Ultrasonics Sonochemistry 21 (2014) 2069–2083

Contents lists available at ScienceDirect

Ultrasonics Sonochemistry

journal homepage: www.elsevier.com/locate/ultson

Cavitation technology – A greener processing technique for the generation of pharmaceutical nanoemulsions

Manickam Sivakumar [a,*], Siah Ying Tang [b], Khang Wei Tan [c]

[a] Manufacturing and Industrial Processes Research Division, Faculty of Engineering, University of Nottingham Malaysia Campus, 43500 Semenyih, Selangor, Malaysia
[b] Chemical Engineering Discipline, School of Engineering, Monash University Malaysia, Jalan Lagoon Selatan, 46150 Bandar Sunway, Selangor, Malaysia
[c] Department of Chemical Engineering, UCSI University, Kuala Lumpur, Malaysia

ARTICLE INFO

Article history:
Received 30 November 2013
Received in revised form 24 March 2014
Accepted 24 March 2014
Available online 3 April 2014

Keywords:
Nano
Emulsion
Ultrasound
Cavitation
Pharmaceutical
Hydrodynamic

ABSTRACT

Novel nanoemulsion-based drug delivery systems (DDS) have been proposed as alternative and effective approach for the delivery of various types of poorly water-soluble drugs in the last decade. This nanoformulation strategy significantly improves the cell uptake and bioavailability of numerous hydrophobic drugs by increasing their solubility and dissolution rate, maintaining drug concentration within the therapeutic range by controlling the drug release rate, and reducing systemic side effects by targeting to specific disease site, thus offering a better patient compliance. To date, cavitation technology has emerged to be an energy-efficient and promising technique to generate such nanoscale emulsions encapsulating a variety of highly potent pharmaceutical agents that are water-insoluble. The micro-turbulent implosions of cavitation bubbles tear-off primary giant oily emulsion droplets to nano-scale, spontaneously leading to the formation of highly uniform drug contained nanodroplets. A substantial body of recent literatures in the field of nanoemulsions suggests that cavitation is a facile, cost-reducing yet safer generation tool, remarkably highlighting its industrial commercial viability in the development of designing novel nanocarriers or enhancing the properties of existing pharmaceutical products. In this review, the fundamentals of nanoemulsion and the principles involved in their formation are presented. The underlying mechanisms in the generation of pharmaceutical nanoemulsion under acoustic field as well as the advantages of using cavitation compared to the conventional techniques are also highlighted. This review focuses on recent nanoemulsion-based DDS development and how cavitation through ultrasound and hydrodynamic means is useful to generate the pharmaceutical grade nanoemulsions including the complex double or submicron multiple emulsions.

© 2014 Elsevier B.V. All rights reserved.

1. What is nanoemulsion?

Nanoemulsions are isotropic colloidal systems composed of oil droplets dispersed in continuous aqueous media and stabilized by surfactant molecules. They are also frequently known as fine-dispersed emulsions, miniemulsions, ultrafine emulsions and submicron emulsions [1]. The nanoemulsions can be in the form of simple emulsion of oil-in-water, O/W or water-in-oil, W/O types. Typically the particle size or the mean droplet diameter covers a size range of 20–500 nm [2]. They are a class of transparent, translucent or sometimes milky emulsion systems which cannot be formed spontaneously as being non-equilibrium systems. Unlike microemulsions, which are also transparent and thermodynamically stable, nanoemulsions have a higher solubilization capacity for lipophilic drugs and better resistance toward droplet collisions induced by Brownian motion, thus giving rise to an excellent kinetic colloidal stability. Although they are kinetically stable, nanoemulsions are thermodynamically unstable dispersions as their free energy of formation is greater than that of their phase separated state. However, due to their nanometer-sized droplets, the long-term physical stability of nanoemulsions makes them unique without any apparent flocculation or coalescence during storage. Therefore these tiny emulsions of nano-dimension are sometimes referred to as "approaching thermodynamic stability" [3]. In the field of pharmaceuticals, nanoemulsion is usually a homogeneous mixture consisting of oil droplets encapsulating bioactive ingredients that are well-dispersed in an aqueous medium in the presence of a surfactant or emulsifier. In pharmaceutical nanoemulsions, the oil droplets serve as the reservoir for hydrophobic drugs. The most widely used oils include flax-seed oil, olive oil, castor oil, soybean oil, and other vegetable oils that are rich in

* Corresponding author. Tel.: +60 3 8924 8156; fax: +60 3 8924 8017.
E-mail address: Sivakumar.Manickam@nottingham.edu.my (M. Sivakumar).

http://dx.doi.org/10.1016/j.ultsonch.2014.03.025
1350-4177/© 2014 Elsevier B.V. All rights reserved.

Omega-3 and Omega-6-fatty acids and contain useful vitamins and minerals. Non-ionic surfactants are preferred since they are of low toxicity and known to be less affected by pH and ionic strength, and they are generally regarded as safe (GRAS) and are biocompatible. Combination of various surfactants has also been used to control droplet size and improve the stability of nanoemulsions. These pharmaceutical nanoemulsions generally appear to be clear or transparent with the mean droplet diameter no larger than 200 nm while some appear optically milky with the droplet size up to 500 nm [4].

2. Why are pharmaceutical nanoemulsions?

Nanoemulsions are useful means of encapsulating, protecting and delivering the poorly water-soluble bioactive components for both functional food and pharmaceutical applications [5,6]. Although nanoemulsions have applications in wider technological areas (Fig. 1), their vital importance could be felt more in the pharmaceutical field. Admittedly, innovations in material chemistry and nanotechnology have synergistically fuelled the development of novel drug delivery systems and nanocarriers that are biodegradable, biocompatible, targeting and stimulus-responsive [7]. Increasing attention has been devoted to these systems due to their unique structure and properties, such as extremely smaller droplet size with larger surface area to volume ratio, increasing drug solubility and dissolution rate, protecting the bioactive compounds against degradation, improving diffusion across intestinal membrane and enhancing mucosal permeability and bioavailability [8–13]. Nanoemulsion formulations offer appealing alternative for the easy administration of poorly water-soluble drugs (hydrophobic bioactive agents) with reduced dosing frequency and drug originated systemic toxic effects and thus they could be considered as a promising drug delivery technology. The outstanding advantages of nanoemulsions over microemulsions in the pharmaceutical area could be mentioned in terms of enhanced drug properties and enhanced dosing requirements as shown in the Table 1. Overall nanoemulsions represent an effective, convenient, flexible formulation strategy and in fact, they are more patient compliant as compared to other existing dosage forms which make them a promising candidate for interesting pharmaceutical applications.

Approximately 40% of the newly discovered drugs or bioactive agents intended for transdermal, parenteral, intravenous route or oral ingestion are highly hydrophobic compounds with low water solubility which reduce their dissolution-rate limited cell absorption. The *in vivo* bioavailability of these drugs remains problematic due to their extremely poor solubility in the body fluids, thus greatly hinders their clinical translations. Several strategies and formulations have been employed to overcome this limitation. For these reasons, many of the hydrophobic drugs are frequently formulated in the conventional dosage forms such as tablets, capsules, pellets and injectable suspensions. Despite their established manufacturing techniques and good reproducibility, these pharmaceutical dosage forms suffer from the disadvantages of low drug absorption rate across gastrointestinal (GI) tract due to the low surface area, uncontrolled drug release profile due to the fast dissolution rate, non cell/tissue-specific drug delivery due to the absence of targeting ligands, higher doses and frequent dosing due to rapid metabolism rate of drugs in gastric fluid. The gastric fluid is essentially a colorless digestive fluid which is produced from the mucous membrane of the stomach, consisting of hydrochloric acid, pepsin, rennin and mucin whereas for GI tract, it is a 9-meter long, hollow digestive tube inside the human body, starting from mouth where food enters, to the rectum and anus where food is expelled, which is also known as alimentary canal. Nanoemulsions, on contrary, offer many crucial benefits over the existing solid dosage forms. By virtue of their fine droplet diameter, nanoemulsions provide ultra low interfacial tension and extremely large surface area that could significantly enhance the drug absorption in GI tract [14]. Therefore, nanoemulsion technology could improve the therapeutic index of drugs by enhancing their efficacy and increasing their tolerability in the human body. Nanoemulsion could also carry large payloads (e.g. drugs, protein, peptides, nucleic acids), protect the therapeutic agents from physiological barriers, as well as enable the development and synthesis of novel classes of polysaccharide nanoparticles [15–17].

The efficiency of drug delivery via different routes of administration is of vital importance in medicine and healthcare. Parenteral route is generally regarded as one of the major routes of drug administration due to its quickest onset of action caused by rapid access to blood circulation. However, it has been proven to be a challenging task to deliver hydrophobic drugs via parenteral route. For a majority of the existing hydrophobic drugs, solvents such as ethanol and propylene glycol are often used to solubilize water-insoluble drugs prior to parenteral administration [18]. Nevertheless, drug precipitation caused by co-solvent [19], severe pain during injection and also hemolysis at injection site often occur which strongly limits its application practically. One strategy to tackle these problems is through intravenous fat emulsion therapy. Commercially available intravenous fat emulsions such

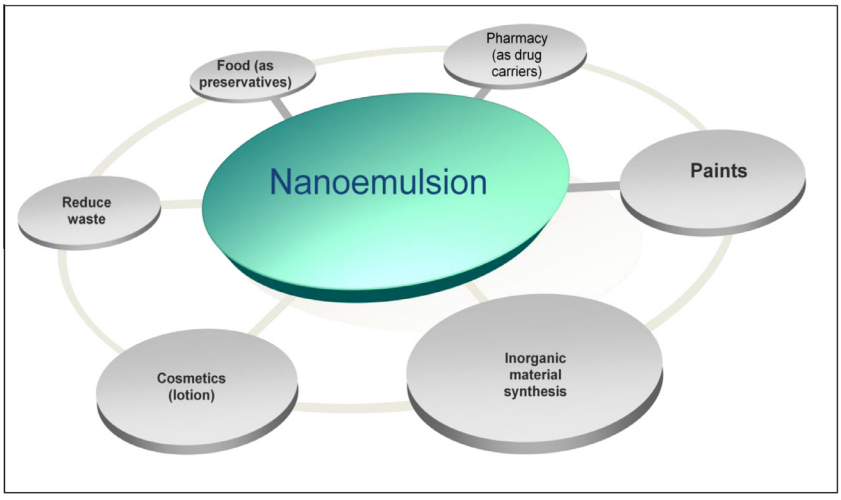

Fig. 1. Applications of nanoemulsions.

Download English Version:

https://daneshyari.com/en/article/1265066

Download Persian Version:

https://daneshyari.com/article/1265066

Daneshyari.com