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Floating Drug Delivery Systems: A Review

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ABSTRACT

Purpose of writing this review on floating drug delivery system was to focus on the principle mechanism of floatation to achieve gastric retention. Technological attempts have been made in the research and development of rate controlled oral drug delivery system to overcome physiological adversities, such as short gastric residence time (GRT) and unpredictable gastric emptying times. It is new drug delivery system maximize effectiveness and compliance. This review summarizes advantages of floating drug delivery system approaches to design single unit and multiple unit floating system, in-vitro and in-vivo technology to evaluate the performance of floating system. At attempt has been made in this review article to introduce the readers to current development in floating drug delivery system.

KEYWORDS

Floating drug delivery systems, its classification and application.

INTRODUCTION

The aim of drug delivery system is to afford a therapeutic amount of drug to the proper site in the body to attain promptly and than maintain desired drug concentration.

Oral administration is most versatile, convenient and most promising route of drug delivery. In needed, for controlled release system, oral route of administration has received more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other.

In oral drug delivery system not all drug (or) therapeutic agent are absorbed uniformly throughout the (GIT) since many drug are well absorbed in upper part of GIT, such high variability may lead to non-uniform absorption and makes the bioavailability unpredicted.[1] Hence, a beneficial delivery system would be one which posses' ability to control and prolonged the gastric emptying time and can deliver drug in higher concentration to the absorption site.[2] The identification of new diseases and resistance shown towards the existing drug caused introduction of new therapeutic molecules. in response, a large number of chemical entities have been introduced, of which some have absorption all over GIT, some have absorption windows some have poor solubility in intestinal media. The entire above requirement can be met and effective drug delivery to absorption window can be achieved by floating drug delivery system.[3]

In recent year scientific and technology and advancement have been made in research and development of rate controlled drug delivery system by overcoming physiological diversities, such as gastric residential time (GRT) and unpredictable gastric emptying time- several approaches currently utilized in prolongation of (GRT), including floating drug delivery system also known as hydrodynamic ally balanced system (HBS) swelling and expanding systems polymeric bioadhesion system, and high density system.[4,5]

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Conventional release drug delivery system do not overcome adversities such as gastric residence time (GRT) and gastric emptying time (GET). One approach to overcome the adversities of (GRT) and (GET) is the floating system also known as hydro dynamically balanced system (HBS).[6]

Advantages

Improved selectively in receptor activation.[7]

1. Administration of prolonged release floating dosage from tablet will result in dissolution of drug in gastric fluid after emptying of the stomach content, the dissolve drug available for absorption in small intestine. It is therefore expected that the drug will be fully absorbed from the floating dosage form if it remain solution form even at alkaline P_H of intestine.
2. Lower dosing and less side effects.
3. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
4. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
5. The main advantage of HBS is it can be used for any class of medicament.
6. Beneficial in treatment of gastric disease. The efficacy of medicaments which are administered using sustain release principal of HBS has been found to be independent of site of absorption of particular medicament.
7. The gastro retentive system is advantageous for drug that is specifically absorbed through stomach example: ferrous salt, antacids.
8. Some acidic substance like aspirin when they come in contact with stomach cause irritation. As it hence HBS formulation may be useful for administration of such drug (aspirin).
9. The efficacy of medicament administered utilizing sustained release principal of floating formulation has been found to be independent of site of particular medicaments.

Disadvantages

1. For swelling system, it is necessary that the formulation should not exist before appropriate swelling.
2. For floating high level of fluid is required in GIT.
3. It is not recommended for drug which are unstable at acidic/gastric PH, in soluble (or) very low soluble drugs and which causes gastric irritation.
4. The drugs that undergo first pass metabolism are not desirable.

Factor Affecting Floating Drug Delivery System[8]

- Absorption: Drug that have poor bioavailability because of site specific absorption from the upper part of gastrointestinal tract are potential candidates to be formulated as floating drug delivery system.
- Density: the density of a dosage form also effects gastric emptying rate. A buoyant dosage form having a density less than that of gastric fluid floats. Density of dosage form should be less than gastric fluids.
- Size: size of dosage form is another factor which effect gastric retention. In most case, larger the size of dosage form, the greater will be retention time became the larger size would not allow the dosage form to pass quickly through pyloric atrium in to the intestine.
- Food intake and nature of food: nature of food and frequency of feeding effects gastric retention of dosage form. Presence of food in stomach usually increases GRT of dosage form and increase drug absorption by

allowing it to stay at site of absorption for long time.

- Effect of gender: Mean ambulatory GRT is comparatively shorter in women than in men. Gastric emptying in slow in women than in man.
- Caloric content: GRT can be increased with meal that is higher in protein and fat.
- Age: elder people (70 above) have longer GRT.

Approaches to Design Floating Dosage Forms

The following approaches have been used for the design of floating dosage forms of single- and multiple unit systems.

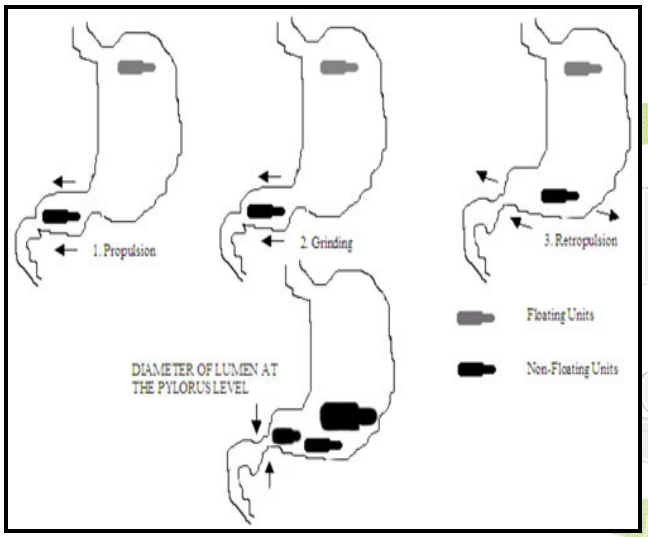

Figure 1: Intragastric Residence Positions of Floating and Non floating Units.

Single Unit Dosage Forms

In Low-density approach the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells24 popcorn, pop rice, and polystyrol have been exploited as drug carriers.[9] Sugar polymeric materials such as methacrylic polymer and Cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethyl cellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid-filled floating chamber25 type of dosage forms includes Incorporation of a gas-filled floatation chamber into a micro porous component that houses a drug reservoir.[10] Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behavior. The device is of swallow able size, remains afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated. Hydro dynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in Acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. The success of HBS capsule as a better system is best exemplified with chlordiazeopoxide hydrochloride. The drug is a classical example of a solubility problem wherein it exhibits a 4000-fold difference in solubility going from pH 3 to 6 (the solubility of chlordiazepoxide hydrochloride is 150 mg/ml and is ~0.1 mg/ml at neutral pH). HBS of chlordiazeopoxide hydrochloride26 had comparable blood level time profile as of three 10-mg commercial capsules.[11]

HBS can either be formulated as a floating tablet or capsule. Many polymers and polymer combinations with wet granulation as a manufacturing technique have been explored to yield floatable tablets.

Multiple Unit Dosage Forms

The purpose of designing multiple unit dosage form is to develop a reliable formulation that has devoid of many of disadvantage of single unit formulation. Multiple unit floating delivery system is developed to overcome drawback of high variability of gastrointestinal tract time, when orally administrated became of their all (or) nothing gastric emptying nature. This multiple unit floating delivery system reduce inter subject variability in absorption and lower the probability of dose dumping.[12]

Floating Drug Delivery Systems and Its Mechanism

Floating drug delivery systems (FDDS) have bulk density lesser than gastric fluids, so they remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system as shown in fig. 2(a). However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side as shown in fig. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.[13]

F = F buoyancy – F gravity

= (Df – Ds) gv--- (1)

Where, F= total vertical force, Df = fluid density,

Ds= object density, v = volume and g = acceleration due to gravity.

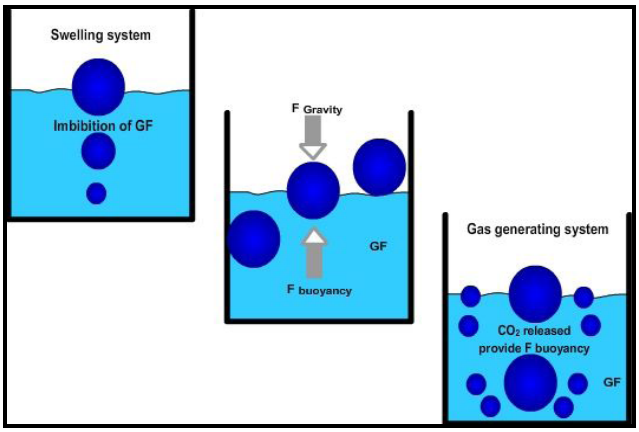

Figure 2 (A): Mechanism of Floating Systems, GF= Gastric Fluid

Classification of Floating Drug Delivery Systems (FDDS)

(A) Effervescent FDDS

(I) Gas generating system (II) volatile liquid containing system

(B) Non- Effervescent FDDS
(I) Colloidal gel barrier system
(II) Microporous compartment system
(III) floating microsphere
(IV) Alginate floating beads.

(C) Raft forming system

(A) Effervescent System FDDS

These are matrix type of system. Prepared with the help of swellable polymer such as methylcellulose and Chitosan and various effervescent compounds.

Ex: sodium bicarbonate, tartaric acid, citric acid.

These are formulated in such a way that when they come in contact with gastric content, co_2 is liberated and gets entrapped in swollen hydrocolloid which provides buoyancy to dosage form. The design of delivery system was based on swellable asymmetric triple layer tablet approach.[14]

(I) Gas Generating Systems

These are low density FDDS is based on the formation of co_2 within the device following contact with body fluids. The materials are fabricated so that upon arrival In stomach, co_2

is librated by acidity of the gastric content and is entrapped in the gellified hydrocolloid this produce upward motion of the dosage form and maintain its buoyancy. Decrease in specific gravity cause dosage form to float on the chyme .the co_2 generating components may be intimately mixed within the tablet matrix in which case a single layer or bilayered is produced which contain the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for a sustained release effect.[15,16,17]

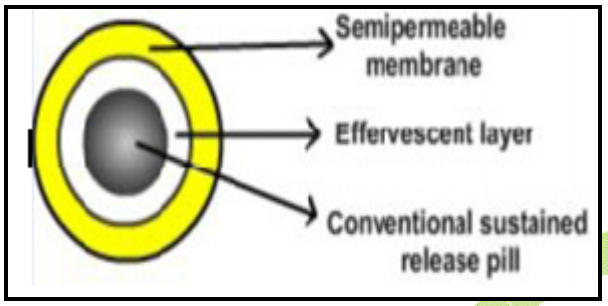

Figure 3 (A): Different layers

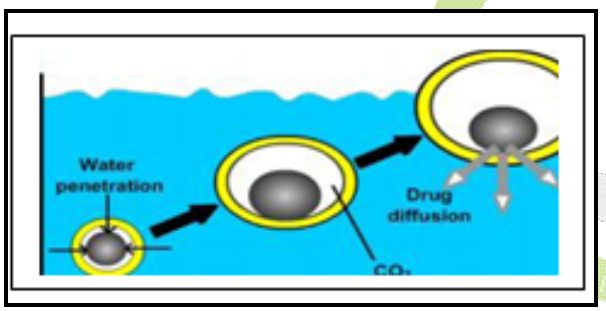

Figure 3(B): Mechanism of floatation via CO2 liberation

(II) Volatile Liquid Containing Systems (Osmotically Controlled DDS)

As an osmotically controlled floating system, the device comprised of a hallow deformable unit that was convertible from a collapsed position after an extended period of time. A housing was attached to the deformable unit and it was internally divided into a first and second chamber with the chambers separated by an impermeable, pressure responsive movable bladder. The first chamber contain an active drug , while the second chamber contain a volatile liquid, such as cyclopentane or ether that vaporises at physiological temperature to produce a gas, enabling the drug reservoir to float. To enable the unit to exit form the stomach, the device contained a bioerodible plug that allowed the vapour to escape.[18]

(B) Non-Effervescent FDDS

Non-Effervescent FDDS use a gel forming (or) swellable cellulose type of hydrocolloids, polysaccharide, matrix forming polymer like polycarbonate, polymethacrylate and polystyrene. One of the formulation method involves the mixing of the drug with gel forming hydrocolloid which swell in contact with gastric fluid after oral administration and maintains integrity of shape and a bulk density barrier, the air trapped by swollen polymer confer buoyancy to the dosage forms.[19]

(I) Colloidal Gel Barrier Systems (Hydrodynamic Balanced Systems)

Such system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption site in the solution form for ready absorption, this system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid e.g.(HPMC),polysaccharides and matrix-forming polymer such as polycarbophil, polystyrene and polyacrylate. On coming in the contact with GI fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.[20]

(II) Microporous Compartment Systems

This technology is based on the encapsulation of a drug reservoir inside a Microporous compartment with pores along its top and bottom walls. The peripheral wall of the drug reservoir compartment is completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the gastric fluid to an extent that it prevents their exist from the drug and carrier the dissolved

drug for continuous transport across the intestine for absorption.[21]

(III) Floating Microspheres / Micro balloons

Hallow microspheres are considerest as most promising buoyant system as they are more advantageous because of central hallow space inside the microsphere. Hallow microsphere is loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method.[22]

(IV) Alginate Beads / Floating Beads

Multi-unit floating dosage forms have been developed from freeze calcium alginate[23]. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride. Causing the precipitation of calcium alginate. The beads are than separated, snap-frozen in liquid nitrogen and freeze-dried at 40^0C for 24 h, leading to the formation of a porous system, which can maintain a floating force for over 12 h. these floating beads gave a prolonged residence time of more than 5.5 h.

(C) Raft forming systems

Raft forming system have received much attention for the delivery of antacid and drug delivery for gastro infection and disorders on contact with gastric fluid a gel forming solution swells and forms a viscous cohesive gel containing entrapped co_2 bubbles. Which forms raft layer on top of gastric fluid which releases drug slowly in stomach. (Often used for gastroesophageal reflux treatment.[24]

Drugs Reported to be Used in the Formulation of Floating Dosage Forms are:

Floating microspheres (aspirin, griseofulvin, p-nitroaniline, ibuprofen, terfinadine and tranilast), floating granules (diclofenac sodium, indomethacin and prednisolone), films (cinnarizine), floating capsules (chlordiazepoxide hydrogen chloride,diazepam, furosemide, misoprostol, L-Dopa, benserazide, ursodeoxycholic acid and pepstatin) andfloating tablets and pills (acetaminophen, acetylsalicylic acid, ampicillin, amoxycillin trihydrate, atenolol, diltiazem, fluorouracil, isosorbide mononitrate, para aminobenzoic acid, piretamide, theophylline and verapemil hydrochloride, etc.).

Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

Various Techniques Used for the Preparation of Gastroretentive Tablets

Wet Granulation

In this method the powdered medicament along with other excipients such as polymers, binding agent, diluents and a part of disintegrating agent are moistened with a sufficient quantity of granulating agent in order to make a coherent mass. The coherent mass is than passed through sieve no 20 to collect the granules of uniform size. The granules are ready to be compressed.[26, 27]

Direct Compression

It is the easiest way to manufacture tablets. Conventional equipment, directly compressible excipients and a number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed than that of other production methods.

Hot-melt Extruded Method

A powder mixture (200g) of given drug (CPM), Eudragit RSPO or Eudragit EPO as retardants, GMS as a thermal lubricant, sodium bicarbonate was first blended The blended powder was then placed in the hopper of a single-screw randcastle Extruder and extruded. The extrusion temperatures for zone 1, zone 2, zone 3 and zone 4(die) were 90, 95, and 100 respectively. The screw rotation speed was 10 rpm and the die diameter was 6 mm. after melt processing manually cut into tablets.[27]

Evaluation of Floating Drug Delivery Systems

I) Buoyancy lag time and Duration of Buoyancy

The buoyancy lag time and the duration of buoyancy were determined in the USP dissolution apparatus II in an acid environment. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of the dissolution medium was taken as buoyancy lag time or floating lag time (FLT) and the duration of buoyancy was observed visually.[28]

II) In Vitro Dissolution Behaviour

The release of the medicament was studied by USP-II type dissolution apparatus (paddle type). Dissolution study was performed at predetermined speed and temperature of about 37 $\pm 0.5^0$ C in an appropriate dissolution medium. 5ml of sample was withdrawn at a predetermined interval and the volume of dissolution medium was maintained by adding same volume of dissolution medium. The absorption of withdrawn sample was measured and the corresponding concentration was determined from the calibration curve.

III) Determination of Density

The tablet density of the floating system was determined by displacement method, using benzene as a displacing medium. A plethysmometer was employed to measure tablet density. Firstly, the instrument was calibrated using benzene (density 08723g/cc) for its volumetric capacity. Benzene was filled till a mark in capillary of the instrument, five tablet of known weight were dropped in wider mouth of plethysmometer. The system was kept undisturbed for 1 min, to let benzene displace the air in the pores of the tablets. After that, displacement in the volume of the benzene in the side capillary in the volume of the benzene in the side capillary in the volume of the benzene in the side capillary was noted. Knowing the weight and volume occupied by the tablets, density of five tablets was determined.[29]

IV) Hardness and Friability

Hardness of the tablet is defined as the force applied across the diameter of the tablet in order to break the tablet, the resistance of the tablet to chipping, abrasion or breakage under condition of storage, transformation and breakage under usage depends on its hardness. Hardness of tablet was measured by using Monsanto hardness tester. Friability of the tablets was determined using roche friabilator. This device subject the tablet to the combined effect of abrasion and shock in plastic chamber revolving at 25 rpm and dropping the tablet at a height of 6 inch. In each revolution pre weight sample of tablet was placed in the friabilator and were subject to 100 revolution tablet were de dusted using a soft muslin cloth and reweight.[30]

The Friability (F%) is given by the formula:

$$F\%=(1-W_o/W)X100$$

Where, Wo is the tablet before the test and W is the weight of the tablets after test.

V) Swelling Index

Tablet were weight individually (W_o) and placed in dissolution medium the temperature was maintained at 37^0 C at regular interval the sample were removed using basket and swollen weight (W_t) of each tablet was determined at pre defined time intervals.[31] The swelling index was calculated by the following equation

Percentage swelling index =$(W_t-W_o/W_o)X100$

Where, W_o is the initial weight of the tablet and W_t is the weight of the tablet at time t.

VI) Weight Variation

USP provide the weight variation test by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average. The tablet meet the USP test if on more than 2 tablet are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

In-vivo Evaluation (Gamma Scintigraphy)

This method helps to locate dosage form in the gastrointestinal tract by which we can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. The inclusion of radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radionucleotide in a γ-camera or scintiscanner. In case of γ-scintigraphy, the γ-rays emitted by the nucleotide are focused on a camera, which helps to monitor the location of the dosage form in the gastrointestinal tract.[32]

Application

Floating multiparticulate drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.[33]

1. Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a low bulk density than that of GI fluid as a result of which they can float on the gastric fluid. These systems are relatively large in size and passing through the pyloric opening is prohibited. Hollow microspheres of non-steroidal anti inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for example floating microspheres of Indomethacin are quiet beneficial for rheumatic patients

2. Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide. A bilayer floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs.

3. Absorption Enhancement

Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extend the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Number of commercial products and patents issued in this field are the evidence of it. The aim is to improve the bioavailability of the drug with narrow absorption window in gastrointestinal tract region. By prolonging the drug resident time in GI region improves the solubility of drug that is less soluble in high PH and reduces drug waste, reduction in plasma level fluctuation.

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