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Formulation Design and Evaluation of Mucoadhesive Buccal Patch of Ketorolac for the Treatment of Periodontitis

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Abstract:- In the present work the aim is to successfully develop a formulation in the form of buccal patch which has prolong residence time also for addressing the problem of osteoporosis in infected teeth. Patients can control the period of administration or terminate delivery in case of emergencies. The buccal drug delivery systems easily administered into the buccal cavity. The novel buccal dosage forms Exhibits better patient compliance. The formulation F4 is selected for best formulation because its show the 98.85% drug release at time 6 hr, folding endurance is 189±4 times and weight of prepared film is 95±4 mg and thickness 43±2 mm of these formulations respectively.

Keywords: *Ketorolac, Mucoadhesive, Formulation and Evaluation of Buccal Film, Solvent Casting, Buccal Film.*

I. INTRODUCTION

Buccal patches are preferable in terms of flexibility and comfort. The application of buccal patches to the site is easy and can be removed according to our need (Raghavendra, 2013). Buccal patch consists of mucoadhesive polymers and other excipients. Due to the adhesive property of the polymer it will binds to the buccal mucosa and the drug will be released to the systemic circulation (Khobragade, 2014).

II. EXPERIMENTAL SECTION

Materials:

Ketorolac tromethamine were obtained as a gift sample from Bioplus life science, Bangalore, HPMC-E15 was purchased from lobachemie,Mumbai,PEG-400,Edudragit RLPO,RSPO and carbopol 934P was purchased from Lobachemie,mumbai, ethanol was purchased from Qualigens fine chemicals, Mumbai.

Method:

Solvent casting:-In the solvent casting process, a specified amount of mucoadhesive polymers is treated with solvent, and the polymer swells after vortexing. The determined amount of plasticizer was applied to the polymer mixture and vortexed again. The necessary amount of medication was liquefied in a small amount of solvent method and then applied to the polymer solution and thoroughly mixed. The entrapped air is then released, and the mixture is transferred to a freshly cleaned Petri plate. The patches are held in a desiccator until the assessment checks are completed (Tarun et al,2013).

Formulation and evaluation of mucoadhesive buccal patches

Ketorolac tromethamine buccal patches are prepared by solvent casting technique using aluminium foil (placed as substrate on glass mold (5*15cm). The composition of multiple formulations of a single square cast patches is stated in the table 1. Ethanol was used as a solvent and PEG as a plasticizer in conjunction with Edudragit RLPO, Eudragit RSPO and Carbopol 934P, and buccal patches were prepared using HPMC-E15(Semalty,2008).

Table 1: Formulation Ingredient for the preparation of mucoadhesive buccal patches

Components	F1	F2	F3	F4	F5	F6
Ketorolac tromethamine (mg)	120	120	120	120	120	120
HPMC-E15 (mg)	1000	1000	1000	1000	1000	1000
Edudragit RLPO (mg)	300	-	-	150	-	100
Eudragit RSPO (mg)	-	300	-	150	150	100
Carbopol 934P (mg)	-	-	300	-	150	100
PEG (ml)	0.5	0.5	0.5	0.5	0.5	0.5
Ethanol (ml)	20	20	20	20	20	20

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In ethanol, the measured concentrations of polymers were dispersed. After levigation with 0.5ml propylene glycol, which acted as a plasticizer and penetration enhancer, 120mg of Ketorolac tromethamine was introduced into the polymeric solutions. To achieve smooth, bubble-free gels, the medicated gels were left overnight at room temperature. Medicated gels is filled into the vials and securely sealed with rubber seals to avoid alcohol evaporation. To shape a versatile patch, the gels were cast into a glass mold and allowed to dry overnight at room temperature (25°C). The dried patches were cut into size of 2.5*2.5cm, packed in aluminium foil and stored in a desiccator until further use. Fig 1 shows the trial batch of mucoadhesive buccal film and fig 2 show the optimized batch of mucoadhesive buccal film.

Dose Calculation

Diameter of the dish (shape) = 5 cm
Distance of the dish (shape) = 15 cm
No. of 2.5 x 2.5 cm film near full (shape) = 12
Each patch carry 5 mg of drug.
12 No. of patches carry mg of drug? = 10×12 = 120mg
The quantity of remedy put in each dish was roughly similar to 120 mg.

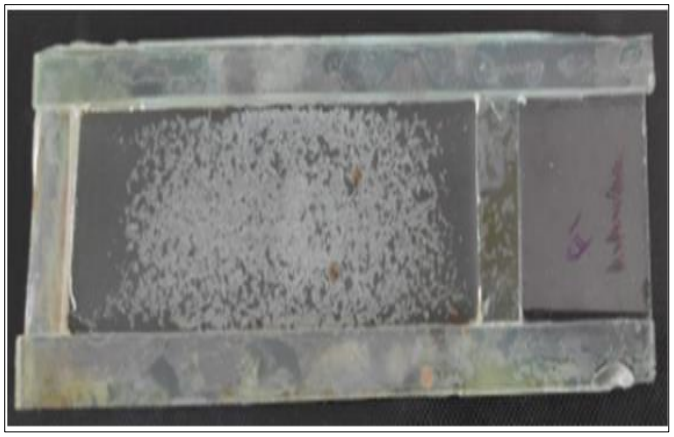

Fig.1 Formulation development of trial batch of mucoadhesive buccal patch

Fig.2 Formulation development of optimized batch of mucoadhesive buccal patch

Evaluation of buccal patches

Thickness

Electronic digital micrometer, digital vernier caliper or micro screw gauge can be used to measure the thickness of the patch. Thickness of the different location (corners and the center) is measured to assess the average thickness of the film (Kashappa,2004).

Weight uniformity

Three patches were chosen at random for each formulation. For the weight variance test, 10 patches from each sample were independently weighted on a digital electronic balance, and the average weight was estimated (Nafee,2003).

Percentage of Moisture Content

The patches were measured individually and stored at room temperature for 24 hours in desiccators containing activated silica. Individual patches were measured repeatedly before a consistent weight was reached. The discrepancy between the original and final weight with respect to the final weight was used to measure the percentage of moisture content (Bharti,2007).

Drug Content Analysis

The patch was dissolved in methanol in a 10 ml volumetric flask, and the amount was filled up of 10 ml methanol. Following that, dilutions were made and UV spectrophotometer at 246nm was used to react them (Alix,2003).

Folding Endurance

This was decided by folding one patch in the same spot over and over before it separated. The value of folding endurance was determined by the number of times the patch could be folded at the same location without splitting or cracking (Baboota,2005).

Percent swelling

The samples were allowed to swell on the surface of an agar plate in an incubator held at 37±0.2°C after the initial patch weight and diameter were determined. After 2 hours, the weight of the patches (n = 3) had increased. The following equation was used to measure the percent swelling percent S (Patel,2009).Percent Swelling (%S) = $(X_t - X_o/X_o) \times 100$, where X_t is the weight of the swollen patch after time t, X_o is the initial patch weight at zero time.

Surface pH of patches

Three patches of each formulation were allowed to swell for two hours on the surface of an agar plate to determine the surface pH. A pH paper was mounted on the surface of the swollen patch to determine the pH. The composite of three readings was taken (Karlsmark,2008).

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***In vitro* residence time**

The in vitro residence time was determined using IP disintegration apparatus (Karlsmark, 2008). The disintegration medium was 800 ml of pH 6.6 phosphate buffer (PB) maintained at 37±2°C. Three-centimeter-long segments of rat intestinal mucosa were fused to the surface of a glass slab, which was then vertically connected to the apparatus. Every formulation's three mucoadhesive patches were hydrated on one surface with pH 6.6 PB before being placed in contact with the mucosal membrane. The glass slab was attached to the mechanism vertically and moved up and down. At the lowest point, the patch was totally submerged in the buffer solution, and at the highest point, it was completely out. Table 2 shows the time taken for total degradation or detachment of the patch from the mucosal surface (n = 3).

vitro release study

The USP XXIV six station dissolution apparatus type 1 (Labindia DS-8000) was used throughout the study(Higuchi, 1965). Using cyanoacrylate adhesive, one patch of each formulation was attached to the central shaft just above the paddle. 900 ml of pH 6.6 phosphate buffer acted as the dissolution medium. The release analysis was carried out at a rotating speed of 50 rpm and a temperature of 37±0.5°C. The release analysis lasted six hours. Per hour, 1 ml of sample was taken from each station and substituted (with the dissolution medium) in the same amount. Each sample was screened, diluted appropriately, and spectrophotometrically analyzed at 246nm. The information given was the average of three tests.

Dissolution apparatus = Type I (paddle apparatus)
Dissolution medium = 6.6 (PB)
Rotating speed = 50 rpm.
Volume = 900 ml
Temperature = 37±0.5°C

Fig no 3. In vitro Dissolution studies

Mathematical treatment of in-vitro release data: When mathematical formulas that express dissolution effects as a function of some of the dosage type characteristics are used, quantitative interpretation of the values obtained in dissolution/release experiments becomes simpler.

Zero-order kinetics: Following this profile, prescription dosage formulations emit the same volume of medication per unit of time, rendering it the perfect type of drug release for achieving pharmacologically extended operation. This model can be represented in a simple way using the following relation:

$$Q_t = Q_o + K_o t$$

Where $Q_t$is the amount of drug dissolved in time t, $Q_o$is the initial amount of drug in the solution (most times, Q_o=0) and $K_o$is the zero order release constant.

First-order kinetics: The following relation expresses this model:

$$\log Q_t = \log Q_o + \frac{K_1 t}{2.303}$$

Where $Q_t$is the amount of drug dissolved in time t, $Q_o$is the initial amount of drug in the solution and $K_1$is the zero order release constant.

A graph of the decimal logarithm of the drug's published number V_s time would be linear as a result. Pharmaceutical dosage formulations that adopt this dissolution profile, such as those containing water-soluble drugs in porous matrices, release medication proportionally to the amount of drug remaining in their interior, resulting in a reduction in the amount of drug released per unit of time.

Higuchi model: Higuchi devised a number of experimental models to investigate the release of water-soluble and low-soluble drugs in semi-solid and solid matrixes. For drug particles scattered in a uniform matrix acting as diffusion media, mathematical expressions were obtained.

The simplified Higuchi model is expressed as:

$$Q = K_H . t^{1/2}$$

The amount of drug released in time t is Q, and the Higuchi dissolution constant is K_H. The Higuchi model depicts drug release as a square root time dependent diffusion mechanism based on Fick's law. This association can be used to explain the degradation of water-soluble medications from a number of modified release prescription dosage formulations, such as transdermal systems and matrix tablets.

Korsmeyer-Peppas model: Korsmeyer *et al.* used a simple empirical equation to describe general solute release behaviour from controlled release polymer matrices:

$$\frac{M_t}{M_\infty} = a\, t^n$$

Where M_t/M_∞ is fraction of drug released, a is kinetic constant, t is release time and n is the diffusional exponent for drug release. 'n' is the slope value of log M_t/M_∞ versus log time curve. Regardless of the release process, Peppas stated that the above equation could accurately explain the release of solutes from slabs, spheres, cylinders, and disks. Peppas used this n value in order to characterize different release mechanisms, concluding for values for a slab, of *n* =0.5 for Fickian diffusion and higher values of *n*, between 0.5 and 1.0, or *n* =1.0, for mass transfer following a non-Fickian model. In case of a cylinder *n* =0.45 instead of 0.5, and 0.89 instead of 1.0. This equation can only be used in systems with a drug diffusion coefficient fairly concentration independent. To the determination of the exponent *n* the portion of the release curve where $M_t/M_\infty <$ 0.6should only be used. To use this equation, the release must be one-dimensional and the device width-thickness or length-thickness relationship must be at least ten. To account for the lag time (l) at the start of drug release from the pharmaceutical dosage type, a modified version of this equation was developed:

$$\frac{M_{t-l}}{M_\infty} = a\,(t-l)^n$$

When there is the possibility of a burst effect, b, this equation becomes:

$$\frac{M_t}{M_\infty} = at^n + b$$

The l and b values would be zero if there was no lag time or burst effect, and only at^n would be used. This statistical model, also known as Power Law, has been used to explain the release of a number of prescription adjusted release dosage types on a daily basis.

III. RESULTS

Thickness

The thickness of patches was measured at three different places using a vernier caliper. The thickness was found 52±2, 48±3, 45±4, 43±2, 40±4 and 42±2 for formulation F1, F2, F3, F4, F5 and F6 respectively. Graph 2 shows the thickness for formulation F1 to F6.

Table no.2 film thickness

Formulation code	General appearance	Thickness* (µm)
F1	Transparent	52±2
F2	Transparent	48±3
F3	Transparent	45±4
F4	Transparent	43±2
F5	Transparent	40±4
F6	Transparent	42±2

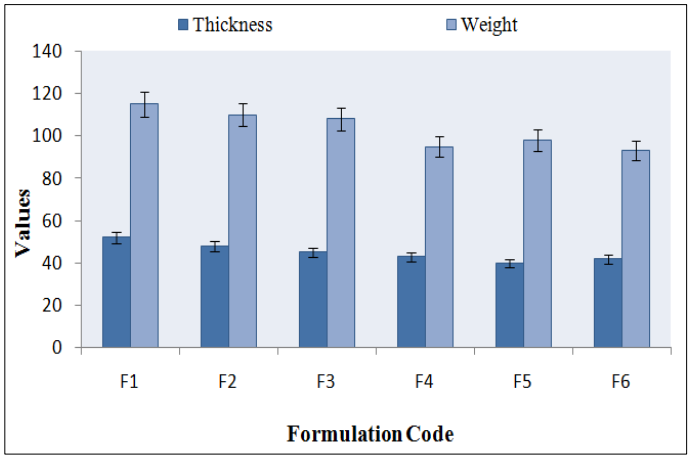
Average of three determination (n=3±SD)

Weight uniformity

For the weight variance test, ten patches from each sample were independently weighted on a digital electronic balance and the average weight measured. All of the formulations were found to have a comparable weight. The weight was found 115±2, 110±3, 108±2, 95±4, 98±5 and 93±2 for formulation F1, F2, F3, F4, F5 and F6 respectively. Results of weigh uniformity reveled the uniform mixing of drug and polymers.

Table no.3 weight uniformity

Formulation	General Appearance	Weight (mg)
F1	Transparent	115±2
F2	Transparent	110±3
F3	Transparent	108±2
F4	Transparent	95±4
F5	Transparent	98±5
F6	Transparent	93±2



Graph no.1 representative of thickness & Weight uniformity for formulation F1 to F6

Percentage of Moisture Content

The discrepancy between the original and final weights with respect to the final weight was used to quantify the percentage of moisture content. The percentage moisture content was found 2.12±0.36, 2.14±0.25, 2.78±0.14, 2.01±0.23, 2.36±0.41 and 2.41±0.32 for formulation F1, F2, F3, F4, F5 and F6 respectively. Formulation F4 had a lower percentage moisture content, which may be attributed to Edudragit RSPO and Carbopol 934's percentage swelling properties. Graph no.2 shows the percentage of moisture content for formulation F1 to F6.

Table no.4 Percentage of Moisture Content

Formulation	General Appearance	Percentage of Moisture Content
F1	Transparent	2.12±0.36
F2	Transparent	2.14±0.25
F3	Transparent	2.78±0.14
F4	Transparent	2.01±0.23
F5	Transparent	2.36±0.41
F6	Transparent	2.41±0.32

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Average of three determinations (n=3)

% Drug Content

The drug quality determination confirms that the API is distributed uniformly across the patch. The percentage drug content of different formulations F1, F2, F3, F4, F5 and F6 were found 98.85±0.32, 98.65±0.25, 98.87±0.14, 99.12±0.23, 98.58±0.12 and 97.65±0.14. The maximum percentage drug content was found in formulation F-4 (99.12±0.23). The drug concentration was observed to be close to 100 in all formulations, indicating standardized drug mixing in solution. Graph 2 shows the % drug content for formulation F1 to F6.

Table no.5 Drug Content

Formulation	General Appearance	% Drug Content
F1	Transparent	98.85±0.32
F2	Transparent	98.65±0.25
F3	Transparent	98.87±0.14
F4	Transparent	99.12±0.23
F5	Transparent	98.58±0.12
F6	Transparent	97.65±0.14

Average of three determinations (n=3)

Surface pH

Given that acidic or alkaline pH will irritate the buccal mucosa and influence the degree of hydration of polymers, the surface pH of the buccal patches was determined to optimize both drug permeation and mucoadhesion. Through using the right polymers for the buccal patches, it was possible to maintain the surface pH as close to the buccal/salivary pH as possible. Surface pH of the formulation F1 to F12 varied from 5.84 ± 0.07 to 6.61 ± 0.1. The results revealed that all the formulations provide an acceptable pH in the range of 5.5 to 7.0 (salivary pH). The pH of different formulations F1, F2, F3, F4, F5 and F6 were found 6.92±0.45, 6.75±0.23, 6.76±0.14, 6.81±0.25, 6.65±0.36 and 6.56±0.41 respectively. All of the patches had a surface pH that was within the salivary pH range. There was no noticeable difference in the pH of the patches' surfaces.

Table no.6 Surface pH

Formulation	General Appearance	Surface pH
F1	Transparent	6.92±0.45
F2	Transparent	6.75±0.23
F3	Transparent	6.76±0.14
F4	Transparent	6.81±0.25
F5	Transparent	6.65±0.36
F6	Transparent	6.56±0.41

Average of three determinations (n=3)

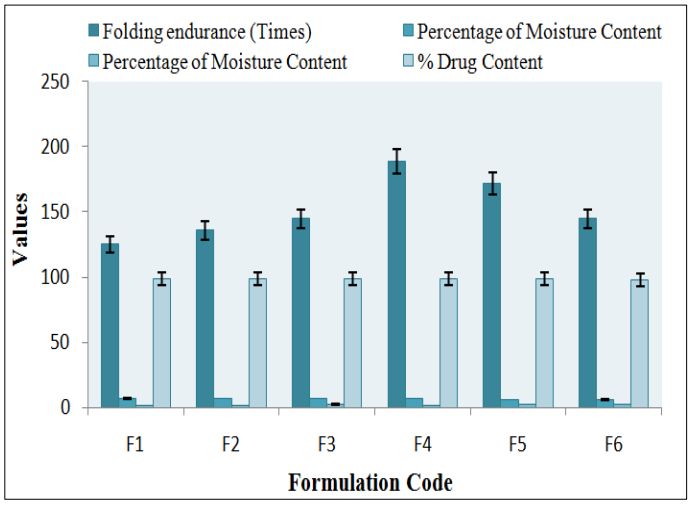
Folding Endurance

Folding stamina was calculated manually by folding the patches over and over before they separated. The end point was determined by the breaking time. Folding endurance was found to be highest for F4 (189±4) and lowest for F1 (125±3) which are within acceptable range. Graph 2 shows the folding endurance for formulation F1 to F6.

Table no.7 Folding Endurance

Formulation	General Appearance	Folding Endurance (Times)
F1	Transparent	125±3
F2	Transparent	136±2
F3	Transparent	145±5
F4	Transparent	189±4
F5	Transparent	172±5
F6	Transparent	145±4

Average of three determinations (n=3)



Graph no 2. representative of folding endurance, percentage moisture content and % drug content

Percent swelling for formulation F1 to F6.

Hydration is needed for a mucoadhesive polymer to extend and create a proper macromolecular mesh of sufficient size, as well as to induce mobility in the polymer chains, in order to promote the process of interpenetration between polymer and mucin. Polymer swelling allows mechanical entanglement by exposing the bioadhesive sites to hydrogen bonding and/or electrostatic interaction with the polymer and the mucous network. However, where maximal swelling and bioadhesion occurs, the mucoadhesive polymer maintains a vital amount of hydration. The swelling behavior and residence time of several mucoadhesive polymers were also affected by Ketorolac tromethamine. The swelling review took two hours to finish. 42.21±1.92, 38.20±1.62, 51.09±1.25, 52.63±1.91, 54.42±2.32 and 49.24±2.12 percent were found to be the proportion of swelling of formulations F1, F2, F3, F4, F5 and F6. The tailored formulation F4 had the greatest percentage of swelling (52.63±1.91 percent).Graph no.3 show the percent swelling for formulation F1 to F6.

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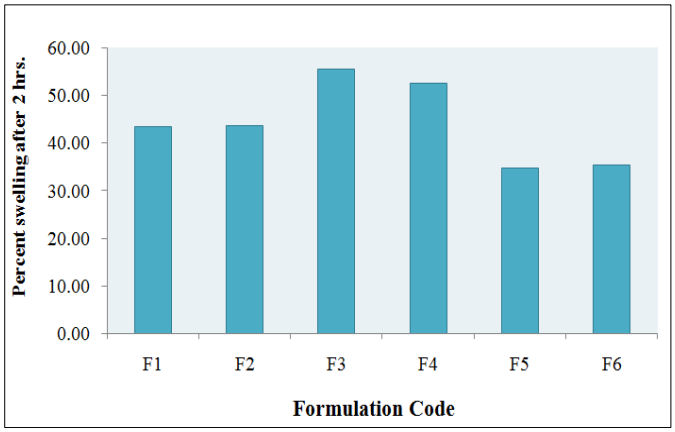
Table no.8 Percent swelling

S. No.	Formulation code	Percent Swelling after 2 hrs		
		Final Weight	Initial Weight	% Swelling
1	F1	165	50	41.21±1.92
2	F2	158	48	38.20±1.62
3	F3	160	52	51.09±1.25
4	F4	145	50	52.63±1.91
5	F5	132	34	54.42±2.32
6	F6	126	33	49.24±2.12



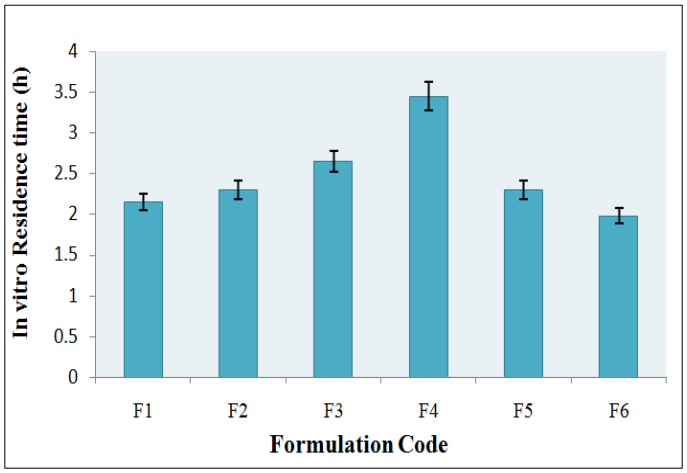
Graph no.3 representative of Percent swelling for formulation F1 to F6

In vitro residence time

Table 9 shows the residence time of different formulations. Non-ionic polymers were found to have a higher rate of erosion (HPMC with Eudragit RLPO and RSPO). The matrix experiences an intra-matrix swelling force as the particle swells, causing the drug to disintegrate leak and leaving a highly porous matrix behind. Water influx weakens the polymer's network stability, affecting the swollen matrices' structural resistance, resulting in marked degradation of the lose gel layer. The residence time was found 2.15±0.2, 2.30±0.3, 2.65±0.2, 3.45±0.1, 2.30±0.2 and 1.98±0.1 for formulation F1, F2, F3, F4, F5 and F6.Graph no 4 show the in vitro residence time for formulation F1 to F6.

Table no.9 in vitro residence time

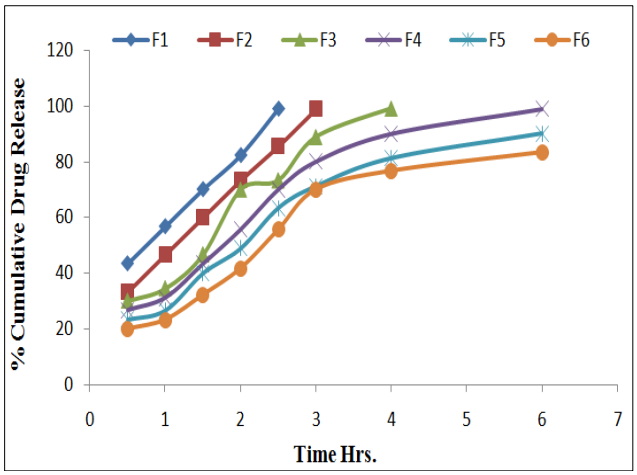
S. No.	Formulation Code	In vitro residence time
1	F1	2.15±0.2
2	F2	2.30±0.3
3	F3	2.65±0.2
4	F4	3.45±0.1
5	F5	2.30±0.2
6	F6	1.98±0.1



Graph no.4 representative of *in vitro* residence time for formulation F1 to F6

Table no.10 In vitro drug release study

S. No.	Time (hr)	% Cumulative Drug Release					
		F1	F2	F3	F4	F5	F6
1	0.5	43.32	33.23	29.98	26.65	23.32	19.98
2	1	56.65	46.65	34.45	31.14	26.65	23.32
3	1.5	69.98	59.98	46.65	43.32	39.98	32.25
4	2	82.23	73.32	69.98	55.65	48.85	41.74
5	2.5	98.89	85.56	73.32	69.98	63.32	55.65
6	3		98.89	88.89	79.98	71.12	69.98
7	4			99.12	89.95	81.12	76.65
8	6				98.85	89.98	83.32

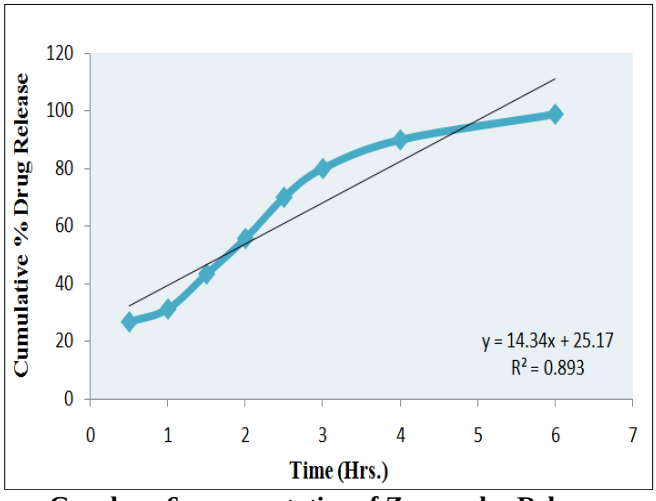


Graph no.5 representative of In-vitro drug release study of formulation F1 to F6

Table no.11 In-vitro drug release data for formulation F-4

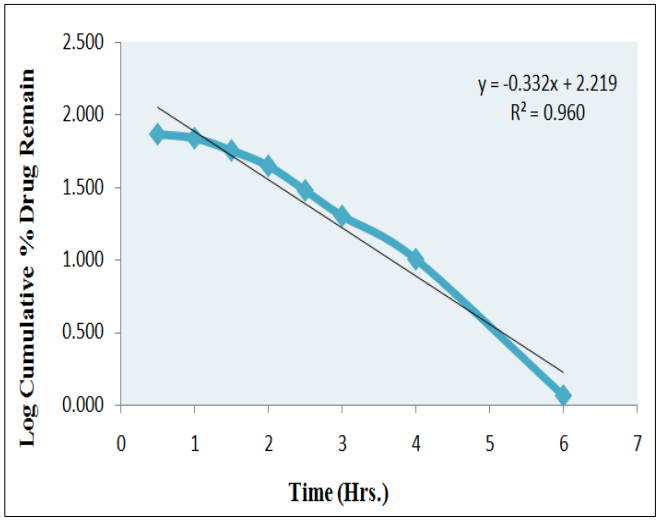
Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	0.301	26.65	1.426	73.35	1.865
1	1.000	0.000	31.14	1.493	68.86	1.838
1.5	1.225	0.176	43.32	1.637	56.68	1.753
2	1.414	0.301	55.65	1.745	44.35	1.647
2.5	1.581	0.398	69.98	1.845	30.02	1.477
3	1.732	0.477	79.98	1.903	20.02	1.301
4	2.000	0.602	89.95	1.954	10.05	1.002
6	2.449	0.778	98.85	1.995	1.15	0.061

1. Zero order Release Kinetics of Prepared Formulation F-4



Graph no.6 representative of Zero order Release Kinetics of Formulation F-4(Cumulative % drug released Vs Time)

2 .First order Release Kinetics of Prepared Formulation F-4



Graph no.7 representative of first order Release Kinetics of Formulation F-4(Log cumulative % drug remaining Vs Time)

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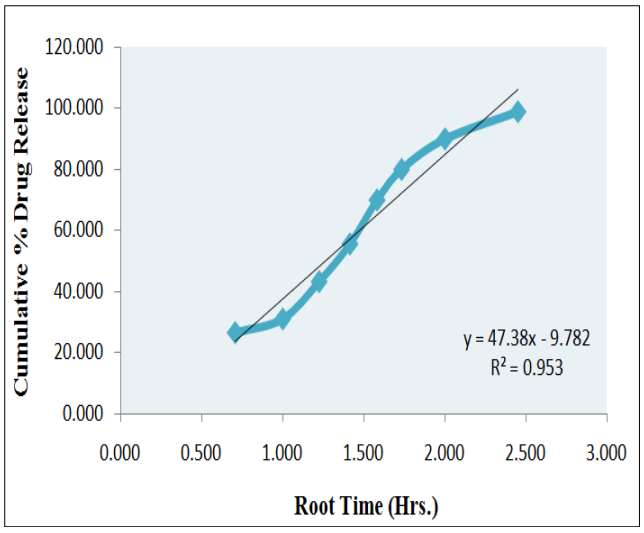
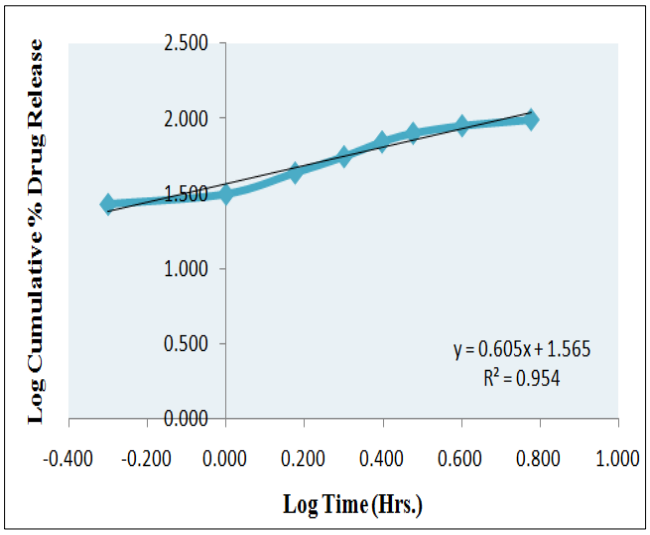


Graph no.8 representative of Higuchi Release Kinetics of Formulation F-4(Cumulative % drug remaining Vs Root Time)



Graph no.9 representative of Korsmeyer-Peppas of Formulation F-4(Log Cumulative % drug release Vs Log Time)

Table no.12 Release Kinetics Regression values of formulation F-4

Formulation code	Zero order	First order	Higuchi	Korsmeyer-Peppas
F-4	0.893	0.960	0.953	0.954

IV. CONCLUSION

The width, weight uniformity, moisture material, drug content analysis, folding endurance, surface pH of patches, percent swelling, in vitro residence time, and in vitro drug release review of different formulations F1 to F6 were all evaluated. A vernier caliper was used to determine the thickness of patches in three distinct locations. The thickness was found 52±2, 48±3, 45±4, 43±2, 40±4 and 42±2 for formulation F1, F2, F3, F4, F5 and F6 respectively.

For the weight variance test, ten patches from each sample were independently weighted on a digital electronic balance and the average weight measured. All of the formulations were found to have a comparable weight. The weight was found 115±2, 110±3, 108±2, 95±4, 98±5 and 93±2 for formulation F1, F2, F3, F4, F5 and F6 respectively.

The discrepancy between the original and final weights with respect to the final weight was used to quantify the percentage of moisture content. The percentage moisture content was found 2.12±0.36, 2.14±0.25, 2.78±0.14, 2.01±0.23, 2.36±0.41 and 2.41±0.32 for formulation F1, F2, F3, F4, F5, and F6 respectively.

The drug quality determination confirms that the API is distributed uniformly across the patch. The percentage drug content of different formulations F1, F2, F3, F4, F5 and F6 were found 98.85±0.32, 98.65±0.25, 98.87±0.14, 99.12±0.23, 98.58±0.12 and 97.65±0.14. The maximum percentage drug content was found in formulation F-4 (99.12±0.23).

Folding stamina was calculated manually by folding the patches over and over before they separated. The end point was determined by the breaking time. Folding endurance was found to be highest for F4 (189±4) and lowest for F1 (125±3).

The pH of different formulations F1, F2, F3, F4, F5 and F6 were found 6.92±0.45, 6.75±0.23, 6.76±0.14, 6.81±0.25, 6.65±0.36 and 6.56±0.41 respectively. All of the patches had a surface pH that was within the salivary pH range. There was no noticeable difference in the pH of the patches' surfaces.

The swelling behavior and residence time of several mucoadhesive polymers were also affected by Ketorolac tromethamine. The swelling review took two hours to finish. Percent were found to be the proportion of 42.21±1.92, 38.20±1.62, 51.09±1.25, 52.63±1.91, 54.42±2.32 and 49.24±2.12 welling of formulations F1, F2, F3, F4, F5 and F6. The highest percentage of swelling was observed in the optimized formulation F4 (52.63±1.91 percent).

Water influx weakens the polymer's network stability, affecting the swollen matrices' structural resistance, resulting in marked degradation of the lose gel layer. The residence time was found 2.15±0.2, 2.30±0.3, 2.65±0.2, 3.45±0.1, 2.30±0.2 and 1.98±0.1 for formulation F1, F2, F3, F4, F5 and F6.

The strengthened patch formulation F-4 releases approximately 26.65 percent medication after 50 minutes and approximately 98.85 percent medication after 6 hours. When the regression coefficient values were compared, it was discovered that first order 'r2' values were the highest, i.e. 0.960, implying that drug releases from the formulation followed first order release kinetics.

The formulation F4 is selected for best formulation because its show the 98.85% drug release at time 6 hr, folding endurance is 189±4 times and weight of prepared film is 95±4 mg and thickness 43±2 mm of these formulations respectively.

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