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REVIEW ARTICLE

# Microemulsion: promising and novel system for drug delivery

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**Abstract**

Microemulsions are based on oil, water and surfactants and mostly in combination of co-surfactant. The resultant mixture is a stable heterogeneous system and has advantage over the conventional emulsion as well as over solution formulations. For topical, oral and parenteral administration, microemulsion acts as a potential carrier system. The main reason of selecting the microemulsion (ME) as drug delivery system is that it is easy to prepare, have ability to incorporate hydrophobic drug, stable and it exhibits more physical stability as compared to other vesicular systems. The purpose of this review is to present the applications of microemulsions and to understand the important facts of this novel delivery system.

**Keywords**

Co-surfactants
Oil
Surfactant
Microemulsion
Drug delivery system

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## Introduction

Microemulsion can be defined as fluid, thermodynamically stable, transparent, isotropic water and oil systems that are stabilized by surfactant, which may be a short chain amine, alcohol or amphiphilic molecule (Lawrence, 1994).

Microemulsion has ability to produce a clear emulsion on mild agitation while conventional emulsions have not. This technology is extensively used to concentrate on the challenges linked with the compounds with poor solubility. MEs comprise of lipid droplets, osmotic agent and an emulsifier (Baker and Naguib, 2005; Kalepun et al., 2013; Kalepua and Nekkanti, 2015). MEs have established a great potential for enhancing the systemic as well as local bioavailability of wide range of hydrophobic therapeutic agents (Tenjarla,1999; Lawrence and Rees, 2000). Hoar and Schulman introduced the term ‘‘MEs” the first time in 1943. They used the term to illustrate the transparent systems that may be obtained, while titrating the normal emulsions to clarity with hexanol (Hoar and Schulman, 1943). Although, Danielsson and Lindman defined the same term “Microemulsion” again in 1981 according to their point of view. ME can be explained as ‘‘a system of amphiphile, water and oil which is optically thermodynamically stable and isotropic liquid solution” (Danielsson and Lindman, 1981).

It was also considered that MEs were perhaps revealed well before the Schulman studies. Since the start of last century, Australian housewives washed wool with water/ soap flake/ eucalyptus oil/white spirit mixtures, and liquid waxes were considered to be the first commercial MEs which was discovered by Rodawald in the year 1928. Attention was given to MEs in 1970's when they come to know that such systems could be helpful in improving oil recovery (Shah, 1981).

**Microemulsion Classification:** Four general types of equilibrium phases were identified by Winsor. On this basis, ME has four types (Winsor, 1948).

**Type I** This is the type of MEs in which ME formed is oil-in-water (O/W) by solubilizing surfactant possibly in aqueous phase. ME this type is known as “Winsor I” ME.

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**Type II** In this MEs type, water-in-oil (W/O) ME is constituted when surfactant is solubilized in oil phase. The surfactant-rich oil phase unites with the surfactant-deprived aqueous phase. This type is called "Winsor II" ME.

**Type III** Middle phase loaded with surfactant combines with both phases i.e.water and oil phases and forms a three phase ME. In this type of ME, both the water and oil phases are deficient in surfactant. This is also known as "Winsor III".

**Type IV** In this type sufficient quantity of surfactant as well as alcohol (amphiphile) is added to formulate an isotropic (single micellar) solution A type IV Winsor ME is Winsor Type III when surfactants are added at higher concentrations, in which the middle phase goes on and turn into a single phase (Winsor, 1948).

As figure 1 shows the phase transitions carried out by increasing either temperature (for non-ionic surfactant) or the concentration of electrolyte. Figure 1 shows three phase systems, the ME (M) in the middle-phase is supposed to be in equilibrium with respect to water (W) and surplus oil (O) (Bellocq, 1984).

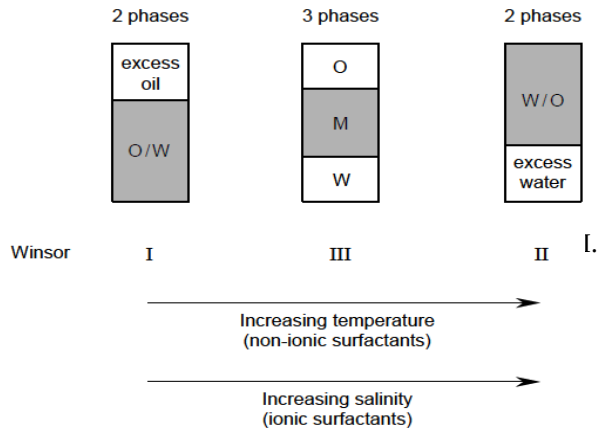


**Figure 1: Phase sequences present in MEs in Winsor classification and effect of salinity and temperature. Shaded area represents surfactants (Bellocq, 1984).**

**Components of Microemulsion:** MEs are composed of an aqueous phase, co-surfactant, a surfactant, and a organic phase. But previous studies showed that co-surfactants can be eliminated by selection of high and low hydrophilic (HLB) surfactants that complements each other structurally (Solans and Garcia-Celmat, 1997).

**(i). Organic phase or oil phase:** The drug should have high solubility in the oil-surfactant system, in view of the fact majority of the drugs show their solubility in O/W ME. The solubility criteria not only enhance the drug release from the system but also raise the concentration gradient and increase the drug penetration across the different biological membranes. A wide range of oils are marketed to be used as the component of ME, but their use become limited due to their irritation causing property, toxicity and vague mechanism of action. The material selected must be clinically acceptable, non-toxic and biocompatible to obtain ME which is non-aggressive and mild.. As the chain of oil increases it results in more positive curvature which in return hinders its penetration into the surfactant tail region (Kibbe, 2000).

Vegetable oilis considered to be an ideal candidate for ME formation in food industries. But the commonly used organic phase for MEs is a mineral oil, as it is more effective in the generation of distinct dispersed phases (Friberg et al., 1994; Sottmann and Strey, 1996). Corn oil, soy oil, cotton oil or sunflower oil has also been used in achieving ME with food grade surfactants (Constantinides and Scalart, 1997; Fanun et al., 2001). While ME formation by using triglycerides (TG) is somewhat difficult, because of their bulky nature and slight polarity in return limits their flexibility and also penetration of interfacial film, thereby hindering optimal dispersed domain curvature (Garti et al., 2005). Long-chain TGs can also be replaced by medium-chain TGs (MCTs) as they have three TG chains of 8–10 carbons which results in greater molecular flexibility permitting the ME formation (Constantinides and Scalart, 1997; Fanun et al., 2001).

**(ii). Aqueous phase:** In case of o/w MEs, water constitutes the continuous phase. As it is immiscible with majority of oils and which results in oil droplets formation (Rousseau et al., 2011).

**Surfactant use in ME:** Before the selection of surfactant, the surfactant's HLB should be considered to understand the behavior of surfactant. The common consideration is that, the surfactant with the HLB value of 3-6 prefers the formation of w/o MEs, while surfactants with HLB value of 8-18 favors the formation of o/w ME. The main consideration is that the ME is formed under the some carefully defined conditions, and the HLB value of the surfactant is used as first step in the component selection for ME formation (Lawrence and Rees, 2000).

Surfactants are the molecules that usually contain a polar head as well as a polar tail (Holmberg, 2002). Surfactant molecules arrange themselves due to various intermolecular as well as intra-molecular forces. For instance, when surfactant is allowed to mix with oil and water, they build up at the interface of oil and water because it is favourable thermodynamically (Lawrence and Rees, 2000).

At low concentrations of dispersed phase or internal phase, the droplets forms in the ME are spherical and isolated. At higher concentrations of dispersed or internal phase, the final structure form depends completely on the interaction among the droplets. If the droplets are repulsive to each other, there will be no droplet overlapping produced due to

colliding droplets. While if there are attractive interactions between the droplets, multi droplet collision may occur and also form some other structures (Capek, 1999).

**a. Nonionic Surfactants:** Majority of nonionic surfactants have similarity in structure with ionic surfactants, apart from for the fact that the head group of ionic surfactants is uncharged. As electrostatic charges are absent in the head groups, the interactions among the nonionic head groups are dominating due to osmotic and steric forces (Lange, 1999). Nonionic surfactants do not have any co-surfactants generally for the formation of MEs. It is considered that the pure nonionic surfactants are generally fabricated of blend of somewhat varying chain lengths (Tadros, 1984).

Nonionic surfactants exhibit excellent biological acceptance (Kibbe, 2000). They have ability to form pH and electrolyte concentration insensitive MEs (Lawrence and Rees, 2000; Djordjevic et al., 2004; Shafiq et al., 2007). Tween 80, Span 80 and Tween 20 are the most commonly used examples of non-ionic surfactants (Lawrence and Rees, 2000).

**b. Ionic Surfactants:** The ionic surfactants are not widely in general pharmaceutical preparations or dosage forms. Large number of ionic surfactants is unable to give balanced MEs in the absence of third component. Therefore, some additives are needed to make them stabilized. The head groups of the ionic surfactants are significantly more lipophobic than polyethylene oxide portion. Salts or co-surfactants addition shifts the HLB on the whole into the favorable range for the formation of ME (Holmberg, 2002). Ionic surfactants are further classified into cationic, anionic, or zwitterionic.

**c. Cationic surfactants:** Cationic surfactants belong to the class of quaternary ammonium alkyl ammonium halides and tetra alkyl ammonium halides are mainly present in this class. The renowned examples from the class of cationic surfactant are di-dodcecyl ammonium bromide (DDAB) and hexa decyl trimethyl ammonium bromide (CTAB) (Lange, 1999).

**d. Anionic surfactants:** Ionized carboxyl group gives anionic charge to these surfactants. This type of surfactant is very understandable according to their structure and function (Lange, 1999). Dioctyl sodium sulfosuccinate (DOSS) and Alkali alkanoates, also referred to as soaps, are the commonly used anionic surfactants (Lawrence and Rees, 2000; Lange, 1999).

**e. Zwitter-ionic surfactants:** Zwitter-ionic surfactants, containing both negatively as well as positively charged groups. Phospholipids and lecithin are common example of zwitterionic surfactants. These surfactants have excellent biocompatibility unlike other ionic surfactants, which are toxic to some extent. This is mainly due to the fact that naturally lecithin is obtained from egg or soybean, which containing diacyl phosphatidylcholine as the main constituents (Holmberg, 2002; Lawrence and Rees, 2000).

**f. Co-surfactants used in ME:** Generally, single surfactant either ionic or non-ionic, is inadequate to form a MEs or it may not result in a favorable MEs forming region. Mixtures of surfactants or occasionally co-surfactants are necessary for the formation of a ME optimally. Co-surfactant is referred to as that component which allows the primitive surfactant to form a ME. Thus, co-surfactant can also be referred as a second surfactant that can used, but it may also termed as an amphiphile with low-molecular-weight, for example an alcohol (Holmberg, 2002).

More often, surfactants with one chain have not the capacity to reducing surface tension up to required ultralow levels needed to form a ME. Short as well as medium alcohols, such as butanol, ethanol, pentanol, propylene glycol or isoproponal, are commonly regarded as co-surfactants (Holmberg, 2002; Giustini et al., 2004; Lawrence and Rees, 2000).

These co-surfactants cause reduction in surface tension and also to fluidize the surfactant film, to accelerate the decay of the system making it thermodynamically stabile. Co-surfactants enhance the flexibility of the surfactant film formed around the ME droplet (Lawrence and Rees, 2000; El Maghraby, 2008; Junyaprasert et al., 2008). A co-surfactant molecule completely distributes themselves in between the water, oil, and oil/water interface. The moderately small co-surfactant moieties eventually get mixed in with the surfactant moieties at the oil/water interface. This in return releases the binding stress and thus allows an easier dispersion (Hait and Moulik, 2007).

Co-surfactant incorporation can increase the micremulsion-forming region (El Maghraby, 2008). The need of a medium chain alcohols as co-surfactant may cause different other problems. Most of the alcohols can be irritating to the biological system, when used chronically. There are serious issues related to toxicity of chemicals, which hinders its use in ME or pharmaceutically (Lawrence and Rees, 2000; Shakeel et al., 2007).

**Microemulsion structures:** ME is not a static dense structure but it is a very labile system. In this system, there is rapid exchange of individual components between different environments and also the interfacial film fluctuates continuously. Depending upon the composition, ME exists in two major phases;

- Droplet phases
- Bicontinuous phases

**(i). Droplet phases:** At higher concentrations of water, ME contain small droplets of oil enclosed by an interfacial film composed of co-surfactant and surfactant moieties and dispersed freely in continuous phase i.e. aqueous phase constituting o/w ME. Whereas, when water concentration is limited or lower,

there will be a reversed situation i.e. the water droplet is dispersed in oil, forming an w/o ME (Gasco et al., 1991).

**(ii). Bicontinuous phase:** The steady transition of o/w to w/o ME is done by altering the quantity of water and oil. The region is formed in the middle has approximately equal fraction of water and oil. It is usually composed of bi-continuous or lamellar structures in which both the phases which is continuously fluctuating with a net curvature of zero (Kreilgaard, 2002). Figure 2 and 3 shows the internal structure of microemulsion (Moulik and Paul, 1998; Kreilgaard, 2002).

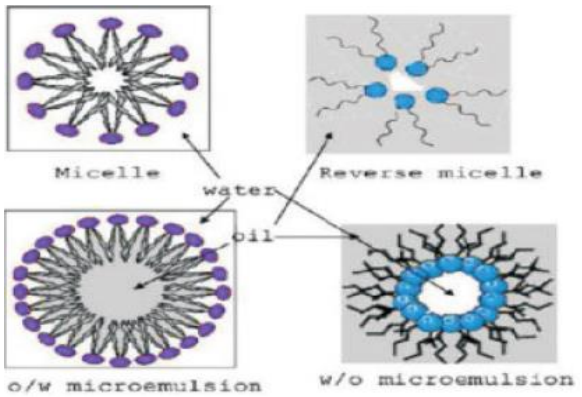


**Figure 2: Schematic diagram of dispersed phase (Kreilgaard, 2002).**

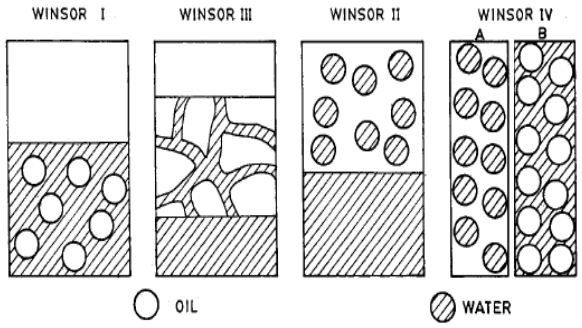


**Figure 3: Different situation during phase formation for water- oil-amphiphile mixture (Moulik and Paul, 1998).**

**Theories of ME:** Many methods have been employed in order to determine the ME formation mechanism as well as its stability. There are some of theories governing these factors.

**(i). Interfacial film or mixed film theories:** The instinctive formation of droplet of ME was generally considered because of complex film formation at the interface of oil-water by the surfactant and co-surfactant. This in return causes a decrease in the oil water tension to very little values i.e. closer to zero to negative.

The film formed is in equilibrium with respect to both oil and water and regarded as liquid and dual in nature having a two dimensional spreading pressure $n_i$, which determine the interfacial tension $\gamma_i$,:

$$\gamma_i = \gamma_{o/w} - n_i \qquad \text{Equation 1}$$

where $\gamma_{o/w}$ is the o/w interfacial tension lacking the film. When surplus amount of co-surfactant and surfactant are adsorbed to create an interface, the spreading pressure $n_i$, may become larger than $\gamma_{o/w}$. There results a negative interfacial tension and energy is offered to enhance the interfacial area, thus the droplet sizes reduce effectively. The negative interfacial tension is a temporary phenomenon, and it has zero or a small positive value at equilibrium (Ktistis and Niopas, 1998).

**(ii). Solubilizing theories:** ME was defined by Shinoda and Friberg (1976) as it is thermodynamically stable monophasic solutions of oil-swollen (o/w) or water-swollen (w/o) spherical micelles. While Rance and Friberg (1977) another researchers illustrated that there exit a relationship between w/o me and reverse micelles with phase diagram wherever by adding p-xylene (50%) to the inverse micelle region of ternary system of pentanol, water and SDS eventually a transparent w/o region appeared which is ME (Shevachman et al., 2008).

**Methods of Preparation of Microemulsion**

**(i). Phase Inversion Method:** In this method, ME is produced by adding surplus dispersed phase (i.e. Phase Inversion Concentration) or by responding to temperature (i.e. Phase Inversion Temperature (PIT). This method is responsible for bringing huge physical changes in the ME system for example variation in particle size.

In case of PIT method, the key factor is the interfacial tension. It decreased upon cooling and it could be found in the region of phase inversion, changing from W/O ME to an O/W ME. While using the nonionic ethoxylated surfactants, the temperature increment enhances their hydrophobicity thereby the ethoxylated surfactants are mainly used in all the practical applications of PIT MEs. Furthermore, as the water volume fraction changes, spontaneous radius of curvature also changes. By adding water in oil phase continuously, primarily water droplets are formed in the continuous oil phase. As the aqueous content increases, the spontaneous curvature of surfactant undergoes a change which is responsible for the transition of W/O ME to an O/W ME at its inversion point. Whereas the phase inversion takes place a specific water concentration inside the phase resembling intermediate ME, thus resulting emulsion formed is entitled as phase inversion concentration (PIC) ME. (Gadhave and Waghmare, 2014).

**(ii). Phase Titration Method:** Spontaneous emulsification (or the phase titration method) method is another method of preparing MEs and it can possibly be explained by the use of phase diagram. Phase diagram is constructed to comprehend the complexity of interactions of various components system occurring because of mixing. MEs are not formed alone but with various related structures such as micelles, emulsions, hexagonal, lamellar, and cubic various gels and oily dispersions (Gadhave and Waghmare, 2014). Figure 4 shows a sample of phase diagram (Gadhave and Waghmare, 2014).

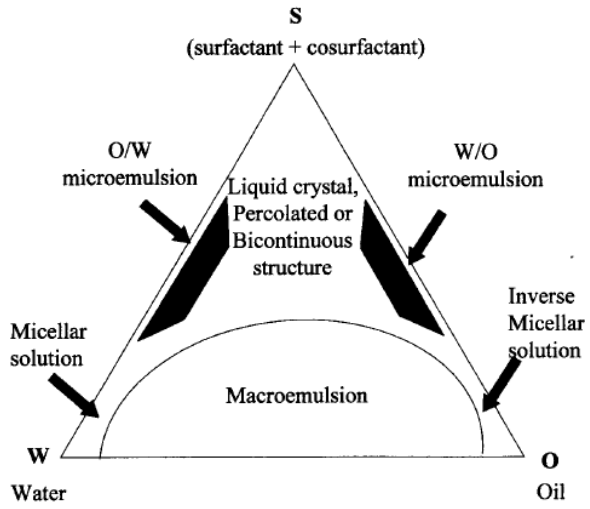


**Figure 4: Hypothetical phase regions of ME systems of oil (o), water (w) and surfactant + cosurfactant (S) (Gadhave and Waghmare, 2014).**

**Evaluation of Microemulsion:** MEs can be evaluated for following parameters; physical examination, viscosity, pH, particle size, zeta potential analysis, electrical conductivity, assay of drug content, *in-vitro* release study and for stability studies.

**Construction of pseudoternary phase diagram:** The dispersion system is composed of oil, surfactant co-surfactant and water are prepared to determine the ME regions. Pseudoternay phase diagram can be constructed by using water titration method. The weight ratios used for surfactant and cosurfactant constant should be same i.e., 1:1 (Junyaprasert et al., 2007; Syed and Peh, 2014).

**(i). Physical examination:** The prepared ME formulations are inspected visually to check its appearance, color, homogeneity and consistency as well. The samples are observed to determine the presence of any precipitates or phase separation visually in the light at room temperature.

**(ii). Viscosity measurement:** Viscosity is checked to find out rheological properties of prepared formulations. Brookfield viscometer (DV-II Pro) is used to determine the viscosity. The temperature to carry out rheological study should be maintained at 25 ± 0.5°C.

**(iii). pH measurement:** The measurement of pH can be done by directly immersing the electrode of pH meter in the ME formulations at room temperature. Every measurement will be performed in triplicates.

**(iv). Droplet size, zeta potential analysis and Polydispersity index:** The average droplet size, zeta potential and polydispersity inex (PDI) of ME formulation can be evaluated by using Malvern zeta sizer. All the samples are analyzed in triplicates.

**(v). Conductivity:** Conductivity test is performed for MEs by using digital conducto-meter to determine ME type either o/w or w/o.

***In-vitro* release study:** The *in-vitro* release of ME formulations is carryout by using a Franz diffusion cell. As franz diffusion cell has two compartments, one is known as the donor and the other as receptor compartment. The temperature should be maintained throughout the study by circulating water bath, which is thermostated at 32.0 ± 0.5ºC and the stirring is maintained at 400 rpm throughout the study. Samples will be taken at regular intervals from the receptor compartment and are analysed by using UV-spectrophotometer.

**Stability studies:** Physical stability of prepared MEs can be determined by their clarity, phase separation and particle size analysis. The selected samples will be kept at room temperature and elevated temperature for a specific time period. Visual inspection of samples will be done at room temperature in dark for determining any physical change.

**Applications of Microemulsion**

**1. Microemulsion in pharmaceuticals**

**a. Oral Delivery:** Solubility and stability are the two important hindrances for oral dosage formulation which can be overcome by the ME system. It is a very suitable delivery system especially for delivery of lipophobic or hydrophilic drugs i.e. proteins and peptides and also for poorly soluble drugs belonging to the BCS class II or IV (Pathan et al., 2012).

**b. Parenteral Delivery:** Hydrophobic and lipophilic drugs are difficult to administer by parenteral formulation. This challenge can be defeated by incorporating them in o/w ME and provide better stability than liposomes and other vesicular system. Etoposide an anticancer drug is investigated by delivering it by using a phospholipid-based ME through parenteral route, which proved good acceptability and safety of the formulation (Date and Nagarsenker, 2008).

**c. Topical Application:** ME when administered topically. It can easily cross SC by changing the arrangement of lipid layer structure and thus enhance the permeation of drug by this route. ME has increased percutaneous absorption of drugs as compared to other

vesicular system. So ME is efficiently used to deliver antifungal agents, antiacne and antiviral agents (Pathan et al., 2012).

**d. Ophthalmic Delivery:** ME in ophthalmic delivery is recently reported. Lecithin, IPM, PG and PEG 200 has been used to formulate ME for the delivery of pilocarpine. This formulation is found to be non irritant to rabbit eye (Lawrence and Rees, 2000).

**e. Pulmonary Delivery:** Water-in-HFA propellant ME is produced for delivering the drug by pulmonary route, which is stabilized by fluorocarbon nonionic surfactant (Patel et al., 1998)

**(i). Microemulsion in cosmetics:** ME has a faster absorption into the skin that's why it is used for cosmetic delivery. The selection of ME for this purpose is done by considering safety, cost and appropriate selection of excipients. Thus ME is widely used as a carrier in cosmetics for skin care, hair care and also to deliver silicon oils (Pathan et al., 2012).

**(ii). Microemulsion in biotechnology:** Biotechnologists are being focused on ME these days to study, immobilization of enzymatic, bioseparation and proteins. ME is preferred over other multiphase systems due to its property that it is simultaneously solubilize both polar as well as nonpolar ingredients in the same solution, thus shifts the equilibrium site of the reaction and consequently product separation occurs by physical means (Pathan et al., 2012).

**Advantages:** They can easily be prepared, clear in appearance, has greater stability, able to be filtered, have low viscosity and no pain when injected. In w/o ME water soluble drugs can be protected, give an increased BA of the drug and can provide sustain release of hydrophilic drugs and in o/w ME it increases solubility and BA of lipophilic drugs (Lawrence, 1994).

**Disadvantages:** Formation of microemulsions requires large amounts of co-surfactants and surfactants. At high concentrations they are irritating, if not slightly toxic, to the biological system (Djordjevic et al., 2005). Many other factors, such as pH and temperature increase the stability of microemulsions.

**Conclusion:** Microemulsions are most interesting drug delivery system as by this system the solubility as well as bioavailability of drug is enhanced. this system can be used for both hydrophilic as well as hydrophobic drugs and by this system we can deliver more than one medicaments simultaneously. As microemulsions are transparent, having low viscosity and thermodynamically stable system, so can be used as potential system for control and for target release of the drug at various sites of the body.

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