

NANOPARTICLE: AS TARGETED DRUG DELIVERY SYSTEM FOR DEPRESSION

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ABSTRACT

Nanoparticles (NP) are defined as particles with a diameter smaller than 100 nm, are increasingly used in different applications, including drug carrier systems and to pass organ barriers such as the blood-brain barrier. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamics properties of various types of drug molecules. Different methods containing various polymers are used for the formulation of the nanoparticle to increase the therapeutic benefit, while minimizing side effect for drug delivery research. While benefits of nanotechnology are widely publicized, the discussion of the potential effects of their widespread use in the consumer and industrial products are just beginning to emerge. This review provides a comprehensive analysis of data available on health effects of nanomaterial's.

Keywords: Nanoparticles, Blood-brain barrier, Polymer

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INTRODUCTION [1, 2, 6]

Depression is a bipolar disorder characterized by a state of low mood and aversion to activity caused by low level of monoamines in the brain that can affect a person's thoughts, behavior, feelings and sense of well-being. About estimated 19 million American adult people suffer from depression. Depression is more than simply feeling unhappy or fed up for a few days. Depressed mood is a feature of some psychiatric syndromes such as major depressive disorder, but it may also be a normal reaction to life events such as grief, a symptom of some bodily ailments or a side effect of some drugs and medical treatments. Tricyclic antidepressants (TCAs), Monoamine oxidase inhibitors (MAOIs) Selective serotonin reuptake inhibitors (SSRIs), Serotonin and norepinephrine reuptake inhibitors (SNRIs) are the medications to depression. These drugs improve symptoms of depression by increasing the availability of certain brain chemicals called neurotransmitters. It is believed that these brain chemicals can help regulate brain circuits that affect emotions [11]. A major National Institute of Mental Health study showed that fewer than 50 percent of people become symptom-free on antidepressants, even after trying two different medications. Furthermore, many who do respond to medication soon slip back into depression, despite sticking with drug treatment.

Nanotechnologies are beginning to change these scientific landscapes in terms of disease diagnosis, treatment. The development of a wide spectrum of nanoscale, and prevention. Nanoparticles, sized approximately between 1 and 100 nanometers, have in some circumstances the ability to pass through many biological obstacles, such as a blood-brain barrier. Many nanoparticles have a large surface area which enables them to be an integral part of effective drug delivery systems. Nanoparticles for drug delivery to the brain is a method for transporting drug molecules across the blood-brain barrier (BBB) using nanoparticles. These technological innovations, referred to as nanomedicines by the National Institutes of Health, have the potential to turn molecular discoveries arising from genomics and proteomics into a widespread benefit for patients. These drugs cross the BBB and deliver pharmaceuticals to the brain for therapeutic treatment of depressive disorders. Part of the difficulty in finding cures for this central nervous system (CNS) disorders.[11] These disorders include Parkinson's disease, Alzheimer's disease, schizophrenia, depression, and brain tumors there is not yet a truly efficient delivery method for drugs to cross the BBB. With the aid of nanoparticle delivery systems, however, studies have shown that certain drugs can now cross the BBB, and even exhibit lower toxicity

and decrease adverse effects throughout the body. Now a day's nanoparticle can be applied as potentially very effective markers of pathological brain tissue, as well as drug carriers. Anti-depressive medications are potential candidates for monotherapy. Most of the disorders today treated with antipsychotic and/or antidepressive medication are a potential candidate for nanotherapy.

Types of nanoparticles for CNS drug delivery [5, 6, 11]

1) Lipid-based nanoparticles

Hydrophilic head, Hydrophobic tail Aqueous Solution

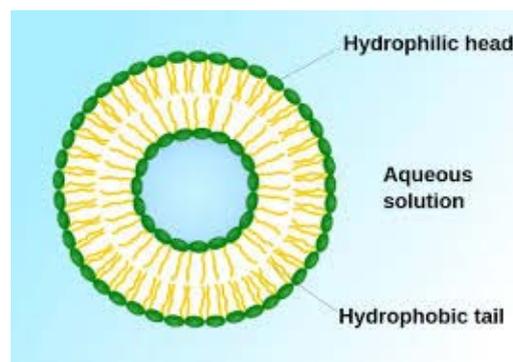


Fig. 1: Lipid-based nanoparticle

Diagram of liposome showing a phospholipid bilayer surrounding an aqueous interior.

One particular type of nanoparticle involves the use of liposomes as drug molecule carriers. The diagram on the right shows a standard liposome. It has a phospholipid bilayer separating the interior from the exterior of the cell. Liposomes are composed of vesicular bilayers, lamellae, made of biocompatible and biodegradable lipids such as sphingomyelin, phosphatidylcholine, and glycerol-phospholipids [6]. Cholesterol, a particular type of lipid, is also often incorporated in the lipid nanoparticle formulation. Cholesterol can increase the stability of the liposome as well as prevent leakage of the bilayer because its hydroxyl group is able to interact with the polar heads of the bilayer phospholipids.

Cationic liposomes

Another type of lipid-nanoparticle that can be used for drug delivery to the brain is a cationic liposome. Cationic liposomes are lipid molecules that are positively charged [6]. One example of cationic liposomes uses bola amphiphiles, which contain hydrophilic groups surrounding a hydrophobic chain to strengthen the boundary of the nano-vesicle containing the drug. Bolaamphiphile nano-vesicles can cross the BBB, and they allow controlled release of the drug to target sites.[5] Lipoplexes can also be formed from cationic liposomes and DNA solutions, to yield transfection agents.[6] Cationic liposome cross the BBB through adsorptive-mediated endocytosis followed by internalization in the endosomes of the endothelial cells. By transfection of endothelial cells through the use of lipoplexes, physical alterations in the cells could be made. These physical changes could potentially improve how certain nanoparticle drug carriers cross the BBB.

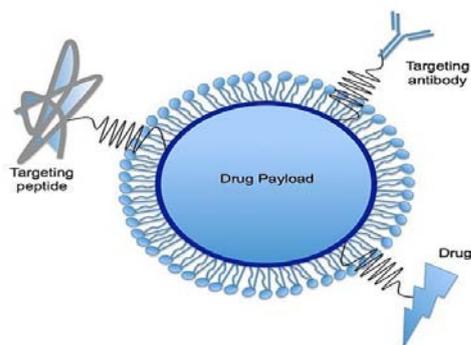


Fig. 2: Solid lipid nanoparticle

3) Solid lipid nanoparticles

Above Diagram displays a solid lipid nanoparticle (SLN). There is only one phospholipid layer because the interior of the particle is solid. Molecules such as antibodies, targeting peptides, and drug molecules can be bound to the surface of the SLN.

Solid lipid nanoparticles (SLNs) are lipid nanoparticles with a solid interior as shown in the diagram on the right. SLNs can be made by replacing the liquid lipid oil used in the emulsion process with a solid lipid. In solid lipid nanoparticles, the drug molecules are dissolved in the particle's solid hydrophobic lipid core, this is called the drug payload, and it is surrounded by an aqueous solution [6] Many SLNs are developed from triglycerides, fatty acids, and waxes. High-pressure homogenization or micro-emulsification can be used for manufacturing. In addition, functionalizing the surface of solid lipid nanoparticles with polyethylene glycol (PEG) can result in increased BBB permeability.

4) Nano emulsions

Another form for nanoparticle delivery systems is oil-in-water emulsions done on a nanoscale [9].

This process uses common biocompatible oils such as triglycerides and fatty acids and combines them with water and surface coating surfactants. Oils rich in omega-3 fatty acids, particularly, contain important factors that aid in penetrating the tight junctions of the BBB [9].

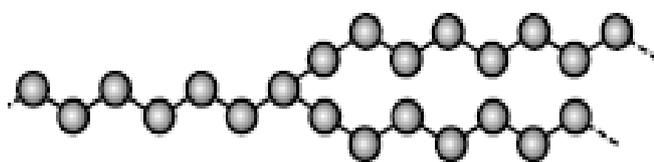


Fig. 3: Polymer-based nanoparticle

5) Polymer-based nanoparticles

Other nanoparticles are polymer-based, meaning they are made from a natural polymer such as polylactic acid (PLA), poly D, L-glycolide (PLG), polylactide-co-glycolide (PLGA), and poly cyanoacrylate (PCA). Some studies have found that polymeric nanoparticles may actually provide better results for drug delivery compared with lipid-based nanoparticles because they may increase the stability of the drugs or proteins being transported. Polymeric nanoparticles may also contain beneficial control release mechanisms.

Polymer branch

Nanoparticles made from natural polymers that are biodegradable have the ability to target specific organs and tissues in the body. They also have the ability to carry DNA for gene therapy, and they have the ability to deliver larger molecules such as proteins, peptides, and even genes. In order to manufacture these polymeric nanoparticles, the drug molecules are first dissolved and then encapsulated or attached to a polymer nanoparticle matrix. Three different structures can then be obtained from this process; nanoparticles, nanocapsules (in which the drug is encapsulated and surrounded by the polymer matrix), and nanospheres (in which the drug is dispersed throughout the polymeric matrix in a spherical form). One of the most important characteristics of nanoparticle delivery systems is that they must be biodegradable on the scale of a few days. A few common polymer materials used for drug delivery studies are poly butyl cyanoacrylate (PBCA), poly (isohexyl cyanoacrylate) (PIHCA), polylactic acid (PLA), or polylactide-co-glycolide (PLGA). Human serum albumin (HSA) and chitosan are also materials of interest. PBCA undergoes degradation through enzymatic cleavage of its ester bond on the alkyl side chain to produce water-soluble byproducts.

PBCA also proves to be the fastest biodegradable material, with studies showing 80% reduction after 24 h post intravenous injection. PIHCA, however, was recently found to display an even lower degradation rate, which in turn further decreases toxicity. PIHCA, due to this slight advantage, is currently undergoing phase III clinical trials for transporting the drug doxorubicin as a treatment for hepatocellular carcinomas. Coating these polymeric nanoparticle devices with different surfactants can also aid BBB crossing and uptake in the brain. Surfactants such as Polysorbate 80, 20, 40, and 60, as well as polaxamer 188, demonstrated positive drug delivery through the blood-brain barrier, whereas other surfactants did not yield the same results. It has also been shown that functionalizing the surface of nanoparticles with polyethylene glycol (PEG), can induce the "stealth effect", allowing the drug-loaded nanoparticle to circulate throughout the body for prolonged periods of time. In addition, the "stealth effect", caused in part by the hydrophilic and flexible properties of the PEG chains, facilitates an increase in localization of the drug target sites in tissue and organ.

Methods of preparation [4, 11]

- 1) Emulsion-Solvent Evaporation Method
- 2) Double Emulsion and Evaporation Method:
- 3) Salting Out Method:
- 4) Emulsions-Diffusion Method:
- 5) Solvent Displacement/Precipitation method

Emulsion-solvent evaporation method

This is one of the most frequently used methods. Emulsification-solvent evaporation involves two steps.1) The first step requires emulsification of the polymer solution into an aqueous phase. 2) Second step polymer solvent is evaporated, inducing polymer precipitation as nanospheres. The nanoparticles are collected by ultracentrifugation and washed with distilled water to remove stabilizer residue or any free drug and lyophilized for storage.

Modification of this method is known as high-pressure emulsification and solvent evaporation method. This method involves preparation of an emulsion which is then subjected to homogenization under high pressure followed by overall stirring to

remove organic solvent. The size can be controlled by adjusting the stirring rate, type and amount of dispersing agent, the viscosity of organic and aqueous phases and temperature. However this method can be applied to liposoluble drugs, and limitation are imposed by the scale-up issue. Polymers used in this method are PLA, PLGA.

Double emulsion and evaporation method

The emulsion and evaporation method have some limitation of poor entrapment of hydrophilic drugs. Therefore to encapsulate hydrophilic drug the double emulsion technique is employed, which involves the addition of aqueous drug solutions to organic polymer solution under vigorous stirring to form w/o emulsions. This w/o emulsion is added into second aqueous phase with continuous stirring to form the w/o/w emulsion. The emulsion then subjected to solvent removal by evaporation and nanoparticles can be isolated by centrifugation at high speed. The formed nanoparticles must be thoroughly washed before lyophilisation.

Salting out method

This method is based on the separation of a water-miscible solvent from aqueous solution via a salting-out effect. It is based on the separation of a water miscible solvent from aqueous solution via a salting-out effect. Polymer and drug are initially dissolved in a solvent which is subsequently emulsified into an aqueous gel containing the salting out an agent (electrolytes, such as magnesium chloride and calcium chloride, or non-electrolytes such as sucrose) and a colloidal stabilizer such as polyvinylpyrrolidone or hydroxyethylcellulose. This oil/water emulsion is diluted with a sufficient volume of water or aqueous solution to enhance the diffusion of solvent into the aqueous phase, thus inducing the formation of nanospheres. Several manufacturing parameters can be varied including stirring rate, internal/external phase ratio, the concentration of polymers in the organic phase, type of electrolyte concentration and type of stabilizer in the aqueous phase. This technique used in the preparation of PLA, Poly (methacrylic) acids, and Ethyl cellulose Nano spheres leads to high efficiency and is easily scaled up. Salting out does not require an increase of temperature and therefore may be useful when heat sensitive substances have to be processed.

Emulsions-diffusion method

This is another widely used method to prepare nanoparticles. The encapsulating polymer is dissolved in a partially water-miscible solvent (such as propylene carbonate, benzyl alcohol), and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. Subsequently, the polymer-water saturated solvent phase is emulsified in an aqueous solution containing a stabilizer, leading to solvent diffusion to the external phase and the formation of nanospheres or nanocapsules, according to the oil-to-polymer ratio. Finally, the solvent is eliminated by evaporation or filtration, according to its boiling point. This technique presents several advantages, such as high encapsulation efficiencies (generally 70%), no need for homogenization, high batch-to-batch reproducibility, ease of scale-up, simplicity, and narrow size distribution. Disadvantages are the high volumes of water to be eliminated from the suspension and the leakage of the water-soluble drug into the saturated aqueous external phase during emulsification, reducing encapsulation efficiency.

Solvent displacement/precipitation method

Solvent displacement involves the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium in the presence or absence of surfactant. Polymers, drug, and or lipophilic surfactant are dissolved in a semipolar water-miscible solvent such as acetone or ethanol. The solution is then poured or injected into an aqueous solution containing stabilizer under magnetic stirring. Nanoparticles are formed instantaneously by the rapid solvent diffusion. Journal of Applied Pharmaceutical Science 01 (06); 2011: 228-234 the solvent is then removed from the suspensions under reduced pressure. The rates of addition of the organic phase into the aqueous phase affect the particles size. It was observed that a decrease in both particles size and drug entrapment occurs as the rate of mixing of the two-

phase increases. Nanoprecipitation method is well suited for most of the poorly soluble drugs. Nanosphere size, drug release, and yield were shown to be effectively controlled by adjusting preparation parameters. Adjusting polymer concentration in the organic phase was found to be useful in the production of smaller sized nanospheres through restricted to a limited range of the polymer to drug ratio.

Nanoparticle characterization [1, 4]

Nanoparticles are generally characterized by their size, morphology and surface charge, using such advanced microscopic techniques as scanning electron microscopy (SEM), transmission electron microscopy (TEM) and atomic force microscopy (AFM). The average particle diameter, their size distribution, and charge affect the physical stability and the *in vivo* distribution of the nanoparticles. Electron microscopy techniques are very useful in ascertaining the overall shape of polymeric nanoparticles, which may determine their toxicity. The surface charge of the nanoparticles affects the physical stability and dispersibility of the polymer dispersion as well as their *in vivo* performance

Particle size

Particle size distribution and morphology are the most important parameters of characterization of nanoparticles. Morphology and size are measured by electron microscopy. The major application of nanoparticles is in drug release and drug targeting. It has been found that particle size affects the drug release. Smaller particles offer larger surface area. As a result, most of the drug loaded onto them will be exposed to the particle surface leading to fast drug release. On the contrary, drugs slowly diffuse inside larger particles. As a drawback, smaller particles tend to aggregate during storage and transportation of nanoparticle dispersion. Hence, there is a compromise between a small size and maximum stability of nanoparticles. Polymer degradation can also be affected by the particle size. For instance, the degradation rate of poly (lactic-co-glycolic acid) was found to increase with increasing particle size *in vitro*. There are several tools for determining nanoparticle size as discussed below.

Dynamic light scattering (DLS)

Currently, the fastest and most popular method of determining particle size is photon correlation spectroscopy (PCS) or dynamic light scattering (DLS). DLS is widely used to determine the size of Brownian nanoparticles in colloidal suspensions in the nano and submicron ranges. Shining monochromatic light (laser) onto a solution of spherical particles in Brownian motion causes a Doppler shift when the light hits the moving particle, changing the wavelength of the incoming light. This change is related to the size of the particle. It is possible to extract the size distribution and give a description of the particle's motion in the medium, measuring the diffusion coefficient of the particle and using the autocorrelation function. The photon correlation spectroscopy (PCS) represent the most frequently used technique for accurate estimation of the particle size and size distribution based on DLS.

Scanning electron microscopy

Scanning electron microscopy (SEM) is giving morphological examination with direct visualization. The techniques based on electron microscopy offer several advantages in the morphological and sizing analysis; however, they provide limited information about the size distribution and true population average. For SEM characterization, nanoparticles solution should be first converted into a dry powder, which is then mounted on a sample holder followed by coating with a conductive metal, such as gold, using a sputter coater. The sample is then scanned with a finely focused beam of electrons. The surface characteristics of the sample are obtained from the secondary electrons emitted from the sample surface. The nanoparticles must be able to withstand vacuum, and the electron beam can damage the polymer. The mean size obtained by SEM is comparable with results obtained by dynamic light scattering.

Moreover, these techniques are time-consuming, costly and frequently need complementary information about sizing distribution.

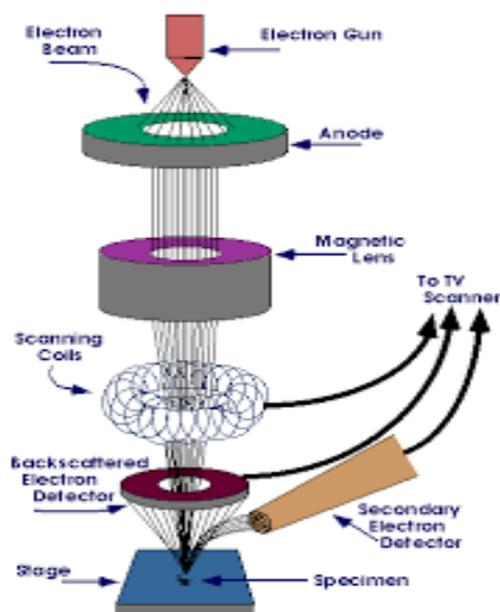


Fig. 4: Scanning electron microscopy

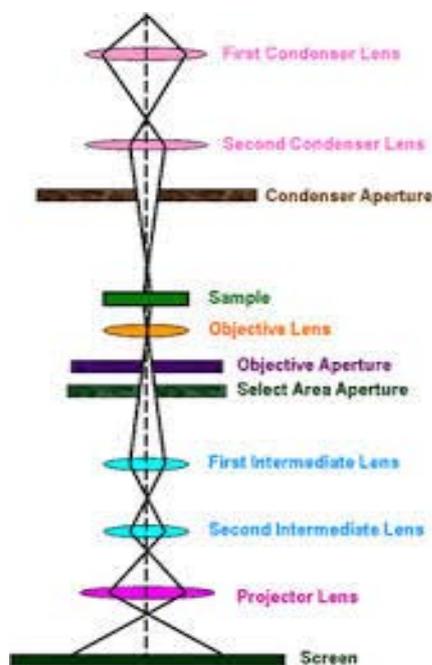


Fig. 5: Transmission electron microscope

Transmission electron microscope

TEM operates on a different principle than SEM, yet it often brings the same type of data. The sample preparation for TEM is complex and time-consuming because of its requirement to be ultra thin for the electron transmittance. The nanoparticles dispersion is deposited onto support grids or films. To make nanoparticles withstand the instrument vacuum and facilitate handling, they are fixed using either a negative staining material, such as phosphotungstic acid or derivatives, uranyl acetate, etc, or by plastic embedding.

An alternate method is to expose the sample to liquid nitrogen temperatures after embedding in vitreous ice. The surface characteristics of the sample are obtained when a beam of electrons

is transmitted through an ultra thin sample, interacting with the sample as it passes through.

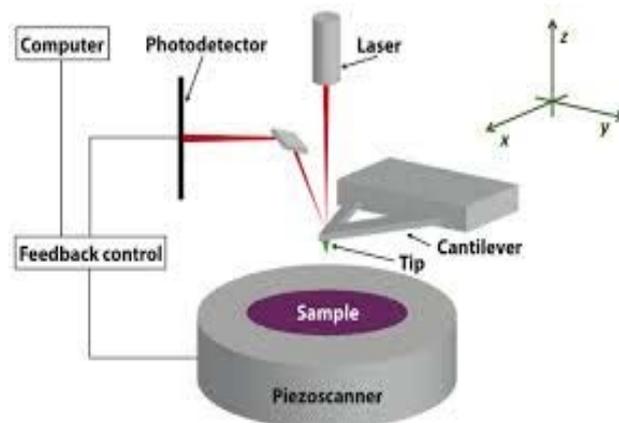


Fig. 6: Atomic force microscopy

Atomic force microscopy

Atomic force microscopy (AFM) offers a ultra-high resolution in particle size measurement and is based on a physical scanning of samples at sub-micron level using a probe tip of atomic scale. The instrument provides a topographical map of the sample based on forces between the tip and the sample surface. Samples are usually scanned in contact or non-contact mode depending on their properties. In contact mode, the topographical map is generated by tapping the probe on to the surface across the sample and probe hovers over the conducting surface in non-contact mode. The prime advantage of AFM is its ability to image non-conducting samples without any specific treatment, thus allowing imaging of delicate biological and polymeric nano and microstructures. AFM provides the most accurate description of size and size distribution and requires no mathematical treatment. Moreover, particle size obtained by AFM technique provides a real picture which helps understand the effect of various biological conditions. Surface Charge: The nature and intensity of the surface charge of nanoparticles is very important as it determines their interaction with the biological environment as well as their electrostatic interaction with bioactive compounds. The colloidal stability is analyzed through zeta potential of nanoparticles. This potential is an indirect measure of the surface charge. It corresponds to the potential difference between the outer Helmholtz plane and the surface of shear. The measurement of the zeta potential allows for predictions about the storage stability of the colloidal dispersion. High zeta potential values, either positive or negative, should be achieved in order to ensure stability and avoid aggregation of the particles. The extent of surface hydrophobicity can then be predicted from the values of zeta potential. The zeta potential can also provide information regarding the nature of material encapsulated within the nanocapsules or coated onto the surface. Surface hydrophobicity: Surface hydrophobicity can be determined by several techniques such as hydrophobic interaction chromatography, biphasic partitioning, adsorption of probes, contact angle measurements, etc. Recently, several sophisticated analytical techniques are reported in the literature for surface analysis of nanoparticles. X-ray photon correlation spectroscopy permits the identification of specific chemical groups on the surface of the nanoparticle.

Advantages of nanoparticle for brain targeting [3]

Advantages of Nanoparticles have several potential advantages over other carrier-mediated drug delivery system.

- 1) Targeting ability of drugs to particular organ or tissue.
- 2) The increase in bioavailability.

- 3) Development of new formulation which is safer.
- 4) Ability to sustained release of drugs.
- 5) High carrier capacity.
- 6) Prolonged circulation time.
- 7) Stable in blood.
- 8) Acquiescent to small molecules, peptides, proteins, or nucleic acids

Disadvantages [5]

- 1) Increase in cost of formulation due to high manufacturing costs, which can be optimized property
- 2) May cause allergic reactions.
- 3) Overuse of polyvinyl alcohol as a stabilizer may have a toxic reaction.

CONCLUSION

Nanoparticles contribute to stronger, lighter, cleaner and “smarter” surfaces and system for brain targeting due to its immense application in the treatment of various CNS diseases because mostly drugs are unable to cross the Blood brain barrier. Nanoparticles have been used extensively for applications in drug discovery, drug delivery, diagnostics and for many others in the medical field. This short review explains that has been developed to target the brain and possess various clinical benefits such as reduced drug dose, less side effects, non-invasive routes, and better delivery of the drug.

CONFLICT OF INTERESTS

Declare none

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