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Original Article

Formulation, characterization and evaluation of bioadhesive buccal patch of venlafaxine

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ABSTRACT

The present study involves the formulation and evaluation of buccal patches of venlafaxine using different polymers like Ethyl cellulose, Hydroxypropyl methylcellulose (HPMC) K4M, Eudragit S100 in various proportion and combination, where propylene glycol and dibutylpthalate are used as plasticizer. All formulations are formulated by solvent casting technique.Venlafaxine; an antidepressant drug has high first pass metabolism so buccal route is excellent for its systemic delivery thereby rendering great bioavailability. Preformulation studies were conducted before formulation and formulated patches were subjected for evaluation of various physicochemical parameters like thickness, wt. uniformity, pH, content uniformity, folding endurance, percentage swelling, tensile strength, vapour transmission rate, percentage moisture loss and muco-adhesion force. *In vitro* drug release study was carried out using Franz diffusion cell. From among all the developed formulations, the formulations FP4, FP7 and FP14 provide a well-controlled release of drugs so these were selected as the best formulations .The optimized fabricated patches were sustained for more than 10 h and obeyed Higuchi kinetics and mechanism of release was fickian diffusion. Optimized patches were also subjected to *ex vivo* study using Goat buccal mucosa. The experimental result revealed that there was no significant difference between *ex vivo* and *in vitro* release profile.

Keywords: Venlafaxine, buccal patch, *in-vitro* and *ex-vivo* study.

INTRODUCTION

The main impediment to the use of many hydrophilic macromolecular drugs as potential therapeutic agents is their inadequate and erratic oral absorption. After oral administration many drugs are subjected to presystemic clearance extensive in liver, which often leads to a lack of significant correlation between membrane permeability, absorption, and bioavailability [1]. Difficulties associated with parenteral delivery and poor oral availability provided the impetus for exploring alternative routes for the delivery of such drugs. These include routes such as pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal.Among the various transmucosal routes, buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. Absorption through the buccal mucosa overcomes premature drug degradation due to the enzyme activity and pH of gastro intestinal tract, avoids active drug loss due to presystemic metabolism, acid hydrolysis and therapeutic plasma concentration of the drug can be rapidly achieved [2]. Moreover buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage from the buccal cavity therefore mucoadhesive drug delivery devices such as patches [3], tablets [4], films, gels, ointments and discs [5] were suggested. Venlafaxine HCl is a selective serotonin and norepinephrine-reuptake inhibitor (SNRI) antidepressant and anxiolytic agent. The oral bioavailability of venlafaxine is about 45 % because of extensive first pass metabolism in liver and gut wall. It was selected as a model drug for investigation because of its suitable properties like dose strength (25 mg), half-life (5 h) and molecular weight (277.40). Disadvantages of drug delivery by this route are the low permeability of the buccal membrane [6], specifically when compared to the sublingual membrane [7], and a smaller surface area. The total

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surface area of the membranes of the oral cavity available for drug absorption is 170 cm^2 [8], of which ~50 cm^2 represents non-keratinized tissues, including the buccal membrane. In the present study, the mucoadhesive buccal patches were developed using polymers such as Ethyl cellulose, Eudragit S100 and HPMC K4M at different proportions to get the controlled release rate from the buccal patches.

The objective of the present research work was to develop buccal patches of Venlafaxine to achieve better therapeutic efficacy by circumventing the hepatic first pass metabolism in effective treatment of depression.

MATERIALS AND METHODS

Venlafaxine was obtained as a gift sample from Ranbaxy Laboratories, Baddi, India. Hydroxypropyl methylcellulose (HPMC) K4M, Eudragit S100 and Ethyl cellulose was provided from S.D Fines chemicals, India. All other reagent and chemicals were of analytical grade.

Preparation of buccal patch by solvent casting method [9]: The buccal patches were prepared using solvent casting technique. In solvent casting (SC), a polymer is dissolved in an organic solvent. Particles (mainly salts), with specific dimensions are then added to the solution. The mixture is shaped into its final geometry. For example, it can be cast onto a glass plate to produce a membrane or in a three dimensional mold. When the solvent evaporates it creates a structure of composite material consisting of the particles together with the polymer. The composite material is then placed in a bath which dissolves the particles, leaving behind a porous structure. Compositions of different formulations are given in Table 1 and 2.

Evaluation of prepared patches:

Thickness [10]: The thickness of three randomly selected buccal patches from every batch was determined using a standard vernier caliper. The average thickness was determined and reported with appropriate standard deviation.

Weight uniformity study [10]: Weight uniformity of patch determined by taking weight of ten patches of sizes 1 cm^2 diameter from every batch and weigh individually on electronic balance. The average weights were then calculated.

Surface pH study: The surface pH of the patches was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The method of Bottenberg *et al* [11] was used to determine the pH; a combined glass electrode was used for this purpose. The patch was allowed to swell by keeping it in contact with 1 ml of distilled water for 1 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 min. The experiments were performed in triplicate, and average values were reported.

Content uniformity [12]: Drug content uniformity was determined by dissolving the patch (1 cm^2 in diameter) from each batch by homogenization in 100 ml of an isotonic phosphate buffer (pH 6.8) for 24 h under occasional shaking. The 5 ml solution was taken and diluted with isotonic phosphate buffer pH 6.8 up to 20 ml, and the resulting solution was filtered through a 0.45 mm Whatman filter paper. The drug content was then determined after proper dilution using UV spectrophotometer.

Folding endurance [13]: Folding endurance of the patch was determined by repeatedly folding one patch at the same place till it broke or folded up to 180 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place on randomly selected three patches from each.

Swelling percentage study [14]: Swelling study of prepared patch was calculated by function of weight and area increase due to swelling, which was measured for each formulation as follows. Weight increase due to swelling: A patch of size (1×1 cm^2) diameter from every batch was weighed on a pre-weighed cover slip. It was kept in a petridish and 10 ml of phosphate buffer, pH 6.8 was added. After 1 h, the cover slip was removed and weighed. The difference in the weights gives the weight increase due to absorption of water and swelling of patch. The study was conducted for 14 h. The percentage swelling ratio was calculated from the average of three measurements using the following equation:

Percentage swelling = $[(Xt - Xo) / Xo] \times 100$

Where, Xt - weight or area of the swollen patch after time t and

Xo - is the original patch weight or area at zero time.

Tensile strength: A tensile strength study of patch is total weight, which is necessary to break or rupture the dosage form and this was done by a device has rectangular frame with two plates made up of Plexiglas's. The one plate is in front and is movable part of device and can be pulled by loading weights on the string, which is connected

to movable part. The 1×1 cm^2 patch equivalent to 2.75 mg drug from each formulation was fixed between the stationary and movable plate. The force needed to fracture the film was determined by measuring the total weight loaded in the string. The weight corresponds to break the patches were taken as tensile strength. The following equation was used to calculate the tensile strength (TS):

TS (g/cm^2) = Force at break (g) / Initial cross sectional area of patch (cm^2).

Vapour transmission test (VTR) [15]: Vapour transmission method was employed for the determination of vapour transmission from the patch. Glassbottle (length = 5 cm, narrow mouth with internal diameter = 0.8 cm) filled with 2 g anhydrous calcium chloride and an adhesive (Feviquick®) spread across its rim, was used in the study. The patch was fixed over the adhesive and the assembly was placed in a constant humidity chamber, prepared using saturated solution of ammonium chloride and maintained at 37 ± 2°C. The difference in weight after 24 h was calculated. The experiments were carried out in triplicate and vapor transmission rate was obtained as follow:

VTR = (Amount of moisture transmitted) / (Area × Time)

Percentage moisture loss (PML) [15]: Percentage moisture loss was also carried to check the integrity of films at dry condition. Three 1cm diameter films was cut out and weighed accurately and kept in desiccators containing fused anhydrous calcium chloride. After 72 h the films were removed, weighed. Average percentage moisture loss of three films was found out.

PML = [(Initial weight – Final weight)/initial weight] × 100

Determination of mucoretention force by Park and Robinson method [16]: With the Park and Robinson method, the patches were placed in contact with the goat soft palate and placed in a modified physical balance. The goat buccal mucosa was placed on the top of a glass vial with smooth surface on top of which was placed the patch, sandwiched between two layers of the buccal mucosa. The other end was attached to a weight for balancing. The weight was added to the left pan until the point of detachment of the patch from the mucosa. The force required to detach the patch from the mucosal surface was determined.

***In-vitro* release study [17]:** The *in-vitro* release study was performed by using the Franz diffusion cell at the salivary pH. The diffusion cell was maintained at 37 ± 0.5°C and 50 rpm. Samples were collected after specific time intervals and subjected for U.V. analysis.

***In vitro* drug release kinetics:** Kinetic models describe drug release from immediate and modified release dosage forms [18].In order to investigate the kinetics and mechanism of drug release from prepared patches of different drug and polymers ratios, the release data were examined using Zero−order kinetic, First order kinetic, Higuchi kinetic, Hixon crowell and Korsmeyer−Peppas model.

RESULTS AND DISCUSSION

The main aim of the present investigation was to develop and evaluate Venlafaxine buccal patches using different polymer in different combination and proportion. Formulated patches were subjected for evaluation of various physicochemical parameters like thickness, weight-uniformity, surface pH, content uniformity, folding endurance, percentage swelling, tensile strength, vapour transmission rate, percentage moisture loss, muco-adhesion force, *in vitro* and *ex vivo* study. Compatibility study was performed by means of FTIR instrument. The result was based on matching the main peak of pure drug with drug and polymer. No incompatibility was found between drug and polymers. The results of physicochemical evaluation are shown in table 3 and 4. The thickness of formulated patches ranges from 0.125±0.005 mm to 0.325±0.006 mm .On increasing the polymer weight the thickness was increased (Fig 1).

The weight of patches of Ethyl cellulose and HPMC K4M ranges from 0.016±0.002 g to 0.033±0.003g, Eudragit S100 and HPMC K4M patches ranges from 0.020±0.001 g to 0.031±0.002 g. Weight of patch was directly proportional with amount of polymer used (Fig 2). The surface pH of patches ranges from 6.3±0.015 to 7.2±0.2 which indicates of no risk of mucosal damage or irritation (Fig 3). For all patches content uniformity was found in range of 87.36±3.1% to 99.07±1.3% which indicate that the drug was uniformly dispersed in patches. The selected patch FP4 shows content uniformity of 98.44±1.3%, FP7 of 97.82±1.8% and FP14 of 96.70±2.9% which shows drug was uniformly dispersed (Fig 4).

The folding endurance of the patches was measured manually and it did not show any cracks (except formulation FP1, FP2 and FP9) even after folding it a number of times (> 180). The folding endurance for most patches was more than 180 ± 5.0 and for optimum ratios it was more than 250, indicating the high flexibility of the patches, which indicate polymers and plasticizer provide the required flexibility to the patches. Further it's also

suggestive that with increasing amount of polymer folding endurance also increases. (Fig 5). The patch FP4, FP7 and FP14 showed the swelling index of 82.59±3.2%, 81.62±4.0% and 70.48 ± 4.2% respectively.Swelling studies reveal that maximum swelling takes place in the patches containing higher amount of the hydrophilic polymers (Fig 6) and the drug release through the patches is by swelling followed by erosion.

The tensile strength gives an indication of the strength and elasticity of the patches.The tensile strength for FP4 with 183.7±1.4 g, FP7 with 193.9±1.9 g and for FP14 181.7±1.3 g respectively.It seen that the patches with higher amount of polymer has higher tensile strength (Fig 7). The result of vapour permeation study showed that all patches were permeable to water vapour and hence the release of drug through the patch takes place by permeation of water (Fig 8). The mucoadhesion force ranges from 2.52 g to 26.91 g. The patches with higher amount of mucoadhesive polymer (HPMC K4M) show good mucoadhesion and result indicate on increasing the amount of mucoadhesive polymer the mucoadhesion force increases (Fig 9). For the formulation batches FP1 to FP15 the polymer like Ethyl cellulose, Eudragit S100 and HPMC K4M were used either alone or in combination. It was clearly observed that on increasing the polymer concentration, the diffusion of the drug from the polymer matrix was retarded and hence resulted in slower release rate (Fig.10 and 11).

All of these buccal patches slowly released the drug incorporated and sustained release for 10 h .Formulation with optimum drug polymer concentration like FP4, FP7 and FP14 provide a well-controlled release of drug from the formulation that is 67.2%, 77.8% and 62.3% respectively. Experimental result also revealed that not only the polymeric concentration affects the diffusion of drug from formulation but also the nature of polymer pose significant role in the release rate. For example formulation FP6 and FP7 having the same amount of drug polymer ratio is 1:5 but in case of FP6 the cumulative release percentage is 62.8% while it is 77.8% for the formulation FP7. It may be due to the nature of polymer that was used in the larger proportion in formulation. More amount of ethyl cellulose in formulation FP6 retards its release more in comparison to formulation FP7 which contained larger fraction of hydrophilic polymer like HPMC K4M.

The model fitting analysis (Zero Order, Higuchi, Hixon Crowell, First Order and Korsmeyer – Peppas Model) were done by comparing the coefficient of regression (r^2) values and corresponding n value of all the kinetic equation. The correlation coefficient values were used as criteria to choose the best model for the drug release from the buccal patch. From the respective table (table 5 and 6) it was observed that the individual formulation having different r^2 value for different model. On the basis of higher value of r^2 we select the best fit model (table 5 and 6). Now Korsmeyer – Peppas Model poses great importance to know the release mechanism of the drug from the formulation. Higuchi model is dominant and shows that the release of venlafaxine, the water–soluble drug through the hydrated gel layer around the buccal patches, is approximately dependent on the square root of time. To predict the mechanism of diffusional release, the following equation $M^t/M^\infty = kt^n$ was used to analyze data of controlled–release of this water soluble drug from the studied polymer matrices. Now n = 0.5 means Fickian diffusion, 0.5 < n < 1.0 non-Fickian diffusion, and n = 1.0 Case II diffusion [19]. Considering the n values calculated for the studied patches (table 5 and 6), almost in most cases a Fickian diffusion mechanism is dominant. Only in case of formulation FP4 non-Fickian or anomalous diffusion is dominant. Which may be due to release from initially dry, hydrophilic glassy polymers that swell in contact of water and become rubbery show anomalous diffusion as a result of the rearrangement of macromolecular chains.The *ex-vivo* venlaflaxine permeation from formulation FP4, FP7 and FP14 showed that drug release across goat buccal mucosa more than 10 h period (Fig 12).As a conclusive result of bioadhesion, physical parameter and *in vitro* and *ex vivo* study; formulation FP4, FP7 and FP14 were selected as best formulations.

CONCLUSION

This study clearly demonstrated that the Venlafaxine can be successfully delivered through buccal route by preparing the buccal patches. The patches were non-irritating and showed ideal properties of patch with an added advantage of circumventing the hepatic first pass metabolism. Well defined residence time of the buccal films in the oral cavity, provide potential therapeutic benefit. It is possible to control the depression at faster rate after buccal administration of venlafaxine from patch by diffusion mechanism. However further work is essential to stabilize venlafaxine in buccal patch for promising controlled drug delivery along with this *In vivo* studies need to be designed and executed to substantiate further *in- vitro in-vivo* correlation.

Table 1: Formulation composition of buccal patches

S.no	Ingredients	Quantity							
		FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8
1	Drug (mg)	100	100	100	100	100	100	100	100
2	Ethyl Cellulose (mg)	100	150	200	250	300	400	100	-
3	HPMC K4M (mg)	100	150	200	250	200	100	400	500
4	Eudragit S100 (mg)	-	-	-	-	-	-	-	-
5	Propylene Glycol (%w/v)	-	-	-	-	-	-	-	-
6	Dibutylpthalate (%w/v)	40	40	40	40	40	40	40	40
7	Methanol (ml)	10	10	10	10	10	10	10	10

FP = Formulation patch, HPMC = Hydroxypropyl methylcellulose

Table 2: Formulation composition of buccal patches

S.no	Ingredients	Quantity						
		FP9	FP10	FP11	FP12	FP13	FP14	FP15
1	Drug (mg)	100	100	100	100	100	100	100
2	Ethyl Cellulose (mg)	-	-	-	-	-	-	-
3	HPMC K4M (mg)	150	200	250	200	400	100	-
4	Eudragit S100 (mg)	150	200	250	300	100	400	500
5	Propylene Glycol (%w/v)	40	40	40	40	40	40	40
6	Dibutylpthalate (%w/v)	-	-	-	-	-	-	-
7	Methanol (ml)	10	10	10	10	10	10	10

FP = Formulation patch, HPMC = Hydroxypropyl methylcellulose

Table 3: Evaluation of buccal patches

S.no	Formulation code	Thickness* (mm)	Wt.uniformity* (g)	pH*	Content uniformity* (%)	Folding endurance*
1	FP1	0.125±0.005	0.016±0.002	6.4±0.15	89.84±1.3	45± 3.0
2	FP2	0.187±0.005	0.023±0.001	6.5±0.17	92.60±2.1	160 ±5.0
3	FP3	0.237±0.007	0.027±0.001	6.4±0.2	95.36 ±3.1	180±3.0
4	FP4	0.325±0.006	0.030±0.002	6.7±0.18	98.44 ±1.3	240±5.0
5	FP5	0.297±0.008	0.029±0.003	6.3±0.1	99.04±1.8	226±5.0
6	FP6	0.314±0.005	0.033±0.002	6.6±0.15	97.84±2.5	219±5.0
7	FP7	0.316±0.006	0.031 ±0.001	6.9±0.2	97.24 ±3.1	225 ±5.0
8	FP8	0.323±0.008	0.032±0.001	6.6±0.12	97.82±1.8	237 ±5.0
9	FP9	0.175±0.006	0.020 ±0.002	6.8 ± 0.1	90.44 ±1.9	140 ±3.0
10	FP10	0.212±0.008	0.021 ±0.001	6.5 ±0.17	93.52 ±2.3	200 ±5.0
11	FP11	0.262±0.005	0.025 ±0.001	6.6 ±0.12	96.60 ±1.7	206 ± 4.0
12	FP12	0.250±0.007	0.029 ±0.002	6.6 ± 0.2	98.44 ±2.1	280 ± 5.0
13	FP13	0.237±0.005	0.028 ±0.001	7.2 ± 0.2	95.36 ±2.4	254 ± 5.0
14	FP14	0.275±0.008	0.029 ±0.003	6.3 ±0.18	96.70 ±2.9	244 ± 5.0
15	FP15	0.225±0.006	0.031 ±0.002	6.7 ± 0.15	99.07±1.3	262 ±5.0

FP = Formulation patch, *=Reflecting data are Mean ± Standard deviation (n=3)

Table 4: Evaluation of buccal patches

S.no	Formulation code	Percentage swelling* (%)	Tensile strength* (g)	Vapour transmission rate* (%)	Percentage moisture loss* (%)	Mucoadhesion force* (g)
1	FP1	57.57±2.5	132.6±1.2	7.13 ±0.6	7.81 ±1.5	18.33±0.2
2	FP2	65.47±2.4	147.2±2.4	6.98 ±0.27	5.33 ±2.1	20.31±0.4
3	FP3	70.61±3.1	161.5±2.1	6.43 ±0.32	8.38±1.6	21.87±0.1
4	FP4	82.59±3.2	183.7±1.4	4.22±0.9	4.33±1.8	23.18±0.5
5	FP5	73.71±3.5	156.8 ±2.1	5.67±0.55	8.76±2.0	20.5±1 .3
6	FP6	46.14 ±2.5	141.3±2.3	6.19 ±0.8	6.62±1.32	16.81±0.2
7	FP7	81.62 ±4.0	193.9 ±1.9	4.53 ±0.32	4.65 ±1.96	24.55±0.1
8	FP8	87.44±3.7	207.1±1.5	7.23±0.55	9.87 ±2.2	26.91±0.5
9	FP9	63.83±3.0	128.3 ±1.8	6.54 ±0.80	8.88± 2.4	20.21 ± 0.3
10	FP10	66.67±4.42	145.7 ±1.4	4.52 ±0.43	9.86±1.1	22.37 ± 0.5
11	FP11	74.21 ±2.9	174.4 ±2.2	7.05 ±0.48	7.57 ±1.30	23.82 ±0.1
12	FP12	67.15 ±2.6	148.7 ±2.4	6.63 ±0.23	10.10 ±1.9	21.36 ±0.3
13	FP13	86.34 ±3.8	132.9 ±3.1	5.13 ±0.89	5.6± 1.6	16.21 ±0.4
14	FP14	70.48 ±4.2	181.7 ±1.3	3.47 ±0.39	4.2± 2.10	24.73 ±0.5
15	FP15	71.42±2.9	120.8±2.1	5.60±0.42	5.92± 2.0	2.52± 0.3

FP = Formulation patch, *=Reflecting data are Mean ± Standard deviation (n=3)

Table 5: Result of correlation coefficients of release data by curve fitting method on zero order, first order, higuchi kinetic , hixon crowell model and there diffusion exponent (n):

Formulation code	Zero order	First order	Higuchi kinetics	Hixson crowell	n*	Best fit model	Mechanism of release
FP1	0.8442	0.9689	0.9061	0.9563	0.2972	First order	Fickian diffusion
FP2	0.9134	0.9397	0.893	0.9513	0.3515	Hixson crowell	Fickian diffusion
FP3	0.948	0.9825	0.8995	0.9791	0.4374	First order	Fickian diffusion
FP4	0.9718	0.9783	0.9029	0.9816	0.5084	Hixson crowell	Fickian diffusion
FP5	0.9124	0.9701	0.8973	0.9607	0.3644	First order	Fickian diffusion
FP6	0.9636	0.987	0.9028	0.984	0.4865	First order	Fickian diffusion
FP7	0.9352	0.9914	0.9081	0.9835	0.4803	Peppas korsmeyer	Fickian diffusion
FP8	0.9303	0.9358	0.8946	0.9622	0.3782	Hixson crowell	Fickian diffusion

FP = Formulation patch, $M^t/M^\infty = kt^{n*}$

Table 6: Result of correlation coefficients of release data by curve fitting method on zero order, first order, higuchi kinetic , hixon crowell model and there diffusion exponent (n):

Formulation code	Zero order	First order	Higuchi kinetics	Hixson crowell	n*	Best fit model	Mechanism of release
FP9	0.9133	0.9366	0.8932	0.9503	0.3519	Hixson crowell	Fickian diffusion
FP10	0.942	0.9842	0.9007	0.9777	0.432	First order	Fickian diffusion
FP11	0.959	0.9837	0.902	0.9814	0.4752	First order	Fickian diffusion
FP12	0.9055	0.974	0.8999	0.9615	0.3618	First order	Fickian diffusion
FP13	0.9217	0.9423	0.8944	0.9585	0.3664	Hixson crowell	Fickian diffusion
FP14	0.9568	0.9894	0.9051	0.9828	0.4924	First order	Fickian diffusion
FP15	0.9479	0.9765	0.9021	0.9727	0.4598	First order	Fickian diffusion

FP = Formulation patch, $M^t/M^\infty = kt^{n*}$

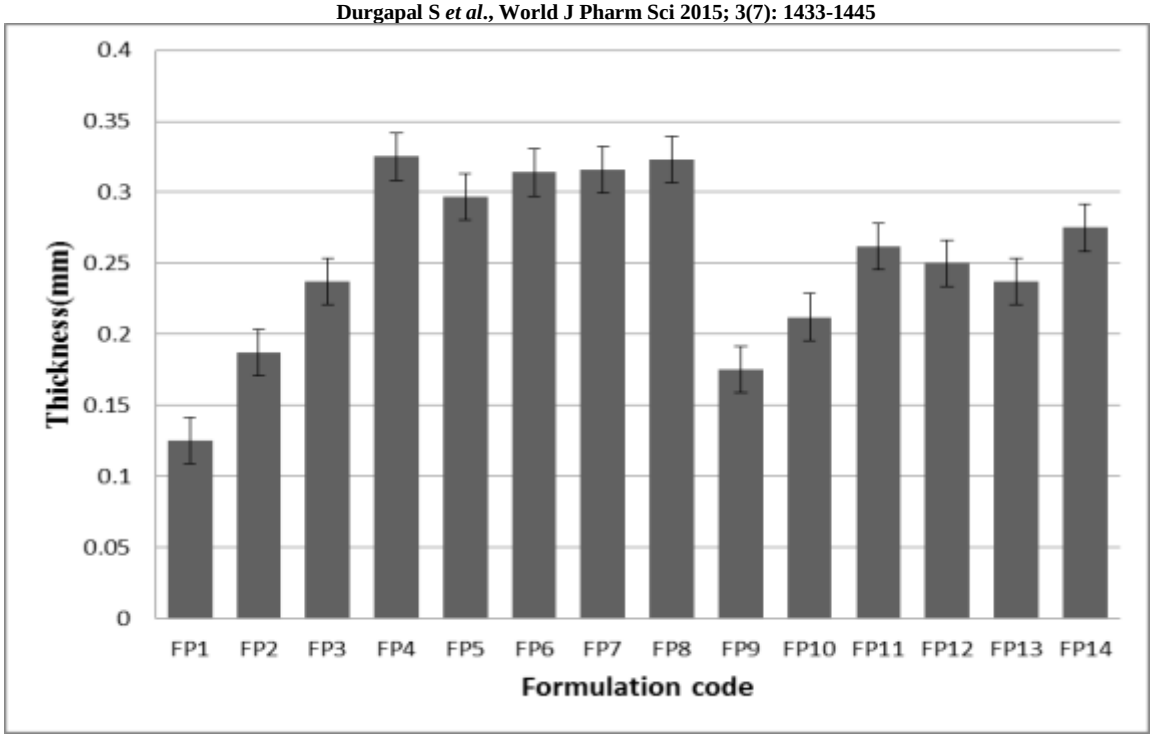

Fig.1: Thickness (mm) of prepared formulations of buccal patch

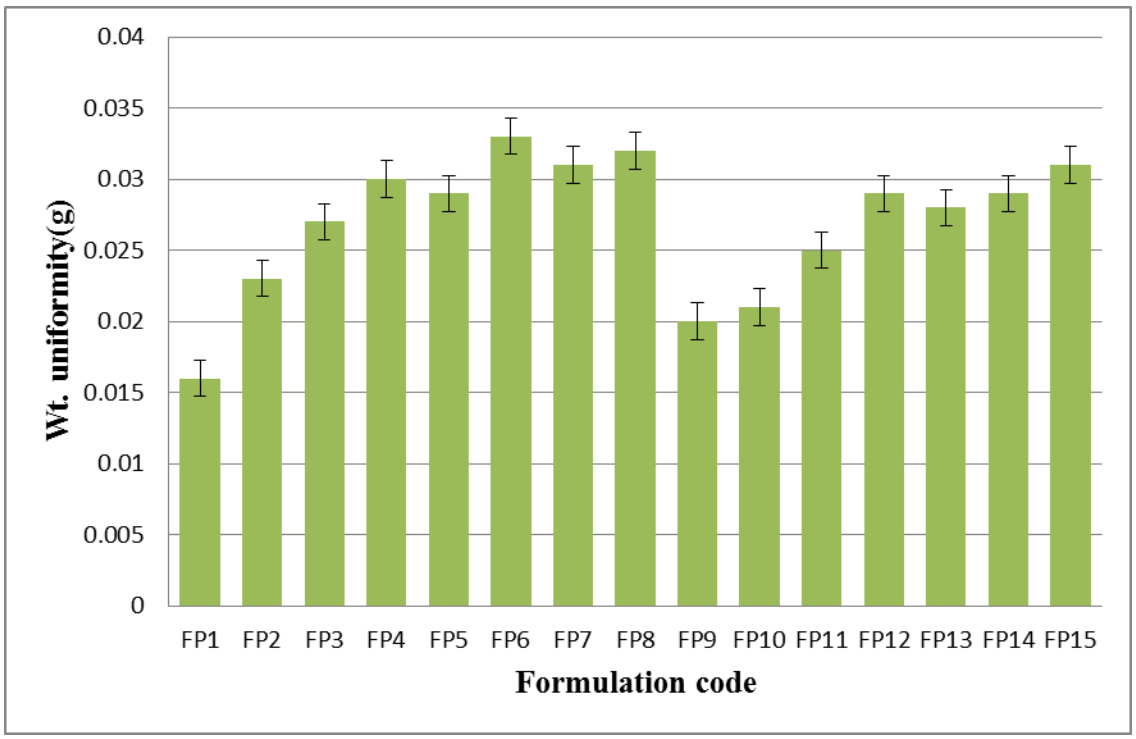

Fig.2: Weight uniformity (g) of prepared formulations of buccal patch

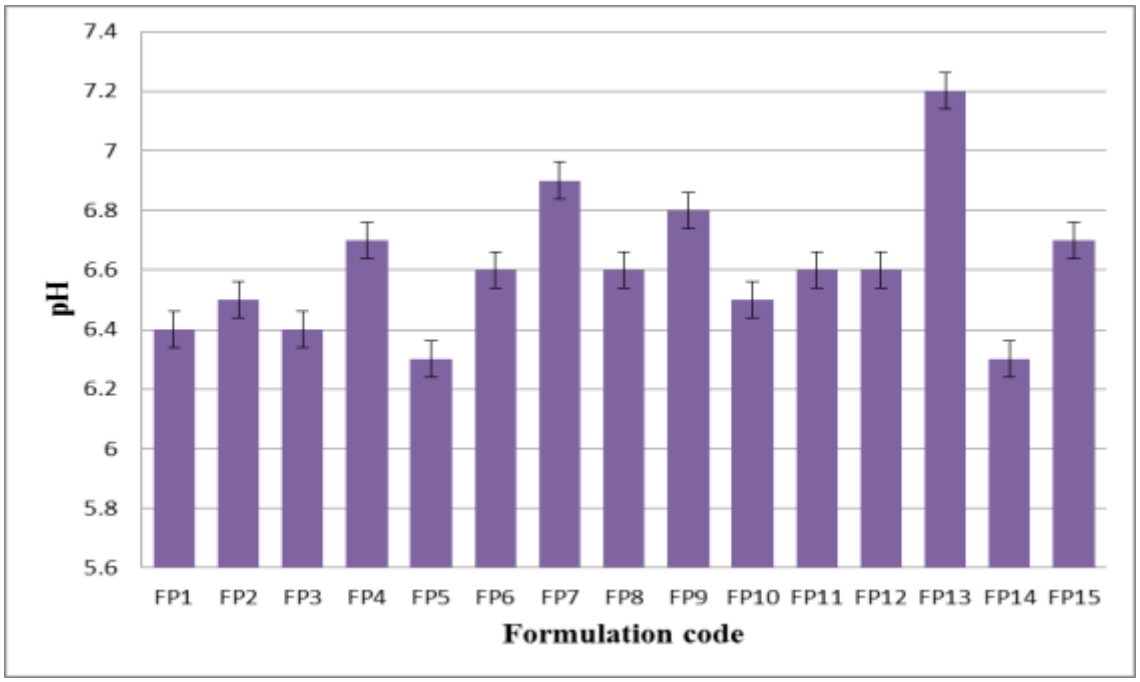

Fig.3: pH of prepared formulations of buccal patch

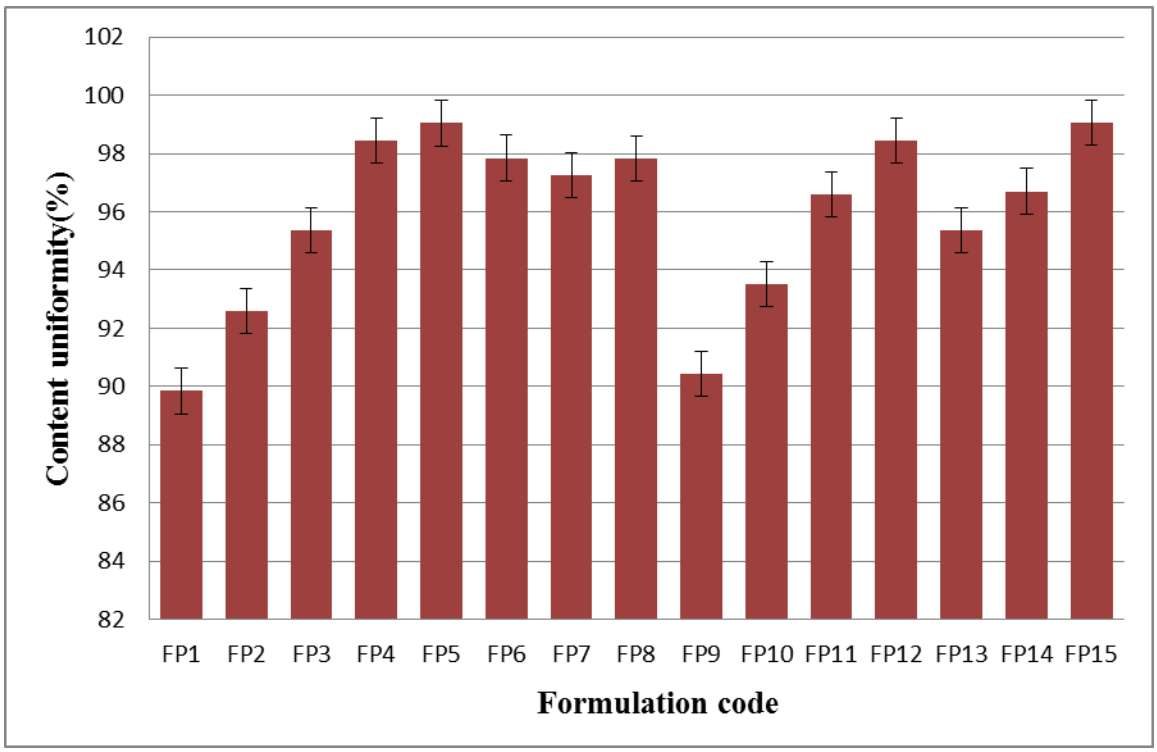

Fig.4: Content Uniformity (%) of prepared formulations of buccal patch

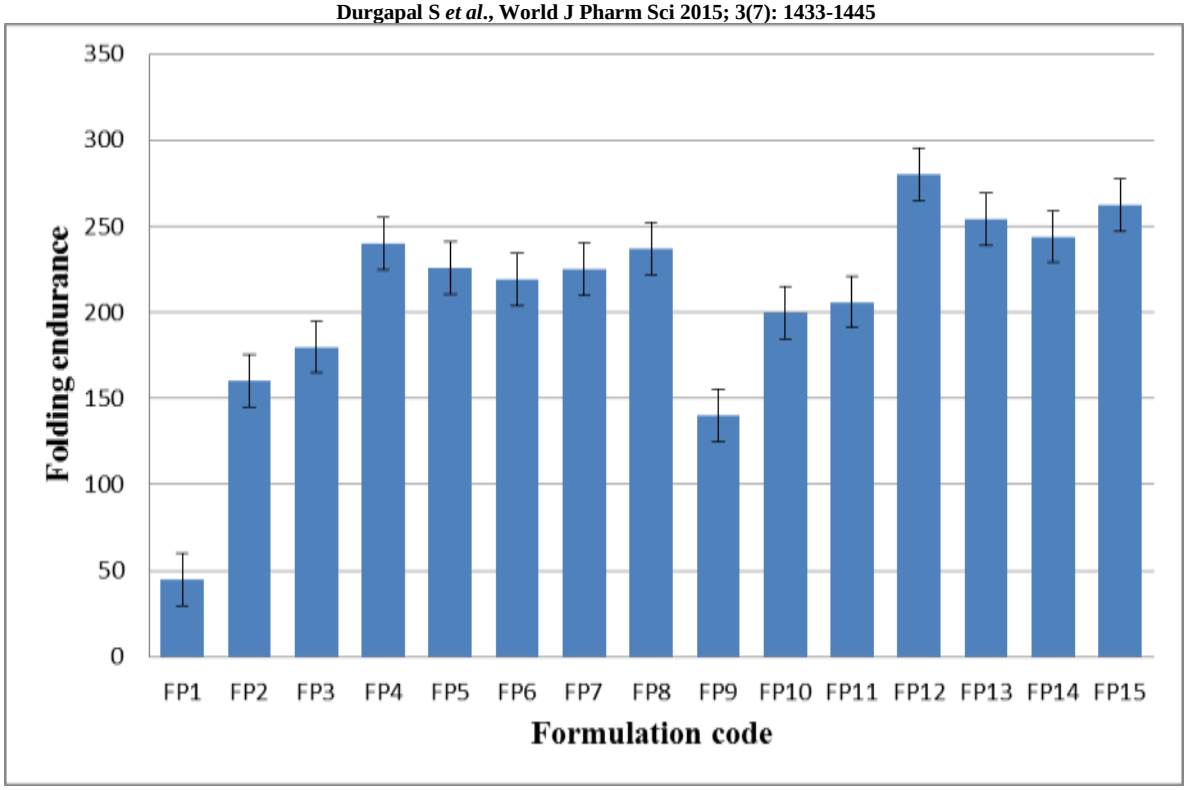

Fig.5: Folding Endurance of prepared formulations of buccal patch

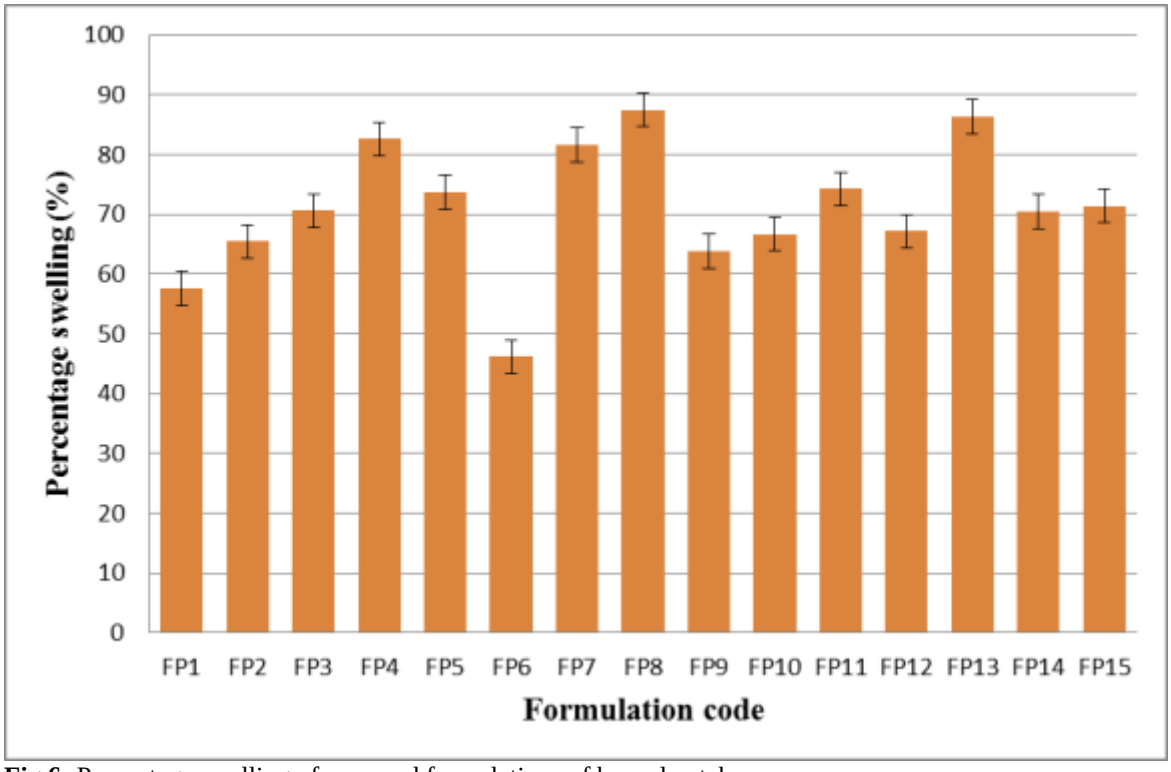

Fig.6: Percentage swelling of prepared formulations of buccal patch

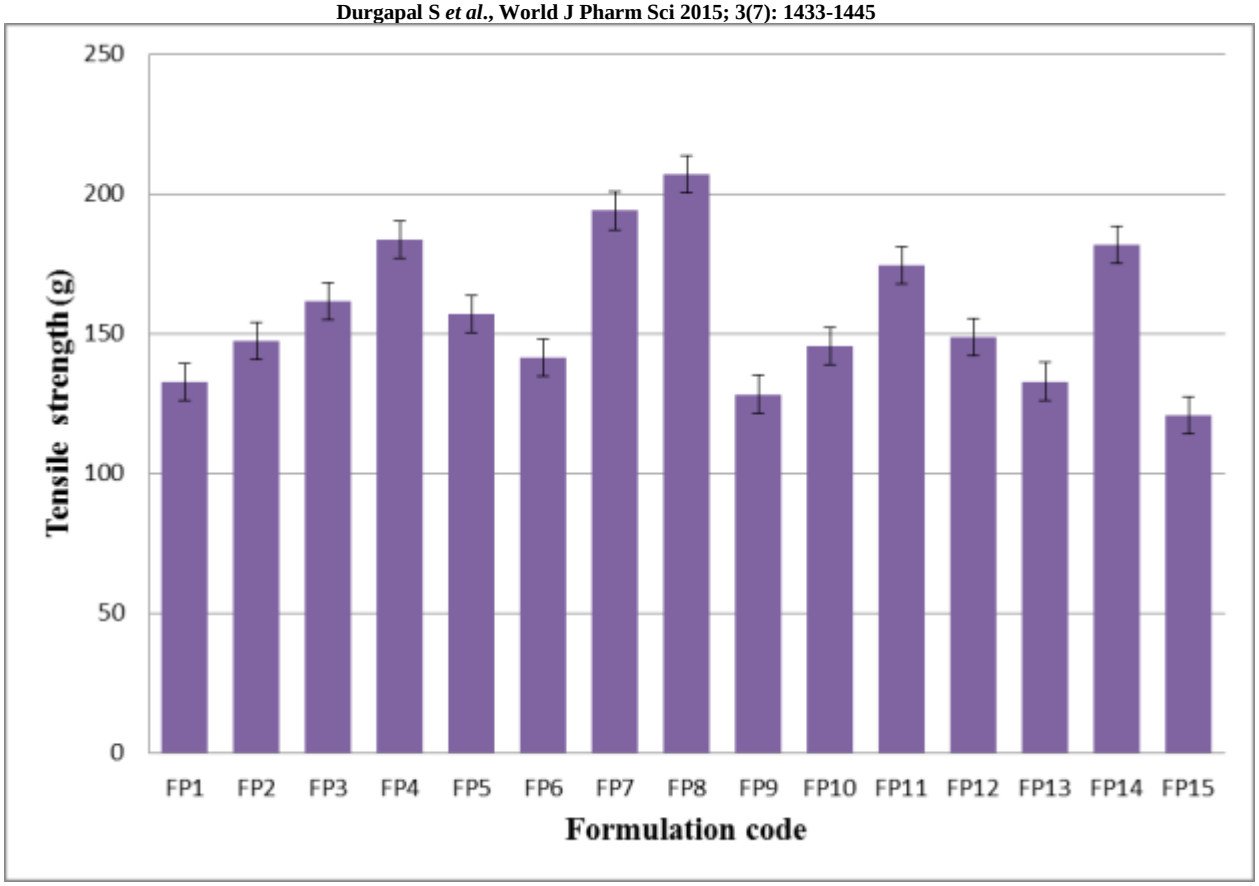

Fig.7: Tensile strength (g) of prepared formulations of buccal patch

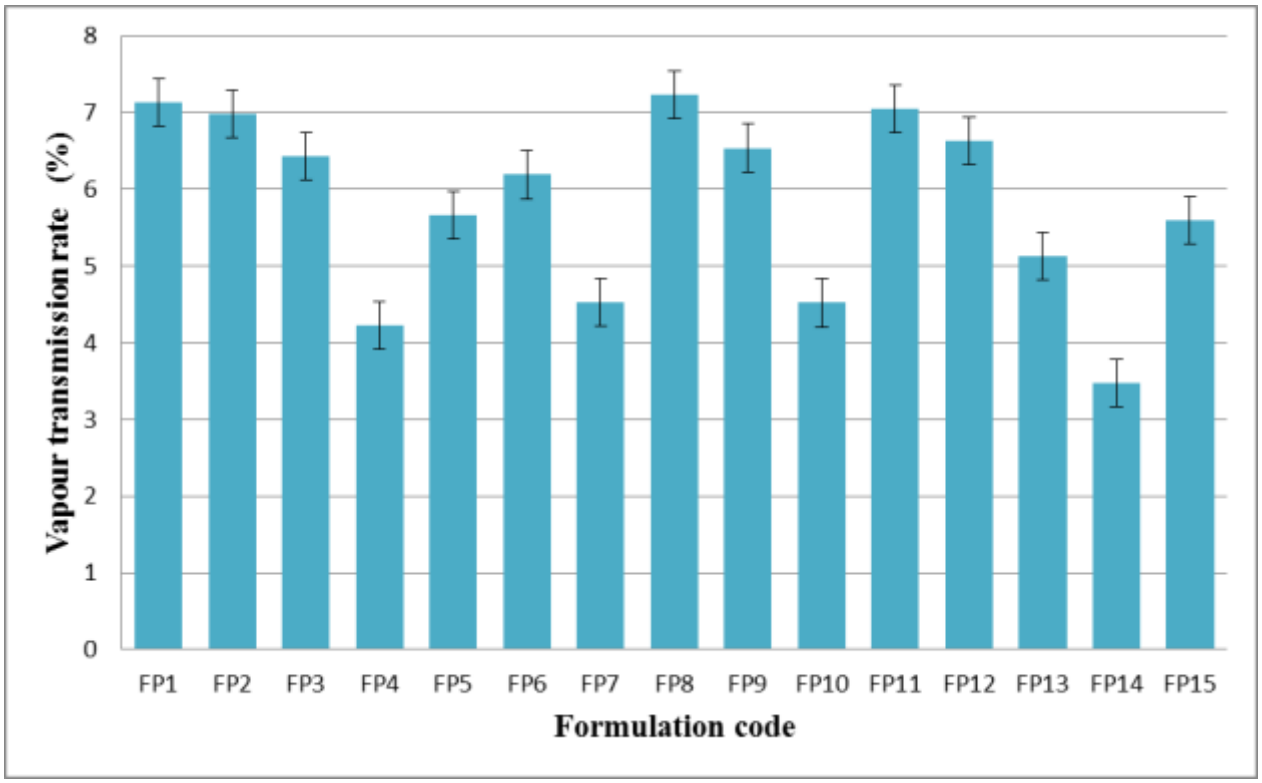

Fig 8: Vapour Transmission (%) of prepared formulations of buccal patch

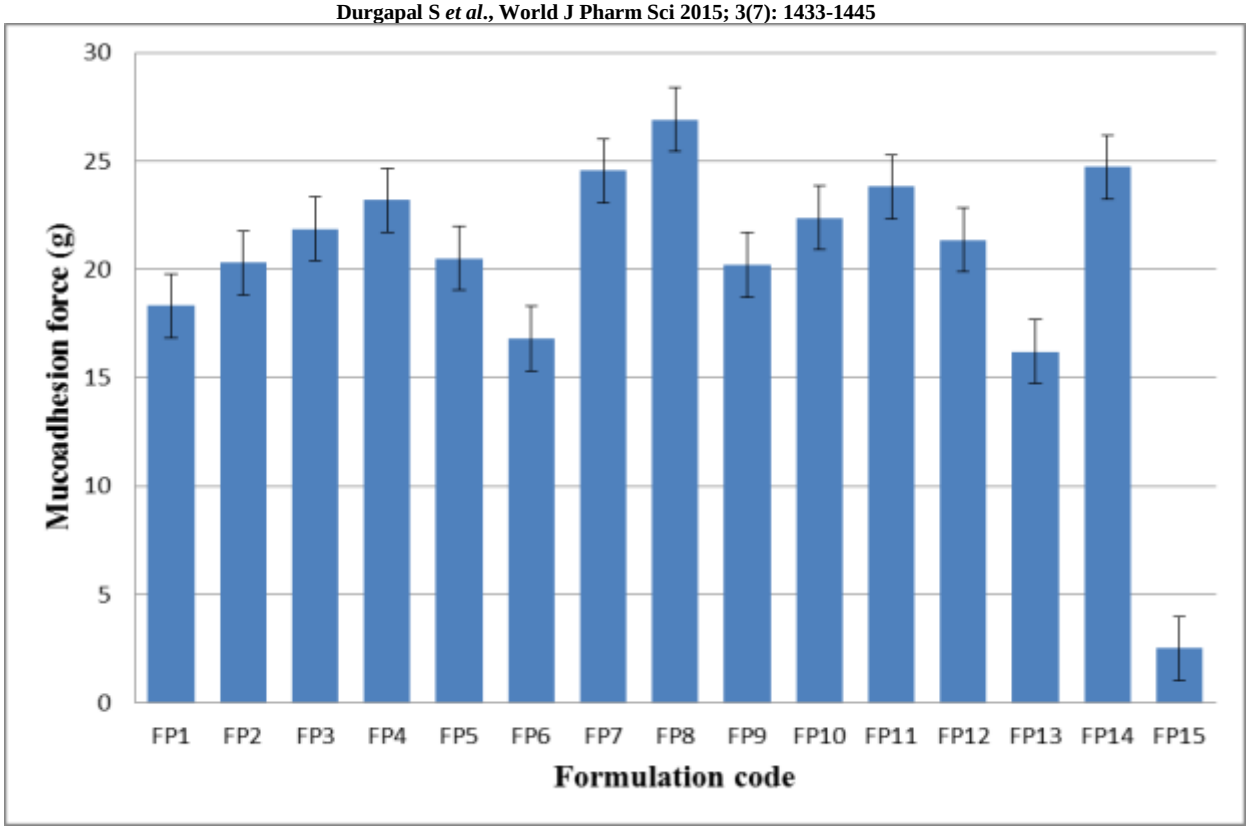

Fig.9: Mucoadhesion Force (g) of prepared formulations of buccal patch

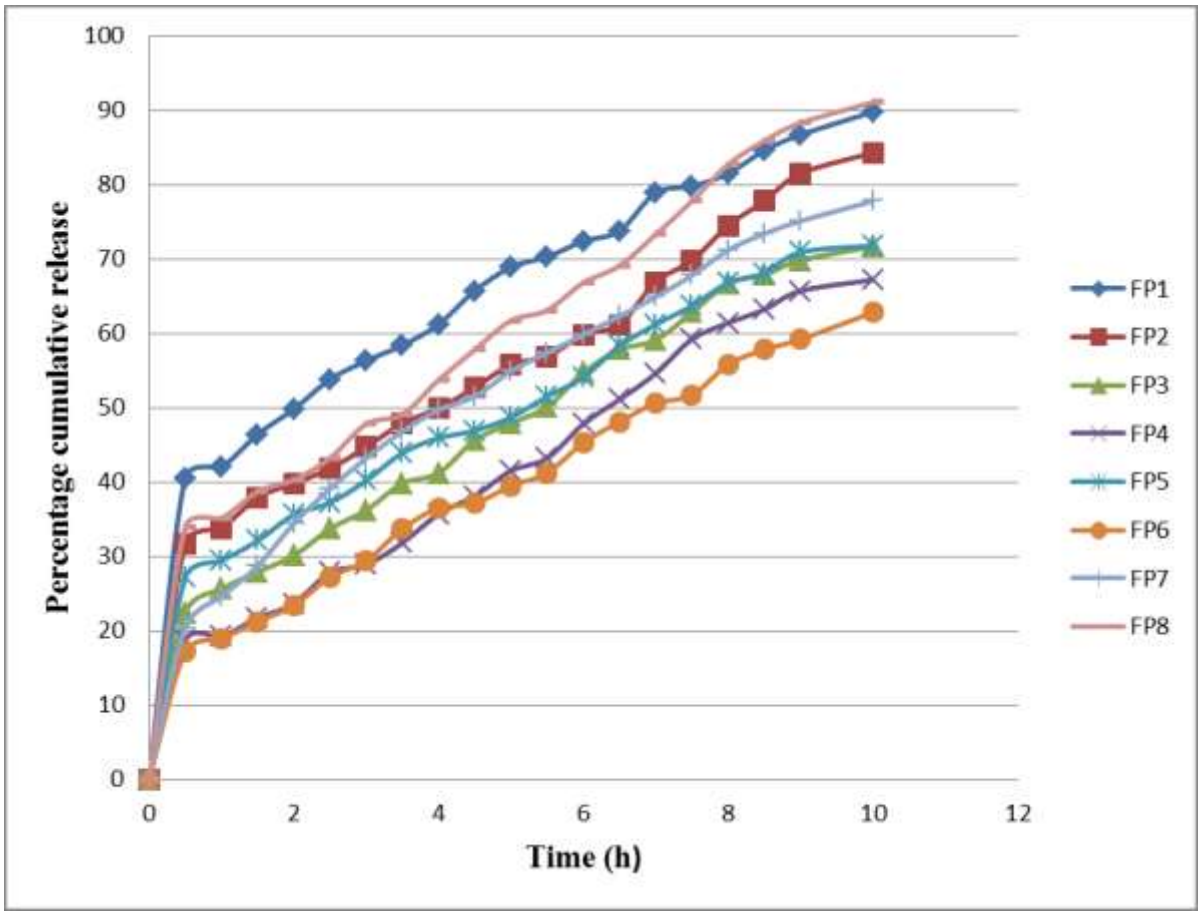

Fig.10: *In Vitro* diffusion study of formulation FP1-FP8

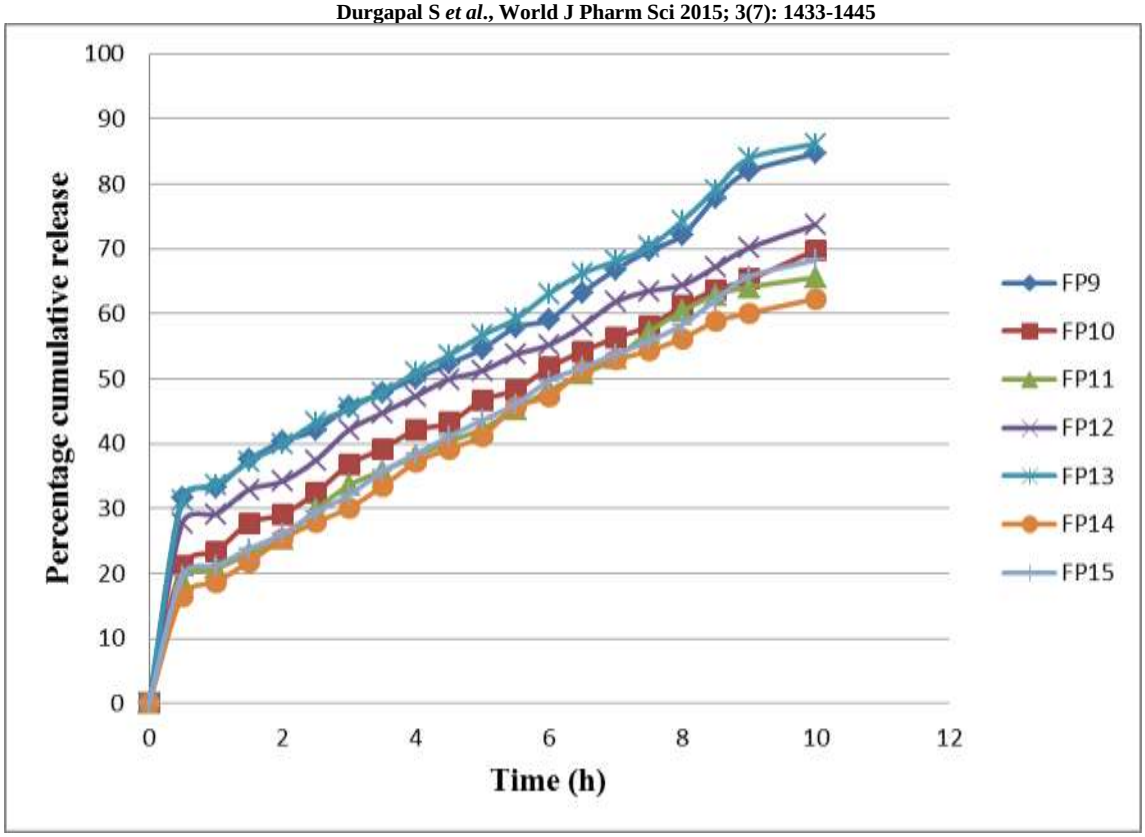

Fig.11: *In Vitro* diffusion study of formulation FP9-FP15

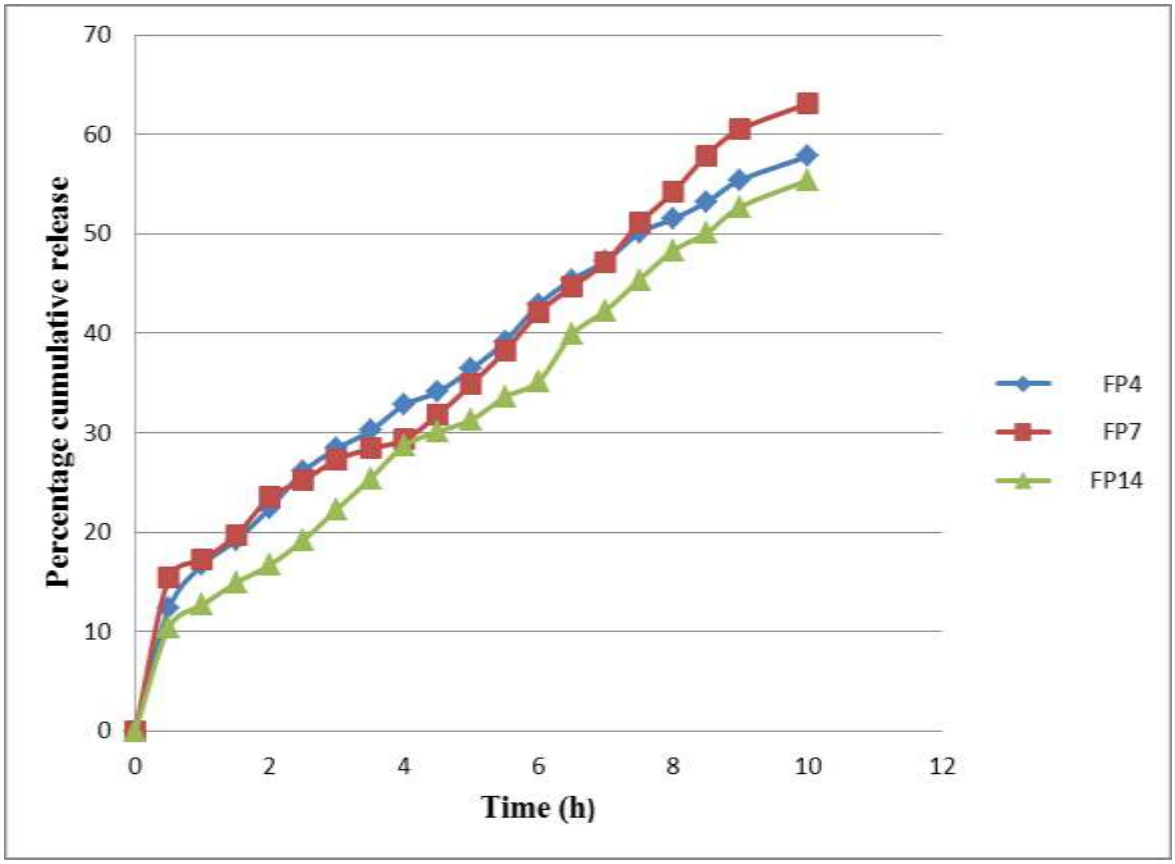

Fig.12: *Ex Vivo* diffusion study of selected formulations

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