WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 13, 1573-1592. Research Article ISSN 2277– 7105

DEVELOPMENT OF FORMULATIONS AND SYSTEMATICALLY EVALUATED IN-VITRO DIFFUSION OF BUCCAL PATCHES OF KETOROLAC

M. Sai Kumar, *H. Parameshwar and A. V. Jithan

*Omega college of Pharmacy Edulabad, Ghatkesar, Affiliated to Osmania University Hyderabad, Telangana, India.

Article Received on
07 August 2022,

Revised on 28 August 2022,
Accepted on 18 Sept. 2022

DOI: 10.20959/wjpr202213-25637

***Corresponding Author**
Dr. H. Parameshwar
Omega college of Pharmacy Edulabad, Ghatkesar, Affiliated to Osmania University Hyderabad, Telangana, India.

ABSTRACT

The objective of present study was to develop matrix type buccal patch therapeutic systems of Ketorolac using various hydrophilic and hydrophobic polymers as matrix formers. Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction was observed. The in vitro release study revealed that F1 formulation showed maximum release in 16 hrs. The release kinetics of formulation F1 followed Higuchi model. Formulation F1 was subjected for accelerated stability studies. The F1 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patchesF1, F2, F3, F4, F5, F6, F7 and F8 formulations showed highest cumulative percentage drug release of 98.38%, 97.92%, 99.10%, 97.32% were obtained during in vitro drug release studies after 16 hrs. The release of Ketorolac appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the in vitro dissolution data the F1 formulation was concluded as optimized formulation.

KEYWORDS: Buccal patch, Buccal delivery system, Ketorolac, Sodium aliginate & Eudragit, Diffusion mechanism.

INTRODUCTION

Buccal Drug Delivery System is the unique environment of the oral cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation, the oral mucosal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first pass effect).

The total area of the oral cavity is about 100 cm^2. Out of this about one third is the buccal surface, which is lined with an epithelium of about 0.5 mm thickness. The oral mucosal surface is constantly washed by the saliva[16] (daily turn out is about 0.5 to 2 liters). The continuous secretion of saliva results in rapid removal of released drug. Conversely, the thin mucin film, which exists on the surface of the oral mucosa, may provide an opportunity to retain a drug delivery system in contact with the mucosa for prolonged periods if it is designed to be mucoadhesive. Such systems ensure a close contact with absorbing membrane, thus optimizing the drug concentration gradient across the biological membrane and reducing the differential pathway. Therefore, the buccal (oral) mucosa may be a potential site for controlled or sustained drug delivery. Drug delivery via the membranes of the oral cavity is traditionally divided into three categories,

- Buccal delivery, which infers drug administration through the lining of the cheek to the systemic circulation.
- Sublingual delivery, which infers drug administration through the administration of drug via membranes of the floor of the mouth for the systemic circulation.
- Local delivery to mouth, which involves treatment conditions within the oral cavity by administration to the affected mucosal tissues.

1.1 Composition of buccal patches

A. Active Pharmaceutical ingredient (API): The buccal film technology has the potential for delivery of variety of APIs. However since the size of the dosage form has limitation, high dose molecules are difficult to be incorporated in buccal film. Generally 5%w/w to 30%w/w of active pharmaceutical ingredients can be incorporated in the buccal patches.

B. Polymers (adhesive layer): Polymer hydration and swelling properties probably play the main role. The polymer hydration and consequently the mucus dehydration could cause an increase in mucous cohesive properties that promote mucoadhesion. Swelling should favor polymer chain flexibility and interpenetration between polymer and mucin chains. So, depending on the type of formulation,polymers with different characteristics have to be

considered. Examples: Hydroxy ethylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, carbopol and other mucoadhesive polymers.

C. Diluents: Lactose DC is selected as diluent for its high aqueous solubility, its flavouring characteristics, and its physico-mechanical properties, which make it suitable for direct compression. Other example: microcrystalline starch and starch.

D. Sweetening agents: Sucralose, aspartame, mannitol, etc.

E. Flavouring agents: Menthol, vanillin, clove oil, Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and etc.

F. Backing layer: Ethyl cellulose, etc.

G. Penetration enhancer: Cyano acrylate, EDTA, Ctric acid etc.

H. Plasticizers: PEG-100, 400, propylene glycol, etc.

1.2 Method of preparation: Two methods used to prepare adhesive patches include,

1. Solvent casting: In this, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation, a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry. The solvent casting method is simple, but suffers from some disadvantages, including long processing time, high cost, and environmental concerns due to the solvents used. These drawbacks can be overcome by the hot-melt extrusion method.

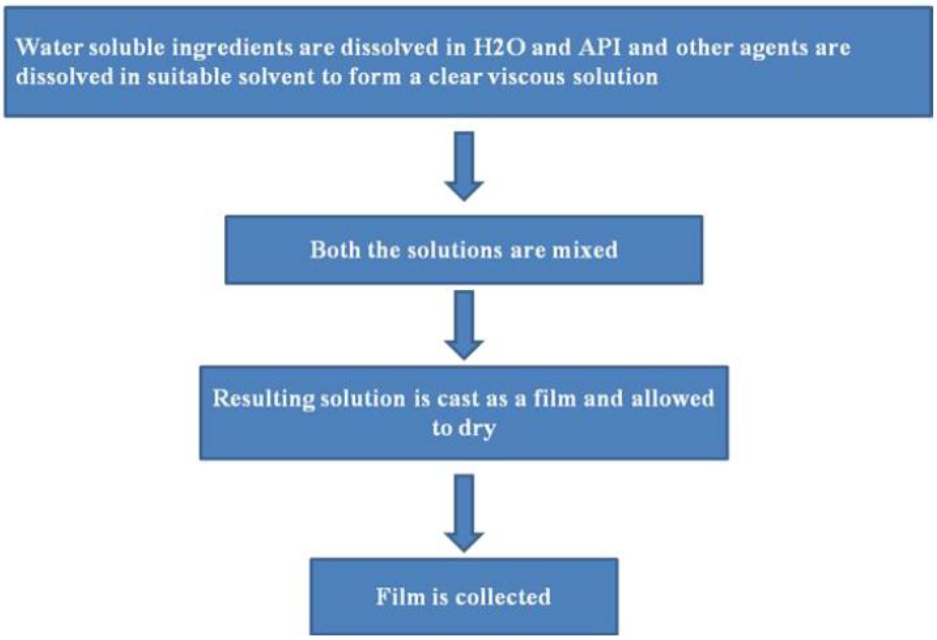


Fig-: Pictorial diagram of Solvent casting method.

2. Direct milling: In this, patches are manufactured without the use of solvents (solvent-free). Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. An impermeable backing membrane may also be applied to control the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device during application period. While there are only minor or even no differences in patch performance between patches fabricated with the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.

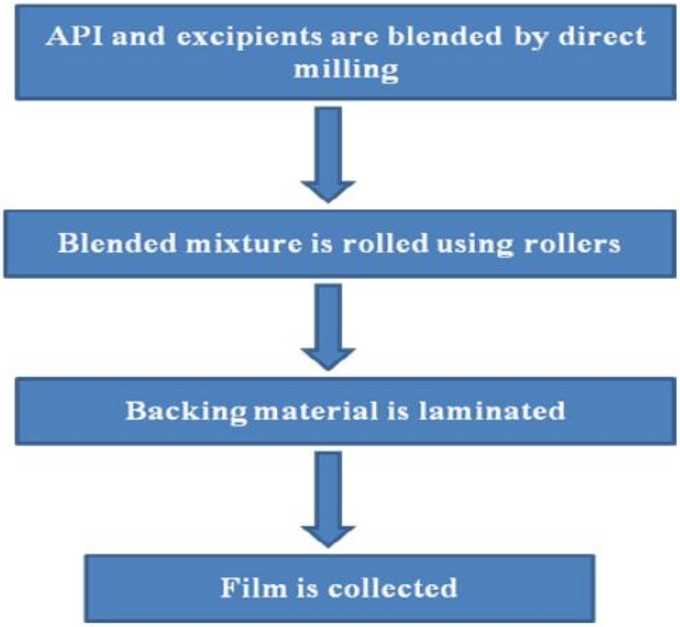


Fig-: Pictorial diagram of Direct milling method.

1.3 Bioadhesive polymers: Bioadhesive polymers are classified into two main categories.

2. Hydrophilic polymers that are water soluble, 2. Water insoluble polymers that are swellable networks joined by cross-linking agents.

In the large classes of hydrophilic polymers[22] those containing carboxylic group exhibit the best mucoadhesive properties. Poly vinyl pyrrolidine (PVP), methyl cellulose (MC), sodium carboxy methyl cellulose (SCMC), hydroxyl propyl cellulose (HPC) and other cellulose derivatives. Hydrogels are the class of polymeric biomaterial that exhibit the basic characteristics of an hydrogels to swell by absorbing water interacting by means of adhesion with the mucus that covers epithelia[23] i.e.

- Anionic group --- Carbopol, Polyacrylates and their cross linked modifications.
- Cationic group --- Chitosan and its derivatives
- Neutral group --- Eudragit-NE30D etc.

DRUG PROFILE: Ketorolac (Ketorolac tromethamine)

Description: A pyrrolizine carboxylic acid derivative structurally related to indomethacin. It is an NSAID and is used principally for its analgesic activity.

Structure

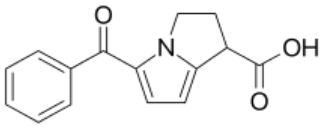


Fig-: Structure of Ketorolac.

Chemical formula: $C_{15}H_{13}NO_3$

Molecular mass: 255.279 g/mol

Solubility: Ketorolac (tromethamine salt) is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide (DMF)

EXCIPIENT PROFILE

Ethyl cellulose

Solubility: Soluble in a wide variety of organic solvents, including aliphatic alcohols, ethers, ketones, aromatic hydrocarbons.

Sodium alginate: Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid. The block structure and molecular weight of sodium alginate samples has been investigated.

Hydroxy propyl methyl cellulose

Solubility: Soluble in cold water, forming a viscous colloidal solution, insoluble in alcohol, ether and chloroform, but soluble in mixture of methyl alcohol and methylene chloride.

Eudragit RL100: Eudragit RL100 is ammonio methacrylate copolymers consisting of fully polymerized copolymers of acrylic acid esters with 10% of functional quaternary ammonium groups.

Methanol: Methanol is highly toxic and unfit for consumption. At room temperature, it is a polar liquid, and is used as an antifreeze, solvent, fuel, and as a denaturant for ethanol. It is also used for producing biodiesel via trans esterification reaction.

Poly ethylene glycol

- BP: Macrogols
- JP: Macrogol 400
- PhEur: Macrogols
- USP-NF: Polyethylene Glycol

MATERIALS AND EQUIPMENTS: Ketorolac- Hetero labs, HYD, Sodium alginate- AR chemicals, HPMC, Ethylcellulose, Eudragit, Methanol (ml), Poly ethylene glycol, Digital weighing machine, Shimadzu at 244, UV-Visible double beam spectrophotometer, Lab India UV-Visible double beam spectrophotometer, Franz diffusion cell, anchor, Mumbai, Magnetic stirrer-Eureka, Bath Sonicator-Wensar.

METHODOLOGY

Preparation of phosphate buffer pH 7.4:17.90gms of di-sodium hydrogen orthophosphate was weighed to it sufficient water was added to get 1000 ml and the pH was adjusted to 7.4 with Orthophosphoric acid. To this solution 0.5% SLS was added.

Determination of λ_{max} using UV- Visible spectrophotometer

Standard stock solution of Ketorolac (10mg/10ml) was prepared by dissolving 10 mg Ketorolac of in 10 ml of methanol. For the selection of analytical wavelength, solution of Ketorolac 10µg/ml was prepared by appropriate dilution of standard solution with phosphate buffer 7.4 and scanned in the spectrum mode from 200- 400nm. The wave length with maximum absorption was chosen for further analysis.

Standard curves of Ketorolac

Standard graph of Ketorolac in phosphate buffer 7.4

Standard stock solution of Ketorolac (10mg/10ml) was prepared by dissolving 10mg of Ketorolacin 10ml of methanol. Diluting the standard stock solution with phosphate buffer 7.4, solution of 10µg/ml concentration was prepared. From this solution serial dilutions were made with phosphate buffer 7.4 to get 2, 4, 6, 8, 10, 12µg/ml concentrations. These solutions were checked for the absorbance using UV- Visible spectrophotometer at λ_{max}273nm against

phosphate buffer 7.4 as blank and standard graph was plotted by taking concentration on X-axis and absorbance on Y- axis.

Standard graph of Ketorolac in phosphate buffer 7.4 containing 0.5% SLS

Standard stock solution of Ketorolac (10mg/10ml) was prepared by dissolving 10mg of Ketorolac in 10 ml of methanol. Diluting the standard stock solution with phosphate buffer 7.4 containing 0.5% SLS, solution of 10µg/ml concentration was prepared. From this solution serial dilutions were made with phosphate buffer 7.4 containing 0.5% SLS to get 2, 4, 6, 8, 10, 12, µg/ml concentrations. These solutions were checked for their absorbance using UV-Visible spectrophotometer at λ_{max} 273nm against phosphate buffer 7.4 containing 0.5% SLS as blank and a standard graph was plotted by taking conc. on X- axis and abs on Y- axis.

Pre-formulation studies

Solubility measurement: 1gm of substance was made to dissolve in various solvents individually and the solvent was added till the drug completely gets dissolved. The amount of solvent consumed is reported as solubility.

Melting point determination: Melting point of drug was determined by taking a small amount of drug in a capillary tube closed at one end and was placed in melting point apparatus and temparature at which the drug melts was noted.

Formulation design: Preparation of buccal patches Transdermal patches containing Ketorolac were prepared by the solvent casting evaporation technique. The drug Ketorolac was dissolved in methanol. Polymers HPMC, Ethylcellulose, Sodium alginate and ERS100 were taken in a beaker, to this add Ketorolac drug which was previously dissolved in methanol. Sufficient care was taken to prevent the formation of lumps. The beaker was kept under magnetic stirrer. PEG was taken as a plasticizer, and added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned petri plate ($40cm^2$), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminium foil and stored in desiccators for further evaluation.

Table-: Formulation Design of Ketorolac buccal Patches.

F.Code	Ingredients (mg)					
	Drug (mg)	HPMC k15M	Carbopol 934	Eudragit RS100	DMSO	PEG
F1	50	500	-	-	0.1ml	1ml
F2	50		500	-	0.1ml	1ml
F3	50	-	-	500	0.1ml	1ml
F4	50	250	250	-	0.1ml	1ml
F5	50	-	250	250	0.1ml	1ml
F6	50	250	-	250	0.1ml	1ml
F7	50	200	-	300	0.1ml	1ml
F8	50	300	-	000	0.1ml	1ml

Evaluation of Buccal patches formulation: Physico- chemical evaluation

Physical appearance: All the prepared Doxofyline films were observed for color, clarity, flexibility, and smoothness.

Folding endurance: Folding endurance of the patches was determined by repeatedly folding at the same place till it broke. The number of times the patch could be folded at the same place without breaking is the folding endurance. This was repeated on all the patches for three times and the mean values plus standard deviation was calculated.

Thickness of the film: The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.

Weight uniformity: The prepared patches are to be dried at 60^0C for 4hrs before testing. A specified area of 4.52 $cm^2$of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Flatness: Flatness was determined by randomly selected five longitudinal strips were cut out from mediated patch of each formulation; the length of each strip was measured before and after kept at room temperature for 30 minutes. Variation in length due to non uniformity of flatness was measured by determining percent constriction, with 0% constriction as 100% flatness.

$$\text{Percent constriction} = \frac{\text{Final length} - \text{Initial length}}{\text{Initial length}} \times 100$$

Drug content: The formulated buccal films were assayed for drug content in each case. Three patches from each formulation were assayed for content of drug. Each formulation was casted in triplicate and one film from each was taken and assayed for content of drug.

Procedure: The buccal films (2 cm^2) were added to conical flask containing 100 ml of phosphate buffer pH 7.4 contain 0.5% SLS. This was then stirred with magnetic bead at 400 rpm for 2 hrs. The contents were filtered and the filtrate was analysed spectrophotometrically for drug content at 310 nm. Similarly a blank was prepared from buccal films without drug.

$$\text{Drug content} = \frac{\text{Weight of drug in patch}}{\text{Total weight of patch}} \times 100$$

Where, Dt = Total amount of the drug in the buccal patch, Da = The amount of drug released

Conditions: Medium: Phosphate buffer pH 7.4 containing 0.5% SLS
RPM: 200, Temperature: 37 ± 0.5^0C, Time intervals: 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 hours.

Moisture absorption studies: The films were weighed accurately and placed in a desiccators containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \qquad (11)$$

Moisture loss studies: Three films were weighed individually and kept in a desiccator containing calcium chloride at 37^0C for 24 hrs. Then the final weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100 \qquad (12)$$

***In vitro* drug permeation studies:** The *in-vitro* study of drug permeation through the Dialysis membrane was performed using a modified Franz type glass diffusion cell. The modified cell having higher capacity is (10 ml) is used to maintain sink condition. The samples were analyzed for drug content spectrophotometrically at 310 nm. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{\text{Da}}{\text{Dt}} \times 100 \qquad (14)$$

Where, Dt = Total amount of the drug in the patch, Da = The amount of drug released

Conditions: Medium: Phosphate buffer pH 7.4 containing 0.5% SLS

RPM: 200, Temperature: 37 ± 0.5^0C, Time intervals: 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 hours

Drug release kinetics

Zero order kinetics: Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation.

$$Qt = Qo + Ko\ t \quad (15)$$

Where, Q_t = Amount of drug dissolved in time t, Q_o = Initial amount of drug in the solution

K_o = Zero order release constant

First order kinetics: To study the first order release rate kinetics the release rate data were fitted to the following equation.

$$\text{Log } Q_t = \log Q_o + K_1 t / 2.303 \quad (16)$$

Where, Q_t is the amount of drug released in time t, Q_o is the initial amount of drug in the solution

K_1 is the first order release constant.

Higuchi model: Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is

$$Qt = K_H.\ t^{1/2} \quad (17)$$

Where, Qt= Amount of drug released in time t,K_H = Higuchi dissolution constant.

Korsemeyer and Peppas release model: To study this model the release rate data are fitted to the following equation $M_t / M_\infty = K.\ t^n$ (18)

Where, M_t / M_∞ = fraction of drug release, K = Release constant, t = Release time

n= Diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form.

Hixson- Crowell model: To study the Hixson–Crowell model the release rate data are fitted to the following equation

$$W_0^{1/3} - W_t^{1/3} = K_{st} \quad (19)$$

Where, W_0 = Amount of drug in the pharmaceutical dosage form, W_t = Remaining amount of drug in the pharmaceutical dosage form, K_s = Constant incorporating the surface- volume relation

Stability studies: Optimized medicated films were subjected to short term stability testing. The buccal films were sealed in Aluminium foils and kept in a humidity chamber maintained at 40 ± ^{0}C and 75 ± 5% RH for 3 months as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week.

RESULTS AND DISCUSSION

Preformulation studies: Melting point determination: The melting points were found to be in the range of 164-166°C the reported melting point is 165°C.

Calibration curve of Ketorolac

Table: Standard calibration curve of Ketorolac.

S. No.	Concentration(µg/ml)	Absorbance
1	0	0
2	10	0.356
3	20	0.487
4	30	0.529
5	40	0.632
6	50	0.795

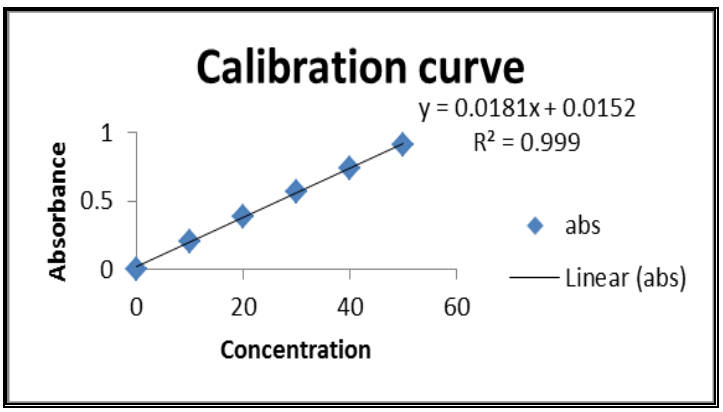


Fig 5: Calibration Curve for Ketorolac.

FTIR Studies: Drug–excipients compatibility studies

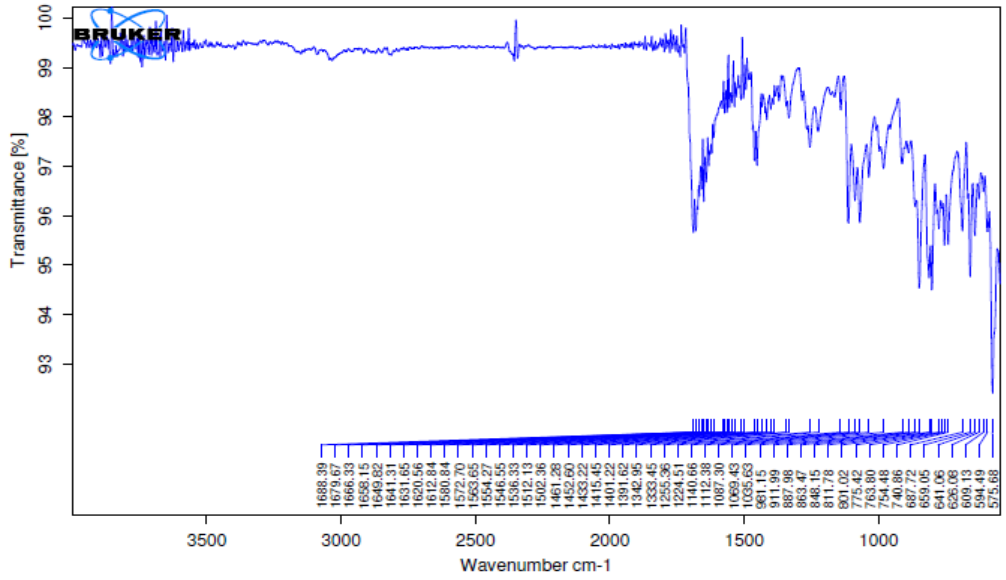


Fig-: FTIR spectra of Pure drug.

Table-: FTIR studies of Pure drug.

Wave number in cm-1	Functional groups	Pure drug
1500-2000	C-H Bending	1115 cm-1
1000-1500	C=C STRETCH	1009cm-1
1000-1500	C=O Stretching	892cm-1
1000	C-H STRETCH	678cm-1

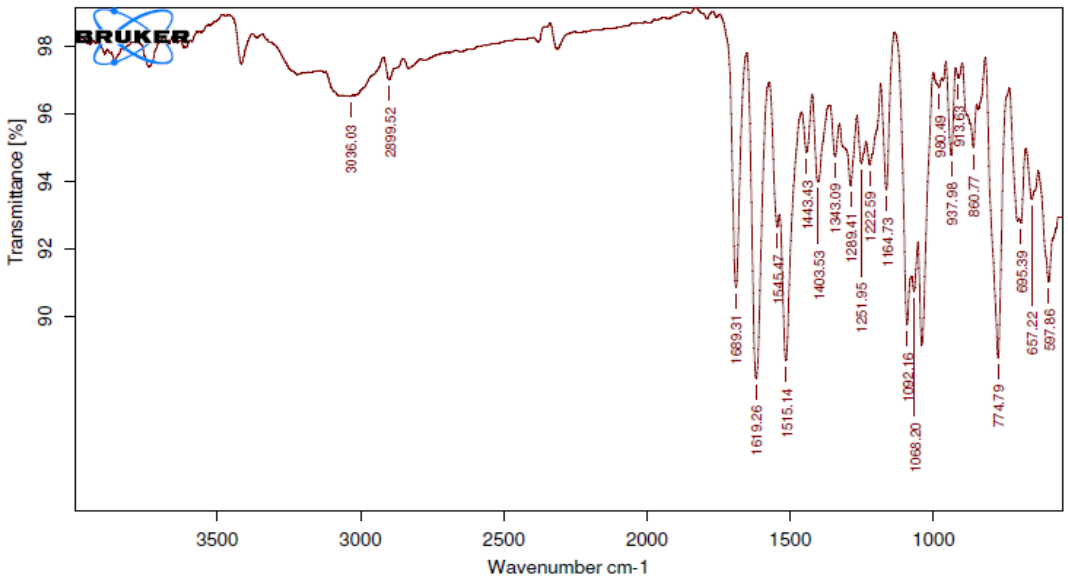


Fig-: FTIR spectra Optimized formula.

Table 8: Fourier Transform Infrared Spectroscopy of optimized formulation.

Wave number in cm-1	Functional groups	Optimized formulation
700-900	C-H Bending	735.55 cm-1
1350-1480	C=C STRETCH	1550.80 cm-1
1760-1550	C=O Stretching	1747.02 cm-1
3010-2850	C-H STRETCH	3008.40 cm-1
3500-3200	O-H Stretching	3305.02 cm-1
3800-3300	N-H STRETCH	3650.48 cm-1

Solubility determination: The solubility of Ketorolac was determined and found very less as78.94 µg/ml in phosphate buffer. The solubility in distilled water was found more than that in phosphate buffer.

Physical appearance and surface texture of patches: These parameters were checked simply with visual inspection of patches and by feel or touch. The observation reveals that the patches are having smooth surface and they are elegant in appearance.

Weight uniformity of patches: The weight of the patches was determined using digital balance and the average weight of all patches.

Thickness of patches: The thickness of the patches was measured using screw gauge and the average thickness of all patches was given.

Folding endurance of patches: The folding endurance gives the idea of flexible nature of patches. The folding endurance was measured manually, patches were folded repeatedly till it broke, and it was considered as the end point. The folding endurance was found optimum and the patches exhibited good physical and mechanical properties and the average folding endurance of all patches.

Swelling index of patches: The swelling index of the patches was determined by immersing preweighed patch of size 10 mm in 50 ml water. The patches were taken out from petridish carefully at 5, 10 upto and 30 min. intervals, blotted with filter paper and weighed accurately and the average swelling index of all patches was given.

Surface pH of patches: Surface pH was determined by bring the patches in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH

paper near the surface of patches and allowing equilibrate for 1 min and the average surface pH of all patches was given.

Drug content uniformity of patches: Ketorolac buccal patches prepared with various polymers were subjected to the valuation for uniform dispersion of drug throughout the patch. In each case three patches were used and the average drug content was calculated.

Table: Physicochemical evaluation data of Ketorolac Buccal Patches.

F. code	F1	F2	F3	F4	F5	F6	F7	F8
Thickness (mm)	0.26	0.20	0.27	0.22	0.25	0.23	0.20	0.19
Weight variation (mg)	49.93	48.93	52.14	50.10	51.25	47.86	51.18	46.62
Drug content Uniformity	94.41	97.26	95.84	96.82	94.50	97.26	98.82	91.25
Folding endurance	77	76	79	78	75	76	72	73
Swelling index	25.22	31.53	34.62	32.60	28.96	29.63	31.28	28.95
Surface pH	5.5	6.6	**7.7**	6.8	5.5	6.2	5.9	6.1

Drug release studies

Table-: *In vitro* release data of film F_1 to F_8.

Time (hrs.)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F8
0	0	0	0	0	0	0	0	0
1	14.90	15.15	15.80	15.56	16.13	15.58	14.89	15.10
2	26.70	25.89	26.50	25.55	26.45	25.55	25.60	24.65
3	37.89	36.87	37.70	38.25	37.89	38.55	33.59	35.65
4	48.18	45.23	44.50	47.59	48.89	48.66	49.89	48.24
5	*69.75*	68.35	67.65	66.55	68.98	67.55	69.12	69.32
6	76.89	79.34	71.98	78.32	79.21	80.55	81.25	82.65
7	88.86	86.77	85.32	84.28	85.90	86.99	88.96	89.23
8	94.45	97.50	98.12	97.22	98.24	99.32	96.92	98.25

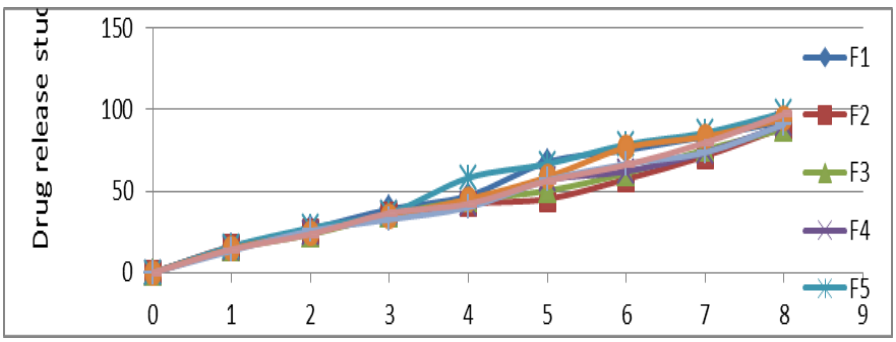
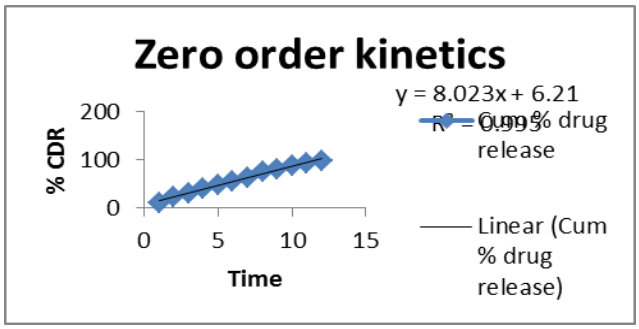


Fig-: In vitro drug release of all formulation.

Release order kinetics

Table-: In vitro release profile of Optimized formulation.

Time (hrs)	Root T	Log T	Cum % drug release	Cum % drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1\backslash 3}$
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	1	15.58	15.58	88.96	1.6541	1.9429	4.9843
2	1.2134	25.55	25.55	76.24	1.3454	1.7143	4.3321
3	1.4328	38.55	38.55	69.73	1.4705	1.7639	4.2189
4	2	48.66	48.66	62.53	1.4858	1.8521	3.4128
5	2.4568	67.55	67.55	52.66	1.6789	1.8543	3.7264
6	2.3585	80.55	80.55	45.92	1.7543	1.9750	3.4321
7	2.5158	86.99	86.99	37.00	1.7814	1.5698	3.2175
8	2.6275	99.32	99.32	26.15	1.8830	1.1342	2.7984



zerorder kinetics: Fig-: Drug release of Zero order kinetics.

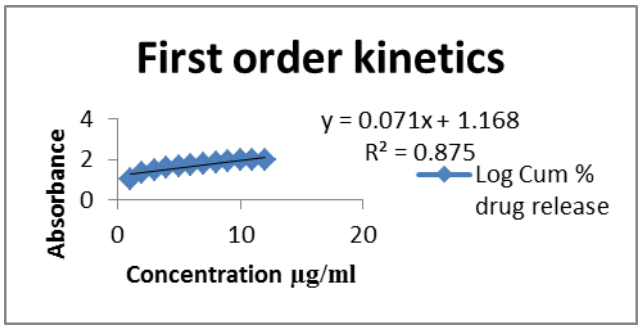


Fig-: Drug release of First order kinetics.

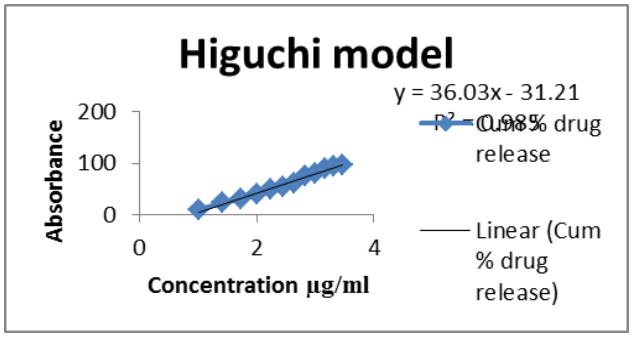


Fig-: Drug release of Higuchi model.

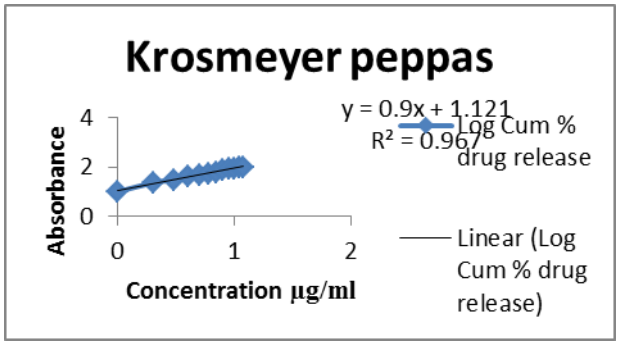


Fig-: Drug release of Krossmayer peppas.

Table-: Drug release kinetics.

S.no	Kinetic model	R^2 value
1	Zero order kinetics	0.995
2	First order kinetics	0.875
3	Higuchi model	0.985
4	Krossmayer peppas	0.967

Stability studies: Optimized formulations F6 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies. The results are tabulated in table 25.

Table-: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months.

Formulation Code	Initial	1st Month	2nd Month	3rd Month
F6	99.32	99.33	99.34	99.35
F6	99.32	99.34	99.35	99.36
F6	99.32	99.36	99.36	99.37

SUMMERY AND CONCLUSION

From the present research work that is development and evaluation of Ketorolac patches for buccal drug delivery, the following points can be concluded:

The patches prepared were elegant in appearance and smooth surface.

- The weights of patches were uniform.
- The thicknesses of patches were uniform.
- The patches were completely dried.
- The patches had good flexibility.
- The patches shows uniform swelling index.

- The surface pH of the patches was uniform.
- There was no drug-excipients interaction between the drug and excipientsused in the formulation.
- The drug was distributed throughout the patch uniformly.
- More than 85 % of the drug was released from all the formulations at the end of 8 hrs.
- In short term stability studies indicate there were no significant changes in thedrug content and *in-vitro* drug release for the period of three month. From the result and conclusion of the research work we can summarize that Ketorolac can be delivered via buccal route.

REFERENCES

1. Shoba Rani R Hiremath; Industrial Pharmacy, Orient Longman private limited, 2008; First edition, 73-77.
2. Sang-Chul Shin, Jin-Pil Bum, Jun-Shik Choi. Enhanced bioavailability by buccal administration of triamcinolone acetonide from the bioadhesive gels in rabbits, Int. J. Pharmaceutics., 2009; 209: 37-43.
3. Giradkar KP, Design development and in vitro evaluation of bioadhesive dosage form for buccal route, International journal of pharma research & development, 2010; 2.
4. Giradkar MA, Channawar AD, Kajale E, Sridhar RS, Kamble BV, Chandewar. Design, development and in vitro evaluation of bioadhesive dosage form for buccal route. Int. J. Pharm. Res. Dev., 2010; 2(6): 1-20.
5. Calum R, Park, Dale L, Munday. Development and evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy. Int. J. Pharm., 2002; 237: 215-26.
6. Subhash V, Madhuri Channawar, Anil V, Unmesh, Kailash R. Chitosan based sustained release mucoadhesive buccal patches Containing verapamil HCl, Int. J. Pharm. Pharm. Sci., 2009; 1(1): 216-29.
7. Shidhaye SS, Mucoadhesive bilayered patches for administration of sumatriptan, AAPS pharm sci tech, 2009; 9(3).
8. Edsman K, Pharmaceutical applications of mucoadhesion for the non-oral routes, Journal of pharmacy & pharmacology, 2005; 57: 3-19.
9. Surender Verma, MahimaKaul, ArunaRawat, SapnaSaini. An overview on buccal drug delivery system. Int J Pharm Sci Res., 2011; 2(6): 1303-21.
10. Miller NS, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery, Advanced Drug Delivery Reviews, 2005; 57: 1666–91.

11. Patel KV, Patel ND, Dodiya HD, Shelat PK. Buccal bioadhesive drug delivery system:An Overview.Int J Pharm Bio Arch, 2011; 2(2): 600-9.
12. Yajaman S., Bandyopadhyay AK. Buccal bioadhesive drug delivery- A promising option for orally less efficient drugs. J Controlled Release, 2006; 114: 15–40.
13. Shimamoto T. Androl J., 1987; 8(1): S14-S16.
14. Amir H, Systemic drug delivery via the buccal mucosal route, Pharmaceutical technology, 2001; 1-27.
15. Sudhakar Y, Knotsu K, Bandopadhyay AK. Bio adhesive drug delivery – A promising option for orally less efficient drugs. J Control Rel., 2006; 114: 15-40.
16. Rajashree Mashru, Vijay Sutariya, Mayur Sankalia, Jolly Sankalia. Transbuccal delivery of lamotrigine across procine buccal mucosa in vitro determination of routes of buccal transport. J Pharm Pharmaceut Sci., 2005; 8: 54-62.
17. Ceschel GC, Maffei P, Moretti MD, Demontis LS, Peana A. International Journal of Pharmaceutics, 2000; 195: 45.
18. Haas J, Lehr CM. Developments in the area of bioadhesive drug delivery systems. Expert Opin Biol Ther., 2002; 2: 287-298.
19. DeVries M.E, Ph.D. Thesis, University of Leiden, Leiden, The Netherlands, 1991.
20. Dixit R.P., Puthli S. P., Oral strip technology: Overview and future potential, Journal of Controlled Release, 2009; 139: 94–107.
21. Rossi Silvia, Sandri Giuseppina, Caramella Carla M., Buccal drug delivery: A challenge already won?, Drug Discovery Today: Technologies, 2005; 2(1).
22. Smart, J.D., The role of water movement and polymer hydration in mucoadhesion. In Bioadhesive drug delivery systems (Mathiowitz, E., Chickering, III D.E., Lehr, C.M., eds), Marcel Dekker, 1999; 11–23.
23. Nazilasalamat M, Montakarn C, Thomas J. The use of mucoadhesive polymers in buccal drug delivery. AdvDrug Del Rev., 2005; 57: 1666-91.
24. Gandhi RB, Robinson JR. Oral cavity as a site for bioadhesive drug delivery. Adv Drug Del Rev., 1994; 13: 43-74.
25. Amir HS. Buccal mucosa as a route for systemic drug delivery: A review. J Pharm Pharmceut Sci., 1998; 1(1): 15-30.
26. Salamat-Miller N, Chittchang M, Johnston TP, The use of mucoadhesive polymers in buccal drug delivery, Advance DrugDelivery Review, Nov, 2005; 57(11): 1666-1691.
27. Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J ContrRel., 1985; 2: 257–75.

28. Bottenberg P, Cleymaet R, Muynek CD, Remon JP, Coomans D, Slop D. Development and testing of bioadhesive, floride-containg slow-release tablets for oral use. J PharmPharmacol, 1991; 43: 457-64.
29. Steward A, The Effect of Enhancers on the Buccal Absorption of Hybrid (BDBB) Alpha-Interferon, Int.J. Pharm, 1994; 104: 145–149.
30. Patel R, Shardul N, Patel J, Baria A. overview on buccal mucoadhesive films. Arch Pharm Sci& Res., 2009; 1(2): 212-7.
31. Anders R., Merkle H., Evaluation of laminated muco-adhesive patches for buccal drug delivery, International Journal of Pharmaceutics, 1989; 49: 231–240.
32. Apoorva M, Neha C, Geeta A. Formulation and characterization of fast dissolving buccal films: A review. Der Pharmacia Lettre., 2011; 3(1): 152-65.
33. Leung SS, Robinson JR. Polymer structure features contributing to mucoadhesion: II. J ContrRel., 1990; 12: 187–94.
34. Amit Khairnar, Parridhi J, Dheeraj B, Dinesh J. Developmement of mucoadhesive buccal patch containing aceclofenac: in vitro evaluations. Int J PharmTech Res., 2009; 1(4): 978-81.
35. Subhash VD, Madhuri A, channavar, Anil VC, Umesh MJ, Kailash RB. Chitosan based release mucoadhesive patches containing verapamil Hcl. Int J Pharm PharmceutSci., Nov-Dec, 2009; 1(1): 216-29.
36. Manishkumar, Garimagarg, Pushpendrakumar, Kulkarni GT, Arunkumar. Design and in vitro evaluation of mucoadhesivebuccal films containing famotidine. Int J Pharm Pharmceut Sci., 2012; 2(3): 86-90.
37. Shalini Mishra, G. Kumar, P. Kothiyal, A Review Article: Recent Approaches in Buccal Patches, The Pharma Innovation, 2012; 1(7).
38. Fiza Farheenet.al. Buccal Patches: A Review. Indo American Journal of Pharm Research, 2013; 3(4).
39. **Sanket Sharma, R. Yogananda,** Buccal Patches: Boon To Oral Drug Delivery System, American Journal of PharmTech Research, 2012.
40. N. Vidyasagar et. al, Journal of Pharmaceutical Research and Development, June, 2012; 1(2): 29-35.
41. Nishan N. Bobade et. al, A Review on Buccal Drug Delivery System, International Journal of Pharmacy and Pharmaceutical Science Research, 2013; 3(1): 35-40.
42. Pradeep Kumar et. al, Buccal Patches: A Review, International Journal of Pharmaceutical Sciences & Research, Jan, 2013; 4(1): 83.

43. Kinesh V. Patel et. al, Buccal Bioadhesive Drug Delivery System: An Overview, International Journal of Pharmaceutical & Biological Archives, 2011; 2(2): 600-609.
44. Navneet verma et al, in-vitro and in-vivo evaluation of mucoadhesive patches containing metoprolol succinate, Asian J Pharm Clin Res., 2012; 5(1): 168-171.
45. Shailaja T et al, A novel bioadhesive polymer: grafting of tamarind seed polysaccharide and evaluation of its use in buccal delivery of metoprolol succinate, Der Pharmacia Lettre, 2012; 4(2): 487-508.
46. Sneh Priyaet. al, Formulation and evaluation of buccal film of Ivabradine hydrochloride for the treatment of stable angina pectoris, Int J Pharm Investig, Jan-Mar, 2013; 3(1): 47–53.
47. Patel, Rajesh Singh; Poddar, S. S. et. al, Development and Characterization of Mucoadhesive Buccal Patches ofSalbutamol Sulphate, Current Drug Delivery, Jan, 2009; 6(1): 140.
48. **N.G. Raghavendra Rao and Keyur Patel,** Formulation and Evaluation of Ropinirole Buccal Patches Using Different Mucoadhesive Polymers, **RGUHS Journal of Pharmaceutical Sciences,** 2013; 3(1): 32-39.
49. Sharma, P; Hamsa, V, Formulation and evaluation of buccal mucoadhesive patches of terbutaline sulphate, *STP PHARM S*, 2001; 11(4): 275-281.
50. http://www.drugbank.ca/drugs/DB00264.
51. http://pubchem.ncbi.nlm.nih.gov/
52. http://www.webmd.com/
53. Rowe, Paul J.S and Sian C.O. Handbook of Pharmaceutical Excipients Fifth edition (2006), Published by the pharmaceutical press publications division of the Royal Pharmaceutical Society of Great Britain, UK.
54. Suvakanta dash et. al., kinetic modeling on drug release from controlled drug delivery systems, Acta Poloniae Pharmaceutica ñ Drug Research, 2010; 67(3): 217ñ223.
55. Amrita Panda, Sukhadakulkarni, Ravi Tiwari, Stability Studies: An Integral Part Of Drug Development Process, IJPRBS, 2013; 2(6): 69-80.