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Research Paper

## Development and *In-Vitro* Evaluation of Budesonide Mucoadhesive Microsphere for Pulmonary Drug Delivery

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### Abstract

The purpose of the study was to develop and evaluate mucoadhesive microspheres of Budesonide for pulmonary drug delivery system having prolonged residence time and sustained drug release. Microspheres were prepared by emulsification solvent evaporation technique using HPMC, carbopol as polymers in varying ratios. The microspheres were evaluated for its percentage yield, drug entrapment efficiency, particle size and shape, in vitro mucoadhesion study and in vitro drug release studies. The FTIR studies revealed no chemical interaction between the drug molecule and polymers and found that drug was compatible with used polymer. The mucoadhesive microspheres showed particle size, drug entrapment efficiency and yield in the ranges of 148 - 164µm, 68.0 - 85.0% and 67.52 - 87.25% respectively. *In vitro* drug release and mucoadhesion study confirms that formulation F5 was the best formulation as it releases 81.8 % at the end of 12 hr. in controlled manner and percentage mucoadhesion of 75.2 % after 10 hr. This confirms the developed budesonide mucoadhesive microspheres are promising for pulmonary drug delivery system.

**Keywords:** Budesonide, Mucoadhesion, Microspheres, Drug entrapment efficiency.

## INTRODUCTION

Pulmonary drug delivery system has been used for the treatment of local and systemic diseases<sup>1</sup>. The local respiratory diseases like chronic obstructive pulmonary disease (COPD) and asthma were the prime focus in the early studies; however the research has been advanced in the treatment of respiratory infectious diseases and also in the transport of therapeutic molecules to the systemic circulation. Respiratory system in itself restricts the entrance of particulate matter by various means: e.g. geometry of the airways and clearance mechanisms of the lungs. The conventional inhalation products have high dosing frequency often leads to local and systemic toxicity. Therefore, novel controlled release carrier systems may provide a probable solution to these difficulties by reducing dosing frequency and increasing drug bioavailability<sup>2,3</sup>.

Drug action can be improved by developing new oral controlled drug delivery system, such as the mucoadhesive microsphere<sup>4</sup>. The concept of bioadhesion and specifically mucoadhesion is one of them to increase gastric retention time of drugs. Mucoadhesion or bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are held together for a prolonged time period by means of interfacial forces. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to

an increase bioavailability and both local and systemic effects<sup>5</sup>. The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation of body. However oral administration of most of the drugs in conventional dosage forms has short-term limitations due to their inability to restrain and localize the system at gastro-intestinal tract.

Mucoadhesive microspheres helps to achieve relatively short residence time by the site of absorption can be overcome by coupling bioadhesion characters developed and to improve localization of oral controlled or sustained release drug delivery system by intimate contact with the mucous layer and by specific targeting of drug to the absorption site<sup>6</sup>. Microspheres of biodegradable or non-biodegradable polymers can be used for sustained delivery<sup>7</sup>.

Budesonide is a locally acting glucocorticoid with high topical anti-inflammatory activity. It has been used for many years in the treatment of inflammatory airway diseases for the low systemic activity of budesonide due to its rapid metabolism to biologically inactive. One of the most common uses of budesonide is in ulcerative colitis and Crohn's disease<sup>8</sup>.

It has a low bioavailability of 9-21%, because of its poor absorption in gastro intestinal tract. It undergoes extensive, primarily hepatic metabolism after oral administration<sup>9</sup>. Therefore, in the present study budesonide is selected as a

suitable drug for the design of mucoadhesive microspheres with a view to improve its oral bioavailability and increase its drug release in a sustained manner<sup>10</sup>.

## MATERIALS AND METHODS

### Material

Budesonide was obtained as gift- sample from Cipla Pharmaceutical Pvt. Ltd. Indore and carbopol 934, HPMC of pharmaceutical grade were procured from Loba chemicals Pvt Ltd and liquid paraffin, Span 80, ethanol, acetone procured from SD Fine chemicals.

### Pre-formulation studies:

Pre- formulation is considered as important phase where researcher characterizes the physical and chemical properties of drug substance which helps to develop stable, effective and safe dosage forms and also check possible interaction with various excipients<sup>8</sup>.

### Compatibility Study FT-IR Spectra Analysis

FT-IR Spectroscopy can be used to investigate and predict any physicochemical interactions between different components in a formulation<sup>11</sup>. While selecting the ingredients, we would choose those which are stable, compatible and therapeutically acceptable. The aim of compatibility study was to test, whether there is any interaction between the excipients and the drug and

compatibility between the drug and excipients. The pellets were prepared and scanned over a wave number range of 4000 – 500 cm<sup>-1</sup> in a FTIR instrument. FT-IR spectrum of budesonide was compared with FT-IR spectra of budesonide with excipients. The pure drug and drug with excipients were scanned separately. Disappearance of budesonide peaks or shifting of peak in any of the spectra was studied<sup>12</sup>.

### Preparation of Mucoadhesive microspheres by Emulsification-solvent evaporation

In the present study, mucoadhesive polymers carbopol 934, HPMC were used in different ratios with the active ingredient for the preparation of mucoadhesive microspheres. These polymers were employed for the fact that they possess good biocompatibility, non-irritant and non-toxic<sup>13</sup>. Accurately weighted amount of the polymers carbopol 934, HPMC as shown in Table No. 1 were dissolved in 50ml of acetone to form a homogenous polymers solution. Budesonide was then dispersed in it and mixed thoroughly. This dispersion quickly injected into 5 ml liquid paraffin containing 1% (w/w) of Span-80 by using a 5 ml of syringe at room temperature with stirring at 1000 rpm to form a uniform emulsion<sup>14,15</sup>. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone evaporated and smooth-walled, rigid and discrete microspheres were formed. The microspheres were collected by decantation and the product was washed with n-hexane and stored in desiccators over fused calcium chloride<sup>16,17</sup>.

**Table 1: Formulation design of Mucoadhesive microspheres**

S.No.	Ingredients	Formulation Code					
		F1	F2	F3	F4	F5	F6
1	Drug(mg)	10	10	10	10	10	10
2	HPMC(mg)	50	100	150	150	150	100
3	Carbopol 934(mg)	50	100	150	50	100	150
4	Light Paraffin(ml)	50	50	50	50	50	50
5	Span 80(ml)	1	1	1	1	1	1
6	Acetone(ml)	50	50	50	50	50	50

### Evaluation of Prepared Mucoadhesive Microspheres:

The mucoadhesive microspheres evaluation was carried out for appropriate assessment of a dispersed system requires characterization of both chemical and physical stabilities. Physical properties are very important with respect to the performance of dispersed systems<sup>18</sup>.

### Percentage yield

The total amount of microspheres obtained were calculated and evaluated for percentage yield<sup>19</sup>.

Percentage yield was calculated using the formula:

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

### Degree of Swelling

The degree of swelling is a property measured to know the behaviour of polymer in physiological solution. It is determined by keeping the microspheres in buffer solution for 24 hrs and washed. The swelling ability of mucoadhesive microspheres in physiological media was determined by swelling them in the PBS pH 6.8. Accurately weighed 20 mg

of microspheres were immersed in little excess of PBS pH 6.8 for 8 hrs and washed<sup>19</sup>.

The degree of swelling was calculated using following formula,

$$\alpha = (W_s - W_o) / W_o$$

Where,  $\alpha$  is the degree of swelling

$W_o$  is the weight of microspheres before swelling

$W_s$  is the weight of microspheres after swelling.

### Particle Size Determination

Determination of average particle size of Mucoadhesive microspheres loaded with Budesonide was carried out by using optical microscopy. A minute quantity of microspheres was spread on a clean glass slide and average size of 300 microspheres was determined in each batch.

### Scanning Electron Microscopy (SEM)

The microspheres were observed under a Scanning Electron Microscopy. They were mounted directly onto SEM sample

stub using double-sided sticking tape and coated with gold film with ion spillter with gold target with resolution 3 nm (30 KV HV Mode), 10 nm (30 KV HV Mode), 40 nm (30 LV Mode) and a vacuum system is fitted to it<sup>20</sup>.

### Drug Loading and Entrapment Efficiency

For determining drug loading and entrapment efficiency, weighed the quantity of microspheres were dissolved in methanol and kept during the night on a mechanical shaker to extract the complete entrapped drug. The obtained solution was filtered through Whatman filter paper and analyzed by using a UV spectrophotometer at 246 nm. The drug loading (DL) and entrapment efficiency (EE) were determined as per equations mentioned below<sup>20</sup>.

$$\% \text{ Drug Loading} = \frac{\text{Actual amount drug loaded in microsphere}}{\text{Weight amount of Microspheres}} \times 100$$

$$\% \text{ EE} = \frac{\text{Actual amount drug entrapped in microsphere}}{\text{Amount of drug added}} \times 100$$

### In vitro Mucoadhesion Study (Wash off test)

The *in-vitro* wash off test was carried out to evaluate the mucoadhesive potential of the microspheres. A small portion of the sheep intestinal mucosa was mounted on a glass slide and accurately weighed microspheres were sprinkled on the mucosa. Around 100 microspheres were spread on the wet mucosa and the prepared slide was hung onto one of the grooves of the USP tablet disintegrating test apparatus filled with Phosphate buffer solution pH 6.8 giving regular up and

down movements for 60 minutes. At the end of 60 min, numbers of microspheres still adhering to the intestinal mucosa were counted<sup>20</sup>. The percentage of mucoadhesion was calculated by following formula:

$$\% \text{ Mucoadhesion} = (W_a - W_l) \times 100 / W_a$$

Where,  $W_a$  = weight of microspheres applied

$W_l$  = weight of microspheres leached out.

### In vitro Drug Release Study

*In-vitro* drug release study was carried out in USP dissolution test apparatus. Mucoadhesive microspheres were loaded into the basket of the dissolution apparatus. Dissolution study was carried out for 24 hrs in media of phosphate buffer pH 6.8 at  $37 \pm 0.5^\circ\text{C}$  and at 100 rpm. 5 ml of the sample was withdrawn from the dissolution media at suitable time intervals and diluted to 10 ml using pH 6.8 phosphate buffer and the same amount was replaced with fresh buffer. The absorbance was measured at 246 nm by using Shimadzu 1700 UV spectrophotometer, against a blank solution<sup>19,20</sup>.

## RESULT AND DISCUSSION

### Compatibility Study FT-IR Spectra Analysis

The comparative FTIR studies of Drug and excipients combination revealed that no chemical interaction between the drug molecule and polymers and found that drug was compatible with used polymer. The FTIR spectra of pure drug and drug with excipients are shown in the Fig 1, 2 & 3.

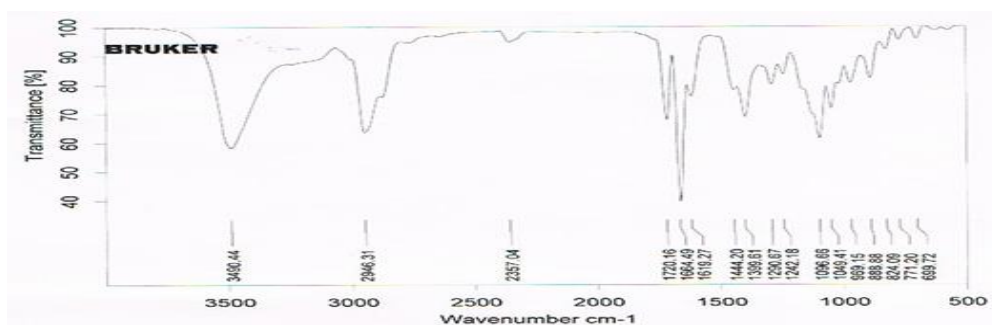


Figure 1: FT-IR Spectra of pure drug (BUDESONIDE)

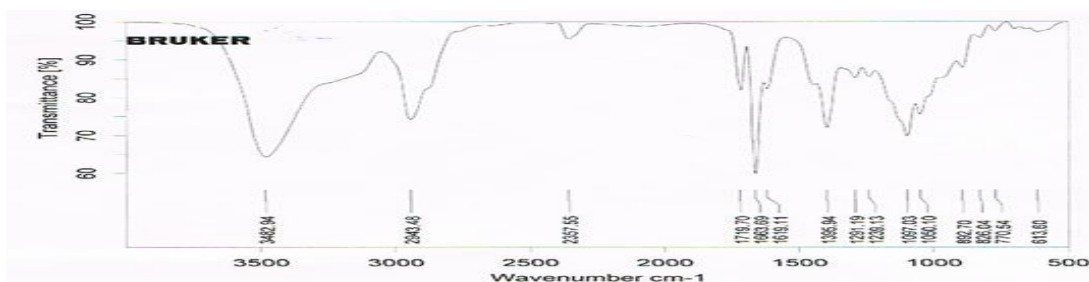


Figure 2: FT-IR Spectra of Budesonide with Polymer (HPMC)

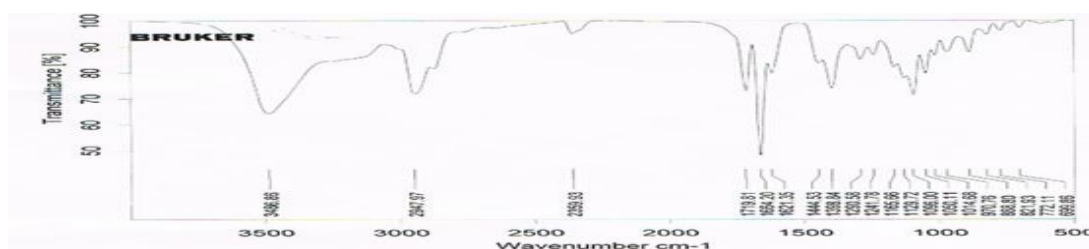


Figure 3: FT-IR Spectra of Budesonide with Polymer (Carbopol)

### Percentage Yield

The percentage yield of microspheres was calculated by using the weight of final product after drying with respect to initial total weight. The maximum percentage yield was found of F5 batch and was noted to be 87.25 % among all the batches. The production yields of microspheres were found to be between 67.52 to 87.25% as shown in Table 2. The percentage yields are shown in Fig 5.

### Degree of Swelling

Degrees of swelling of the formulations were carried out and found to be within the range between 1.38 - 1.85.

### Particle Size Determination

With increase in polymer concentration, the mean particle size of the microspheres significantly increased and range was between 148 to 164  $\mu\text{m}$ . The particle sizes of Budesonide microspheres are shown in Fig 5.

### Scanning Electron Microscopy (SEM)

The morphology of the mucoadhesive microspheres of best formulation F5 was examined by scanning electron microscopy. SEM confirms the outer surface of F5 formulation was smooth and dense, while the internal surface was porous. The shell of microspheres also showed some porous structure it may be caused by evaporation of solvent entrapped within the shell of microspheres after forming smooth and dense layer. The scanning electron microscopy of F5 batch is shown on Fig 4.

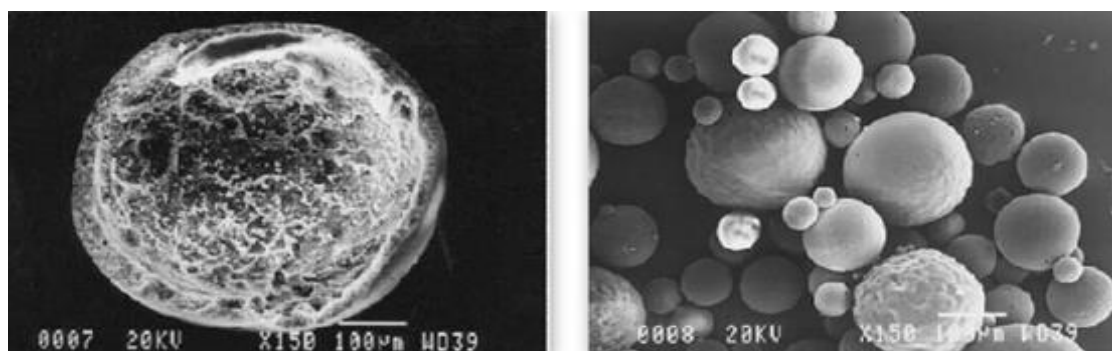


Figure 4: Scanning Electron Microscopy

### Drug Loading and Entrapment Efficiency

Percent Entrapment Efficiency of the formulations was found to be within the range between 68.0 to 85.0%. The maximum percentage yield was found of F5 batch and was noted to be 85.4 % among all the batches. The percentage entrapment efficiency is shown in Table 2& Fig 5.

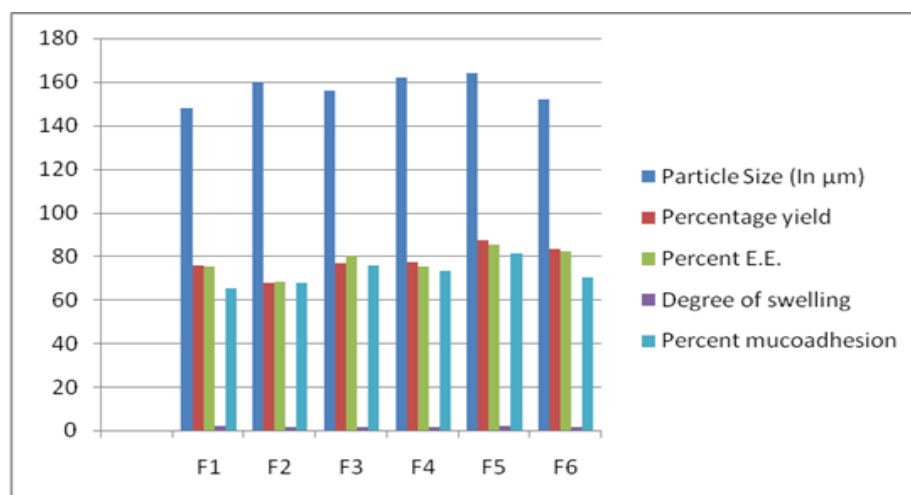
### In vitro Mucoadhesion Study

Prepared microspheres were found good mucoadhesion strength. Percent mucoadhesion of the all batches of microspheres were found to be in the range of 65.0 to

81.42%. On increasing the polymer concentration, the bioadhesive property of the microspheres also increased as shown in Fig. 5. Increase in polymer concentration was attributed to increase in viscosity; produce stronger mucus gel network which helps to increase mucoadhesion<sup>21</sup>. The percentage mucoadhesion of microspheres adhering to tissue after 60 min. is displayed in Table 2. The F5 batch showed highest % mucoadhesion which was attributed to increase in concentration of polymers.

Table 2: Physicochemical Properties and Characterization of Budesonide Mucoadhesive Microspheres

Formulation code	Particle Size (in $\mu\text{m}$ )	Percentage yield (in %)	Entrapment Efficiency (in %)	Degree of swelling	Percent mucoadhesion (in %)
F1	148	75.82	75.2	1.82	65.0
F2	160	67.52	68.6	1.73	67.71
F3	156	76.64	80.3	1.38	75.71
F4	162	77.17	75.6	1.55	73.42
F5	164	87.25	85.4	1.85	81.42
F6	152	83.37	82.5	1.36	70.0



**Figure 5: Graphical representation of Physicochemical Properties and Characterization of Budesonide Mucoadhesive Microspheres**

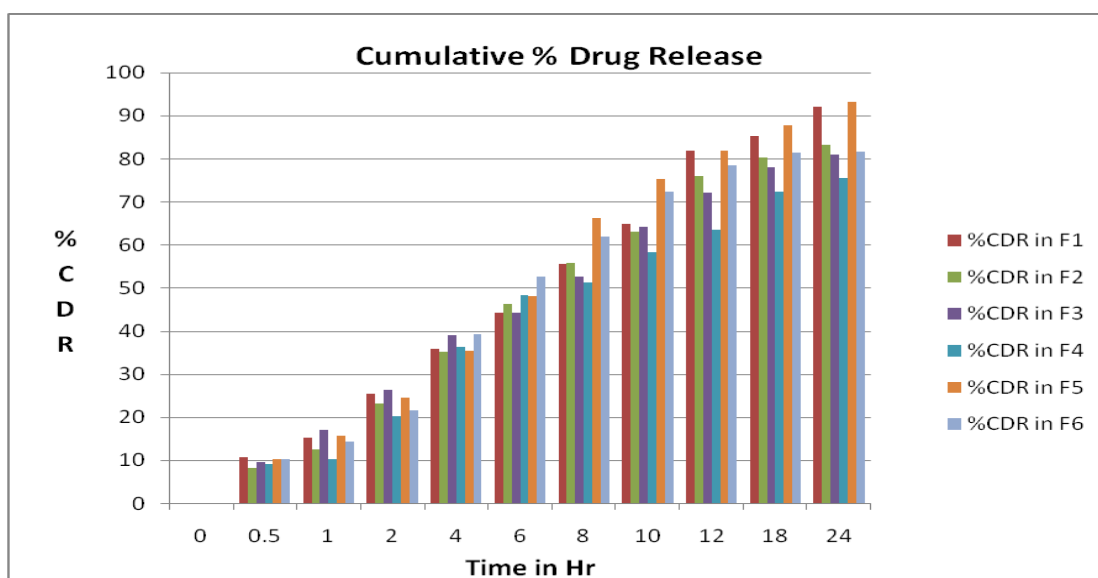
#### *In vitro* dissolution study

The drug release from budesonide microsphere was carried out in pH 6.8 buffers as a dissolution medium for a period of 24 hrs respectively. The *in-vitro* budesonide release profile for all batches was shown in Fig. 6. Drug release from these mucoadhesive microspheres were slow, controlled release and dependent upon the nature and concentration of mucoadhesive polymers used<sup>22,23</sup>. It was found that there

was decrease in budesonide release with increase in mucoadhesive polymer content. Hence it is considered as the best microsphere formulation which seems to be a good candidate for controlled release. The microspheres were subjected to *in-vitro* drug release rate by dissolution profiles are shown in Table 3. In vitro drug release study confirms that the formulation F5 was the best formulation as it releases 81.8 % at the end of 12 hr. in controlled manner

**Table 3: *In vitro* release of Mucoadhesive microspheres in media**

Time(hr)	%CDR in F1	%CDR in F2	%CDR in F3	%CDR in F4	%CDR in F5	%CDR in F6
0	0	0	0	0	0	0
0.5	10.7	8.2	9.6	9.1	10.2	10.3
1.0	15.2	12.5	17.1	10.2	15.6	14.3
2.0	25.5	23.2	26.3	20.2	24.6	21.6
4.0	35.9	35.1	39	36.2	35.3	39.3
6.0	44.3	46.3	44.3	48.3	48.1	52.6
8.0	55.5	55.8	52.5	51.2	66.2	61.9
10.00	64.82	73.3	72.2	74.7	75.2	72.3
12.00	81.8	76	75.3	63.6	81.8	78.4
18.00	85.3	80.2	78	72.3	87.7	81.3
24.00	92.07	83.2	81	75.5	93.2	81.6



**Figure 6: *In vitro* release of Mucoadhesive microspheres**



## CONCLUSION

In the present study, a satisfactory attempt has been made to formulate mucoadhesive microspheres of budesonide for pulmonary drug delivery. Budesonide undergoes extensive hepatic metabolism. Hence mucoadhesive microspheres were developed to enhance the bioavailability and to prepare sustain microspheres having slow release in gastrointestinal tract. Microsphere formulation of budesonide was prepared by using emulsion solvent evaporation method. From the experimental study, it was concluded that *in vitro* drug release and mucoadhesion study confirms that formulation F5 was the best formulation as it releases 81.8 % at the end of 12 hr. in controlled manner and percentage mucoadhesion of 75.2 % after 10 hr. *In vitro* release of mucoadhesive microspheres of budesonide was found to be in sustained manner and is dependent on the concentration of polymer used. It was found that there was decrease in budesonide release with increase in mucoadhesive polymer content and increased bioadhesive property of the microspheres with increasing the polymer concentration. Hence, it was concluded that the prepared mucoadhesive microspheres of budesonide prove to be potential system for safe and effective sustained release over an extended period of time for pulmonary drug delivery. In future the research can be extended to *in-vivo* studies to prove the increased bioavailability statistically.

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## Conflict of Interest

There is no conflict of interest.

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