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Research Article

FORMULATION AND EVALUATION OF VENLAFAXINE HYDROCHLORIDE MUCOADHESIVE BUCCAL TABLETS

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ABSTRACT
The present study involves the formulation and evaluation of buccal tablets of venlafaxine hydrochloride, an antidepressant drug to circumvent the first pass metabolism. Buccal route is excellent for the systemic delivery, there by rendering great bioavailability. A significant reduction in dose and dosing frequency can be achieved, thereby reducing dose dependent side effects, patient compliance and prolonging duration of action. Tablets of venlafaxine HCl were prepared by direct compression method. Twelve formulations were prepared with varying concentrations of bioadhesive polymers like hydroxypropylmethylcellulose K4M (HPMC K4M), carboxymethylcellulose (CMC), carbopol 934P and chitosan. Buccal tablets were evaluated by different parameters such as thickness, hardness, weight uniformity, content uniformity, swelling index, surface pH, ex vivo bioadhesive strength, in vitro drug release, ex vivo drug permeation and FTIR studies. The modified in vitro assembly was used to measure the bioadhesive strength of tablets with fresh porcine buccal mucosa as model tissue. The tablets were evaluated for in vitro release in pH 6.8 phosphate buffer for 8 hours in standard dissolution apparatus in order to determine the mode of release, the data was subjected to model fitting, the optimized formula followed non-fickian release mechanism with zero order kinetics. The formulation containing venlafaxine HCl and HPMC K4M in the ratio of 1:1 could be used to design effective and stable buccoadhesive tablets of venlafaxine HCl.
KEYWORDS: Buccal tablets, Venlafaxine hydrochloride, Swelling index, Mucoadhesive.

INTRODUCTION

The oral cavity is an attractive site for drug delivery due to ease of administration, avoidance of possible drug degradation in the gastrointestinal tract and first-pass metabolism. Buccal delivery system involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Prolonged release of the drug and increased bioavailability leads to the significant reduction in the dose and dose related side effects. Moreover buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage from the buccal cavity therefore mucoadhesive dosage forms were suggested for oral drug delivery which includes various mucoadhesive devices such as patches[1], tablets, films, gels, disc[2], strips and ointment[3]. Venlafaxine hydrochloride is selective serotonin reuptake inhibitor used in the treatment of depression; it was selected as model drug for investigation because of its suitable properties like dose (25 mg), half life of 5 hours and molecular weight (277.40). A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in oral cavity for the desired duration. In present study, the mucoadhesive tablets were developed using polymers such as HPMC K4M, CMC, carbopol 934P and chitosan to get controlled and zero order drug release[4,5].

MATERIALS AND METHODS

Materials

Venlafaxine hydrochloride was gift sample from Lupin pharmaceuticals, Pune, India. Carbopol 934P, hydroxypropylmethylcellulose (HPMC K4M), chitosan and CMC from Zydus Cadila, India. Mannitol and Aspartane by Dr Reddy's laboratories, Hyderabad, India.

Mucoadhesive Tablets Preparation

Buccal tablets were prepared by a direct compression method. Venlafaxine hydrochloride was mixed manually with different ratios of HPMC K4M, CMC, carbopol 934P, chitosan, and mannitol as diluent for 10 min. The blend was lubricated with magnesium stearate for 3 to 5 min. The mixture is compressed using 8 mm flat faced punch on Cemach 12 stages rotary tablet compression machine. Compositions of formulations were given in Table 1.

Evaluation of buccal tablets

Thickness

The thickness of buccal tablets was determined using digital micrometer. Ten tablets from each batch were evaluated and the results averaged.

Weight variation

Weight variation was performed for twenty tablets from each batch using an electronic balance and average values were calculated.

Hardness

Hardness was conducted for three tablets from each batch using Monsanto hardness tester and average values were calculated[7,8].

Friability

Friability test was conducted by testing twenty tablets from each batch, using Roche friabilator.

Content uniformity

Ten tablets were weighed and grounded in a mortar with pestle to get fine powder; powder equivalent to the mass of one tablet was dissolved in methanol by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 224 nm using an UV spectrophotometer.

Measurement of bioadhesion strength

Bioadhesive strength of the tablets was measured on a modified physical balance. The apparatus consisted of a modified double beam physical balance in which a lighter pan had replaced the right pan and the left pan had been replaced by a glass slide (4 cm length and 2.5 cm width) with plastic hang suspended by teflon rings and copper wire. The left-hand side of the balance was exactly 5 gm heavier than the right side .The height of the total set up was adjusted to

accommodate a glass container of 6.6 cm height. All parts of modified physical balance. In order to find out the bioadhesion strength first buccal tablet (n=3) was stacked to the glass slide with the help of knob, which was situated at the base of physical balance. Now five grams weight from the right pan was then removed. This lowered the glass slide along with the tablet over the membrane with a weight of 5.0 g. This was kept undisturbed for 5 min. Then the weights on the right-hand side were slowly added in increments of 0.1 g till the tablet just separated from the membrane surface. The excess weight on the right pan, i.e. total weight minus 5 g was taken as a measure of the bioadhesive strength[10].

Surface pH Study

Buccoadhesive tablets were allowed to swell for 2 hours on the surface of agar plate. The surface pH was measured by means of a pH paper placed on the core surface of the swollen tablet. A mean of three readings was recorded[11].

Swelling Studies

Buccal tablets were weighed individually (designated as W1) and placed separately in Petri dishes containing 15 ml of phosphate buffer (pH 6.8) solution. At regular intervals (1, 2, 3, 4, 5, 6, 7 and 8 hrs), the buccal tablets were removed from the Petri dishes and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W2). This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following Equation[5,12].

$$\text{Swelling index} = [(W2-W1)/W1]$$

In vitro drug release of buccal tablets

The United States Pharmacopeia (USP) II rotating paddle method was used to study the drug release from the buccal tablets. The dissolution medium consisted of 500 ml of phosphate buffer pH 6.8. The release was performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was placed in to the bottom of the dissolution vessel. Samples (5 ml) were withdrawn at predetermined time intervals and replaced with fresh medium. Dissolution for the conventional marketed product was conducted without glass slide. The samples were filtered through filter paper and analyzed after appropriate dilution by UV spectrophotometer at 224 nm.

Release kinetics and mechanism

To know the release mechanism and kinetics of venlafaxine HCl, optimized formulation was attempted to fit in to mathematical models and n, r^2 values for zero order, First order, Higuchi and Peppas models were represented in Table 6 .The peppas model is widely used, when the release mechanism is not well known or more than one type of release could be involved. The semi-empirical equation[13] was shown as equation.

$$Mt/M\infty = ktn$$

Where, $Mt/M\infty$ is fraction of drug released at time't', k represents a constant, and n is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-fickian release, the value of n falls between 0.5 and 1.0; while in case of fickian diffusion, n = 0.5; for zero-order release (case II transport), n = 1; and for supercase II transport, n > 1. Observation of all the r2 values indicated that the highest r2 (value was found for Zero order release. According to 'n' value it is one, so it follows non-fickian diffusion with zero order release (case II transport).

Ex vivo permeation of drug solution

Ex vivo permeation study of venlafaxine HCl through the porcine buccal mucosa was performed using dissolution cell and membrane assembly, at 37°C ± 0.2°C and 50 rpm. This temperature and rpm was maintained by magnetic stirrer. Porcine buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The tissue was stored in Krebs buffer at 4°C upon collection. The epithelium was separated from underlying connective tissues with surgical scissors and tied to the one side of open tube. The membrane contain side of the tube (donor chamber) was brought in to contact with the surface of the 50 ml pH 6.8 buffer solution[15] which was taken in 100 ml beaker (receiver chamber). After the buccal membrane was equilibrated for 30 min with the buffer solution between both the chambers, the receiver chamber was filled with fresh buffer solution (pH 7.4) and the donor chamber was charged with 5 ml (1mg/ml) of drug solution. Aliquots (5 ml) were collected at predetermined time inter wells up to 8 hours and the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 224 nm using a UV spectrophotometer. The medium of the same volume (5 ml), which was pre warmed at 37°C, was then replaced into the receiver chamber. The experiments were performed in triplicate (n = 3) and mean values were used to calculate flux (J) and permeabilitycoefficient (P).

$$J = (dQ/dt)\, A$$

$$P = \frac{(dQ/dt)}{\Delta CA}$$

J is Flux ($mg.hrs^{-1}cm^{-2}$); P is permeability coefficient (cm/hr); dQ/dt is the slope; SC, the concentration difference across the mucosa and A the area of diffusion (cm^2).

Fourier transform infrared spectroscopic studies

FTIR spectroscopic studies were conducted for optimized formulation and venlafaxine HCl pure drug.

RESULTS AND DISCUSSION

The main aim of this work was to develop mucoadhesive tablets to release the drug at mucosal site in unidirectional pattern for extended period of time. Carbopol 934, HPMC K4M, chitosan and CMC were selected as buccoadhesive polymers for retaining the drug for extended period. All the formulations passes test for weight variation, hardness, content uniformity and show acceptable results with respect to drug content (98.15 to 101.13) and friability (0.08 to 0.46%). The bioadhesive property of the prepared tablets containing drug and HPMC K4M in 1:1 ratio showed good adhesive nature at salivary pH whereas Carbopol have highest strength will damage the epithelial lining of the buccal mucosa. The surface pH values of 5.81 to 6.92 indicate no risk of mucosal damage or irritation. Swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration as shown in Table 3. Swelling index measurements increased with increasing amounts of HPMC K4M whereas carbopol and CMC decreases. The ex vivo permeation showed satisfactory results, summarized in Table 6. The stability of venlafaxine HCl mucoadhesive tablets in human saliva was evaluated by their appearance, such as color and shape, and the concentration as within acceptable limits. FTIR indicates there was no interaction took place between drug and the polymer, shown in Figure 4. In vitro drug release studies revealed that venlafaxine HCl from different formulations

varies with characteristics and composition of polymers. The release rate of drug decreased with increasing concentration of HPMC K4M and chitosan respectively. The ability of HPMC to form complex matrix network which leads to delay in release of drug from the device. The maximum cumulative percent release of venlafaxine HCl from formulation F1 was 99.53% as promote dissolution and hence the release, of the highly water soluble drug. To examine further the release mechanism of venlafaxine HCl from mucoadhesive tablets, the result were analyzed according to the equation

$$Mt/M\infty = ktn$$

The obtained values of 'n' lie between 0.5 and 1.0 in optimized formulation for release of venlafaxine HCl indicates non-fickian release kinetics, which is indicative of drug release mechanism involves diffusion an chain relaxation, shown in Table 7. In light of above discussion it can be concluded that formulation F1 could be used to release the venlafaxine HCl uni-directionally in buccal cavity for extended period of time without the risk of mucosal irritation

CONCLUSION

Development of bioadhesive buccal drug delivery of venlafaxine HCl tablets is one of the alternative routes of administration to avoid first pass effect and provide prolonged release. Venlafaxine HCl-HPMC K4M at the ratio of 1:1 is with complementary physical properties. From the results, it was concluded that the in vitro drug release, Bioadhesion strength of the optimized formulation is suitable for buccal delivery. The release pattern followed non-fickian diffusion with zero order release. FTIR studies concluded that there was no interaction between drug and excipients.

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Table 1: COMPOSITION OF VENLAFAXINE HYDROCHLORIDE MUCOADHESIVE TABLETS

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ingredients (mg)	1:1	1:1.5	1:2	1:1	1:1.5	1:2	1:1	1:1.5	1:2	1:1	1:1.5	1:2
Venlafaxine HCl	25	25	25	25	25	25	25	25	25	25	25	25
HPMC K4M	25	37.5	50	-	-	-	-	-	-	-	-	-
CMC	-	-	-	25	37.5	50	-	-	-	-	-	-
Carbopol 934P	-	-	-	-	-	-	25	37.5	50	-	-	-
Chitosan	-	-	-	-	-	-	-	-	-	25	37.5	50
Mannitol	65	52.5	40	65	52.5	40	65	52.5	40	65	52.5	40
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3
Aspartam	2	2	2	2	2	2	2	2	2	2	2	2
Total weight(mg)	120	120	120	120	120	120	120	120	120	120	120	120

Table 2: THE BIOADHESIVE STRENGTH AND SURFACE pH VALUES OF FORMULATIONS

Formulation Code	Bio adhesion Strength (gm)	Bioadhesive Force(N)	Surface pH
F1	12.5±0.09	1.22±0.08	6.81±0.010
F2	12.1±0.07	1.18±0.06	6.40±0.515
F3	12.9±0.16	1.26 ±0.15	6.21±0.015
F4	14.0±0.31	1.37±0.29	5.91±0.040
F5	15.5±0.07	1.52±0.06	6.63±0.050
F6	16.1±0.16	1.57±0.15	6.92±0.015
F7	29.3±0.21	2.87±0.19	5.81±0.035
F8	31.5±0.06	3.09±0.05	6.85±0.005
F9	33.9±0.27	3.32±0.21	6.75±0.010
F10	24.5±0.10	2.40±0.29	6.56±0.515
F11	18.2±0.11	1.78±0.06	6.23±0.010
F12	15.9±0.15	1.55±0.15	6.55±0.015

Each value represents the mean ±SD (n =3).

Table 3: SWELLING INDEX PROFILE OF FORMULATIONS (F1 – F12)

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	0.31	0.35	0.40	0.08	0.24	0.30	0.42	0.48	0.15	0.24	0.25	0.43
2	0.55	0.57	1.02	0.35	0.81	0.67	0.36	0.75	0.41	0.57	0.73	1.04
3	1.02	1.12	1.74	0.71	1.23	1.08	0.73	1.14	0.63	1.18	1.08	1.58
4	1.42	1.52	2.26	1.18	1.44	1.51	1.18	1.26	0.91	1.51	1.42	2.10
5	1.64	1.95	2.36	1.43	1.75	1.84	1.32	1.5	1.11	1.64	2.03	2.65
6	2.01	2.25	2.44	1.68	2.12	2.26	1.61	1.71	1.30	1.82	2.53	2.91
7	2.41	2.38	2.49	2.04	2.27	2.59	1.73	1.63	1.52	1.39	2.35	2.73
8	2.49	2.51	2.52	1.95	2.10	2.37	2.46	2.48	2.54	1.17	2.05	2.36

Each value represents the mean ±SD (n =3).

Table 4: IN VITRO CUMULATIVE DRUG RELEASE PROFILE OF FORMULATIONS OF HPMC K4M AND CMC

Time (hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	12.1±0.7	11.8±0.6	11.5±0.9	15.6±0.6	18.6±0.5	11.8±0.7
2	22.6±0.4	21.29±0.5	19.1±0.9	46.3±0.8	40.9±0.7	44.1±0.6
3	46.9±0.2	59.7±0.6	58.78±0.4	57.4±0.7	51.9±08	53.5±0.6
4	53.8±0.3	63.1±0.2	69.1±0.5	61.3±0.6	60.3±0.9	61.9±0.2
5	61.1±0.3	77.6±0.5	76.15±0.6	68.7±0.8	64.8±0.2	63.9±0.3
6	88.39±0.3	82.23±0.4	82.9±0.4	74.2±0.7	67.6±0.3	66.3±0.7
7	91.73±0.4	87.60±0.2	87.31±0.8	76.4±0.7	72.4±0.6	68.2±0.6
8	99.53±0.5	90.73±0.6	89.46±0.9	78.6±0.7	76.5±0.5	72.4±0.7

Table 5: IN VITRO CUMULATIVE DRUG RELEASE PROFILE OF FORMULATIONS OF CARBOPOL 934P & CHITOSAN

Time (hr)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	18.1±0.7	16.9±0.8	15±0.9	11.2±0.4	11.5±0.7	11.4±0.2
2	45.8±0.4	25.3±0.5	23.4±0.8	21.6±0.9	19.6±0.5	19.7±0.7
3	61.3±0.2	56.2±0.6	48.5±0.5	65.6±0.7	65.8±0.8	62.4±0.6
4	66.9±0.3	64.3±0.2	61.4±0.4	72.5±0.6	71.1±0.7	64.9±0.2
5	73.2±0.3	72.6±0.5	69.8±0.6	79.1±0.9	76.8±0.2	70.7±0.6
6	76.8±0.4	75.1±0.4	72.3±0.4	81.2±0.7	78.5±0.3	73.2±0.7
7	80.1±0.3	78±0.3	76.5±0.6	82.9±0.7	81.6±0.4	77.2±0.8
8	81.9±0.6	79.3±0.7	76.9±0.8	84.3±0.7	82.4±0.5	81.6±0.7

Table 6: EX VIVO DRUG PERMEATION PROFILES OF DRUG SOLUTION AND OPTIMIZED FORMULATION

	Flux($mg.hrs^{-1}cm^{-2}$)	permeability coefficient (cm/h)
Drug solution	0.1077	0.0172
Optimized formulation(F6)	0.1127	0.0180

Table 7: RELEASE KINETICS AND MECHANISM OF OPTIMIZED FORMULATION (F1)

Formulation code	Mathematical models(Kinetics)				
	Zero order	First order	Higuchi	Peppas model	
	r^2	r^2	r^2	n	r^2
F1	0.9707	0.7757	0.9704	0.806	0.9802

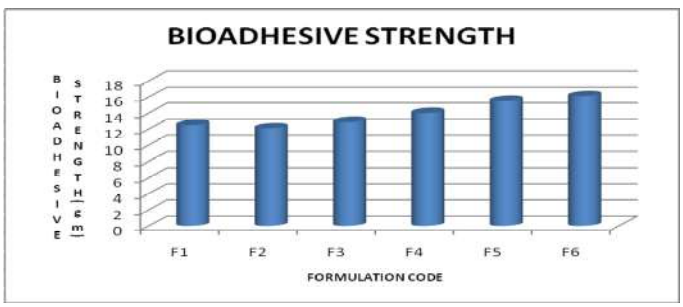

Figure 1a: Bioadhesion strength profile of HPMC K4M & CMC

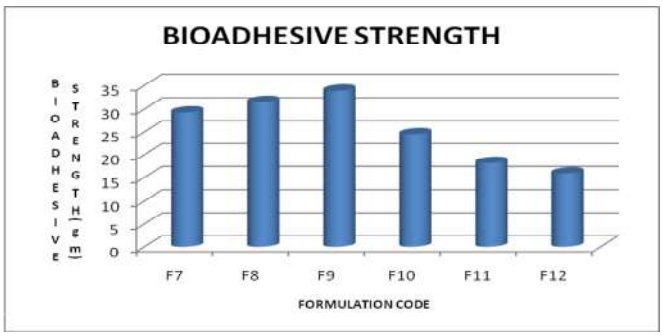

Figure 1b: Bioadhesion strength profile of carbopol 934P & chitosan

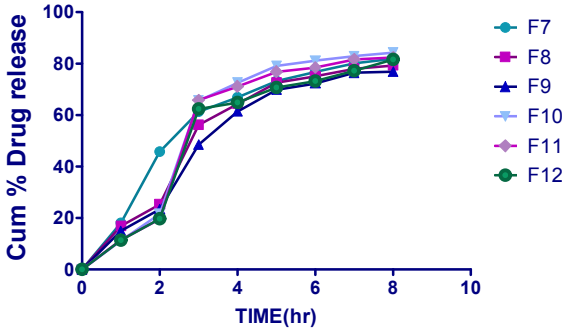

Figure 3b: In vitro cumulative percentage drug release profile of carbopol 934P & chitosan

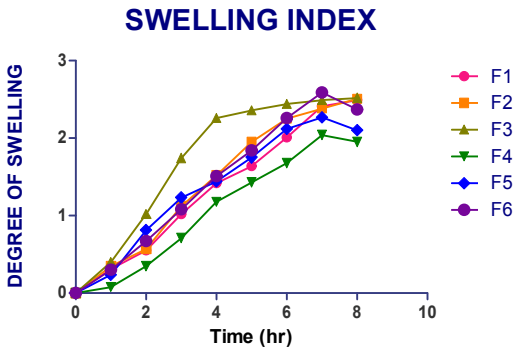

Figure 2a: Swelling index profile of formulations containing HPMC K4M & CMC

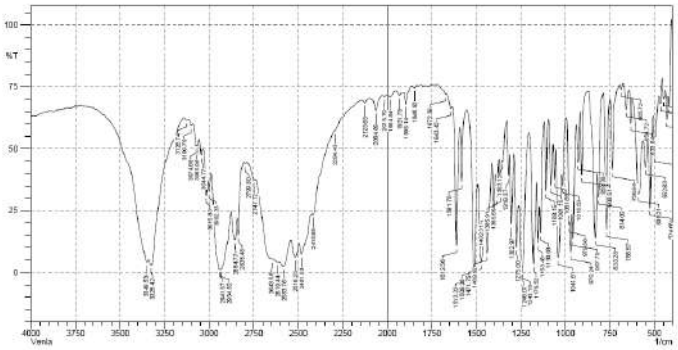

Figure 4a: FTIR spectra of venlafaxine HCl pure drug

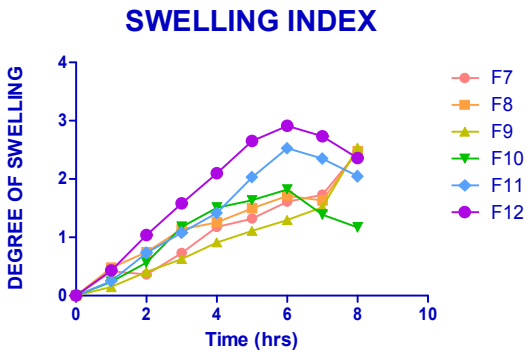

Figure 2b: Swelling index profile of formulations containing carbopol 934P & chitosan

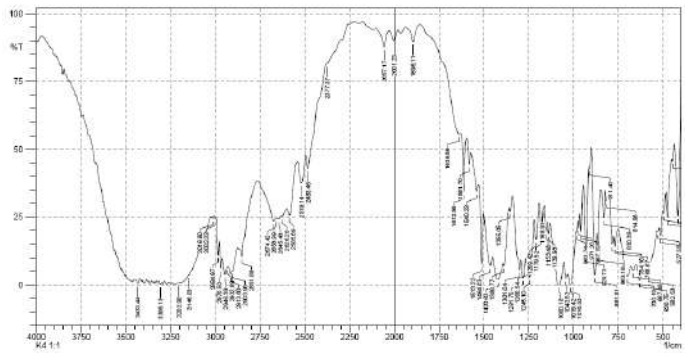

Figure 4b: FTIR spectra of optimized formulation (F1)

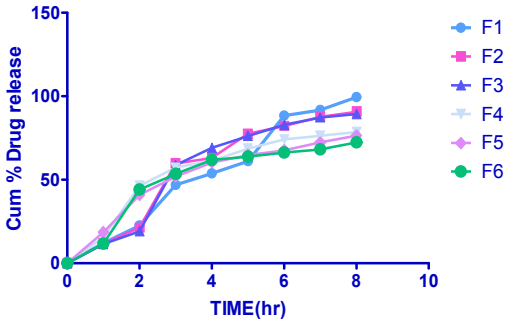

Figure 3a: In vitro cumulative percentage drug release profile of HPMC K4M& CMC

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