mucoadhesive Buccal tablets formulation of Favipiravir
5. 5)To perform the stability study of developed Mucoadhesive Buccal tablets formulation of Favipiravir
6. 6)To propose an effective strategy for Mucoadhesive Buccal tablets formulation of Favipiravir formulation.

NEED OF RESEARCH WORK

In the trend of drug repurposing for the treatment of the COVID-19 many drugs such as hydroxychloroquine, remdesivir, lopinavir, ritonavir, and some other drugs favipiravir which is previously existing drug for diseases like SARS-CoV and MERS (Middle East Respiratory Syndrome) has shown a quick service in treating the pandemic before the vaccine. Favipiravir (T705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is an antiviral agent that selectively inhibits the RNA dependent RNA polymerase (RdRp) of RNA viruses. It is a synthetic prodrug that was initially used in the treatment of influenza infections. The recommended dosage regimen of favipiravir is 1800 mg twice a day on day1, followed by 800 mg twice a day for 7 days if needed continued up to maximum 14 days. The Cmax is attained after 2Hrs of administration. Both Tmax and half-life increase after multiple doses. It is having a very short half-life of 2.5-5 h which is rapidly eliminated in the hydroxylated form. Mucoadhesive dosage forms are specially designed to adhere to the mucosal surface, thus intensifying retention of the drug at the site of application, while providing a controlled rate of drug release for better therapeutic outcome. The conventional dosage form of Favipiravir may leads to a lot of inconvenience and fluctuations in therapy, with some adverse effects. Thus, devising mucoadhesive medication is a good alternative for reducing its dosing frequency, for prolonged effect with improved bioavailability, while also improving safety and efficacy of the medication So, in this research work it is hypothesized that,

the development of Mucoadhesive Buccal tablet of Favipiravir by using different polymers which will also help to resolves the issues related with Favipiravir. So, this is attempted to develop novel formulation approach system to get the stabilized, more effective strategy for the model drug Favipiravir.

MATERIALS AND METHODS :

MATERIALS

Equipment's used in present work are enlisted in table 1.

Sr. No.	System	Model	Manufacturer
1	Fourier Transform Infrared(FT-IR) Spectrometer	Alpha	Bruker
2	UV-Visible spectrophotometer	Microprocessor double beam spectrophotometerLI-2702	Labindia
3	Ultrasonic cleaning bath	UCB-40	Spectrabab
4	pH meter	LI-120	Elico
5	Water purification system	MilliQ	Millipore
6	Digital Microscope	DMWBI-223ASC	Motic
7	Weighing balance	ViBRA HT	Essae
8	Vortexer	SLM-VM-3000	Genei Merck Specialities Pvt Ltd.
9	Dissolution Test Apparatus	Tablet Dissolution TesterUSP	Labindia

List of Chemicals and Reagents

Chemical and reagents used in present work are enlisted in table

Table 2: List of Chemicals and Reagents

Sr. no.	Materials	Manufacturer	Application
1	Favipiravir	Obtained from Tokyo Chemical Industry (India) Pvt. Ltd. Hyderabad	API
2	Carbopol grade 934	Dipa Chemical Industries	Mucoadhesive polymer
3	PVP K30	Dipa Chemical Industries	Mucoadhesive polymer
4	Ethyl Cellulose	Dipa Chemical Industries	Mucoadhesive polymer
5	Magnesium stearate	Dipa Chemical Industries	Lubricant
6	Talc	Dipa Chemical Industries	Glidant

Formulation of mucoadhesive buccal tablets of Favipiravir

Favipiravir mucoadhesive tablets were prepared by direct compression method as per the formulations as shown in Table 3. Before direct compression, all the ingredients were shifted through sieve No. 40 and then thoroughly blended in glass mortar and pestle. Blending was carried out separately for core tablet (polymer and drug) and backing layer (ethyl cellulose). The mixture of core tablet was lubricated with magnesium stearate and talc which was already passed through sieve 60. At first, the core tablets were compressed by using compression machine with 9.5 mm round shape punch. Then, one compressed core tablet was placed in die cavity manually. Over it, accurately weighed 50 mg of ethyl cellulose was added to each die cavity. It was then leveled and compressed again to obtain Favipiravir buccal tablets having one sided backing layer of ethyl

cellulose. After compression, the tablets were weighed to check that it lies within the range of 100±10 mg.

Table 3: Formulations batches prepared by direct compression method

Formulationcode	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core tablet									
Drug(mg)	200	200	200	200	200	200	200	200	200
Carbopol 934 (mg)	18	25	16	18	25	16	8	15	20
PVP K30 (mg)	25	18	27	-	-	-	15	8	15
Ethyl Cellulose (mg)	-	-	-	25	18	27	20	20	8
Mg stearate (mg)	2	2	2	2	2	2	2	2	2
Talc (mg)	1	1	1	1	1	1	1	1	1
Backing Layer									
Ethyl Cellulose (mg)	50	50	50	50	50	50	50	50	50
Total (mg)	**296**	**296**	**296**	**296**	**296**	**296**	**296**	**296**	**296**

Evaluation of Favipiravir Mucoadhesive Buccal compressed tablets

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

Weight variation Study

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

Table 4. Limits for Tablet Weight Variation

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

Thickness of tablet

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

Hardness of Tablet :

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

Friability :

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

Friability (%) = initial weight − final weight/initial weight x 100

Differential Scanning Colorimetry

DSC analysis was performed using PERKINELMER DSC PYRIS 6 (USA) on 2 to 8 mg sample. Sample was heated in an aluminum pan at a rate of 10 °C / min within a 30 to 300°C temperature range under a nitrogen flow of 20 ml/min. An empty sealed pan was used as a reference.

Determination of surface pH of tablets

Mucoadhesive buccal tablets from each batch were left to swell for 2 h on surface of agar plate. The

surface pH was measured using pH paper placed on core surface of the swollen tablet.

Mucoadhesive strength test

A modified physical balance was used to measure the strength of muco-adhesiveness. The apparatus consisted of a double beam physical balance in which the right side has a pan, and the left side of the balance has a string that was hanged and at the bottom of the string was were evaluated using 2% w/v agar gel plate. For each formulation, 10 tablets were weighed and average weight of each 10 tablets were calculated (W1). Then the tablets were placed with the core facing the gel surface in Petri dishes which are placed in an incubator at 37±0.1°C. The tablets were removed at time intervals of 1, 2, 3, 4, 5 and 6 hours, excess water on surface was absorbed using filter paper and swollen tablets were weighed. The average weight (W2) was determined and then swelling index was calculated suctioned glass slide. This was the place where the tablets were placed using an adhesive. The porcine buccal mucosa was placed on top of an inverted 50 mL beaker which was placed inside a 500 mL beaker that was filled with phosphate buffer with pH 6.8 kept at 37 ºC. The buffer amount was just enough so that it reaches the buccal mucosa surface. Exactly five gram of weight was placed on the right pan before putting the porcine buccal tablet in place. The weight was then removed to lower the glass slide with the attached buccal tablet. The tablet was to be in contact with the porcine buccal mucosa membrane and this was not disturbed for 5 minutes. After 5 minutes, weights were added on the right side of the pan to separate the tablet from the membrane. The accumulated weight on the right side was then noted and subtracted with 5 g. The value was taken as the measure for the bio-adhesive strength of the tablet. The bio-adhesive force was calculated using the formula:

N= W X g/1000

Where,

N= Bio-adhesive force

W= weight required for detachment of the tablet from the porcine buccal mucosa in grams g = acceleration due to gravity at 9.81 m/sec2

In-vitro swelling studies

The swelling rate of mucoadhesive tablets were evaluated using 2% w/v agar gel plate. For each formulation, 10 tablets were weighed and average weight of each 10 tablets were calculated (W1). Then the tablets were placed with the core facing the gel surface in Petri dishes which are placed in an incubator at 37±0.1°C. The tablets were removed at time intervals of 1, 2, 3, 4, 5 and 6 hours, excess water on surface was absorbed using filter paper and swollen tablets were weighed. The average weight (W2) was determined and then swelling index was calculated using this formula.

% Swelling index = [(W2-W1)/ W2] x 100

In-vitro release studies

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8 ±0.5. The release was performed at 37 ± 0.5°C, with a rotation speed of 50 rpm. The tablet was supposed to release drug from one side only hence one side (backing layer) of tablet was fixed to glass disk with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through filter paper and analyzed by UV spectrophotometer at 235 nm.

Ex-vivo mucoadhesion time (wash off test)

The ex-vivo mucoadhesion time was performed after application of the buccal tablet on freshly cut goat buccal mucosa. A segment of fresh goat buccal mucosa (2 cm) was glued to the surface of glass slide, and a mucoadhesive buccal tablet was wetted with 1 drop of phosphate buffer pH 6.8±0.5 and pasted to the goat buccal mucosa by applying a light force with a fingertip for 30 seconds. The

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

Release kinetics study

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

Zero order equation

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

C =Kot……...Equation 1

Where,

Ko = Zero order constant in conc. / time t = Time in hours

First order equation

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

Log C = log Co + Kt/2.303 Equation 2

Where,

Co = Initial drug concentration K = First order constant t = Time in hours.

Higuchi Kinetics

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

Q = Kt½ Equation 3

Where,

K = Constant reflecting design variable system (Differential rate constant) t = Time in hours.

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

Korsmeyer – Peppas equation

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

Mt/Mα= Ktn Equation 4

Where,

Mt/Mα= Fraction of drug released at time t = Release time

K = Kinetics constant (Incorporating structural and geometric characteristics of the formulation) n = Diffusional exponent indicative of the mechanism of drug release.

Table 5: Release mechanisms based on n-value

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

Stability Study

The tablets were stored for 3 months and the samples were tested after a period of 30, 60, and 90 days. The samples were analyzed using the quality control tests such as hardness, friability, Drug content and in-vitro drug release.

RESULT AND DISCUSSION :

Construction of calibration curve for Favipiravir

λmax for Favipiravir was found at 235 nm. The standard calibration curve of Favipiravir was obtained by plotting the absorbance of the standard solution against its concentration at 235 nm. The standard solution of Favipiravir showed the linear curve with correlation coefficient of 0.9996. Their equations of lines were y = 0.1016x + 0.071 at selected λmax. Following table shows absorbance

of respective standard solution. The standard curve for Favipiravir at 235 nm is shown in Figure .

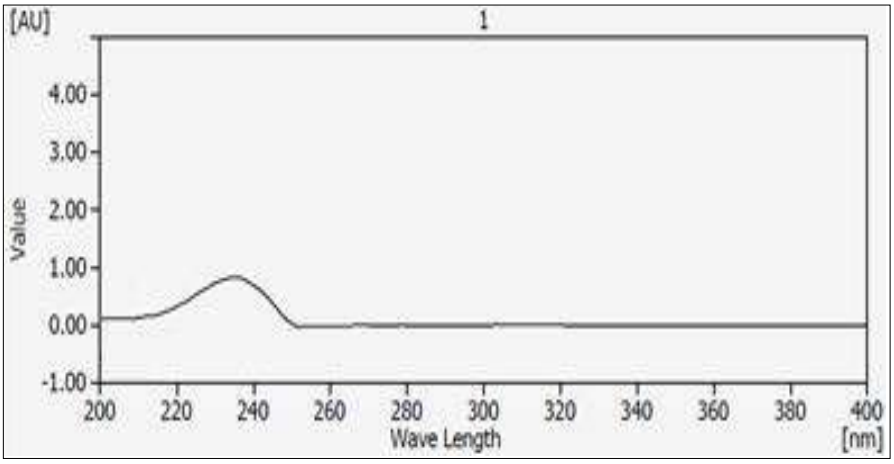
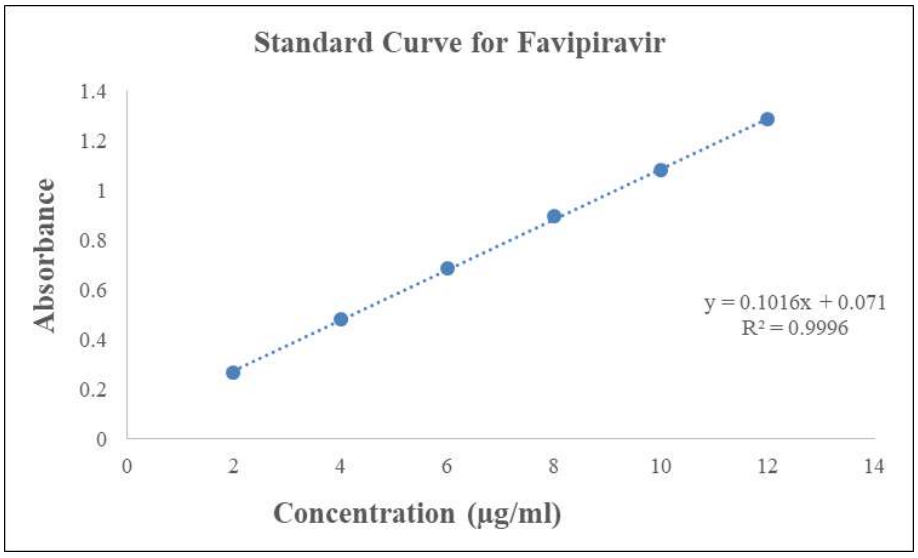


Fig.no 2 Maximum wavelength of Favipiravir

Calibration range for Favipiravir :

Sr. No.	Concentration (µg/mL)	Absorbance
1	2	0.265
2	4	0.481
3	6	0.687
4	8	0.894
5	10	1.082
6	12	1.286



Calibration curve for Favipiravir

Drug (Favipiravir) polymer compatibility study:

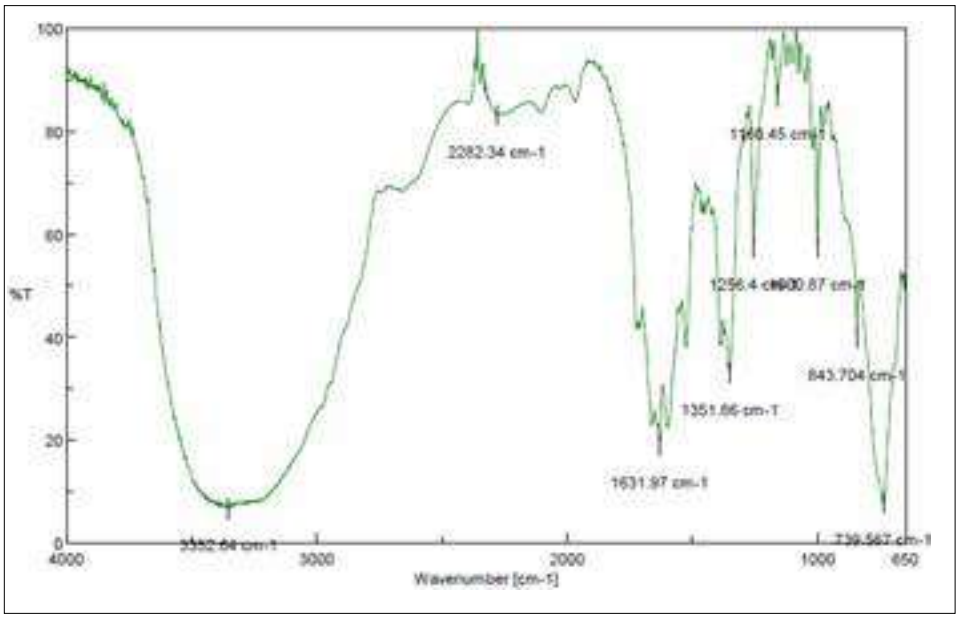
FT-IR Study

FT-IR studies were conducted for Favipiravir alone and combination of polymers and Favipiravir to determine any interactions between drug and polymers. The Characteristic peaks for Favipiravir, Carbopol 934, PVP K30 and Ethyl cellulose were identified and any notable shift in characteristic peaks was not observed in Mucoadhesive Buccal tablet of Favipiravir

spectra. So that it was concluded that there were no interactions between drug and polymer.

1. IR absorbance bands of pure Favipiravir

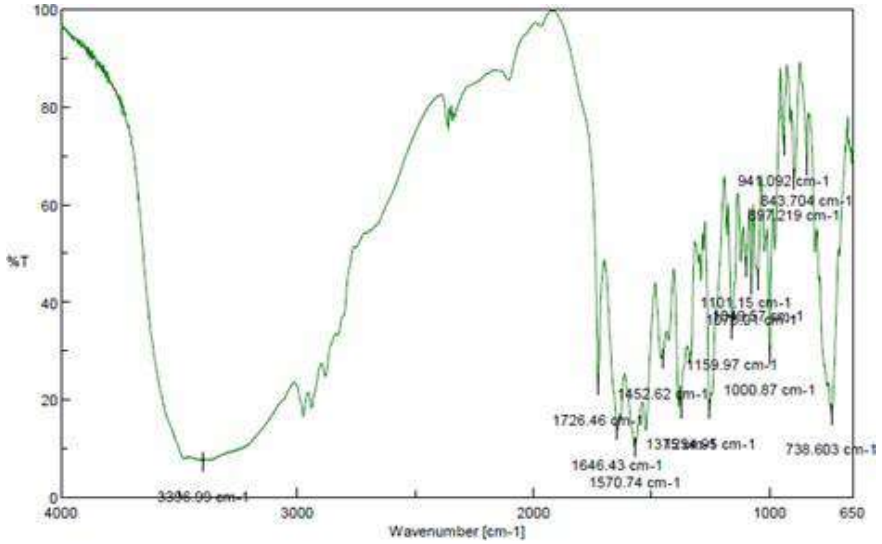
Functional Group	Observed frequencies (in cm^{-1})
O-H (hydroxyl)	3352.81
C=C (aromatic double bond)	1631.97
-C-H bending	1351.86
C-O stretch	1160.45



FTIR Spectra of Favipiravir

2. IR absorbance bands of Favipiravir and Carbopol 934 mixture

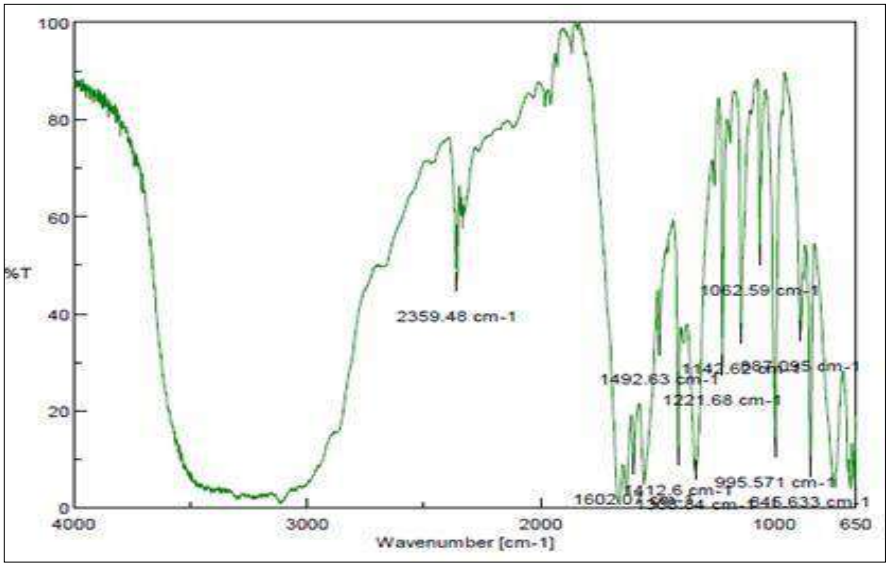
Functional Group	Observed frequencies (in cm^{-1})
Carbonyl (C=O)	1726.46
Hydroxyl (O-H)	3336.00
Ether (C-O-C)	1101.15
Aromatic C=C	1570.74



FTIR Spectra of Favipiravir and Carbopol 934 mixture

3. R absorbance bands of Favipiravir and Ethyl Cellulose mixture

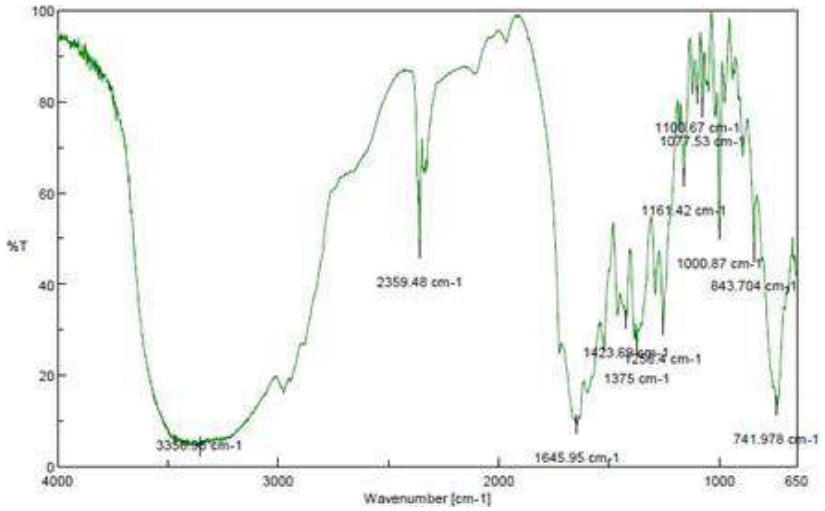
Functional Group	Observed frequencies (in cm^{-1})
Amide C=O	1645.95
Amide N-H	3350.95
Alkene C=C	1645.95
Pyrrolidone Ring C=O	1645.95



FTIR Spectra Favipiravir and Ethyl Cellulose mixture

4. IR absorbance bands of Favipiravir and PVP K30 mixture

Functional Group	Observed frequencies (in cm^{-1})
Amide C=O	1645.95
Amide N-H	3350.95
Alkene C=C	1645.95
Pyrrolidone Ring C=O	1645.95



FTIR Spectra of Favipiravir and PVP K30 mixture

Evaluation of mucoadhesive buccal tablet of favipiravir

Pre-compression parameters of powder blends

Batches	Angle of repose(θ)	Bulk density	Tapped density	% compressibility	Hausner ratio
F1	21.32	0.384	0.481	24.34	1.467
F2	23.46	0.368	0.423	22.46	1.346
F3	20.23	0.346	0.476	23.78	1.426
F4	22.59	0.382	0.489	26.12	1.291
F5	24.10	0.367	0.426	25.84	1.346
F6	21.18	0.376	0.438	27.27	1.271
F7	23.48	0.468	0.354	25.37	1.147
F8	20.76	0.367	0.486	24.76	1.341
F9	21.46	0.385	0.418	23.94	1.284

Flow properties are parameter to evaluate the compression parameter of sustained release tablet of FPV. From the literature it is stated that, smaller the value of angle of repose (<30°), lesser the internal friction or cohesion between the particles and greater the flow characteristics & vice-versa and Carr's index and Hausner's ratio are also less than 21 & 1.25 respectively indicating the good flow properties. The angle of repose of pre compression powder blend was obtained in the range of 20.23-24.10 showed the excellent flow. Carr's index and Hausner's ratio in the range of 22.46 – 27.27 and 1.147-1.467 respectively indicates good flow properties

Specification of Favipiravir Tablet

Average weight of 1 Tablet	296 mg
Appearance	Yellowish Color, round shape with one side break line
Thickness of 1 tablet	3.70±0.2 %
Hardness of 1 tablet	4.12 ± 0.2 kg

Physical characterization of tablet

1. **Identification of FPV Tablet**

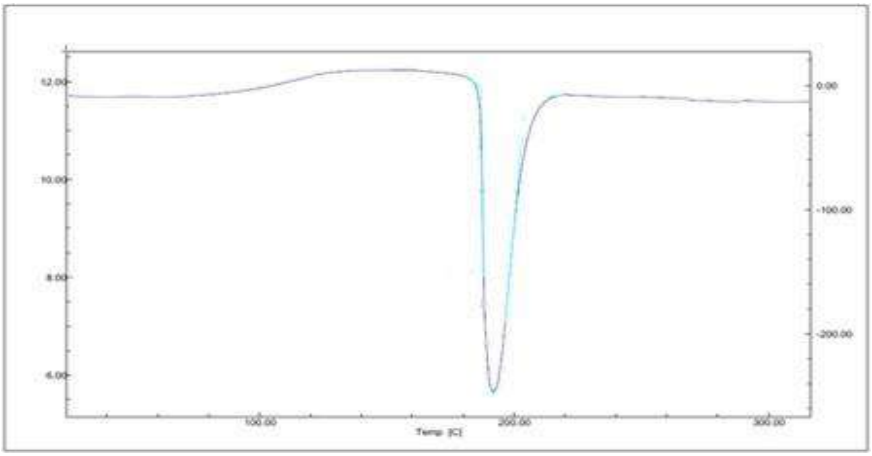
Post Compression parameters of FPV Tablet

Batches	Weight variation (mg) SD (n=3)	Hardness (Kg/cm^2) SD (n=3)	% Friability	% Drug content SD (n=3)
F1	292± 2.0	4.26 ± 0.2	0.405	91.62± 0.2

F2	295± 3.0	4.12 ± 0.2	0.374	88.10± 0.4
F3	290± 2.0	4.24 ± 0.3	0.184	98.28± 0.5
F4	298± 4.0	4.19 ± 0.3	0.267	92.61± 0.3
F5	291± 5.0	4.28 ± 0.2	0.568	93.26± 0.4
F6	302± 3.0	4.06 ± 0.4	0.367	90.37± 0.2
F7	295± 4.0	4.86 ± 0.1	0.458	91.34± 0.3
F8	301± 5.0	4.28 ± 0.3	0.311	92.43± 0.2

Post- compression parameter like weight variation, hardness, friability and drug content was evaluated. Weight variation test was passing and the variability in the weight was observed in the range of 290± 2.0-302± 3.0. Hardness and the drug content of the tablet was obtained in the range of 4.12 ± 0.2 to 4.86 ± 0.1and 88.10± 0.4 to 98.28± 0.5 respectively. Results are showed in Table .

2.Differential Scanning Colorimetry



DSC Thermogram of Favipiravir

The DSC of the Favipiravir was carried out by using instrument. The standard range of melting point of Favipiravir is 187℃ to 193℃. The peak of Favipiravir was observed on the 188°C which is in the standard range of FPV melting point which confirms the presence of Favipiravir.

The results for the surface pH of the Favipiravir buccal tablets are tabulated in table 14. The surface pH of all the tablets is within the range of 6.16 ± 0.01to 7.29 ± 0.05 which is close to neutral PH. There is negligible or no change in the surface pH of the tablets. Hence, no irritation to the buccal cavity is assumed.

Determination of surface pH of tablets

Surface pH of the Favipiravir Buccal tablets

Sr. No.	Formulation code	Surface pH
1	F1	6.51 ± 0.01
2	F2	6.37 ± 0.16
3	F3	6.16 ± 0.01
4	F4	7.29 ± 0.05
5	F5	6.46 ± 0.02
6	F6	6.47 ± 0.31
7	F7	6.38 ± 0.15
8	F8	6.46 ± 0.26
9	F9	0.21

Mucoadhesive strength test

In our study, all the formulated batches exhibited satisfactory mucoadhesive strength ranging from 0.257 N to 0.471 N force. The results for the Mucoadhesive strength of the Favipiravir buccal tablets are tabulated in table.

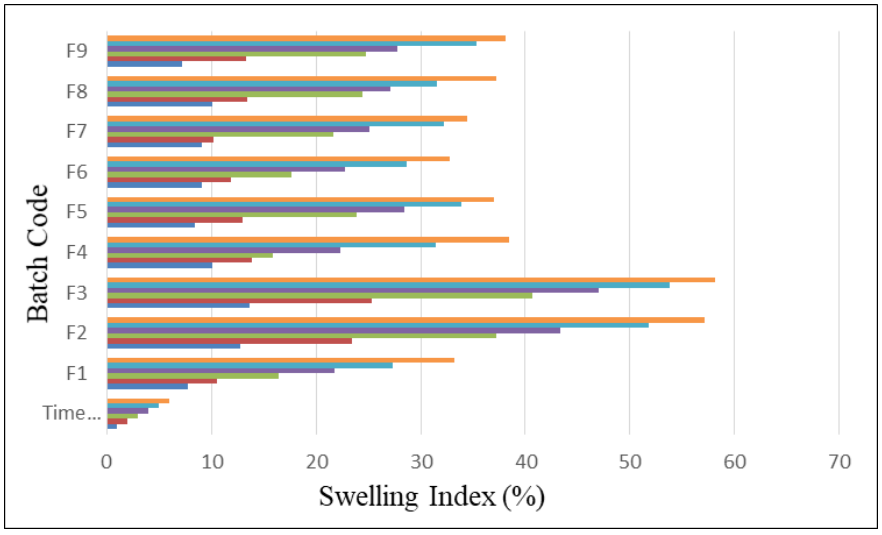
Mucoadhesive strength (N) of the Favipiravir buccal tablets

Sr. No.	Formulation code	Mucoadhesive strength (N)
1	F1	0.368
2	F2	0.471
3	F3	0.428
4	F4	0.396
5	F5	0.257
6	F6	0.341
7	F7	0.354
8	F8	0.421
9	F9	0.416

In-vitro swelling studies

The swelling property of all the batches was performed by evaluating the swelling index at different time intervals (1, 2, 3, 4, 5 and 6 h). All the formulations showed an appreciable increase in swelling index, proportional to the time increased, and achieving maximum swelling effect at 6 h. The tablets did not show any significant change in their morphological shape and form, throughout the study. Appropriate swelling behavior of mucoadhesive buccal system is essential for uniform and prolonged drug release and effective mucoadhesion. The swelling index after 6 h. is in the range from 0.257 to 0.428 % for formulation containing Carbopol 934 with PVP 30.

% swelling index of tablet

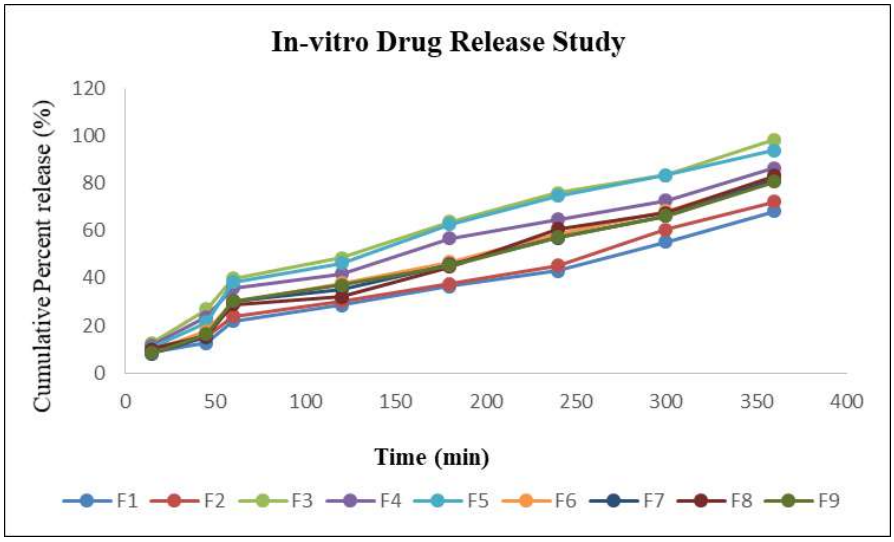


Swelling index (%) of the Favipiravir buccal tablets

Code	Time (h)					
	1	2	3	4	5	6
F1	7.76±1.21	10.54±0.71	16.48±0.61	21.78±1.17	27.31±0.39	33.27±0.61
F2	12.74±1.31	23.41±0.75	37.23±0.17	43.39±1.21	51.76±0.57	57.16±0.64
F3	13.64±0.87	25.36±0.82	40.67±1.74	46.98±0.57	53.79±1.12	58.10±1.34
F4	10.14±0.68	13.86±0.74	15.84±0.75	22.37±0.65	31.48±0.61	38.46±1.13
F5	8.45±0.47	12.97±1.12	23.84±1.2	28.47±0.51	33.87±0.64	36.95±0.50
F6	9.15±0.74	11.84±2.14	17.67±1.31	22.72±1.27	28.64±0.64	32.76±0.56
F7	9.15±0.32	10.16±1.21	21.62±1.3	25.13±0.45	32.24±0.48	34.42±0.43
F8	10.13±0.37	13.48±1.21	24.48±1.5	27.10±0.53	31.53±0.46	37.17±0.40
F9	7.16±0.24	13.27±1.10	24.73±1.6	27.82±0.61	35.38±0.52	38.14±0.40

In-vitro release studies

The in-vitro dissolution profile for the various Favipiravir buccal tablet formulations is given below in Figure 23. In vitro drug release studies of the mucoadhesive buccal tablet of FPV were conducted for a period of 6 hours. From the results, it can be concluded that an increase in Carbopol content delays the drug release from the tablets. Also, the formulation which showed highest swelling index also exhibit high extent of drug release.



In-vitro release profile of Formulation 1 to Formulation 9

Time (min)	% Release of FPV								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
15	8.64±0.52	10.67±0.46	12.76±1.24	11.67±0.71	10.58±0.84	9.48±0.63	8.16±0.63	10.16±0.52	8.36±0.53
45	12.67±0.68	15.43±1.02	26.76±1.31	23.74±0.83	21.49±0.69	17.63±1.17	15.24±1.02	15.73±1.11	16.42±1.10
60	21.84±0.53	23.78±0.41	39.71±0.72	35.78±0.74	38.36±0.52	29.67±0.84	30.25±0.76	28.86±0.68	30.38±0.74
120	28.68±0.72	30.47±0.68	48.52±0.83	41.86±0.48	46.28±0.63	37.92±0.73	35.42±0.62	32.02±0.71	36.96±0.52
180	36.67±0.72	37.64±0.34	63.76±0.56	56.83±0.68	62.84±0.71	46.81±0.81	45.76±0.73	44.68±0.61	45.28±0.53
240	43.18±0.63	45.38±1.13	75.86±0.87	64.82±0.81	74.67±0.65	58.64±0.67	57.12±0.56	60.80±0.59	57.37±0.57
300	55.38±0.46	60.38±0.48	83.41±0.64	72.64±0.46	83.42±0.97	68.19±0.58	66.15±0.58	67.52±0.38	66.19±0.34
360	68.19±0.51	72.31±0.53	98.31±0.73	86.37±0.34	93.84±0.72	82.67±0.76	81.46±0.52	83.15±0.62	80.67±0.53

This may be due to the fact that the higher amount of water uptake by the polymers may lead to considerable swelling of polymer matrix, allowing the drug to diffuse out at a faster rate. The mucoadhesive polymer PVP K30 and swelling polymer Carbopol 934 are playing the major role to release of Favipiravir up to 6 hrs. The percent release was obtained in the range of 68.19 ±0.51 to 98.31±0.73 which is highly variable due to the different composition in tablet formulation.

Ex-vivo mucoadhesion time (wash off test)

The data from the Wash off test are tabulated in table 18. The ex-vivo mucoadhesion time for the prepared buccal tablets of Favipiravir varies from 5 h to more than 6 h. The difference between the values of the ex-vivo mucoadhesion time for buccal tablets can be attributed to the combination of the various amounts of the polymer which affect the mucoadhesion. e range of the ex-vivo mucoadhesion time was found to be 5 h 10 min to more than 6 hr which showed the good adhesion of Favipiravir Buccal tablet to the buccal mucosa.

Sl. No.	Formulationcode	Mucoadhesivetime
1.	F1	> 6 h
2.	F2	5 h 13 min
3.	F3	5 h 45min
4.	F4	> 6h
5.	F5	5 h 51 min
6.	F6	5 h 40 min
7	F7	5 h 36 min
8	F8	5 h 10 min
9	F9	5 h 55 min

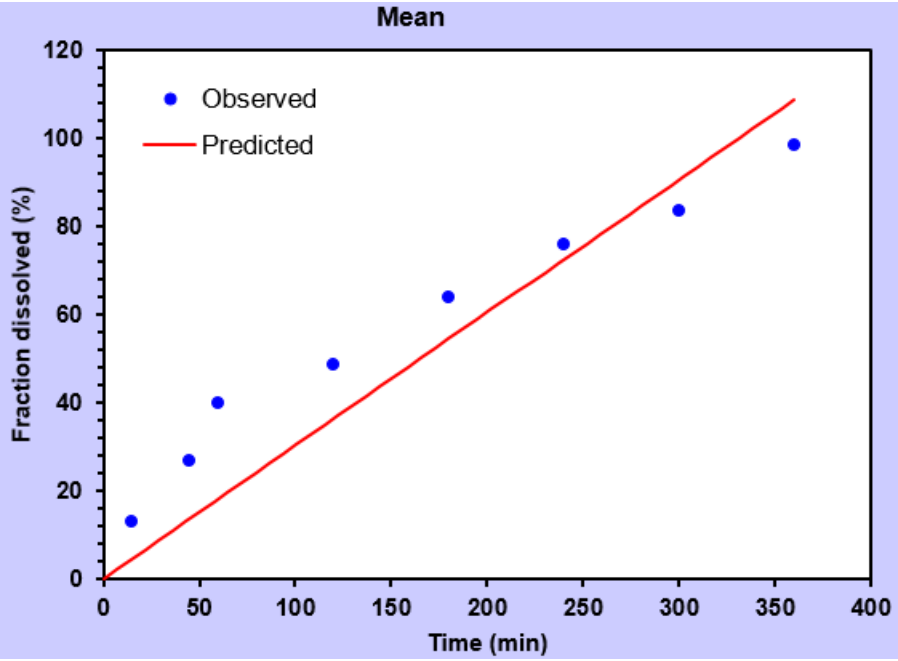
Time duration of attachment of the Favipiravir Buccal Tablets

Release kinetics study

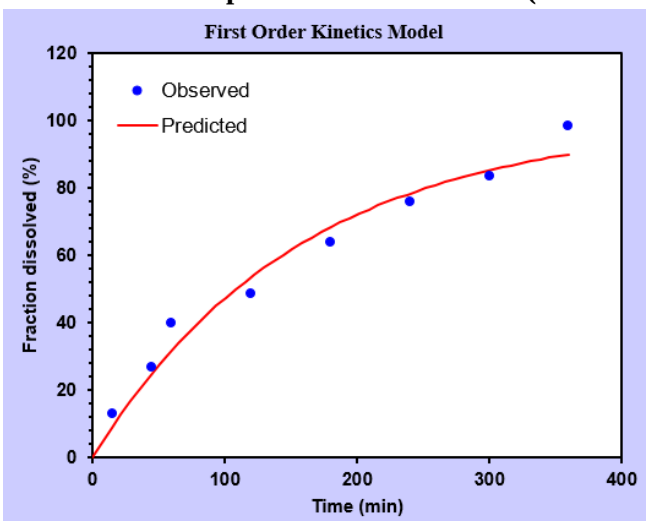
Out of all the prepared formulations, formulation 3 (F3) was selected as optimized formulation as it gave the best results for percentage drug release. The drug release kinetics for the optimized formulation (F3) was calculated and the results obtained are represented in table 19. The zero order profile, first order profile, Higuchi profile and Korsmeyer-Peppas plot is represented in Fig. 24, 25, 26 and 27 respectively. Examination of the correlation coefficient (R2) value indicated that the drug permeation followed a diffusion-controlled mechanism for the buccal tablet of best formulation (F3) as the R2 value for Korsmeyer Peppas plot (0.9881) was higher in comparison to the zero-order plot (0.8150) first-order (0.9663), Higuchi plot (0.9773), kinetic models, as shown in Table 23. The drug release is independent of concentration. Also, the n value of Korsmeyer-Peppas lies within $0.45<n<0.89$, which indicates that it undergoes anomalous diffusion or Non-Fickian diffusion.

Release kinetics and mechanisms of Favipiravir buccal tablet of optimized formulation (F3)

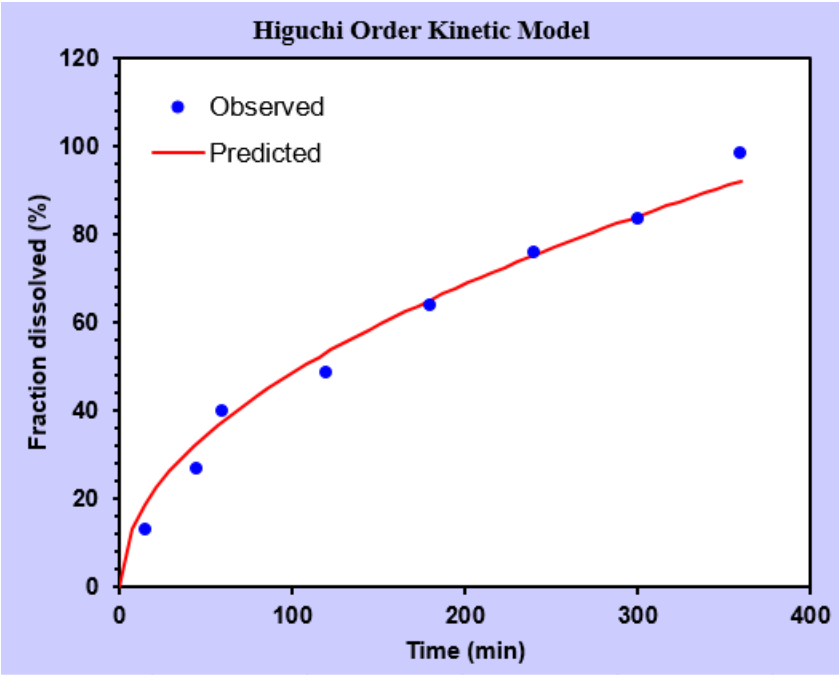
code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsmeyer-Peppas	Possible drug release mechanism	code
				(R^2)	N	
F3	0.8150	0.9663	0.9773	0.9881	0.585	Non-Fickian transport



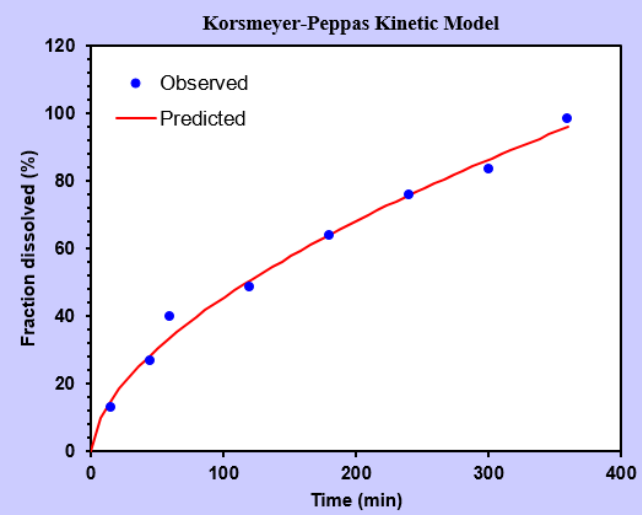
Zero order profile for Formulation (F3



First order profile for Formulation (F3)



Higuchi order profile for Formulation (F3

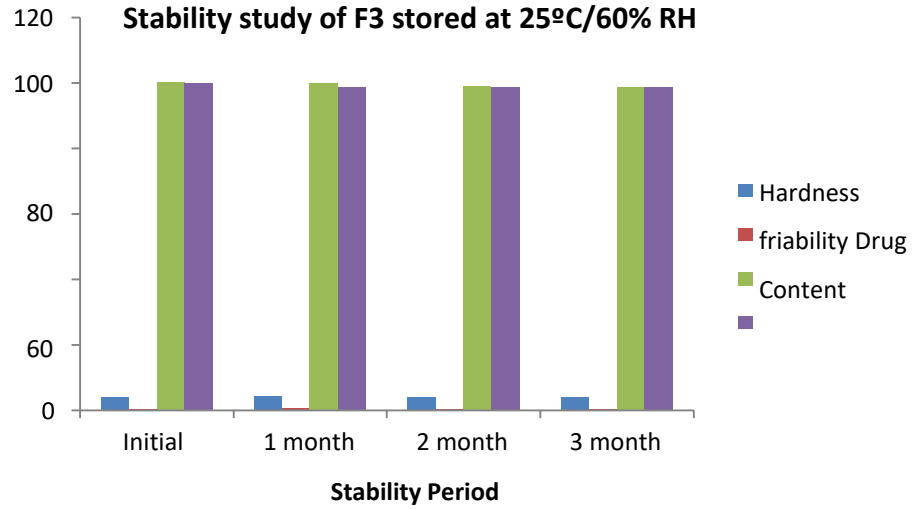


Korsmeyer-Peppas order profile for Formulation (F3)

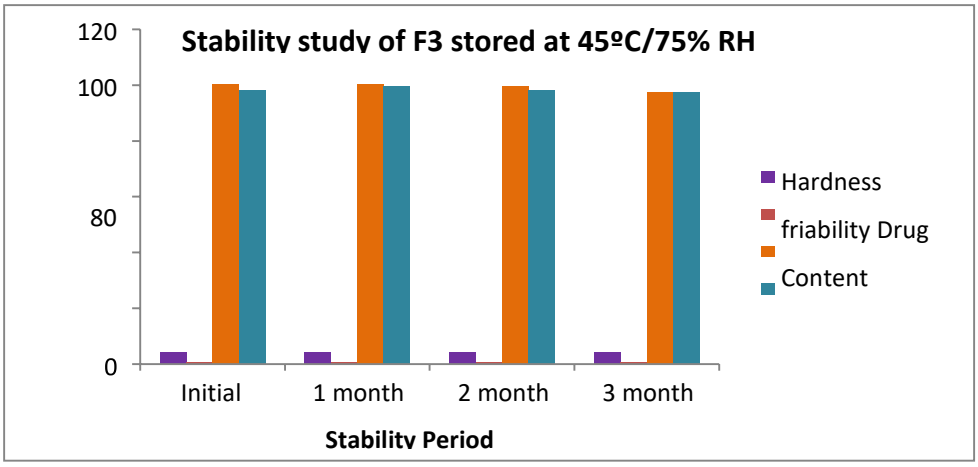
Stability Study

Based on the results of in-vitro drug release two best formulations F3 was selected for three month stability studies at 25ºC/60% RH and at 45ºC/75% RH. The stability studies were conducted according to the method described in section four. The selected formulations were evaluated for physical appearance, hardness, friability, and drug content. The results showed that there was no significant change in physical appearance, hardness, friability, drug content and drug release profile throughout the study period. Three months of stability studies revealed that; there was no any significant degradation of the drug. Thus prepared formulations were physically and chemically stable. The result of stability studies were tabulated in table

Stability study of formulation F3 at 25ºC/60% RH



Stability study of formulation F3 at 47ºC/75% RH



Results of stability studies for formulation F3 stored at 25ºC/60% and 45ºC/75% RH

Storage period	Stored at 25ºC/60% RH				Stored at 40ºC/75% RH			
	FormulationF3				FormulationF3			
	Hardness Kg/cm^2	% friability	% Drug content	% CDR	Hardness Kg/cm^2	% friability	% Drug content	% CDR
Initial	4.36±0.07	0.614±0.1	100.16±0.3	98.17±0.4	4.31±0.07	0.564±0.2	100.34±0.3	99.84±0.2
After 1 month	4.32±0.12	0.576±0.3	100.41±0.1	99.37±0.4	4.34±0.098	0.624±0.1	99.84±0.2	99.67±0.3
After 2 month	4.31±0.46	0.634±0.2	99.67±0.2	98.12±0.4	4.28±0.07	0.571±0.3	98.97±0.3	98.61±0.2
After 3 month	4.21±0.13	0.624±0.1	97.23±0.3	97.46±0.4	4.14±0.07	0.538±0.1	98.76±0.3	98.72±0.2

CONCLUSION:

In the present work, an attempt was made to design efficacious and prolonged release mucoadhesive buccal tablets of Favipiravir using various polymers to reduce dosing frequency, decrease gastric irritation and to improve patient compliance. Two polymer combinations (Carbopol 934 and PVP K30 as well as Carbopol and Ethyl cellulose) were taken at varying proportions. The buccal tablets were tested for

weight uniformity, thickness, friability and hardness. Tablets were then evaluated for their swelling index, in vitro drug release, mucoadhesion time (wash-off time) and in-vitro drug release study. The best polymer composite was selected from the various ratios of the polymers. The best polymer ratio was found to be Carbopol 934 and PVP K30 in the ratio 16:27 mg. The mucoadhesive strength of buccal tablets increases as the concentration of secondary polymer increases. The above polymer composite showed satisfactory results in the parameters such as thickness, hardness, drug content, swelling index, mucoadhesive time and in-vitro dissolution.

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HOW TO CITE: Nishigandha Pandurang Gite , Vinayak Munde , Formulation And Evaluation Of Mucoadhesive Buccal Tablet Of Favipiravir, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 8, 3733-3754. https://doi.org/10.5281/zenodo.13371490