Formulation and Evaluation of Mucoadhesive Buccal Film of 5-Fluorouracil by Liposomal Formulation Method

Shalini Dixit[1]*, Shivangni Rathore[1], Revathi A Gupta[1]

[1]Institute of Pharmacy, Dr. A.P.J. AKU, Indore

Corresponding Author- Shalini Dixit email- rs5880840@gmail.com

Abstract: The aim of this study was for cancers of the mouth, throat, colon, stomach, and cervical regions, fluorouracil is the recommended medication. 5 FU has a pKa value of 8.0 and 13.0, making it a highly polar substance that is classified as BCS class III (Highly soluble & Low permeable). Due to its limited permeability, the medication is poorly absorbed, and its bioavailability is low at 28% (first pass metabolism). Following intravenous injection, 5 Fu is quickly removed, with an apparent terminal half-life of 8–20 minutes. The medication has serious side effects, including as impacts on the gastrointestinal tract, the bloodstream, the brain, the heart, and the skin. 5FU is a good option for trans buccal, vaginal, and rectal drug delivery systems because of these issues.

Since fluorouracil has a limited permeability, permeability must be increased. The thin film hydration process is used to create liposomes, which are then further described and assessed. When fluorouracil reaches the gastrointestinal tract (GIT), it undergoes first-pass metabolism and produces toxic effects that harm normal cells. To counteract this effect, buccal films are made using the solvent casting process. The medicine diffuses straight into the systemic circulation through the jugular vein when it is delivered buccal. It was discovered that the polymer ratio was 4.9:2.5 (F4), using HPMC and SCMC. In terms of weight, thickness, surface pH, % moisture absorption and loss, folding endurance, drug content, and diffusion investigations, the F4 formulation performs satisfactorily. Buccal films have the ability to regulate the release over a ten-hour period. The Buccal film formulation improves the drug's bioavailability, lowers cytotoxicity, avoids first pass metabolism, reduces the frequency of doses, and prevents gastrointestinal discomfort.

Key words: 5-fluorouracil, anti-cancer drug, Buccal film, mouth dissolving film, HPMC

1. INTRODUCTION

The buccal route was the best option when compared to injectables and parenteral, and it has a number of benefits over other methods. In the same way that the parenteral route has poor patient compliance, allergy, and some other infections, it also gives great bioavailability. Patients may experience some inconvenience when using the parenteral method. This allows for the quick release of medication at the desired area, where it is absorbed, disseminated, and readily metabolised. As a result of this restriction, alternate administrative paths are created. Buccal mucosa has an absorptive role and provides several advantages, such as avoiding the first pass effect, which was a noninvasive method, increasing bioavailability, enabling a quick action, and lowering adverse effects (5).

In the oral cavity, the buccal, sublingual, palatal, and gingival regions exhibit efficient drug delivery. The most common medication delivery routes for treating both local and systemic effects are buccal and sublingual. The oral mucosa's permeability indicates the tissues' physical characteristics. When a quick beginning of effect was required, the buccal mucosa, which was thinner and had a high blood flow and surface area, was a viable location. The sublingual mucosa was the permeable region. Although the sublingual route was favoured for treating acute diseases, its surface rinsed by saliva, which made formulation in the oral cavity difficult.

These days, mucoadhesive drug delivery systems are a hot topic for study. These are delivery systems that make use of some polymers' bioadhesion properties. Compared to conventional methods, mucoadhesive buccal drug delivery systems are easier to use, can be quickly stopped in the event of toxicity by removing the dosage from the buccal cavity, and can be used to give medication to patients who are unable to take it orally. The design and assessment of buccal medication

delivery systems have received a lot of attention lately due to its potential for the future market. Therefore, it is necessary to create and optimise a buccal medication delivery system.

The mechanism of the polymer-mucus contact that results in muccoadhesion has been explained by a number of ideas. Intimate contact between the bioadhesive polymer and the biological tissue during appropriate wetting of the bioadhesive surface and bioadhesive swelling, as seen in Figure 2, is the first of the sequential processes that take place during bioadhesion. Subsequently, the bioadhesive polymer chain and the mucus chains interpenetrated the tissue, allowing the bioadhesive to penetrate. Low chemical bonds may then start to function.

2. MATERIALS AND METHODS

Apparatus and chemicals: 5 Fluorouracil by M/s Vopec Pharmaceuticals Chennai, Lecithin by Cipla, Pithampur, Aspartame, Mannitol by S.D.Fine Chem. Ltd., India, Hydroxy Propyl Cellulose by Loba Chemie, Mumbai.

Methods: Solvent casting is the most commonly used method for the preparation of ODFs using water soluble excipients, polymers and drug which are dissolved in de-ionized water; consequently, a homogenous mixture is obtained by applying high shear forces generated by a shear processor. Then, the prepared solution is poured onto petri plate and the solvent is allowed to dry by exposing it to high temperature in order to attain good quality films. An orodispersible film of tianeptine sodium was successfully prepared through solvent casting technique using different grades of Lycoat and HPMC. In solvent casting technique, film forming polymer is usually soaked in an appropriate solvent for overnight.

3. EXPERIMENT

3.1 Preparation of liposomal

Formulation of Buccal Films

The HPMC and SCMC polymers were selected for the Buccal film due to their excellent flexibility, plasticity, and sophisticated look, as demonstrated by the placebo study. The solvent casting process was used to create buccal film filled with FU liposomes. Using a magnetic stirrer, precisely weighed HPMC was dissolved in 10 millilitres of water and stirred for 15 minutes. After dissolving SCMC separately in 10 millilitres of water, the two polymeric solutions were completely combined and heated to 60 degrees Celsius for forty-five minutes. Liposomes were added to the polymeric solution in an amount equal to 20 mg of 5FU. As plasticisers, sweeteners, and flavourings, respectively, propylene glycol, sorbitol, and menthol were employed. For 24 hours, the prepared solution was cast on a Petri dish and heated to 40°C.

Table 1: Composition of Buccal Films

INGREDIENTS	F1	F2	F3	F4	F5
Liposomal suspension equivalent to 20 mg of 5FU	20	20	20	20	20
HPMC (%)	1	2	4	4.9	6
SCMC (%)	1.5	2	2.5	1.5	2.5
Propylene Glycol (ml)	0.4	0.4	0.4	0.4	0.4
Sorbitol (ml)	1	1	1	1	1
Menthol (ml)	0.5	0.5	0.5	0.5	0.5

3.2 Preformulaion study

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. These studies are designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical and analytical investigation in support of promising experimental formulations.

3.2.1 Melting point determination

Melting point of drug was determined by Open capillary method.

3.2.2 Determination of λmax

Using a phosphate buffer with a pH of 6.8, the 5-fluorouracil standard curve is calculated at 266 nm using a UV spectroscopic technique. The linearity is determined to be r2 = 0.9989 and y = 0.0521x-0.0027.

4. RESULTS AND DISCUSSION

4.1 Preformulation Studies

4.1.1 Description of Drug

Visual observations were made on the 5 Fluorouracil's appearance. It was discovered to be a white powder that conforms with IP.

4.1.2 Solubility:

Five Fluorouracil medication solubility tests were conducted. According to the solubility study's findings, 5-fluorouracil dissolves somewhat in chloroform and is soluble in water and 95% ethanol at room temperature.

4.1.3 Drug polymer compatibility study:

Drug, lipid, and polymer FTIR spectra were captured, and the corresponding peaks were assessed. Figures 13 through 17 show the outcomes.

The peak values derived from spectra under stressful conditions demonstrate that the excipient has no effect on the drug's distinctive peaks. There was no discernible shift in the relative intensities or peak location of the drug's endothermic peak. This suggests that the medication and polymer are not interacting.

5 Fluorouracil -FTIR Spectrum

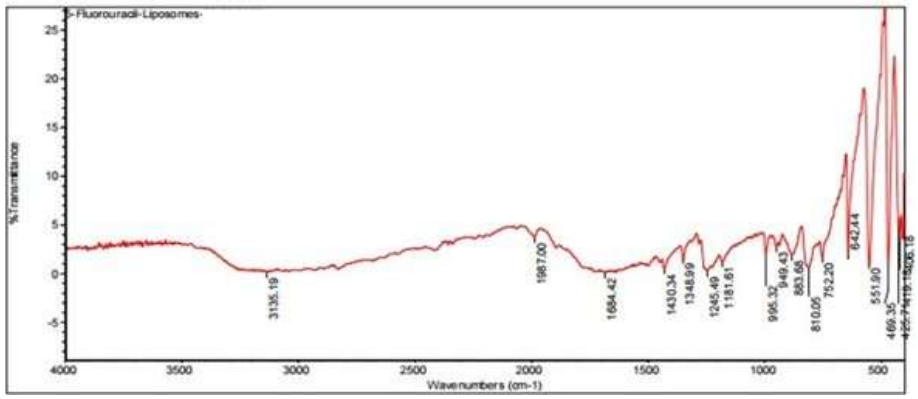


Fig 1: 5 Fluorouracil FTIR Spectrum

Table 2: Interpretation of FTIR Spectrum of 5 Fluorouracil:

S.no	Peak Value	Characteristics functional group
1.	C-F	469
2.	C-H	1245
3.	C=C	1684
4.	C-N	1430
5.	N-H	3135

The buccal film was clean and translucent overall upon visual inspection, indicating that the medication is evenly dispersed throughout the film. The film's surface was smooth, and its structure was exquisite.

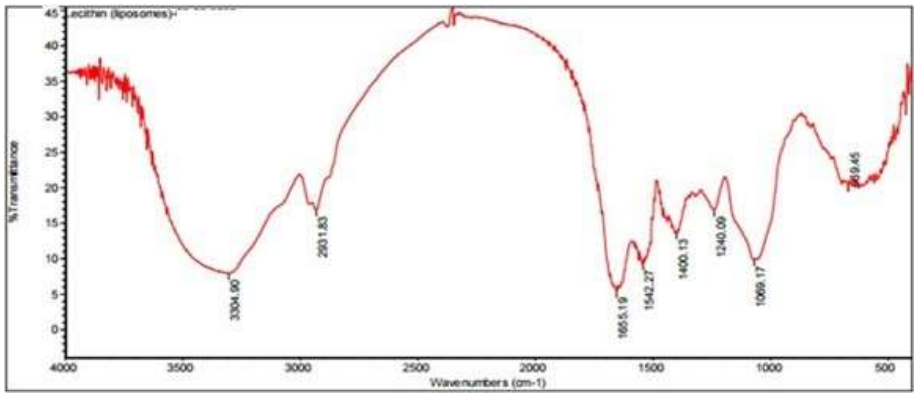


Fig 2: FTIR Spectrum of Lecithin

Table 3: Interpretation of FTIR Spectrum of Lecithin:

S.no	Peak Value	Characteristics functional group
1.	C=O	1655
2.	C-OH	1400
3.	C-O	1240
4.	C-C	1069
5.	CH_2	694

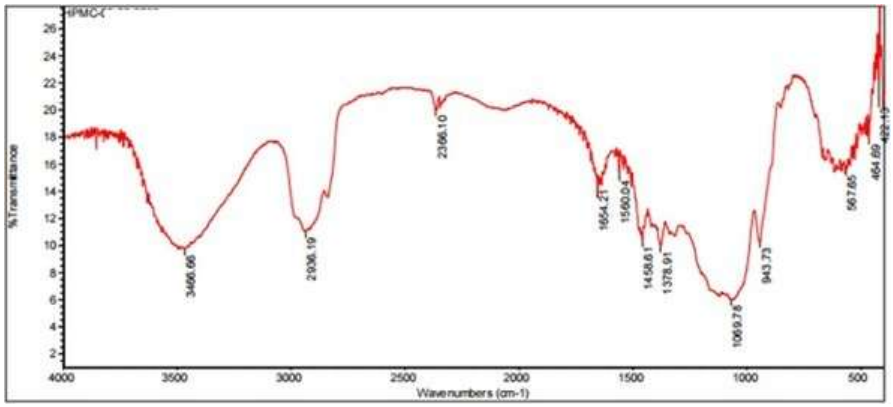


Fig 3: FTIR Spectrum of HPMC

Table 4: Interpretation of FTIR of HPMC:

S.no	Peak Value	Characteristics functional group
1.	O-H	3466
2.	C-H	2936
3.	C=O	1654
4.	C-0	1069
5.	CH2	694

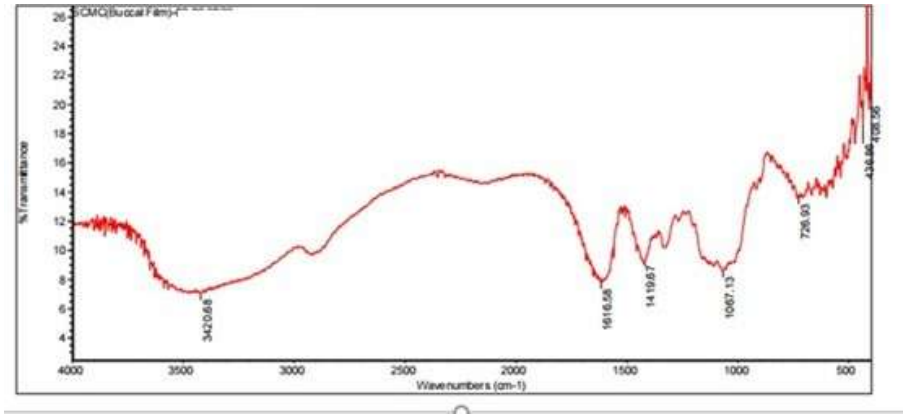


Fig 4: SCMC FTIR Spectrum

Table 5: Interpretation of FTIR Spectrum of SCMC

S.no	Peak Value	Characteristics functional group
1.	O-H	3420
2.	COOH	1616
3.	COO	1419

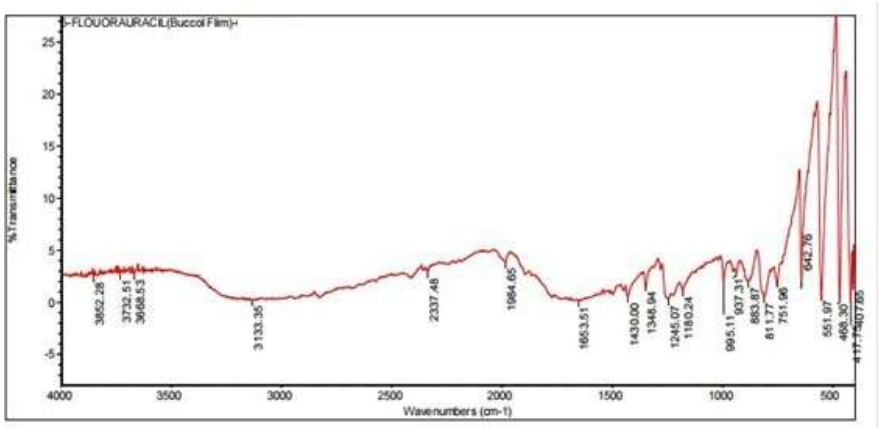


Fig 5: FTIR Spectrum of 5-FU Buccal Film:

Table 6: Interpretation of FTIR Spectrum of Formulation

S.no	Peak Value	Characteristics functional group
1.	C-F	468
2.	C-H	1245
3.	C=C	1653
4.	C-N	1430
5.	N-H	3133

The potential interactions between 5Fu and lecithin in the liposomal formulation were investigated using FTIR Spectroscopy. The pure drug's FTIR spectrum shows a distinctive peak at around 3135 cm-1 for N-H stretching, 1245 cm-1 for C-H stretching, 1684 cm-1 for C=C stretching, 1430 cm-1 for C-N stretching, and C-F stretching of the 5-fluorouracil uracil ring.

C-OH exhibited the largest peak in the lecithin spectrum at 1400 cm-1, followed by C-C stretching at around 1060 cm-1, C-O stretching at about 1239 cm-1, and C=O stretching at about 1600 cm-1.

The main peak in the HPMC spectrum was located at 3466 cm-1 for O-H, C-H stretching at around 2939 cm-1, CH2 stretching at about 694 cm-1, and C=O stretching at about 1654 cm-1.

The main peak in the SCMC spectrum was located at 3420 cm-1 for O-H, with COOH stretching at around 1616 cm-1 and COO stretching at about 1419 cm-1.

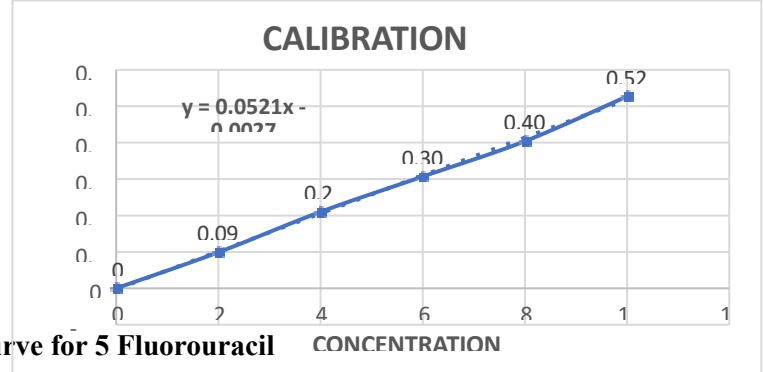
N-H stretching was detected near 3133 cm-1, C-H stretching was detected near 1245 cm-1, C=C stretching was detected near 1653 cm-1, C-N stretching was detected near 1430 cm-1, and C-F stretching of the uracil ring of 5-fluorouracil was detected around 468 cm-1, according to the formulation's FTIR spectrum.

The main peaks of 5-FU are easily evident in the spectrum of formulation, which seems to be an overlay of the distinct spectra with the peaks appearing in their proper places. The aforementioned findings demonstrate that the medicine and formulation excipients do not interact and that there is no discernible difference between the FTIR spectra of the two.

4.1.4 Calibration Studies

Table 7: Value for calibration Curve of 5 FU

S.no	Concentration (µg\ml)	Absorbance(nm)
1	2	0.099
2	4	0.162
3	6	0.307
4	8	0.392
5	10	0.527



GRAPH 1: Calibration curve for 5 Fluorouracil

Using a phosphate buffer with a pH of 6.8, the 5-fluorouracil standard curve is calculated at 266 nm using a UV spectroscopic technique. The linearity is determined to be r2 = 0.9989 and y = 0.0521x-0.0027**.**

5. EVALUATION OF BUCCAL FILM:

5.1 Appearance of the film

The buccal film was clean and translucent overall upon visual inspection, indicating that the medication is evenly dispersed throughout the film. The film's surface was smooth, and its structure was exquisite.

5.2 Film Morphology

The shape and surface characteristics of 5-Fluorouracil liposomal film was assessed by

SEM

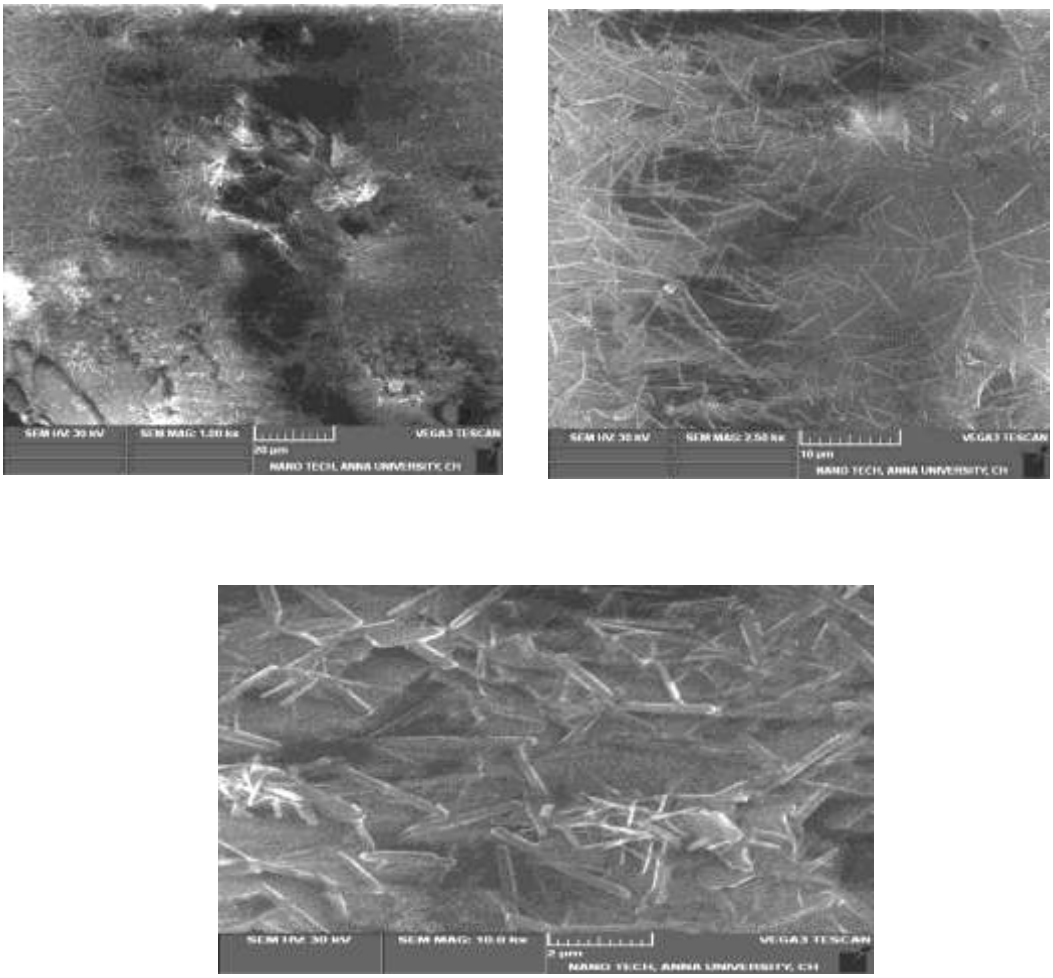


Fig 6: SEM IMAGES OF LIPOSOMAL LOADED BUCCAL FILMS

The Buccal film formulation's morphology is seen in the SEM photographs. The optimised film has an uneven texture, looks slightly rough, and is tortuous. Nevertheless, the typical micrograph showed no obvious holes or fissures, which are required to regulate the hydration and release of medication molecules.

The micrographs' lack of drug crystals indicated that the drug particles were evenly distributed throughout the polymer matrix. In fact, the drug-entrapped film's exterior features possessed the right surface morphology, making it suited for buccal administration.

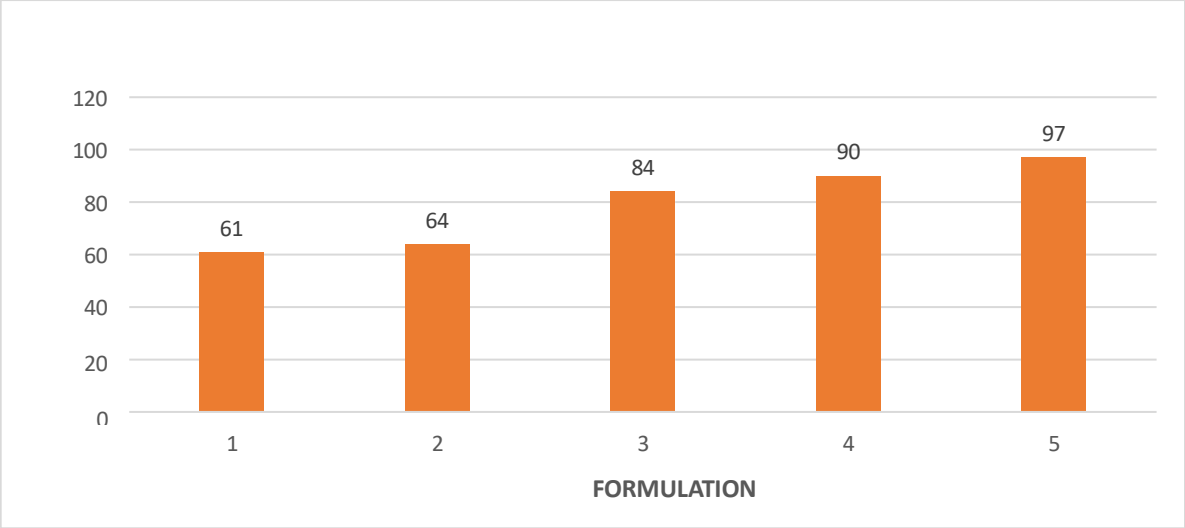
5.3 Weight of the film

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

Table 8: Weight of the buccal film

Formulation	Weight (mg)
F1	61±0.89
F2	64±0.74
F3	90±0.80
F4	90±0.48

F5	97±0.48



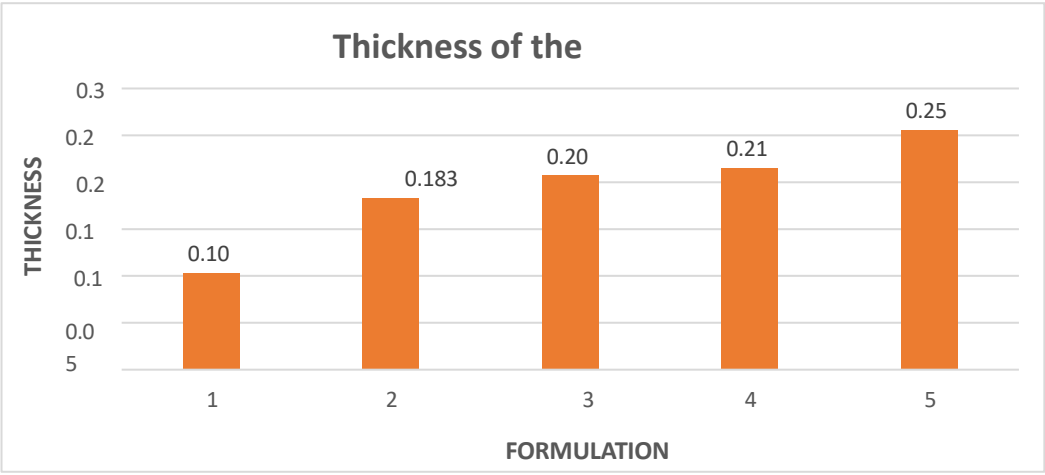
Graph 7: Weight of the buccal films

5.4 Thickness of the film

Thickness is measured by calibrated digital vernier Caliper. The thickness was measured at different spots of the film and average was taken. The film thickness ranged from 0.366 to 0.498 mm.

Table 9: Thickness for buccal film

Formulation	Thickness (mm)
F1	0.103±0.013
F2	0.183±0.007
F3	0.207±0.014
F4	0.215±0.008
F5	0.256±0.036



Graph 8: Thickness for buccal film

5.5 Surface pH study

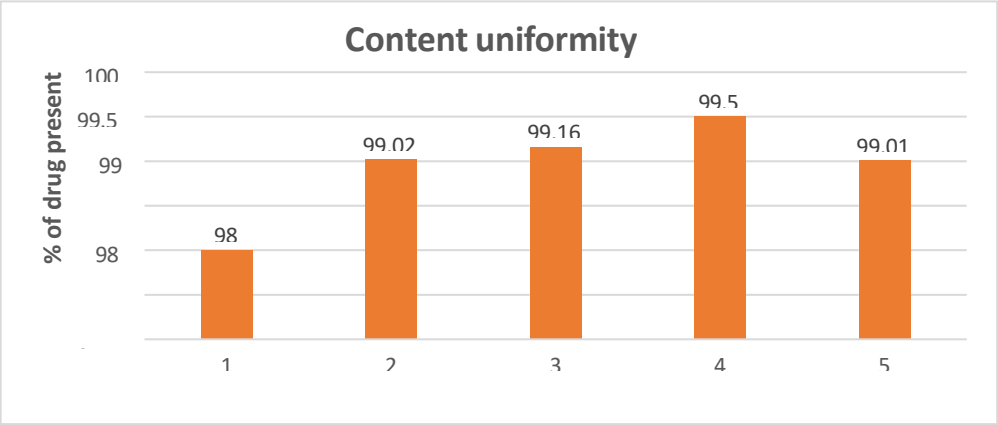
The surface pH study was performed by using distilled water and pH were measured, which suggests that the surface pH of all films was found to be uniform within the salivary range (pH 6.6). This suggests that the films would show no irritation within the surface of mucosa and therefore is suitable for the buccal administration.

5.6 Content uniformity of film

To ensure uniform distribution of drug within the buccal film, content uniformity test was performed.

Table 10: Content uniformity for buccal films

Formulation	Drug content
F1	98.0±1.0
F2	99.02±0.11
F3	99.16±0.29
F4	99.50±0.50
F5	99.01±0.05



Graph 9: Drug Uniformity for buccal films

The drug content of all formulation was determined using a UV Spectroscopy at 266nm. The drug content was found to be in the range of 98.00-99.5%. It indicates negligible drug loss from the film.

5.7 Percentage moisture absorption and loss

The percentage moisture absorption test was carried out to ensure physical stability or integrity of buccal films.

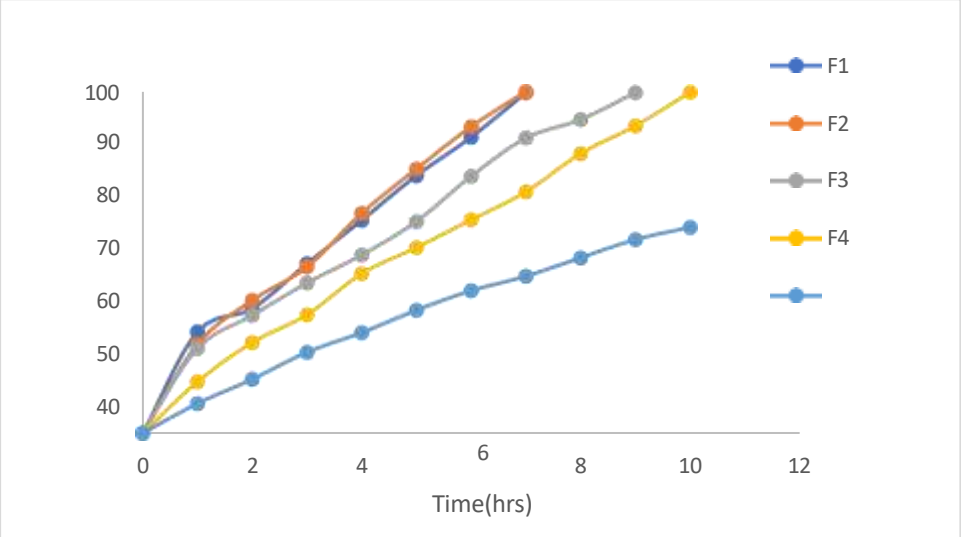
5.8 Ex vivo permeation studies of buccal films:

The drug permeation data for various 5 Fluorouracil buccal film formulation was given below in table

Table 11: Ex vivo permeation of 5 Fluorouracil buccal films

S.NO	Time in (hrs)	F1 %	F2 %	F3 %	F4 %	F5 %
0	0	0	0	0	0	0
1	1	29.63	26	24.8	15.01	8.67

2	2	36.45	38.86	34.43	26.52	15.78
3	3	49.54	48.59	43.9	34.63	23.67
4	4	62.26	64.28	52.12	46.65	29.41
5	5	75.29	77.28	61.9	54.28	35.98
6	6	86.56	89.65	75.11	62.39	41.67
7	7	99.56	99.87	86.32	70.56	45.9
8	8	-	-	91.7	81.78	51.3
9	9	-	-	99.6	89.87	56.6
10	10	-	-	-	99.67	60.2



Graph 10: Ex vivo permeation of 5 Fluorouracil buccal films

Table 12: Data analysis for permeation of buccal films

FORMULATION	Jss mg/cm^{2}h	ER fllux	Tlag, h
Control	1.1106	-	2.07
F4	9.4802	8.53	0.36
F5	7.917	7.12	0.60

Conclusion

The Jss o 5-Fluorouracil from F4 was found 9.4802 Jss mg/cm2h, the result indicates 8.53 times higher than compared to free drug. The study confirms that amount of polymers in buccal film formulation plays an essential role in the physicochemical properties and permeability through Goat buccal skin.

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