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Formulation and evaluation of 5-fluorouracil buccal mucoadhesive buccal tablet

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Abstract
Objective: The present formulation was developed with the intention to formulate versatile 5-fluorouracil (5-FU) mucoadhesive tablet that fulfill the therapeutic need that is lacking in current cancer treatment and aimed at minimizing toxic effect, enhancing efficacy and increasing patient compliance.
Method: Mucoadhesive tablets of 5-fluorouracil were prepared by direct compression technique using different grades of polymer with varying concentration. The tablets were compressed using 10 mm flat faced punch on a single stroke-punching machine. The formulations were tested for drug content, hardness, friability, weight variation, thickness, swelling studies, *in vitro* drug release, *ex vivo* permeation studies, mucoadhesive strength.
Result and Discussion: The formulated mucoadhesive buccal tablet was evaluated for various parameter and formulation F7 was found as the optimum batch.
Conclusion: From the above study it was concluded that Formulation F7 was found optimized formulation showing optimum results for all the evaluated parameters. The drug content was 98.75%, swelling index 130 at 6 hours, Mucoadhesive Strength 22.1 and force (N) 0.216801, Residence time was more than 8hours and drug release was found to be 96.78%.

Keywords: Residence time, mucoadhesion, versatile 5-fluorouracil, cancer

Introductions
Cancer is a disease involving all organs, races, ages, and sex of humans. Among all types of cancer, Oropharyngeal cancer, colorectal cancer contributes to the world most burden and cervical cancer accounts for little extent. Oropharyngeal cancer develops in the part of the throat just behind the mouth called the oropharynx. Oropharynx includes the base of the tongue, soft palate, tonsils, tonsillar pillars and the back wall of the throat [1].
Cervical cancer involving the cervix that is narrow and lowers part of the uterus. About 90% of Oropharyngeal and cervical cancers are squamous cells carcinoma that begins in the epithelial lining in mouth and vagina. Whereas in colorectal cancer columnar cells are affected. Surgery, radiation therapy and chemotherapy are the most common therapies for treating cancer [2].
5-FU is the drug of choice in oropharyngeal cancer, colorectal cancer, stomach cancer, and cervical cancer. Chemically, 5-FU is a dipodic acid and highly polar in nature with pka values of 8.0 and 13.0. After oral administration, 5-FU is poorly absorbed with erratic variation in bioavailability ranging between 0 to 80%. 5-FU after parenteral administration it is rapidly eliminated with the apparent terminal half-life of approximately 8-20 min [3]. On intravenous administration 5-FU produces severe systemic toxic effects including gastrointestinal, hematological, neural, cardiac and dermatological origin. These problems make 5-FU suitable candidate for Transbuccal/vaginal and rectal delivery.
Polymeric drug delivery systems are mainly designed for the efficient delivery of the active drug. Among various polymeric drug delivery systems, interpolyelectrolyte complexes are the newest, efficient form of polymeric carriers for novel drug delivery systems. Carbopol 934, HPMC (K4M and K15 M), Xanthan gum and Gaur gum has established its potential in drug delivery and have been most efficient. Most publications on 5-FU focused only on a single

drug delivery system like buccal gels, cervical patches, colorectal drug delivery. Hardly any articles reported on permeation studies and histological effects of 5-FU. A literature review revealed that there is no single drug delivery system available that can be given either through buccal, vaginal or rectal route. The prime goal has to design 5-FU multipurpose tablets with greater efficacy, potency, adaptability to need, minimal toxic effects and better patient compliance than the established marketed product [4, 5].

Materials and Methods

Materials

5-fluorouracil (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

Mucoadhesive tablets 5-fluorouracil (5-FU) were prepared by direct compression technique using different grades of polymer with varying concentration. All the ingredients except magnesium stearate were blended in glass mortar uniformly. After the sufficient mixing of the drug as well as other components, magnesium stearate was added and further mixed for additional 2-3 minutes. The tablets were compressed using 10 mm flat faced punch on a single stroke-punching machine. The compositions of all formulation are given in Table 1.

Table 1: Composition of -fluorouracil (5-FU) mucoadhesive buccal tablets containing Carbopol 934, HPMC K15M, with different concentration, (F1 to F9)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5-fluorouracil	30	30	30	30	30	30	30	30	30
HPMC K15M	22.5	45	60	90	7.5	15	7.5	6	--
Carbopol 934	7.5	15	30	30	22.5	15	15	24	--
Xanthan gum	--	--	--	--	--	--	--	--	92
Guar gum	--	--	--	--	--	--	--	--	--
Dibasic Calcium Phosphate	169	139	109	79	169	169	169	169	107
Magnesium Stearate	1	1	1	1	1	1	1	1	1

Table 2: List of chemicals used

Name of Chemicals	Manufacturers
5-fluorouracil (5-FU)	Ozone international, Mumbai.
Carbopol 934	Wockhardt Limited
HPMC (K4M and K15 M)	Wockhardt Limited
Xanthan gum	Wockhardt Limited, Aurangabad
Guar gum	Wockhardt Limited, Aurangabad
Magnesium Stearate	Wockhardt Limited, Aurangabad
Dibasic Calcium Phosphate	Wockhardt Limited, Aurangabad

Uniformity of tablet thickness

A digital Vernier caliper was used for measurement of the thickness of 10 tablets from each batch, and the results were presented as the mean (± standard deviation [SD]) of 10 measurements.

Friability test

Ten tablets were previously weighed, transferred to the drum of the friabilator (Pharma Test, Hainburg, Germany), rotated at 25 rpm for 4 min and finally reweighed. The percentage loss in weights was calculated and taken as a measure of friability [6].

Uniformity weight of the tablet

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 3.

Table 3: Limits of percentage deviation allowed underweight variation test

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

Surface pH

The surface pH of the formulation was determined in order to investigate their possible side effects *in vivo.* An acidic or alkaline formulation will cause irritation of the mucosal membrane and hence this is an important parameter in developing a mucoadhesive dosage form. A combined glass electrode was used for determination of surface pH. pH was measured at time intervals of 15, 30, 60, 90 and 120 min. The discs were first allowed to swell by keeping them in contact with 5 ml phosphate buffer pH 6.8 for two hours in 50 ml beakers. pH was then noted by bringing the electrode near the surface of the formulation and allowing equilibrating for 1 min. The experiments were carried out in triplicate [7].

Drug Content uniformity

In this test, 10 tablets were used where each tablet was mashed and transferred into 100 mL volumetric flask. The flasks were brought to the volume by phosphate buffer pH 6.8. Each flask was sonicated using Sonix IV SS-Series (Sonix IV Ultrasonic Cleaning Systems, North Charleston, SC, USA) till dissolution occurred. Then 1 mL of the solution was filtered, suitably diluted, and the final absorbance of the solution was measured at 266 nm using a UV spectrophotometer (V-530; Jasco, Tokyo, Japan) against phosphate buffer (pH 6.8) as a blank [8].

Swelling study

The tablets were weighed and transferred individually into Petri dishes filled with 20 mL of phosphate buffer (pH 6.8), and the study was conducted for 10 h. Then the tablets were removed from the Petri dishes and excess water was wiped off by a filter paper. The test was done in triplicate. The swelling index was calculated by applying the following equation:

$$\text{Swelling index} = \frac{W2 - W1}{W1} \text{x } 100$$

Where W1 is the buccal tablet weight before being dipped into the Petri dish and *W*2 is the buccal tablet weight after being dipped and wiped [9].

Ex vivo Mucoadhesive strength (g)

A modified physical balance method was used for

determining the ex vivo buccoadhesive strength [13, 14]. Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 and two sides of the balance were made equal before the study. The sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8 at 37°C+1 °C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive and adds weight on the right hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min). To the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of then buccal tablet in grams.

Force of adhesion (N) = (Bioadhesive strength (g) ×9.8)/1000
Bond strength (Nm^{-2}) =Force of adhesion / surface area [10, 11].

***In vitro* release Studies**

In order to carry out *In-vitro* release studies dissolution test apparatus type II (USP) rotating paddle method was used. The studies were carried out for all formulation combination in triplicate, using 900 ml (37 °C, 100 rpm) of isotonic phosphate buffer (pH 6.8) as the dissolution medium. An aliquot of 5ml sample was withdrawn at 0.5, 1, 2, 3, 4,5,6,7 and 8 hours intervals and similar volume was replaced with fresh phosphate buffer (pH 6.8) maintained at the same temperature. 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 [12].

***Ex vivo* residence time**

The *Ex vivo* residence time was determined using a modified USP dissolution apparatus. The phosphate buffer of pH 6.6 is used as dissolution medium which is maintained at 37C± 2° C. A segment of porcine buccal mucosa each of 4 cm length was glued to the surface of glass slide which was then vertically attached to the apparatus. Three tablets of each formulation were hydrated using 15µl pH 6.6 buffer on one side and the hydrated surface was brought into contact with the mucosal membrane. The tablets secured on the glass slide were completely immersed in the buffer solution. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm the time for complete erosion or detachment from the mucosa was recorded [13].

Evaluation of mucoadhesive buccal tablet

All the prepared mucoadhesive buccal tablets were evaluated for following official parameter:

1) Hardness
2) Thickness
3) Weight variation
4) Content uniformity
5) Percentage friability

The details of the evaluated parameters are shown in table 4.

Table 4: Evaluation of prepared mucoadhesive buccal tablets

Batch code	Evaluation Parameters				
	Uniformity of Weight(mg)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Thickness
F1	230±6.66	5-7	0.2	96.02	1.7±0.04
F2	231±9.94	5-7	0.1	97.21	1.82±0.015
F3	232±7.88	5-7	0.51	96.58	2.2±0.015
F4	233±6.74	5-7	0.6	98.45	2.5±0.058
F5	229±9.94	5-7	0.59	100.23	1.68±0.025
F6	226±6.99	5-7	074	97.48	1.68±0.025
F7	232±7.85	5-7	0.37	98.75	1.7±0.04
F8	231±7.37	5-7	0.23	99.0	1.67±0.01
F9	228±7.88	5-7	0.19	102.23	1.81±0.025

* Values are represented as mean ± S.D (n = 3)

Weight variation data for all the formulations batches indicated no significant difference in the weight of individuals tablets from the average value and weight variation were found to be within IP limits. The average weight all batches F1-F9 were in the range of 226 to 233 mg and with standard deviation within ± 9.94 showed good uniformity in batches.

The thickness of all batches F1-F9 (except batch E3 and E4) were in the range of 1.67 to 1.81 mm with standard deviation within ± 0.01 to ± 0.087 showed good uniformity in batches. Batches F3 and F4 showed a thickness of 2.20 mm ± 0.015 and 2.50 ± 0.058 respectively.

The hardness values were found to be in the range of 5 to 7 kg/cm^2.

The friability values were found to be within IP limits.

The drug content was found to be within the range of 96.02-103.34%.

***In- vitro* swelling study of mucoadhesive buccal tablets**

The swelling percentage of formulated tablets was determined by measuring increased weight after a specific time interval. The results are shown in table 5 and a graphical representation of it is shown in. figure no.1.

Table 5: *In vitro* Swelling Study of Mucoadhesive Tablet

Batch code	%Swelling index				
	Time (hrs)				
	0.5	1	2	4	6
F1	21.12	41.78	63.06	88.42	93.2
F2	25.00	43.42	74.31	90.06	111.56
F3	40.12	70.05	105.90	120	141.5
F4	35.4	65.09	95.08	101	124
F5	31.51	58.11	85.56	108.09	121.00
F6	30.12	50.03	75.17	93.00	105.99
F7	32.79	52.00	75.00	117.77	130.00
F8	34.77	58.22	92.21	102.27	125.00
F9	28.35	64.52	92.00	135.5	172

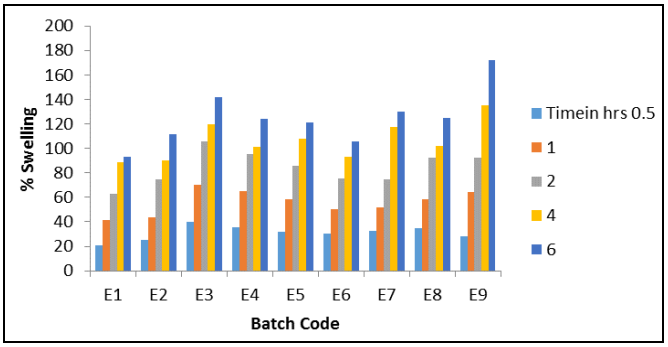

Fig 1: *In- vitro* swelling study of mucoadhesive buccal tablets

The result of swelling study indicates that all batches shown good swelling index, appropriate swelling is an essential parameter for uniform and prolonged drug release. The formulation F3 containing HPMC K15 M: CP 934 as 1:2 shows maximum swelling index. Guar gum at 35% w/w concentration shows higher swelling than Xanthan gum at the same concentration.

Surface pH determination of mucoadhesive buccal tablets

The surface pH of the tablets was determined in order to investigate the possibility of any side effects, on the oral cavity. The surface pH was measured by means of a pH paper placed on the surface of the swollen tablets. Tablets from all batches had shown a surface pH in the range of 5 to 7.

***In -vitro* Mucoadhesive Study**

The force required for the detachment of mucoadhesive tablets was measured in gm. The weight is then converted into a force of adhesion measured in Newton.

The results obtained are shown in table 6 and the graphical representation of it is shown in fig no 2.

Table 6: *In –vitro* mucoadhesive study

Batch code	Mucoadhesive strength(g)	Force of adhesion (N)
F1	18.15	0.178052
F2	20.12	0.197377
F3	25.19	0.247114
F4	22.22	0.217978
F5	19.2	0.188352
F6	23.2	0.227592
F7	22.1	0.216801
F8	18	0.17658
F9	21.4	0.209934

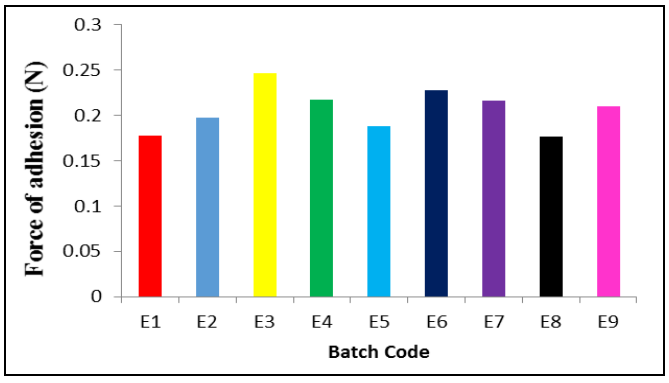

Fig 2: In -vitro mucoadhesive study

The maximum mucoadhesive strength was obtained for formulation E3 containing HPMC K 15M: CP 934 as 1:2. Xanthan gum and Guar gum at 40% w/w concentration in batch E9 and E10 does not show a significant difference in mucoadhesive strength.

***In –vitro* residence time**

Residence time is an important factor which correlates bioadhesion time of dosage form to the buccal mucosa. The study was carried out for 8 hrs using modified disintegration apparatus.

The time for which tablets remain adhered to buccal mucosa shown in table no.8.5.

Table 7: *In –vitro* residence time

Batch code	Time (hrs)
F1	More than 8 hrs
F2	More than 8 hrs
F3	More than 8 hrs
F4	More than 8 hrs
F5	More than 8 hrs
F6	More than 8 hrs
F7	More than 8 hrs
F8	More than 8 hrs
F9	Around 7 .5 hrs

It was found that HPMC K 15M and CP in combination (batch F1to F9) showed optimum residence time for more than 8 hrs. Gums (xanthan and guar) 35% w/w alone and in combination does not show optimum residence time.

***In –vitro* drug release study**

Drug release study was carried out for all formulations F1 to F9 according to official pharmacopeia. It was found that all formulations showed optimum drug release up to 8 hrs except F1 to F9.

The percentage drug release study for batches F1 to F9 shown in table no.8 and fig 3.

Table 8: The percentage drug release study

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	21.6	19.91	18.66	15.17	28.97	29.63	28.01	33.26	24.98
2	31.32	28.48	30.32	22.3	43.59	46.45	46.52	48.36	37.81
3	39.7	29.7	39.14	30.23	52.23	56.54	58.63	57.01	47.38
4	40.11	32.45	45.53	35.4	59.41	64.76	66.45	63.56	52.77
5	40.12	43.59	54.99	42.47	65.98	70.21	74.28	70.8	59.43
6	45.8	46.52	60.83	47.6	77.44	75.2	82.39	75.86	63.07
7	52.34	48.36	65.92	50.89	80.32	80.1	89.56	80.52	67.25
8	59.23	56.57	71.52	63.57	82.57	85.92	96.78	86.78	76.89

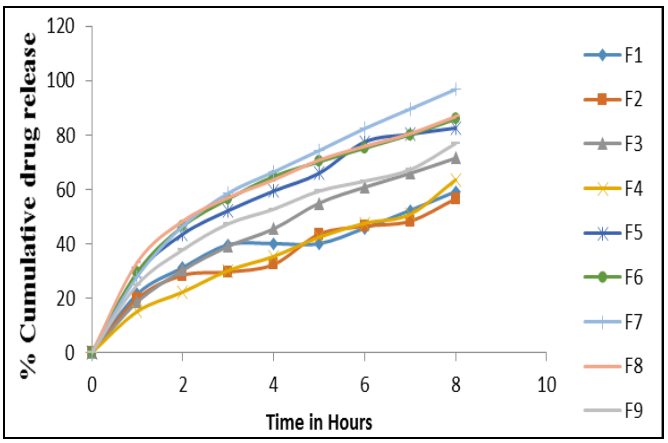

Fig 3: Percentage drug release of Batches F1-F9

Drug release kinetic study

Table 9: Model fitting

	R	K
Zero-order	0.8811	13.3268
T-test	4.93	(Passes)
1st order	0.997	-0.275
T-test	33.915	(Passes)
Matrix	0.9974	32.3764
T-test	36.455	(Passes)
Pepas	0.9918	30.2099
T-test	20.572	(Passes)
Hexon Crow.	0.9835	-0.0697
T-test	14.388	(Passes)

From all the batches Batch F7 was taken for kinetic study as it showed good results for all the evaluation parameters. From kinetic study and R^2 it was concluded that best fit model was Matrix, R^2 was 0.9974.

Conclusion

From the above study it was concluded that Formulation F7 was found optimized formulation showing optimum results for all the evaluated parameters. The drug content was 98.75%, swelling index 130 at 6hours, Mucoadhesive Strength 22.1 and force (N) 0.216801, Residence time was more than 8hours and drug release was found to be 96.78%.

References

1. Gupta AK, Dhakar RC, Siddiqui AW, Maurya SD. Interpenetrating polymeric network hydrogel for stomach-specific drug delivery of clarithromycin: Preparation and evaluation, Asian Journal of Pharmaceutics. 2010; 4(4):184-189.
2. Dhiman MK, Dhiman A, Sawant K. Transbuccal delivery of 5-flurouracil: permeation enhancement and pharmacokinetic study. AAPS Pharma Sci. Tech. 2009; 10(1):258-265.
3. Calavresi P, Chabner BA. The pharmacological basis of therapeutics. In Goodman and Gilmans. 9th edition. Edited by Hardman JG, Limbird LE, Perry BM, Raymond WR. New Delhi: McGraw-Hill, 1996, 125-1232.
4. Singh BN, Singh RB, Singh J. Effects of ionization and penetration enhancers on the Transdermal delivery of 5-flurouracil through excised human stratum corneum. Int J pharm. 2005; 298(1):98-107.
5. Nam K, Watanabe J, Ishihara K. The characteristics of spontaneously forming physically cross-linked hydrogels composed of two water soluble phospholipids polymers for oral drug delivery carrier I: Hydrogel dissolution and insulin release under neutral pH condition. Eur J Pharm Sci. 2004; 23:251-270.
6. Moustanfine RI, Kabonova TV, Kemonova VA, Van den Mooter G. Characteristics of interpolyelectrolyte complexes of Eudragit E100 with Eudragit L100. J control rel. 2005; 103:191-198.
7. Rahim Bahri-Najafi, Zahra Rezaei, Mohammad Peykanpour, Leyla Shabab, Reza Solooki2, Pooya Akbari. Formulation of nicotine mucoadhesive tablet for smoking cessation and evaluation of its pharmaceuticals properties, abr. 2013; 2(4):284-292.
8. Mohamed AEl-Nabarawi, Adel AAli, Heba M Aboud, Amira H Hassan, Amany H Godah. Transbuccal delivery of betahistine dihydrochloride from mucoadhesive tablets with a unidirectional drug flow: in vitro, ex vivo and *in vivo* evaluation, Drug Design, Development and Therapy. 2016; 10 4031-4045.
9. Rosen T. Pragmatic and profound benefits of acyclovir buccal adhesive tablets. J Drugs Dermatol. 2016; 15(6):775-777.
10. Ritthidej GC, Phaechamud T, Koizumi T. Moist heat treatment on physicochemical change of chitosan salt films. Int J Pharm. 2002; 232(1):11-22.
11. Sahini J, Raj S, Ahmad F, Khar RK. Design and in vitro characterization of buccoadhesive drug delivery system of insulin. Indian J Pharm Sci. 2008; 70:61-5.
12. Singh B, Ahuja N. Development of controlled release buccoadhesive hydrophilic matrices of diltiazem hydrochloride: Optimization of bioadhesion, dissolution and diffusion parameters. Drug Dev Ind Pharm. 2002; 28:431-42.
13. Kaur A, Kaur G. Mucoadhesive buccal patches based on interpolymer complexes of chitosan-pectin for delivery of carvedilol. Saudi Pharm J. 2012; 20:21-7.
14. Naga Raju K, Velmurugan S, Deepika B, Sundar Vinushitha. Formulation And *In vitro* Evaluation Of Buccal Tablets Of Metoprolol Tartrate, Int. J Pharm Pharm Sci. 2011; 3:(2):239-246.