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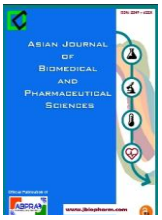

REVIEW ARTICLE

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Potential Application of Non Aqueous Emulsion for Drug Delivery

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Abstract

Conventional emulsions are heterogeneous system in which one immiscible liquid is dispersed as droplets in another liquid. That may be water-in-oil or oil-in-water emulsions. However emulsion can be formulated waterless or without an aqueous phase to produce anhydrous or non-aqueous or oil-in-oil emulsions may be used as reservoirs to deliver lipophilic or hydrolytically unstable drugs, could be considered as depot formulations for sustained release drug delivery. Such systems, presence of water to be avoided. Some drugs are unstable or not soluble in water, formulation of such drug for oral administration has more difficult. Oral drug delivery vehicles must be capable of maintaining sufficient drug concentration in a bioavailable form that will enable expected absorption and biological activity. Such drug delivery vehicles must also be capable of maintaining the drug in its dissolved state and maintain stability of drug. This can be achieved by formulating the non aqueous emulsion. Most important factor considering formulation of stable anhydrous emulsion for oral delivery is concentration of surfactant. At high surfactant concentration may inhibit lipolysis and is disadvantageous to the intestinal mucous and has potential of causing local irritation side effects. So there is a need for such vehicle that will not comprise high and significant portion of surfactants that are irritating to the gastro intestinal mucous.

Keywords: Oil-in-Oil emulsions, lipophilic drug, Oral drug delivery

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INTRODUCTION

Two types of emulsion are known: An emulsion of oil droplets in a continuous phase of water, and an emulsion of water droplets in a continuous phase of oil.[4] Macroscopic separation of the phases is prevented by the addition of a suitable surfactant. In the vast majority of emulsion research, one of the liquid phase is water.[5] The terms oil and water, as used in the literature, denote nonpolar and polar liquids in general. If "immiscible oils" or "immiscible waters" could be found, the possibility would arise that not one, but three classes of emulsions could be made, namely oil-oil (O/O) emulsions, oil-water (O/W) emulsions, and water-water (W/W) emulsions. Each of these three classes of emulsions would then consist of two emulsion types (Fig. 1). Depending on which phase is the continuous and which is the disperse phase. Within each class, the two emulsion types should be invertible, as oil-in-water emulsion in which the oil is dispersed and water forms the continuous phase can be inverted into water-in-oil in which the water is an internal phase dispersed in oil phase and vice versa. Of the three conceivable classes of emulsions, only the combination oil in water or, in more general term, the combination nonpolar-polar, is described in the literature.

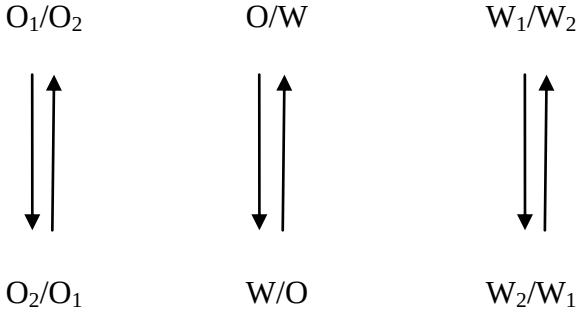

Figure 1: Emulsion Types

The combination oil-oil or nonpolar-nonpolar and the combination water-water or polar-polar have been either not recognized or not seriously considered.[4]

Emulsion is one of the most convient and advantageous formulation in which one of the liquid phases is water. However emulsion can be formulated without an aqueous phase to produce anhydrous, non-aqueous or oil-in-oil emulsions. Such systems, which can replace conventional emulsions where the presence of water to be avoided.[6] Non aqueous microemulsions have attracted a great deal of attention not only because of their importance in industrial application but also intrinsic interest. Non aqueous microemulsions are suitable for poorly aqueous soluble drug and thermodynamically stable multicomponent fluid of polar solvent, oil and mixture of a.[3] Liquid administration of drug is one of the convient and often advantageous delivery, especially when dealing with children or the elderly for whom pill swallowing can be difficult or even hazardous.[1, 3] In the past few years, recognizing that the literature was relatively sparse, we have studied some emulsions of two non-aqueous or "oil" phases. Not only are there no rules for their stabilization, but the normal rules elaborated for the formulation of emulsions containing a non-polar oil phase and an aqueous phase do not hold. There is thus some challenge in producing stable anhydrous emulsions, which might be useful in formulating hydrolytically unstable drugs for oral drug delivery or to provide reservoir vehicles for transdermal systems.[3,7]

Oil-in-anhydrous solvent emulsions may be prepared in various hot or cold methods. In hot method, the oily and anhydrous solvent phases are heated separately to 80^0 C. until all ingredients melt and are Well dissolved. The phases are combined while mixing. Mixing may be performed with any mixer, blender, homogenizer, etc. Which is used for producing emulsions. Oil-in-non-hydrous emulsions may also be prepared by heating all the ingredients, including oil, non-hydrous solvent and emulsifying stabilizers in a single batch, heating to achieve melting of solids and with continued mixing to promote emulsification until cooled to room temperature.[2]

Several novel approaches have been attempted to increase the solubility and bioavailability of biological classification system (BCS) class II drugs. The novel approaches can be divided into two main categories: Solid dosage forms and liquid dosage forms. Both are developed with the purpose of increasing dissolution rate and bioavailability simultaneously.

Advantages of oil-in-oil emulsion:

High drug loading capacity

oil-in-oil emulsion increases the bioavailability of the drug

oil-in-oil emulsion can be used as carriers for lipophilic compounds

Convenient for Parenteral, topical, ocular and oral administration

oil-in-oil emulsion as a potential for controlled drug release

oil-in-oil emulsion can be used for water unstable compounds

Better penetration through membranes and higher bioavailability

Disadvantages:

Due to incorporation of oily solvent there may chances of oxidation of oil phase.

Intra venous, Intra muscular, Subcutaneous or other form of injection is possible following preparative dilution step, before the administration, with physiological fluid such as saline or sucrose sterile

solution, to obtain physiologically acceptable sterile and isotonic product.[2]

For stabilization of such system development of special surfactant is require.

In case of oral drug delivery at high surfactant concentration may inhibit lipolysis and is disadvantageous to the intestinal mucous and has potential of causing local irritation side effects.[2]

Noteworthy Contribution in the field of non aqueous emulsion:

Gunther E. M. had been introduced a novel class of polymeric oil-in-oil emulsions. Emulsions of the class comprise two immiscible polymer solutions and a graft copolymer as an emulsifying agent. The name polymeric oil-in-oil emulsions (PO0 emulsions) has been suggested for the new emulsions. The concept has been verified with several eyetema of polymer solutions. The polymers used here are poly (ethy1 acrylate), poly(methy1 methacrylate), polystyrene, polyvinyltoluene, poly-ptercbutyletyrene, and a styrene/acrylonitrile copolymer.[4] Peterson, R.V. were used liquids representing the polar phase include glycerin, propylene glycol, and polyethylene glycol 400. Olive oil as the nonpolar phase liquid. Representative anionic, cationic, and nonionic surfactants were employed. Conventional theories and methodology are not readily translatable to the nonaqueous systems in many instances. Concluded that combinations of glycerin and olive oil emulsified more readily than either propylene glycol or polyethylene glycol 400 and olive oil. Further, the emulsions of glycerin and oil were more stable, exhibited a wider range of physical characteristics, and required much lower levels of surfactant. [17] Sakthivel T. designed to evaluate some design criteria for hydrocarbon–formamide systems. The effect of various parameters such as surfactant concentration and solvophilicity of the surfactant was observed. The surface activities of polysorbate 20, 40, 60 and 80 in formamide and critical micellar concentrations were determined. The latter were several orders of magnitude higher in formamide than in water, and the areas per molecule larger. The addition of water to the dodecane formamide systems did not destabilise the emulsion. Release of the model drug dehydroepiandrosterone from dodecane in formamide emulsions was studied in distilled water, the rate of release being dependent on the volume fraction of dodecane. [19] Dyab, A. K.F. worked on series of nonionic polymerisable nonyl phenol ethoxylates has been prepared as organic solvent-soluble surfactants in which straight, branched and cyclic alkyls and phenyl acted as solvophilic segment and polyoxyethylene, chains as solvophobic segment. The new bifunctional reactive surfactants were prepared by reacting polyoxyethylene 4-nonyl -2-propylene-phenol nonionic reactive surfactant with maleic anhydride followed by esterification with poly (ethylene) glycol. The ^{13}C and ^{1}H NMR was used to determine chemical structure of the prepared surfactants. Surface activities of these surfactants in organic solvents including formamide, toluene and aqueous water solvent were determined by surface tension measurement. The results showed that these polymerisable nonyl phenol ethoxylates surfactants can reduce the surface tension of both polar and non-polar organic solvents. A stable non-aqueous emulsion of formamide/toluene system was prepared and exhibited excellent stability against coalescence for more than 6 months when stabilized by the modified surfactants. [11]

Payghan, S. A. gave a conceptual idea about non-aqueous system; such system provides reservoir vehicles for transdermal systems and controlled drug delivery systems or hydrolytically unstable drugs and explained that non-aqueous systems are well known as solvents for drugs, suspension vehicles, oleogels, soft gelatin drug delivery system.[8] Also examined the effect of accelerated-aging conditions on the performance of piroxicam (PX) non aqueous formulated emulsions. Concluded although storage conditions affected the dissolution behavior of all PX emulsion formulations, but did not have a significant effect on PX chemical stability. And formulation had acceptable dissolution stability when stored at room temperature throughout their storage periods.[40] Also developed piroxicam non aqueous emulsion and to understand the kinetics of drug release by applying mathematical and model-dependent approaches.[41] Suitthimeathegorn, O. Investigated biodistribution and intramuscular absorption of dexamethasone from non-aqueous emulsions in the rat. Emulsions of castor oil-in silicone oil (co/so) release drugs slowly in vitro. To investigate the potential use of such formulations as depot preparations in vivo, drug absorption and distribution from an intramuscular injection site to various organs in the rat was studied. 3H-dexamethasone (0.1 mg/kg) was incorporated into the castor oil (disperse phase) of co/so emulsions and in castor oil-in-water (co/w) emulsions as control and found that Administration of 3H-dexamethasone in the co/so emulsion improved the mean residence time (MRT) and the elimination half-life ($t_{1/2}$) in comparison to the co/w emulsion. The clearance of 3H-dexamethasone from the co/so emulsions at the injection site was also slower and at 4.0 h post-injection the amount of drug remaining in the muscle was found to be eight times higher than with the co/w emulsions. [7] Chien Lin, C., worked on to enhance the stability of skin-whitening agent, deoxyArbutin in formulations, they chose the polyol-in-silicone, anhydrous emulsion system as the basic formulation for investigation. The quantity of

DeoxyArbutin and the accumulation of hydroquinone in both hydrous and anhydrous emulsions at various temperatures were analyzed through an established high performance liquid chromatographic method. The results indicated that water increased the decomposition of deoxyArbutin in the formulations and that the polyol-in-silicone, oil-based, anhydrous emulsion system provided a relatively stable surrounding for the DeoxyArbutin that delayed its degradation at 25 °C and 45 °C. The deoxyArbutin is a potent tyrosinase inhibitor that is safer than hydroquinone and arbutin. However, DeoxyArbutin is thermolabile in aqueous solutions, where it decomposes to hydroquinone. [25]

Ha, J. W., and Yang, S. M. the rheological responses of oil-in-oil emulsions in a dc electric field were investigated experimentally. Concluded that emulsions consisted of a less conducting dispersed phase and a more conducting continuous phase. The positive electro rheological (ER) effect, which is produced at low shear rates, is diminished instantaneously at high shear rates. When the shear flow becomes strong and dominant, the contribution of electric field to the rheological responses of the emulsions can be ignored. The negative ER effect is observed when the shear flow and electric fields are competitive. The magnitude of the viscosity reduction increases with both the viscosity and conductivity ratios. [18] Jaitely, V. formulated oil in oil emulsion by using various non-ionic surfactants. Emulsions of castor oil in silicone oil with a range of viscosities from 1-100 cSt were studied using a range of non ionic surfactants as emulsifiers. Stable emulsions were obtained using Triton-X-100. Formulated emulsion was found to be stable up to around 37^0C but the system are destabilized above 50^0C. They studied that the release of dexamethasone and dehydroepiandosterone from oil in oil emulsion across dialysis membrane in to aqueous medium and observed slow release over several hour. [15] Suitthimeathegorn, O. were formulated oil in oil emulsion using castor oil as the disperse phase and dimethicone or cyclopentasiloxane as the continuous phase. Among the emulsifiers studied only silicone surfactants which were miscible in silicone oil stabilized the emulsions. Cyclomethicone/PEG/PPG-18/18 Dimethicone and Cyclopentasiloxane/PEG/PPG-18/18 Dimethicone were more effective in lowering the interfacial tension between castor oil and both dimethicone and cyclopentasiloxane. Emulsions formulated using either of these two surfactants were found to be stable against phase separation and exhibited least globule growth over 168 h. [14]

Loudet, J. C. et al. studied nonaqueous emulsions that are composed of liquid crystal and silicone oils. New surfactant molecules are specifically synthesized to stabilize these emulsions. The behavior of the present surfactants is reminiscent of the behavior of classical surfactants used for aqueous emulsions. Depending on their affinity for the liquid crystal or the silicone oils, they may either stabilize silicone in liquid crystal emulsions or stabilize liquid crystal in silicone emulsions. Worker had also showed that liquid crystal/silicone emulsions can be stabilized against Ostwald ripening by using an additional component in the dispersed phase of the formulation. Finally pointed out that the inclusion of liquid crystal droplets in silicone materials is potentially useful for imparting specific optical properties to materials traditionally employed for coatings or cosmetics. [20] Verma, S. worked on formulating stable non aqueous emulsions of castor oil and silicone oil, exploring also the possibility of using such systems as anhydrous vehicles for controlled drug release and concluded that The significant factor in the stabilization of the emulsion was the solubility of the surfactants in the continuous phase, lowering of interfacial tension being not in itself sufficient. As there are no guidelines for the selection of surfactants to stabilize two immiscible non-polar oils we are continuing to study a wider range of non aqueous systems to develop a better understanding of stabilization. [6] Imhof A. examined the stability of emulsions of oil in several non aqueous polar liquids using commercially available nonionic surfactants. Stable concentrated oil-in-formamide and oil-in-dimethylthe sulfoxide emulsions could be prepared using commercially available nonionic surfactants. Several other polar liquids turned out not to produce stable nonaqueous emulsions with these surfactants. It is unclear exactly which combination of molecular properties determines the emulsifying capacity, but hydrogen bonding clearly plays a more important role than polarity. Ostwald ripening was shown to be a very important factor in the stability of these nonaqueous emulsions. The process is considerably faster than in aqueous systems because of the higher solubility of oils in nonaqueous polar solvents. [16]

Wide range of drugs for oil in oil emulsion: [2]

The selection of the drug is manly depending up water solubility. Certain drug are not freely dissolve in water, decomposes when contact with aqueous environment up on storage, aqueous solution of certain drug gives unpleasant taste and smell. Such a type of drug selected for preparation of non aqueous emulsion which are lipophilic in nature.

Preferred classes of drugs include, but are not limited to, antihypertensive, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatory, antipsychotic agents, cognitive enhancers, anti-

atherosclerotic agents, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti Alzheimer's disease agents, antibiotics, anti-depressants, antiviral agents, glycogen phosphorylase inhibitors, and cholesterol ester transfer protein inhibitors.

Vitamins and co-enzymes that may be delivered using this, include but are not limited to Water or fat soluble vitamins such as thiamin, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, biotin, camitine, vitamin C, etc

Example of botanical bioactive agents, are: polyphenols, isoflavones, resveratrol, soy isoflavones, grape seed extract polyphenols, curcumin, epigenin.

Anti-inflammatory plant extracts such as aloe vera, echinacea, etc

anti-psoriatic such as Chinese zizipus jujuba.

Astringents such as hammamelis

Anti bacterial such as arte misia, chamomile, golden seal.

Immune modulators such as echinacea,

Anti-aging or anti-cancer or anti-photo damage, anti-inflammatory such as feverfew parthenolides, rejuvenation agents, carotenoids, beta-carotene, lycopene, etc.

Example of cholesterol and triglycerides lowering drug: fenofibrate, lovastatin, simvastatin, pravastatin, fluvastatin, etc.

Anxiolytics, sedatives & hypnotics: diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, etc;

Anti-emetics: ondansetron, tropisetron, granisetrone, metoclopramide, etc.

Chemotherapeutics agents include but are not limited to cisplatin (CDDP), procarbazine, mechlorethamine, cyclophosphamide, camptothecin, ifosfamide, melphalan, chlorambucil, bisulfan, nitrosurea, etc.

Antimicrobial agents that may be used include but are not limited to naficillin, oxacillin, vancomycin, clindamycin, erythromycin, trimethoprim-sulphamethoxazole, rifampin,

ciprofloxacin, broad spectrum penicillin, etc.

Antifungal agents that may be delivered include but are not limited to ketoconazole, fluconazole, nystatin, itraconazole, clomitrazole, and amphotericin B.

Antiviral agents that may be used include but are not limited to acyclovir, trifluridine, idoxorudine, foscarnet, ganciclovir, zidovudine, etc.

Antihistamines are represented by but are not limited to cimetidine, ranitidine, prylamine, diphenydramine, promethazine, chlorpheniramine, chlorcyclizine, etc.

Decongestants and antitussives include agents such as dextromethorphan, carbetapentane, caramiphen, chlophedianol, diphenhydramine, glaucine, pholcodine, etc.

Anesthetics include etomidate, ketamine, propofol, and benodiazapines (e.g., flurazepam, diazepam, clorezepate, etc.), benzocaine, dyclonine, lidocaine, bupivacaine, etidocaine, prilocalne, etc. Other useful agents may include amobartital, aprobarbital, paral, thiopental, butabarbital, etc

Analgesics include opioids such as morphine, mepidine, dentanyl, sufentranil, alfentanil, aspirin, acetaminophen, ibuprofen, indomethacine, naproxen, etc Ergot and ergot derivatives (Wigraine, cafergot, ergostat, etc), imitrex, etc.

Anti-inflammatories include but are not limited to salicylic acid derivatives (e. g. aspirin) paraminophenol derivative (e. g. acetaminophen) indole and indene acetic acids (sulindac indomethacin, etc) heteroaryl acetic acids (tolmetin diclofenac and ketorolac) aryl propionic acid derivatives (ibuprofen, naproxen, etc.), anthranilic acids (mefenamic acid, meclofenamic acid) enolic acids (piroxicam, tenoxicam, etc.)

Diuretics include but are not limited to acetazolamide, dichlorphenamide, methazolamide, furosemide, bumetanide, ethacrynic acid torseimde, azosemideetc.

Psychotherapeutic agents include thorazine, serentil, mellaril, millazine, tindal, permitil, prolixin, trilafon, stelazine, suprazine, taractan, navan, etc.

Cardiovascular agents include but are not limited to nitroglycerin, isosorbide dinitrate, sodium nitroprisside, captopril, enalapril, enalaprilat, etc.

Preferred Solvent System:

Which are oily in its nature that is not mixing or dissolving with water or hydrous mediums. And/ or other oil phase. They are immiscible in each other, Such oily solvent may be natural or synthetic or semi-synthetic.

Oil solvents are mineral oil, vegetable oil, silicon oil, lanolin, refined animal oil, hydrocarbon esters derived from vegetable animal or marine origin.

Vegetable oils may included such as: isopropyl miristate, jojoba oil, almond oil, avocado oil, coconut oil, capric-caprylic tryglyceride of fractionated coconut oil, nutmeg oil, castor oil,

olive oil and oleic acid, soybean oil, sunflower oil,

canola oil, citrus seed oil, carrot seed oil,

corn oil, cottonseed oil, cucumber oil, peanut oil,

rapeseed oil, safflower oil, whale oil, wheat germ oil,

sesame oil, etc.

Animal oils may included such as: egg oil, shark liver oil, tallow (beef) oil, tallow (mutton) oil, turtle oil,

Semi-synthetic oil is a product of inter-esterification of hydrogenated palm oil palm kernel oil, peach kernel oil.

Hydrophobic solvents may be selected comprising isostearic acid derivatives, isopropyl palmitate, lanolin oil, diisopropyl dimerate, maleated soybean oil, octyl palmitate, isopropyl isostearate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, glyceryl oleate, tocopheryl linoleate, Wheat germ glycerides, arachidyl propionate, myristyl lactate, isopropyl palmitate, decyl oleate, propylene glycol ricinoleate, isopropyl lanolate, pentaerythrityl tetrastearate, neopentylglycol dicaprylate/dicaprate, hydrogenated
coco-glycerides, isononyl isononanoate, isotridecyl isononanoate, myristal myristate, isocetyl stearate and isoadipate.

Continuous Non-Hydrous and Hydrophilic Phases:

The continuous non-hydrous and hydrophilic phase is made of organic solvents that are completely and immediately miscible with water and physiological fluids Preferred pharmaceutically acceptable water-miscible non-aqueous solvents suitable for use in the non-aqueous compositions, but are not limited to, glycols such as propylene glycol and glycerin, polyethylene glycols of various molecular weights and the like and their mixtures.

Less preferable are organic solvents that are only moder ately or partially miscible With water. Example of other preferred solvents and possible co-solvents are: polyols or amides or esters, butanediols and isomers thereof, pentaerythritol, sorbitol, mannitol, dimethyl
isosorbide, polypropylene glycol, ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG or methoxy PEG; Amides, such as 2-pyrrolidone, 2-piperidone, e-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide;

Esters, such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl butyrate, triacetin, propylene glycol diacetate, .epsilon.-caprolactone
and isomers thereof, .delta.-valerolactone and isomersthereof, .beta.-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide,
dimethyl isosorbide, N-methylpyrrolidones, transcutol.etc

Emulsifying System: [1, 2, 8, 9, 10, 22, 23]

The emulsifying stabilizer is any surface active agent of pharmaceutical cosmetic or food grade that has an amphiphilic nature and that is able to stabilize the emulsion. The surfactant can by hydrophilic, hydrophobic, or a mixture of hydrophilic and hydrophobic, Anionic, Cationic, Non-ionic, Ampholytic and Zwitterionnic surfactants.

The fabrication of stable non-aqueous emulsions is not as advanced as the stabilization of aqueous emulsions. The selection of suitable stabilisers is still challenging due to a lack of general knowledge about the underlying stabilizations mechanisms.[21] The hydrophilic-lipophilic balance (HLB) introduced by Griffin for aqueous emulsions in 1949, for instance, does not hold with these systems.[11, 12, 13]

It has been found that low concentration of emulsifier stabilizer is practically applied to obtain required shelf life stability and obtain and maintain below one micron mean particle size. Typical low surfactant ration is below 20%, preferably below 10% and more preferably below 5% and more preferably from 1% to 5%.

In contrast to significant load of surfactants in "Self Emulsifying Delivery Systems", in the range of 20% to 50%, it has been unexpectedly discovered that low surfactant ration compositions maintain sub-micron or nano-size mean oil globules size When diluted With physiological fluids such as gastrointestinal content or simulated content. The nano-size mean globule diameter is maintained for the period relevant for physiological drug absorption and for the relevant pH and physiological conditions of gastro intestine system.

Ampholytic and Zwitterionnic Type of Surfactants Used:

Ampholytic:

3-[N,N—Dimethyl (3-palmitoyl aminopropyl) ammonio]-propane sulfonate
N-Dodecyl-N,N-dimethyl-3-ammonio-1-propane sulfonate
Sodium 2,3-dimercapto Propane sulfonate monohydrate

Zwitterionnic:

3-(N,N-Dimethyloctylammonio) propane sulfonate
3-(N,N-Dimethyl palmityl ammino) propane sulfonate
3-(Decyl dimethylammonio) -propane- sulfonate
N-Dodecyl-N,N-dimethyl-3-ammonio-1-propane sulfonate
N-Dodecyl-N,N-dimethyl-3-ammonio-1-propane sulfonate

Anionic Type of Surfactants Used In Non-Aqueous Emulsion:

Cholic acid from ox or sheep bile.
Glycolithocholic acid ethyl ester
Lithium 3,5-diiodosalicylate
N,N-Dimethyl dodecyl amine N-oxide
N-Lauroyl sarcos-ine
Niaprof
Sodium taurolitho cholate

Cationic Type of Surfactants Used In Non-Aqueous Emulsion :

Girard's reagentT 99%
N,N′,N′-Polyoxy ethylene(10)-N-tallow-1,3-diamino propane liquid
Saponin
4-Nonyl phenoxy polyglycidyl ether
6-Cyclohexyl hexyl β-D-maltoside
Brij 30,35,56,72,97,58,
Nonidet P 40

Non-Ionic Type of Surfactants Used :

Glucopone 215,600 CS UP and 600,650 EC
Triton CF 10, N-57, 60, X-100, 207, 45,305,405.
Triton X-15
Tergitol NP-9
Tween (Polysorbate) 20,21,40, 60,61,65,80,81,85,
Span 20,40,60, 65,80,83,85,
propylene glycol stearate

Silicone surfactants:[6, 14]

PEG/PPG-18/18 Dimethicone (DC 190),
PEG/PPG-15/15 Dimethicone (DC 5330),
PEG-12 Dimethicone (DC 193),
Cyclomethicone/PEG/PPG-18/18 Dimethicone (DC 3225C),
Lauryl PEG/PPG-18/18 Methicone (DC 5220),
Cyclopentasiloxane/PEG/PPG- 18/18 Dime-thicone (DC 5225C),
Cyclopentatasiloxane/PEG-12 Dime-thicone Cross polymer (DC 9011)

Applicability of oil-in-oil system:

For personal care applications:[1, 8, 17, 24, 35] The anhydrous emulsions may be employed include, but are not limited to, deodorants, antiperspirants, skin creams, facial creams, hair care products such as shampoos, mousses, styling gels, protective creams, such as sunscreen, pre-shave and after-shave lotions, liquid soaps, shaving soaps, and shaving lathers, color cosmetics such as lip products or lipsticks, foundations, blushes, makeup, and mascara, , oil removers, color cosmetic removers, and powders. And other cosmetic formulations where silicone components have been added. These cosmetic compositions will in all probability also contain other materials designed to improve appearance or functionality of the composition and as such cosmetic compositions prepared with the compositions of the present invention may additionally comprise emollients, pigments, colorants, fragrances, preservatives, hormones, medicinal compounds, anti-microbial agents, anti-fungal agents, vitamins, salts, absorbing agents for ultraviolet (UV) radiation and botanical extracts. The compositions of the present invention also have utility as drug delivery systems for topical application of medicinal compositions that are to be applied to the skin. Based on the desirable physical characteristics and stability properties of these emulsions and the inherent values of the components which they contain, it appears that these preparations can be used advantageously in cosmetic technology

Successful treatment for hyperpigmentation diseases: [25] In the literature found that deoxyArbutin, is a potent tyrosinase inhibitor, tyrosinase is an enzyme is mainly involved in the formation of pigments, such as melanin accumulation of melanin leads to many hyperpigmentation diseases such as melasma, solar lentigines, and post-inflammatory hyperpigmentation but found that this skin whitening agent was thermolabile in aqueous solutions and decomposes to hydroquinone under these conditions.[32] Instability in water posed developmental and practical problems for using deoxyArbutin in cosmetics and medication. Thus, enhanced the stability of this skin-whitening agent by incorporation in to non aqueous system.

Beyond/ Exceed from Pharmaceuticals: The obtained stable non-aqueous emulsions, or their polymeric materials if one or both oils is a monomer, will open up interesting avenues of research particularly those require the absence of water as coating, paints and anticorrosion areas. The emulsions are also capable of running as carriers for biocides, herbicides, pesticides, and other biologically active substances; and they have utility as additives for cellulosic or synthetic nonwoven carrier substrates used in wet-like cleansing wipes such as wet-wipes, tissues, and towels, marketed generally for personal hygiene and household cleaning tasks [5,8,33]

Magnetic Systems: Incorporation of magnetite nanoparticles into the disperse phase of these oil-in-oil emulsions has allowed control of the flow of droplets of the phase in capillaries, important in microfluidic systems and also in the design of pulsatile drug release systems.[8, 18,34] Magneto- and electrorheological systems are of increasing interest in controlling the properties of delivery devices.

Solvent for Capsule: The resulting composition comprising the low solubility bioactive agent, may be dosed directly will allow capsule filling at a later stage and it can be filling in to soft gelatin capsule or hard vegetable capsules.[2] It has been suggested that these liquid systems can be administered in gelatin capsules and subsequently result in the formation of a fine emulsion within the gastric space. This process may favorably influence the Bioavailability of lipophilic drugs or help to avoid the irritancy which can be caused by high concentration of certain drugs.[8, 43.] One area in which published literature is lacking is the field of non-aqueous emulsions filled into capsules, still some researchers have used polyethylene glycol (PEG) propylene glycol as a continuous phase for such emulsions.[37, 38] Non-aqueous emulsion is inert to the

capsule shells and did not compromise the seal of these systems over an extended period of time.[36]

Controlled Release Drug delivery vehicle: Formulating stable non aqueous emulsions of castor oil and silicone oil, In vitro release slow release patterns of ^{3}H dehydroepiandrosterone (DHEA) and ^{3}H-dexamethasone solubilize in the disperse castor oil phase into an aqueous dialysing medium (pH 7.4) were observed over 48 h. The release was observed to follow first-order release kinetics. Certain literature showed stable anhydrous emulsions of castor oil and silicone oil. The significant factor in the stabilization of the emulsion was the solubility of the surfactants in the continuous phase, lowering of interfacial tension being not in itself sufficient.[6, 8, 16]

High temperature reactions: Non-aqueous emulsions can also be applied for conducting reactions requiring high temperature to be proceeded. Indeed high boiling solvents can be used to build the dispersed phase and the continuous phase. An example employing reaction temperature >100^{0}C is the anionic polymerization of 3-caprolactam. The reactions were performed at 150 ^{0}C. The temperature could be even increased above 150 ^{0}C to perform the reduction of silver nitrate by ethylene glycol in the dispersed phase of non-aqueous inverse miniemulsions. Ionic liquids are ideal candidates to perform reactions at high temperature and at atmospheric pressure due to their low vapor pressure. Another advantage of high temperature reactions is that reactions are usually faster when increasing the temperature of the reaction.[27]

CONCLUSION

Up to now non-aqueous emulsions did not attract much attention although their unique features are useful for many applications. It is usually more difficult to stabilize non-aqueous emulsions than aqueous emulsions. In particularly, there is a need for such vehicle that will not comprise high and significant portion of surfactants that are irritating to the gastro intestinal mucous. It is the objective of the present invention to furnish a carrier system for bioactive agents having limited water solubility, whereas an admixture to body fluid is possible or better dissolution and enhanced absorption is obtained while avoiding the side effects associated with high emulsifiers' concentration. Unfortunately, many drugs are unstable or not soluble in water, formulation of such drug for oral administration has more difficult. Well-stabilized systems will, find uses in controlled release.

CURRENT & FUTURE DEVELOPMENT:

Keeping the above in view, efforts would be made to develop a stable Non-aqueous emulsion system for water unstable compounds. We emphasize mainly on incorporation of stable non aqueous emulsion as a vehicle for soft gelatin capsule dosage form, also trying to develop Intra venous, Intra muscular, subcutaneous dosage form

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