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Non-aqueous Emulsion for Pharmaceutical Applications: Part 1 Fundamental and Component

นิพนธ์ต้นฉบับ

Original Article

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บทคัดย่อ

อิมัลชันชนิดไม่มีน้ำเป็นองค์ประกอบสามารถเตรียมได้จากการผสมของเหลวที่ไม่เข้ากันสองชนิด เช่น ของเหลวชนิดมีขั้วที่ไม่ใช่น้ำ-ของเหลวที่ไม่มีขั้ว โดยใช้สารอิมัลซิไซเออร์เพื่อเพิ่มความคงตัวของระบบ ปรากฏการณ์ออสวาร์ดริพเพ่นนิ่งมีบทบาทสำคัญต่อความคงตัวของอิมัลชันชนิดไม่มีน้ำเป็นองค์ประกอบ ปัจจัยหลักที่สำคัญประการหนึ่งในการพัฒนาอิมัลชันชนิดนี้ คือ ตัวทำละลายชนิดที่มีขั้วที่ไม่ใช่น้ำควรสามารถเป็นตัวทำละลายที่ดีสำหรับส่วนที่ชอบน้ำของโมเลกุลสารลดแรงตึงผิวและมีความไม่เข้ากับของเหลวที่ไม่ชอบน้ำหรือน้ำมัน ปัจจัยอื่นที่ควรคำนึงถึง คือ การเลือกสารลดแรงตึงผิวที่มีความสามารถละลายได้ในของเหลวที่ไม่เข้ากันนั้นได้ โดยมีข้อพิจารณาเพิ่มเติม คือ การเลือกใช้สารลดแรงตึงผิวที่ไม่ระคายเคืองเยื่อบุหรือเนื้อเยื่อของร่างกาย ความไม่คงตัวของอิมัลชันชนิดนี้ประกอบด้วยการเกิดการแยกชั้นครีมและการแยกตัวของส่วนผสม สามารถเตรียมอิมัลชนิดนี้ให้คงตัวได้ด้วยการใช้สารลดแรงตึงผิวชนิดบล็อกโคพอลิเมอร์ร่วมกันและการใช้ของเหลวที่มีขั้วแต่ไม่เข้ากับน้ำมันชนิดที่เหมาะสม

คำสำคัญ: อิมัลชันชนิดไม่มีน้ำเป็นองค์ประกอบ, การประยุกต์ทางเภสัชกรรม, หลักสำคัญ, ส่วนประกอบ

Abstract

Non-aqueous emulsions are prepared by mixing two immiscible liquids such as a non-aqueous polar liquid and a non-polar liquid with emulsifier to stabilize the system. Ostwald ripening plays a critical role in the stability of these non-aqueous emulsions. One of the main factors to develop a non-aqueous emulsion is the choice of non-aqueous polar liquids that should have the ability of a good solvent for the solvophillic part of the surfactant molecules and to make it immiscible with non-polar liquid or oil. The other factor is to select the surfactant having the ability of selective solubility in either of immiscible liquids. In addition, it is necessary to choose the surfactant that will not irritate the mucosa or tissue. This emulsion shows two types of crucial instability including creaming and breaking. The stable non-aqueous emulsions could be prepared by using two block copolymer surfactants and suitable oil-immiscible polar liquid.

Keywords: non-aqueous emulsion, pharmaceutical application, fundamental, component

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Introduction

The delivery of poorly water-soluble drugs has been the subject of intense research, as approximately 40% of new chemical entities are hydrophobic in nature.[1] Emulsion has been developed as a delivery system for these poorly water soluble compounds. An emulsion is a system in which one liquid is dispersed in another with which it is immiscible. Macroscopic phase separation of these immiscible liquids is prevented by the addition of suitable emulsifiers such as surfactants. In general, pharmaceutical emulsions are oil-in-water (O/W) or water-in-oil (W/O) systems.[2-4] However, there are some limitations with regards to water. First, water is not appropriate for certain drugs, which are unstable in the presence of water or are water insoluble and therefore cannot be incorporated into aqueous formulations. Second, bacterial growth and drug crystallization are common in aqueous phase.[5] To overcome these problems, a water-free liquid preparation is desirable. Emulsions can be formulated without an aqueous phase to produce anhydrous, non-aqueous or oil-in-oil emulsions to replace regular aqueous emulsions wherever the presence of water is undesirable.[2] For example, the production of polymer particles where catalysts or monomers were sensitive to water such as polyurethane particles which monomer diiocyanate and catalyst reacted with water quickly.[6] In addition, the non-aqueous emulsion (also known as oil-in-oil or anhydrous emulsion) is formed from two immiscible liquids, a non-aqueous polar liquid used instead of water and a non-polar liquid and emulsifier to stabilize the system by preventing a phase separation.

There are several advantages of non-aqueous emulsion systems over aqueous emulsions. For example, it is suitable

for the hydrophobic drugs or substances that are sensitive to water or degraded by hydrolysis. Also, it can be used as a carrier for lipophilic compounds or used for controlled drug release. Moreover, these systems have low viscosity and lower boiling vaporization temperature compared to aqueous system, which makes them particularly suitable for spraying application of paints.[6,7] Non-aqueous emulsions were developed since the early 1960s. The first formulation was a system of olive oil-in-glycerin.[8] Another example of an early application of non-aqueous emulsions system was polyol-in-oil emulsion system with polar phase that included glycerin, propylene glycol and polyethelene glycol 400 (polyol compound). Olive oil was used as a non-polar liquid phase and representative anionic, cationic and nonionic surfactants were employed as an emulsifier.[9] Up to now, although their unique features are useful for many applications, non-aqueous emulsions did not attract much attention.

This review offers a general idea about non-aqueous emulsion systems, as well as information about its components, types, preparation techniques and stability. A non-aqueous emulsion (also known as oil-in-oil or anhydrous emulsion), similar to an aqueous emulsion, is formed from two immiscible liquids which employs, a non-aqueous polar liquid which is used instead of water, a non-polar liquid and emulsifier to stabilize the system by preventing a phase separation.

Fundamental of the non-aqueous emulsion system

Several non-aqueous emulsion formulations prepared by a broad range of compounds have been reported. The non-aqueous emulsion system constitutes three main compartments: (1) polar phase, which is formed by a non-aqueous polar liquid, (2) oil phase, and (3) emulsifier. In the next section, each of these compartments will be discussed in detail.

(1) Non-aqueous polar liquid

For non-aqueous emulsion preparations, the selection of solvents is of critical importance, while the key determining factor is polarity of the solvents.[10] A liquid capable of replacing water in an emulsion should have an appreciable polarity to make it immiscible with oils and to make it a good solvent for the solvophillic part of the surfactant's molecules. The hydrogen bond formation of polar liquid may play a crucial role in the solvating ability of both ionic and non-ionic surfactants.[2,3] Preferentially, the polar liquid which exhibits a dipole moment from 0.9 - 4.5 should be selected. Moreover, if the emulsions are intended for personal care application, then the non-aqueous polar liquid should be physiologically compatible and can be formulated into desirable dosage forms. Examples of solvents which were used as a non-aqueous polar phase such as propylene glycol, ethanol, propyl alcohol, iso-propyl alcohol, acetyl triethyl citrate and acetyl tributyl citrate.[10]

Reagents commonly used as the dispersed phase or the continuous phase which are the non-aqueous polar liquids include glycerin, propylene glycol, polyethylene glycol, ethylene glycol dimethyl ether, tetraethylene glycol dimethyl ether, triacetin, medium chain (C_8-C_{10}) triglycerides and propylene glycol C_8 diester.[7,10] There was the formulation of non-aqueous *in situ* PLGA microparticle forming emulsion using the injectable water miscible liquid such as DMSO as the non-aqueous polar liquids. The transformation from emulsion into microparticle was owing to solvent exchange mechanism.[11] In addition, as non-aqueous polar liquids, the water miscible organic solvents such as *N*-methyl pyrrolidone (NMP) and 2-pyrrolidone (PYR) were utilized in the *in situ* forming microparticle emulsion. Owing to their thermal stability and biocompatibility, these polar aprotic solvents have been used.[12] Previously, DMSO, NMP and PYR were used as the non-aqueous solvents for the oil in oil emulsion containing doxycycline hyclate to prepare *in situ* forming microparticle (ISM) with solvent exchange for periodontal pocket delivery.[13]

In this regard, the development of a system to aid in the solvent selection process could predict the miscibility and behavior of surfactant will greatly facilitate the formulation of non-aqueous emulsions. The influence of solvents on the fluid characteristic of oil in oil emulsion of ISM had been investigated which DMSO and 2-pyrrolidone could be used to fabricate the emulsion with suitable manner of injection.[14,15]

(2) Oil phase

The composition and type of oil also play an important role in the non-aqueous emulsion. The oil components in the external phase not only influence the viscosity but also impart the lubrication of the system.[13] Examples of solvents successfully used as oil phase in non-aqueous emulsion

preparations were, for example, hexamethyldisiloxane, octamethyltrisiloxane, vegetable oils and synthetic oils.[7,10]

(3) Emulsifier

The emulsifying stabilizer is any surface active agent of pharmaceutical cosmetic or food grade that has an amphiphillic nature to stabilize the emulsion. It can be divided into 2 groups: surfactant and amphiphillic block copolymers. The consideration for hydrophilic-hydrophobic balance (HLB) value could facilitate the selection of suitable emulsifier for non-aqueous emulsion systems.

(3.1) Surfactant

Emulsions may comprise one or more emulsifying agents to stabilize the system. The range of industrial surfactants was screened using subjective visual assessment for their ability to form a non-aqueous system with medium-chain and long-chain triglycerides. The concentration of surfactant or emulsifier is necessary to be considered for stabilizing the emulsion. For the injectable non-aqueous *in situ* forming microparticle (ISM) emulsions, the 5% glyceryl monostearate (GMS) showed a superior stabilizing potential prolonging the emulsion stability from a few minutes to more than 12 h.[11] In a previous study, the 2.5% GMS dissolved in olive oil was the most suitable component when prepared using 1:1 of the external and the internal phase ratio.[13]

(3.2) Amphiphillic block copolymer

In comparison to low molecular weight surfactants, such as sodium dodecylsulfonate (SDS), much lower concentration of an amphiphillic block copolymer are required to form a stable micelle.[16] Poly(styrene)-b-poly(dimethyl methacrylate), poly(styrene)-b-poly(methyl methacrylate), poly(styrene)-b-poly(ethylene propylene), poly(styrene)-b-poly(isoprene) and poly(isoprene)-b-poly(methyl methacrylate) are used to prepare dispersions with non-polar continuous phase. For example, aliphatic hydrocarbons and silicone oil.[6] The relatively large size of tri-block copolymers may contribute to the emulsion stabilization. It proved that large surfactant molecules such as PEO-PPO-PEO triblock copolymer surfactants are more effective stabilizers for formamide emulsions than low molecular weight surfactants which has received a considerable interest in recent years.[2,3] Another report documented the stabilization of non-aqueous emulsions by poly(2-vinylpyridine)-b-poly(butadiene) in the system of polyethylene glycol (PEG 400) dispersed in a typical liquid glycerin ester (Miglyol 812).[17] Very recently, a biocompatible non-aqueous emulsion preparation has been reported. Being stabilized by a well-defined poly(butadiene)-poly(2-vinylpyridine)-poly(ethylene oxide) triblock copolymer, the emulsions were developed for the system Miglyol 812 dispersed in PEG 400.[18]

Types of non-aqueous emulsion

Similar to an aqueous emulsion system which is classified as O/W and W/O emulsion, non-aqueous emulsion is classified into 3 types: (1) those using a non-aqueous polar liquids as an oil-in-polar solvent, (2) polar solvent-in-oil, and (3) oil-in-oil system which is formulated without a non-aqueous polar liquid but using two immiscible oils. In this section, examples of each type will be discussed.

1. Oil-in-non-aqueous polar liquid emulsion

Examples of this subtype of non-aqueous emulsion are olive oil in polar phase including glycerin, propylene glycol and PEG 400. In this particular system, anionic, cationic and nonionic surfactants were used as an emulsifier to investigate the effect of emulsifier type on the stability of the system.[9] Another example is the system of dichloromethane in perfluorohexane. Copovidone or Eudragit® RS is used as an emulsifier to form microparticles by microencapsulation method.[19] This type of emulsion is more similar to aqueous systems than systems comprising two non-polar oils due to the fact that they both have a polar continuous phase.

2. Polar solvent-in-oil emulsion

Amphiphillic block copolymers in dimethyl formamide or acetonitrile was employed as a dispersed phase and alkanes as a continuous phase. The designed amphiphillic block and copolymers, such as polyisoprene-b-poly(methyl methacrylate) were used as the additives to stabilize these emulsions.[16]

3. Oil-in-oil emulsion

The example of this subtype is non-aqueous emulsion formulated for controlled release by using castor oil as the disperse phase and dimethicone or cyclopentasiloxane as the continuous phase. This study used only silicone surfactants (cyclomethicone/dimethicone copolyols) which were miscible in silicone oil to stabilize the emulsions. Another preparation

is a development of castor oil-in-silicone oil using varying type of silicone surfactants to stabilize the system.[4]

Polymer

In addition, polymers have been widely used in emulsions for sustained drug release profile. Non-aqueous emulsions formulated with polymers can also achieve such propose. Various types of hydrophobic and hydrophilic polymers are available for the preparation of non-aqueous emulsions. The presence of polymer in non-aqueous emulsion could be in the dispersed phase or the continuous phase as in the following examples.

(1) In dispersed phase of polar solvent-in-oil emulsion for *in situ* forming microparticles

The *in situ* microparticle has been fabricated from polar solvent-in-oil emulsion comprising polymer solution phase dispersed in external oil phase. Polymer solution phase can be prepared by dissolving a biodegradable polymer such as poly(lactide-co-glycolide) (PLA) or poly lactic-co-glycolic acid (PLGA*)* in a water-miscible biocompatible solvent such as N-methyl pyrrolidone (NMP), 2-pyrrolidone, dimethyl sulphoxide (DMSO), triacetin or low molecular weight polyethylene glycol which are able to form highly concentrated polymer solution in the combination of surfactants such as tween 80 or polyoxyethylene-polyoxypropylene copolymer (Pluronic F 68). Peanut oil and sesame oil can be used as a biocompatible external phase with surfactant such as span 80 or Miglyol 812 with/without aluminium stearate or aluminium mono stearate.[20] The injectable biodegradable *in stiu* forming o/o emulsion microparticles was developed comprising PLGA polymer solutions dissolved in NMP or 2-pyrrolidone as the internal phase which was mixed with 2-syringe connector with the external phase of peanut oil stabilized with 2% (w/w) Span 80. It was observed that this system was more easily injectable with smaller needle size thus expected to be less painful and provide a better patient comfort/compliance.[21,22]

(2) In the continuous phase of poly(ethylene glycol) (PEG) droplets in non-polar solvent system

Some investigators prepared the non-aqueous emulsions where the dispersed phase consists of poly(ethylene glycol) (PEG) droplets and the continuous phase formed by a polymer solution consisting of a film forming polymer dissolved in a volatile organic solvent. The stability of these emulsions is achieved with either polybutadiene-poly (ethylene oxide) or poly (terbutylstyrene)-b-poly(ethylene oxide) block copolymer. The emulsifying stabilization efficiency of polybutadiene-b-poly(ethylene oxide) and poly (ter butylstyrene)-poly(ethylene oxide) diblock copolymers is examined in non-aqueous emulsions. These emulsions are formed by a dispersion of polyethylene glycol mixed with a cationic surfactant acting as a biocide, in a continuous phase of a thermoplastic elastomer dissolved in methylcyclohexane. Emulsions with controlled droplet size and excellent stability were obtained by solvent evaporation which leads to elastomeric films containing droplets of confined disinfecting liquids.[23]

Preparation techniques

There are many techniques for the preparation of a non-aqueous emulsion system. However, perhaps the simplest method is manual shaking. In this method, an emulsion is prepared by adding both internal phase and external phase into a small container then shaking it by hand until a viscous emulsion is formed.[3] Alternatively, the high mechanical force such as homogenization[24], Rotamixer[5] and sonication/probe sonication[4] have also been used. Another preparation technique is used in the *in situ* forming microparticles preparation, also known as the 2-syringes connector method as presented in Figure 1. In this approach, the internal and external phase are filled separately, one phase in separate syringe. The syringes are connected through a connector. The formation of emulsion is achieved by pushing one phase through the syringe to mix it with the other phase repeatedly for about 50 cycles at a speed of 2 cycles/second.[25,26]

Linking the internal phase and the external phase in 2 syringes coupled with a connector.

Non-aqueous emulsion after mixing the internal phase and the external phase.

Figure 1 Preparation technique of non-aqueous emulsion using the 2-syringes connector method.

Stability of non-aqueous emulsions

Stability has long been a major concern which limits the usage of non-aqueous emulsions. In general, the emulsions showed two types of instability. The first is creaming caused by the inner phase going upward direction. This is called upward creaming. On the other hand, if it is going downward direction, it is called as downward creaming or sedimentation. The other is breaking, caused by coalescent of droplets, which ultimately leads to a complete separation of the two phases.[2,27]

(1) Creaming

This process always started immediately after emulsions were formed. Creaming is caused by density difference between the two phases. Density difference normally gives rise to a diffusion boundary as larger droplets rise faster than smaller ones. However, the process is strongly enhanced by clustering of droplets, which is caused by the flocculation.[2]

(2) Breaking/coalescence and Ostwald ripening

Coalescence is a phenomenon that small droplets of internal phase fuse together to form a larger droplet, whereas Ostwald ripening is a phenomenon that smaller droplets of emulsion disappear but the larger droplets gradually grows. Both coalescence and Ostwald ripening lead to a complete separation of the two phases called breaking. Ostwald ripening plays a major role of destabilization of non-aqueous emulsion.[2] This Ostwald ripening can be prevented by adding a small amount (1%) of an oil that has a very low solubility in the continuous phase or using larger size of surfactant molecules such as triblock copolymers.[2]

Stabilization technique

There are two basic strategies for the preparation of stable non-aqueous emulsions, specifically using two incompatible block copolymer surfactants and using suitable oil-immiscible polar liquid.

(1) Using two incompatible block copolymer surfactants

The design of block copolymer surfactant system constitutes two incompatible blocks, each of which is selectively soluble in different immiscible liquids. This approach needs to be characterized as a new surfactant for each combination of liquids. For example, diblock copolymers of polystyrene and polyisoprene were able to stabilize DMF and hexane emulsions for almost 24 h.[26] For stable emulsions, the surfactant must lower interfacial tension. On the other hand, it provides the interfacial film to be sufficiently viscoelastic to protect the surface.[27,28] In addition, another factor needs to be considered. Some investigations compared the dominant factor for stability of non-aqueous emulsion. When both alkyl and aryl poly(oxyethlyene) ethers and silicone-based surfactants have the ability to lower the interfacial tension at the castor oil-silicone interface, a dominant factor for stabilization is the solubility of the surfactant in the continuous phase.[28]

(2) Using suitable oil-immiscible polar liquid

For the investigation of a suitable oil-immiscible polar liquid which can effectively replace water, the one criterion is to be a good solvent for the solvophillic part of the surfactant molecule. For example, non-ionic surfactants with HLB numbers around 12 were found to stabilize oils dispersed in formamide.[27]

There are no guidelines for stabilization of two immiscible non-polar oils or polar-solvent phases, because HLB system was not applicable for this system.[27] An optimized non-aqueous emulsion can be obtained through the implementation of pseudo-ternary phase diagram constructed by the titration method.[27] The most significant factors affecting the stability of a non-aqueous emulsion system is the surfactant concentration in continuous phase by using the factorial design based on a reduced-fit quadratic model to confirm contribution of various factors on the stability of the emulsions.[29]

Although there have been only occasional reports for non-aqueous emulsion systems, a non-aqueous emulsion could be used to replace an aqueous emulsion where the presence of water is undesirable. In the pharmaceutical field, this system is developed as the vehicle for hydrophobic drugs or drug susceptible to hydrolysis. A major problem of non-aqueous emulsions is due to its limited stability resulting from Ostwald ripening. The most important factor affecting the stability is the concentration of surfactant. A challenge in this field awaits further development for the methods to generate a fairly stable non-aqueous emulsion. The role of physical properties in the development of non-aqueous emulsions and their pharmaceutical applications are further mentioned in Part II. To provide an overall perspective as to the diversity of

reagents which may be used to formulate a non-aqueous emulsion, the components of previously established non-aqueous emulsion preparations are summarized in Table 1.

Table 1 Components of previously established non-aqueous emulsion preparations.

Dispersed phase	Continuous phase	Surfactant/Combination of surfactant	Ref.
Olive oil	Glycerin	Anionic, cationic	8
Olive oil	Glycerin	Non-ionic	9
Olive oil	Glycerin	Saponifying agent of ammonia and 2-amino-2-methyl-1,3-propanediol (AMP)	30
Glycerin, propylene glycol or polyethylene glycol 400	Olive oil	Gleceryl monostearate or sodium stearate or sorbitan monosterate	9
Mineral oil	Glycerin	Anionic, cationic and non-ionic	31
Dodecane	Formamide	Non-ionic	2
Dodecane	DMSO	Non-ionic	2
Castor oil	Silicone oil (dimethylsiloxane)	Non-ionic	29
Castor oil	Dimethicone or cyclopentasiloxane	Silicone surfactant (cyclomethicone/dimethicone copolyols)	4
N,N'-dimethyl-formamide (DMF)	n-hexane	Poly(isoprene)-poly(methylmethacrylate) block copolymer	32
Acetonitrile	Cyclohexane	Poly(isoprene)-*b*-poly(methyl methacrylate) block co-polymer and poly(methylmethacrylate) block copolymer	32
Acetonitrile	Tetradecane	Poly(isoprene)-poly(methylmethacrylate) block copolymer	32
Castor oil	Silicone oil	Silicone surfactant	33
Acetone	Triglyceride (Myglyol 812)	Sorbitan monooleate	19
Dichloromethane	Perfluorohexane	Perfluoro polyester	19
Polyethylene glycol 400	Glycerin ester (Myglyol 812)	Poly(2-vinylpyridine)-*b*-poly(butadiene) (P2VP-*b*-PBut) copolymers	17
DMF or acetonitrile	Alkanes	Polyisoprene-*b*-poly(methyl methacrylate) (PI-*b*-PMMA)	16
Acetonitrile	Cyclohexane	Iron(III)-induced synthesis of poly(ethylenedioxythiophene) (PEDOT)	16
Alkanes	Perfluoroalkanes	Amphipolar polymeric emulsifier with fluorous and aliphatic side chain	16
Olive oil or Glycerin	Glycerin or Olive oil	Span 20,40,60,80, 85,Tween 20,40,60,80, SLS, GMS	27
Glycerin ester (Myglyol 812)	Polyethylene glycol 400	Poly(butadiene)-poly(2-vinylpyridine)-poly(ethylene oxide) (PBut-P2VP-PEO) tri block copolymers	18

Conclusion

Non-aqueous emulsion is prepared from two immiscible liquids which employs a non-aqueous polar liquid instead of water, a non-polar liquid and emulsifier to stabilize the system by preventing a phase separation. There are three types of non-aqueous emulsion including oil-in-non-aqueous polar liquid emulsion, polar solvent-in-oil emulsion and oil-in-oil emulsion. The fairly stable non-aqueous emulsion is mainly from Ostwald ripening. The use of suitable emulsifier is necessary for preparation of stable non-aqueous emulsion. In addition, it is necessary to choose the surfactant that will not irritate the mucosa or tissue. The review for the role of physical properties in the development of non-aqueous emulsions, and also the evaluation and application of non-aqueous emulsion will also be mentioned in Part II.

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