

CHALLENGES TO OPTIMISATION AND SCALE-UP OF THE PROCESS OF LYOPHILISATION OF PHARMACEUTICALS

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ABSTRACT

With the advent of biopharmaceuticals into the market, lyophilisation or freeze-drying forms an essential step in their manufacturing technique. Stability and sterility are achieved more easily with the process than with other conventional techniques. Design, development, control, optimisation and scale-up of the process requires consideration of several aspects such as theoretical knowledge of the stages of freeze-drying cycle, determination of end-point of primary drying stage, evaluation and analysis of the process and the product, techniques for optimization in practice and their relevance to the variables in question. Application of the process in commercial scale throws up challenges in terms of design of dryer, batch size, duration of process. Description of factors responsible for problems related to scale-up should be investigated in details and should be appropriately controlled to reduce the production cost to a minimum without compromising with the process efficiency or product quality.

KEYWORDS: lyophilisation, freeze-drying cycle, commercial scale.

INTRODUCTION

Freeze-drying or lyophilisation is most commonly employed to enhance the shelf-life of labile active pharmaceuticals and biopharmaceuticals like proteins, peptides, vaccines, antibodies, enzymes, hormones, blood products, nanoparticles etc., by removal of water or any other solvent, under controlled conditions.^[1-5] It is highly recommended for parenterals for which low moisture content (<1%) is essential for preservation of the product and maintenance of sterility.^[6] Since drying is carried out at very low temperatures, thermal

degradation of pharmaceuticals can be avoided which is a problem with conventional drying techniques.^[7]

In spite of the high expenditure involved, lyophilized products are widely accepted commercially because of the advantages of immediate and complete reconstitution, easy, safe and accurate administration in hospital setting, ease to ensure sterility and protection against oxidation by providing nitrogen atmosphere.^[1,8]

The main disadvantage of the process of lyophilisation is its prolonged cycle time which may vary from less than 24hrs to more than one week. Energy requirement is also high since the process involves constant cooling and/or heating at its various stages.^[1] Involvement of numerous process parameters at various stages of freeze-drying makes it a process where scale-up from laboratory scale to commercial or industrial scale through pilot scale is difficult to implement. An essential criterion during scale-up is to obtain the same product temperature history throughout the drying process independent of the dryer scale.^[4]

Monitoring and optimization of process parameters requires detailed knowledge about the theory of heat and mass transfer. Design of an optimized process based on sound scientific principles necessarily enables achieving highest permissible product temperature with adequate safety margins, reduces cycle time as also cost factor.^[4,9]

The present/review focuses on the various issues pertaining to rationale, design and control of lyophilisation and aspects related to scale-up challenges during process development and optimization in industrial scale operation.

A knowledge about the ideal characteristics of a successful freeze-dried formulation is essential before understanding the mechanistic part of the process of lyophilisation. Process development and optimization is only possible after establishing the critical quality attributes of a freeze-dried product. The ideal characteristics of a freeze-dried product include several physical qualities, level of moisture, solid-state stability, solution stability.^[2,3]

a. Desirable physical attributes

The product should possess an elegant appearance or desirable morphological characteristics and uniform particle size distribution.

b. Residual moisture content

Freeze-dried products should contain very low amount of moisture after completion of the cycle to maintain the stability and flow property of the material.

c. Solid-state stability

- i. The freeze-dried product should not exhibit any signs of collapse or melt-back. The collapsed product is characterized by slower reconstitution time due to reduced porosity and lower specific surface area. In case of proteins, collapse may also lead to disruption of protein structure.
 - ii. The lyophilized product should possess sufficient stability to be formulated as reconstituted product quickly as and when required.
- d. Solution stability: Following reconstitution, the freeze-dried product should possess physical, chemical and microbiological stability at desired storage conditions for the specified shelf-life. There should not be any compromise on the potency and efficacy of the product.

1. STAGES OF FREEZE-DRYING (FD) CYCLE

The entire FD cycle may be assumed to occur in three distinct stages

1. Freezing stage: At the onset, a vitreous or highly viscous state of the substance is attained by freezing at a sufficiently low temperature when crystallization of free water occurs.^[9] A small percentage of water, bound water, still remains entrapped in the unfrozen state in the amorphous solid phase constituted by different excipients as also the active pharmaceutical ingredient.^[2]

2. Primary drying stage: Following the initial freezing stage, occurs the most important step of FD cycle, which is commonly known as primary drying stage. The main event of this stage is sublimation of crystallized water at a critical product temperature which should be less than glass transition (T_g) or collapse temperature (T_c). The collapse temperature is so called because at or above this temperature the dried cake collapses with complete loss of structural integrity. Due to structural breakdown, the channels or paths through which the water molecule may escape during sublimation are clogged thereby reducing the rate of sublimation. This may lead to retention of higher percentage of moisture in the product than that in absence of collapse.^[3,10] During sublimation, the sublimation interface or the front is formed initially at the outer surface or top of the product which recedes to the interior or

towards the bottom of the vial with time. The water vapor moves towards the condenser serpentines. For sublimation to occur, chamber pressure must be significantly reduced and shelf temperature should be higher than that in the previous step to provide energy for sublimation.^[6,9,11]

At the end of primary drying stage, the product temperature should be increased slowly at a controlled rate to allow evaporation of residual moisture in such a way so as not to cause collapse of the cake.^[3]

3. The last step or secondary drying is also known as desorption since removal of bound or sorbed solvent(usually water) occurs at a comparatively elevated ambient temperature (25-50°C)and at a slower rate via the process of diffusion. During this step, only 10-35% of water is removed at a temperature which is determined by the user requirement of the product.^[9, 10] The final product temperature at the end of secondary drying depends on shelf temperature and it is crucial for quantification of moisture content in the product.^[3] The moisture level becomes highly significant for protein-based formulations.

Sometimes, an additional step of annealing is carried out prior to sublimation in order to increase the size of ice crystals and control particle size distribution of ice crystals, increase glass transition temperature of the product, accelerate the primary drying rate, improve the appearance and ruggedness of the dried cake. Pre-sublimation annealing involves thermal treatment of the frozen product (at a temperature determined from differential scanning calorimetry or freeze-drying microscopy) to induce crystallization of specific excipients like mannitol and glycine which actually results in enhanced storage stability of the product by reducing the tendency of amorphous excipient to crystallize out during storage. The crystalline form of mannitol is preferred because more robust tablets are obtained which do not show any sign of shrinkage or cracking as a result of stress during freeze-drying. The annealing temperature should be greater than devitrification temperature by 10°C but lower than the eutectic melting temperature for complete crystallization in less time. The duration of annealing depends on the nature of excipients.^[3,12] Annealing has been reported to improve the storage stability of proteins by lowering the rate and extent of protein aggregation. The global molecular mobility was also decreased as evident from comparatively higher value of structural relaxation time constant with respect to the unannealed sample.^[13]

Most of the products amenable to freeze-drying are kept in sealed or stoppered containers for the need of the process. However, in case of Zydis Orally Disintegrating Tablets(ODTs), the rapidly dissolving porous matrix tablets are obtained by passing the blister trays containing formulation in the form of suspension through a freeze tunnel (temperature reduction achieved by spray of liquid nitrogen) during which the liquid formulation freezes completely.^[12]

2. MONITORING AND EVALUATION OF FD PROCESS

2.1 End-point determination of primary drying stage

Determination of end-point of primary drying is crucial to reduce time and money since excess drying at this stage does not provide any extra benefit. Moreover, premature transition to secondary drying stage leads to partial collapse of the cake. Accurate determination of this end-point is a great hurdle for the technicians since the time interval between the completion of sublimation in the first and last vial may extend up to several hours.^[6]

In pilot scale, end-point can be detected as^[3]

1. Rise in product temperature and end of product cooling
2. Insignificant fluctuation in chamber pressure
3. Allowing chamber pressure to rise by temporary isolation of the chamber from the vacuum pump. Incomplete sublimation results in rise in chamber pressure.
4. Weight of the vials by removing them from the chamber without disturbing the vacuum.
5. Determination of moisture content or vapor pressure

Advancements have been made by introducing different probes and sensors into single vials such as TEMPRIS sensors, TrackSense Pro, Near Infra-red(NIR) probes, Raman probes.^[1]

In commercial scale, end-point is estimated by measurement of temperature or pressure. Detection of end of sublimation is usually done by inserting temperature sensors or thin wire thermocouples in some of the vials. However, this method suffers from a serious drawback. Variation has been found to exist between the non-thermocouple containing vials and thermocouple-containing vials with respect to properties of frozen matrix like size of pores, product resistance to vapor flow, temperature and time required for drying. This problem has been overcome in laboratory scale by including delay or soak time before proceeding to the next step of secondary drying. Moreover, use of thermocouples requires intervention by humans which can cause a serious threat to the sterility of products and can also interfere

with the process dynamics.^[1,6,7] In case of freeze-drying of biological tissue (bovine pericardium), the thermocouples should be placed at the geometric centre of the sample as freeze-drying proceeds from edges to the centre.^[3, 11]

2.2 Testing for equipment qualification^[14]

Identification of limiting conditions for operating a particular freeze-dryer is done by carrying out a series of ice slab tests. Choked flow may happen depending upon the pressure since the mass flow rate choke point is directly proportional to pressure.

2.3 Evaluation of freeze-drying process and characterisation of freeze-dried product

Evaluation of the process of freeze-drying is essential in order to validate the technique for a particular formulation and to improve the robustness of the process. It should include investigation and characterization of the physical, chemical and biological properties of the product. Highly sophisticated techniques should be adopted for proteins since the configuration and biological activity of proteins may undergo a substantial alteration (denaturation) as a result of exposure to low temperature and subsequent dehydration.^[15]

The process of lyophilisation is evaluated on the basis of determination of specific critical product quality attributes such as cake quality, cake volume, reconstitution time, microscopic characteristics, final product temperature etc.^[2,9]

Cake quality

The quality of the cake is visually observed with respect to attributes like elegance in appearance, evidence of collapse or melting, presence of holes etc.

Recently, a fuzzy logic system has been developed for analyzing cake quality parameters without consuming large amount of material. Extent of cake collapse, glassiness and color uniformity were determined visually, images taken and analysed with suitable imaging solutions. The fuzzy logic-based system demonstrated equivalence with visual observation tests and can be used for screening of lyophilized products in development stage.^[16]

Cake volume

The final volume of the intact lyophilized mass should occupy same volume as that of the original frozen mass.

Reconstitution time

The lyophilized product should be capable of being reconstituted immediately after addition of water volume that has been lost during the process.

Microscopic characterization

The microscopic structure of the frozen matrix can be observed by different high resolution techniques such as transmission electron microscopy (TEM), atomic force microscopy (AFM), scanning electron microscopy (SEM) etc. This technique is very suitable for quantification of sublimation rate of very thin biological tissue specimen at various conditions by measurement of thickness of dried layer formed during the process.^[11] Moreover, freeze-drying microscopy (FDM) enables identification of temperatures at which visible changes occur and measurement of relative drying rates.

2.4 Characterisation of thermal events

Detection of thermal events in the lyophilized mass and determination of critical formulation temperatures has been made possible by thermal analytical methods such as differential scanning calorimetry (DSC) and differential thermal analysis (DTA). Glass transition temperature of the maximally freeze-concentrated solute is measured with the help of these techniques.^[1,17]

3. OPTIMISATION OF FREEZE-DRYING CYCLE**3.1 Process parameters important for optimisation**

Process optimization requires an in-depth knowledge about the various variables affecting the process efficiency and output, range of permissible deviations from the optimum values without affecting the quality of the finished product. The objective of optimization is to establish functional relationship between sublimation rates, product temperature, shelf heat transfer fluid temperature, total gas pressure and several other variables depending on the purpose and scale of operation.^[18] Once the objective is fulfilled, it will lead to optimal cycles. Otherwise, the cycles are aggressive (i.e. too high temperatures or too short cycle times) or conservative (too prolonged cycle time). However, before initiating any detailed discussion on control of different process parameters, one should have an idea about the mechanisms of heat transfer in case of freeze-drying. Heat transfer during lyophilisation may occur through either of the three processes: conduction, convection and radiation. Radiation occurs primarily through shelves, walls and the door of the freeze-dryer. Conduction operates at the bottom of the tray or the vial. The processes of convection and radiation occur

throughout the entire length of the container for which the composition and shape of the container are important.^[9]

3.1.1 Product temperature

For amorphous components, product temperature should not be allowed to exceed collapse temperature since higher than optimum temperature reduces the product viscosity leading to fusion of pores, loss of microstructure, formation of holes in the cake, inelegant appearance, irreversible melting, deleterious effect on reconstitution time and finally rejection of the entire batch.^[1, 9, 14]

Similarly, for crystalline components, the product temperature should be maintained below eutectic melting temperature (T_e) to prevent melt-back phenomenon in the frozen formulation. At this temperature, the solute material melts and impedes the formation of any rigid structure after solvent removal. This characteristic temperature is affected by amorphous components in the formulation and other additives capable of forming a ternary or higher-level eutectic mixture.^[3, 17] As in case of collapse, here also, the partially dried product loses pharmaceutical acceptability.^[14]

Optimum product temperature is attained by striking a delicate balance between heat transfer rate to the product and water vapor (mass) transport rate.^[10]

For orally disintegrating tablets, either of the two phenomena of collapse or melt-back can adversely affect the disintegration time owing to the negative impact on the porous structure of the matrix.^[12]

3.1.2 Shelf temperature

Shelf temperature should be closely monitored to prevent product collapse and shrinkage due to generation of localized hot spots.^[9]

3.1.3 Chamber pressure

For successful completion of various stages of drying and to produce dried cake of high quality, the chamber pressure at a critical temperature should be reduced to a value which is lower than the vapor pressure of ice.^[10] It has been observed that high values for chamber pressure increases product resistance to mass transport (transport of water vapor molecules) from ice interface within the frozen mass to the chamber and lowers the rate of sublimation.^[14]

3.1.4 Formulation variables

Physicochemical properties of the formulation affect the collapse temperature. It should exhibit as high as glass transition temperature or collapse temperature as possible. If the product possesses a low collapse temperature, then lyophilisation cycle of longer duration is required exposing it to greater risks.^[3] The formulation criteria essential for lyophilisation are achieved by inclusion of specific excipients or additives which help in imparting a rigid macroscopic structure to the cake. Incorporation of additives of correct type will prevent collapse of the entire structure. Mannitol is a commonly employed bulking agent and can also act as a stabilizer. It facilitates lyophilisation at a higher temperature thereby reducing duration of the entire process. It is to be kept in mind that mannitol may crystallize out in different polymorphic forms depending on the concentration used in the formulation and also freezing rate. However, crystallization of the bulking agent can cause vial breakage during expansion of the frozen phase. Such crystallisation can also disrupt structure of the protein molecules in protein-based formulations. In case of nanoparticles, success of lyophilisation depends greatly on the composition of nanoparticles (type and concentration of polymer, surfactant) and interaction between specialized excipients and formed nanoparticles.^[2] Cryoprotectants and lyoprotectants are added to stabilize the systems against stresses induced by freezing and dehydration respectively. Cryoprotectants which include different sugars like trehalose, sucrose, glucose, mannitol induce immobilization of nanoparticles in the glassy, vitrified matrix thereby preventing aggregation and also protecting against the stress generated by ice crystals. This specific class of excipients is selected on the basis of results obtained from freeze-thawing study. Addition of crystallizing salts like buffers or amorphous excipients with high glass transition temperature (e.g. dextrans, cyclodextrins) enhance the critical formulation temperature and prevent the product against collapse or melt-back.^{[1-3], [10,17]}

Special care needs to be taken for formulations containing an organic co-solvent since its volatilization may cause loss of solid content from the vial thereby affecting biological activity and also affecting container-closure integrity.^[14]

3.1.5 Loading condition

In order to promote faster growth of ice crystals of bigger size compared to nucleation, it is advised to load the filled containers on to pre-chilled trays (e.g. -50°C). This will cause quenching of the lowest portion of the sample in the container.^[3]

3.2 Techniques for optimisation of FD cycle

Process optimization results in faster and efficient process at a lower cost with expenditure of less energy. This is especially true for commercial-scale lyophilisation for large batches. Application of suitable optimization techniques will enable release of a lyophilized product into the market at a competitive price. Mathematical modeling is an effective tool for studying the process conditions of freeze-drying. A good model helps in analysis of drying rates and prediction of surface-temperature profile. Models based on both the processes of heat and mass transfer have been developed from time to time. Depending on the objective of modeling, either the whole process or any particular stage can be subjected to modeling to predict the process behavior. Model parameters, with their probable intra-batch and inter-batch variability should be accurately estimated. In one particular model, the heat transfer coefficient has been assumed to vary with the position of the vial in the array and also the material of construction of the loading tray. Development of mathematical model of secondary drying step is based on the estimation of kinetics of desorption, desorption rate through determination of rise of chamber pressure and assessment of dependence of output variables on the operating variables. Mathematical model for off-line secondary drying process helps in optimizing the process variables by calculation of the design space after deciding on the final product requirements. Once the target product profile is achieved, the operating conditions are said to fulfill the criteria. Maximisation of sublimation flux and maintenance of product temperature well below limit temperature have been estimated in short time by using soft-sensor. Model parameters(heat and mass transfer coefficients) and product dynamics have been determined very easily.^{[8, 11], [19-22]}

In another study, mathematical modeling of secondary drying step involves investigation of effect of input variables (e.g. temperature of the tray, duration of the process) on the output responses(e.g. final product temperature, residual moisture content). Attempts to optimize primary drying phase for a parenteral formulation through utilization of a non-steady state mathematical model has met with success.^[20]

Both in-line and off-line optimizations should be taken into consideration by exploiting the strengths and weaknesses of different tools. Some of the tools that have been implemented to develop and optimize laboratory-scale in-line freeze-drying protocol include SMART™ freeze-dryer, LyoDriver, Model Predictive Control (MPC) algorithms, Thermodynamic Lyophilisation Control(TLC), Dynamic Parameters Estimation (DPE) model, Lyotrack

humidity sensor etc. Advancements have been made by introducing novel approaches with single vials such as TEMPRIS sensors, TrackSense Pro, Near Infra-red(NIR) probes, Raman probes.^[1,7,23,24]

4. FACTORS RESPONSIBLE FOR SCALE-UP PROBLEMS

Scaling up becomes a problem since a freeze-dryer actually is a multi-purpose equipment capable of drying, creating a vacuum chamber and preserving sterility and stability. Therefore, numerous variables associated with the main process, equipment, container-closure system are important at each stage of operation, each of which contributing differently to scale-up challenge.

4.1 Process variables

4.1.1 Process parameters during primary drying stage

It is the longest of all the stages of FD cycle marked by low product temperature and low vapor pressure. It has been reported that an increase in product temperature by 10⁰C reduces the duration of primary drying stage by 13%. Hence its optimization actually improves the process economics.^[1,4]

Although loading of containers on to pre-chilled trays has yielded successful lyophilized product on small scale, it is tough to adapt the rapid quenching approach to large-scale process when it becomes very difficult to attain precise temperature control and batch-to-batch variation is more pronounced. Even if possible, it can cause damage to automated loading systems due to frost build-up while using pre-chilled shelves.^[3]

4.1.2 Freezing rate and hold temperature

Additionally, with large-scale operation, it is not feasible to achieve high freezing rates (e.g. 0.5-1.0⁰C/min). After the freezing rate has been optimized the next parameter to be established is the hold temperature which should be such that all the vials during industrial scale process are maintained at equilibrium with the shelf temperature.^[3]

4.2 Equipment variables

4.2.1 Monitoring devices

For precise determination of primary drying time in commercial scale, the approach of “time-based” cycle is adopted while monitoring temperature in vials. Insertion of thermocouples becomes problematic in large-scale freeze-dryers with fully automated loading/unloading

operations. More accurate monitoring can be achieved by measurement of chamber pressure by capacitance manometer reading. Limit for pressure rise is determined on the basis of batch size and sublimation rate expected at the end of primary drying. An additional monitoring device, the Pirani gauge (thermal conductivity gauge) is employed in some lyophilisers. It is sensitive to gas composition inside the chamber and cannot be used for formulations using flammable solvents.^[3,6] This technique is also not totally devoid of flaws and other techniques such as tunable diode laser absorption spectroscopy, electronic moisture sensor have also been used. Primary drying end-point has also been predicted from dry layer mass transfer resistance parameters. Resistance is affected by solid content, nature of the product and the ice nucleation temperature. Distribution of nucleation temperature is more uniform in a controlled environment (Class 100) in case of production-scale lyophilisers.^[6, 14]

4.2.2 Design of dryer

Owing to large batch sizes, the commercial scale dryer possesses more inertia and intermediate stages of freeze-drying may continue for longer periods compared to laboratory-scale or pilot scale processes.^[3] Geometry of freeze-dryer controls the product temperature at the interface of sublimation of water crystals and water flow to the condenser. Differences in design of freeze-dryers between laboratory-scale and industrial scale units may result in improper assessment of the heterogeneity factor. Since the emissivities of the different surfaces of the dryer vary with the type of the dryer, the mean vial heat transfer coefficient also varies.^[4]

Maximum sublimation rate and minimum attainable chamber pressure are operating parameters that are determined by the dryer design.^[4]

Non-uniformity or heterogeneity in rate of sublimation from the vials placed on the shelf due to differences in the rates at the edge and the rest occur as a result of atypical radiation effects. Moreover, the shelf surface temperature is not uniform throughout and there are instances of localised hot and cold spots.^[4]

4.2.3 Design of condenser and refrigeration system

The surface area of the condenser and its temperature affect the condensation capacity of the freeze-dryer. The refrigeration system governs the maximum allowable condensation rate for the water molecules.^[9,14]

Design of condenser restricts the water vapor transport rate that can be condensed without unnecessarily increasing the condenser temperature. This restriction is imposed by the limitations in the refrigeration capacity as the surface area of condenser is fixed or limits on water vapor flow rate around the condenser create some inaccessible surfaces.^[14]

4.2.4 Heat transfer system

Heat transfer system of a freeze-dryer is responsible for supplying the necessary heat for sublimation of ice in the desired formulation. However, the amount of heat that is transferred depends on the electrical power that is supplied to heat the heat-transfer fluid like silicone oil, nature of heat –transfer fluid, heat-transfer coefficient of shelf which is again determined by the design of heat flow paths in the trays and finally flow rate.^[14]

4.2.5 Effect of dryer load

An important process variable that needs to be considered and optimized during development and scale-up of FD cycle is the dryer load. Operating the machine under partial load condition improves the efficiency of the drying process by keeping better control over chamber pressure, maintaining gas composition in the chamber (i.e. the ratio of water vapor to nitrogen), reducing the drying time and by minimizing the number of edge vials.^[4]

4.2.6 Effect of gas composition in the chamber

The total pressure exerted by water and gas determines the mass of water molecules that will vaporize. Once the dried layer starts forming at the surface due to sublimation and proceeds towards the centre of the container, it restricts the escape of water molecules.^[9]

If the number of vials on the shelf is less than optimum, the levels of molar fluxes of water vapor and nitrogen in the chamber vary with percentage of nitrogen being much higher than required. This reduces the overall vial heat transfer coefficient leading to lowering of product temperature and prolongation of drying time.^[4]

4.3 Container-closure related variables

Freeze-drying is usually done in standard primary packages like vials and dual chamber systems. A new closed vial filling system has been developed to ensure better sterility of the product during the process.^[25, 26]

The type, geometry of the vial affects the process of heat transfer and stopper type and design has a significant impact on the mass transfer. Moreover, similar processing conditions for

stoppers and vials should be employed at all scales of production to ensure uniformity in the composition of the extractable components.^[3] Judicious selection of container-closure system in freeze-drying is an essential pre-requisite, especially in commercial scale since the principles governing heat and mass transfer in large-scale vary significantly from those in glass vials. Intensity of heat transfer through radiation depends on the composition and geometry of the container.^[9] It may be noted that the conditions found to be suitable for vials may not be appropriate for pre-filled syringes. Other alternative container-closure systems include ampoules, 96-well plates depending on the end-use. Long-term storage stability of freeze-dried pharmaceutical and biological products is affected by closure system.^[4] Rubber closure is a potential source of problem in laboratory scale. However, the problem becomes magnified while operating on large scale because of large batch size. Rubber has a tendency to absorb moisture which may be desorbed during different stages of freeze-drying and can alter the operating conditions.^[27]

CONCLUSION

Development and optimization of the process of lyophilisation in industrial scale is related to the target product profile. Design of process parameters and product quality attributes should be considered as an integrated process and not as a sum total of some unit operations with no relation among them. Scaling up needs a precise knowledge about the capability and limitations of a large-scale dryer. The goal of designing a control system for the process is to minimize drying time and hence operating cost.

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