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Review Article

Present scenario of pulsatile drug delivery system

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ABSTRACT

In current years, pulsatile drug release systems (PDRS) are ahead raising attention as compared to conventional drugs. In this delivery system, the drug is liberated quickly after a well defined insulate-time, could be helpful for many medicines or treatments. It can be labeled in single and a couple of-pulse structures. Other structures consist of a drug-enclosed core, enclosed by means of a swelling layer and an outer layer is insoluble, however coating with semipermeable polymer. The lag time earlier to the rupture is specifically controlled via: the penetration and mechanical houses of the coated polymer and the behaviour of swelling depend on the swelling layer. As is within the residing frame frequently observed that, many fundamental capabilities are regulated with the aid of brief or pulsed launch of bioactive substances at a precise site and time. Therefore its miles grave to expand novel drug transport systems to attain pulsed launch of a sure amount of medicine a good way to imitate the feature of the dwelling systems, whilst reduce undesirable side results. Particular interest has been given to the thermally receptive poly (N-isopropylacrylamide) and its imitative hydrogels. Pulsatile drug transport is a machine that, by means of handing over drug at the right vicinity, right amounts and in proper time, grips suitable assures of benefit to the patients affected by continual problems like high blood pressure, allergies, arthritis.

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1. Introduction

Conventional oral formulations are the top leading dosage form in global market. It is the preferential route for drug administration and management. The oral controlled-release systems show a distinctive model of drug targets to liberate in which the drug absorption is sustained in the curative window for an extended phase of time, thus safeguarding sustained therapeutic action. In certain situations this release pattern isn't always appropriate that insists discharge of a drug after an interval of time. The pulsatile system is in advance quite a few attention, as the drug is launched

entirely after described insulates time (Figure 1). PDD is website online and time-specific drug shipping, as a consequence imparting spatial and chronological shipping and accumulative patient fulfillment. This drug transport gives the fast and fleeting delivery of certain amount of selected molecules within a small span of time immediately after a programmed duration, i.e., lag time, and these system have the process of handling the drug substance quickly and completely after an insulated time. Such a release model is called as pulsatile release.¹⁻⁴ Human's body show a particular circadian rhythms that are synchronized by the master circadian clock, the suprachiasmatic center. Chronopharmacotherapy of diseases (myocardial infarction,

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bronchial asthma, rheumatic disease, angina pectoris, ulcer and hypertension) that explain circadian rhythm in their etiology and management of such diseases entail PDDS, by which drug is released quickly and entirely as a pulse after insulate time.⁴⁻⁶ There are several other conditions that require release of the drug in pulsatile manner, like many frame capabilities that trace circadian rhythms, consisting of secretion of hormones like luteinizing hormone, follicle stimulating hormone, progesterone and estrogen, acid secretion in the gastric emptying, stomach and GI blood transfusion. There are abundant benefits of the PDDS. These are:

1. Can be used extensively for day and night time action.
2. Low cost, side effects are low as dose frequency and dose size is less.
3. Adapts to body circadian rhythms.
4. Drug targeting is easy.
5. Defends the GI mucosa from irritating drugs.
6. First pass metabolism is lease.
7. Steady drug level is maintained in the blood plasma.⁷⁻¹⁰

1.1. Disadvantages

1. Loading capacity of drug is less.
2. Release of drug is less.
3. Formulation steps are complex.
4. Reproducibility and efficacy is poor.
5. Skilled/trained persons needed for manufacturing.

Present review focus on advanced methodologies for pulsatile manufacturing and up-gradation in the technologies for manufacturing.

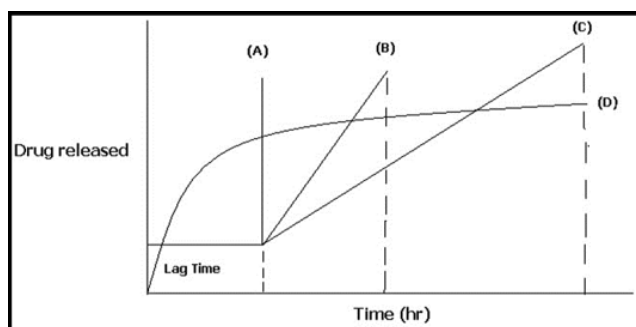


Fig. 1: Schematic representation of different drug delivery systems, with (A) sigmoidal release after lag time, (B) delayed release after lag time, (C) sustained release after lag time and (D) extended release without lag time. [Reproduced from: Jain D., Raturi R., Jain V., Bansal P., Singh R. Recent technologies in pulsatile drug delivery systems. Biomatter. 2011; 1: 57-65.]

1.2. Chronopharmacotherapy

The phrase chronopharmaceutics includes two words chronobiology and pharmaceutics. Chronobiology is the area which includes study of biological rhythms and their mechanisms in the body. Chronotherapeutic drug shipping machine is the drug delivery device that's based at the biological rhythms of frame. Chronomodulated machine is also recognized as pulsatile device or sigmoidal release system. There are 4 styles of mechanical rhythms in our body, which manage ordinary and disease associated body structure of the body (Figure 2). They are:

1. **Circadian:** The oscillation is completed in 24hrs.
2. **Ultradian:** The oscillation completed in shorter duration i.e. less than 24 hrs.
3. **Infradian:** The oscillations is longer than 24 hrs.
4. **Seasonal:** In the short days of winter, seasonal affected illness reasons melancholy in prone people. Out of four biological rhythms, circadian rhythm is the main rhythms in the body which maintains all the physiological, chemical, biological and behavioral processes.¹¹⁻¹³

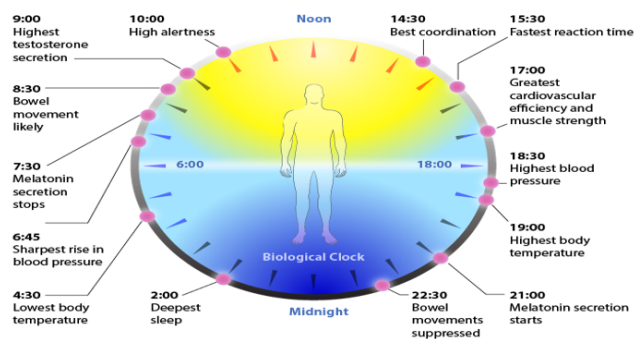


Fig. 2: Cycle of circadian rhythms [Reproduced from: <https://cpavictoria.com.au/blog/>.]

1.3. Necessitate of pulsatile drug delivery systems

1. Circadian rhythm follows many body functions which fluctuates according to the time.
2. Acid secretion, cholesterol synthesis, gastric emptying and GI blood transfusion might change with circadian rhythm.
3. Chronopharmacotherapy of illnesses which give an explanation for circadian rhythms of their path body structure.

1.4. Mechanism of drug release from pdds

The release happens from PDDS in different ways.¹⁴

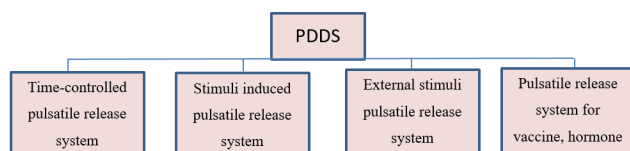
- a) Diffusion H_2O diffuses to the internal particle as soon as it comes in contact with aqueous fluids.

Erosion With time few particles erode slowly to release the drug.

Osmosis Osmotic pressure develops between the outside aqueous fluid and internal particle which can be one pathway of release of drug.

1.5. Classification of PDDS

Pulsatile system are essentially time-controlled drug delivery system in which the system manages the lag time independent of environmental factors like enzyme, pH, GI motility etc. Pulsatile drug delivery systems can be generally categorized into four classes.¹⁵



1.6. Time-controlled pulsatile release system

These time-controlled systems can be classified as a single units (e.g., tablet or capsule) or multiple unit systems.

1.6.1. Single unit systems

1.6.1.1. Capsular systems. Single-unit systems are mostly developed in capsule form. The insulate time is managed by way of a plug, which finds pushed away by erosion or swelling and the drug is launched as a Pulse from the insoluble pill frame. Polymers used for designing of the hydrogel plug are as following:¹⁶

1. Swellable materials coated with but permeable polymer (polymethacrylates).
2. Erodible compressed polymer (polyvinyl alcohol, HPMC).
3. Congealed melted polymer (glyceryl mono oleate).
4. Enzymatically controlled erodible polymer (pectin).¹⁷

These structures are made in a way that drug reservoir is covered with soluble or erodible layer that dissolves when in contact with fluid and drug is released after an insulated tiem.¹⁸ For instance the biological clock of body.¹⁹ It includes a strong dosage shape protected with lipid limitations containing surfactants.²⁰ The insulate time and movement of drug is managed by the thickness and grade of viscosity of polymer (Figure 5).

The system is coated with a rupturable membrane. The outer layer or membrane gets ruptured due to pressure by effervescent agents. In such a system sodium bicarbonate and citric acid are used as effervescent agents.²¹ Ethyl cellulose coating is done in the core tablet when the system comes in contact with water it releases carbon dioxide which

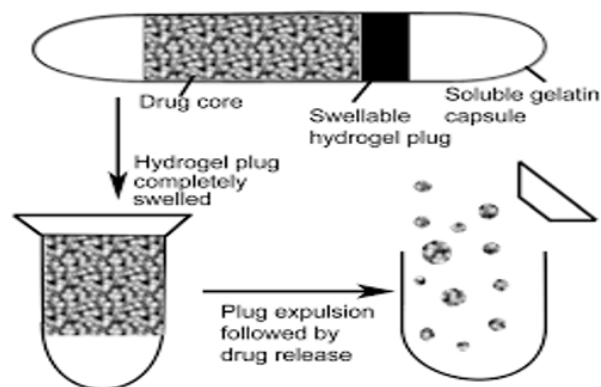


Fig. 3: Schematic design of pulsincap system. [Reproduced from: Shidhaye S.S., Lotlikar V.M., Ghule A.M., Phutane P.K., Kadam V.J. Pulsatile delivery systems: An approach for chronotherapeutic diseases. *Sys. Rev. Pharm.*2010; 1: 55-61.]

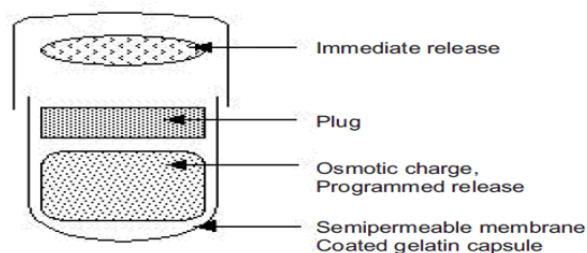


Fig. 4: Schematic design of osmotic system. [Reproduced from: Arora S., Ali J., Ahuja A., Baboota S., Qureshi J. Pulsatile drug delivery systems: An approach for controlled drug delivery. *Indian J. Pharm. Sci.* 2006; 68: 295-300] Pulsatile delivery by solubilisation (or) erosion of membrane

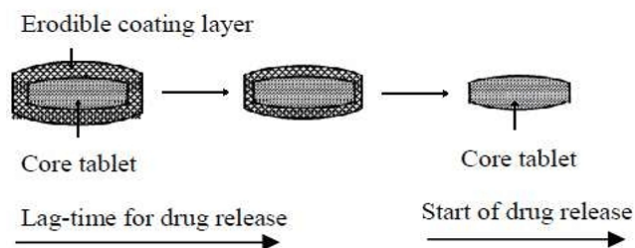


Fig. 5: Schematic diagram of delivery system with erodible coating layers [Reproduced from: Kotha R.K., Raghavapally S.G., Adavi S.L., Taranalli S., Pandey D. Current techniques in pulsatile drug delivery: a review. *Int. Res. J. Pharm.* 2013; 4:77-84.] Drug delivery system with rupturable layers/ membranes

creates pressure and after some time the membrane ruptures due to pressure (Figure 6). The lag time is controlled by way of the composition of the outer polymeric membrane.²²⁻²⁵

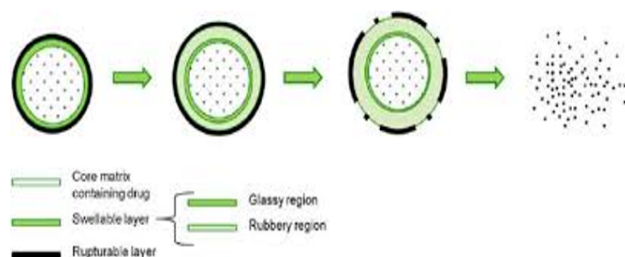


Fig. 6: Drug Release Mechanism from System with Rupturable coating Membrane [Reproduced from: Devi R., Kumar S. Pulsatile drug delivery system: new paradigms. *Int. J. Innov. Pharm. Sci. Res.* 2017; 5: 34-49.]

1.7. Multiple unit pulsatile systems

Gastric emptying pattern differs for multi-particulate formulations, such system are dispersed freely throughout the GIT and is affected by transit time of food²⁶ (Figure 7). These systems are of two types.

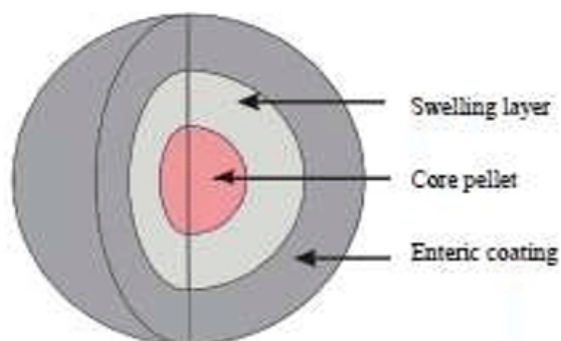


Fig. 7: Hypothetical design of multiparticulate pulsatile systems [Reproduced from: Kotha R.K., Raghavapally S.G., Adavi S.L., Taranalli S., Pandey D. Current techniques in pulsatile drug delivery: a review. *Int. Res. J. Pharm.* 2013; 4:77-84.] Pulsatile system based on the change in membrane permeability

This system incorporates the interface of some acrylic polymers with quaternary ammonium corporations. The inside core is having drug and succinic acid coated with AMC USP/NF type

The water is responsible for liquefying the succinic acid. This scheme was used to design an acid-containing core and tested in beagle dogs. It shows a good in vitro/in vivo relationship of lag time.²⁷

1.8. Stimuli-induced pulsatile release system

This system release the drug in response to stimuli by the external surroundings.²⁸

1.9. Thermo-responsive pulsatile release

Hydrogel are the better example for thermo-sensitive drug delivery. The polymer is crosslinked and the transition in temperature is linked in the formation of hydrogel. Temperature-sensitive polymer used are ethyl, methyl, and propyl groups. Poly (N-isopropyl acrylamide) (PINPAM) are extensively used polymers.²⁹

1.10. Chemical stimuli-induced pulsatile release

The factor responsible for drug release is biological factors like pH, enzymes or any other chemical stimuli. Example is automatic release of insulin when glucose level rises in blood. Kazunori et. al., reported a gel that showed a remarkable change in swelling caused by glucose using phenylboronic acid.^{30,31}

1.11. Externally regulated pulsatile release system

Electro responsive pulsatile release

Application of electric field as an external stimulator. Electrically response delivery uses polyelectrolytes and are also sensitive to pH change. Poly (2-acrylamide-2-methyl propane sulfonic acid-co butyl methacrylate) hydrogels are example of such delivery system.^{32,33}

1.12. Micro electro-mechanical systems

The device made by this system have the ability to store and release many chemical moiety by moving mechanism. Better control over drug release is possible. Another advancement is microchip, which contains such reservoirs of impermeable substrate through an electrolyte.³⁴ Prototype microchip is made of silicon and contains drug reservoir which is covered at one end by gold that provides the electrochemical reaction and melts on application of electric potential.^{35,36}

1.13. Pulsatile release systems for vaccine and hormone products

The major mechanism involved in therapeutic benefit from vaccines is development of immunity.³⁷ Vaccine are administered to protect the body and hence co-administration is also needed to maintain the immunity.³⁸ PDDS can be used for delivery of vaccines.³⁸⁻⁴²

2. Marketed Technologies of Pulsatile Drug Delivery

Pharmaceutical companies worldwide are focusing on development of such PDDS which can help to treat major

Table 1: Example of FDA approved pulsatile drug delivery systems in market

Proprietary name	Active pharmaceutical ingredient	Chronopharmaceutical technology	Drug release mechanism
Concerta® tablet	Methylphenidat HCl	Oros	Osmotic regulation
Cardizem LA	Diltiazem Hcl	Ceform microsphere technology	Diffusion/ erosion
Uniphyll ^R	Theophylline	Contin ^R	Controlled release
Innopran ^R XL	Propranolol Hcl & Verapamil	Diffucaps	Rapid/sustained release
Covera-HS ^R	Verapamil	Oros	Osmotic regulation
Verelan ^R PM	Verapamil	Codas	Delayed release
Pepcid	Famotidine	Physicochemical modification of API	Tablet
Lipovas ^R ,	Simvastatin	Physicochemical modification of API	Tablet
Invega TM	Paliperidone	OROS	Osmotic regulation
Glucotrol	Glipizide	OROS	Osmotic regulation
Glizid-MR30	Gliclizide	Hydrophilic matrix technology	Swelling/diffusion/erosion
Kapidex TM	Dexlansoprazole	DDR Technology	Dual drug release
Coruno®	Molsidomine	Geomatrix technology	Swelling/erosion
Theiform	Diclofenac sodium	3DP	Immediate release/controlled release
Pulsincap TM	Dofetilide	Pulsincap TM	Rupturable system
Moxatag®: ER tablets	Amoxicillin	Pulsystem	Multiparticulate system
Theiform	Diclofenac Na	Three dimensional printing	Externally regulated system
Opana®	Oxymorphone	Timerx®	Erodible/ soluble barrier coating ER Tablets
Cardiazem® LA	Diltiazem HCl, Verapamil HCl	Ceform®	Extended Release tablet
Procardia XL	Nifedipine	Procardia XL®	Sustained release
Hokunalin® tape	Tulobuterol	Transdermal chronodelivery System.	

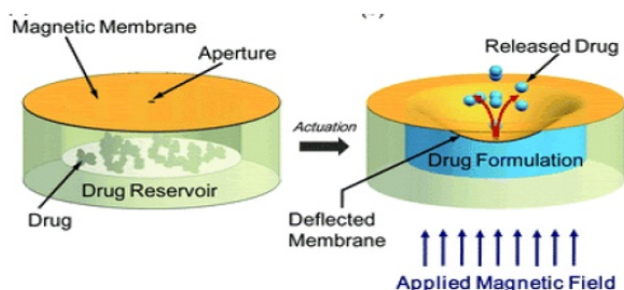


Fig. 8: Drug release from magnetically induced pulsatile systems [Reproduced from: Shanmugan P., Bandameedi R. Chronotherapeutic drug delivery systems. J. Drug Meta. Toxicol. 2015; 6: 2-7.]

chronic disorders. Recently developed technologies used are listed in Table 1.

3. Recent Advances in the Pulsatile Drug Delivery System

There are many diseases that require pulsatile release like asthma, cancers, arthritis, ulcers, cardiovascular diseases,

allergic problems.²⁷ The recent trend is multi particulate system that offers many advantages. The release pattern of drug is dependent upon pH, internal flora of GI, time release. For increasing therapeutic efficacy of oral delivery various technologies are developed.⁴²

4. Accubreak Technology

Dose modification becomes easy by this technology. In this small dose of the tablet is taken and a controlled release medication is prepared. When it releases in the body the membrane ruptures and the drug is reduced to half prior to its release.⁴³

5. TMDS Technology

In single tablet the release rate of multiple ingredients can be optimized.

6. Geoclock Technology

In this active drug is surrounded by an outer layer which contains a hydrophobic mixture and a brittle material. E.g. LODOTRA – for rheumatoid arthritis.

Table 2: Recent patent on pulsatile/controlled drug delivery systems/devices

S. No.	Based on API/Device	Topic	Inventor	Status/Date	Patent No.
1	Device	Multi-dose drug delivery device and method	Robert Farra	Granted/ 2014-03-25	US8679093B2
2	Device	Medical device for controlled drug delivery and cardiac monitoring and/or stimulation	Barry M. Yomtov Stephen J. Herman	Granted/ 2011-03-29	US7917208B2
3	Device	Low-permeability, laser-activated drug delivery device	Jonathan Robert Coppeta Kenneth N. Horne John T. Santini, Jr. John A. Scholl Gregory J. R. Spooner Cynthia L. Stevenson Naveed Shams Andrew Poutiatine	Grant/ 2014-12-16, 2014-01-08	US8911426B2, EP2533737B1
4	Device	Portable drug delivery device including a detachable and replaceable administration or dosing element	Joseph Zhili Huang Guy DiPierro	Grant/2013-02-12,	US8372040B2
5	Device & different APIs	Oral drug delivery system	Su Il Yum Grant Arthur J. Tipton John W. Gibson John C. Middleton	Grant/ 2012-03-13, 2015-09-23, 2012-02-01, 2013-06-12, 2013-09-17, 2010-11-11, 2016-01-11, 2011-01-26	US8133507B2, EP2218448B1, JP4865330B2, CN101797221B, CA2810477C, DE6033440ID1, DK2218448T3, ES2350689T3
6	Delivery system	Drug delivery system	James M. Olsen	Granted/ 2010-08-03, 2007-11-14, 2008-09-11	US7766885B2, EP1755703B1, DE602005003355T2
7	Device	Cartridge insertion assembly for drug delivery system	Oz Cabiri	Granted/ 2012-04-17, 2014-08-13, 2014-07-02, 2014-05-07	US8157769B2, EP2477679B1, JP5535321B2, CN102639169B
8	Ionizable pharmaceutical agent & lipophilic species	Transmucosal drug delivery system	John A. McCarty	Granted/ 2015-03-31, 2014-04-16, 2013-01-02, 2012-02-07, 2013-07-08, 2013-07-18, 2009-01-10	US8992974B2, JP5475215B2, CN1777411B, CA2516816C, DK1599186T3, ES2414084T3, RU2342953C2
9	Devices	Drug delivery devices, kits and methods there for	Gilbert H. KLIMAN	Granted/ 2013-08-27	US8521273B2
10	Devices	Gastric retention controlled drug delivery system	Kamlesh Mohanlal Dudhara Nitin Bhalachandra Dharmadhikari Vaishali Vijay Dhavse	Granted/ 2010-08-17, 2012-12-05, 2012-08-08, 2010-12-01, 2011-06-14, 2010-09-30, 2013-03-15, 2008-05-27	US7776345B2, EP2238975B1, JP4994570B2, CN1520286B, CA2452738C, DE60237372D1, ES2398348T3, RU2325152C2
11	Device	Transmucosal drug delivery device and method including chemical permeation enhancers	Scott Uhland Eric Peeters Hussain Fatakdawala	Granted/2014-11-11, 2014-11-19, 2015-05-07	US882748B2, EP2308465B8, JP5715368B2
12	Delivery System	Controlled dose drug delivery system	Amir Shojaei Stephanie Read Richard A. Couch Paul Hodgkins	Granted/ 2014-09-30	US8846100B2

7. Duredas Technology (Dual release drug absorption system)

In this there are two layers in which one layer is responsible for immediate release of second layer and sustained action is produced.

7.1. Innoherb

In this the herbal compound are converted into beads or pellets and coated within capsule. The coating is done by semi-permeable membrane which is also used to mask the bad taste.⁴⁴

7.2. Orbexa technology

Granulation is done for loading of drugs. Polymers are used for coating and this technology can be imparted in proteins.¹⁹

8. Conclusion

Oral delivery of drugs is the most suitable and cost-effective approach followed. The chrono pharmacology principles can be used and be a fairly promising delivery in many chronic illnesses. The new drug delivery system is need of the hour for better therapeutic efficacy and pulsatile release is one of them. While, controlled release delivery offer the desired therapeutic impact, however, drop brief of diseases following organic rhythms, circadian issues together with peptic ulcer, high blood pressure, osteoarthritis, and asthma which want chrono pharmacotherapy. Circadian rhythm of the body is a widespread concept for knowledge of the most reliable want of drug within the body. Pulsatile drug delivery helps patients to handle the drugs in proper manner in proper time in chronic problems also. Drug transport will help in achi 'eving outcomes. We are sure that with an increase in technological development and higher design parameters those obstacles can be overcome inside the close to destiny and wider variety of patients will be significantly benefited from this system.

9. Source of Funding

None.

10. Conflict of Interest

None.

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