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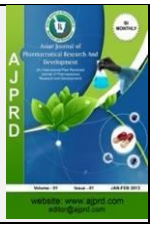

Open Access Research Article

Design and characterization of PH responsiveopthalmic in-situ gel of Brimonidine Tartrate

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ABSTRACT

Glaucoma is a progressive ocular disorder characterized by elevated intraocular pressure (IOP), leading to irreversible optic nerve damage and vision loss if left untreated. Conventional ophthalmic eye drops exhibit poor ocular bioavailability due to rapid precorneal elimination, tear turnover, and nasolacrimal drainage, resulting in frequent dosing and reduced patient compliance. The present study aimed to formulate and evaluate a pH-triggered ophthalmic in-situ gel of Brimonidine Tartrate using Carbopol 980 and HPMC K100M to improve precorneal residence time and sustain drug release. Preliminary optimization studies were carried out to select suitable concentrations of Carbopol 980 and HPMC K100M. A total of nine formulations (F1–F9) were prepared using a 3^2 factorial design and evaluated for physicochemical properties, including pH, viscosity, gelling time, gelling capacity, gel stability, drug content, in-vitro drug release, sterility, and stability. The prepared formulations showed acceptable clarity, homogeneity, and pH suitable for ocular administration. Rheological studies demonstrated pseudoplasticbehavior with viscosity increasing after gelation. The optimized formulation (F5) exhibited optimum viscosity, rapid gelation (4.76 s), satisfactory gel stability (>8 h), drug content of 100.37%, and sustained drug release of 52.12% over 12 h. Sterility testing confirmed the absence of microbial growth, while stability studies indicated no significant changes in physicochemical properties during storage. The developed Brimonidine Tartrate ophthalmic in-situ gel demonstrated sustained drug release, prolonged ocular residence, and improved formulation stability, suggesting its potential as an effective alternative to conventional ophthalmic eye drops for glaucoma management.

Keywords: Brimonidine Tartrate, Ophthalmic in-situ gel, Carbopol 980, HPMC K100M, Glaucoma, Sustained drug delivery, Ocular drug delivery.

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INTRODUCTION

Glaucoma is one of the leading causes of irreversible blindness worldwide and is characterized by progressive degeneration of the optic nerve, primarily associated with elevated intraocular pressure (IOP). According to the World Health Organization, millions of people are affected by glaucoma, and the prevalence continues to increase due to population aging. Effective control of IOP remains the primary therapeutic strategy for preventing vision loss in glaucoma patients. Brimonidine Tartrate, a selective α_2-adrenergic receptor agonist, is widely prescribed for reducing aqueous humor production and enhancing uveoscleral outflow, thereby lowering intraocular pressure.Although conventional ophthalmic eye drops are the most commonly used dosage form for glaucoma therapy, they suffer from several limitations, including rapid precorneal drug elimination due to tear turnover, blinking, and nasolacrimal drainage. Consequently, less than 5% of the instilled drug reaches intraocular tissues, resulting in poor ocular bioavailability and the need for frequent administration. Repeated dosing not only decreases patient compliance but also increases the likelihood of systemic absorption and adverse effects.To overcome these limitations, ophthalmic in-situ gel systems have emerged as a promising drug delivery approach. These systems are administered as low-viscosity solutions and undergo sol-to-gel transition upon exposure to physiological conditions such as pH, temperature, or ionic composition of tear fluid. The gel formed on the ocular surface prolongs precorneal residence time, minimizes drug loss, enhances ocular bioavailability, and provides sustained drug release, thereby improving therapeutic efficacy and patient compliance.Among the available pH-sensitive polymers, Carbopol 980 is widely used because of its excellent gelling ability, biocompatibility,

and rapid gel formation at tear fluid pH. However, Carbopol formulations alone often exhibit low viscosity before gelation and may produce brittle gels after neutralization. Therefore, viscosity-enhancing polymers such as Hydroxypropyl Methylcellulose (HPMC K100M) are incorporated to improve rheological properties, gel strength, and sustained drug release. The synergistic combination of Carbopol 980 and HPMC K100M produces a stable ophthalmic formulation with desirable viscosity, prolonged ocular retention, and controlled drug release.In the present investigation, Brimonidine Tartrate ophthalmic in-situ gel formulations were developed using Carbopol 980 and HPMC K100M. Preliminary optimization studies were conducted to determine suitable polymer concentrations, followed by formulation of nine experimental batches employing a 3^2 factorial design. The prepared formulations were evaluated for physicochemical characteristics, rheological behavior, gelling properties, drug content, in-vitro drug release, sterility, and stability to identify an optimized formulation capable of improving ocular drug delivery.

Novelty of the Study:The present work focuses on the development of a pH-triggered ophthalmic in-situ gel by combining Carbopol 980 with HPMC K100M to achieve improved gelation behavior, prolonged ocular retention, enhanced drug stability, and sustained release of Brimonidine Tartrate. The optimized formulation offers a promising alternative to conventional eye drops by reducing dosing frequency and improving patient compliance in glaucoma management.

Materials and Methods

Materials

Brimonidine Tartrate was used as the model anti-glaucoma drug. Carbopol 980 (pH-sensitive polymer) and Hydroxypropyl Methylcellulose (HPMC K100M) (viscosity-enhancing polymer) were used for preparation of the ophthalmic in-situ gel. Triethanolamine was used as a pH-adjusting agent to induce gelation. Benzalkonium chloride was used as a preservative, while disodium EDTA served as a chelating agent. Sodium chloride was added to maintain isotonicity. Water for Injection (WFI) was used as the vehicle for all formulations. All chemicals and reagents used were of analytical or pharmaceutical grade.

Instruments

The following instruments were employed during the study:Digital pH meter,Brookfield Digital Viscometer (LV Series),UV–Visible Spectrophotometer,Magnetic Stirrer with Hot Plate,AnalyticalBalance,Autoclave,Laminar Air Flow Cabinet,Incubator,Franz Diffusion Cell,Dissolution Assembly with Magnetic Stirrer,Refrigerator,Glassware (Class A)

Experimental Design (3^2 Factorial Design)

A 3^2 full factorial design was adopted to optimize the formulation variables. Carbopol 980 (X_1) and HPMC K100M (X_2) were selected as the independent variables, each at three concentration levels. Nine formulations (F1–F9) were prepared and evaluated.

The responses studied includeincludeed:

pH

Viscosity

Gelling time

Gelling capacity

Gel stability

Drug content

In-vitro drug release

The optimized formulation was selected based on acceptable physicochemical properties and sustained drug release.

Optimization of Carbopol 980

Carbopol 980 concentrations ranging from 0.25% to 2.0% w/v were prepared to determine the optimum concentration for ophthalmic in-situ gel formulation. The prepared placebo formulations (C1–C6) were evaluated for pH before and after gelation, viscosity before and after gelation, gelling time, gelling capacity, and gel stability.

The pH of all formulations before gelation was acidic and increased to approximately 7.4 after neutralization with triethanolamine. Higher polymer concentrations produced increased viscosity and rapid gel formation. Batch C3 (0.75% Carbopol 980) exhibited optimum viscosity, acceptable gelling characteristics, and satisfactory gel stability and was selected for further formulation studies.

Optimization of HPMC K100M

HPMC K100M concentrations of 0.5%, 1.0%, 1.5%, and 2.0% w/v were evaluated (H1–H4). The formulations were examined for pH, viscosity, gelling capacity, and gel stability.

The viscosity Increased proportionally with polymer concentration. Among the tested batches, H3 (1.5% HPMC K100M) demonstrated optimum viscosity, improved gel strength, and prolonged gel stability without producing excessively viscous gels. Therefore, H3 was selected for formulation development.

Preparation of Ophthalmic In-situ Gel Formulations (F1–F9)

The ophthalmic in-situ gel formulations were prepared by the cold method under aseptic conditions. HPMC K100M was dispersed in a portion of Water for Injection with continuous stirring and allowed to hydrate completely. Carbopol 980 was dispersed separately in Water for Injection under continuous stirring until a uniform solution was obtained.

Brimonidine Tartrate was dissolved in Water for Injection, followed by the addition of benzalkonium chloride, disodium EDTA, and sodium chloride. The Carbopol and HPMC solutions were mixed gradually with continuous stirring. The drug solution was then incorporated into the polymeric solution under gentle stirring until a clear and homogeneous formulation was obtained.

The pH was adjusted using triethanolamine to achieve physiological pH and induce sol-to-gel transition. The final volume was adjusted with Water for Injection, filtered through a sterile membrane filter, filled into sterile ophthalmic containers, and stored under refrigerated conditions until further evaluation.

Table 1: formulation of opthalmic in-situ gel with Brimonidine Tartrate.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Brimonidine Tartrate	0.1g	0.1g	0.1g	0.1g	0.1g	0.1g	0.1g	0.1g	0.1g
Carbopol 980	0.125 g	0.125 g	0.125 g	0.250 g	0.250 g	0.250 g	0.375 g	0.375 g	0.375 g
HPMC k100 m	0.250 g	0.500 g	0.750 g	0.250 g	0.500 g	0.750 g	0.250 g	0.500 g	0.750 g
Sodium chloride	0.45g	0.45g	0.45g	0.45g	0.45g	0.45g	0.45g	0.45g	0.45g
Disodium EDTA(0.01%)	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g
Benzalkonium chloride (0.	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g
Triethanolami ne	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Distilled water	50 ml	50ml	50ml	50ml	50ml	50 ml	50ml	50ml	50ml

Evaluation Methods

Determination of pH: The pH of each formulation was measured using a calibrated digital pH meter at room temperature before and after gelation. Measurements were performed in triplicate, and results were expressed as mean ± SD.

Viscosity Measurement: Viscosity was determined using a Brookfield Digital Viscometer at different spindle speeds (10–100 rpm). Measurements were performed before and after gelation to evaluate rheological behavior. The viscosity values were recorded as mean ± SD.

Gelling Time: Gelling time was determined by adding a specified volume of formulation into simulated tear fluid maintained at physiological temperature. The time required for complete gel formation was recorded using a stopwatch.

Gelling Capacity:Gelling capacity was evaluated visually after addition of the formulation into simulated tear fluid and graded according to gel strength and persistence as +, ++, +++, and ++++.

Gel Stability: The formed gels were observed in simulated tear fluid for their ability to retain gel structure. The duration for which the gel remained intact without erosion or dissolution was recorded.

Drug Content: Drug content was determined by diluting an accurately measured quantity of formulation with simulated tear fluid (pH 7.4). The absorbance was measured using a UV–Visible spectrophotometer at the λmax of Brimonidine Tartrate. Drug content (%) was calculated using the previously established calibration curve.

In-vitro Drug Release Study: In-vitro drug release was performed using a Franz diffusion cell fitted with a dialysis membrane. Simulated tear fluid (pH 7.4) served as the receptor medium and was maintained at 37 ± 0.5°C with continuous stirring. Samples were withdrawn at predetermined intervals up to 12 hours, replacing an equal volume of fresh medium after each withdrawal. The samples were analyzed spectrophotometrically, and cumulative drug release was calculated.

Sterility Test: Sterility testing of the optimized formulation was carried out using nutrient agar and CLED agar plates under aseptic conditions. The plates were incubated at 37°C for 24 and 48 hours and examined for microbial growth. Absence of colonies confirmed sterility.

Stability Study: The optimized formulation (F5) was subjected to stability testing for 30 days. Samples were evaluated at 0, 15, and 30 days for clarity, homogeneity, pH, viscosity, gelling time, gelling capacity, and gel stability. No significant changes in physicochemical properties indicated good formulation stability.

Statistical Analysis: All experimental studies were performed in triplicate, and the results were expressed as Mean ± Standard Deviation (Mean ± SD). The optimized formulation was selected by comparing the physicochemical properties, rheological behavior, drug content, gel characteristics, and in-vitro drug release profile of all formulations. Statistical evaluation was carried out using the 3^2 factorial design to determine the influence of Carbopol 980 and HPMC K100M concentrations on formulation performance.

Results and Discussion

Optimization of Formulation: A total of nine formulations (F1–F9) were prepared using a 3^2 factorial design by varying the concentrations of Carbopol 980 and HPMC K100M. Carbopol 980 acted as the pH-sensitive gelling polymer, while HPMC K100M enhanced viscosity and sustained drug release. All formulations were evaluated for clarity, pH, viscosity, gelling characteristics, drug content, in-vitro drug release, sterility, and stability.Among all formulations, F5 exhibited the most desirable physicochemical characteristics and sustained drug release profile and was therefore selected as the optimized formulation.

Physical Appearance: All formulations were visually inspected for clarity, colour, homogeneity, and presence of particulate matter.The prepared formulations were clear,

transparent, colourless, homogeneous, and free from visible particles. No precipitation or phase separation was observed, indicating compatibility of Brimonidine Tartrate with Carbopol 980 and HPMC K100M.

DSC Studies:

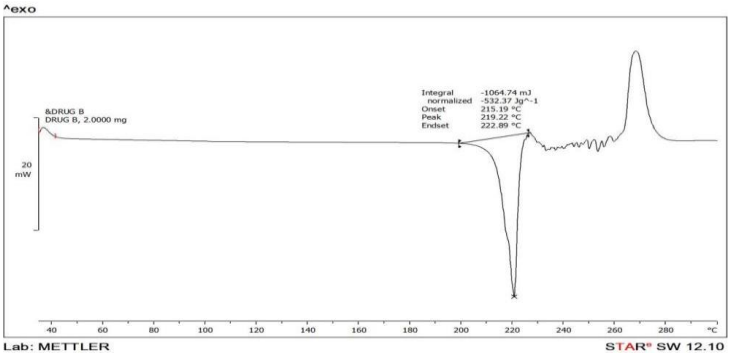

Figure 1: DSC of drug

The DSC thermogram of pure Brimonidine Tartrate showed a sharp endothermic peak at approximately 219.22°C, with onset temperature at 215.19°C and endset temperature at 222.89°C. The sharp peak indicates the crystalline nature and purity of the drug sample. The enthalpy value observed was −532.37 J g^{-1}, corresponding to the melting endotherm of the drug. The presence of a distinct melting peak confirms that the drug exists in crystalline form and possesses good thermal stability.

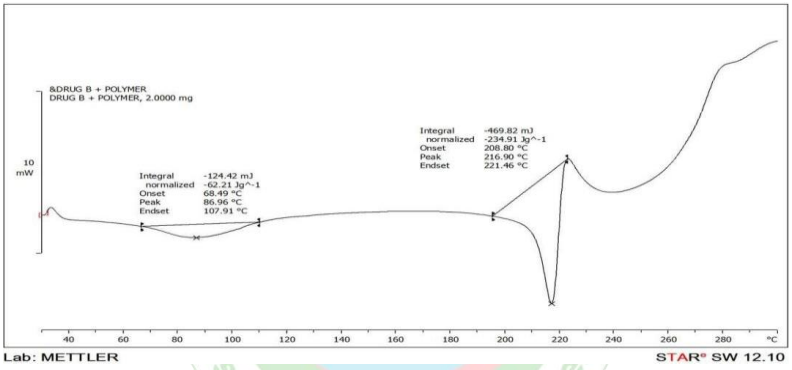

Figure 2: DSC drug and polymer (Brimonidine tartrate+carbopol980+HPMC K100M)

The DSC thermogram of the drug–polymer physical mixture exhibited a broad endothermic peak in the range of 68.49°C to 107.91°C with a peak temperature at 86.96°C, which may be attributed to the loss of absorbed moisture or dehydration of polymeric material. Another characteristic endothermic peak corresponding to the drug was observed at 216.90°C with onset at 208.80°C and endset at 221.46°C. The slight shift in melting peak compared to the pure drug may be due to mixingof the drug with polymer and reduction in crystallinity. However, the characteristic drug peak was retained without disappearance or formation of additional peaks, indicating the absence of significant chemical interaction between Brimonidine Tartrate and the polymer used in the formulation.

pH Evaluation: The pH of all formulations ranged between 7.1 and 7.3, which lies within the acceptable physiological pH range for ophthalmic administration.The optimized formulation (F5) showed a pH of 7.2 ± 0.03, indicating that the formulation is expected to be non-irritating to ocular tissues while maintaining effective gel formation after instillation.

Table 2: PH of formulations batches

Batches	Before Gelation	After Gelation
F1	3.59	7.4
F2	3.44	7.4
F3	3.30	7.4
F4	3.18	7.4
F5	3.45	7.4
F6	3.53	7.4
F7	3.66	7.4
F8	3.70	7.4
F9	3.69	7.4

Rheological Behaviour (Viscosity):Viscosity studies demonstrated that viscosity increased with increasing concentrations of Carbopol 980 and HPMC K100M.The optimized formulation (F5) exhibited a viscosity of 285 ± 3 cPs, which was sufficient to maintain the formulation in liquid form before administration while providing adequate gel strength after contact with tear fluid.The polymer combination produced desirable pseudoplasticbehaviour, facilitating easy instillation into the eye while prolonging precorneal residence time.

Table 3: Rheological behaviour of formulation batches

RPM	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	978 ± 4.1	1088 ± 4.5	1185 ± 5.0	1235 ± 4.8	1291 ± 3.0	1398 ± 4.5	1552 ± 5.2	1688 ±5.5	1815 ± 6.0
20	882 ± 3.8	992 ± 4.2	1092 ± 4.6	1132 ±4.5	1185 ±3.0	1288 ± 4.3	1425 ± 4.8	1545 ± 5.0	1662 ± 5.5
30	807 ± 4.0	905 ± 4.0	988 ± 4.4	1036 ± 4.2	1078 ± 3.0	1172 ± 4.0	1292 ± 4.5	1398 ± 4.8	1508 ± 5.0
50	702 ±3.5	798 ± 4.1	885 ± 4.0	928 ± 4.0	931 ± 3.0	1045 ±3.8	1155 ± 4.2	1245 ± 4.5	1345 ± 4.8
60	655±3.6	745 ± 3.9	832 ± 4.1	872 ± 3.8	868 ± 3.5	958 ± 3.7	1065 ± 4.1	1165 ± 4.3	1262 ± 4.5
100	522 ± 3.2	670 ± 3.5	698 ± 3.8	735 ± 3.5	745 ± 3.0	845 ± 3.5	925 ± 3.8	1015 ± 4.0	1098 ± 4.2

Gelling Time: The gelling time of all formulations was determined by adding the formulation into simulated tear fluid.The optimized formulation (F5) formed gel rapidly within 8 ± 1 seconds, indicating rapid sol-to-gel transformation after ocular administration.Rapid gel formation minimizes drug loss due to tear drainage and improves ocular retention.

Gelling Capacity: The gelling capacity of all formulations was evaluated visually. Optimized formulation exhibited +++ gelling capacity, indicating immediate gel formation with prolonged retention. The gel remained intact without rapid erosion, demonstrating excellent in-situ gel-forming ability.

Gel Stability: The prepared formulations were evaluated for gel stability in simulated tear fluid.The optimized formulation remained stable for more than 8 hours, indicating prolonged gel integrity and sustained residence at the ocular surface.Such prolonged gel stability supports controlled drug release and improved therapeutic efficacy.

Table 4: Gelling time, gelling capasity, gel stability of formulation batches

Formulation	Gelling time (sec)	Gelling capacity	Gel stability
F1	6 sec	+	Stable for 4 hr
F2	5 sec	+	Stable for 4.5 hr
F3	6.73 sec	++	Stable for 5 hr
F4	4.98 sec	++	Stable for 6 hr
F5	4.76 sec	++	Stable for 8 hr
F6	4.72 sec	++	Stable for 7.5 hr

Drug content: Drug content analysis demonstrated uniform distribution of Brimonidine Tartrate throughout all formulations.The optimized formulation showed drug content within acceptable pharmacopeial limits (approximately 99–101%), confirming accuracy of formulation and uniform drug distribution.No evidence of drug degradation or incompatibility was observed.

Table 5: drug content of formulation batches

Formulation batches	Drug content %
F1	95.86%
F2	94.36%
F3	95.86%
F4	92.85%
F5	100.37%
F6	97.36%
F7	88.34%
F8	97.36%
F9	95.86%

In-vitro Drug Release: Drug release studies were performed using a Franz diffusion cell containing simulated tear fluid (pH 7.4).The optimized formulation (F5) exhibited a controlled and sustained release pattern over 12 hours. Drug

release was gradual without an initial burst effect, indicating effective entrapment of Brimonidine Tartrate within the polymeric matrix.The sustained release behaviour can be attributed to the combined effect of Carbopol 980 and HPMC K100M, which increased gel viscosity and reduced drug diffusion.The prolonged release profile Is expected to decrease dosing frequency and improve patient compliance in glaucoma therapy.

Table 6: in vitro release study of formulation batches

Batch code (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	5.71%	4.66%	3.83%	4.29%	3.31%	2.78%	2.33%	1.88%	1.43%
1	8.61	8.14	7.00	7.53	6.38	5.77	5.08	4.47	3.86
2	15.80	13.72	12.32	13.34	11.41	10.32	9.47	8.54	7.60
3	22.42	19.70	17.67	19.09	16.68	14.97	14.02	12.73	11.58
4	28.35	25.49	23.05	24.65	21.59	18.64	18.58	17.04	15.51
5	33.94	30.64	28.23	29.93	26.67	24.26	23.08	21.28	19.49
6	39.17	35.81	32.91	34.93	31.47	28.81	27.50	25.53	23.32
7	43.74	40.69	37.26	39.73	35.91	33.94	31.78	29.54	27.22
8	47.33	44.83	41.27	44.23	40.18	37.36	35.76	33.48	30.94
9	50.08	48.11	44.64	47.33	43.86	41.13	39.51	37.11	34.48
10	52.65	50.75	47.49	50.07	47.14	44.52	42.87	40.43	37.58
11	55.03	52.99	49.66	52.32	49.88	47.50	45.83	43.48	40.43
12	56.71	54.99	51.53	54.31	52.12	49.93	48.36	46.09	42.92

Sterility Test:The optimized formulation was evaluated for sterility using nutrient agar and CLED agar media.No microbial colonies or visible growth were observed after 24 and 48 hours of incubation at 37°C.These findings confirmed that the optimized ophthalmic in-situ gel was sterile and microbiologically safe for ocular administration.

Figure 3: Sterility test of optimized batch

Stability Study: The optimized formulation (F5) was subjected to stability studies for 30 days, and samples were analyzed at 0, 15, and 30 days.No significant changes were observed in clarity, homogeneity, pH, viscosity, gelling time, gelling capacity, or gel stability throughout the study.These observations indicate that the optimized formulation remained physically and chemically stable throughout the storage period.

Table 7: stability study of formulation batches

Parameter	0 Days	15 Days	30 Days
Clarity	Clear	Clear	Clear
Homogeneity	Homogeneous	Homogeneous	Homogeneous
pH	7.2 ± 0.03	7.2 ± 0.04	7.1 ± 0.05
Viscosity (cPs)	285 ± 3	283 ± 4	281 ± 5
Gelling Time (sec)	8 ± 1	8 ± 1	9 ± 1
Gelling Capacity	+++	+++	+++
Gelling Stability	Stable for >8 h	Stable for >8 h	Stable for >8 h

Discussion

The present investigation successfully developed a Brimonidine Tartrate ophthalmic in-situ gel using Carbopol 980 and HPMC K100M through a 3^2 factorial design. Carbopol 980 imparted pH-triggered gelation, while HPMC K100M enhanced viscosity and sustained drug release. The optimized formulation (F5) demonstrated acceptable pH, rapid gelation, excellent gel stability, uniform drug content, sterility, and prolonged drug release for up to 12 hours. Stability studies further confirmed that the formulation retained its physicochemical properties during storage. These findings indicate that the developed ophthalmic in-situ gel has the potential to improve ocular bioavailability, prolong precorneal residence time, reduce dosing frequency, and enhance patient compliance in the management of glaucoma.

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this research work.

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