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Formulation and Evaluation of Mucoadhesive Buccal Patches of Aceclofenac

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ABSTRACT

Mucoadhesive buccal patches of Aceclofenac were prepared using different polymers like hydroxypropyl methylcellulose, Carbopol 934-P, polyvinyl alcohol, polyvinyl pyrrolidone K-30, Eudragit L-100 in various proportion and combinations by solvent casting method. The prepared patches were smooth, elegant in appearance, uniform in thickness, mass and drug content. All the formulation showed folding endurance of 100. A 3^2 full factorial design was employed to study the effect of variable polymers like Carbopol 934-P and PVP K-30, hydroxypropyl methylcellulose, which significantly influenced characteristics like swelling index and ex vivo residence time of Aceclofenac buccal patches. In vitro drug release and in vitro drug permeation study showed that, from the formulation F10, the drug is released and permeated fastly. All the formulations are best fitted to Higuchi model.The stability study of selected patches were done in natural human saliva and it was found that all the patches were stable in human saliva.

Keywords: Aceclofenac, buccal patches, *in-vitro* release, residence time, swelling index.

INTRODUCTION

The various transmucosal routes, buccal route is an alternative oral route of administration owing buccal mucosa has excellent convenience and region of smooth muscles and relatively immobile mucosa, hence suitable for administration of mucoadhesive dosage form. The oral cavity has rich blood supply that drains directly into the systemic circulation and bypasses drugs from hepatic first pass metabolism by increasing the bioavailability [1,2]. These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery [3]. Mucoadhesion is the phenomenon between two materials which are held together for prolong period of time by interfacial force. It is generally referred as mucoadhesion when interaction occurs between polymer and epithelial surface [4,5].

Aceclofenac is a non steroidal anti-inflammatory drug (NSAID'S) belongs to class phenyl acetic acid. It is used as analgesic, antipyretic and it is widely used in the treatment of rheumatoid arthritis, osteoarthritis, management of dental pain and post operative pain. Aceclofenac is poorly insoluble in water and gastric fluids, leads to poor bioavailability.due to this, it will remains in the stomach wall for a prolonged period of time which may cause ulceration, gastric perforation, bleeding.the bioavailability of Aceclofenac is 60-70% and half life is 4-5 hrs [6].

The main drawbacks behind the oral rote of Aceclofenac are poor bioavailability due to first-pass metabolism and enzymatic degradation in the gut wall. But the intravenous administration is painful and difficult to administer in unconscious patient and geriatric patient. Attempt has been made earlier to formulate various mucoadhesive buccal devices, including tablets [7], films [8] and patches [9], strips [10], ointments [11] and gels [12]. Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets and also ensures more accurate dosing of the drug compared to gels and ointments [13].

Hence In the present work, the main aim was to develop unidirectional buccal patches of Aceclofenac to improve the bioavailability by avoiding hepatic first-pass metabolism and there by improve the patient compliance and also to reduce the frequency of administration.

MATERIALS AND METHODS

Materials

Aceclofenac was a free gift sample from Karnataka antibiotics Pvt Ltd, Bangalore, India. Carbopol 934-P was obtained from Sarabhai Chemicals Ltd, Baroda, India. Eudragit-L100 was procured from Helios Pharmaceuticals Ltd, Ahmadabad, India. Polyvinyl pyrrolidone (PVP K-30) were purchased from Themis laboratory, India. Polyvinyl alcohol (PVA), poly ethylene glycol (PEG 400), hydroxypropyl methylcellulose (HPMC K-4M) and propylene glycol (PG) was purchased from S.D fine chemicals, Bangalore, India. The biaxially-oriented polypropylene (BOPP) film was obtained from Pedilite, India. All other reagents used were analytical grade.

Methods

Formulation of mucoadhesive buccal patches of Aceclofenac

Aceclofenac buccal patches were prepared by solvent casting method using different hydrophilic and hydrophobic polymers (HPMCK-4M (2%), Carbopol 934-P (1%), PVA (2% w/v), Eudragit L-100 (2% w/v) and PVP (2% w/v) Different concentrations and ratios of polymer solution is prepared as mentioned in **Table 3**. The above polymeric solution 2 mL PEG 400 or PG was added and stirred on a magnetic stirrer for 1 hour at low rpm until homogenous clear solution formed. The drug (404mg in 1mL of methanol) and sodium saccharin (0.75%) were added to the above solution .the homogenous solution keep it aside till air bubbles free solution obtained and poured into a Teflon coated circular Petridish having 9.0 cm diameter. The patches were initially dried at room temperature and then dried for 36 hrs at 60 ^{o}C in a hot air oven. The dried patches were carefully removed and checked for any cracks and cut into 2 cm diameter patches using specially fabricated stainless steel patch cutter. One side of patch was laminated with impermeable backing layer (BOPP) and packed in an aluminium foil and stored in a desicator for further analysis [14].

Table1.Compositions of Aceclofenac buccal patches

Formulations		HPMC-K4M (2%) (mL)	Carbopol-934p (1%) (mL)	Eudragit L-100(2%) (mL)	PVA (2%) (mL)	PVPK30 (mL)	Aceclofenac (mg)
F1	**F11**	10	-	10	10	-	20
F2	**F12**	12	12	-	6	-	20
F3	**F13**	12	-	12	6	-	20
F4	**F14**	10	15	-	5	-	20
F5	**F15**	10	10	-	8	-	20
F6	**F16**	10	10	-	-	10	20
F7	**F17**	13	-	10	-	7	20
F8	**F18**	12	-	9	-	9	20
F9	**F19**	10	14	-	-	6	20
F10	**F20**	14	12	-	-	4	20

**F1-F10 plasticizer used is PEG-400; F11-F20 plasticizer used is PG*

Evaluation of patches

Mass uniformity and thickness of patches

Mass uniformity and thickness (selected buccal patches) was done for randomly selected ten individual patches. The thickness and mass uniformity is measured by using screw gauge and digital weighing balance carefully.

Folding endurance

The folding endurance of randomly selected patches (without backing membrane) was determined by repeatedly folding one patch at the same place till it break or folded maximum 250 times [13].

Drug content uniformity

Aceclofenac buccal patches are allowed dissolve in 10 mL of simulated saliva pH (6.2), under occasional shaking for 3 hr, withdraw 2 mL sample solution filter with filter paper after that suitable dilutions was made and amount of drug present in per patch was determined by using UV spectrometer (Shimadzu 1800, Japan) at 272nm [15].

Measurement of surface pH

Buccal patches were placed on the surface of agar plate (the agar plate is prepared by dissolving agar 2% w / v in warmed phosphate buffer pH 6.2 under stirring then poured to Petridish to solidify at room temperature) allow to swell for some time. The surface pH is measured bringing a glass electrode in contact with surface of the patch and allow to equilibrate for 1 min. Averages of three readings are recorded [16].

Swelling studies

The weight of the patch, without backing membrane was determined by digital electronic weighing balance. Patches are placed on the surface of an agar plate and allowed to swell by keeping it an incubator at 37 ºC and the diameter is measured at predetermined time intervals for 90 minutes.

Swelling index was calculated from following equation.

$$\text{Swelling index} = (W_2 - W_1 / W_1) \times 100$$

Where SI (%) is percent swelling, W_2 is the swollen patch weight, W_1 is the initial weight of the patch [17].

***Ex vivo* residence time**

The *in vitro* residence time was determined using a locally modified USP disintegration apparatus (Electrolab ED-2L), the disintegration medium was composed of 500 mL simulated saliva pH 6.2 maintained at 37 ºC. A segment of pig buccal mucosa (3 cm long), was glued to the surface of a glass slide, vertically attached to the apparatus and allowed to move up and down so that the patch was completely immersed in and out buffer solution .The time taken by the patch to detach from the mucosal surface was recorded and the averages of three readings were recorded [18].

***In vitro* drug release**

The amount of drug release from Aceclofenac buccal patches was studied using the USP type II dissolution test apparatus (Electrolab TDT-08L) 100 mL simulated saliva pH (6.2) at 37 ± 5 ºC stirred at 50 rpm, patch having 2 cm diameter was fixed to square shaped glass disk by using instant adhesive (cyanoacrylate) glass disk is placed inside a dissolution beaker contains simulated saliva pH (6.2) [19]. 2 mL of samples are withdrawn at pre determined intervals of 240 min and replaced with fresh buffer solution. Collected samples are filtered through 0.45 µm filter paper and diluted with buffer solution pH (6.2) and the amount of drug release is assayed by UV spectrophotometer (Shimadzu 1800, Japan) at 272 nm. Drug release mechanism was determined by Higuchi and Korsmeyer-Peppas plots [20-22].

***In vitro* permeation**

The *in vitro* buccal permeation study of Aceclofenac buccal patches through the pig buccal mucosa was performed using Franz diffusion cell at 37 ºC ± 0.2 ºC. Pig buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. Freshly obtained pig buccal mucosa was mounted between the donor and receptor compartments. The patch was placed on the mucosa so the smooth surface of the mucosa placed towards receptor compartment and the compartments were clamped together. The donor compartment was wetted phosphate buffer (pH 6.2). The receptor compartment was filled with isotonic phosphate buffer (pH 7.4) stirred with a magnetic bead at 50 rpm. 1 mL sample was withdrawn at predetermined intervals and replaced with fresh buffer solution and assayed by UV spectrophotometer (Shimadzu 1800, Japan) at 272nm [23].

Stability studies

Selected Aceclofenac buccal patches were packed in an aluminium foil and stored in an amber coloured glass bottles. These bottles were subjected to stability testing using stability chambers maintained at 37 ± 0.5 ºC and 75 ± 5% RH for 6 months. Stability of selected patches is also carried out in human natural saliva. Patches are examined for changes in weight variation, thickness and drug content [24].

RESULTS AND DISSCUSION

Mass uniformity, thickness, Folding endurance, Drug content uniformity and surface pH

A total of 20 formulations were prepared using HPMC K-4M, PVP, Cp 934-P, Eudragit L -100 and PVA by solvent casting technique. The formulation F1-F10, PEG-400 was used as plasticisers and in case of F11-F20, PG was used as plasticisers. All the prepared patches showed uniform size, shape and smooth in appearance. Physical characteristics of prepared patches like mass uniformity, folding endurance, thickness, drug content and surface pH are shown in **Table 2.** The mass of the patches increased with PEG-400 as plasticizer. This may be due to the high molecular weight of the PEG-400 while compare to PG. The thickness of the patches varied between 28 ± 0.0030 to 42 ± 0.002 mm. Drug content of all formulations was found to be

uniform from 66% to 97% and shoed favourable drug loading efficiency. This indicates that the drug was dispersed uniformly throughout the patches. Surface pH of the patches lies between 5.2 to 6.3. All most all patches shows satisfactory folding endurance i.e. >100. The formulations F5, F8, F10, F15, F18, and F20 shows folding endurance of >250. Therefore these patches are selected for further evaluation studies like swelling index, mucoadhesion time, *in vitro* drug release studies, *in vitro* drug permeation and stability studies.

Table 1. Mass uniformity, thickness, Folding endurance, drug content and surface pH of Aceclofenac buccal patches

Formulation codes	Mass uniformity	Film thickness	Folding endurance (Times)	Surface pH	Drug content	Drug loading efficiency (%)
F1	93±2.8	0.31±0.003	170	6.1	15.6±0.3	78
F2	100±5.1	0.29±0.002	125	6.1	16.4±0.4	82
F3	94±4.1	0.34±0.006	132	5.9	13.3±0.8	66
F4	92±5.2	0.31±0.003	140	6.1	14.7±0.6	73
F5	91±4.2	0.39±0.008	>250	6.2	19.8±0.1	99
F6	95±4.3	0.41±0.004	180	5.9	15.3±0.4	76
F7	93±4.8	0.33±0.006	192	5.9	18.6±0.3	93
F8	100±5.1	0.32±0.004	>250	6.1	19.5±0.5	97
F9	92±3.2	0.42±0.002	120	5.9	14±0.6	70
F10	90±2.1	0.32±0.001	>250	6.1	19.5±0.2	98
F11	92±2.9	0.28±0.006	180	6.3	16.6±0.9	83
F12	90±4.2	0.24±0.005	130	5.9	17.8±0.3	89
F13	91±4.5	0.31±0.006	140	5.9	14.4±0.6	72
F14	90±3.9	0.30±0.004	180	6.1	15.6±0.7	78
F15	91±5.2	0.35±0.002	>250	6.2	19.5±0.1	97
F16	90±6.2	0.32±0.001	140	6.0	16.4±0.4	82
F17	89±5.0	0.31±0.004	197	5.9	18.5±0.5	92
F18	87±7.2	0.30±0.007	>250	5.9	19.0±0.3	95
F19	89±5.8	0.36±0.005	130	6.0	15.1±0.8	75
F20	89±2.8	0.28±0.003	>250	6.1	19.4±0.3	97

** Mean ± SD, n=3*

Table 3. Swelling index of selected Aceclofenac buccal patches

Time (min)	Swelling Index					
	F5	F8	F10	F15	F18	F20
5	91±1	103±2	100±2	96±1	100±1	92±3
10	92±3	103.5±2	103±3	96±2	102±1	93±3
15	93±2	104±3	108±2	100±3	105±2	95±2
30	97±2	108±2	115±3	103±2	106±2	98±1
45	101±3	112±1	116±4	109±2	110±3	102±1
60	103±2	115±2	118±2	109±3	115±2	105±2
90	115±3	110±3	120±3	109±4	111±3	114±2

** Averages of three readings*

Swelling studies

Swelling behaviour of selected patches as a function of time is showed in **Table 3.** The swelling indices of the patches were increased up to 120 ± 3 for formulation F10 after 90 min and followed by F5, F8, F15 and F18. The higher swelling index may be due to the presence of water soluble polymers. But F8 and F18 composed of hydrophilic and hydrophobic polymers and the presence of Eudragit polymer might have affected the swelling indices. The formulation prepared with PEG-400 showed maximum swelling index and this could be due to higher water

uptake of PEG-400 compared to PG. During the study all the maintained its integrity and did not show any appreciable changes in shape and form.

Ex vivo residence time

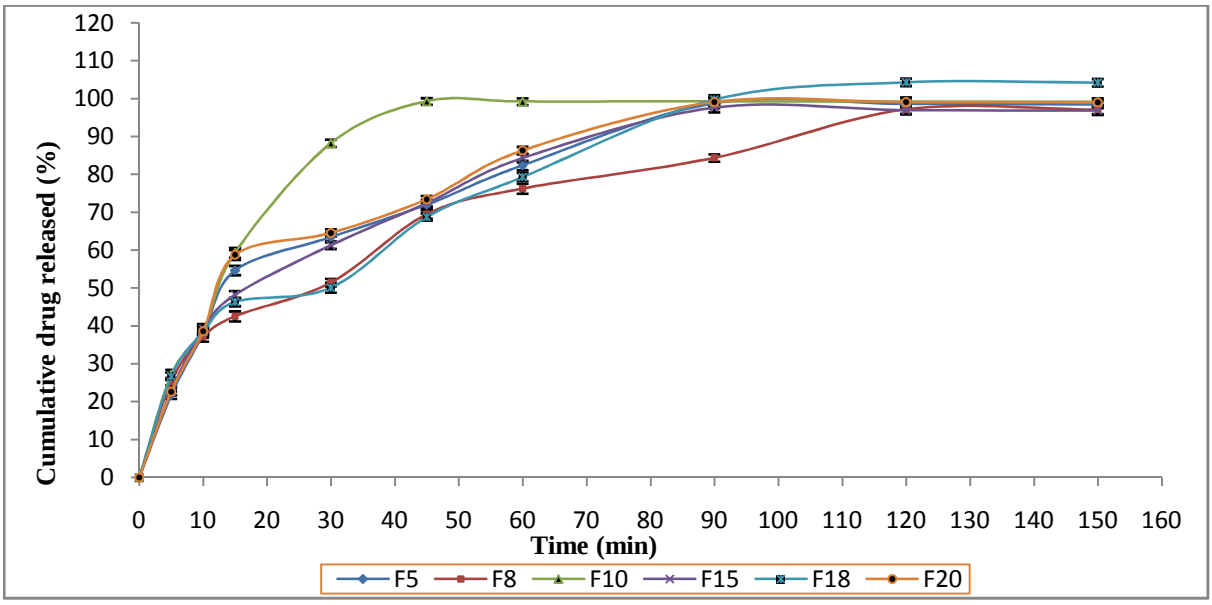
The values of *ex vivo* mucoadhesion time are shown in **Table 4.** The residence time of the tested patches ranged between 109 ± 1.8 and 120 ± 1.7 min. All the selected patches retained on the pig buccal mucosa over the study period and which is indicated that the residence time of all the patches was sufficient to retain on the buccal mucosa.

Table 4. *Ex vivo* residence time of selected Aceclofenac buccal patches

Formulations	Mucoadhesion time (min)
F5	112 ± 1.2
F8	118 ± 2.2
F10	120 ± 1.7
F15	109 ± 2.4
F18	115 ± 2.1
F20	109 ± 1.8

** Averages of three readings*

Fig 1. *In vitro* release of Aceclofenac from selected patches



In vitro drug release

The *in vitro* release of selected patches is shown in **Fig.1.** The maximum drug release was shown to be 99.28 after a period of 45 min from F10.The formulations F5, F15 and F20 showed maximum release after 90 min and F8 and F18 showed after 120 min. We could notice other relations in formulaions with PEG-400, that there was a good correlation between the percentage drug release, swelling index and percentage drug permeation. From the beginning of the study, the drug release profile of all patches showed faster drug release and was not appropriate for a controlled drug delivery system. The drug release mechanism from controlled release devices is very complex and either purely diffusional or purely erosion controlled or by both. Drug release mechanism was determined by ploting release data to Higuchi and Korsmeyer-Peppas model. All the formulations are best fitted to Higuchi model, according to this model the drug releases from

theses patches may be controlled by diffusion through the micropores. The r^2, '*k*' and '*n*' values are shown in **Table 5.**

Table 5. The r^2, '*k*' and '*n*' values of selected Aceclofenac buccal patches

Formulations	Higuchi		Kosmeyer-Peppas		Mechanism of drug release
	r^2	k	r^2	n	
F5	0.930	8.314	0.823	0.802	Diffusion
F8	0.970	7.965	0.817	0.778	Diffusion
F10	0.792	8.317	0.788	0.802	Diffusion / Non fickian
F15	0.937	8.281	0.821	0.796	Diffusion
F18	0.967	7.758	0.803	0.769	Predominatly Higuchi
F20	0.917	8.332	0.815	0.800	Predominatly Higuchi

In vitro permeation

The *in vitro* permeation of selected patches are shown in **Fig.2.** The drug permeation was fast and showed a similar profile to that of the *in vitro* drug release. The formulation F10 showed maximum permeation over a period of 45 min. Formulation F20 and F5 showed after 90 min and F8 and F18 showed after 120 min. From this it is noticed that F10 showed the maximum swelling index, *in vitro* release and *in vitro* permeations. The drug was released from the patches and permeated through the porcine buccal mucosa and hence could possibly permeate through the human buccal membrane also. There was a good correlation between the *in vitro* drug release and *in vitro* drug permeation results and are shown in **Fig. 3.** The correlation coefficient (r^2) of formulations was 0.9988.

Fig 2. *In vitro* permeation of Aceclofenac from selected patches

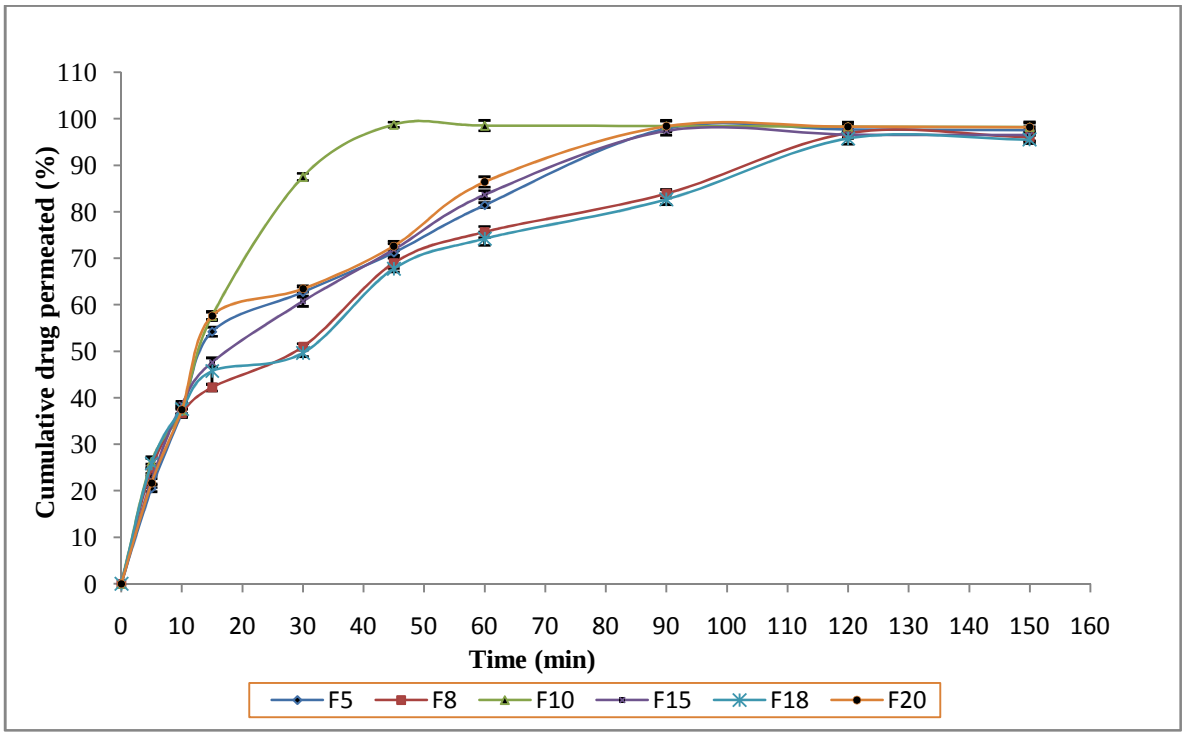
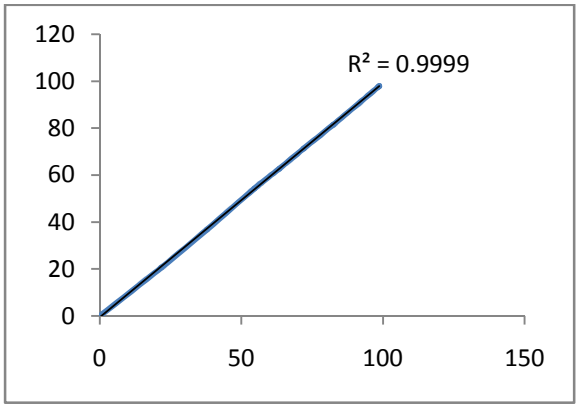
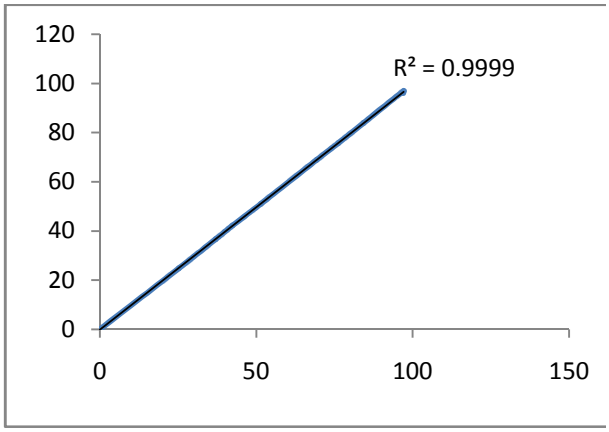


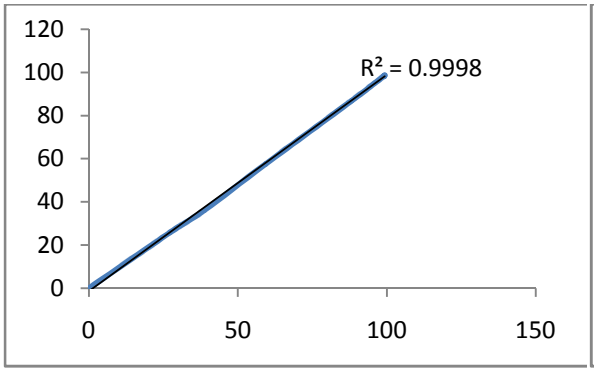
Fig 3. Correlation between *in vitro* release and *in vitro* permeation of Aceclofenac from selected patches



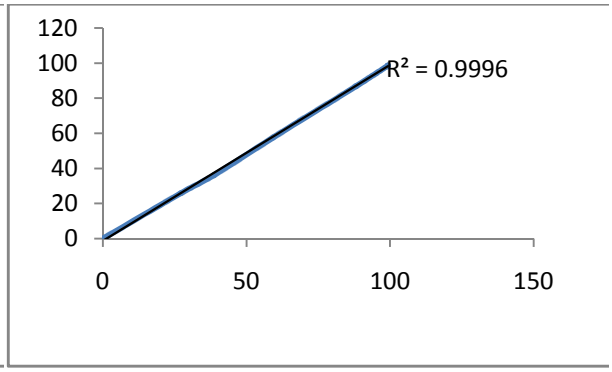
F5



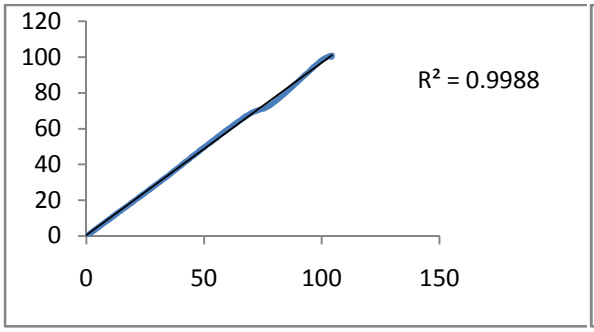
F8



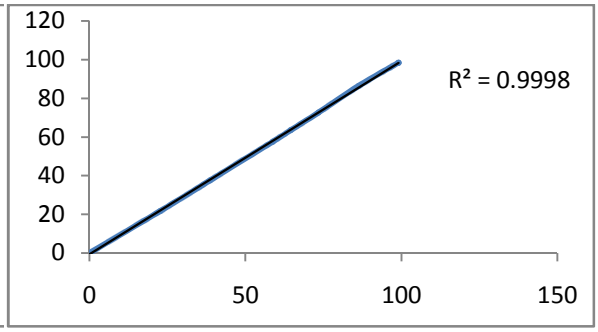
F10



F15



F18



F20

Stability studies

Stability studies of Aceclofenac buccal patches are shown **Table 5**. During the end of accelerated stability study of tested patches shows almost same drug content as observed in beginning of the study and also shows satisfactory mass uniformity and thickness properties during the end of the stability study. No colour change or no any changes in texture were observed when patches were tested in human saliva.

Table 5. Stability studies of selected Aceclofenac buccal patches

Evaluation parameter	Formulation code	1st month	2nd month	3rd month	5th month	6th month
Drug content*	F5	19.7±0.8	19.7±0.6	19.5±0.6	19.4±0.6	19.2±0.6
	F8	19.3±0.5	19.2±0.5	19.2±0.5	19.0±0.5	18.8±0.5
	F10	19.2±0.4	19.1±0.7	19.1±0.7	19.0±0.7	18.9±0.7
	F15	19.4±0.3	19.3±0.3	19.3±0.3	19.3±0.3	19.2±0.3
	F18	18.9±0.2	18.9±0.3	18.8±0.4	18.7±0.4	18.6±0.4
	F20	19.2±0.3	19.1±0.5	19.1±0.5	18.9±0.5	18.8±0.5
Residence Time*	F5	110 ± 0.9	108 ± 0.7	106 ± 0.9	105± 0.9	104± 0.9
	F8	117 ± 2.2	115 ± 1.8	112 ± 1.7	110± 1.7	109± 1.7
	F10	119 ± 1.3	118 ± 0.9	116 ± 0.5	114± 0.5	112± 0.5
	F15	107 ± 2.1	105 ± 1.4	104 ± 1.9	103± 1.9	101± 1.9
	F18	114 ± 1.1	113 ± 0.8	111 ± 0.7	109± 0.7	107± 0.7
	F20	108 ± 0.9	105 ± 0.9	102 ± 1.5	101± 1.5	100± 1.5
Thickness*	F5	0.38±0.06	0.37±0.08	0.37±0.08	0.36±0.07	0.35±0.07
	F8	0.31±0.02	0.29±0.03	0.28±0.05	0.27±0.05	0.26±0.05
	F10	0.30±0.03	0.29±0.02	0.28±0.06	0.27±0.06	0.25±0.06
	F15	0.34±0.02	0.33±0.04	0.32±0.05	0.31±0.04	0.30±0.04
	F18	0.27±0.02	0.28±0.03	0.28±0.03	0.27±0.02	0.25±0.02
	F20	0.28±0.003	0.26±0.04	0.25±0.07	0.24±0.06	0.23±0.06

** Averages of three determinations*

CONCLUSION

Mucoadhesive buccal patches of Aceclofenac with unidirectional drug release were formulated to overcome first pass metabolism. There was a good correlation between *in vitro* drug release and *in-vitro* drug permeation study. The drug was released from the patches and permeated through the porcine buccal mucosa and hence could possibly permeate through the human buccal membrane also.

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