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FORMULATION AND EVALUATION OF GASTRORETENTIVE IN SITU GELLING SYSTEM OF MITIGLINIDE

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ABSTRACT

In-situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. The polymers (Na alginate and gellan gum) as primary polymers and the secondary polymer (iota carrageenan, sodium CMC) play an important role in gel strength. As the concentration of Na alginate and gellan gum increases in, the gel strength increased significantly.

Moreover, presence of $CaCl_2$ was significant increase in gel strength, the degree of rigidness of gel increases due to increasing degree of crosslinking of divalent Ca^{2+} ions with the polymer chains. The $CaCl_2$ which upon contact with 0.1N HCl (pH 1.2) the liquid polymeric solution should undergo a rapid sol-to-gel transition by means of ionic gelation. The composition of gastric fluid is rich in Cl^- ions; hence on interacting with $CaCl_2$ as cross-linking agent, in-situ gel formed rapidly. The in-situ gel formed should preserve its integrity without dissolving or eroding so as to localize the drug at absorption site for extended duration. In-vitro and buoyancy study test gave a good indication about the gastroretentive property of the selected formula (F3) in the activity of drug and it agreed with the in-vitro results and the proposed mathematical modeling for release kinetic.

Keywords: In-situ Gel, polymer, bioavailability, Gastroprotective floating, Hydrogels, Photo-polymerization.

1 INTRODUCTION

In-situ is a Latin word which means ‘In its original place or in position’ Extensive researches focused on the development of new drug delivery systems with improving efficacy and bioavailability together, thus reducing dosing frequency to minimize side effects. As a progress, they design in-situ forming polymeric delivery systems sparked by the advantages of easy administration, accurate dose as well as prolong residence time of drug in contact with mucosa compared to conventional liquid dosage form, improved patient compliance and comfort[1].

In-situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition upon administration. Gels are an intermediate state of matter containing both solid and liquid components. The solid component comprises a 3D network of inter connected molecule or aggregates which immobilizes the liquid continuous phase. Gels may also be classified (based on the nature of the bonds involved in the 3D solid network): chemical gels arises when strong covalent bonds hold the network together and physical gels when hydrogen bonds, electrostatic and Vander walls interaction maintain gel network. Hydrogels are aqueous gel having high molecular weight, hydrophilic, cross-linked polymers or copolymers that form a 3D network in water. These gels have been shown to combine significantly longer residence time with increased drug bioavailability. The hydrogels are polymers which have the ability to absorb and retain large amounts of water and biological fluids; in addition, they swell and induce a liquid-gel transition[2].

Gastroretentive floating In-situ gel refers to a polymer solution of low viscosity which upon coming in contact with the gastric fluids; undergoes change in polymeric conformation and a viscous

strong gel of density lower than the gastric fluids is produced. The gelation can be triggered by temperature modulation, pH change, and ionic crosslinking. Insitu gels can be administered by oral, ocular, rectal, vaginal, injectable and intra-peritoneal routes[3].

2 APPROACHES OF DESIGNING IN-SITU GEL SYSTEM

2.1 Physically Induced In-Situ Gel Systems

2.1.1 Swelling

In situ formation occurs when material absorbs water from surrounding environment and expands to give the desired space. Example of substance is myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to form liquid crystalline phase structures. It has some bioadhesive properties and can be degraded in vivo by enzymatic action.

2.1.2 Diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for such system.

2.2 Chemically Induced In-Situ Gel Systems

2.2.1 Ionic crosslinking

Certain ion sensitive polysaccharides such as iota carrageenan, gellan gum(Gelrite®), pectin, sodium alginate undergo phase transition in presence of various ions such as k^+ , Ca^{2+}, Mg^{2+}, Na^+ · In- situ gel formation involves administration of aqueous liquid solutions, once administered they form gel under certain conditions involve the use of gelling agent which can form a system that contain the dispersed drug and other excipients. The gelling of this system is achieved by using polymer solutions such as gellan gum & sodium alginate triggered by ionic complexation that contains divalent-ions complexed with Na-citrate which breakdown in acidic environment of stomach to release free divalent ions (Ca^{2+}) due to change in pH. The free Ca^{2+} ions get entrapped in polymeric chains thereby causing cross linking of polymer chains to form matrix structure causes the in situ gelation of orally administered solution as shown in equation.

In-situ gel involves formation of double helical junction zones by aggregation of double helical segments to form dimensional network by complexation with cations& hydrogen bonding with water. While the system is floating in the stomach the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach[4].

2.2.2 Enzymatic crosslinking

In-situ gel formation catalyzed by natural enzymes. For example, cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin. Thus adjusting the amount of enzyme controls the rate of gel formation, which allows the mixtures to be injected before gel formation.

2.2.3 photo-polymerization

A solution of monomers such as acrylate or other polymerizable functional groups and initiator can be injected into tissue site and the application of electromagnetic radiation used to form gel designed to be readily degraded by chemical or enzymatic processes or can be designed for long term persistence in-vivo. Typically; long wavelength ultraviolet and visible wavelengths are used, while short wavelength ultraviolet is not used because it has limited penetration of tissue and biologically harmful [5].

3 IN-SITU GEL FORMATION BASED ON PHYSIOLOGICAL STIMULI

3.1 Temperature Dependent In-Situ Gelling

These hydrogels are liquid at room temperature (20ºC-25ºC) and undergo gelation when contact body fluids (35ºC-37ºC), due to an increase in temperature. This approach exploits temperature-induced phase transition. Some polymers undergo abrupt changes in solubility in response to increase in environmental temperature (lower critical solution temperature, LCST) and formation of negative temperature sensitive hydrogel in which hydrogen bonding between the polymer and water becomes unfavorable, compared to polymer–polymer and water–water interactions. Also an abrupt transition occurs as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure[6].

3.2 pH Dependent In-Situ Gelling

Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers. The pH is an important signal, which can be addressed through pH-responsive materials. Gelling of the solution is triggered by a change in pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. For example: carbomer and its derivatives as anionic polymer[7].

4 MECHANISMS OF DRUG RELEASE FROM IN-SITU GEL SYSTEM

4.1 Diffusion–Controlled Mechanism

4.1.1 Matrix system

The active agent is homogenously dispersed as a solid into a hydrogel inert bio-degradable polymers matrix as in Figure 1.15a. The release of drug depends on

- Diffusion of water into the matrix followed by the dissolution of the drug and finally the diffusion of the dissolved drug from the matrix.
- Polymers interact with drugs leading to modulate the release of the drug.
- Thickness of the hydrated matrix is considered as the diffusional path length of the drug. If we consider the polymer matrix to be inert and the drug release is diffusion-controlled, then the release rate of the drug could be described by Higuchi equation.

4.1.2 Reservoir devices

The drug is contained in a core (often termed as reservoir) which is surrounded by a rate-controlling polymeric membrane of hydrogel which allows the diffusion of drug. As the system comes in contact with water, water diffuses into the system and dissolves the drug, and then drug transport (from the core through the external polymer membrane) occurs by dissolution at one interface of the membrane and diffusion driven by a gradient in thermodynamic activity Drug transport can be described by Fick's first law, if the activity of the drug in the reservoir remains constant and infinite sink conditions are maintained, then the drug release rate may be continued to be constant since it depends on the membrane permeability and it will be independent of time, thus zero-order kinetics can be achieved. Once drug is exhausted, the release becomes concentration dependent following first order kinetics. These kinds of drug delivery systems are mainly used to deliver the active agent by oral routes [8].

4.2 Swelling-Controlled Mechanism

4.2.1 Solvent activated system

It occurs when diffusion of drug is faster than hydrogel swelling. When a hydrogel is placed in an aqueous solution, water molecules will penetrate into the polymer network that occupy some space, and as a result some meshes of the network will start expanding, allowing other water molecules to enter within the network. But, swelling is not a continual process; the elasticity of the covalently or physically cross-linked network will counter-balance the infinite stretching of the network to prevent its destruction. For example the release of drugs from (HPMC) hydrogel is commonly modeled using this mechanism. If the drug delivery system is a true swelling-controlled system then it is described by Ritger and Peppas equation[9].

4.2.2 Osmotic swelling

For hydrogels, the total swelling pressure of gel could be related to volume fraction, relaxed volume of network, and cross-link density while it is independent on gel pH and swelling time.

4.3 Chemically-Controlled Mechanism

It can be categorized according to the type of chemical reaction occurring during drug release within a delivery matrix into:

- Pendant chain system is the most common reaction where the drug is covalently attached to a polymer backbone. The bond between the drug and the polymer is labile and can be broken by hydrolysis or enzymatic degradation and then the drug release.
- Erodible drug delivery system where the release of the drug is controlled by the dissolution during surface-erosion or bulk-degradation of the polymer backbone then the drug diffuses from erodible systems.

Depending on whether diffusion or polymer degradation controls the release rate, the drug is released following different mechanisms; if erosion of polymer is much slower than diffusion of the drug through the polymer, then drug release can be treated as diffusion controlled process. While if diffusion of the drug from the polymer matrix is very slow, then polymer degradation or erosion is the predominate mechanism, for example hydrophobic erodible polymers[10].

5 EXPERIMENTAL WORK

5.1 Characterization of Mitiglinide

5.1.1 Determination of mitiglinide melting point

The melting point of drug was determined by capillary tube method according to the USP which is 180-184°C

5.1.2 Determination of mitiglinide solubility

Solubility of drug in two different solvents 0.1N HCl and distilled water was checked by preparing saturated solutions of drug in respective solvents by using the shake-flask method at 37° C. Saturated solutions were prepared by adding excess of drug to vehicles, then samples were allowed to shaken in sonicator for 24 hrs overnight. After 24 hours, the solutions were filtered and analyzed spectrophotometrically**.** Freely soluble in methanol, soluble in 0.1N HCl and slightly soluble in water[11].

5.2 Preparation of Oral Mitiglinide Solution to Act As In- Situ Gel

Different polymers were used to prepare Mitiglinide to act as in-situ gelling preparation. The methods of preparation for the required formulas were as follows: Using the magnetic stirrer, fluidity enhancer agent was added in 100 ml of distilled water. Gelling agent was added when the temperature reached 70˚ C, and then release retard polymer was added. The temperature was maintained at 70˚ C and then stirred continuously to obtain a clear solution. The obtained clear solution was cooled to 40˚ C and then cross-linking agent was added. The temperature was maintained at 40˚ C, finally the drug, preservative and sweetening agent were added in the solution along with gas generating agent. The solution was stirred continuously till a uniform solution was obtained. Table represents composition of preliminary formulations prepared[12].

Table-1: Composition of preliminary formulations

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Mitiglinide (mg)	20	20	20	20	20	20	20	20	20	20	20	20
Sodium alginate (% w/v)	0.2	0.5	0.7	-	-	-	-	-	-	-	-	-
Iota Carrageenan (% w/v)	-	-	-	0.2	0.5	0.7	-	-	-	-	-	-
Gellan gum (% w/v)	-	-	-	-	-	-	0.2	0.5	0.	-	-	-
Sodium CMC (% w/v)	-	-	-	-	-	-	-	-	-	0.2	0.5	0.7
Tri-sodium citrate (% w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMC K100M (% w/v)	1	1	1	1	1	1	1	1	1	1	1	1
Calcium chloride (% w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium bicarbonate (% w/v)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Methyl paraben (% w/v)	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Saccharin sodium (% w/v)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Distilled water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

6 EVALUATION OF FLOATING IN-SITU GEL MITIGLINIDE SOLUTION

6.1 Gel Strength Determination

Gel strength is indicative of the tensile strength of the gelled mass. It signifies the ability of the gelled mass to withstand the peristaltic movement. The gel strength of the formulation is an important variable dependent on the type and concentration of the polymer, combination of polymers, gas generating agent and cation source ($CaCl_2$). The method to measure gel strength of gelled mass was modified; by using fabricated gel strength apparatus and it was done triplicate as shown in Figure 2.1. Solution of 5 ml was taken in the cylinder followed by addition of 25 ml of GF 0.1 N HCl (pH 1.2) for gelation. After gelation the HCl was drained off leaving the formed gel mass, and then the device was rested on to surface of the gel. At the free end of the device a light weight pan (4 g) was attached to which the weights were added. The gel strength was reported in terms of weight required to pass the apparatus through the gel mass[13].

6.2 Swelling Index

The percentage of swelling index of in-situ gel of the formulations was determined. In situ gel formed by putting 5 ml of each formula in a petri dish and 40 ml of GF 0.1 N HCl (pH 1.2) was added. Then 0.1N HCl solution was removed from the gel and the excess of 0.1N HCl solution was blotted out with whatman filter paper. The initial weight (W_o) of the gel was recorded, to this gel 10 ml of distilled water was added and after 60 minutes the water was decanted and the final weight (W_t) of the gel was recorded, this process was repeated for 5 hrs and the difference in the weight was calculated and reported [(105)]. The % weight gain (swelling index) for formulations is calculated by the following equation (1):

$$\% \text{ Swelling index} = (W_t - W_0 / W_t) \times 100 \quad (1)$$

Where, W_0 =Initial weight of the gel. W_t =weight gain by the gel[15].

6.3 Viscosity Measurements

The viscosity of the prepared solutions were measured out using sample of 100ml. Measurements were performed using suitable spindle number 64 and sheared at a rate of 3, 4, 5, 6, 10, 12, 20, 30, 50, 60, 100 rpm, and the temperature was maintained at 37° C. The viscosity was read directly after 30 seconds. All measurements were made in triplicate. The rheological velocity was explained by plotting viscosity against angular velocity[16].

6.4 In-Vitro Buoyancy Study

The in vitro buoyancy study is characterized by floating lag time and total floating duration. In vitro buoyancy study was carried out triplicate using USP dissolution apparatus type II using 900 ml medium of 0.1N HCl (pH 1.2). The medium temperature was kept

at 37 ± 0.5° C. Accurately 10 mL of the prepared in-situ gel formulation was drawn up using disposable syringe and placed into the petri dish (4.5 cm internal diameter) and finally the petri dish containing the formulation was placed carefully in the dissolution vessel. Then the dissolution test apparatus was run at 50 rpm, this speed was slow enough to avoid breaking of gelled formulation and maintaining the mild agitation conditions believed to exist in vivo. The time the formulation took to emerge on to the medium surface (floating lag time) and the time over which the formulation constantly floated on the dissolution medium surface (duration of floating) were reported [17].

6.5 pH Measurement

The pH of the prepared solution for all formulations was measured by digital pH meter at 25 ± 0.5° C after it is calibration using standard buffer solutions of pH 4, 7, 9 then the measurements of pH were recorded.

6.6 Determination of Drug Content

Accurately, 5 ml of liquid solution (containing 20 mg of the drug) from all formulations was taken and to which 70 ml of 0.1N HCl was added, then the sample was sonicated for 30 min until clear solution is made. The volume completed to 100 ml and filtered using Whatman filter paper No. 41. From this solution, 1ml sample was withdrawn and diluted to 10 ml with 0.1N HCl. Contents of drug was determined spectrophotometrically at 259 nm using double beam UV-Visible spectrophotometer[18].

6.7 Water Uptake Study

A simple method was adopted to determine the water uptake by the gel. The in situ gel formed in 0.1 N Hydrochloric acid was used for this study. From each formulation the gel portion from the 0.1 N Hydrochloric acid separated and the excess solution was blotted out with a tissue paper. The initial weight of the gel taken was weighed and to this gel 10 ml of distilled water was added and after every 30 minutes of the interval water was decanted and the weight of the gel recorded and the difference in the weight was calculated and reported[19].

7 EVALUATION OF MITIGLINIDE FLOATING IN-SITU GEL

All the formulations (F1-F12) prepared were evaluated for different parameters like: gel strength, gelation time, content uniformity, floating lag time, floating duration, pH measurement, water uptake and swelling index, the results are summarized[20].

Table-2: Evaluation of preliminary formulations F1 – F12.

Formulation	pH determination	Viscosity in cPs		Floating Lag time In sec.
		Solution	Gel	
F1	7.56 ± 0.028	265.66 ± 2.04	1353.3 ± 1.69	4.66 ± 0.47
F2	7.59 ± 0.012	288.20 ± 2.33	1450.0 ± 2.16	4 ± 0.81
F3	**7.4 ± 0.021**	**327.26 ± 2.77**	**1536.6 ± 2.86**	**3 ± 0.43**
F4	7.26 ± 0.028	247.6 ± 2.98	1045.0 ± 1.41	35 ± 3.74
F5	7.23 ± 0.016	265.83 ± 4.01	1152.0 ± 3.74	42.66 ± 2.05
F6	7.30 ± 0.020	296.93 ± 4.04	1224.3 ± 3.39	50.33 ± 2.05
F7	7.66 ± 0.038	312.33 ± 3.23	882 ± 3.74	22.66 ± 1.24
F8	7.61 ± 0.038	333.56 ± 4.56	1008.3 ± 4.64	25.33 ± 2.05
F9	7.69 ± 0.030	363.23 ± 1.91	1250.3 ± 2.86	22 ± 2.44
F10	7.84 ± 0.024	254.03 ± 4.39	942.66 ± 3.39	54.66 ± 3.09
F11	7.86 ± 0.026	283.73 ± 2.90	1135.6 ± 3.29	48.66 ± 2.62
F12	7.87 ± 0.028	318.03 ± 2.77	1216 ± 4.32	56.33 ± 1.24

7.1 In Vitro Drug Release Study

The in vitro release of drug from buoyant in-situ gel solutions was studied using USP type II (paddle type) dissolution test apparatus. Five ml (containing 20 mg of drug) from each formulation was transferred using disposable syringe, the needle was wiped clean and excess formulation was removed from needle end. The syringe plunger depressed slowly to extrude 5 ml into a petri dish with an internal diameter of 4.5 cm already containing 10 ml of 0.1N HCl. This petri dish containing formulation was placed on the surface of the medium and plunged into a dissolution vessel containing 900 ml of 0.1N HCl (pH 1.2) without much disturbance. The dissolution test apparatus was run at 50 rpm for maximum up to 12 hrs at a temperature 37± 0.5° C. This speed was slow enough to avoid the breaking of gelled formulation and was maintaining the mild agitation conditions believed to exist in vivo. Five ml samples were withdrawn form dissolution medium with disposable syringe at predetermined time intervals of one hour and replenished with 5 ml of pre-warmed fresh medium. Samples were filtered using whatman filter paper No.41 and furosemide contents in the aliquots was determined spectrophotometrically using double beam UV-Visible spectrophotometer at a wavelength of 259 nm after suitable dilution[21].

Table-3: Evaluation of preliminary formulations F1 – F12.

Formulation Code	Total Floating time (hours)	% Drug content (n=3, ± S.D.)	% Water uptake study (n=3, ± S.D.)	Gelling strength (n=3, ± S.D.) in sec.	Swelling index (%)	Gelation time (sec)
F1	> 12	98.13 ± 0.11	9.04 ± 2.51	12.09 ±0.81	46.1	11±0.05
F2	> 12	96.85 ± 0.26	11.69 ± 0.75	14.04 ±1.01	65.6	2±0.01
F3	> 12	99.14 ± 0.63	14.46 ± 0.30	15.32 ±0.47	90.2	2±0.01
F4	> 12	94.65 ± 0.67	4.77 ± 1.46	4.11 ± 0.68	63.7	10±0.07
F5	> 12	95.29 ± 0.82	8.06 ± 1.48	6.65 ± 0.33	75.6	6±0.11
F6	> 12	96.15 ± 0.48	10.31 ± 2.10	8.07 ± 0.43	84.2	7±0.06
F7	> 12	89.06 ± 0.15	5.90 ± 1.40	3.31 ± 0.07	8.3	2±0.01
F8	> 12	88.08 ± 0.26	8.00 ± 1.10	5.74 ± 0.30	10.1	10±0.09
F9	> 12	85.19 ± 0.45	9.13 ± 1.26	6.3 ± 0.74	12.2	3±0.02
F10	> 12	87.54 ± 0.14	3.18 ± 0.69	7.45 ± 1.78	60.9	5±0.03
F11	> 12	89.37 ± 0.34	6.19 ± 0.67	10.98 ±0.54	64.4	4±0.08
F12	> 12	91.57 ± 0.93	8.42 ± 0.25	12.39 ±0.84	43.5	6±0.04

Table-4: *Invitro* Drug release of trial formulations.

Time	% CDR											
	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	14.26	13.09	21.67	11.47	12.67	60	14	11.75	15.07	7.42	6.52	5.85
2	26.67	25.49	35.53	17.02	22.52	14.71	25.72	27.56	17.22	13.09	11.60	10.60
3	40.18	40.98	52.74	32.50	27.91	20.68	37.30	47.33	29.65	20.81	17.83	18.27
4	52.19	53.18	57.39	37.14	37.42	39.52	52.94	54.12	48.31	32.17	24.22	23.23
5	54.73	55.63	60.59	47.82	52.21	46.08	56.29	57.56	53.70	42.97	28.32	29.30
6	58.50	58.81	63.98	52.63	57.63	50.65	58.49	59.18	54.90	54.86	37.47	38.95
7	62.28	61.11	67.66	58.05	59.83	54.89	61.69	61.98	58.26	56.74	51.22	53.52
8	65.77	65.09	70.82	60.35	62.81	58.57	66.30	65.87	62.54	60.83	53.62	56.42
9	75.35	73.68	73.85	64.45	65.90	62.53	67.65	71.36	66.66	63.50	58.55	58.98
10	79.40	77.32	78.03	67.77	67.88	64.85	69.5	74.58	69.40	64.56	60.17	62.45
11	80.73	78.81	81.33	72.01	70.22	69.56	72.30	76.87	74.50	66.67	68.51	70.71
12	82.60	80.31	89.50	74.64	72.04	73.09	76.24	77.78	79.58	71.79	77.83	75.5

8 CONCLUSIONS

Oral mitiglinide solution can be formulated as in-situ gel preparation by using Na alginate and iota carrageenan. Viscosity of the solution increased significantly with increasing concentrations of Na alginate and iota carrageenan. Gelation time reduced significantly with addition of $CaCl_2$. Swelling index increased significantly with increasing Na alginate concentration and it is affected by type of secondary polymer. Floating duration and floating lag time reduced significantly by the presence of $NaHCO_3$. In-vitro test gave a good indication about the gastroretentive property of the selected formula (F3) in the activity of drug and it agreed with the in-vitro results and the proposed mathematical modeling for release kinetic. It was concluded that the formulation of mitiglinide as a floating in-situ gel is promising.

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