Asian Journal of Pharmaceutical Education and Research
Vol -7, Issue-2, April-June 2018
ISSN: 2278 7496

REVIEW ARTICLE Impact Factor: 4.101

REVIEW ON NANO EMULSION BASED DRUG DELIVERY SYSTEM

Swati Patel*, Grijesh Pandey, S.K. Yadav

Technocrats Institute of Technology- Pharmacy Education and Research, Bhopal (M.P.)

*Corresponding Author's E mail: Swati1995patel@gmail.com

Received 03 Mar. 2018 ; Revised 18 Mar. 2018; Accepted 03 Apr. 2018, Available online 15 Apr. 2018

ABSTRACT

The most emerging branch in pharmaceutical sciences known as "Pharmaceutical nanotechnology" presents new tools, opportunities and scope, which are expected to have significant applications in disease diagnostics and therapeutics. Recently nano-pharamceuticals reveal enormous potential in drug delivery as carrier for spatial and temporal delivery of bioactive and diagnostics. Nanotechnology, shortened to nanotech, is the study of the controlling of matter on an atomic and molecular scale. Nanoemulsions (also referred as miniemulsions, submicron emulsions, ultrafine emulsions, fine-dispersed emulsions and so forth) are a group of dispersed particles used as vehicles for pharmaceutical aims and seem to be promising for the future of cosmetics, diagnosis, drug therapies and biotechnologies. Nanoemulsions are transparent or translucent dispersions, having the droplet size of less than 100 nm (the same droplet length-scale as microemulsions) with ultra low interfacial tension, large o/w interfacial areas and long-term physical stability. Literature review reveals that nanoemulsions containing solubilized drugs have been studied extensively as nanocarriers for the treatment of various diseases. Antibiotics, anticonvulsants and antihypertensives are among the drugs solubilized in nanoemulsions. The present review outlines the advantages and disadvantages of nanoemulsion with its preparation methods and therapeutic applications of nano-emulsion based drug delivery system of drugs published over the past decade.

Keywords: Nanoemulsion, Nano-pharamceuticals, Nanocarriers, drug delivery system.

INTRODUCTION

New opportunities to prevent and to treat diseases are by emerging the understanding of disease pathways. The intrinsic limitations of therapeutic biomacromolecules, such as proteins and nucleic acids, can be avoid through rationally-designed delivery vehicles. Drug delivery is becoming an increasingly important aspect for medicine field, as more potent and specific drugs are being developed.

Nanotechnology comprises technological developments on the nanometer scale, usually 0.1-100 nm. The use of nanotechnology in pharmaceuticals and medicine has grown over the last few years. The pharmaceuticals developed on the basis of nanotechnology are termed as "nanopharmaceuticals." The various nanopharmaceuticals currently being used or in the process of development are nanoemulsions (NEs) (submicron sized emulsions), nanosuspensions (submicron sized suspensions), nanospheres (drug nanoparticles in polymer matrix), nanotubes (sequence of nanoscale C60 atoms arranged in a long thin cylindrical structure), nanoshells (concentric sphere nanoparticles consisting of a dielectric core and a

metal shell), nanocapsules (encapsulated drug nanoparticles), lipid nanoparticles (lipid monolayer enclosing a solid lipid core) and dendrimers (nanoscale three-dimensional macromolecules of polymer). NEs are a group of dispersed particles used for pharmaceutical and biomedical aids and vehicles that show great promise for the future of cosmetics, diagnostics, drug therapies, and biotechnologies. NEs can be defined as oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size is between 100 and 500 nm. The particles can exist as water-in-oil and oil-in water forms, where the core of the particle is either water or oil, respectively. NEs are made from surfactants approved for human consumption and common food substances that are "Generally Recognized as Safe" (GRAS) by the FDA. These emulsions are easily produced in large quantities by mixing a water-immiscible oil phase into an aqueous phase with a high-stress, a mechanical extrusion process that is available worldwide. The NEs are also referred as miniemulsions, ultrafine emulsions and submicron emulsions. [1-4]

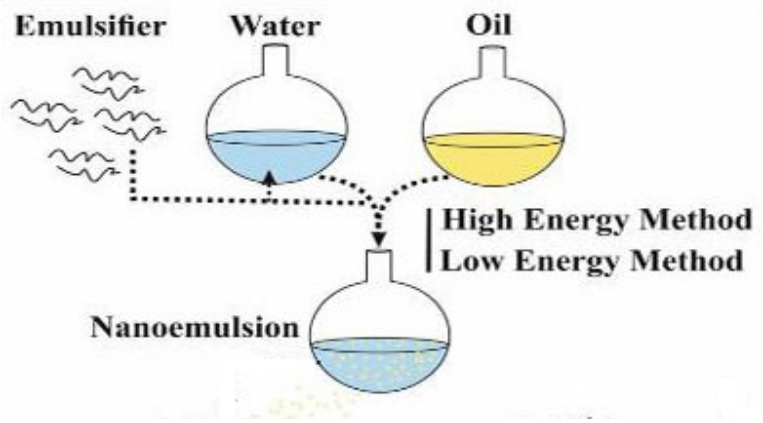

Figure 1: Nanoemulsions: colloidal topical delivery systems

NE formulations offer several advantages for the delivery of drugs, biologicals, or diagnostic agents. Traditionally, NEs have been used in clinics for more than four decades as total parenteral nutrition fluids. Several other products for drug delivery applications such as Diprivan®, Liple®, and Ropion® have also reached the marketplace.[5] Although NEs are chiefly seen as vehicles for administering aqueous insoluble drugs, they have more recently received increasing attention as colloidal carriers for targeted delivery of various anticancer drugs, photosensitizers, neutron capture therapy agents, or diagnostic agents. Because of their submicron size, they can be easily targeted to the tumor area. Moreover, the possibility of surface functionalization with a targeting moiety has opened new avenues for targeted

delivery of drugs, genes, photosensitizers, and other molecules to the tumor area. Research with perflurochemical NEs has shown promising results for the treatment of cancer in conjugation with other treatment modalities and targeted delivery to the neovasculature. It is expected that further research and development work will be carried out in the near future for clinical realization of these targeted delivery vehicles.

Table 1: Components of nanoemulsion formulations [6]

Oils	Emulsifiers
Castor oil, coconut oil, corn oil, cottonseed oil, evening primrose oil, fish oil, jojoba oil, lard oil, linseed oil, mineral oil, olive oil, peanut oil, PEG-vegetable oil, perflurochemicals, pine nut oil, safflower oil, sesame oil, soybean oil, squalene, sunflower oil, wheatgerm oil.	Natural lecithins from plant or animal sources, phospholipids, PEG-phospholipids, poloxamers (e.g. F68), polysorbates, polyoxyethylene castor oil derivatives, polyglycolized glycerides, stearlyamine, oleylamine. Additives Antioxidants (a-tocopherol, ascorbic acid) Tonicity modifiers (glycerol, sorbitol, xylitol) pH adjustment agents (NaOH or HCl) Preservatives.

Table 2: Commercial nanoemulsion (sub-micron emulsion) formulations [6]

Drug therapeutic	Brand	Manufacturer	Indication
Propofol	Diprivan	Astra Zeneca	Anesthetic
Dexamethasone	Limethason	Mitsubishi Pharmaceutical, Japan	Steroid
Palmitate alprostadil	Liple	Mitsubishi Pharmaceutical, Japan	Vasodilator platelet inhibitor
Flurbiprofen axetil	Ropion	Kaken Pharmaceuticals, Japan	Nonsteroidal analgesic
Vitamins A, D, E, K	Vitalipid	Fresenius Kabi, Europe	Parenteral nutrition

Table 3: List of patented nanmoemulsion formulations [7]

Patent application title	Patent app no.	Date
Topical compositions and methods of detection and treatment	20120039814	2012/02/16
Cancer vaccine compositions and methods of using the same	20110280911	2011/11/17
Methods of using nanoemulsion compositions having anti-inflammatory activity	20110200657	2011/08/18
Stable nanoemulsions for ultrasound-mediated of drug delivery and imaging	20110177005	2011/07/21
Method for the preparation of nanoparticles from nanoemulsion	20110135734	2011/06/09
Nanoemulsion formulations for direct delivery	20110045050	2011/02/24
Lyophilized nanoemulsion	20110015266	2011/01/20
Antimicrobial nanoemulsion compositions and methods	20110070306	2011/03/24
Nanoemulsion vaccines	20100316673	2010/12/16
Perfluorocarbon nanoemulsion containing quantum dot nanoparticles and method for preparing the same	20100233094	2010/09/16
Nanoemulsion of resveratrol-phospholipid complex and method for preparing the same and applications thereof	20100297199	2010/11/25
Compositions for treatment and prevention of acne, methods for making the compositions, and methods of use thereof	20100226983	2010/09/09
Stable mixed emulsions	20100069511	2010/03/18
Oil-in-water nanoemulsion, a cosmetic composition	20090208541	2009/08/20

The proficiency of any therapeutic agent is highly reliant on the extent of the drug reaches the systemic circulation by voyage number of barriers, smaller the particle size of drug maximum the absorption of any therapeutic agent. The attractiveness of nanotechnology is majorly due to the smallest particle size at the nanoscale. The nanoemulsion is the latent outcome of nanotechnology. In this review, we have discussed nanoemulsion based drug delivery system of antibiotic drugs, as nanoemulsion will solve the various problems that current therapeutic agents fronting and has been open new prospects to formulate

nanoemulsions with various therapeutic agents with heightened efficiency along with some other applications.

Antibiotic drugs as nanoemulsions

The rise in antibiotic-resistant bacteria has received much attention over recent years, but the rate of development of new antibiotics to treat these emerging "superbugs" is very slow. Encapsulating lipophilic drugs into oil droplets was first introduced in 1960 using the submicron emulsion o/w (Intralipid®) for parentral nutrition via injection. Microemulsions were reviewed for their parenteral use.[8] The low viscosity of the droplets causing fast release and susceptibility of the incorporated actives towards degradation by the aqueous continuous phase were the main drawbacks from such systems. More interesting, injectable liposomal products were commercialized such as AmBisome® (Amphotericin B), Doxil® /Caelyx® (Doxorubicin) and DaunoXome® (Daunorubicin) and a large array of investigational products which clearly indicates the potential advantages of liposomes as novel lipid carriers.[9]

A nanoemulsion can incorporate hydrophobic drug in oil droplets and due its very small particle size, it be used to improve oral bioavailability of poorly to soluble drug. Drugs such as steroids, hormones, diuretic and antibiotics can be delivered in nanoemulsion form through oral route.

It is not only important to design the most appropriate new drug for empirical therapy, but it is equally necessary to modify the drug delivery system in a way that makes the existing antibiotics useful. This can be done by studying the mechanism of antibiotic resistance and challenging the bacterial defense system with innovative mechanisms that can prove useful in combating infectious diseases such as UTI. Over the decades, the strategy for effective delivery of antibiotics has been gradually shifting towards the use of nanocarriers based on the fact that they can deliver the drug more efficiently inside the cell owing to their particle size and excipient properties.[10] A simple approach towards the problem of extracellular hydrolysis of antibiotics can be overcome by intracellular targeting of drugs. This can be done by encapsulating it in a stable nano-system that prevents the hydrolysis of drugs in the external vicinity and allows easy permeation through the cell membrane of the pathogens. Since microemulsions are thermodynamically stable solutions, with ultra-low interfacial tension, large interfacial area and inner structure of nanodroplets, they can solubilize a varied number of soluble as well as partly soluble drugs, as well as other biologically important components.[11] Moreover, the ease of formulation of micro-emulsion favors its use in pharmaceuticals where the pathogens can be exposed to the optimum concentration of drugs using such systems. [12]

Santos-Magalhães *et. al.,* 2000 formulated benzathine penicillin G nanoemulsion and nanocapsules to evaluate their physicochemical and stabilising characteristics, and to determine their antimicrobial

activity and penicillin in vitro release kinetics. Nanoemulsions were produced by the spontaneous emulsification approach and nanocapsules of poly (d,l-lactic acid-co-glycolic acid) polymer (PLGA) were prepared by the method of interfacial deposition of a pre-formed polymer. A 207±8 nm mean diameter nanoemulsion formulation maintained stability for more than 5 months at 4°C. Stable nanocapsules with 224±58 nm mean diameter were obtained, which remained stabilised over 120 days at 4°C. The penicillin encapsulation ratio in the nanocapsules was 85%. The in vitro release profiles indicated that penicillin released from the nanoemulsion was similar to the one observed from nanocapsules. However it can be clearly deduced from the in vitro kinetic analysis that the antibiotic cannot be protected in colloidal delivery systems. Nevertheless, stable formulations obtained in this investigation supply a potential dosage form to encapsulate more easily soluble drugs.[13]

Sanmukhani *et. al.,* 2014 conducted study to assess the comparative efficacy and safety of a nano-emulsion gel formulation of clindamycin with its conventional formulation in the treatment of acne vulgaris of the face. A total of 200 patients (97 males) were included for Intention to Treat analysis in the trial with 100 patients in each group. A trend towards better safety profile of the nano emulsion gel formulation was reported. In the treatment of acne vulgaris of the face, clindamycin nano emulsion gel formulation appears to be more effective than the conventional gel formulation and is also well tolerated.[14]

Yang *et. al.,* 2016 formulated the nano-emulsion through a spontaneous emulsification method for efficient delivery of ampicillin into the citrus phloem using bark application. Based on various physiochemical characteristics of oils, surfactants, and organic solvents, an oil-in-water (O/W) nano-emulsion formulation was developed and optimized to combat citrus HLB. The nano-emulsion that was prepared from Cremophor EL (viscous oil), acetone (water miscibility organic solvent), and Span 80/Tween 80 (surfactant) formed a small droplet size (17.33 ± 0.52 nm) and exhibited an improved absorption rate. Peak concentration was detected at 2 days posttreatment and the maximum concentration (C_{max}) and relative bioavailability (RBA) of ampicillin in HLB-affected citrus were 71.86 ± 35.38 ng/g and 267.25% ± 44.1%, respectively. The peak concentration of Amp appeared at 6 days post treatment in the citrus trees that were treated with Amp alone and their C_{max} and RBA were 56.44 ± 32.59 ng/g and 100%, respectively. The same nano-emulsion was used to deliver five different antimicrobials to control citrus HLB through bark application. Researchers found that the droplet size of the antimicrobials in the nano-emulsion was significantly reduced and the nano-emulsion also enhanced the therapeutic efficiency of validoxylamine A alone and in combination with actidione as well as sulfadimoethoxine sodium

against Las. Therefore, this study provides an efficient bark application nano-emulsion formulation for citrus HLB control. [15]

Vatsraj *et. al.,* 2014 aimed at development of a novel oil-in-water (o/w) nanoemulsion (NE) system having ability to function as carrier for poorly soluble drugs with clarithromycin as a model antibiotic. The therapeutically effective concentration of clarithromycin, 5 mg/mL, was achieved using polysorbate 80 combined with olive oil as lipophilic counterion. A three-level three-factorial central composite experimental design was utilized to conduct the experiments. The effects of selected variables, polysorbate 80 and olive oil content and concentration of polyvinyl alcohol, were investigated. The particle size of clarithromycin for the optimized formulation was observed to be 30 nm. The morphology of the nanoemulsion was explored using transmission electron microscopy (TEM). The emulsions prepared with the optimized formula demonstrated good physical stability during storage at room temperature. Antibacterial activity was conducted with the optimized nanoemulsion NESH 01 and compared with free clarithromycin. Zone of inhibition was larger for NESH 01 as compared to that with free clarithromycin. This implies that the solubility and hence the bioavailability of clarithromycin has increased in the formulated nanoemulsion system. [16]

Nicolaos *et. al.,* 2003 found the oil-in-water submicron emulsion was proven to be effective in protecting the prodrug from the enzymatic attack in rabbit intestinal washings. The aim of the study was to perform a pharmacokinetic study in conscious rats to confirm o/w submicron superiority in comparison to other oral formulations (hydro-alcoholic solution, suspension and coarse emulsion). The pharmacokinetic study was performed in conscious rats implanted with permanent aortic catheters. A parenteral solution of cefpodoxime was injected via this catheter, and oral formulations were administered orally. The cefpodoxime plasma level was performed by a HPLC validated method. The pharmacokinetic parameters, $t_{1/2}$, C_{max}, t_{max}, AUC and absolute bioavailability (F) were determined with a non-compartmental analysis. The results show a significant increase of F for submicron emulsion (97.4%) between the other oral formulations. No significant difference of F was found between the other oral formulations, even with the coarse o/w emulsion. The o/w submicron emulsion made the enhancement of the absolute bioavailability of cefpodoxime proxetil possible. This benefit could be explained by the low droplet size of the submicron emulsion which improve the absorption process of the prodrug. [17]

Eke *et. al.,* 2017 studied the stability and antibacterial activities of erythromycin oil-in-water nanoemulsion in batches F1, F2, F3 (160 mg of erythromycin) and a control having varying amounts of soy oil, soy lecithin and Tween 80 made up to 20 ml with distilled water, homogenising at 7500 rpm for 30 min. They were centrifuged and verified for electrical conductivity, pH, viscosity, droplet size,

polydispersity index (PDI), zeta potential, acute toxicity, in vitro antibacterial study against Staphylococcus aureus, Pseudomonas aeruginosa and Streptococcus pneumoniae together with in vivo antibacterial activity in rats besides a commercial erythromycin suspension. The nanoemulsions exhibited no cracking, creaming, phase separation or flocculation. Conductivities and viscosities remained stable through 90 days. The viscosity improved as the oil content increased across the formulations resulting in enlarged particle size and PDI of 237.2 nm and 0.467 for F1, F2 and F3 each had particle sizes of 290.6 nm and PDI of 0.670. The pH was fairly stable between 5 and 6. There was no sign of toxicity or death with the highest dose of the nanoemulsions. There was enhanced antimicrobial activity against S. aureus and S. pneumoniae similar to those of the commercial erythromycin suspension with the activities of the nanoemulsions higher at 0.14mg/ml compared to 0.78mg/ml of the commercial product. The in vivo antibacterial activity of nanoemulsions compared with the commercial product in rats. With the stability of the nanoemulsions up to 90 days, it could be concluded that the erythromycin soy lecithin nanoemulsion had improved solubility, stability and bioavailability. [18]

Nirmala*et. al.*, 2013 tried to work on a novel cinnamon oil based nanoemulsion drug delivery system for azithromycin using sonication technique at laboratory scale. Cinnamon oil, tween 80 and water were prepared at a ratio of 6:18:76 v/v to produce fine droplets in the range of 68.39 ± 2.19 nm after a sonication period of 30 min. Also, the polydispersity index confers better stability of the system as it recorded a lower value. Cinnamon oil was mainly chosen as it enhances the solubility to greater extent in azithromycin as it is highly lipophilic in nature. Moreover, the surfactant concentration was reduced greatly compared to other microemulsion systems. Hence, this system would be more efficient with mild or no toxic effects. [19]

Cefpodoxime proxetil (marketed under the trade name Vantin® by Pharmacia & Upjohn) is an oral cephalosporin antibiotic with poor aqueous solubility and low bioavailability and is therefore also a candidate for lipid-based formulations. Nicolaos et al. [20] demonstrated an improvement of the absolute oral bioavailability after administration of a phospholipid-based microemulsion (IMWITOR® 742 (Sasol) (blend of mono-, di- and triglycerides, these being chiefly acrylic and caproic acid), MCT, LIPOID S 40 (Lipoid GmbH) (40% phosphatidylcholine, 12–15% phosphatidylethanolamine, 3% phosphatidylinositol, 4% Lysophosphatidylcholine, 3% triglycerides)). Compared to an ethanolic solution, a suspension and an emulsion of the active ingredient, the microemulsion exhibited the highest absolute bioavailability in rats (97.4%) amongst the formulations tested. In addition, the microemulsion

formulation was shown to protect the active ingredient from enzymatic decomposition within the intestine.

Future perspectives

Nanoemulsions are proposed for numerous applications in pharmacy as drug delivery systems because of their capacity to solubilize non-polar active compounds. Future perspectives of nanoemulsion are very promising in different fields of therapeutics or application in the development of cosmetics for hair or skin. One of the versatile applications of nanoemulsions is in the area of drug delivery where they act as efficient carriers for bioactive, facilitating administration by various routes. The advantages and applications of nanoemulsions for oral drug delivery are numerous, where the droplet size is related to their absorption in the gastrointestinal tract. Due to the renewed interest in herbal drug formulation, nanoemulsion may be the ideal delivery platform for these difficult-to-formulate phytopharmaceuticals. The prospects of nanoemulsions lie in the ingenuity of formulation experts to utilize the advantages of nanoemulsion carriers in overcoming peculiar problems of drug delivery such as absorption, permeation, and stability of both orthodox and herbal drugs. Nanoemulsions offer several advantages for the delivery of drugs and are thus receiving increasing attention as drug carriers for improving the delivery of active pharmaceutical ingredients. They are applicable for almost all routes of delivery and therefore hold promise for different fields, be it cosmetics, therapeutics or biotechnology. This new technology could be developed to overcome the poor absorption of some phytopharmaceuticals and poor miscibility of these compounds with the lipid contents of cell membrane linings.

Conclusion

Nanoemulsion formulations offer several advantages for the delivery of drugs, biologicals, or diagnostic agents and able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Traditionally, Nanoemulsions have been used in clinics for more than four decades as total parenteral nutrition fluids. Nanoemulsions are chiefly seen as vehicles for administering aqueous insoluble drugs, they have more recently received increasing attention as colloidal carriers for targeted delivery of various anticancer drugs, photosensitizers, neutron capture therapy agents, or diagnostic agents. Because of their submicron size, they can be easily targeted to the tumor area. Moreover, targeting moiety has opened new avenues for targeted delivery of drugs, genes, photosensitizers, and other molecules to the tumor area. It is expected that further research and development work will be carried out in the near future for clinical realization of these targeted delivery vehicles.

References

1. Sing AF, Graciaa A, Lachaise J, Brochette P and Salager JL. Interaction and coalescence of nanodrops in transluscent o/w emulsions. Colloid Surface A. 1999; 152: 31-9.
2. Sarker DK. Engineering of nanoemulsions for drug delivery. Curr Drug Deliv. 2005; 2: 297- 310.
3. Chiesta M, Garg J, Kang YT and Chen G. Thermal conductivity and viscosity of water-in-oil nanoemulsions. Colloid Surface A. 2008; 326: 67-72.
4. Fernandez P, Andre V, Reiger J, Kuhnle A. Nanoemulsion formation by emulsion phase inversion. Colloid Surface A 2004; 251: 53-8.
5. Tiwari SB and Amiji MM. Nanoemulsion formulations for tumor targeted delivery In: Amiji M.M., Nanothechnology for cancer therapy. New York: CRC press. 2007; pp. 723-40.
6. Tiwari SB and Amiji MM. Nanoemulsion formulations for tumor-targeted delivery, nanotechnology for cancer therapy. Mansoor M. Amiji, Taylor and Francis Group, editors. 2006. p. 723-39.
7. Kreilgaard M. Dermal Pharmacokinetics of Microemulsion, Formulations Determined by In-Vitro Microdialy-sis. Pharmaceutical Research. 2001; 18(3): 367-373.
8. Date AA and Nagarsenker, M.S.," Parenteral microemulsions: An overview. " Int J Pharm, 2008,355 (1-2)19-30.
9. 1 4. Joshi, M.D. and Müller, R.H.," Lipid nanoparticles for parenteral delivery of actives". Eur J Pharm Biopharm, 2009,71 161-172.
10. Nagahara, N, Akiyama Y, Tada M, Nakao M, Kitano M and Ogawa Y. Mucoadhesive microspheres containing amoxycillin for clearance of Helicobacter pylori. Antimicrob Agents Chemother. 1998; 42: 2492-2494.
11. Spernath A and Aserin A. Microemulsions as carriers for drugs and nutraceuticals. Advances in colloidal and interface science. 2007; 130: 47-64.
12. Fattal, E. Intracellular targeting of antibiotics by means of biodegradable nanoparticles. J Control Rel. 1992; 19: 259-267.

13. Santos-Magalhães NS, Pontes A, Pereira VMW and Caetano MNP. Colloidal carriers for benzathine penicillin G: nanoemulsions and nanocapsules. International Journal of Pharmaceutics. 2000; 208(1-2): 71–80.
14. Bhavsar B, Choksi B, Sanmukhani J, Dogra A, Haq R, Mehta S, Mukherjee S, Subramanian V, Sheikh S and Mittal R. Clindamycin 1% nano-emulsion gel formulation for the treatment of Acne Vulgaris: Results of a randomized, active controlled, multicentre, phase IV clinical trial. Journal of Clinical and Diagnostic Research. 2014; 8(8): YC05-YC09
15. Yang CY, Powell CA, Duan YP and Zhang MQ. Characterization and antibacterial activity of oil-in-water nano-emulsion formulation against Candidatus Liberibacter asiaticus. Plant Disease 2016; 100(12); 2448-2454.
16. Vatsraj S, Chauhan K and Pathak H. Formulation of a novel nanoemulsion system for enhanced solubility of a sparingly water soluble antibiotic, clarithromycin.Journal of Nanoscience. 2014; 1-7.
17. Nicolaos G, Crauste-Manciet S, Farinotti R and Brossard D. Improvement of cefpodoxime proxetil oral absorption in rats by an oil-in-water submicron emulsion. International Journal of Pharmaceutics. 2003; 263(1–2): 165-171.
18. Eke OU, Oluchi IC, Chinedu UK and Umale AM. Formulation and evaluation of erythromycin stearate soy lecithin nanoemulsion. AASCIT Journal of Nanoscience. 2017; 3(5): 24-34.
19. Nirmala MJ, Allanki S, Mukherjee A and Chandrasekaran N. Azithromycin: Essential oil based nanoemulsion drug delivery system. Int J Pharm Pharm Sci. 2013; 5(4): 236-238.
20. Nicolaos G, Crauste-Manciet S, Farinotti R and Brossard D. Improvement of cefpodoxime proxetil oral absorption in rats by an oil-water submicron emulsion. Int J Pharm. 2003;263: 165–71.