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Formulation, Characterization and *In Vitro* Evaluation of Sustained Release Bilayered Buccal Patches of Ranitidine Hydrochloride

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ABSTRACT

Buccal bilayer patch is a non-dissolving thin matrix modified release dosage form composed of one or more polymer films or layers containing the drug and/or other excipients. The ranitidine bilayer buccal patches were prepared by solvent casting method with the combination of HPMC K4M, K15M, K100M and polyvinyl alcohol for drug layer and ethyl cellulose for backing layer to produce 6 formulations (F1- F6). The formulation F6 was considered as optimized formulation which showed best drug permeation till 8 h and drug release up to 8 h. The data obtained from *in vitro* release study were fitted to various mathematical models like zero order, first order, higuchi model, korsmeyer peppas model *etc.* The result of FTIR analysis showed that there was no physical and chemical interaction between drug and other excipients. The present research proved that buccal patches are potential drug delivery systems that will have significant impact in the community, as this will protect drug from first pass metabolism and degrading effects of pH and different enzymes.

INTRODUCTION

The buccal patches has gained prime relevance in pharmaceutical areas as a novel, convenient, patient friendly and excellent accessible product. When compared to the tablets and capsules the buccal patches has improved patient compliance due to its small size and reduced thickness. The patches can be formulated to exhibit a systemic or local action because its mucoadhesion property implies the attachment to the buccal mucosa for extended period of time[1,2].

The concept of mucoadhesion was introduced in the field of controlled release drug delivery systems in the early 1980 s. For drug delivery purpose, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Mucoadhesion is the relatively new and emerging concept in drug delivery. Mucoadhesion keeps the delivery system adhering to the mucus membrane[3].

Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption[3,4].

BIOADHESION

The term bioadhesion can be defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces. In biological systems, bioadhesion can be classified into 3 types:

✓ Type 1, adhesion between two biological phases.

- For example: platelet aggregation and wound healing.

✓ Type 2, adhesion of a biological phase to an artificial substrate.

- For example, cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts.

✓ Type 3, adhesion of an artificial material to a biological substrate.

- For example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel [4,5].

MATERIALS AND METHODOLOGY

MATERIALS

All the materials used in the formulations, evaluation and other experiments are listed below. The chemicals used were of laboratory reagent grade and were used as they were procured. The distilled water was used in all experiments.

Table No. 1: List of chemicals and reagents used

MATERIALS	SUPPLIERS
Ranitidine hydrochloride	Yarrowchem Products, Mumbai, India
HPMC K4 M	Yarrowchem Products, Mumbai, India
HPMC K15M	Yarrowchem Products, Mumbai, India
HPMC K100M	Yarrowchem Products, Mumbai, India
Poly vinyl alcohol	Yarrowchem Products, Mumbai, India
Propylene Glycol	Yarrowchem Products, Mumbai, India
Ethyl Cellulose	Yarrowchem Products, Mumbai, India
Acetone	Yarrowchem Products, Mumbai, India
Dibutyl Pthalate	Yarrowchem Products, Mumbai, India

METHOD OF PREPARATION

FORMULATION OF BILAYER BUCCAL PATCH OF RANITIDINE HYDROCHLORIDE

a) DESIGN OF BACKING LAYER

Backing membrane of ethyl cellulose was fabricated by slowly pouring a solution containing 500mg of ethyl cellulose and 2%v/v dibutyl pthalate in 10ml acetone in a petriplate of 7.5cm internal diameter. It was allowed to air dry for 1h[6,7].

b) FORMULATION OF DRUG LAYER

Solvent casting method

Ranitidine hydrochloride buccal patch was formulated using solvent casting method. The hydrophilic polymer PVA was allowed to soak for 30 min in distilled water. Ranitidine hydrochloride was dissolved in water. HPMC was properly dispersed in distilled water and kept in the refrigerator to form a clear solution. The drug solution is the poured to the PVA solution and allowed to be stirred for 1h. Then the drug polymer solution is poured to the HPMC solution and then propylene glycol is added to the viscous solution with continuous stirring for 15-20 min. The polymeric solution was sonicated for 30 min in order to completely remove air bubbles. The resultant clear solution was then poured on ethyl cellulose pre-prepared backing layer in a glass petri dish. Drying was carried out at room temperature for 24 h. The drying rate was controlled by placing an inverted glass funnel. For complete drying, the petri dish was kept in a hot air oven maintained at 50°C for another 12 h. After complete drying, the patches were removed from the petridish. The films were smooth, flexible and could be cut to any desired shape and size[8,9].

Table No. 2: Formulation ingredients

Ingredients	F1	F2	F3	F4	F5	F6
Ranitidine hydrochloride	150	150	150	150	150	150
PVA	100	100	100	100	100	100
HPMC K4M	150	-	-	75	-	50
HPMC K15M	-	150	-	75	75	50
HPMC K100M	-	-	150	-	75	50
Propylene glycol	1	1	1	1	1	1

(Propylene glycol in ml and other excipients are in mg)

EVALUATION

Organoleptic evaluation

Organoleptic properties of drug like color, appearance and odor were observed[9].

Melting point determination

Melting point of drug sample was determined by melting point apparatus. The small quantity of drug was taken in a capillary tube sealed at one end and was placed in digital melting point apparatus and temperature range at which the drug melts is noted[10].

UV spectroscopy-determination of lambda max

The stock solution of ranitidine hydrochloride was made in 0.1N methanolic hydrochloride. 100 mg of ranitidine hydrochloride was accurately weighed and dissolved in 100 ml of 0.1N methanolic hydrochloride. The stock solution was further diluted with phosphate buffer of pH 6.8 to obtain a working standard of 100µg/ml. By appropriate dilutions of standard solutions, ranitidine hydrochloride was scanned in the range of 200-400 nm to determine the wavelength of maximum absorbance for the drug[11,12,13].

Preparation of standard calibration curve of ranitidine hydrochloride

100 mg of ranitidine hydrochloride was dissolved in 20 ml phosphate buffer of pH 6.8 and volume was made up to 100 ml in a volumetric flask with phosphate buffer of pH 6.8. From this stock solution different dilutions were prepared in the concentration range of 20, 40, 60, 80 and 100 µg/ml in 10 ml volumetric flask and absorbance was taken at 313 nm. Standard curve was prepared by the observations recorded by taking concentration on X axis and absorbance on Y axis[14-20].

Solubility determination

Solubility test of ranitidine hydrochloride was performed by using various solvents. Water, methanol, ethanol, acetic acid, 0.1 N hydrochloric acid, sodium hydroxide, dichloromethane were used as solvents.

FTIR study

The drug and excipients were prepared and scanned from 4000-400 cm-1 in FTIR spectrophotometer and evaluated using FTIR peak matching method and the shift in the major peaks are noted for any incompatibility detection[21].

EVALUATION OF BILAYER BUCCAL PATCH

Mass uniformity and film thickness

Mass uniformity of the patches was studied with 6 different randomly selected patches from each batch was determined using analytical balance. Thickness of 6 patch of each formulation was determined using micrometer screw gauge and average was determined[22].

Folding endurance

Folding endurance of the patch was determined by repeatedly folding the film at the same place up to 200 times till it broken or folded. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance of patch. This study was performed in 6 patches, and the average of six readings was calculated [23,24].

Tensile strength measurement

The tensile strength was determined by an apparatus. Three strips of patch were cut having 1×1 dimention. The thickness and breadth of strips was noted at three sites and average value was taken for calculation. The rate of change of stress was kept constant with increment. The elongation was observed and the total weight taken was used for calculation. The tensile strength was calculated using the following formula:

$$\text{Tensile strength(S)}=\frac{m\times g}{b\times t}$$

Where S is tensile strength in dynes/cm^2, m is mass in grams, g is acceleration due to gravity (980 cm/sec), b is breadth of strip in cm, and t is thickness of strip in cm[25,26].

Swelling index

Ranitidine hydrochloride buccal patch of 2cm^2 allowed to swell on the surface of petridish containing 5ml of phosphate buffer pH 6.8 and weight of the swollen patch was recorded in the duration of 4 h. Three patches from each batch were cut and weighed and average weight was calculated (W_1). The patches were placed in the buffer and removed at time intervals 1, 2, 3, 4 h and water on the surface was carefully absorbed using filter paper and the swollen patches were reweighed[27].The average weight was calculated (W_2), and the swelling index was calculated by the formula:

$$S\ I = \frac{W2-W1}{W1} \times 100$$

Where,

SI = swelling index

W_2 = final weight

W_1 = initial weight

Drug content uniformity

Drug content for each of the formulations of patch (without backing layer) was determined by dissolving it in phosphate buffer 6.8 pH and allowed for continous stirring for 1 h and kept for 24 h. The resultant solution has been filtered, and then required dilution has been diluted and measured at UV spectrophotometer at 313nm[28-36].

Surface p^H of the patches

Three patches of each formulation are allowed to swell by keeping in contact with 0.5ml of distilled water (p^H 6.5) for 1 h at room temperature. The p^H was determined by bringing electrode in contact with the surface of the patch allowing it to equilibrate for 1 min[37-42].

Percentage moisture absorption

In order to evaluate the physical stability of the patches in high humidity condition, it is accurately weighed and placed in a desiccators containing saturated solution of aluminium chloride (79.5% relative humidity) for 3 days. The patches were reweighed and percentage moisture absorption was calculated by using the formula[43].

$$\text{Percentage moisture absorption} = \frac{\text{Final weight-Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss

This is to evaluate the percentage of moisture loss from the freshly prepared film. The prepared patch is accurately weighed and placed in a desiccators containing fused anhydrous calcium

chloride for 72 h. After 72 h again reweighed and percentage moisture loss was calculated using the formula[44].

$$\text{Percentage moisture loss} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100$$

Ex vivo bioadhesion time

The *ex-vivo* bioadhesion time was evaluated after application of the patches onto freshly cut goat buccal mucosa. The mucosa was fixed in the inner side of the beaker, above 2.5cm from the bottom with cyanoacrylate adhesive. The bioadhesive side of each patch was wetted with one drop of isotonic phosphate buffer p^H of 6.8 and affixed to the goat buccal mucosa by applying a light force with a fingertip for 30 s. The beaker was filled with 500ml of isotonic phosphate buffer p^H of 6.8 and temperature was maintained at 37 ± 1°C. After 2 min, a 50 rpm stirring rate was applied to simulate the buccal cavity environment and patch adhesion duration *i.e.* the time taken for the patch to detach from the mucosa was recorded as the bioadhesion time[45-48].

Ex vivo bioadhesion strength

The apparatus used for bioadhesion testing was assembled in the laboratory. Mucoadhesion strength of tablet was measured on a modified physical balance using the method using goat cheek pouch as model mucosal membrane. A double beam physical balance was taken, the left pan was removed. A thick thread of suitable length was hanged to left arm. To the bottom side of thread a glass stopper with uniform surface was tied. A clean 500 ml glass beaker was placed below hanging glass topper and another glass beaker of 50 ml was placed in inverted position and weighted 50gm to prevent floating. The balance was so adjusted that right hand side was exactly 5 gm heavier than the left.

Method

The balance adjusted as described above was used for the study. The goat buccal mucosa excised and washed was tied tightly with mucosal side upward using thread over the base of inverted 50 ml glass beaker. The beaker suitably weighed was lowered into 500 ml beaker, which was then filled with isotonic phosphate buffer pH 6.8 kept at 37^{o}C such that the buffer reaches the surface of mucosal membrane keep it moist. This was then kept below left handside

of balance. The buccal patch was then stuck to glass stopper through its backing membrane using cyanoacrylate adhesive. The 5 gm on right hand side is removed; this causes application of 5 gm of pressure on buccal patch overlying buccal mucosa. The balance was kept in this position for 3 min and then slowly weights were increased on the right pan, till tablet separate from mucosal membrane. The total weight on right pan minus 5 gm gives the force required to separate the patch from mucosa. This gives bioadhesive strength in grams. The mean value of 3 trials was taken for each set of formulations. After each measurement, the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 min before reading a new tablet of same formulation to get reproducible multiple results for the formulation [49-56].

***Ex vivo* permeation studies**

The study was carried out in franz diffusion cell. Cellophane membrane fixed between the donor compartment and the receptor compartment so that soft surface will face the donor compartment. The drug loaded patch placed above cellophane membrane and the two compartments were clamped together. The donor compartment was wetted with 2 ml of phosphate buffer of 6.8 p^H, receptor compartment was filled with isotonic phosphate buffer of 7.4 p^H, the diffusion cell was thermo stated at 37°C and the receptor compartment was stirred at 50 rpm. 2 ml sample was withdrawn at predetermined time intervals. The buffer was immediately replaced using blank buffer. After filtration through 0.45µm, an appropriate dilution of samples was analyzed for drug concentration by measuring the λ max at 313 nm[57-61].

***In-vitro* drug release studies**

Dissolution studies were carried out for all the formulations in triplicate, employing USP-II paddle method and 200ml of p^H 6.8 phosphate buffer as the dissolution medium for remaining 8 h. The medium was allowed to equilibrate to temperature of 37°C ±0.5°C. Buccal patch of dimension 3×6 cm, equivalent to 50 mg ranitidine hydrochloride patch was glued to a glass slide with instant adhesive from one side in order to ensure unidirectional drug release. The glass slide was put in the bottom of the dissolution vessel so that the patch remained on the upper side of the slide and the apparatus was operated for 8 h at 50 rpm. At definite time intervals of 5 ml of sample was withdrawn and filtered through whatman membrane filter (0.45µm). The volume replaced with equivalent amount of fresh dissolution medium. The samples were analyzed spectrophotometrically at 313 nm using UV-

spectrophotometer[37,62,63]. The amount and percentage of drug release can be calculated from the given formula,

$$\text{Concentration} = \frac{\text{absorbance}}{\text{Slope}}$$

$$\text{Amount of drug release} = \frac{\text{Concentration} \times \text{Bath volume} \times \text{Dilution factor}}{1000}$$

$$\text{Percentage of drug release} = \frac{\text{Amount of drug release} \times 100}{\text{Drug loaded}}$$

Kinetic study

The drug release kinetic studies were done by various mathematical models like zero order, first order, higuchi model, Hixson crowell model and korsmeyer peppas model. The model that best fits the release data is selected based on the correlation coefficient (r^2) values in various models. The model that gives high 'r^2' value is considered as the best fit of the release data.

RESULTS AND DISCUSSIONS:

Organoleptic evaluation

Table No. 3: Organoleptic evaluation

Color	**White to off white**
Odor	**Odorless**
Taste	**Bitter Taste**

Melting point determination

Melting point of Ranitidine was found to be 134° C which indicates the purity of the sample.

UV spectroscopy-determination of lambda max

The lambda max determination of ranitidine was done in phosphate buffer of p^H 6.8, which was scanned between 200-400 nm in the UV spectrophotometer. It was found to be 313 nm.

Standard Calibration curve for Ranitidine Hydrochloride

The standard calibration curve of pure drug ranitidine hydrochloride was determined as per methodology. The results were tabulated as shown in the **table 4.** The obtained results were used to plot a graph with absorbance v/s concentration. It gave straight line that passes through the origin.

Table No. 4: Standard graph of ranitidine hydrochloride

Sl. No	Concentration (µg/ml)	Absorbance(313nm) *± SD
1	0	0
2	10	0.042 ± 0.002
3	20	0.078 ± 0.004
4	40	0.155 ± 0.001
5	60	0.216 ± 0.003
6	80	0.302 ± 0.002
7	100	0.412 ± 0.004

*Average of three determinants, **SD=** standard deviation

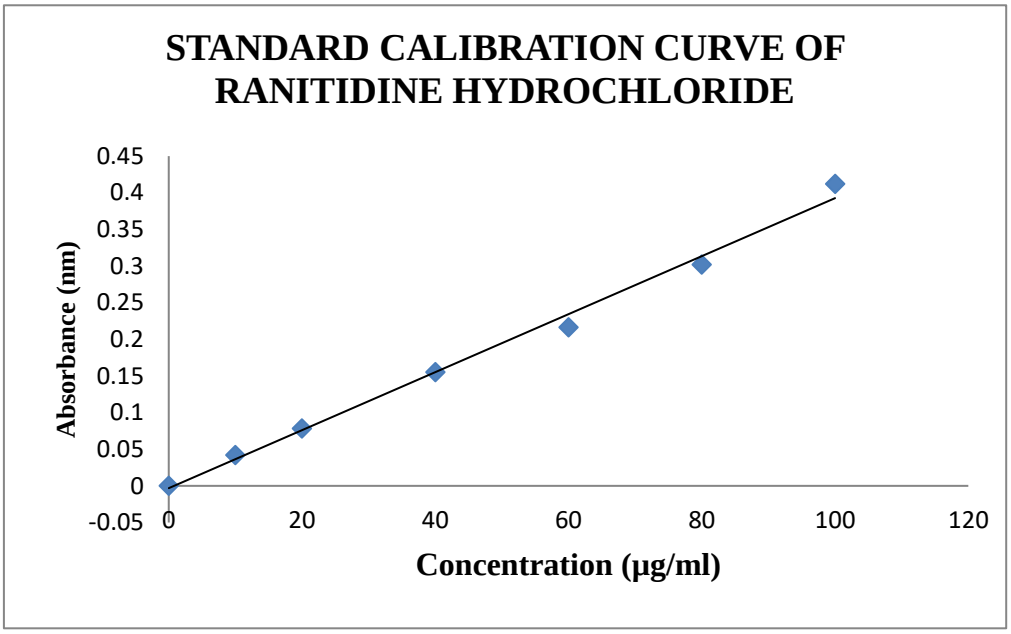


Figure No. 1: Standard calibration curve of ranitidine hydrochloride

Solubility determination

The solubility of the pure drug ranitidine hydrochloride was determined as per methodology**.** The results were showed in the **table 5.**

Table No. 5: Solubility analysis of ranitidine hydrochloride

Sl. No	Solvent	Solubility
1	Water	Soluble
2	Alcohol	Soluble
3	Acetic acid	Soluble
4	Distilled water	Soluble
5	pH 6.8 buffer	Soluble
6	Dichloromethane	Slightly soluble

Drug excipient compatibility studies

FTIR analysis was carried out on the basis of methodology.

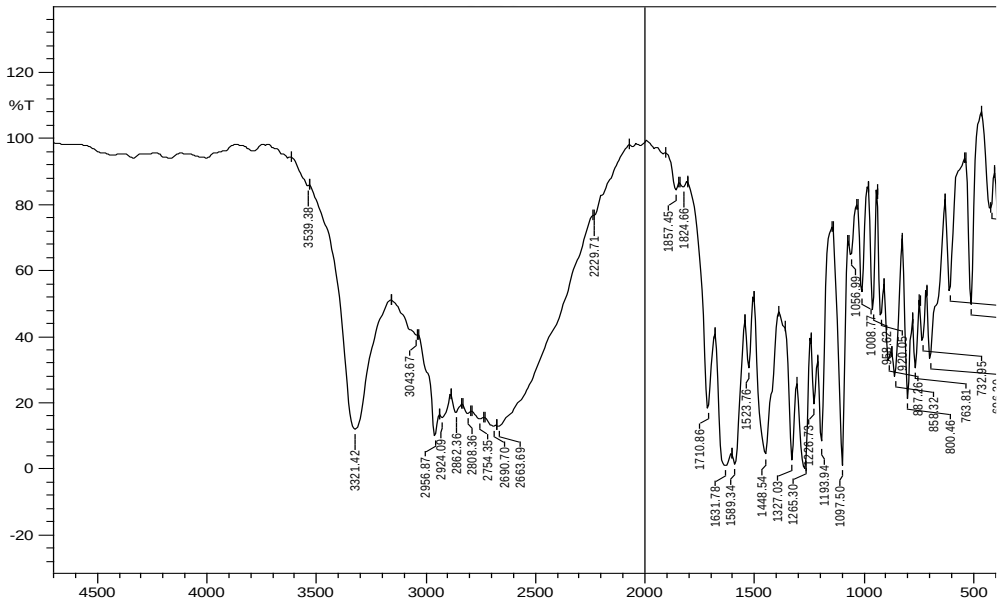


Figure No. 2: FTIR spectrum of ranitidine hydrochloride

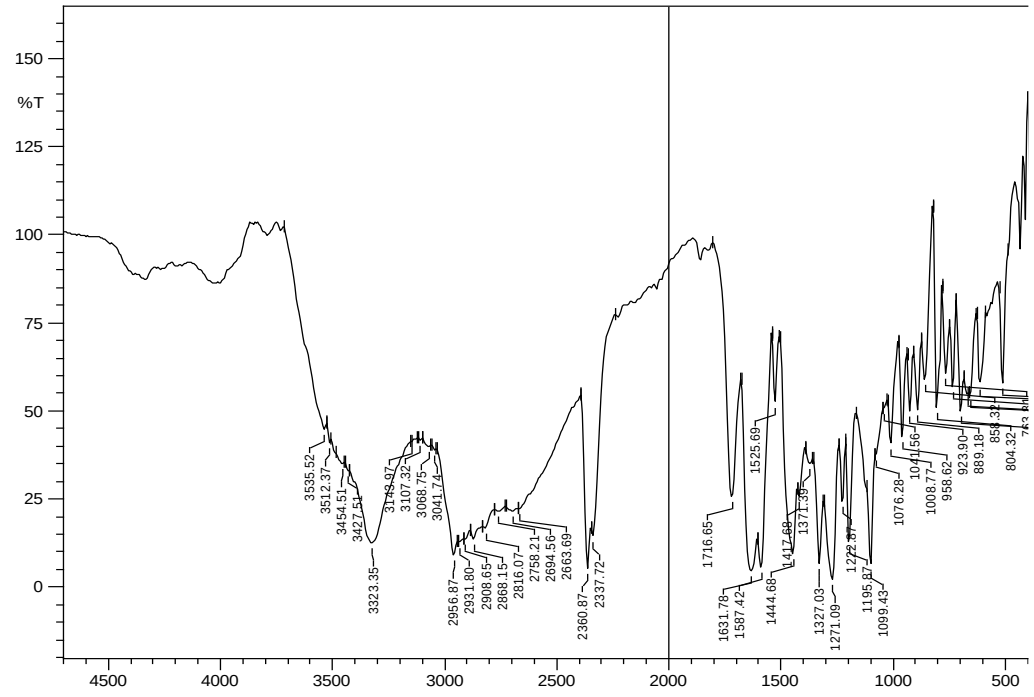
e 

Figure No. 3: FTIR spectrum of ranitidine hydrochloride with HPMC(K4M,K100M,K15M)+acetone+PVA+dibutyl pthalate+propylene glycol+ethyl cellulose

Table No. 6: Spectral analysis of ranitidine hydrochloride

Sl. No	Functional group	Characteristic peak range cm^{-1}	Characteristic peak cm^{-1}
1	C-H	3000-3250	3013.77
2	N-H	3250-3450	3321.42
3	C-N	1266-1342	1285.32
4	NO_2	1370-1390	1378.13

The interpretation of FTIR spectrum of ranitidine hydrochloride is given in **table 6.** The spectrum of ranitidine hydrochloride gave intense peaks for alkyl, amino, cyano and nitro groups. Some peaks were seen as overlapped.

FORMULATION DEVOLOPMENT

Figure No. 4: Ranitidine hydrochloride bilayered buccal patch

EVALUATION OF BILAYERED BUCCAL PATCHES

Mass uniformity

Weight of the patches was found to be uniform for each formula in the range of 79 ± 0.18 mg and 96.5± 0.16 mg**.**

Thickness

The thickness of all patches samples was uniform within each formulation in the range of 0.64 ± 0.74 mm and 0.88 ± 0.47 mm.

Folding endurance

All patches haven't showed any cracks even after folding for more than 160 times. This reflects that all formulations had good patch properties. Folding endurance of **F6** was high due to the higher amount of the HPMC polymers in combination. From the study it is understood that the folding endurance increases as the concentration of HPMC increases.

Surface p^H

Considering the fact that the acidic or alkaline p^H may cause irritation to the buccal mucosa, attempts were made to keep the surface p^H as close as to that of the salivary p^H (5.5 - 7). The p^H values of all formulations were within the range of the salivary p^H. No significant difference was observed in the surface p^H of different formulations in the range of 6.8 ± 0.86 - 7.2 ± 0.69, consequently, these patches can be considered non irritant to the buccal cavity and could achieve patient compliance.

Drug content

The result showed the drug content in the range of 92 ± 0.35 % to 98 ± 0.43 % they are within the acceptable pharmacopoeial limits.

Table No. 7: Evaluation of bilayered buccal patches

Sl. No	Batch code	Mass uniformity (mg) *± SD	Thickness (mm) *± SD	Drug content (% w/w) *± SD	Folding endurance *± SD	Surface pH *± SD
1	F1	82 ± 0.77	0.69 ± 0.17	97 ± 0.55	160 ± 0.45	6.9 ± 0.67
2	F2	79 ± 0.18	0.79 ± 0.87	92 ± 0.35	185 ± 0.75	7.1 ± 0.57
3	F3	90 ± 0.65	0.64 ± 0.74	93 ± 0.95	180 ± 0.34	6.8 ± 0.86
4	F4	858 ± 0.15	0.88 ± 0.47	95 ± 0.35	188 ± 0.27	7.2 ± 0.69
5	F5	96 ± 0.16	0.81 ± 0.16	95 ± 0.52	190 ± 0.36	7.1 ± 0.33
6	F6	92 ± 0.28	0.77 ± 0.82	98 ± 0.43	196 ± 0.68	6.8 ± 0.27

*****Average of six determinants, SD = Standard deviation

Measurement of swelling index

The swelling state of the polymer was reported to be crucial for its bioadhesive behaviour. Adhesion occurs shortly after the beginning of the swelling but the bond formation between the mucosal layer and polymer is not very strong. The faster the swelling of the polymer, the faster is the initiation of diffusion and formation of adhesive bonds; resulting in faster initiation of bioadhesion. All formulation was swelled within 10 min and the constant weight of the buccal patch was seen after 4 h. The degree of swelling index was in the order **F3>F1>F2** *i.e.*, the bilayer patch made up of HPMC K100M posses more swelling percentage as compared to HPMC K4M and HPMC K15M. The degree of swelling was obtained as **F6>F5>F4** *i.e.,* the bilayer patch formulated using three polymer combinations (HPMC K100: HPMC K15M: HPMC K4M) showed higher swelling index compared to the patches made up of two polymer combinations (HPMC K100: HPMC K15M & HPMC K15M: HPMC K4M).

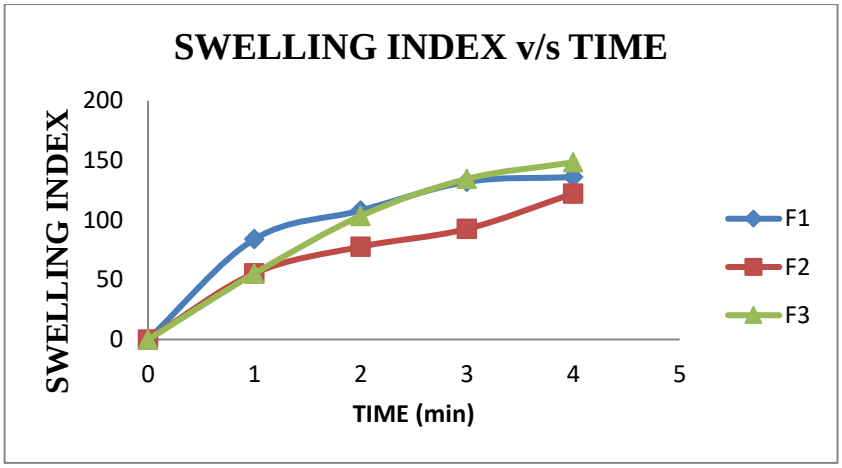


Figure No. 5: Swelling index v/s time profile of F1 - F3

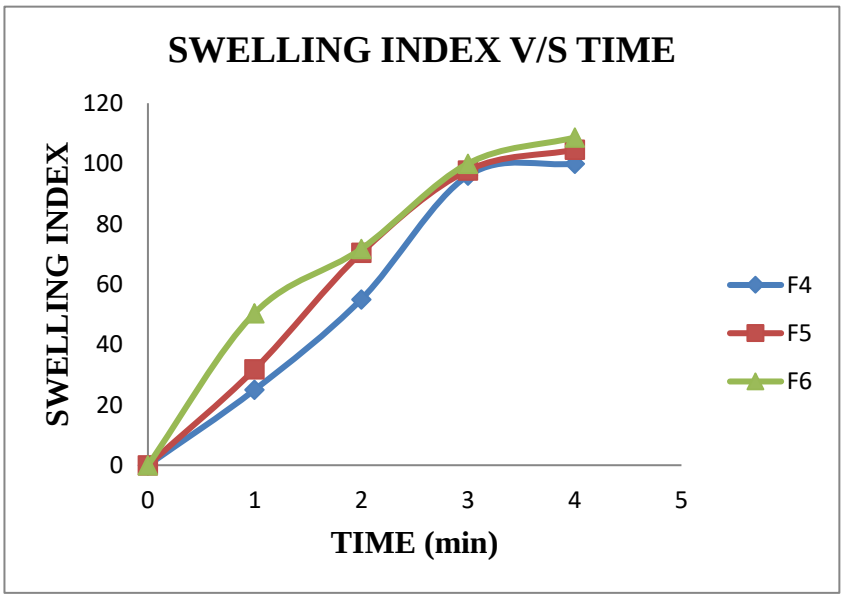


Figure No. 6: Swelling index v/s time profile of F4– F6

Measurement of tensile strength

The tensile strength was determined by the methodology**.** Tensile strength was varied with the polymers. The observed tensile strength in case of bilayer patches formulated using single polymers was **F2>F3>F1** *i.e.*, patches prepared with HPMC K15M was having increased tensile strength than those prepared with HPMC K100M and HPMC K4M. In case of patches formulated using combination polymers, the tensile strength was observed as **F6>F5>F4** *i.e.* the patches that was formulated using three polymer combinations (HPMC K100M: HPMC K15M: HPMC K4M) showed higher tensile strength compared to the patches that was formulated using two polymer combinations (HPMC K100: HPMC K15M & HPMC K15M: HPMC K4M).

Table No. 8: Tensile strength of bilayered buccal patches

Sl. No	Formulation	Tensile strength (N/cm^2) *± SD
1	F1	1.07 ± 0.28
2	F2	2.61 ± 0.47
3	F3	2.19 ± 0.37
4	F4	2.82 ± 0.31
5	F5	3.27 ± 0.55
6	F6	3.42 ± 0.40

***** Average of three determinants, SD = Standard deviation

Percentage moisture loss

The percentage of moisture content of all the batches was in the limit of 18.60 ± 0.34 - 28.57 ± 0.54**.**

Table No. 9: Percentage moisture loss

Sl. No	Formulation	Percentage Moisture loss (%) *±S.D
1	F1	26.13 ± 0.65
2	F2	22.5 ± 0.18
3	F3	28.4 ± 0.53
4	F4	18.60 ± 0.34
5	F5	21.57 ± 0.54
6	F6	19.51 ± 0.17

*****Average of three determinants, **SD =** Standard deviation

Percentage moisture content

The moisture uptake content was increased with increasing the concentration of polymers. Low moisture content of the formulation leads to the more protection from microbial contamination,

so they remained stable. The percentage moisture content of ranitidine hydrochloride patches was varied between 7.38 ± 0.13 - 8.5 ± 0.19.

Table No. 10: Percentage Moisture content

Sl. No	Formulation	Percentage Moisture Content (%) *± S.D
1	F1	8.75 ± 0.56
2	F2	7.38 ± 0.13
3	F3	8.29 ± 0.68
4	F4	7.8 ± 0.29
5	F5	8.09 ± 0.23
6	F6	7.25 ± 0.19

*Average of three determinants, **SD=** standard deviation

***Ex-vivo* bioadhesion time**

All the patches were subjected to *Ex-vivo* bioadhesion time test and the results are shown in the **table 11.** The residence time of the formulations ranged between 5 h to 7 h. None of the patches were detached over the study period from the mucosal membrane and this indicated that this period of time was sufficient to retain the patch on the mucosal membrane. Out of all the formulations, formulation **F6** showed the highest *ex-vivo* bioadhesion time.

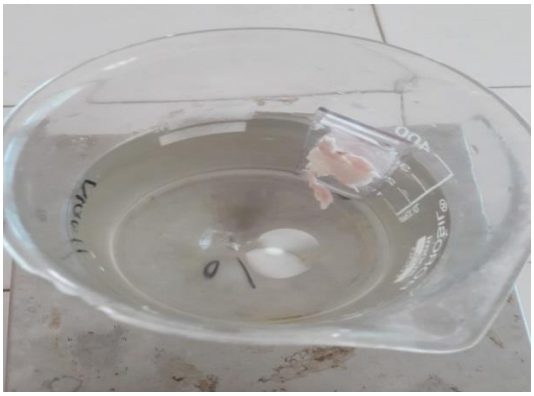


Figure No. 7: *Ex-vivo* bioadhesion time determination

Table No. 11: *Ex-vivo* bioadhesion time

Sl. No	Formulation	Bioadhesion time
1	F1	5 h 6 min
2	F2	6 h 5 min
3	F3	6 h 8 min
4	F4	6 h 7 min
5	F5	7 h 3 min
6	F6	7 h 6 min

***Ex vivo* bioadhesion strength**

All the patches were subjected to *ex vivo* bioadhesion strength test and the results are shown in the **table 12.** All the patches showed good bioadhesive strength, out of all the formulations, formulation **F6** showed the highest *ex vivo* bioadhesion strength.

Table No. 12: *Ex-vivo* bioadhesion strength

Sl. No	Formulation	Bioadhesion Strength *± S.D
1	F1	11.2 ± 0.17
2	F2	11.6 ± 0.13
3	F3	12.3 ± 0.11
4	F4	18.1 ± 0.16
5	F5	18.7 ± 0.14
6	F6	19.2 ± 0.12

*Average of three determinants, **SD=** standard deviation

***Ex-vivo* Permeation Study**

From the results obtained in **table 13** the patch **F6** showed 83.3% after 8 h.

Table No. 13: *Ex-vivo* permeation study

Time (h)	Percentage of drug Permeated (%)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	20.17	21.17	24.45	23.4	22.12	25
2	27.77	30.18	32.97	28.6	31.5	35.7
3	34.06	36.31	38.34	34.5	37.14	44.04
4	44.07	45.70	47.05	40.19	46.4	48.74
5	52.56	54.6	56.08	47.8	55.05	54.08
6	64.05	66.66	68.7	56.11	63.5	66.7
7	71.05	73.04	74.77	68.45	73.04	76.47
8	76.80	77.15	78.90	77.15	80.15	83.13

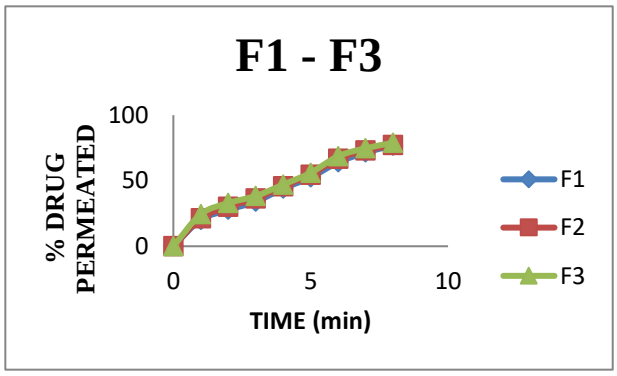


Figure No. 8: *Ex-vivo* permeation study of F1– F3

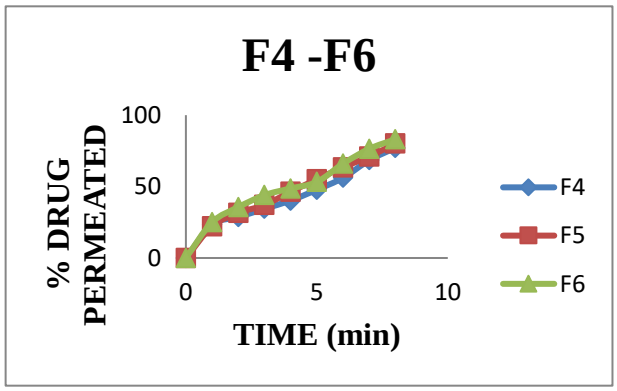


Figure No. 9: *Ex-vivo* permeation study of F4– F6

***In-vitro* drug release study**

The *in-vitro* release study was conducted as per the methodology**.** The results were obtained as follows.

F1

Table 14: *In-vitro* release study of F1

Sl. No	Time (h)	Percentage of drug release (%) *± S.D
1	0	0
2	1	27.2 ± 0.21
3	2	32.5 ± 0.19
4	3	37.03 ± 0.13
5	4	45.00 ± 0.18
6	5	55.64 ± 0.24
7	6	66.07 ± 0.22
8	7	74.65 ± 0.18
9	8	80.12 ± 0.21

*Average of three determinants, **SD=** standard deviation

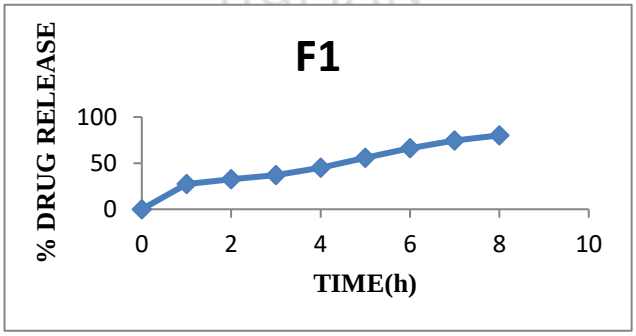


Figure No. 10: *In-vitro* release study of F1

F2

Table No. 15: *In-vitro* release study of F2

Sl. No	Time (h)	Percentage of drug release (%) *± S.D
1	0	0
2	1	24.01 ± 0.11
3	2	33.9 ± 0.23
4	3	47.12 ± 0.18
5	4	56.09 ± 0.28
6	5	64.98 ± 0.16
7	6	78.11 ± 0.15
8	7	83.85 ± 0.23
9	8	91.03 ± 0.21

*Average of three determinants, **SD=** standard deviation

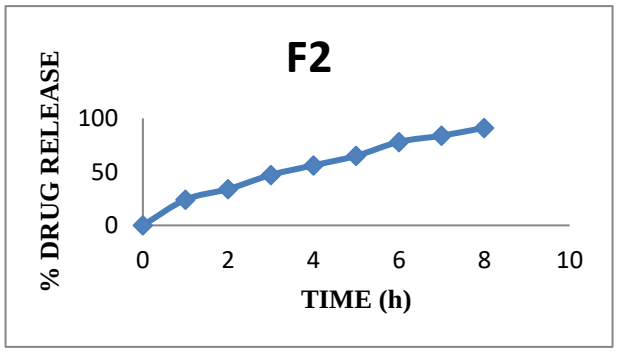


Fig 11: *In vitro* release study of F2

F3

Table No. 16: *In-vitro* release study of F3

Sl. No	Time (h)	Percentage of drug release (%) *± S.D
1	0	0
2	1	22.6 ± 0.16
3	2	35.7 ± 0.12
4	3	43.06 ± 0.25
5	4	57.21 ± 0.16
6	5	65.43 ± 0.17
7	6	71.98 ± 0.20
8	7	84.33 ± 0.19
9	8	91.0 ± 0.22

*Average of three determinants, **SD=** standard deviation

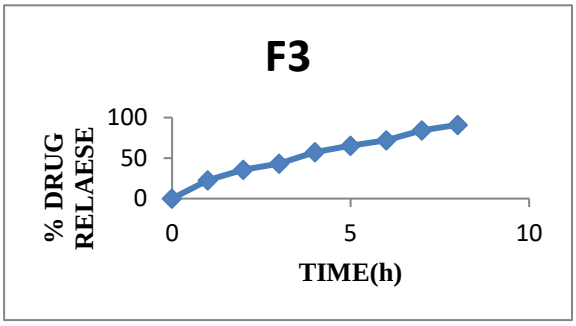


Figure No.12: *In-vitro* release study of F3

F4

Table No. 17: *In-vitro* release study of F4

Sl. No	Time (h)	Percentage of drug release (%) *± S.D
1	0	0
2	1	23.9 ± 0.24
3	2	32.04 ± 0.13
4	3	45.66 ± 0.18
5	4	54.7 ± 0.23
6	5	62.67 ± 0.22
7	6	77.03 ± 0.14
8	7	83.45 ± 0.17
9	8	91.5 ± 0.21

*Average of three determinants, **SD=** standard deviation

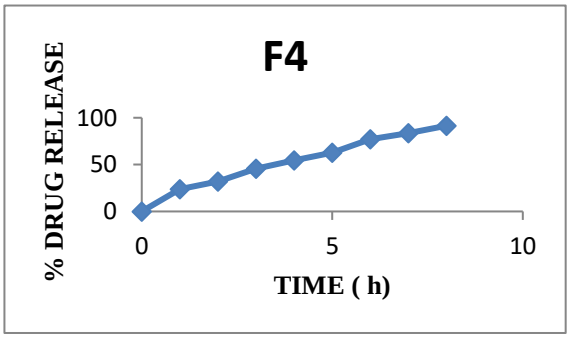


Figure No. 13: *In-vitro* release study of F4

F5

Table No. 18: *In-vitro* release study of F5

Sl. No	Time (h)	Percentage of drug release (%) *± S.D
1	0	0
2	1	21.2 ± 0.26
3	2	32 ± 0.19
4	3	48.8 ± 0.22
5	4	56.4 ± 0.15
6	5	61.05 ± 0.12
7	6	77.21 ± 0.21
8	7	85.12 ± 0.18
9	8	92.2 ± 0.14

*Average of three determinants, **SD=** standard deviation

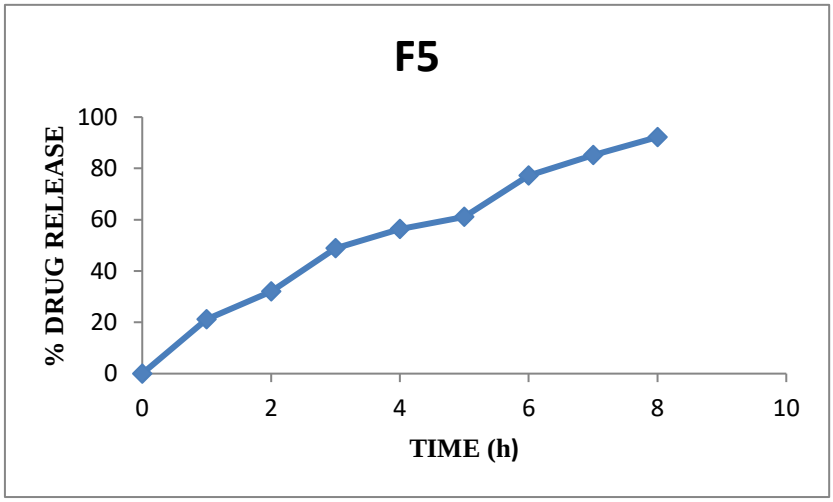


Figure No. 14: *In-vitro* release study of F5

F6

Table No. 19: *In-vitro* release study of F6

Sl. No	Time (h)	Percentage of drug release (%) *± S.D
1	0	0
2	1	28.6 ± 0.15
3	2	34.96 ± 0.19
4	3	49.05 ± 0.23
5	4	59.8 ± 0.17
6	5	66.5 ± 0.22
7	6	75.9 ± 0.17
8	7	88.90 ± 0.22
9	8	95.8 ± 0.12

*Average of three determinants, **SD=** standard deviation

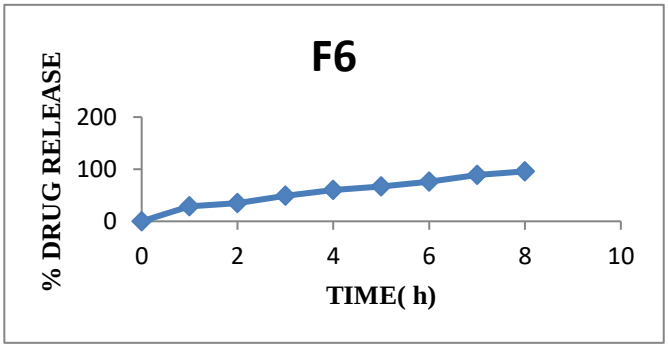


Figure No. 15: *In-vitro* release study of F6

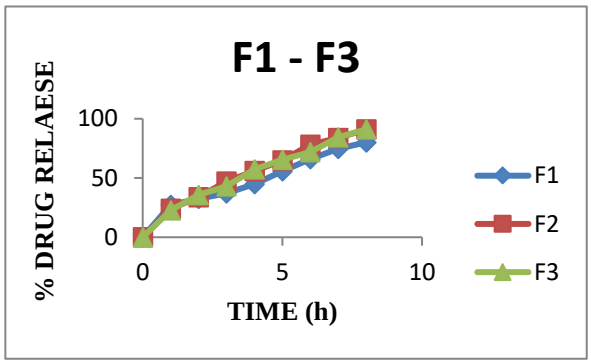


Figure No. 16: Comparative *in-vitro* release study of F1 - F3

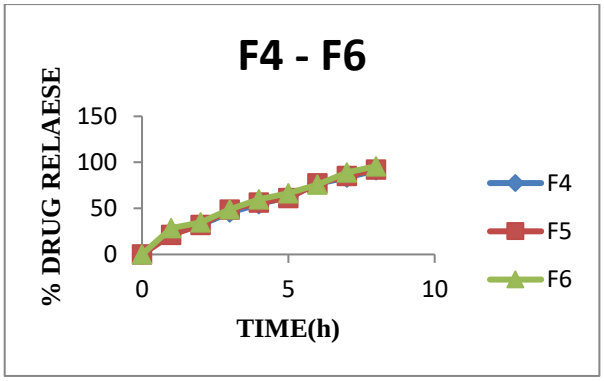


Figure No. 17: Comparative *in-vitro* release study of F4 - F6

The *in-vitro* drug release studies were carried out in phosphate buffer (pH 6.8) using USP dissolution apparatus. The *in-vitro* release profile from **F6** showed maximum release 95.8 % of drug within 8 h.

Kinetic study

The kinetic study of ranitidine hydrochloride buccal patches was carried out as per methods. The study was observed as in **table 20.**

Table No. 20: Regression value of kinetic models

Formulation	**Kinetic Models**			
F6	Zero Order	First Order	Korsemeyer-Peppas plot	Higuchi
R^2 Value	0.97	0.885	0.895	0.916

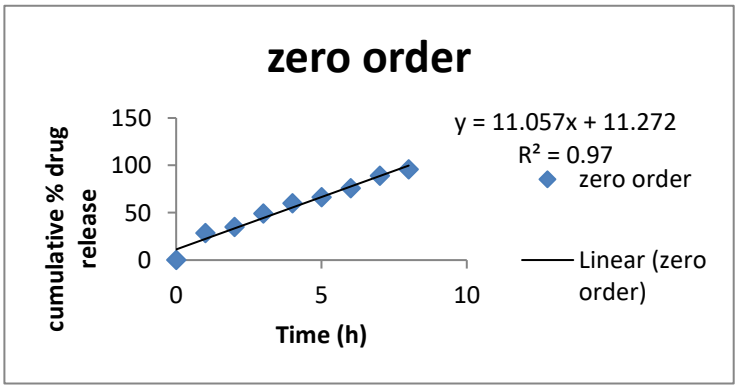


Figure No. 18: Zero order plot for F6

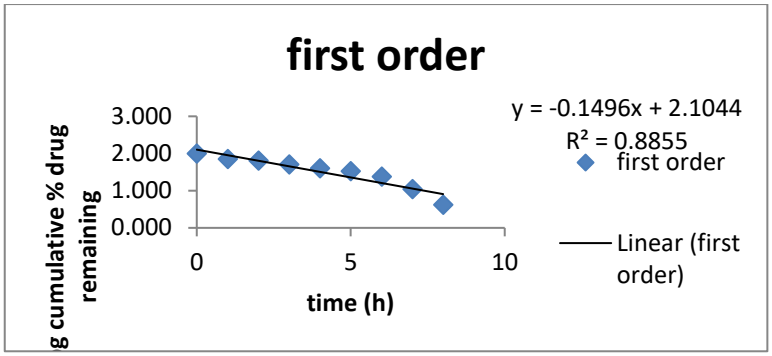


Figure No. 19: First order plot for F6

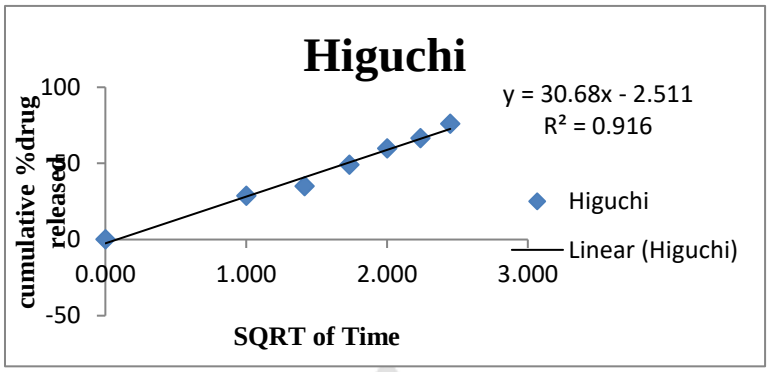


Figure No. 20: Higuchi plot of F6

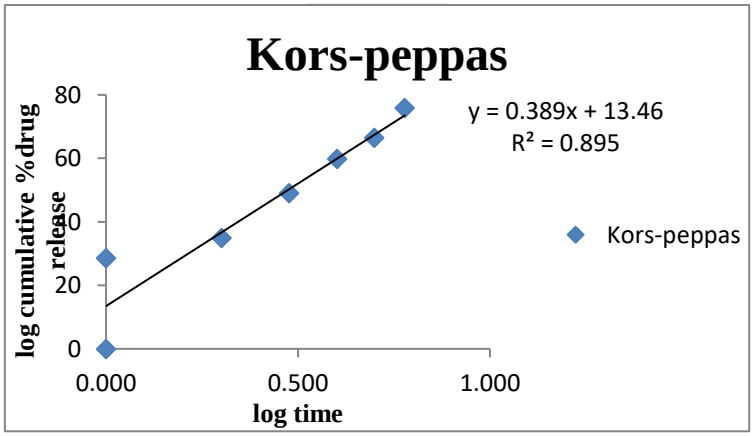


Figure No. 21: Kors-Peppas plot of F6

The dissolution profile of optimized formulation **F6** was fitted to various kinetic models like zero order, First order, Higuchi model and Korsmeyer-Peppas models were used. The values of co-efficient of correlation were found to be best fitted to Higuchi models as shown in **table 20**. Higuchi model describes the release of drugs from an insoluble matrix as a square root of a time dependent process based on Fickian diffusion. The release constants were calculated from the slope of the appropriate plots, and the regression coefficient was determined. It was

found that the *in vitro* drug release of drug from bilayer buccal patch was best explained by zero order model as it showed the highest value for R^2 (0.97), followed by Higuchi model (0.916) indicates that drug released by diffusion mechanism. The formulation indicates that the drug release continues and constant until drug at absorption site.

CONCLUSION

In the present research work an attempt was made to prepare bilayer buccal patches of ranitidine hydrochloride. The bilayer buccal patches were prepared by solvent casting method with the combination of HPMC K4M, K15M, K100M and polyvinyl alcohol for drug layer and ethyl cellulose for backing layer, they proved that they can meet the ideal requirement for buccal device, which are good potential to bypass or avoids the extensive hepatic first pass metabolisms. Thus it was concluded that, as per the pre-established objectives the physio-chemical characterization and *in vitro* evaluation of ranitidine hydrochloride bilayer buccal patches were performed and obtained satisfactory results. The present research proved that buccal patches are potential drug delivery systems that will have significant impact in the community, as this will protect drug from first pass metabolism and degrading effects of p^H and different enzymes.

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