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SOLID DISPERSION – BASED DRUG DELIVERY SYSTEMS: FOR ENHANCED SOLUBILITY AND BIOAVAILABILITY

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ABSTRACT

Solid dispersion is an effective formulation technique to enhance the solubility, dissolution rate and bioavailability of poorly water-soluble drugs. It included the dispersion of a suitable carriers that are either mostly hydrophilic or mostly hydrophobic containing this active pharmaceutical ingredient (API). These common carriers are polyvinylpyrrolidone (PVP), Soluplus, hydroxypropyl methylcellulose (HPMC) and ethyl cellulose. The preparation of these techniques is widely available: fusion technique, solvent evaporation, hot-melt process and spray drying. Besides solubility enhancement, the proper selection of the polymers may also enable of controlled and/or sustained drug release in solid dispersions. Recrystallization, moisture sensitivity and physical instability are challenges that must be taken into account, however. The present review highlights the various types of solid dispersion systems including the methods of preparation, characterization and application in augmenting drug bioavailability and formulation of controlled release dosage forms.

KEYWORDS: Solid dispersion; Solubility enhancement; Amorphous Solid dispersion; Controlled drug release; Polymeric carriers; Bioavailability.

1. INTRODUCTION

1.1 Overview of solid dispersion systems

Solid dispersion is a formulation technique employed in manufacturing of poorly soluble and less bioavailable API. This technique involves dispersion of a water insoluble API in a water-soluble carrier, thereby enhancing the solubility and improving the bioavailability of the formulation. The utilization of polymeric carriers has an impact on the stability of the amorphous API. The concept of solid dispersion systems was first introduced by Sekiguchi and Obi in the year 1961 and first utilized in the year 1966 by Mayersohn and Gibaldi. This method can be employed in improving the biopharmaceutics of BCS class II and class IV drugs. Conversion of crystalline compounds to amorphous compounds leads to an increase in the effective surface area of a particle thereby increasing the solubility. This technique is conventionally utilized to improve the solubility of poorly soluble drugs but the thermodynamically unstable nature of amorphous compounds is a drawback to this method, which can be overcome by the utilization of amorphous solid dispersion systems commonly known as ASD. ASDs have proven to be an excellent alternative to improve the poor solubility drugs.[1]

1.2 Challenges of conventional systems and need of solid dispersion systems

The various drawbacks of conventional dosage forms such as increased toxicity, less patient compliance, immediate drug release has led to the need for development of controlled drug delivery systems. Controlled drug delivery systems usually are formulated to release the drug at a predetermined rate and target site thereby reducing the side effects of the drugs. The biggest drawback of controlled drug delivery systems is dose dumping or burst release which is the release of large amounts of drug before the specified time this leads to decreased effectiveness of the drug or may lead to systemic toxicities. Solid dispersion systems have been utilized as an alternative to conventional drug delivery systems. Use of different water soluble and water

swellable polymers to modify the solid dispersion systems can lead to the formulation-controlled delivery systems. Methods such as rapid solvent evaporation, fusion, lyophilization, melt extrusion have been extensively utilized in the preparation of solid dispersion systems. This review aims to cover the various aspects of solid dispersion systems its major utilization in enhancing solubility of poorly soluble drugs and its application in formulation of controlled drug delivery systems. It includes the information about various carriers utilized in preparation and methods utilized along with other aspects of solid dispersion technique.[2]

2. CARRIERS

Carriers are a major part of the formulation of solid dispersion systems. They primarily determine the solubility of the drug that is a water-soluble carrier enhances the solubility of the formulation thereby increasing the dissolution and bioavailability whereas a water insoluble carrier helps in formulation of a controlled drug delivery system. Polymers are the most commonly used carriers in solid dispersions. Polymers can be broadly classified into natural, semi-synthetic and synthetic polymers based on their origin. Polymers of plant origin are proven to have suitable characteristics of a carrier so are widely used in SDs. Synthetic polymers such as polyvinyl and acrylate derivatives are one of the most commonly used once. Semi synthetic ones like cellulose and its derivatives are also found to be used widely. Various synthetic and semi synthetic polymers commonly used and their properties are listed below:

2.1 Polyvinylpyrrolidone [PVP]

Polyvinylpyrrolidone structurally contains a carbonyl and amide functional groups which are said to be responsible for the interactions with drug molecules thereby inducing more solubility to the drug. The carbonyl group acts as a hydrogen bond acceptor and the amide group helps in formulation of a suitable drug delivery system. It is the most commonly used polymeric carrier with a molecular weight around 2,500 to 3,000,000 Da. PVP helps in stability of amorphous solid dispersion by inhibiting the phase separation thereby facilitating the formulation of ASDs. This property of PVP can be justified using the study of curcumin where the ASD showed complete dissolution compared to the crystalline form. PVP is highly hygroscopic in nature contributing to the instability due to moisture absorption.

2.2 Copovidone [PVP/VA]

PVP-VA is a copolymer made up of polyvinyl pyrrolidine and vinyl acetate manly used in the ratio of 6:4. It is comparatively less hygroscopic than PVP alone and has high stability to greater temperatures. Owing to this property it is mainly used to formulate SDs using fusion and solvent methods. The element responsible for drug polymer interaction in PVP-VA is vinyl acetate. PVP-VA62 is used for preparation of controlled release solid dispersions as it is amphiphilic in nature, thereby solubilises in both hydrophilic and hydrophobic solvents. This property can be supported by the itraconazole solid dispersion prepared by hot stage extrusion method.[3]

2.3 Soluplus

Soluplus is a co polymer composed of PEG, Polyvinyl caprolactam, Polyvinyl acetate. It enhances the solubility by micellar solubilisation owing to its amphiphilic nature. The solid dispersions of rivaroxaban and 9-nitrocamptotecin with soluplus suggest the same. It is less hygroscopic, remains as a dry powder at normal conditions where others tend to form sticky masses. It has a high molecular weight around 1,00,000g/mol and high degradation temperature.

2.4 Acrylates and methylacrylates

These are commercially known as Eudragit. They are glassy substances available as powders, dispersions and organic solutions. The various forms of Eudragit are Eudragit L, Eudragit RL, Eudragit RS, Eudragit RLPO, Eudragit RSPO, Eudragit EPO, Eudragit S100, Eudragit L100-55. Eudragit L is an anionic copolymer of metylacrylic acid and methyl methacrylate. It is soluble in alkaline solvents. It is mainly used in enteric coated formulations. Eudragit RL and RS are polymers of ammonium methacrylate. They contain quaternary ammonium group which is responsible for permeability of polymers. Eudragit EPO is a cationic polymer which is soluble at low pH and swells at higher pH. It is used as a carrier for acidic drugs. Eudragit S100 is an anionic carrier which gets fully ionized at basic pH. Solid dispersion of celecoxib using the same has been proved to have more bioavailability than the conventional forms. Eudragit S100 has shown increased stability in case of ASDs. Eudragit L100-55 is a copolymer of methyl acrylic acid and ethyl acrylate. It has been proved to slow the drug release in acidic environment in the ezetimib and lovastatin SD. It is shown to reduce crystal growth and nucleation.[4]

2.5 Ethyl cellulose

It is a long chain polymer having repeating units of beta anhydrous glucose joined by acetyl groups as linkers. It is a cellulose ether and is hydrophobic in nature. It is in commercial use as a binder and coating material. It has been used in formulation of drugs ranging from soluble to sparingly soluble. Studies suggest that the rate of drug release is affected directly by the quantity of polymer used. Higher the polymer concentration lower is the rate of drug release. Drugs such as indomethacin, acetaminophen, ketoprofen have been formulated into SDs using ethyl cellulose as carrier.

2.6 Hydroxypropyl cellulose

Hydroxypropyl cellulose (HPC) is a thermoplastic, nonionic cellulose ether having excellent thermo plasticity, low melt viscosity, film forming property, mechanical strength, which is suitable for hot-melt extrusion and amorphous solid dispersion (ASD) formulations. HPC is present in different molecular weights and various grades of viscosity, and has a broad

range of applications, such as binder, film-coating agent and controlled-release matrix former. Research shows that HPC can enhance drug dissolution, bioavailability and therapeutic effectiveness by facilitating the formation of amorphous drug and hydrogen bonding. It has an effect on the drug release rate, viscosity, and possible drug–polymer interactions, making it useful in pharmaceutical formulation and controlled-release drug delivery.[5]

2.7 Hydroxypropyl methyl cellulose

Hydroxypropyl methyl cellulose commonly known as HPMC is a cellulose ether that is a combination of both alkyl and hydro alkyl components. HPMC 1828, HPMC 2208, HPMC2906, HPMC2910 are the four different types specified in the USP. Research has been done to produce sustained release verapamil with HPMC which showed increased release time compared to other polymers. It is suitable for both hydrophilic and lipophilic drugs. The drawback with HPMC is its high melt viscosity which is why ASDs using HPMC are prepared by the method of spray drying.

2.8 Hydroxypropyl methyl cellulose phthalate

HPMCP is a phthalyl acid ester of HPMC where the phthalyl acid is the group responsible for bonding with the drug. Two forms HPMCP 55 AND 50 are available commercially. It is most commonly used in enteric coated formulations and is proved to increase the stability of drug as in the case of clofazimine. It has a molecular weight around 20,000 to 2,00,000. Sustained release formulation prepared using the same is acetaminophen along with chitosan as a carrier, using spray drying method.

2.9 Hypromellose acetate succinate

HPMCAS is an ester form of HPMC prepared using acid anhydrides and succinates. It is proved to have various advantages over other carriers such as inhibition of crystallization, enhanced stability to moisture, increased solubility etc.[6]

2.10 Other carriers

PEGs, Poly acrylic acids, PEOs are also in use as polymeric carriers. Recent studies are based on various plant based natural polymers including gummy exudates of T. catappa linn for a sustained release formulation of dexomethorphan. Methyl cellulose, chitosan, ethyl vinyl acetate has also been tested for formulation of controlled delivery SD s. Other plant polymers include Aegle marmelos gum, caffeine, chitosan, Neem gum etc.[7]

3. PREPARATION METHODS

There are a number of methods for making a solid dispersion, depending on the physicochemical properties of the drug and the carrier, their thermal stability and miscibility, and what their intended function be is for the drug to be released. Classical methods include melting or fusion of the material and solvent evaporation or a combination of these methods, with more modern methods such as hot-melt extrusion, spray drying, lyophilization and techniques using supercritical fluids. Appropriate processing is especially important when producing amorphous solid dispersions (ASDs). In such cases, the goal is to disperse the drug in the carrier, preferably at the molecular level, with a minimum of crystallization.[8]

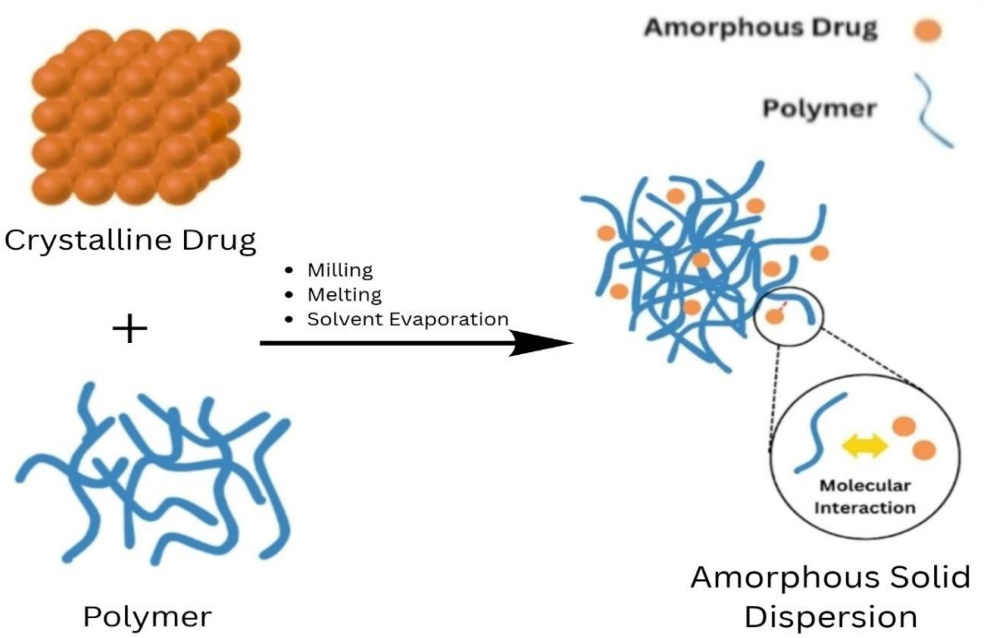


Fig. 1: Schematic representation of crystalline and amorphous drug in a polymeric carrier.

3.1 Fusion or melting method

The fusion method requires preparation of the drug-carrier physical mixture and then heats to melt the mixture until the drug and carrier are fused together. The molten material is then quickly chilled and the material that has solidified is crushed, pulverised and sieved. Rapid quenching may establish a super-saturated system thus minimising molecular rearrangements, leading to drug formation inside the carrier in a finely dispersed or amorphous state. These drawbacks include need for high temperatures, medicaments degradation during melting and lack of miscibility between the medicament and the carrier.[9]

It is also possible to use a melting method to incorporate a drug into a water-insoluble or water-swellable carrier for controlled-release solid dispersions. These types of carriers affect the diffusion and dissolution of the drug incorporated in them, but do not give the rapid dissolution of drug which 100% hydrophilic solid dispersions provide. Therefore, the type of carrier can alter the significant role of solid dispersion from being a solubility enhancing to a sustained or controlled release agent.[10]

3.2 Solvent evaporation method

Solvent evaporation involves dissolution of the drug in a common solvent which is volatile, and then evaporation of the solvent to yield the matrix of the drug. It is desirable if mixing is done at the molecular level as this results in favourable dissolution properties. There are two particular formulation problems that can arise: firstly, if the drug and polymer are very polar, they may not be soluble in the same solvent and one strategy would be to find a solvent system such that they are both soluble; secondly, the drug and/or the polymer may crystallise or phase separate during film removal.

The same is true for controlled-release formulations when using the solvent evaporation method. Carriers can be water insoluble polymers like ethyl cellulose (EC) and other polymers controlling the release. The quantity and characteristic of the polymer plays an important role to control the drug release. For instance, increase of the EC concentration is correlated to a decrease in drug release rate from solid dispersions.

3.3 Hot-melt extrusion

The Hot Melt Extrusion is similar to the fusion method, but intensive mixing is done through an extruder. This process may be divided into the following stages: feeding and conveying of components; flow of components through the die; flow of components out of the die down stream processing. A major benefit is that the heated drug–polymer combination could be moulded into various drug products, such as oral dosage items, implants, and ophthalmic inserts.

The use in marketed ASD FORMULATIONS is another indication of the practical importance of HME. In the recent review, HME is mentions as one of the processing technologies in commercial ASD products with drugs like verapamil, ritonavir/lopinavir, itraconazole, posaconazole, suvorexant and venetoclax.[11]

3.4 Spray drying and lyophilization

Rapid solvent removal processes are beneficial to the production of ASDs. Spray drying is especially relevant to the current advancement of the ASD field, and a number of commercial spray dried medications found in the 2023 review are made by this technology (such as those for etravirine, tolvaptan, everolimus, telaprevir and ivacaftor.

Another alternative to the usual method of solvent evaporation is lyophilization, or freeze drying. In these processes, the drug and carrier are both dissolved in the same solvent, the solution is frozen and then the solvent is removed by sublimation to form the lyophilized molecular dispersion.[12]

3.5 Supercritical-fluid processing

An alternative technique for solid dispersions is supercritical-fluid methods. A supercritical carbon dioxide co-extrusion process can use carbon dioxide as an antisolvent, with the spray of drug containing organic solution being given into the continuous supercritical phase. After processing carbon dioxide may be removed relatively easily from polymeric materials, and is regarded as an environmentally preferred process. A technique mentioned in the literature that is related to the rapid expansion of supercritical solution (Ress) is described below.[13]

In general, the preparation technology should be chosen in combination with carriers. The stability, solubility, dissolution behaviour and bioavailability of an ASD are, apart from the substance's actual properties, related to the type of polymers used.[14]

4. CHARACTERIZATION AND STABILITY

Characterization is fundamental to establish if a solid dispersion has reached the desired solid-state from the start and if this solid-state can be maintained throughout the manufacturing and storage processes.[15] Amorphous drugs have higher free energy than crystalline drugs and therefore exhibit a thermodynamic preference for dissolution and higher solubility as compared to crystalline drugs which is highly useful for ASDs. Polymeric carriers are therefore also important as dispersions that can help prevent the crystallization of the drug as well as suppress drug crystallization their stabiliser properties.[16]

4.1 Solubility Studies

Solubility studies are carried in the evaluation of the capability of solid dispersions to improve the aqueous solubility of poorly water-soluble medicines. It is often used to determine the differences between the solubility of pure drug powder and solid dispersions by using

saturation solubility studies. To the appropriate solvent, an excess of samples is added and the temperature is controlled until equilibrium is reached. The samples are filtered or centrifuged then the amount of drug in the liquid solution is measured by a suitable analytical technique (UV-visible spectrophotometry or HPLC). High degree of the increase in the apparent solubility of the drug suggests better solubilisation provided by polymer carrier. This yields results that help to evaluate the solid dispersion formulations for enhancing the solubility of poorly water-soluble drugs.[17]

4.2 In-vitro Dissolution Studies

In vitro dissolution is carried out to evaluate the amount and rate of drug release from solid dispersion formulations. The dissolution test is performed at a controlled temperature and agitation in a suitable dissolution apparatus by means of an appropriate medium. Samples are taken at regular time intervals, passed through a filter and then tested by an appropriate analytical method to measure the quantity of drug dissolved. The percent of the drug being released is calculated and plotted at regular intervals, thus yielding the dissolution profile.[18] The results are compared with that of pure dose or physical mixture to determine the effect of solid dispersion on the drug dissolution. The increase in the dissolution rate can be explained by the reduced crystalline form, enhanced wettability, decrease effective particle size and increase in the interaction of the drug–conferring composition. Drug–polymeric dispersion studies are equally useful with controlled-release dosage forms for determining the ability of the polymer to control drug release.[19]

4.3 Powder X-ray diffraction

One particularly important technique for determining if a material is crystalline or amorphous is powder X-ray diffraction (PXRD). A better signal resolution for diffraction peaks means a higher level of crystallinity; if these characteristic peaks are absent, or there is a decrease in resolution, they can be indicative of amorphization. The problem of non-crystalline material quantification can be solved using the conventional PXRD method, and if the alteration is temperature and/or environmental dependent, then the PXRD measurements can be combined with temperature and/or environmental control, as described earlier, to follow the phase transformation kinetics. Controlled-release solid dispersions have also been employed in X-ray diffraction analysis to determine if the drug molecule is either crystalline or amorphous.[20]

4.4 Differential scanning calorimetry

One measurement technique is differential scanning calorimetry (DSC) which is also very common for detecting crystalline material. The DSC is sensitive to detecting thermal events such as the glass to rubber transition, crystallization/recrystallization, melting and degradation under controlled heating. Energy associated with melting and recrystallization can also be recorded, which is related to the amount of crystalline material present.[21] Information is added by using temperature-modulated DSC (TMDSC), which is a conventional DSC program with a sinusoidal modulation, on top of the conventional DSC program. The approach can yield quantification of amorphous content by means of the heat capacity difference based on the heat-capacity change in the glass transition region.[22] DSC has also been coupled to X-ray diffraction in controlled release solid dispersion studies for evaluation of physical state of drugs in polymer matrix.[23]

4.5 Solids NMR and spectroscopic characterization

Solid State Nuclear Magnetic Resonance (ss-NMR) is a non-destructive technique that provides structural data and may be used to estimate amorphous content or mixture of phases. It is useful specifically in the study of molecular interactions in ASDs.[24]

4.6 Dynamic vapor sorption

(DVS) is a test to determine the sorption and desorption behaviour of water. Moisture exposure is a significant part of the ASD stability issue because of changes in humidity that can cause crystallization of the amorphous material. DVS is able to identify the crystallization response and can thus be used to investigate partially amorphous and amorphous powders.[25]

In case of hygroscopic polymers, moisture has a particular relevance. The physical stability, for instance, of a PVP-based ASD, for example can be significantly affected by water uptake due to the fact that water uptake leads to an increase in molecular mobility, thereby reducing physical stability.[26]

This significance of humidity is further confirmed in case of controlled release solid dispersions of ethyl cellulose. In one of the reported systems, no significant drug crystallinity change was observed after 40% and 68% relative humidity exposure while 100% R.H. exposure for a specific drug: polymer composition led to the hydration of the drug to form a hydrate.[27]

4.7 Other characterization techniques

Other characterization techniques used include dissolution calorimetry that would distinguish between the dissolution properties of a crystalline and an amorphous sample, and inverse gas chromatography (IGC) which could be used to investigate surface properties and interactions with these drugs and crystallinity.[28]

Therefore, the stability of solid dispersion is a function of the drug physical state, the mobility of the drug molecules, the nature of drug-polymer interactions, the drug-polymer compatibility and the environment conditions including humidity. The selection of polymer is especially significant since polymers affect the production of ASD, physical stability, dissolution and bio availability.[29]

5. MARKETED PRODUCTS

Many drugs are already on the market and have been manufactured using the various methods of solid dispersion. Some of the products are listed in Table 1.[30]

S.No	Brand Name	Active pharmaceutical ingredient	Manufacturer	Method used
1.	Zelboraf	Vemurafenib	Roche	Solvent controlled
2.	Zepatier	Elbasvir/Grazoprevir	Merck	Spray drying
3.	Braftovi	Encorafenib	Array	HME (holt melt extrusion)
4.	Sporanox	Itraconazole	Janssen	Fluid-bed bead layering
5.	Samsca	Tolvaptan	Otsuka	Spray drying
6.	Cesamet	Nabilon	Valeant	Solvent evaporation
7.	Kaletra	Ritonavir/ Lopinavir	Abbott	HME (hot melt extrusion)
8.	Isoptin	Verapamil	Abbott	HME (holt melt extrusion)
9.	Astagraf XL	Tacrolimus	Astellas Pharma	Wet granulation
10.	Zortress	Everolimus	Novartis	Spray drying

6. USE IN DRUG DISCOVERY & DEVELOPMENT

Important applications of solid dispersion technology are for the development of drug candidates with poor aqueous solubility, especially regarding slow dissolution that restrict oral absorption of the drugs. The amorphous to crystalline transformation may lead to decreased solubility, dissolution rate and oral bioavailability of the crystalline drug. Polymeric carriers also enhance the performance by making the material wettable and stabilize the amorphous structure and prevent the drug from precipitation within the gastrointestinal tract.[31]

This is especially relevant when the drug candidate in pharmaceutical development is difficult to deliver, such as a compound with poor properties. That's a factor that makes ASD technology highly applicable during the pharmaceutical development of unusual and challenging drug candidates. Amorphization can overcome solubility limitations and may decrease the amount of API and manufacturing resources needed during the pre-clinical evaluation and provide a means to investigate the bioavailability and toxicology and clinical performance.

Not surprisingly, solid dispersion technology is not limited to improving dissolution. The same formulation concept can be adapted to controlled drug delivery with the use of water insoluble or water swellable polymers. The resultant system is monolithic with the drug homogeneously distributed throughout the dosage form, which may help to prevent the “burst release” seen in some reservoir-type controlled release dosage forms.[32]

The commercial relevance of the technology is supported by many pharmaceutical-based commercial products from the solvent evaporation, spray drying and hot-melt extrusion etc. group, that are produced using gaseous technology. Thus, the dispersion to be called solid dispersion is a very general formulation platform which covers from solubility and bioavailability enhancement to the development of clinically relevant oral formulations and controlled oral delivery systems.[33]

CONCLUSION

Solid dispersion-based drug delivery system provides a feasible solution in enhancing the solubility, dissolution and bioavailability of poorly water-soluble drugs. Appropriate polymeric vehicles and preparation methods are important for drug release and stability of the formulation. The hydrophilic carriers aid in dissolution while the water insoluble or water swellable polymers can be used to aid in sustained and controlled drug release. Formulation development is flexible with techniques like hot melt extrusion, spray drying and solvent evaporation. Other problems are recrystallization, moisture and physical instability. Rational characterization and stability testing are critical factors that should be carried out to assure formulation quality and performance. Overall, solid dispersion technology looks like it has a huge potential to become a flexible platform to develop better drug delivery systems that yield improved bioavailability and customized release curves in order to release the drug at a more desirable rate. The applications in the pharmaceutical field can be extended with additional research in polymer selection and optimization of the formulation of this polymer and optimization of the manufacturing process.

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