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FORMULATION AND EVALUATION OF BUCCAL PATCHES OF VENLAFAXINE

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Research Article

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ABSTRACT

Mucoadhesive buccal patches containing venlafaxine were prepared using the solvent casting method. Chitosan and pectin were used as bioadhesive polymer and different ratios. The patches were evaluated for their physical characteristics like mass variation, drug content uniformity, folding endurance, surface pH, and in vitro drug release, in vitro buccal permeation study, ex vivo bioadhesion strength and ex vivo mucoadhesion time. Patches exhibited controlled release and released the entire contents with a period of 10 hrs. Incorporation of PVP K-30 generally enhanced the release rate. Swelling index was proportional to the concentration of chitosan. Optimized patches (F) showed satisfactory bioadhesive strength of 17.53 ± 0.47 g, and ex vivo mucoadhesion time of 10.32 hrs. The surface pH of all batches was within ± 0.4 units and thus no mucosal irritation is expected. Patches containing 1:4 of chitosan and pectin had higher bioadhesive strength with sustained drug release as compared to patches with other ratios of polymer. The optimized patch demonstrated good in vitro and ex vivo results.

KEYWORDS: Mucoadhesion, buccal patch, venlafaxine, buccal delivery, chitosan, pectin

Introduction

Venlafaxine is a representative of new class of antidepressants. It acts by inhibiting selectively the uptake of serotonin and noradrenaline but shows no affinity for neurotransmitter receptors[1]. Hence it lacks the adverse anticholinergic, sedative and cardiovascular effects of tricyclic antidepressants. However, the main limitation to therapeutic effectiveness of venlafaxine is its poor bioavailability (40-45%) and short biological half life (5hr) necessitating the administration, two or three times daily so as to maintain adequate plasma levels of drug. This necessitates the development of sustained delivery system which permits direct access of the active constituent to the systemic circulation thereby by-passing first-pass metabolism. Buccal delivery is one such system which has been attracting much attention in the recent years. The potential pharmacokinetic benefits of such systems such as lower peak plasma drug concentration and smaller fluctuations between peak and trough plasma drug concentration makes it suitable for the treatment of depression. Moreover, it offers easy administration and increases patient compliance.

In the present study, the natural bioadhesive polymers chitosan and pectin were chosen for the formulation of patches. These polymers have been widely used because of their biocompatible and biodegradable nature. Pectin is a polysaccharide containing (1 4) α-D-galactouronic acid units partially esterified with methanol. The mucoadhesive

performance of pectins largely depends on their characteristics, i.e. higher degree of esterification and molecular weight which give a stronger mucoadhesion[2]. Inspite of good bioadhesive potential, pectin alone cannot be used because of acidic nature which may cause irritation to gastric mucosa[3]. Chitosan is a polysaccharide containing amino groups. The mucoadhesive property of chitosan is due to either ionic interactions between the positively charged amino groups and the negatively charged mucin at low pH or due to hydrogen bonding via the unionized amine groups and mucin at higher pH values. However, the adhesive interactions of chitosan with mucin have been questioned. Moreover, uncontrolled fast release of drug from the formulation related to the use of chitosan and pectin alone is a challenge which has to be overcome [4]. Therefore, various combinations of chitosan and pectin have been explored for improved delivery of venlafaxine to the systemic circulation.

MATERIALS AND METHODS

Materials

Venlafaxine was obtained as a gift sample from Ranbaxy Laboratories, Gurgaon. Chitosan was provided from HiMedia Laboratories Pvt. Ltd Mumbai. Pectin, PVP K-30, glycerol, glacial acetic acid were obtained from S.D. Fine Chemicals, India. All other reagent and chemicals were of analytical grade.

Methods

Preparation of mucoadhesive buccal patches

Buccoadhesive patches containing varying amounts of chitosan and pectin were prepared by solvent casting method as reported by Kaur *et al.,* [3] with slight modification. Chitosan and drug were dissolved in 2% v/v glacial acetic acid solution and pectin was dissolved separately in distilled water. Chitosan solution containing drug was added to pectin solution with stirring. Glycerol 5% v/v was added as plasticizer under constant stirring. To improve patch performance and release characteristics, a water soluble hydrophilic additive, 1% w/v PVP K-30 was added. The resulting viscous solution was casted into petridish (1.6mm diameter) and dried in an oven at 50^{o} C for 48 hours. The dried films were carefully removed and checked for any imperfection or air bubbles. The patches were packed in an aluminium foil and stored in an air tight glass container to maintain the integrity and elasticity of the patches. **Table 1** shows the composition of different patches.

EVALUATION OF BUCCAL PATCHES

Mass uniformity and Thickness:

The assessment of weight and patch thickness was done in 10 different randomly selected patches from each batch. For determination of mass, patches were directly weighed on a digital balance and the patch thickness was measured at 5 different randomly selected spots on patches using a screw gauge [2].

Folding endurance:

Folding endurance of patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 200 times without breaking[5].

Drug content uniformity:

The amount of drug contained in the patch was determined by dissolving the patch by homogenization in 100 ml of an isotonic phosphate buffer (pH 6.8) for 8 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 μm Whatman filter paper. The drug content was

then determined after proper dilution by UV spectrophotometer (Shimadzu-1700 Japan) at λ_{max} of 224 nm[3]. The experiments were carried out in triplicate.

Surface pH Determination:

The surface pH was determined by the method similar to that used by Bottenberg *et al.*, [6]. A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping them in contact with 1 ml of distilled water (pH pH 6.8±0.1) for 2 h at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute. The surface pH of the patches was determined in order to investigate the possibility of any side effects, in the oral cavity. As acidic or alkaline pH is bound to cause irritation to the buccal mucosa, hence attempt was made to keep the surface pH of the patch close to the neutral pH.

***In vitro* Swelling Studies of Buccoadhesive patch:**

The degree of swelling of bioadhesive polymer is important factor affecting adhesion. Upon application of the bioadhesive material to a tissue a process of swelling may occur. The swelling rate of buccoadhesive patch was evaluated by placing the film in phosphate buffer solution pH 6.8 at 37±0.5 ^{o}C. Buccal patch was weighed (W_1), placed in a 2% (w/v) agar gel plate and incubated at 37 ±1^{0}C. At regular one-hour time intervals (upto 3 h), the patch was removed from the petridish and excess surface water was removed carefully using the filter paper. The swollen patch was then reweighed (W_2) again and the swelling index was calculated [7].

Swelling index = W_2- W_1 / W_1

Tensile strength and Elongation at break:

The tensile strength of the patch is the measure of bioadhesion performances and was measured using tensile strength instrument locally assembled. One end of the patch was fixed between the two iron screens to give support to the film and another end was connected to the paper holder in which hook was inserted. A thread was tied to this hook, passed over the pulley and a small pan attached to the other end to hold the weight. A small pointer was attached to the thread, which travels over the scale affixed on the base plate. To determine tensile strength, the patch was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the patch was broken and the elongation was determined by recording the distance travelled by the pointer before break of the patch on the scale. The weights required to break the patch was considered as a tensile strength and it was calculated as Kg/cm^2 using following formula[8, 9].

Tensile strength = F/a*b(1+L/l)

Where, **F** is force required to break; a, b, and L are width, thickness and length of patch respectively and l is elongation of patch at break point

Elongation at break = $\frac{l_b - l_o}{l_o} \times 100$

Where, **lo** = original length of the patch and $\mathbf{l_b}$ = length of the patch at break when stress is applied.

Bioadhesion properties:

The bioadhesive strength was measured using a modified version of the apparatus previously applied by Parodi *et al.,*[10]. The device was mainly composed of a two-arm balance. Both the ends are tied to glass plate for keeping weight. The right and left pans were balanced

by adding extra weight on the left hand. The piece of goat buccal mucosa was tied to the two glass slide separately. Buccal patch was placed between these two slides containing goat buccal mucosa, and extra weight from the left pan was removed to sandwich the two pieces of glass and some pressure was applied to remove the presence of air. The balance was kept in this position for 5 min. Weight was added slowly to the left hand pan until the two glass slides got detached from each other the weight require to detach the patch from buccal mucosa of goat gave the measure of bioadhesive strength.

Force of adhesion (N) = Bioadhesive strength/1000*9.81

Bond strength (Nm^{-2}) = Force of adhesion/Surface area

***In vitro* release Studies:**

USP dissolution test apparatus type II (Electrolab dissolution Tester) was used to carry out the *in-vitro* release studies [1]. The studies were carried out using 900 ml of isotonic phosphate buffer (pH 6.8) as the dissolution medium at 37±0.5^{0}C and 50 rpm. To provide unidirectional release, one side of buccal patch was attached to a glass disk with the help of two sided adhesive tape. The disk was introduced in the bottom of the dissolution vessel such that patch surface is exposed to the dissolution medium. An aliquot of 5ml sample was withdrawn at predetermined time intervals and similar volume was replaced with fresh phosphate buffer (pH 6.8) maintained at same temperature. Samples were then analyzed spectrophotometerically.

Permeation studies:

The *in vitro* study of Venlafaxine permeation through the goat buccal mucosa was performed using a Franz diffusion cell with 15 ml capacity. Freshly obtained goat buccal mucosa was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The patch was placed on the mucosa and the compartments clamped together. The donor compartment was filled with 1 ml of simulated saliva pH 6.8 (sodium chloride 4.5g, potassium chloride 0.3g, sodium sulphate 0.3g, ammonium acetate 0.4g, urea 0.2g, lactic acid 3g and distilled water up to 1000ml, adjusting pH of solution to 6.8 by 1 M sodium hydrooxide solution). The receptor compartment (15 ml capacity) contained isotonic phosphate buffer pH 6.8 [12]. The hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm and maintaining the temperature at 37^o±0.5^{o}C. One ml sample was withdrawn at predetermined time intervals and analyzed for drug content at 224 nm. The graph of % drug permeated v/s time was plotted and flux, permeability coefficient was determined.

***Ex vivo* mucoadhesion time:**

The selected batch was subjected to *ex vivo* mucoadhesion test[11] using a disintegration apparatus. The disintegration medium was composed of 800 ml isotonic phosphate buffer pH 6.8 maintained at 37^{o}C. A segment of freshly isolated goat buccal mucosa, 3 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive patch was hydrated from one surface using 15 µl of phosphate buffer pH 6.8 and then the hydrated surface was brought into contact with the mucosal membrane.

The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary

for complete erosion or detachment of the patch from the mucosal surface was recorded.

Table 1: Composition of different batches of Venlafaxine buccal films.

Batch code	Polyelectrolyte complex Ratio (Chitosan:Pectin)	Chitosan (mg)	Pectin (mg)	Venlafaxine (mg)	Glycerol (5%) ml	PVP (1%)
A	-	100	-	10	0.5	100
B	-	-	100	10	0.5	100
C	1:1	50	50	10	0.5	100
D	1:2	33	66	10	0.5	100
E	1:3	25	75	10	0.5	100
F	1:4	20	80	10	0.5	100
G	2:1	66	33	10	0.5	100
H	3:1	75	25	10	0.5	100
I	4:1	80	20	10	0.5	100

RESULTS AND DISCUSSION

Physiochemical characteristics of the patches:

The prepared patches were smooth in appearance, uniform in thickness, mass and drug content and showed no visible cracks. The patches exhibited variable thickness because of differences in their composition. The mass ranged from 48-55mg. The surface pH was within ± 0.4 units of the pH of saliva and thus no mucosal irritation is expected[13]. The patches prepared from pure chitosan and pure pectin was found to be acidic in nature. So they alone cannot be used for formulation of batches due to chances of damage to buccal mucosa. Further, it is evident from Table 2 that the patches exhibited good folding endurance (> 150 times).

Table 2: Physical parameters of formulated Venlafaxine patches

Batch code	Mass (mg)	Thickness (mm)	Drug content (%)	Folding Endurance	Surface pH
A	55	0.42±0.08	99.34±0.62	179	4.32±0.18
B	52	0.51±0.05	98.86±0.48	183	4.12±0.13
C	50	0.48±0.06	99.26±0.42	169	6.7±0.19
D	49	0.62±0.04	98.96±0.56	198	6.8±0.21
E	52	0.54±0.09	99.62±0.62	201	6.9±0.12
F	55	0.46±0.02	98.74±0.44	152	6.5±0.11
G	48	0.48±0.06	99.16±0.46	169	6.7±0.16
H	53	0.50±0.06	98.64±0.56	175	6.4±0.13
I	54	0.44±0.04	98.99±0.46	188	6.8±0.17

Swelling indices of the patches:

The swelling behaviour of formulation governs its bioadhesion and drug release pattern. The patches did not show any marked physical change of deterioration during 3 hrs of swelling study. **Batch A** showed highest swelling index (90%) within 3hr due to greater swelling of chitosan. Batch B exhibited a swelling index of 84.32 % within 3hr due to hydrophilic nature of pectin. **Figure 1** depicts the degree of swelling of formulations **A-I**. An increase in pectin concentration in batches D, E, F as compared to batch C showed increased swelling index. This can be explained on the basis that when the patch is placed in an aqueous medium, liquid penetrates into the patch and a gel is formed due to uncoiling of the structure of pectin molecules and formulation of hydrogen bonds with water molecule. As a result, the diameter of patch increases progressively and a distinct gel sol boundary develops. Thus the overall dimensions of the patch are affected and rate of swelling is increased [14].

Moreover, an increase in chitosan concentration (batches G, H, I) also showed increased swelling. This observation can be

explained by the presence of chitosan in the cationic (protonated) form in the polymer complex. It has been reported that in ionically crosslinked polymer pomplexes swelling is favoured by the protonation and repulsion of free ammonium groups of chitosan[15]. Further, addition of hydrophilic polymer PVP K-30 also increased the surface wettability and penetration of water within the matrix [3]

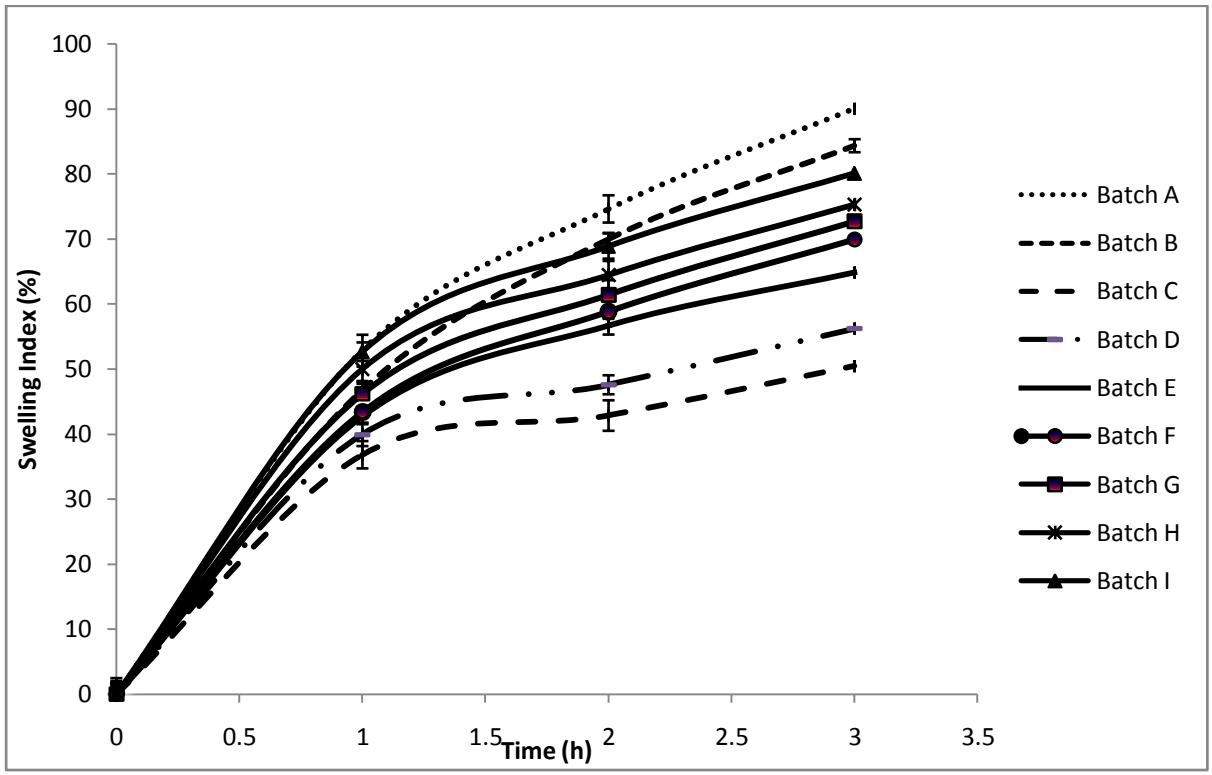

Fig 1 Swelling index of buccal batches from batches A to I (Mean ± SD, n=3).

Mechanical properties of the patch:

These studies were carried out to evaluate the flexibility and elasticity of the buccal film. An ideal buccal film should possess high tensile strength and elongation at break [1]. The tensile strength and elongation at break increased with increase in polymer content. The batch A showed highest tensile strength (0.164±1.21) indicating the tensile property of chitosan while least strength was exhibited by batch B containing pectin only. As observed from **Figure 2**, batches G, H, I possessed greater tensile strength in comparison to batches C to F because of higher amounts of chitosan. With respect to elongation at break, the formulation F showed max value of 35.12±0.66 and the lowest was observed for formulation A. From the figure, it is evident that except for formulations F and G, all other show statistically significant difference ($p < 0.05$).

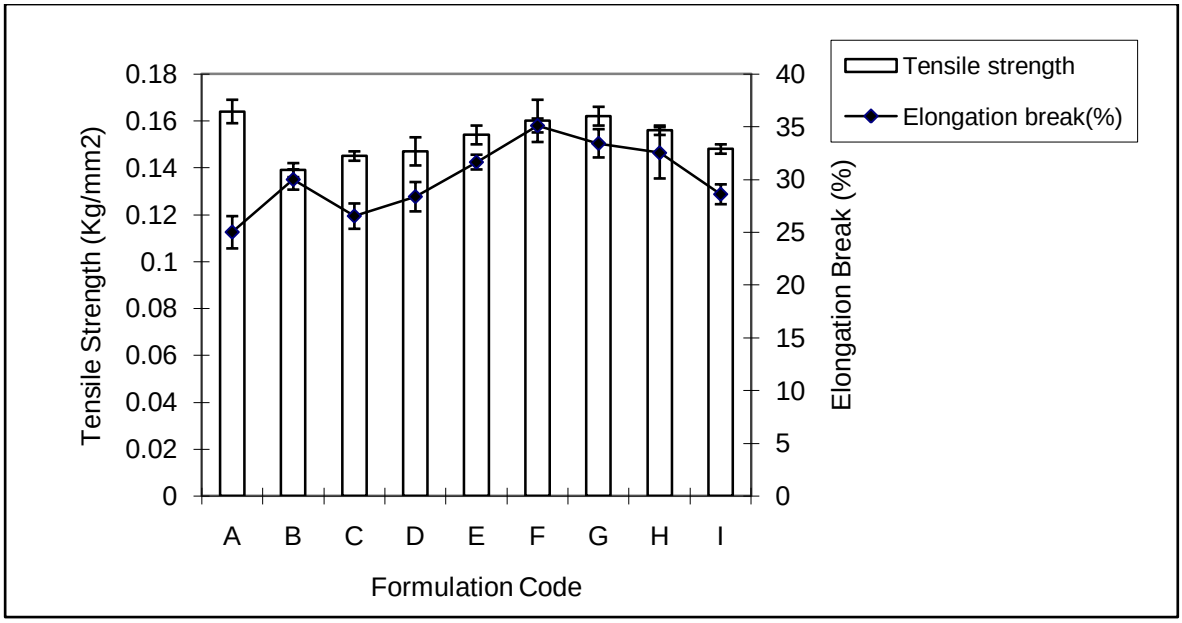

Fig 2 Tensile Strength of buccal patches from batch A to I (Mean ± SD, n=3)

On the other hand, bioadhesive strength studies have shown variable results. Figure 3 clearly indicates that bioadhesive strength varied widely due to differences in polymer type and composition of the film. Bioadhesive strength of buccal patches may be defined as the adhesion between buccal patches and buccal mucosa. The strength of bioadhesion is affected by various factors like biological membrane used in the study, molecular mass, and swelling rate of polymers present in the formulation. In this study, fresh goat buccal mucosa was used as biological membrane. Various bioadhesive parameters like bioadhesive strength, force of adhesion, and bond strength exhibited by these patches was satisfactory. Among all these formulated patches, formulation no. F showed maximum bioadhesive strength (17.53 g), force of adhesion (0.17 N), and bond strength (0.08 N m−2). Because of inappropriate and undesirable results, patches A and B were excluded from further studies.

***In-vitro* release studies:**

The dissolution profile for the different formulations is shown in **Fig 4**. The drug release from batches G, H and I decreased to almost 2 fold with increase in chitosan concentration (**Table 2**), probably because of the swelling behaviour of cross-linked chitosan which creates a thick gel and restricts drug diffusion [16]. Approximately, 80% of the drug was released from the formulations C, D and E within 10 hrs. The patch F released the drug at a faster rate than the rest of the formulations. The release of Venlafaxine from batches C to F can be attributed to the swelling nature of pectin. It has been reported by Sujja-areevath *et al.,* [17] that the swelling behaviour of the patches due to pectin results in moving boundary condition which continuously modifies the effect of the drug. The continued swelling of the polymer mixture causes the drug to diffuse from the formulation at faster rate [18]. Further, to confirm the mechanism of drug release Higuchi's plots were drawn for all the

formulations, which is depicted in **Fig 4**. The regression coefficients were found to be 0.9672, 0.9637, 0.9551, 0.9708, 0.8757, 0.991, 0.9806 for batches C to I respectively. From the values, it was concluded that the release followed diffusion controlled mechanism.

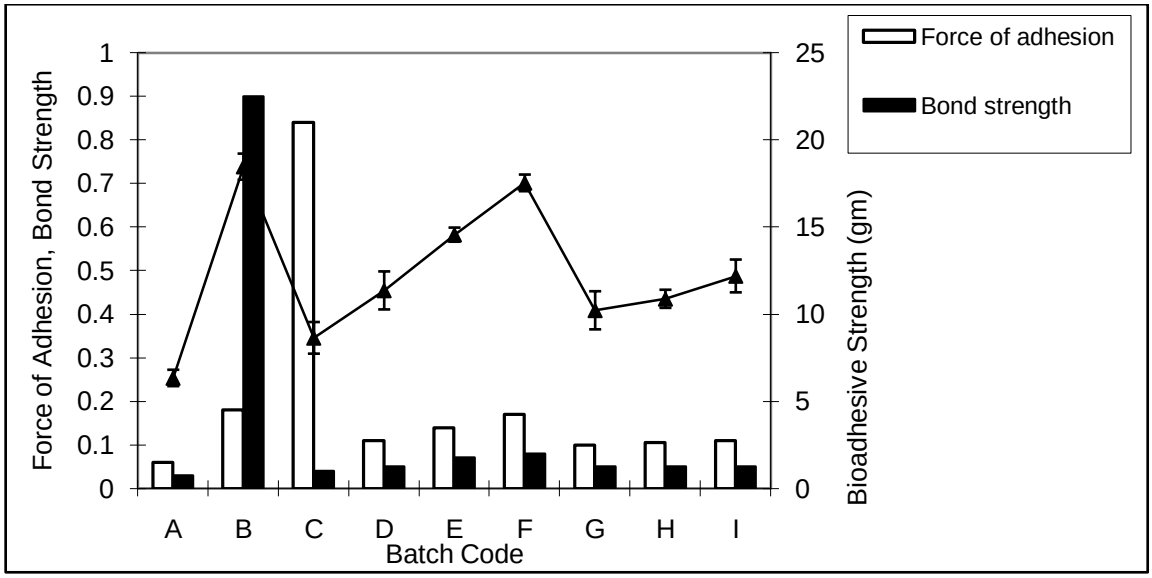

Fig 3- Bioadhesive strength of different patches (Mean ± SD, n=3)

Table 6 *In vitro* release profile of Venlafaxine from batches C to I

S.No	Time (hrs)	Batch C	Batch D	Batch E	Batch F	Batch G	Batch H	Batch I
1	0.5	36.96	35.55	34.95	38.17	25.48	33.12	20.42
2	1	38.97	37.17	41.4	44.83	28.14	41.57	23.24
3	2	44.01	43.62	45.04	46.85	38.22	47.49	25.46
4	3	49.68	47.26	49.47	60.57	42.39	51.73	26.47
5	4	59.31	51.69	52.3	70.46	55.21	58.46	31.31
6	5	61.11	56.34	59.16	78.57	62.85	60.94	33.94
7	6	69.84	64.81	67.84	89.03	67.03	68.29	34.94

8	7	73.26	69.25	72.08	90.44	76.16	73.03	38.78
9	8	77.56	74.87	79.95	95.08	82.21	76.61	50.48
10	10	77.59	79.46	80.95	99.32	90.23	82.48	53.71

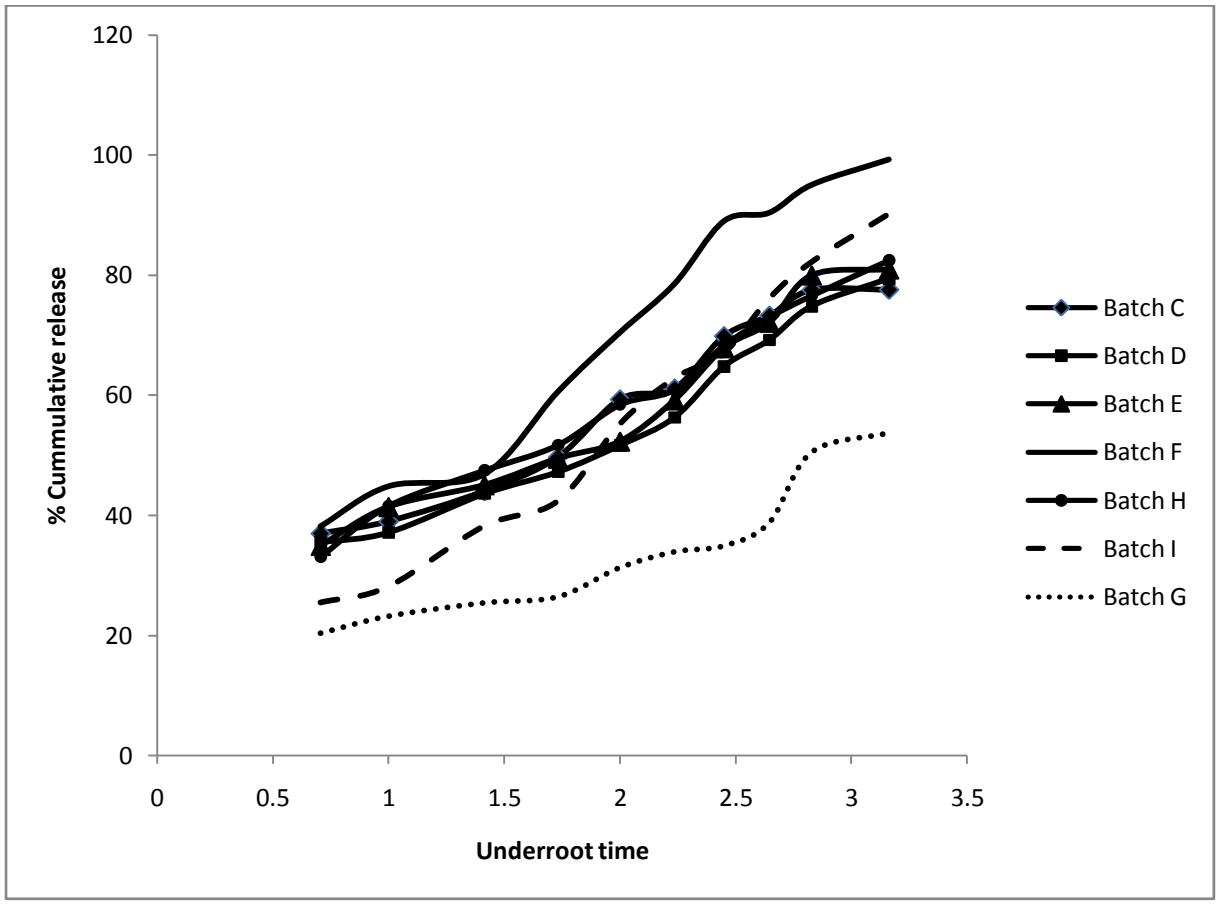

Fig 4 Higuchi diffusion plots for different Buccal patches

Selection of best batch:

Selection of best batch was done on the basis of result obtained from mechanical studies and *in vitro* performance of patches. Batch F was selected from physical mixture batches of chitosan and pectin. Selection of this batch was done because batch F had shown good bioadhesive strength 11.10 g and was releasing 99.32% of drug till 10 h. These characteristics of polymer complex are prerequisites for the development of buccoadhesive dosage form. After selection of best batch residence time study and permeation studies were performed.

Permeation of Venlafaxine from bioadhesive batch:

The permeation studies were conducted using Franz diffusion cell assembly. The

study was carried out on batch F which showed 63% drug release within 10 hour. Good correlation was observed between *in-vitro* drug release and *in-vitro* drug permeation, as the correlation coefficient was found out to be 0.98.

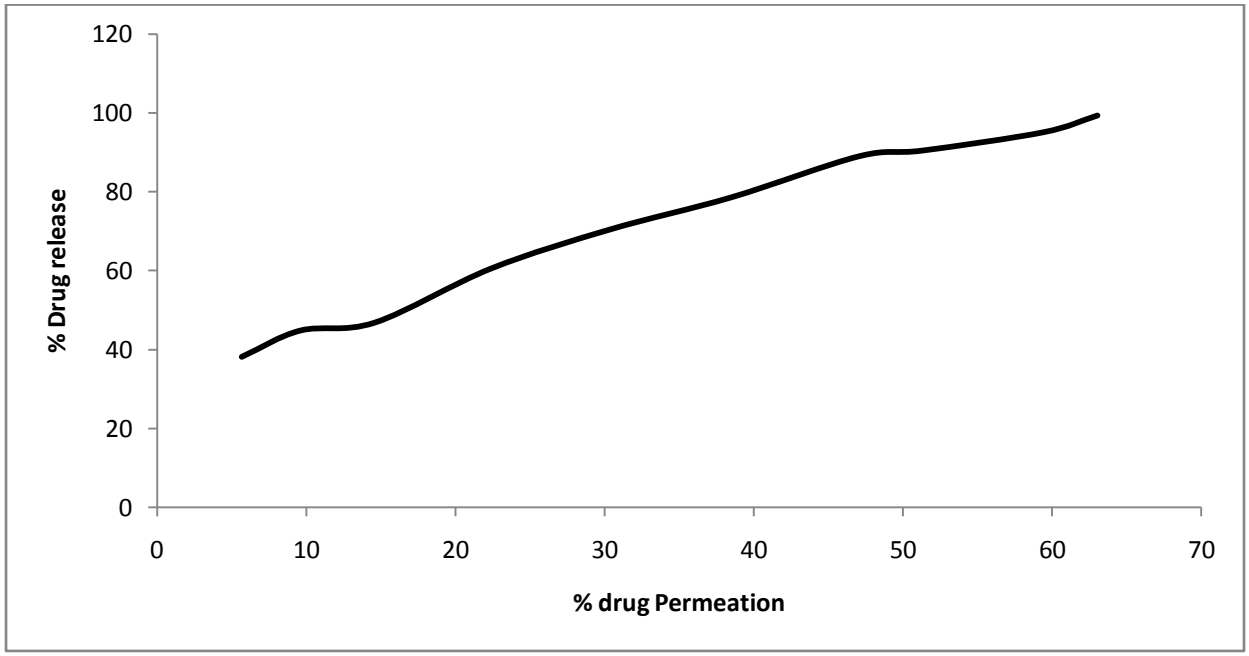

Fig 5 Correlation between *in vitro* drug release and *in vitro* drug permeation. Mean ± SD, n=3

Mucoadhesion time:

When designing a buccal adhesive patch, it is important to guarantee its adhesivity to the buccal mucosa for a few hours. It was observed that patch F exhibited residence time of 10.32 hr ± 0.17 which was sufficient till almost considerable amount of drug is permeated from the buccal membrane.

Conclusion:

This study clearly demonstrated that Venlafaxine can be successfully delivered through buccal route. The patches were non-irritating with favourable film properties and showed sufficient mucoadhesive potential until the drug is absorbed from the formulation. Further, it is also proved that the combination of chitosan and pectin meets the ideal pre-requisites for a buccal device which can be a good way to by-pass hepatic first pass metabolism of Venlafaxine.

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