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Nanosuspension: A Bridge between Drug Discovery and Formulation?

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ABSTRACT

Delivering the therapeutic agent to the desired site is a major problem in the ailment of various diseases. The most important branch in the pharmaceutical sciences called as 'Pharmaceutical nanotechnology' presents numerous new tools, scope, opportunities and potential drug delivery which are expected to have various applications in the field of diagnosis and therapeutics. The interest in preparation and its application of nanomaterials is increased due to their potential drug delivery system. Currently, the nanoscale formulation has received tremendous interest to solve the solubility issues. Nanosuspension brought a revolution in the pharma industry by overcoming the solubility, dissolution and bioavailability problems also it improves the drug safety and efficacy. An alarming increase in new drug formulation based on nanoscale reduces the gap between drug discovery and formulation.

INTRODUCTION

Site-specific delivery of a therapeutic agent is a serious problem faced in the treatment of diseases. The utilization of drugs characterized by poor biodistribution, unwanted side effects, limited or minimal effectiveness, and limited selectivity is achieved at higher risk.

Nanotechnology is a newer approach towards problem-solving and is a collection of tools, ideas, and opportunities that considered to be applied in the pharmaceutical industry. Nanotechnology application in Pharmaceutical R&D field is expected to move the industry from "blockbuster model" drug to "personalized drug therapy".

Pharmaceutical scientists face a formulation problem in poorly water-soluble drugs which becomes a challenge for them and nearly 40% of new chemical molecules are poor water-soluble one. A Pharmaceutical nanosuspension is "drug particles very finely dispersed in the aqueous vehicle, followed by surfactant stabilization administered orally, topical, parenteral and or pulmonary route with reduced particle size leading to improved dissolution rate and thus the enhanced bioavailability." As a consequence of improved solubility, the concentration of active compound increases and plasma maximum is reached fast. Also, the nanosuspension has the added advantages of formulating the insoluble drugs, oils, reduction of the dosage volume and can achieve passive drug targeting [(1)].

Currently, nanomedicine science is the fascinating field of research and numerous drugs have been formulated and marketed with the aid of nanotechnology. This field offers a profound influence on better treatment strategy by providing better insights into the molecular basis of various diseases[(2)].

Solubility

The success of a formulation depends on drug availability at the site of action. Solubility is the process of dissolution of solid particles in a liquid phase to get a homogenous system. In a saturated solution, the solute will be in equilibrium with the solvent. The solubility can be expressed as a percentage, parts, molality, molarity, volume fraction etc. Estimation shows that nearly 40% of new chemical entities (NCEs) which are active are poorly water soluble. As per the Biopharmaceutical Classification System(BCS), a guide for predicting intestinal drug absorption by USFDA all the available drugs are classified into 4 types. The drugs under

class II and IV suffers from low solubility issue. As per USP and BP the solubility criteria is given as [3, 4, 5]:

Table 1: Descriptive terms of solubility

Descriptive term	Part of the solvent required per part of the solvent
Very soluble	Less than 1
Freely soluble	1-10
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble	10,000 and above

Poorly soluble drugs often require higher doses in order to reach therapeutic plasma concentrations. Some techniques involved in enhancing the solubility are altering the pH, adding co-solvents, particle size reduction, complexation, supercritical fluid process, micellar solubilization etc. The various advantages and disadvantages of the above-said methods are tabulated below.

Table 2: Advantages and disadvantages of solubility enhancement techniques

Method	Advantage	Disadvantage
pH adjustment	Simple and rapid to formulate and analyze Amendable and use a small quantity of material	Risk of precipitation(and form thrombi or emboli) Tolerability and Toxicity related problems. Alteration in pH may affect the stability of the formulation
Adding cosolvents	Simple and rapid to formulate and analyze	Stability issues. Toxicity and Tolerability related problems.
Particle size reduction	Can formulate rapidly Low cost of production Can maintain stability Can increase bioavailability	Particle agglomeration plays a difficult task Sterilization becomes challenging.
Microemulsions	Easy and rapid formulation Increase bioavailability	Tolerability for surfactants Precipitating nature Challenge for validation

Out of this, the size reduction has the maximum utilization in the day to day processing of drug materials for formulation. The size reduction technology has the positive effects like Increased Surface Area, Enhanced Solubility, Increased Dissolution rate, Increased Bioavailability, Rapid Onset of Therapeutic Action, reduced dose Required, Decreased Fed/Fasted Variability, and decreased Patient-To-Patient Variability.

Nanotechnology

Nanotechnology and nanoscience are widely seen as having great potential to bring benefits to many areas of research and applications. The term "nanotechnology" was first used in 1974, when Norio Taniguchi, a scientist at the University of Tokyo, Japan, referred to materials in nanometers 1.

Nanotechnology is a multidisciplinary field which literally means any technology on a nanoscale that has applications in the real world. Nanotechnology is the science that deals with the processes that occur at the molecular level and of nano length scale size (i.e. 10-9) [(6)].

The term nanotechnology was first used by Taniguchi in the year 1974. The different fields of applications of nanotechnology are Health, Medicine, Electronics, Transportation, Space exploration, Energy and Environment [(2)]. In technological advancements, Nanoparticles gained a prominent role due to their adjustable physiochemical characteristics such as flow properties, melting point, wettability, thermal and electrical conductivity, light absorbance and scattering which enhances their performance in the formulation. In the International system of units, nm represents 10^{-9} meter in length. The USFDA represents nm as "materials which have at least one dimension in the approximate range of 1-100nm and exhibit dimensional dependent phenomena"[(7)].

At the level of nanoscale, the nanoparticles exhibit unique properties of physical, chemical and biological when compared to their respective particles at higher scales. The nanoparticles possess various dimensions, size, and shapes. It can be tubular, cylindrical, spherical, hollow core, spiral, flat, conical etc. or irregular with variation in their surface. Some of the nanoparticles are amorphous or crystalline with loose or agglomerated single or multicrystal solids.

Many synthesis methods are being developed or either improved to reduce the production cost and enhances their properties. Some modified methods of producing nanoparticles increase their physical, mechanical, optical and chemical properties. A wide development in the field of instrumentation led to improvement in characterization and subsequent application of nanoparticles. Nanoparticles are now flooded in every sector for production and improving product quality.

Classification of Nanoparticles

The nanoparticles are classified mainly into organic, inorganic and carbon-based particles [8].

Organic nanoparticles

These types of nanoparticles are nontoxic, biodegradable and some of the particles like micelles and liposomes have a hollow core (nanosuspension) and are sensitive to heat and light. Examples of such particles are dendrimers, liposomes, ferritin, and micelles. These types of nanoparticles are widely used in the biomedical field as they possess efficient and targeted drug delivery system.

Inorganic nanoparticles

These particles are made up of metal and metal oxides and not of carbon. Metals like aluminum, cobalt, copper, cadmium, gold, lead, silver, iron and zinc are used for the synthesis of nanoparticles either by the destructive or constructive process. The metal oxide nanoparticles like aluminum oxide, titanium oxide, zinc oxide, iron oxide, magnetite oxide, and silicon dioxide are commonly synthesized. These compounds have distinct properties like surface characteristics, shape, color, sensitivity and reactivity.

Carbon-based nanoparticles

These nanoparticles are made up of carbon and are further subclassified into graphene, fullerenes, carbon nanotubes, carbon nanofibres etc.

Synthesis of nanoparticles The method of synthesis of Nanoparticles can be categorized into the bottom-up or top-down method.

Bottom-up method: This is a constructive method which involves building up of materials from atoms to nanoparticles. The methods in this category are sol-gel, chemical vapor deposition, spinning, pyrolysis and biosynthesis.

Top-down method: This involves destructive method which employs the reduction of bulk material to nanoparticles. The methods of this category are nanolithography, laser ablation, thermal decomposition, mechanical milling and sputtering.

Properties of Nanoparticles(Ealias AM)

Physical

The physical properties of the nanoparticles include optical properties such as color, light penetration, absorption, and reflection and the UV absorption properties. The mechanical properties such as elastic, tensile and ductile strength and flexibility offer a significant role in their application. Other properties such as suspension, hydrophilicity, hydrophobicity, diffusion and settling characters found its way in the modern day to day things. Also, the magnetic and electrical properties of the nanoparticles are used in modern electronic tools for their energy applications.

Chemical

The properties such as reactivity with target, stability, and sensitivity to factors such as heat, moisture, atmosphere, and light determine its application in the particular field. Corrosive-anticorrosive, oxidation-reduction and flammability characters of nanoparticles determine their usage.

Nanosuspension

In the field of biomedicine, the nanoparticle plays an important role in the diagnosis and efficient, targeted drug delivery. Nanosuspensions are favored for water-insoluble compounds with a high melting point, high log P value and high doses. This technology can also be used for water and organic solvent insoluble drugs. Hydrophobic drugs can be formulated as nanosuspension[9, 10].

Nanosuspensions are defined as colloidal dispersions of nano drug particles stabilized by surfactants. It can also be defined as a biphasic system which consists of pure drug particles

dispersed in an aqueous vehicle with the diameter of the suspended particle just less than 1µm in size.

Preference for Nanosuspension Approach

The compounds that are water-insoluble (soluble in oil) with high log P value.

The drugs that are water-insoluble but soluble in the oil phase system are formulated in the liposome, emulsion systems.

Formulation approaches not applicable to all drugs.

Nanosuspensions are used as a formulation approach for drugs that are insoluble in both water and in organic media instead of using lipidic systems[11, 12].

Nanosuspension formulation is most suitable for the compounds with high log P value, high melting point, and high dose.

Potential Advantages of Nanosuspension Technology in poorly soluble drugs

Particle size reduction, increase in drug dissolution rate and absorption, increased bioavailability, AUC versus time, onset and peak drug level, reduced variability and fasted/faded effect[13, 14, 15].

The nanoparticles can adhere to the mucosal lining of the gastrointestinal tract thus prolonging the contact time of the drug and enhancing its absorption.

Nanosuspension can be administered through various routes such as parenteral, oral, dermal, pulmonary, and ocular.

Nanosuspension drug delivery has a low incidence of side effects with its excipients.

Nanosuspension overcomes drug delivery issues. It also improves the resistance to oxidation and hydrolysis thus enabling physical stability.

It reduces the administration volumes and also it encompasses the passive targeting[16].

Methods for Preparation of Nanosuspension

The conventional bottom up and top down technologies are used for the preparation of nanosuspensions. The various methods employed and their advantages and disadvantages are summarized below[17].

Bottom-up technology

The process starts with molecular level and goes through its association to form solid particles. Example: pouring the solvent to nonsolvent, changing the temperature or combining both. The classic technique is precipitation in the pharmaceutical chemistry and technology field.

Advantages

Simple in preparation

Low cost of equipment.

High saturation solubility needed for achieving precipitation.

Disadvantages

Need to be soluble in at least any one solvent

Need Solvent miscibility with one nonsolvent

Removal of solvent residue increases the production cost.

Need precaution to preserve the particle character.

Top-down technology The technologies of this method are

Media milling The method was developed by Liversidge *et al.* in 1992. The nanosuspensions are produced by the use of high shear mills or pearl mill. It consists of a milling chamber, the recirculation chamber, and shaft. The aqueous drug suspension fed into the mill contains grinding balls and these balls rotate at a high shear rate with controlled temperature. The forces of friction and impact produce particle size reduction. The balls are made up of

ceramic sintered aluminum oxide or highly cross-linked polystyrene resin or zirconium oxide with high abrasion resistance. Example: production of Zn –Insulin by wet milling technology.

Advantages

Simple and easy for the formulation of nanosuspension of poorly soluble drugs.

Low cost

Production on a large scale and flexibility in handling drug quantity.

Disadvantages

Product contamination by erosion of the mill.

A long duration of the process can engage the growth of germs.

More time and cost for the separation procedure of the milling materials is required.

High-Pressure Homogenization

Dissocubes/Homogenization in water

This method was developed by Muller *et al.* in 1999. It involves forcing the suspension under pressure through a small orifice which results in reduced static pressure below the boiling point of water and forms gas bubbles. On leaving the gap the suspension reaches the normal air pressure, the bubbles start to implode and the drug particle in the surrounding rushes to the center and colloid thus causing the particle size reduction. This is called cavitation. (Shid RL).

Advantage

It can be employed for the production of both diluted and concentration suspension.

It allows for aseptic production.

Narrow size distribution of drugs can be achieved.

It doesn’t cause and erosion of the processed materials.

Disadvantages

It needs pretreatment for obtaining the nanoparticles before the commencement of homogenization. (A. Kumar, G. A. Reddy).

Nano pure/Homogenization in nonaqueous media The suspension is homogenized in water mixtures or water free media. The drug suspension in aqueous media was homogenized at 0^{o} C or below the freezing point and called as deep freeze homogenization.

Advantages

It can be used for thermolabile materials at milder conditions.

Nano edge/Combined precipitation and homogenization

The production technique involves a microprecipitation step (a solvent-antisolvent technique) followed by a high-energy homogenization process. It employs the homogenization of precipitated suspension leading to particle size reduction and minimizes the crystal growth. For effective nano edge technology, an evaporation step is included for the solvent-free starting material.

Disadvantages

The residual solvent is the major problem associated.

More tedious and expensive to achieve the particle size compared to other methods.

Emulsion Diffusion Method

The Emulsion can also be used as a template for nanosuspension production. This can be applied to drugs that are soluble in a volatile organic solvent and or water-miscible solvent. The so formed emulsion was further homogenized with high pressure. After repeated cycles, the emulsion was diluted with water and homogenized to diffuse the solvent and convert the drop into solid particles. (Venkatesh T).

Advantages

No need of specialized equipment.

Particle size can be controlled by controlling the emulsion droplet.

Disadvantages

Drugs of poor solubility in both aqueous and organic solvents cannot be formulated by this method.

High quantity of surfactant and or stabilizer is required.

A need for di ultrafiltration may render the process costly.

Microemulsion template

This method employs the organic solvent or mixed solvent loaded drug in an aqueous phase with suitable surfactants for emulsion formation. The organic solvent is then evaporated under reduced pressure to produce drug particle precipitate which instantaneously forms nanosuspension stabilized by surfactants. (Paun JS, Vaghela A).

Advantages

No need for specialized equipment and consumes less energy.

Increase in drug solubilization and long shelf life.

Particle size can be controlled by controlling the droplets of an emulsion.

Disadvantages

Poorly soluble drugs cannot be formulated.

Need for di ultrafiltration purification which makes the process costly.

Surfactant and or stabilizer are required in high amount.

Supercritical fluid method

The various process of this method is a rapid expansion of supercritical solution (RESS), Precipitation along with compressed antisolvent process (PCA) and supercritical antisolvent process. The rapid expansion of supercritical solution (RESS) involves the expansion of the drug-containing solution as supercritical fluid through a nozzle which leads to loss of solvent

power of supercritical fluid which results in drug precipitation as fine particles. By PCA method the atomized drug solution is compressed in the CO_2 chamber. The solution is supersaturated as the solvent is removed and thus the fine crystals are precipitated. In the supercritical antisolvent process the supercritical fluid on which a poorly soluble drug and the solvent for that drug are also miscible is used. The solution of the drug is injected into the supercritical, solvent extracted by supercritical fluid and the drug is supersaturated and precipitated into crystals.

Advantages Same as emulsion diffusion method with an added advantage of less energy input needed for production.

Disadvantages

Need for hazardous solvents, surfactants, and stabilizers for the production.

Nucleation overgrowth may appear due to supersaturation.

Melt emulsification method

The method involves the drug dispersion in aqueous solution with stabilizer, heated above the melting point of drug and homogenized to produce emulsion (Verma KAK).

Dry Co Grinding

This method uses dry milling techniques and employs the grinding of poorly soluble drugs with polymers and copolymers which are soluble. Polymers and copolymers such as sodium dodecyl sulfate (SDS), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), cyclodextrin and polyethylene glycol (PEG) were used in this preparation.

Advantages

Provide improvement in surface polarity and it aids in the transformation of crystalline to amorphous form. (Sunder S).

Formulation consideration in a Nanosuspension

Organic solvents

An Organic solvent is required for the formulation of nanoparticles in case of using emulsion or microemulsion template method. The solvent selection criteria are based on the acceptability, toxicity potential and ease of removal from the formulation. The pharmaceutically acceptable, less hazardous and their water miscibility of the solvents are given below.

Water-miscible solvents: ethanol and isopropanol.

Partially water-miscible solvents: ethyl acetate, ethyl formate, triacetin, benzyl alcohol, butyl lactate, and propylene carbonate [(18)].

Stabilizer

Stabilizers are used to help the formulations to maintain the desirable properties of the product until it is consumed by the user. The function of the stabilizer is to wet the drug particles, to prevent Ostwald's ripening and agglomeration in order to yield a physically stable nanosuspension by providing a steric and or ionic barrier. The type and the quantity of stabilizer have a sound effect on physical stability and behavior of nanosuspension. In certain conditions, a mixture of stabilizers is used to get a stable nanosuspension formulation. Various ratios of drug to stabilizer ratio can be used (from 1:20 to 20:1). The explored stabilizers are poloxamers, lecithins, povidones, polysorbates, and cellulose. Lecithin is the choice of stabilizer to develop parenteral and autoclavable nanosuspension[(19)].

Co-surfactants

It is critical to choose co-surfactant in microemulsion for the formulation of nanosuspension since it can influence greatly on phase behavior. Literatures describes the use of dipotassium glycyrrhizinate and bile salts as cosurfactants and a number of solubilizers like ethanol, isopropanol, glycofurol, and transcutol can be used as co-surfactants.

Other additives

The nanosuspension may contain various additives such as polyols, osmogent, cryoprotectant, salts, and buffers depending upon the properties of the drug or its route of administration.

Post-production process

The post-production processing for nanosuspension is essential when the drug is greatly susceptible to chemical degradation or hydrolytic cleavage. It is also required to achieve the stability of the formulation in its desired route of administration after adding the stabilizer. To overcome this problem lyophilization and or spray drying can be employed to give a dry powder of nano drug particles. Consideration should be given to post-production processing for particle size and moisture of the dried nanoparticles.

Characterization methods of Nanosuspensions

Colour, Taste, Odor

These characters are very important in oral formulations. The change in particle size, crystal structure, and altered dissolution may attribute to change in taste. Instability can also be indicated by a change in color, odor, and taste.

Particle size distribution

Particle size and polydispersity index are very important characteristics of nanoformulation. The particle size of a nanoformulation determines the following characteristics such as physical stability, drug saturation solubility, dissolution rate, and bioavailability. Particle size distribution nanoformulation can be determined by coulter counter ultisizer, photon correlation spectroscopy, and laser diffraction.

Particle Charge/Zeta Potential

The charge of a particle plays a major role in the stability of nanoformulation. The electric charge of a particle surface provides an electrostatic repulsion between the nanoparticles of the drug and in this way it prevents the particle from aggregation and precipitation. A minimum of ±30mV Zeta potential is required for a stable nanosuspension. The particle charge can be measured by electrophoretic mobility by application of electric field which can

be converted of zeta potential and by the application of ultrasound wave which in turn induces the electroacoustic phenomenon.

Dissolution velocity and Saturation solubility

The important advantage of nanosuspension over other techniques is that it can increase the velocity of dissolution and saturation solubility. These two parameters must be assessed in various physiological solutions. This assessment of the two parameters helps to determine the *in-vitro* behavior of the nanoformulation.

Crystal Morphology

The polymorphic changes of the crystalline drug due to high-pressure homogenization can be characterized by an X-ray diffraction analysis technique in combination with differential thermal analysis or differential scanning calorimetry. A change in the crystalline nature of a nanosuspension from amorphous to another polymeric form can occur due to high-pressure homogenization.

Density

It is an important parameter of the nanoformulation. Density must be measured at a given temperature by well-mixed uniform formulation. A drop in density indicates the entrapped air present within the formulation. Precision hydrometer facilitates the measurement of density.

pH value

For aqueous formulations, the pH should be measured at a given temperature only after reaching the settling equilibrium to minimize the pH drift and electrode surface coated with the formulation particles. Electrolytes are not supposed to add to the external phase of the formulation to stabilize the pH.

Stability

The higher surface energy of nanoparticles induces crystal drug agglomeration. The important function of a stabilizer is wetting of drug particles for prevention of Ostwald ripening and agglomeration of the nanoformulation by providing a steric or an ionic barrier thus forming a physically stable formulation.

Viscosity measurement

In lipid-based formulations, the viscosity of several compositions can be measured at various shear rates at different temperatures by the use of Brookfield type rotary viscometer. The instrumentation room for sample measurement must be maintained at 37^0 by using a Thermo bath.

Droplet size:

The size of a droplet of microemulsion vesicles can be determined by electron microscopy or light scattering technique. The Spectrophotometer of dynamic light scattering with the neon laser can be used at a wavelength of 632nm.

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***In-vivo* Biological evaluation**

A successful formulation needs an establishment *in-vitro*/*in-vivo* correlation along with monitoring of the *in-vivo* drug performance which is an essential area of the study. The *in vivo* behavior nanoformulation depends on the organ distribution of drug which in turn is dependent on surface properties like surface hydrophilicity and plasma protein interaction. The qualitative and quantitative protein absorption pattern is observed which recognize the organ distribution of the nanoformulation. Suitable and updated techniques must be followed for the evaluation of surface properties, adhesion properties, and protein interaction.

Applications

Some of the significant applications of nanoparticles are cosmetics, sunscreens, catalysis, food, construction, electronics, and medicine.

Intra-venous route

The intravenous route provides a quicker onset of action, targeting and reduced drug dosage. It is the most preferred route for drugs following first pass metabolism, drugs that are not absorbed in GIT or undergo degradation in GIT. Intravenous administration of nanoparticles has several advantages such as the administration of poorly soluble drugs without toxic cosolvents, increasing the therapeutic effect of the drug as in conventional formulation and drug targeting.

Pulmonary route

The nanosuspension used in the pulmonary route can eliminate systemic toxicity and focused delivery promotes localized action and effective therapy.

Oral route

The major problem of the oral route for drug delivery is poor solubility, low dissolution, and reduced efficacy. Because of small particle size and large surface-volume ratio, oral nanoformulations are especially used to increase the rate of absorption and bioavailability of hydrophobic drugs.

Ocular route

Ocular route of delivering nanosuspension of drugs provides a sustained release and provides improved shelf life and increased bioavailability of the drug.

Enhanced bioavailability

The poorly bioavailable drugs due to its poor solubility, permeability, and stability through its conventional dosage form can be resolved by switching to nanoformulation.

Targeted drug delivery

As the surface properties of the particles and the *in-vivo* behavior of particles can be altered easily the nanosuspension can be aimed for targeted drug delivery. Careful engineering of nanosuspensions by using various technologies the active or passive drug targeting can be achieved.

Mucoadhesion nanoformulation

The orally administered nanosuspension contains nanoparticles that diffuse into the media and rapidly encounters the surface of mucous. By the mechanism of bioadhesion, the particles are immobilized at intestinal wall. The direct contact of the intestinal wall to the particles by bioadhesion phase is the initial step in particle absorption. This adhesiveness of the particles helps to improve bioavailability and drug targeting. This bioadhesion can be improved by using mucoadhesive polymer during formulation.

The nano-formulated drugs can improve drug stability, increase bioavailability and can be used for drug targeting. Some of the examples for nano formulation have been reported below.

Table 3: Examples for nano formulation

Drug	Route of administration	Manufacturing method
Diclofenac sodium	Dermal	Controlled crystallization during freeze drying
Rutin, Hesperidin	Dermal	Wet milling and high- pressure homogenization
Hydrocortisone	Ocular	Wet milling and Microfluidic precipitation
Forskolin	Ocular	Wet Milling
Itraconazole	Pulmonary	Wet Milling
Budesonide	Pulmonary	Wet Milling

CONCLUSION

Nanosuspension is a unique and historical approach to remove drug formulation issues like poor bioavailability of hydrophobic drugs. This technology can be combined with traditional dosage forms. Since this technique is simple, cost-efficient, increase the dissolution and bioavailability many poorly soluble drugs of BCS II & IV drugs can be formulated through this technology. This technology is boon to the pharmaceutical industry as it reduces the gap between drug discovery and formulation. Also, many plant-based medicines with proved biological activity which suffers from formulation issues can be solved with nanoformulation without destruction of its active constituents. Thus this technology can play a significant role in drug discovery and its formulations.

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