Journal of Diseases
2017 Vol. 4, No. 1, pp. 14-20
ISSN(e): 2410-6550
ISSN(p): 2413-838X
DOI: 10.18488/journal.99.2017.41.14.20

NANO FORMULATIONS OF NATURAL COMPOUNDS FOR ENHANCED DELIVERY

Zahangir Alam *Executive, Research and Development, ORION Pharma Ltd., Dhaka, Bangladesh*

Article History
Received: 10 April 2017
Revised: 18 May 2017
Accepted: 14 June 2017
Published: 4 July 2017

Keywords
Nano emulsions
Natural compounds
Nano particles
Formulations.

ABSTRACT

Natural products were always the key elements in ancient history that are promising to treat various diseases including cancer and prevent any health disorders. They have seen a breakthrough since they were used in cancer chemotherapy and prevention with selective phytochemicals. Fruits and vegetables contain nutrient constituents that are bioactive in disease states. Extensive in vitro and in vivo research data is available to prove their efficacy. While few compounds have successfully transitioned to the clinical trials, few of them are still facing problems due to their poor bioavailability and lack of targeting. The lack of efficacy in human studies can be attributed to the complexity of the biological system and complexity of food. In recent years, identification of molecular targets made it necessary to develop efficient formulations for delivery. Nano formulations such emulsions, nanoparticles and nano vesicles are few of the advancements that showed promising faith in natural product chemotherapy. This paper reviews few of the techniques employed for natural compound delivery which can be applied to various compounds.

1. INTRODUCTION

The use of natural products has main advantage of disease prevention rather than cure. One of the main health conditions that require attention now-a-days is the cancer. Because of its variability, aggressiveness, metastasis and poor prognosis [1-7]. It is even very difficult to diagnose at early stage or predict its occurrence [8-10]. Several natural compounds are being used in treatment for cancer [11]. Research is showing evidence that phytochemicals have pharmacological effect in the human body by altering cell fate such as apoptosis, carcinogenesis, oxidative stress and aging [12, 13]. Phytochemicals can be given in diet due to their nontoxic advantages over other synthetic chemicals. However, achieving the desired genomic or cellular response depends upon the concentrations of compounds at site of action. If properly employed they can be used against carcinogenesis. While nature has huge sources of bioactive compounds, it is very critical to identify the desired ones out of them. Various approaches are needed to classify the natural compounds into categories and enhance their bioactivity. Semisynthetic derivatives were also used to enhance their in vivo activity in various diseases [14-17].

Any health disorder is result of deviation of regular cellular signaling pathways from normal. This can occur at genomic levels due to mutations. Hence it is important to identify the cellular targets in health disorders [18-21]. Especially in cancer, the mutations lead to aggressive form of disease that can result in altered disease prognosis,

difficulty in treatment and death of patient. Identifying the molecular targets is also useful to targeting the drugs by using various formulations. Cancer requires prolonged drug treatment to ensure the complete eradication of disease and prevention of recurrence [21-23]. Sustained release formulations that showed efficiency in other disorders can be employed in chemotherapy also [24, 25]. Especially nano formulations hold promise as they can penetrate the vascular endothelium and also tumor stroma [26]. As the natural products do not have tendency to accumulate in the body for long periods of time, it is necessary to use specific formulations in chemotherapy.

Nano-emulsions are effective due to their droplet size of 20–200 nm. Depending upon the solubility nature of natural compounds, we can employ either oil-in-water (O/W) or water-in-oil (W/O) nano-emulsions. Nano-emulsions can be formulated using high and low energy methods such as simple stirring and passing through homogenizer. Stable formulations can be formed using surfactants. Recent complex materials such as polymers and other inorganic materials are used to make polymeric nanospheres [27]. Similar to nanoemulsions, nano particles are also used. These are the particulate systems to improve pharmacokinetic and pharmacodynamics nature of compounds and protect them in vivo. They restrict the access of drug to unwanted site of action and ensures controlled release. Polymers can be used in nano particles to increase therapeutic effect with no or low toxicity [28].

1.1. Self-Emulsifying Nanoemulsions

Oil soluble vitamins including D and E are essential for the human body for nutritional and other health purposes [29-33]. Vitamin D is essential to maintain bone, teeth and cartilage development. According to preliminary in vitro and in vivo studies, it is also shown to prevent cancer, heart diseases and immune diseases [34, 35]. However, supplementation if these oil soluble vitamins through oral route is critical due to their poor aqueous solubility and low absorption [36, 37]. Studies are being conducted for effective delivery of these types of supplements in the form of self-emulsifying nano emulsions [38]. In a recent study, several factors such as oil phase composition, surfactant to oil ratio, surfactant type and mechanical conditions were tested to make most stable and easy to absorb nano emulsions [39]. According to this, oil phase and aqueous phase were prepared separately and titrated slowly to make emulsion. Oil phase consists of Vitamin E itself, medium chain triglycerides (MCTs) and non-ionic surfactants (Tweens) and aqueous phase consists of buffer solutions (0.8% citric acid, 0.08% sodium benzoate, in Water). When various Tweens surfactants (20, 40, 60, 80 and 85) were used at 10%, the smallest droplets (d < 200nm) with optimum polydispersity index were formed in the presence of Tween 80 [39]. This can be because of surfactant's molecular geometry, according to which Tween 80 has one unsaturated tail and Tween 20, 40, and 60 have saturated chains. At the same time, Tween 85 did not make spontaneous emulsion of smaller droplets irrespective of its three unsaturated tails [40, 41]. This explains the necessity of optimum surfactant geometry required that was achieved by Tween 80 itself. In this case, presence of MCTs and vitamin D at various concentrations had little or no effect on particle size formation. Dynamic light scattering and polydispersity index studies indicated that surfactant concentration of 10% is optimum for smaller droplet diameters as the oil to surfactant ratio is 1:1. As the process requires spontaneous emulsification, too low and too high concentrations of surfactants will result in liquid crystalline state or improper micro emulsion state with large droplets, respectively [42, 43]. Moreover, with these conditions, emulsification occurs at lower stirring speeds just to ensure even distribution of surfactant/oil phase into aqueous phase. In addition, these low-energy nanoemulsions can be stored at room temperature for more than 1 month if diluted with water or anionic surfactant solution which can reduce particle size growth and further variability in droplet size distribution [44, 45]. At higher temperatures, the turbidity will be increased due to progressive dehydration of polar head group of nonionic surfactant, Tween. This process is irreversible in this present formulation type.

In a similar self-emulsifying nanoemulsions preparation containing 10% Vitamin E with MCT as carrier oil, glycerol was used to further reduce the droplet size to 50nm [44, 45]. When the glycerol concentration was

increased from 10 to 50%, smaller droplets with less size distribution were formed. In addition, glycerol increases the system viscosity to aid the mass transport kinetics of surfactant and oil molecules at the boundary between the organic and aqueous phases [46]. In addition, glycerol at 50% increased optical clarity of the final nanoemulsion which can be important to acceptability to the patients. Glycerol mediated optical clarity is because of decreased droplet size and increased refractive index of the aqueous phase. Moreover, 80% Vitamin E and 20% MCT mixture is better option to use with glycerol in terms of clarity. Similar to the vitamin D nanoemulsions discussed above, glycerol (40%) containing vitamin E nanoemulsions can be stored better after diluting with aqueous buffer. If not diluted, glycerol is maintaining the stability of emulsion at 5-20°c in terms of lower droplet size variation and increase. At 37°c, the refractive index is dropping down to 0.06 indicating high droplet size and unstable formulation. This is because of decrease of phase inversion temperature of the nonionic (Tween) containing nanoemulsion.

1.2. Solid Lipid Nanoparticles of Vitamin A

Solid lipid nanoparticles (SLN) showed significant use in delivery of vitamin A. In one study, SLNs containing Vitamin A-retinol or its ester retinyl palmitate were tested comparing with nanoemulsions [47]. Additional studies were also conducted with SLNs of hydrogels and oil-in-water cream. SLNs were prepared by adding Vitamin A to glyceryl behenate and further dispersing it in surfactant solution. Passing the mixture through high pressure homogenizer will yield desired SLNs. In case of nanoemulsions, vitamin A was added into oil Miglyol 812 before adding to the surfactant solutions. In case of SLNs, the vitamin A is entrapped or immobilized in solid matrix while the nanoemulsions contain vitamin A in liquid oil phase. This makes significant difference in drug release kinetics following applying to the skin. In addition, hydrogels were prepared by adding the SLNs or nanoemulsion into a mixture of glycerol (85%), water and gelling agent under continuous stirring. In a similar way oil-in-water (o/w) cream was prepared. All the formulations were tested by applying on to the porcine skin due to their similarity with human skin in terms of thickness and few other characteristics [47, 48]. After 6 hours of application, SLNs were effective as they release vitamin A into upper stratum corneum significantly higher compared to the nanoemulsion formulation due to the difference in drug carrier system. SLNs continued to localize the drug in upper skin after 6 hours but not in dermis and subcutaneous tissue in proportional way. When observed the drug absorbing pattern for 24 hrs, the retinol concentration was increased in deeper layers with correlated decrease in upper layers in case of SLNs. This is because of formation of thick gel film on skim and further water evaporation which makes the retinol permeation into deeper layers. Similar to the SLN formulation, the hydrogel containing SLNs also showed high retinol deposit in the upper skin layer for the first 6 hrs. And after 24 hrs, the retinol concentration also increased in the deeper layers unlike the previous case because of hydrogel formulation [47].

1.3. Nano vesicles of Vitamin E

Natural compounds such as tocotrienols that belong to the vitamin E group of compounds showed potential anticancer activity against various types of cancer [49-51]. However, they have limitations to show effect in vivo due to their poor absorption and lack of targeting to the tumor [52, 53]. Several studies were conducted to increase their site targeting by design of vesicles, nanoemulsions and nanoparticles [54, 55].

Transferrin (Tf) containing vesicle formulations were used increase their targeting towards melanoma tumors and epidermoid carcinoma [56]. The vesicles contain Span 60, cholesterol, TPGS (Tocopherol derivative) and dioleolphosphatidylethanolamine (DOPE). The vesicles were tagged with Transferrin so that they can be travelled to the tumors after in vivo administration. After the final formulation, they were studies with transmission electron microscopy for uniformity and measured drug loading. As the tocopherol is lipid soluble, vesicle loading of the same can be increased by increasing bilayers in vesicles. Transferrin concentration on surface is around 25%. Size of the vesicles was found to be 341nm after transferrin tagging which makes them sufficient to extravasate to reach

tumors. When tested in vitro on cell lines, uptake of TRF (Tocotrienol rich fraction) was increased in targeted vesicles compared with the TRF solution [56]. In addition, Tf-vesicles will be taken up by the cells by endocytosis pathway, which enabled them to localize in the perinuclear region and concentrate TRF in nuclear and perinuclear regions. This phenomenon is not available in TRF solutions so that the TRF was distributed only in the cytosol. After ensuring the efficient cell uptake, therapeutic studies were conducted on A431, T98G and B16-F10 cells by treating them with transferrin labelled and unlabeled vesicles. Tf labeling enhanced therapeutic activity by many folds higher compared to unlabeled vesicle and TRF solution alone treatments. Even in vivo anticancer effect was observed in Tf targeting vesicles. Targeting suppressed tumor growth and long term survival in all the mice was observed. In 10-40% of the animal based upon the type of tumor, there was complete regression and disappearance of tumor which was confirmed even by bioluminescence imaging. TRF solution treated mice extended mice survival by 2-4 days, however, Tf targeting vesicle treatment increased mice survival by more than 20 days. No significant toxicity was observed in the treatment [56].

2. CONCLUSION

Natural compounds have various health benefits and they cannot be neglected to employ in health problems. The limitations such as poor solubility, oral absorption, and poor bioavailability should be overcome by nanotechnology. Various nano formulations are being used in research in recent years that can be used on natural compounds also. Drugs that are formulated in nano formulations hold the future of treatment.

Funding: This study received no specific financial support.
Competing Interests: The author declares that there are no conflicts of interests regarding the publication of this paper.

REFERENCES

[1] J. E. Moulder and S. Rockwell, "Tumor hypoxia: Its impact on cancer therapy," *Cancer and Metastasis Reviews*, vol. 5, pp. 313-341, 1987. *View at Google Scholar | View at Publisher*

[2] T. Ozben, "Oxidative stress and apoptosis: Impact on cancer therapy," *Journal of Pharmaceutical Sciences*, vol. 96, pp. 2181-2196, 2007. *View at Google Scholar | View at Publisher*

[3] S. B. Hosain, R. A. Hill, and Y.-Y. Liu, "The Role of Sphingolipids in Modulating Pluripotency of Stem Cells," in *Trends in Stem Cell Proliferation and Cancer Research*, ed: Springer, 2013, pp. 167-191.

[4] B. Stewart and C. P. Wild, World Cancer Report, 2014.

[5] M. Mignogna, S. Fedele, and L. L. Russo, "The world cancer report and the burden of oral cancer," *European Journal of Cancer Prevention*, vol. 13, pp. 139-142, 2004. *View at Google Scholar | View at Publisher*

[6] S. Ananthula, A. Sinha, M. El Gassim, S. Batth, G. D. Marshall Jr, L. H. Gardner, Y. Shimizu, and W. M. ElShamy, "Geminin overexpression-dependent recruitment and crosstalk with mesenchymal stem cells enhance aggressiveness in triple negative breast cancers," *Oncotarget*, vol. 7, p. 20869, 2016. *View at Google Scholar | View at Publisher*

[7] S. B. Hosain, S. K. Khiste, M. B. Uddin, V. Vorubindi, C. Ingram, S. Zhang, R. A. Hill, X. Gu, and Y.-Y. Liu, "Inhibition of glucosylceramide synthase eliminates the oncogenic function of p53 R273H mutant in the epithelial-mesenchymal transition and induced pluripotency of colon cancer cells," *Oncotarget*, vol. 7, pp. 60575-60592, 2016. *View at Google Scholar | View at Publisher*

[8] J. Russo and I. H. Russo, "Toward a physiological approach to breast cancer prevention," *Cancer Epidemiology and Prevention Biomarkers*, vol. 3, pp. 353-364, 1994. *View at Google Scholar*

[9] F. Shahidi, *Natural antioxidants: chemistry, health effects, and applications*: The American Oil Chemists Society, 1997.

[10] K. N. Bhinge, V. Gupta, S. B. Hosain, S. D. Satyanarayanajois, S. A. Meyer, B. Blaylock, Q.-J. Zhang, and Y.-Y. Liu, "The opposite effects of doxorubicin on bone marrow stem cells versus breast cancer stem cells depend on

glucosylceramide synthase," *The international journal of biochemistry & cell biology*, vol. 44, pp. 1770-1778, 2012. View at Google Scholar | View at Publisher

[11] S. Nobili, "Natural compounds for cancer treatment and prevention," *Pharmacological Research*, vol. 59, pp. 365-378, 2009. View at Google Scholar | View at Publisher

[12] F. Shahidi, "Natural antioxidants: Chemistry, health effects, and applications," *American Oil Chemists Society*, 1997.

[13] S. B. Hosain, S. Sultana, and A. Haque, "Studies on antibacterial, cytotoxic and antioxidant properties of the seeds and leaves of Ficus racemosa," *International Journal of Pharmaceutical Sciences and Research*, vol. 2, p. 1040, 2011. View at Google Scholar

[14] D. J. Newman, "Natural products and derivatives as leads to cell cycle pathway targets in cancer chemotherapy," *Current Cancer Drug Targets*, vol. 2, pp. 279-308, 2002. View at Google Scholar | View at Publisher

[15] S. Ananthula, *Mechanisms mediating tocotrienol derivative in vitro and in vivo anticancer effects and inhibition of compensatory responses to hypoxia in the highly malignant mouse+ SA mammary cancer cells*: University of Louisiana at Monroe, 2014.

[16] S. Fiorito, "Growth inhibitory activity for cancer cell lines of lapachol and its natural and semi-synthetic derivatives," *Bioorganic & Medicinal Chemistry Letters*, vol. 24, pp. 454-457, 2014. View at Google Scholar | View at Publisher

[17] M. S. Butler, "Natural products to drugs: Natural product-derived compounds in clinical trials," *Natural Product Reports*, vol. 25, pp. 475-516, 2008. View at Google Scholar | View at Publisher

[18] J. L. Bos, "Prevalence of ras gene mutations in human colorectal cancers," *Nature*, vol. 327, pp. 293-297, 1987. View at Google Scholar | View at Publisher

[19] F. Ichida, "Novel gene mutations in patients with left ventricular noncompaction or Barth syndrome," *Circulation*, vol. 103, pp. 1256-1263, 2001. View at Google Scholar | View at Publisher

[20] G. Hetet, "Association studies between haemochromatosis gene mutations and the risk of cardiovascular diseases," *European Journal of Clinical Investigation*, vol. 31, pp. 382-388, 2001. View at Google Scholar | View at Publisher

[21] S. B. Hosain and Y. Y. Liu, "Missense mutants of p53 tumor suppressor contributes to drug-resistance and epithelial-mesenchymal transition in colon cancer cells," ed: AACR, 2015.

[22] M. Michael and I. F. Tannock, "Measuring health-related quality of life in clinical trials that evaluate the role of chemotherapy in cancer treatment," *Canadian Medical Association Journal*, vol. 158, pp. 1727-1734, 1998. View at Google Scholar

[23] P. H. Sylvester, A. r. Malayan, P. Perttjtrlt'rtrto'Rasher, and V. Titvtrrt, "Statins as Anticancer Agents."

[24] D. R. Janagam, L. Wang, S. Ananthula, J. R. Johnson, and T. L. Lowe, "An accelerated release study to evaluate long-acting contraceptive levonorgestrel-containing in situ forming depot systems," *Pharmaceutics*, vol. 8, p. 28, 2016. View at Google Scholar | View at Publisher

[25] B. W. Barry, B. A. Mulley, and P. York, "Sustained-release formulations," ed: Google Patents, 1991.

[26] S. Hamdy, "Targeting dendritic cells with nano-particulate PLGA cancer vaccine formulations," *Advanced Drug Delivery Reviews*, vol. 63, pp. 943-955, 2011. View at Google Scholar | View at Publisher

[27] C. Solans, "Nano-emulsions," *Current Opinion in Colloid & Interface Science*, vol. 10, pp. 102-110, 2005. View at Google Scholar

[28] V. Mohanraj and Y. Chen, "Nanoparticles-a review," *Tropical Journal of Pharmaceutical Research*, vol. 5, pp. 561-573, 2006. View at Google Scholar

[29] M. F. Holick, "Vitamin D: Extraskeletal health," *Endocrinology and Metabolism Clinics of North America*, vol. 39, pp. 381-400, 2010. View at Google Scholar | View at Publisher

[30] H. Reichel, H. P. Koeffler, and A. W. Norman, "The role of the vitamin D endocrine system in health and disease," *New England Journal of Medicine*, vol. 320, pp. 980-991, 1989. View at Google Scholar

[31] R. Zhang and D. P. Naughton, "Vitamin D in health and disease: Current perspectives," *Nutrition Journal*, vol. 9, p. 65, 2010. View at Google Scholar | View at Publisher

[32] I. M. Lee, "Vitamin E in the primary prevention of cardiovascular disease and cancer: The women's health study: A randomized controlled," *Trial Jama*, vol. 294, pp. 56-65, 2005. *View at Google Scholar*

[33] S. Ananthula, "Bioavailability and Bioequivalence Issues Associated With Oral Anticancer Drugs and Effect on Drug Market," *Journal of Bioequivalence & Bioavailability*, vol. 6, 2014.

[34] R. Bouillon, "Vitamin D and cancer," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 102, pp. 156-162, 2006. *View at Google Scholar*

[35] T. J. Wang, "Vitamin D deficiency and risk of cardiovascular disease," *Circulation*, vol. 117, pp. 503-511, 2008. *View at Google Scholar*

[36] P. W. Sylvester, M. R. Akl, A. Malaviya, P. Parajuli, S. Ananthula, R. V. Tiwari, and N. M. Ayoub, "Potential role of tocotrienols in the treatment and prevention of breast cancer," *Biofactors*, vol. 40, pp. 49-58, 2014. *View at Google Scholar*

37] F. A. Behery, M. R. Akl, S. Ananthula, P. Parajuli, P. W. Sylvester, and K. A. El Sayed, "Optimization of tocotrienols as antiproliferative and antimigratory leads," *European journal of medicinal chemistry*, vol. 59, pp. 329-341, 2013. *View at Google Scholar | View at Publisher*

[38] F. Donsì, "Design of nanoemulsion-based delivery systems of natural antimicrobials: Effect of the emulsifier," *Journal of Biotechnology*, vol. 159, pp. 342-350, 2012. *View at Google Scholar | View at Publisher*

[39] M. Guttoff, A. H. Saberi, and D. J. McClements, "Formation of vitamin D nanoemulsion-based delivery systems by spontaneous emulsification: Factors affecting particle size and stability," *Food Chemistry*, vol. 171, pp. 117-122, 2015. *View at Google Scholar | View at Publisher*

[40] D. K. Chou, "Effects of Tween 20® and Tween 80® on the stability of albutropin during agitation," *Journal of Pharmaceutical Sciences*, vol. 94, pp. 1368-1381, 2005. *View at Google Scholar | View at Publisher*

[41] B. A. Kerwin, "Polysorbates 20 and 80 used in the formulation of protein biotherapeutics: Structure and degradation pathways," *Journal of Pharmaceutical Sciences*, vol. 97, pp. 2924-2935, 2008. *View at Google Scholar | View at Publisher*

[42] A. Forgiarini, "Formation of nano-emulsions by low-energy emulsification methods at constant temperature," *Langmuir*, vol. 17, pp. 2076-2083, 2001. *View at Google Scholar | View at Publisher*

[43] C. Solans and I. Solé, "Nano-emulsions: Formation by low-energy methods," *Current Opinion in Colloid & Interface Science*, vol. 17, pp. 246-254, 2012. *View at Google Scholar | View at Publisher*

[44] A. H. Saberi, Y. Fang, and D. J. McClements, "Fabrication of vitamin E-enriched nanoemulsions: Factors affecting particle size using spontaneous emulsification," *Journal of Colloid and Interface Science*, vol. 391, pp. 95-102, 2013. *View at Google Scholar | View at Publisher*

[45] A. H. Saberi, Y. Fang, and D. J. McClements, "Effect of glycerol on formation, stability, and properties of vitamin-E enriched nanoemulsions produced using spontaneous emulsification," *Journal of Colloid and Interface Science*, vol. 411, pp. 105-113, 2013. *View at Google Scholar | View at Publisher*

[46] S. Magdassi and S. G. Frank, "Formation of oil-in-glycerol/water emulsions," *Journal of Dispersion Science Andtechnology*, vol. 7, pp. 599-612, 1986. *View at Google Scholar | View at Publisher*

[47] V. Jenning, "Vitamin A loaded solid lipid nanoparticles for topical use: Occlusive properties and drug targeting to the upper skin," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 49, pp. 211-218, 2000. *View at Google Scholar | View at Publisher*

[48] E. G. De Jalón, "Topical application of acyclovir-loaded microparticles: Quantification of the drug in porcine skin layers," *Journal of Controlled Release*, vol. 75, pp. 191-197, 2001. *View at Google Scholar | View at Publisher*

[49] K. Kline, "Vitamin E and cancer," *Vitamins & Hormones*, vol. 76, pp. 435-461, 2007. *View at Google Scholar*

[50] S. Ananthula, P. Parajuli, F. A. Behery, A. Y. Alayoubi, S. Nazzal, K. El Sayed, and P. W. Sylvester, "-Tocotrienol Oxazine Derivative Antagonizes Mammary Tumor Cell Compensatory Response to CoCl2-Induced Hypoxia," *BioMed research international*, vol. 2014, pp. 1-13, 2014. *View at Google Scholar | View at Publisher*

[51] S. Ananthula, P. Parajuli, F. A. Behery, A. Y. Alayoubi, K. A. El Sayed, S. Nazzal, and P. W. Sylvester, "Oxazine derivatives of γ-and δ-tocotrienol display enhanced anticancer activity in vivo," *Anticancer research*, vol. 34, pp. 2715-2726, 2014. *View at Google Scholar*

[52] S. Yap, K. Yuen, and J. Wong, "Pharmacokinetics and bioavailability of α-, γ-and δ-tocotrienols under different food status," *Journal of Pharmacy and Pharmacology*, vol. 53, pp. 67-71, 2001. *View at Google Scholar | View at Publisher*

[53] J.-Y. Fu, H.-L. Che, D. M.-Y. Tan, and K.-T. Teng, "Bioavailability of tocotrienols: evidence in human studies," *Nutrition & metabolism*, vol. 11, p. 5, 2014. *View at Google Scholar | View at Publisher*

[54] B. S. Abuasal, "Enhancement of intestinal permeability utilizing solid lipid nanoparticles increases γ-tocotrienol oral bioavailability," *Lipids*, vol. 47, pp. 461-469, 2012. *View at Google Scholar | View at Publisher*

[55] P. P. Constantinides, A. Tustian, and D. R. Kessler, "Tocol emulsions for drug solubilization and parenteral delivery," *Advanced Drug Delivery Reviews*, vol. 56, pp. 1243-1255, 2004. *View at Google Scholar | View at Publisher*

[56] J. Y. Fu, "Novel tocotrienol-entrapping vesicles can eradicate solid tumors after intravenous administration," *Journal of Controlled Release*, vol. 154, pp. 20-26, 2011. *View at Google Scholar | View at Publisher*