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Research Article

FORMUALTION AND DEVELOPMENT OF MUCOADHESIVE SUSTAINED RELEASE BUCCAL TABLETS AND PATCHES OF 5-FLUOROURACIL USING DIFFERENT POLYMERS

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ABSTRACT

Objective: The present research study was undertaken to formulate mucoadhesive sustained release buccal tablets and patches of 5-fluorouracil (5-FU).

Method: For the research experiment work design expert software version 10, stat-ease, Inc. has been used. A 3^2 full factorial design was selected for the formulation of the buccal tablet as well as buccal patches. In this research work, formulated tablets and patches using different polymers such as carbopol 974p, polyvinylpyrrolidone-K 30, sodium deoxycholate, microcrystalline cellulose, and polyvinyl alcohol. An after formulation of batches formulated products studied for characterization, namely, Fourier transform infrared (FTIR) and differential scanning calorimeter (DSC). Evaluation parameters studied such as weight uniformity, thickness, hardness, friability, and content uniformity also carried out. For drug release purpose from the formulation of buccal tablet and patches *in vitro* drug released performed. *In vivo* drug releases study also carried out using Rabbit for drug reaction point of view.

Results: Design expert showed the significant results on independent and dependent variables. The R-Squared 0.9943 for drug release and 0.9985 for swelling index is in reasonable agreement with the formulations. FTIR and DSC indicating compatibility of the drug and polymers in the tablet formulation and patch formulations at the molecular level. The drug release of buccal tablet showed 75.10–99.34% and buccal patches showed 58.41–81.43%. These formulations showed good results when compared to the conventional tablet.

Conclusion: Formulation of mucoadhesive sustained release buccal tablets and patches of 5-FU successfully done using different polymers, which would definitely help in increasing bioavailability of the drug.

Keywords: Mucoadhesive sustained release, 5-Fluorouracil, Carbopol 974p, Polyvinylpyrrolidone-K 30, *In vitro* drug release, *In vivo* drug release.

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INTRODUCTION

Among the various routes of drug delivery, the oral route is perhaps the most preferred to the patient and the clinician alike. However, administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the gastrointestinal (GI) tract, that prohibit oral administration of certain classes of drugs [1]. Bioadhesive drug delivery formulations were introduced in 1947 when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa [2]. Buccal delivery of drugs provides an attractive alternate to other conventional methods of systemic drug administration since buccal mucosa is relatively permeable with rich blood supply and acts as an excellent site for the absorption of drugs. The administration of drugs through buccal route facilitate a direct entry of drug molecules into the systemic circulation, avoiding the first-pass metabolism and drug degradation in the harsh GI environment, which are often associated with oral administration. The buccal cavity is easily accessible for self-medication, and hence, it is safe and well accepted by patients since buccal patches can be very easily administered and even removed from the application site, terminating the input of drug whenever desired. Moreover, buccal patches provide more flexibility than other drug deliveries [3]. Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the middle of the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period [4].

The oral mucosa has many properties, which not only makes it an attractive site for drug delivery but also provides several challenges for researchers investigating novel delivery techniques to overcome many different formulations including sprays, tablets, mouthwashes, gels, pastes, and patches are presently used for delivery into and/or across the oral mucosa [5].

In recent years, delivery of therapeutic agents through mucoadhesive drug delivery system has become highly interesting. Certain drugs have the lack of efficacy due to decreased bioavailability, GI intolerance, unpredictable, and erratic absorption or presystemic elimination of other potential route for administration. The recent development in the drug delivery has intensified the investigation of mucosal drug delivery. Such route includes oral, buccal, ocular, nasal, and pulmonary routes, etc. Mucoadhesive drug delivery systems are delivery systems, which utilized the property of bioadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for an extended period. The ability to maintain a delivery system at a particular location for an extended period has great appeal for both local as well as systemic drug bioavailability. Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because it provides the possibility of avoiding either destruction by GI contents or hepatic first-pass inactivation of the drug [6,7].

5-Fluorouracil (5-FU) is a medication used to treat cancer. By injection into a vein, it is used for colon cancer, esophageal cancer, stomach cancer, pancreatic cancer, breast cancer, and cervical cancer. When used by injection most people develop side effects. Common side effects include inflammation of the mouth, loss of appetite, low blood

cell counts, hair loss, and inflammation of the skin [8]. When used as a cream irritation at the site of application may occur [9]. The use of either form in pregnancy may harm the baby. FU is in the antimetabolite and pyrimidine analog families of medications [10,11]. How it works is not entirely clear but believed to involve blocking the action of thymidylate synthase and thus stopping the production of DNA. FU has been given systemically for anal, breast, colorectal, esophageal, stomach, pancreatic, and skin cancers (especially head-and-neck cancers). It has also been given topically (on the skin) for actinic keratoses, skin cancers, and Bowen's disease [12] and as eye drops for the treatment of ocular surface squamous neoplasia [13].

The present research study was undertaken to formulate mucoadhesive sustained release buccal tablets and patches of 5-FU using different polymer and excipients.

MATERIALS AND METHODS

Materials

5-FU, polyvinyl alcohol, talc, and sodium deoxycholate was procured from ozone international, Mumbai. Carbopol 974p, polyvinylpyrrolidone K30 was procured from Wockhardt Ltd, Aurangabad. Microcrystalline cellulose was procured from RanQ remedies Pvt. Ltd., Pune. All other ingredients were used for laboratory scale.

Methods

Formulation and preparation of mucoadhesive buccal tablets of 5-FU

The mucoadhesive buccal tablets were prepared by a direct compression method using direct compression (Cadmach, Ahmadabad). The mucoadhesive drug/polymer mixture was prepared by homogeneously mixing the carbopol 974P, polyvinylpyrrolidone (PVP) K-30, complex (CP+PVP), sodium deoxycholate, microcrystalline cellulose, and Talc. All the ingredients of the mucoadhesive buccal tablet of 5-FU were weighed (Table 1) sifted and mixed in mortar with the help of pastel. The 150 mg mixture was then compressed using 8 mm punch in a single stroke on single punch tablet machine. Each tablet weighed 150 mg [14].

Experimental design

For the research experiment work design expert software version 10, stat-ease, Inc. has been used. A 3^2 full factorial design was selected because an experiment may be designed to focus attention on a single independent variable or factor. An alternative approach is to study the influence of one independent variable in conjunction with variations in one or more additional independent variables. In this research study, not only the effects of the two independent variables separately but also how they combine to influence the dependent variable. The amount of carbopol (X1) and the amount of polyvinylpyrrolidone (X2) were selected as independent variables. Two-factor (X1, X2), three-level (−1, 0, +1) design can be developed. Two-factor were evaluated each at three-level, and experimental trials were performed for all nine possible combinations. *In vitro* drug release and mucoadhesion were selected as dependent variables. The actual and coded formulation design of swellable gastro-retentive tablets according to factorial design (3^2) layout is shown in Tables 2 and 3 [15].

Formulation and preparation of mucoadhesive buccal patches of 5-FU

The calculated amount of polymer was dissolved in distilled water with magnetic stirring for 24 h, and then, the drug (5-FU) was incorporated into the polymeric solution with continuous stirring. The desired quantity of the plasticizer (propylene glycol) was added and kept aside for 1 h at room temperature. The mixture of the polymeric solution and drug of all formulas was poured on aluminum foil in a glass petri dish having 15 cm diameter. The petri dishes were kept on leveled surface and covered by inverted funnel to allow controlled evaporation of solvent at room temperature until a flexible patch was formed. Dried patches were carefully removed, checked for any imperfections or air bubbles and cut into small patches. The patch was packed in aluminum foil and stored in desiccator to maintain the integrity and elasticity of the patches. The composition of buccoadhesive patches is listed in Table 4 [16].

Characterization

Fourier transform infrared (FTIR)

The FTIR (IR-Affinity 1S, Shimadzu) spectra of drug, polymers, and formulations were recorded using KBr pellet method. The materials were triturated in porcelain mortar pestle with dry potassium bromide in the ratio (1:100). The pellets were prepared in KBr press at pressure 8 tones. The pellet was scanned over the range of 4000–600/cm and the spectra obtained were reported [17].

Differential scanning calorimeter (DSC)

DSC was performed on drug, polymers, and formulations. The physical mixtures of drug, polymers, and formulations were prepared by triturating (1:1) in a dried mortar for 5 min and kept as it is for 24 h. The materials were weighed, 2–7 mg and sealed in aluminum pans. The sealed aluminum pan was heated at a scanning rate of 20°C/min over a temperature range of 90 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the drug, and drug-polymer mixture [18].

Evaluation parameters for buccoadhesive dosage form

Uniformity weight of tablet and patch

Twenty tablets were selected at random from each batch, weighed individually, and the average weight was calculated. The batch passes the test for uniformity of weight if not more than two of the individual tablet weight deviates from the average weight by more than the 7.5% as shown in Table 5.

Each patch was weighed individually on an analytical balance (Shimadzu. AUX220, Japan) and the average weights were calculated [19,20].

Thickness

The thicknesses of buccal tablets were determined using digital vernier caliper (Mitutoyo, Japan) and the average was calculated. Ten individual tablets and patches from each batch were used and the average thickness was calculated [21].

Friability

The friability of the 6 tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasion sand shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions [22]. Tablets were de-dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F=(1-W0/W)\times 100 \quad \text{Eq. (1)}$$

Where,
W0 is the weight of the tablets before the test
W is the weight of the tablet after the test.

Hardness

Pfizer hardness tester (Monsanto Rolex) was used for the determination of the tablets hardness. For each formulation the hardness of 6 tablets was evaluated [22].

Surface pH study

The surface pH of the buccal tablet was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping

Table 1: Composition of 5-fluorouracil mucoadhesive buccal tablet

Ingredients (mg)	Formulation batches								
	FT_1	FT_2	FT_3	FT_4	FT_5	FT_6	FT_7	FT_8	FT_9
5-fluorouracil	20	20	20	20	20	20	20	20	20
Complex (CP+PVP)	80	80	80	80	80	80	80	80	80
Carbopol	5	12.5	5	5	12.5	20	20	12.5	20
Polyvinylpyrolidone	12.5	20	20	5	12.5	12.5	5	5	20
Sodium deoxycholate	3	3	3	3	3	3	3	3	3
Microcrystalline cellulose	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5

PVP: Polyvinylpyrrolidone

Table 2: Experimental range and levels of the independent variables

Coded values	Actual values (% w/w)	
	Carbopol (X_1)	Polyvinylpyrrolidone (X_2)
−1	5	5
0	12.5	12.5
+1	20	20

Table 3: Presentation of real values of 3 levels for the statistical design

S. No	Batch	Variable levels in coded form	
		Carbopol (X_1)	Polyvinylpyrrolidone (X_2)
1	FT1	−1	0
2	FT2	0	1
3	FT3	−1	1
4	FT4	−1	−1
5	FT5	0	0
6	FT6	1	0
7	FT7	1	−1
8	FT8	0	−1
9	FT9	1	1

it in contact with 1 mL of phosphate buffer (pH 6.8) for 2 h at room temperature. The pH was identified by bringing the electrode into contact with the tablet surface and allowing the surface to equilibrate for 1 min [23,24].

Swelling study

Buccal tablets and patches were weighed individually; initial weight was considered as W1 and placed separately in Petri dishes containing 10 mL of phosphate buffer (pH 6.8) solution in such a way that the side of tablet and patch, which attaches to the buccal membrane was positioned to the bottom of the petri dishes with the backing membrane being viewable from the top. Tablets and patches were soaked in such a way that they completely immersed in the buffer solution. At time intervals of 12 h, the buccal tablets and patch were removed from the petri dishes using coverslips and excess surface water was removed carefully using the Whatman filter paper. The swollen tablets and patches were then reweighed (W2). This experiment was performed in triplicate [25]. The degree of swelling (water uptake) was calculated according to the following formula:

$$\text{Degree of swelling} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \qquad \text{Eq.(2)}$$

Drug content uniformity

Five tablets were selected at random and were powdered in a mortar; and the amount of powder equivalent to single dose was dissolved in phosphate buffer pH 6.8 up to 10 ml by sonication (Dolphin, Mumbai) for 15 min and filtered through Whatman filter (0.45 µm) paper. The drug content was analyzed spectrophotometrically at 261.4 nm using a UV spectrophotometer (Shimadzu 1601). Each measurement was carried out in triplicate and the average drug content was calculated.

Drug content uniformity was determined by dissolving the patch in 100 ml of phosphate buffer (pH 6.8) for 24 h with stirring. From the solution 5 ml was diluted with the drug content was then determined after proper dilution of the filtered solution at 266 nm using a UV spectrophotometer [26].

Ex vivo mucoadhesive strength and force of adhesion

A modified balance method was used for determining the *ex vivo* mucoadhesion strength. Goat buccal mucosa was used as the model substrate, and phosphate buffer pH 6.8 was used as the moistening fluid. Freshly excised goat buccal mucosa was obtained from the local slaughterhouse used within 3 h of slaughter. The tablet and patch were laid onto the model membrane under a manual pressure of 5 min. Bioadhesive strength was measured in terms of weight in grams of water required to detach the tablet and patch from the goat buccal mucosa. The addition of water was stopped when tablet and patch was detached from goat buccal mucosa. The weight of water required to detach the tablet and patch, respectively, from buccal mucosa was noted as *ex vivo* mucoadhesive strength. Mucoadhesive strength was performed in duplicate, and average mucoadhesive strength was determined [23]. From this mucoadhesive strength, the force of adhesion was calculated using the following formula.

$$\text{Force of adhesion } (\text{N}) = \frac{\text{Mucoadhesive strength}}{100} \times 9.81 \qquad \text{Eq. (3)}$$

Ex vivo mucoadhesive time

The *ex vivo* mucoadhesion time studies were performed after application of tablet and patch, respectively, on freshly cut goat stomach mucosa. The mucosa was fixed on a glass slide using double-sided adhesive, and one side of glass slide was fixed to thread whose another end was fixed with the arm of tablet disintegration test apparatus. A side of each tablet and patch was wetted with dissolution medium and was attached to the mucosa by applying a light force with a fingertip for 20 s. The beaker was filled with 800 mL of phosphate buffer of pH 6.8 maintained at 37±0.50°C were used as disintegration medium and after 2 min the slide was placed in a beaker, and the apparatus was started. Care was taken that while up and down motion of the arm tablet and patch should remain in the medium. Behavior and mucoadhesive time of tablet and patch were monitored until complete detachment occurred [21].

Folding endurance

Randomly selected three films from each batch were taken to measure the folding endurance. The films were repeatedly folded at the same place until it broke. The films folded up to 300 times manually was considered satisfactory value. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance [27].

Table 4: Composition of preliminary batches for formulation of buccal patches

Ingredients	FP-1	FP-2	FP-3	FP-4	FP-5	FP-6	FP-7	FP-8	FP-9
5-fluorouracil (mg)	200	200	200	200	200	200	200	200	200
Carbopol 974p (mg)	100	100	33.5	66.5	66.5	33.5	33.5	100	66.5
PVP k30 (mg)	33.5	100	66.5	33.5	100	33.5	100	66.5	66.5
PVA (g)	5	5	5	5	5	5	5	5	5
PEG (ml)	30	30	30	30	30	30	30	30	30
Ethanol (ml)	20	20	20	20	20	20	20	20	20
Water (ml)	150	150	150	150	150	150	150	150	150

PVP: Polyvinylpyrrolidone, PEG: Polyethylene glycol, PVA: Polyvinyl alcohol

Table 5: Limits of percentage deviation allowed underweight variation test

Average weight of tablet	% Deviation
80 mg or less	10
80 mg <×<250 mg	7.5
250 mg or more	5

Tensile strength (TS) measurement

Dried patch samples were cut into uniform strips (2.5 cm×5 cm). Two pieces of cardboard (1 cm×2.5 cm) were attached to the upper and the lower end of the patch using cyanoacrylate resin adhesive. Attaching the patch to the cardboard facilitates clamping it to the jaws of the modified device used for TS measurement, thus preventing pressure on the patches and slipping before or during application. The modified device contains a rectangular frame with two jaws made up of aluminum. One jaw is stationary in the front, and the other one is movable and can be pulled by loading weights on the pan attached with string to the movable part. The patch on the cardboard was clamped between the two jaws of the device positioned at a distance of 3 cm. The weights were gradually added to the pan until the patch was broken. The weight necessary to break the patch was noted as breaking force, and the simultaneous distance traveled by the pointer on the graph paper indicated the elongation at break (E/B) [28]. TS and percent elongation can be obtained by following formula:

$$\text{Tensile strength} = \frac{\text{Force at break (N)}}{\text{Initial cross sectional area of the sample } (\text{mm}^2)} \quad \text{Eq. (4)}$$

$$\text{Elongation percent} = \frac{\text{Increase in length}}{\text{Original length}} \times 100 \quad \text{Eq. (5)}$$

Ex vivo permeation study

Permeation study was carried out for the optimized formulation using Franz diffusion cell. The tablet and patches, respectively, were placed in the donor compartment on the sheep mucosa. The mucosal layer is on donor compartment. The receptor compartment was filled with phosphate buffer pH 6.8. The temperature was maintained at 37±0.5°C and 50 rpm. The amount of 5-FU permeated through sheep mucosa was determined by withdrawing 3 ml of aliquots from the receptor compartment using a syringe and immediately replacing the same volume of the solution [14].

In vitro drug release buccal tablets

The United States pharmacopoeia (USP) type II dissolution apparatus (Veego Scientific DA6D, Mumbai) was used to study the release of drug from buccal tablets. Tablets were supposed to release the drug from one side only; therefore, an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2 cm × 2 cm glass slide with a solution of cyanoacrylate adhesive. *In vitro* drug release studies were carried out in 900 ml of phosphate buffer solution pH 6.8 for 10 h at 100 rpm and 37±0.5°C. At predetermined time intervals, 1 ml of samples were withdrawn and replaced with 1 ml fresh medium. The samples were filtered, diluted suitably then analyzed spectrometrically at 266 nm [28]. All dissolution was performed in triplicate.

In vitro drug release buccal patches

The drug release study from the patches was carried out using a USP 23 Type 2 rotating paddle dissolution test apparatus (Electrolab). A total of 250 ml of solution (pH 6.8) at 37°C±5°C was used as the dissolution medium with a stirring rate of 50 rpm. A patch of 2.5 cm diameter was fixed onto a glass disc with the help of cyanoacrylate adhesive. The disc was put at the bottom of the dissolution vessel such that the patch remained on the upper side of the disc. Samples (5 ml) were withdrawn at a predetermined time interval of 30 min and replaced with an equal volume of dissolution medium. The samples were filtered through a 0.45 mm filter and appropriately diluted with SHS solution (pH 6.8) and assayed spectrophotometrically at 266 nm [28]. The experiment was performed in triplicate, and average values were reported.

In vivo drug release study for tablets and films

Six male New Zealand white rabbits (2.6 kg) were selected for the *in vivo* study. The dose of 5-FU was adjusted based on the rabbit weight, and the optimized formulations were cut and placed in the buccal membrane with the help of a clip and tablets placed in the buccal membrane with the adhesive layer. Dextrose solution was transfused continuously throughout the period of the study. Periodically, 1 ml of blood sample was taken by syringe containing 1 ml of heparin solution to prevent blood clotting. These blood samples were centrifuged at 2500 rpm for about 30 min. One milliliter of the supernatant was taken, and after suitable dilution analyzed at 266 nm spectrophotometrically by the method described under *in vitro* analysis [29,30].

Stability studies

Stability studies were carried out on the formulation, according to the ICH guidelines. The optimized formulations were selected, and the stability studies were carried out at the accelerated condition of 40±2°C, 75±5% RH conditions, stored in desiccators, the formulations were packed in amber color screw cap container and kept in above-said condition for 3 months. The formulations were analyzed periodically for their physical appearance, buccoadhesive strength, and *in vitro* drug release [29,31].

RESULT AND DISCUSSION

Evaluation parameters for factorial batches (tablet formulation)

The evaluation parameters of tablets and patches are given in Tables 6 and 7, respectively. The friability found in tablet formulations shows a good strength of tablets to withstand abrasion during transportation and general handling.

The hardness of all tablet batches was in the range of 3.1–4.2 kg/cm^2. Such hardness range is enough to give mechanical strength indicating good compressibility of blends. The content uniformity of drug is found in tablet between 97.98–99.87% and 90–99% in patch formulation.

Characterization

FTIR

The IR spectrum of pure drug, polymers and physical mixture are used to establish the characteristic behavior of the drug and in its formulations. The pure drug 5-FU Figs. 1a and 2a shows peaks at 3500/cm to N-Hstretching, at 3100/cm to C-Hstretching (aromatic), at 2800/cm to C-Hstretching (aliphatic), at 1730/cm to C=Ostretching, at 930/cm to C-Fstretching. It is evident from the spectral study, that there is no difference worth mentioning in the portions of characteristic absorption bands of various functional groups and bonds present in the drug molecule and the formulations prepared from it. The drug has not lost its characteristic properties when it is converted into its different formulations. These observations support the fact that the drug has maintained its integrity in its formulations as it retained its physical characteristics without undergoing any change in its properties. This suggests that there is no interaction of the drug with polymer and excipients used in preparation of the formulations. Hence, it can be concluded that the drug has not under gone any type of interaction with the excipients used in the formulation development. From the result, it was observed that the entire characteristic peaks of 5-FU, were present in the tablet formulation and patch formulation spectrum. Thus, indicating compatibility of the drug and polymer in the tablet formulation and patch formulation at molecular level.

DSC

DSC thermogram of 5-FU pure drug and polymer was studied and it was found that drug 5-FU Fig. 3a shown endothermic peak at 283.17°C. Fig. 3b Carbopol 974p showed endothermic peak at 82.34°C, 142.87°C, 204.90°C. Fig. 3c Polyvinylpyrolidone showed endothermic peak at 96.94°C, 193.30°C, 253.71°C and Fig. 3d complex of Carbopol+PVP showed endothermic peak at 85.05°C, 161.92°C, and 238.66°C. This suggests that there is no interaction of the drug with polymer and excipients used in preparation of the formulations.

Mucoadhesive strength study and in vitro retention time of 5-FU buccal tablets

Carbopol and PVP have been reported to possess good mucoadhesive properties in buccal tablet formulations. When these polymers come in contact with water forms mucilage and swells, thus are responsible for mucoadhesion by simple bonding with mucus components. Mucoadhesion strength and mucoadhesion force were found good enough results, namely, 11.42–14.56 g and 1.079–1.428, respectively. Mucoadhesion time was found in the range of 7.5–11.10 h shown in Table 8. The results of mucoadhesion study indicate that it will definitely help to retain the tablet for longer period. The swelling of the polymers is studied by their ability to imbibe water and swell

Table 6: Evaluation parameters for factorial batches (tablet formulation)

Formulation batches	evaluation parameters				
	Weight uniformity (g)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Content uniformity (%)
FT1	132.2±0.51	1.03	3.3±0.13	0.13	99.28±0.20
FT2	146.1±0.15	2.01	4.2±0.11	0.22	99.63±0.12
FT3	138.5±0.26	1.02	3.5±0.20	0.15	99.58±0.10
FT4	123.0±0.72	1.01	3.1±0.10	0.15	98.72±0.04
FT5	139.2±0.35	1.01	3.2±0.18	0.12	99.87±0.03
FT6	146.4±0.49	2.02	3.1±0.16	0.16	99.46±0.01
FT7	138.2±0.38	1.02	3.4±0.30	0.16	99.32±0.16
FT8	130.4±0.23	1.02	4.1±0.19	0.14	99.84±0.28
FT9	153.1±0.42	2.03	4.0±0.25	0.12	97.98±0.5

Table 7: Evaluation parameters for factorial batches (patch formulation)

Formulation Batches	Evaluation parameters					
	Surface pH	Weight Uniformity (g) ±SD	Thickness (mm)	Folding endurance	Content uniformity (%)	Ex-vivo resistance time in hrs
FP1	6.45±0.173	241±2.17	0.269±0.023	>290	90.3±1.02	3.22±0.56
FP2	6.11±0.173	245±6.42	0.289±0.025	>290	93.0±0.67	4.07±0.86
FP3	6.08±0.173	263±10.6	0.205±0.015	>290	98.3±0.12	4.28±0.46
FP4	6.36±0.208	278±4.25	0.260±0.015	>290	90.0±0.99	3.77±0.33
FP5	5.90±0.152	265±1.76	0.348±0.045	>290	96.4±0.56	3.77±0.33
FP6	7.06±0.200	212±5.78	0.256±0.025	>290	94.6±0.98	4.94±0.54
FP7	6.52±0.155	282±3.24	0.370±0.010	>290	99.0±0.19	3.55±0.99
FP8	5.98±0.251	269±2.65	0.234±0.011	>290	97.0±0.49	3.98±0.33
FP9	7.32±0.360	277±5.36	0.245±0.028	>290	96.3±0.85	4.57±0.33

*SD: Standard deviation, n=10, n=3, n=3

Table 8: Mucoadhesive strength study and *in vitro* retention time of 5-FU buccal tablets

Formulation batches	Mucoadhesive strength (gm)	Mucoadhesive force (N)	*In vitro* retention time	Swelling index (%)
FT1	11.42±0.10	1.120	8 h 42 min	48.16
FT2	12.86±0.12	1.261	9 h 40 min	53.24
FT3	11.00±0.08	1.079	7 h 50 min	41.23
FT4	11.69±0.61	1.146	9 h 01 min	38.46
FT5	12.82±0.50	1.257	9 h 35 min	43.19
FT6	13.94±0.31	1.367	10 h15 min	58.32
FT7	13.19±0.31	1.293	9 h 55 min	49.17
FT8	12.46±0.31	1.222	9 h 15 min	40.59
FT9	14.56±0.31	1.428	11 h 10 min	62.12

5-FU: 5-fluorouracil

enormously. In the present study, polymers used in the formulation carbopol and PVP have been reported to show good swelling properties. These polymers in combination showed good swelling properties ranging from 38.46% to 62.12% as shown in Table 8 and Fig 4. This increase in swelling was possible only due to imbibitions and mucilage formation of polymers when it comes in contact with biological and or aqueous medium and due to which swelling took place.

Mucoadhesive strength of buccal patch formulation

Mucoadhesive strength

From the mucoadhesive strength data, it was found that the drug release study the patch prepared carbopol in the amount of 100 mg (FP1), 200 mg (FP2), and 400 mg (FP3) were about 8.70±0.17, 9.10±0.14, and 9.56±0.24, respectively. Patch containing PVP in the amount of 100 mg (FP4), 1200 mg (FP5), and 400 mg (FP6) were about 9.23±0.09, 14.5±0.70, and 10.6±0.12, respectively.

The patch prepared with carbopol and PVP with the amount of 50 mg (FP7) shows maximum mucoadhesive strength of 18.5±0.23. The patch prepared with carbopol and PVP with the amount of 100 mg (FP8) shows mucoadhesive strength of 14.5±0.23. The patch prepared with carbopol and PVP with the amount of 100 mg (FP9) shoes mucoadhesive strength of 13.01±0.23 as shown in Table 9 and Fig. 5 [32].

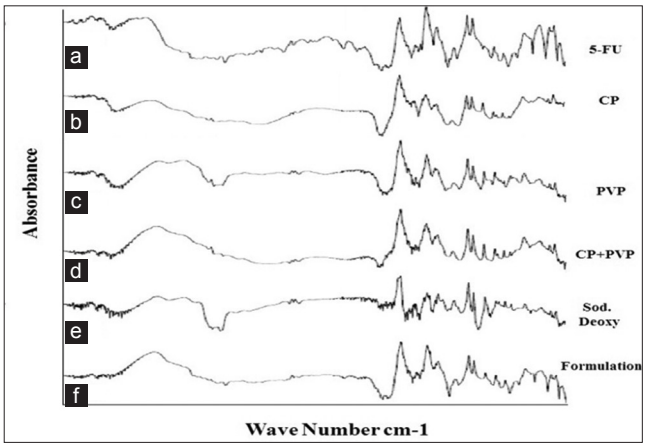

Fig. 1: Fourier transform infrared, (a) 5-fluorouracil, (b) CP, (c) polyvinylpyrrolidone (PVP), (d) complex CP+PVP, (e) sodium deoxycholate, (f) tablet formulation

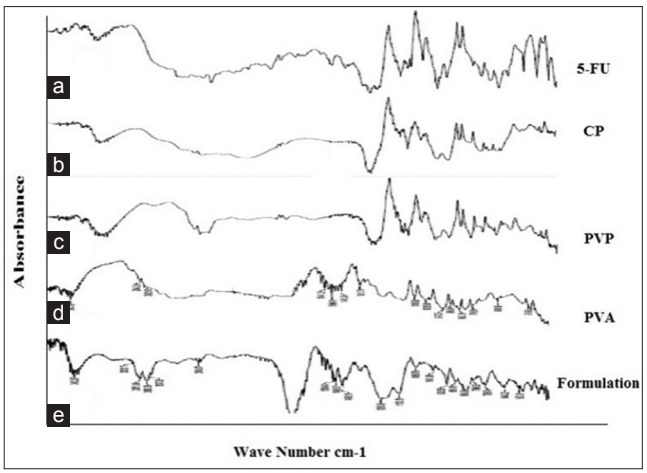

Fig. 2: Fourier transform infrared, (a) 5-fluorouracil, (b) CP, (c) polyvinylpyrrolidone, (d) polyvinyl alcohol, (e) patch formulation

Surface pH of patch

Surface pH was determined by the patch were allowed in contact with 1 ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of patch and allowing equilibrate for 1 min and the average surface pH of all patches are given in Table 10. From the surface pH data, it was found that patch prepared carbopol in amount of 100 mg (F1), 200 mg (F2), 400 mg (F3) were about 6.45±0.173, 6.11±0.173, and 6.08±0.173, respectively. Patch containing PVP in the amount of 100 mg (F4), 200 mg (F5), and 400 mg (F6) were about 6.36±0.208, 5.90±0.152, and 7.06±0.200. The patch prepared with carbopol and PVP with the amount of 100 mg (F7), 120 mg (F8), and 80 mg (F9) were about 6.52±0.155, 5.98±0.251, and 7.32±0.360 [33].

Drug content uniformity of patch

In each case, three patches were used and the average drug content was calculated. From the in folding endurance data, it was found that patch prepared carbopol in amount of 100 mg (F1), 200 mg (F2), and 400 mg (F3) were about 90.3±1.02, 93.0±0.67, and 98.3±0.12, respectively. Patch containing PVP in the amount of 100 mg (F4), 200 mg (F5), and 400 mg (F6) were about 90.0±0.99, 96.4±0.56, and 94.6±0.98, respectively. The patch prepared with carbopol and PVP with the amount of 100 mg (F7), 120 mg (F8), and 80 mg (F9) were about 99.0±0.19, 97.0±0.49, and 96.3±0.85 shown in Table 10 [34].

Folding endurance of patch

The folding endurance of the patch was determined by repeatedly folding a small strip of the patch at the same place until it broke and the average folding endurance of all patch is given in Table 10. From the in folding endurance data, it was found that patch prepared carbopol in amount of 100 mg (F1), 200 mg (F2), and 400 mg (F3) were about >290, >290, >290. Patch containing PVP in amount of 100 mg (F4),

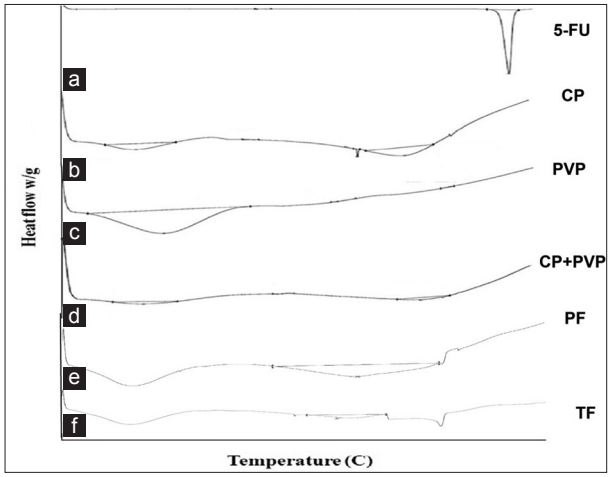

Fig. 3: Differential scanning calorimeter (a) 5-fluorouracil, (b) CP, (c) polyvinylpyrrolidone, (d) complex CP+PVP, (e) buccalpatches formulation (PF), (f) buccaltablet formulation (TF)

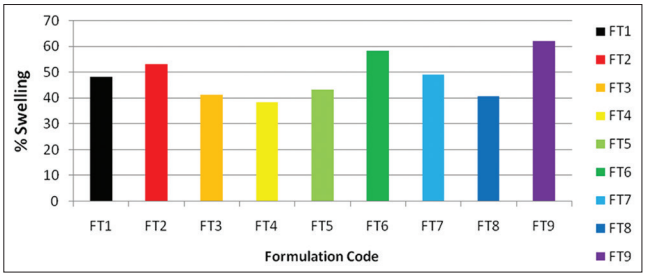

Fig. 4: Swelling index of tablet formulation

200 mg (F5), and 400 mg (F6) were about >290, >290, >290. The patch prepared with carbopol and PVP with amount of 100 mg (F7), 120 mg (F8), 80 mg (F9) were about >290, >290, >290 [34].

Thickness of patch

The thickness of the patch was measured using vernier caliper and the average thickness of all patches is shown in Table 10. Thickness of film prepared of carbopol in amount of 100 mg (F1), 2000 mg (F2), 400 mg (F3) were found to 0.269±0.023, 0.289±0.025, 0.205±0.015. Patch containing PVP in amount of 100 mg (F4), 200 mg (F5), and 400 mg (F6) were found to be 0.260±0.015, 0.348±0.045, 0.256±0.025, respectively. The patch prepared with carbopol and PVP with amount of 100 mg (F7), 120 mg (F8), and 80 mg (F9) were about 0.370±0.010, 0.234±0.011, 0.245±0.028 [34].

Weight uniformity of patch

The weight of prepared patch was determined using digital balance and the average weights of all patches are given in Table 10. Patch prepared carbopol in amount of 100 mg (F1), 200 mg (F2), 400 mg (F3) were about 241±2.17, 245±6.42, 263±10.6, respectively. Patch containing PVP in amount of 100 mg (F4), 200 mg (F5), and 400 mg (F6) were about 278±4.25, 265±1.76, 212±5.78, respectively. The patch prepared with carbopol and PVP with amount of 100 mg (F7), 120 mg (F8), and 80 mg (F9) were about 282±3.24, 269±2.65, 277±5.36 [33].

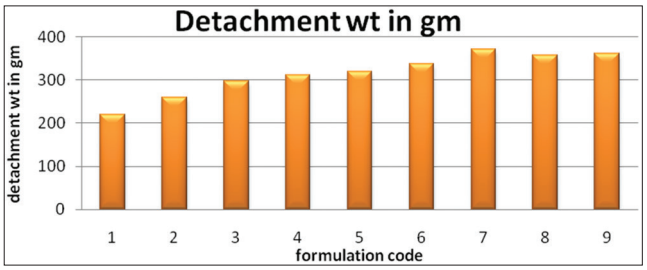

Fig. 5: Mucoadhesive strength of buccal patches

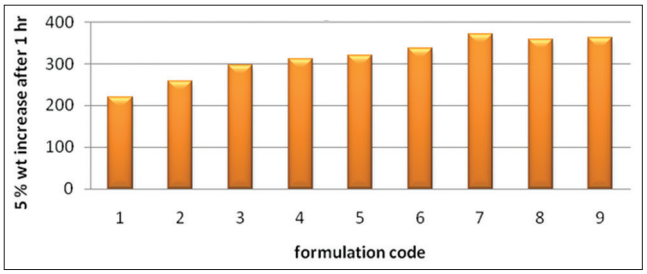

Fig. 6: Swelling index after 1 h

Swelling index

From the swelling index data, it was found that, the drug release study the patch prepared carbopol in the amount of 100 mg (F1), 200 mg (F2), 400 mg (F3) were 16.12±1.32, 16.76±0.95, and 17.40±1.10, respectively. Patch containing PVP in amount of 100 mg (F4), 1200 mg (F5), and 400 mg (F6) were about 18.12±0.76, 18.95±0.89, and 20.05±2.52, respectively. The patch prepared with carbopol and PVP with amount of 50 mg (F7) shows maximum swelling index of 25.12±1.26. The film prepared with carbopol and PVP with amount of 100 mg (F8) shows swelling index of 23.51±3.06. The film prepared with carbopol and PVP with amount of 100 mg (F9) shows swelling index of 24.01±4.80 shown in Table 11 and Fig 6 [32].

TS

From the TS data, it was found that the drug release study the patch prepared carbopol in amount of 100 mg (F1), 200 mg (F2), and 400 mg (F3) were 220.15, 259.32, and 297.57, respectively. Patch containing PVP in amount of 100 mg (F4), 1200 mg (F5), and 400 mg (F6) were about 312.45, 320.54, and 337.56, respectively. The patch prepared with carbopol and PVP with the amount of 50 mg (F7) shows maximum TS of 371.81. The film prepared with carbopol and PVP with amount of 100 mg (F8) shows TS of 358.66. The patch prepared with carbopol and PVP with amount of 100 mg (F9) shows TS of 361.95 shown in Table 11 and Fig 7 [32].

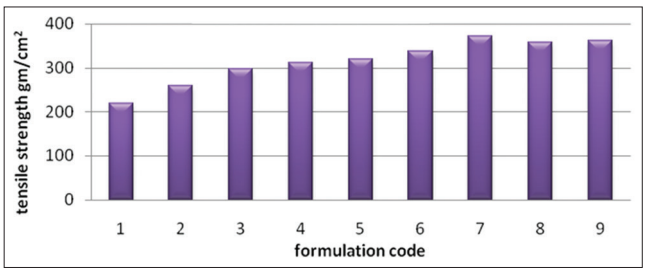

Fig. 7: Tensile strength g/cm²

Table 9: Mucoadhesive strength of formulation

Formulation code	Detachment weight in g
FP1	8.70±0.17
FP2	9.10±0.14
FP3	9.56±0.24
FP4	9.23±0.09
FP5	14.5±0.70
FP6	10.6±0.12
FP7	18.5±0.23
FP8	14.5±0.23
FP9	13.01±0.23

Table 10: Mucoadhesive strength study and *in vitro* retention time of 5-FU buccal patches

Formulation batches	Evaluation parameters					
	Surface pH	Weight uniformity (g) ±SD	Thickness (mm)	Folding endurance	Content uniformity (%)	Ex-vivo resistance time in hrs
FP1	6.45±0.173	241±2.17	0.269±0.023	>290	90.3±1.02	3.22±0.56
FP2	6.11±0.173	245±6.42	0.289±0.025	>290	93.0±0.67	4.07±0.86
FP3	6.08±0.173	263±10.6	0.205±0.015	>290	98.3±0.12	4.28±0.46
FP4	6.36±0.208	278±4.25	0.260±0.015	>290	90.0±0.99	3.77±0.33
FP5	5.90±0.152	265±1.76	0.348±0.045	>290	96.4±0.56	3.77±0.33
FP6	7.06±0.200	212±5.78	0.256±0.025	>290	94.6±0.98	4.94±0.54
FP7	6.52±0.155	282±3.24	0.370±0.010	>290	99.0±0.19	3.55±0.99
FP8	5.98±0.251	269±2.65	0.234±0.011	>290	97.0±0.49	3.98±0.33
FP9	7.32±0.360	277±5.36	0.245±0.028	>290	96.3±0.85	4.57±0.33

In vitro study of buccal tablet

A 3^2 full factorial design was constructed to study the effect of the amount of carbopol 974p (X1) and PVP (X2) on drug release from tablets. The dependent variables chosen were drug release and mucoadhesion. In drug release study of 5-FU was found to be a function of the polymer concentration. It was observed that the variation in concentration of polymer from factorial batches FT1 to FT9 have variability on release rate of drug. The influence of carbopol 974p and PVP ratio on the release of 5-FU from the tablets in phosphate buffer having pH 6.8 at 37±0.5°C. It is clear that increase in concentration of carbopol 974p and PVP in formulae decreased the release rate. The formulation FT-5 showed the best 99.34% drug release.

Formulations FT-6, FT-7, and FT-9 containing higher concentrations of carbopol 974p showed less drug release from 79.61% to 85.42% as compared to other formulation batches, out of which batch FT-9 showed very less drug release due to higher concentrations of carbopol 974p and PVP. The formulations FT-1, FT-2 and FT-3 showed increase in drug release from 80.76% to 92.46% due to decrease in concentration of carbopol 974p and PVP. The Formulations FT-4, FT-5, and FT-8 showed drug release from 75.10% to 99.34%, in which the polymer concentration was found optimum in batch F-3 which showed drug release up to 99.34%. The batch FT-4 showed less drug release. Cumulative drug release buccal tablet shown in Fig. 8.

Final equation in terms of coded factors

% Drug release = +97.48-6.06* A-2.16* B-6.82* AB-10.52* A^2-13.46* B^2

In vitro study of buccal patch

From the *in vitro* dissolution data, it was found that the drug release study the patch prepared Carbopol in amount of 100 mg (FP1), 200 mg (FP2), 400 mg (FP3) were about 73.07±0.72%, 60.06±0.68%, 76.61±0.32% drug release, respectively. Patch containing PVP in amount of 100 mg (FP4), 200 mg (FP5), and 400 mg (FP6) were about 59.54±0.55%, 58.41±0.52%, 54.27±0.51% drug relSease, respectively. The patch prepared with carbopol and PVP with Amount of 100 mg (FP7) shows maximum dissolution of 81.43±0.54. The patch prepared with carbopol in amount of 100 mg with PVA in 50 mg (FP8) shows dissolution of 71.84±0.69%. The patch prepared with carbopol in amount of 50 mg with PVA in 100 mg (FP9) shows dissolution of 67.17±0.74%. From the above results, it can be concluded that increasing concentration of polymer that is carbopol and PVP increases drug release. Combined effect of carbopol and PVP in (1:1) shown much better drug release profile. Cumulative % drug release of buccal patches shown in Fig. 9 [16,35].

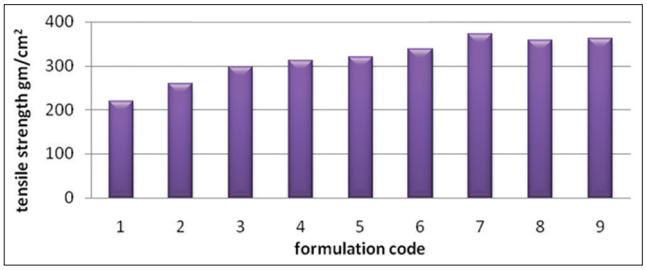

Fig. 7: Tensile strength g/cm²

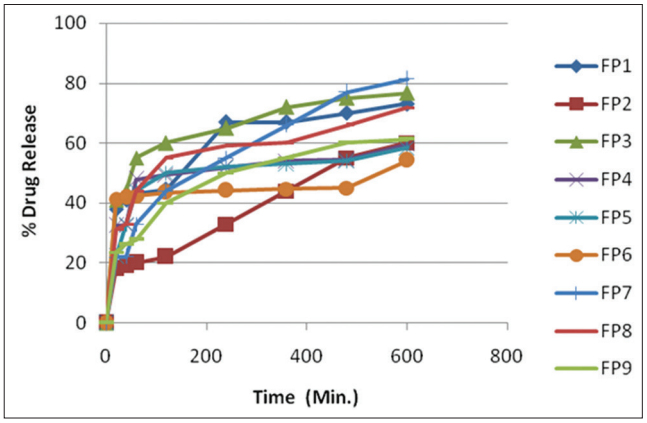

Fig. 8: Cumulative drug release buccal tablet

Ex vivo permeation studies

5-FU permeation from formulations FT-5 across sheep mucosa over 10 h is shown in Fig 10. The maximum permeation of 5-FU from FT-5 and FP-5 was 96% and 69% at 10 h and 8 hrs, respectively. Regression of the linear portions of the two plots gave slopes and intercepts from which the permeation flux (slope divided by mucosal surface area) of FT-5 and FP-5 were calculated to be 8.366 and 5.233 mg/cm2/h, respectively. While permeation coefficients were found be 2.36 and 1.43 cm/h for FT-5 and FP-5 formulations, respectively. In formulation FT-5 and FP-5 addition of sodium deoxycholate and polyethylene glycol increased the cumulative percentage of drug permeated. This may be due to sodium deoxycholate and Polyethylene glycol extracted only mucosal lipid from the intercellular spaces. Thus, this enhances the diffusivity of the 5-FU through the par cellular or polar route, along with the extraction of mucosal lipid from the intercellular spaces by the formation of micelles. This resulted in enhancing passive diffusivity of the 5-FU throughtranscellular (crossing the cell membranes and entering the cell) and par cellular routes.

ANOVA analysis for drug release and mucoadhesion

Evaluation and interpretation of research findings are important and the p-value serves a valuable purpose in these findings. ANOVA for the dependent variables drug release and Mucoadhesion was done. The coefficients of X1 and X2 were found to be significant at $p<0.05$, hence confirmed that both the variables have significant effect on the selected responses. Overall, both the variables caused significant change in the responses. ANOVA and response surface analysis were performed using design expert software.

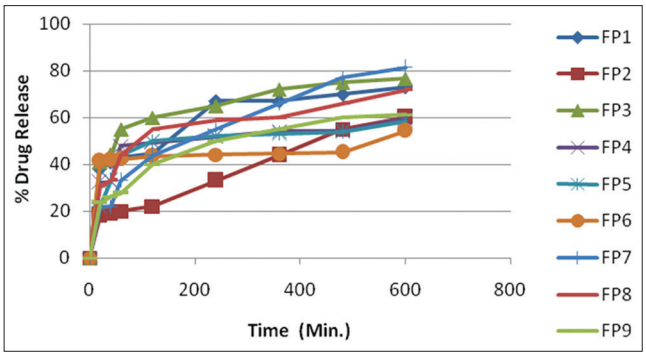

Fig. 9: Cumulative % drug release of buccal patches

Table 11: Swelling index and tensile strength

Formulation code	Swelling index (% wt increase after 1 h)	Tensile strength (g/cm)
FP1	16.12±1.32	220.15
FP2	16.76±0.95	259.32
FP3	17.40±1.10	297.57
FP4	18.12±0.76	312.45
FP5	18.95±0.89	320.54
FP6	20.05±2.52	337.56
FP7	25.12±1.26	371.81
FP8	23.51±3.06	358.66
FP9	24.01±4.80	361.95

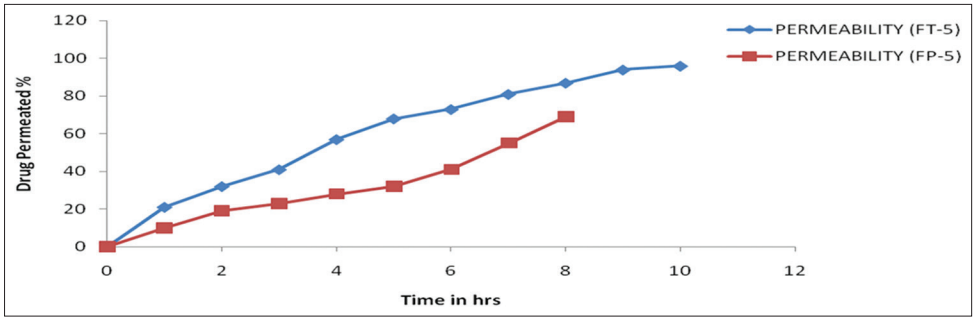

Fig. 10: *Ex vivo* permeation studies of FT-5 and FP-5 formulation

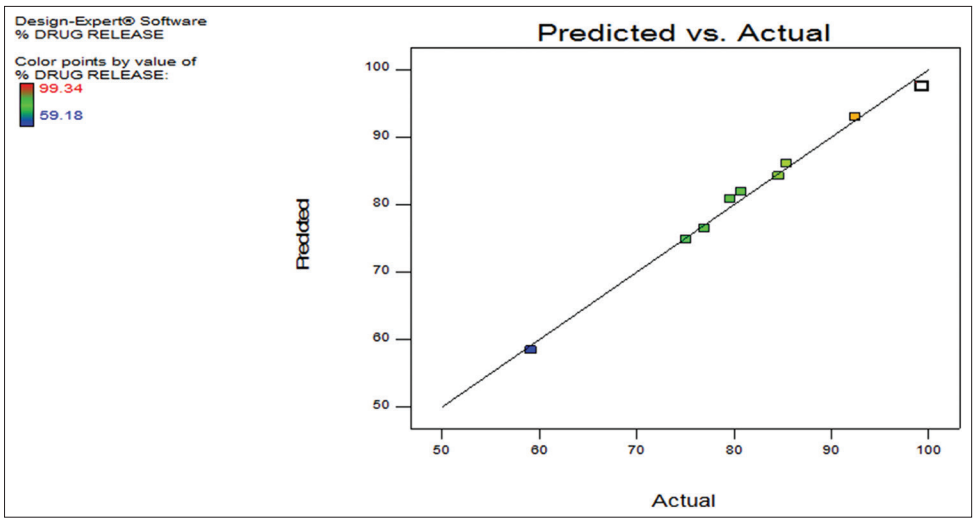

Fig. 11: Predicted versus actual plot of % drug release for tablet formulation

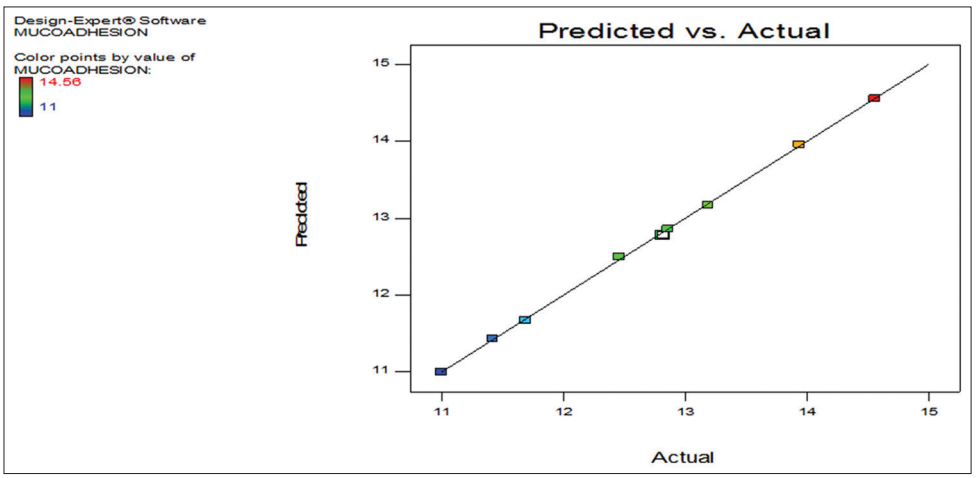

Fig. 12: Predicted versus actual plot of mucoadhesion for tablet formulation

Table 12: Analysis of variance table (Partial sum of squares - Type III)

Source	Sum of source	Df	Mean squares	F value	p-value Probe>F	Observation
Model	1018.76	5	203.75	74.24	0.0024	Significant
A-Carbopol	220.58	1	220.58	80.37	0.0029	Significant
B-Polyvinylpyrilidone	28.04	1	28.04	10.22	0.0495	Significant
AB	186.19	1	186.19	67.84	0.0037	Significant
A^2	221.34	1	221.34	80.65	0.0029	Significant
B^2	362.61	1	362.61	132.12	0.0014	Significant
Residual	8.23	3	2.74			
Core Total	1026.99	8				

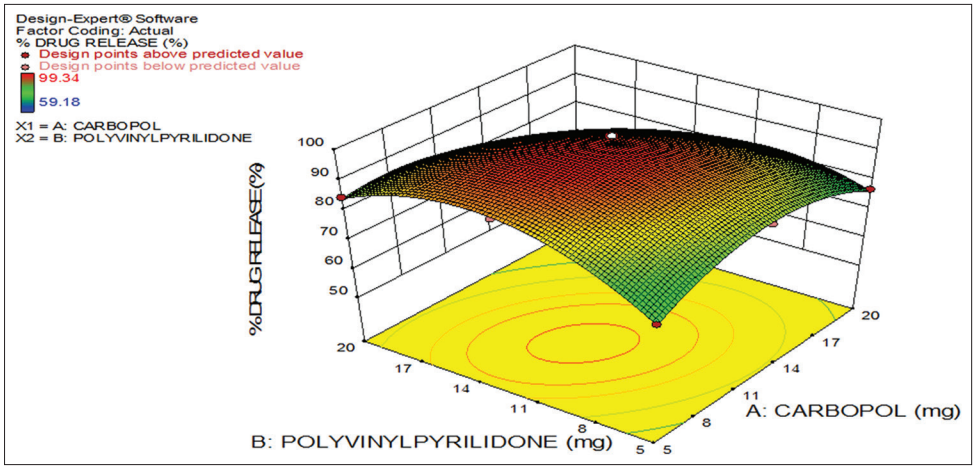

Fig. 13: 3D graph of % drug release for tablet formulation

Table 13: Standard deviation, mean and R^2 for dissolution

Std.Dev	1.66	0.75	R^2	0.9920
Mean	81.49	92.30	Adj R-Squared	0.9786
C.V.%	2.03	0.82	Pred R-Squared	0.9382
PRESS	63.52	13.96	Adeq Precision	28.856

Table 14: Analysis of variance table (Partial sum of squares - Type III)

Source	Sum of source	Df	Mean squares	F value	p-value Probe>F	Observation
Model	10.86	5	2.17	1348.66	<0.0001	Significant
A-Carbopol	9.58	1	9.58	5943.77	<0.0001	Significant
B-Polyvinylpyrilidone	0.19	1	0.19	120.66	0.0016	Significant
AB	1.06	1	1.06	658.49	0.0001	Significant
A^2	0.013	1	0.013	7.94	0.0668	Significant
B^2	0.020	1	0.020	12.41	0.0388	Significant
Residual	4.833E-003	3	1.611E-003			
Core total	10.87	8				

Response surface analysis

The quadratic model obtained from the regression analysis was used to build a 3-D graphs in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots presented in Figs. 11-14. Predicted plots (Figs. 11 and 12) are representations of the responses for the selected factors and shows that the predicted results and practically obtained results are similar. Three dimensional (3-D) surface plots (Figs. 13 and 14) for the obtained responses were drawn based on the model polynomial functions to assess the change of the response surface and also indicates that increase in concentration of carbopol decreases the % drug release. These plots explain the relationship between the dependent and independent variables, i.e., the effects of two factors on the response at one time. The response surface analysis for drug release and mucoadhesion was studied which showed significant results. The Model F-value of 74.24 and 1348.66 for drug release and mucoadhesion implies the model is significant. Values of p<0.0500 indicate model terms are significant. The results are shown in Tables 12-15.

Final equation in terms of actual factors

% Drug Release=+25.61528+5.38322* Carbopol+7.21233* Polyvinylpyrilidone-0.12129* Carbopol* Polyvinylpyrilidone-0.18702* Carbopol^2-0.23938* Polyvinylpyrilidone^2

Final equation in terms of coded factors

Mucoadhesion=+12.78+1.26* A+0.18* B+0.52* AB-0.080* A^2-0.100* B^2

Table 15: Standard deviation, mean and R^2 for mucoadhesion

Std.Dev	0.040	0.75	R-Squared	0.9996
Mean	12.66	92.30	Adj R-Squared	0.9988
C.V. %	0.32	0.82	Pred R-Squared	0.9962
Press	0.042	13.96	Adeq Precision	108.524

Table 16: Summary of mean pharmacokinetic parameters for buccal patch, buccal tablet and reference (conventional tablet) in healthy rabbits

SN	Pharmacokinetic parameters	Buccal patch	Buccal tablet	Conventional tablet
1	Cmax (ng/ml)	215	231	227
2	T max (h)	3	8	4
3	$AUC_{0-\infty}$ (ng.h/ml)	2534	2754	1603
4	Slope	−3.865	−4.119	−0.351

Final equation in terms of actual factors

Mucoadhesion=+11.30500+0.089556*Carbopol-0.046000* Polyvinylpyrilidone+9.15556E-003* CARBOPOL* Polyvinylpyrilidone-1.42222E-003* Carbopol^2-1.77778E-003* Polyvinylpyrilidone^2

From the equation for dissolution, the information conveyed was: R^2 was high indicating the adequate fitting of the quadratic model. As carbopol and polyvinylpyrolidone (−ve coefficient) showed −ve

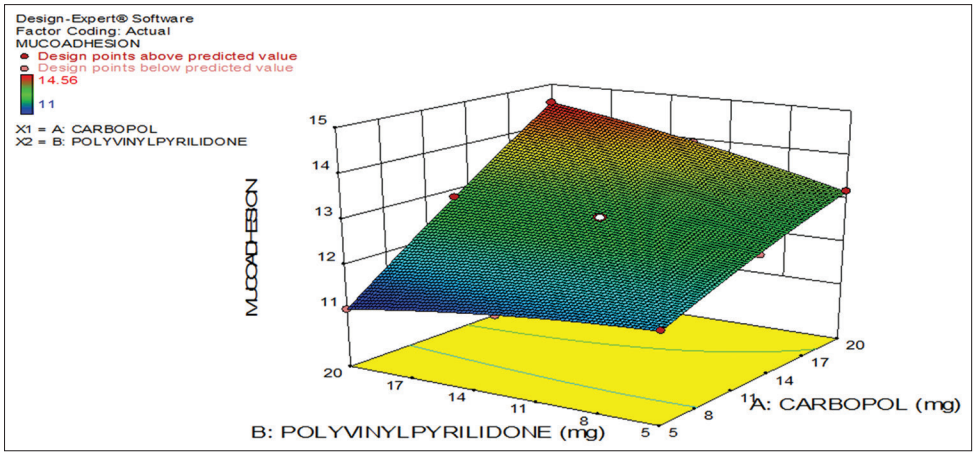

Fig. 14: 3D graph of mucoadhesion for tablet formulation

Table 17: Stability studies for buccal tablet

No. of months	Hardness (kg/cm^2)	Friability (%)	% Swelling	Mucoad-hesive strength (mg)	Mucoadhesive time (hr)	*In vitro* drug release study (%)
1	3.2±0.01	0.12±0.03	42.18	12.82±0.32	More than 9.4 h	99.65
2	3.2±0.03	0.12±0.01	43.25	12.89±0.046	More than 9.4 h	99.16
3	3.2±0.02	0.12±0.02	43.38	12.72±0.062	More than 9.4 h	99.25
4	3.2±0.03	0.12±0.01	43.10	12.90±0.37	More than 9.3 h	99.18
5	3.2±0.0	0.12±0.01	43.32	12.45±0.086	More than 9.3 h	99.84
6	3.1±0.01	0.11±0.02	44.10	12.85±0.10	More than 9.4 h	99.41

sign it also indicated that drug delivery system gained more control over the release from prepared dosage form. From the equation for mucoadhesion, the information conveyed was: R^2 was high indicating the adequate fitting of the quadratic model. As carbopol and polyvinylpyrolidone (+ve coefficient) showed +ve sign it also indicated that drug delivery system gained more mucoadhesion. Graphical presentation of data shows relationship between response and independent variables. The information given by graph was similar to that of mathematical equations obtained from statistical analysis. The response surface plots showed that various combinations of independent variables X1 and X2 satisfy specific requirement (i.e. drug release with mucoadhesion while taking into consideration of various factors involved in dosage form).

ANOVA for response surface quadratic model (For mucoadhesion study)

***In vivo* study**

Six male New Zealand white rabbits (2.6 kg) were selected for the *in vivo* study. The dose of 5-FU was adjusted based on the rabbit weight and the optimized formulations were cut and placed in the buccal membrane with the help of a clip and tablets placed in the buccal membrane with the adhesive layer. The results are shown in Table 16.

Stability study of optimized batch

Stability study was done to see the effect of temperature and humidity on tablets and patches. Storage conditions:

1. Accelerated temperature 40°C±2°C
2. Accelerated temperature at 75% RH±5%.

Time period of 6 months, at intervals of every 1 month, the tablets and patches were visually examined for any physical changes, changes in hardness, friability, swelling index, mucoadhesion strength, mucoadhesion time, and *in vitro* drug release study. The results indicate no significant change in the tablet properties. Hence, it can be concluded that the formulated buccal tablets are stable under appropriate storage conditions. The results for stability studies are shown in Table 17.

CONCLUSION

FTIR and DSC indicating compatibility of the drug and polymers in the tablet formulation and patch formulation at molecular level. The drug release of buccal tablet showed 75.10–99.34% and buccal patches showed 58.41–81.43%. These formulations showed good results when compared to the conventional tablet. Formulation of mucoadhesive sustained release buccal tablets and patches of 5-FU successfully done using different polymers, which would definitely help in increasing bioavailability of the drug. ANOVA study showed the "R^2" of 0.9943 for drug release and 0.9985 for swelling index is in reasonable agreement with the "Adj R-Squared" of 0.9849 for drug release and 0.9960 for swelling index. The ratio of 29.120 for drug release and 60.670 for swelling index indicates an adequate signal. The probablity value, i.e, p value found was also less than 0.0500. Therefore, this model can be used to develop the design. The desirability result was found equal to 1 and hence, the results were found valid.

CONFLICTS OF INTERESTS

None.

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