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Synthesis of Dutasteride Loaded Nanoemulsion

Chemistry

KEYWORDS : Dutasteride, nanoemulsion, in vivo, oleic acid, eucalyptus oil, ethanol, tween80, and double distilled water.

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ABSTRACT

The effectiveness of a drug changes with size as well as molecular confirmation. The physical properties of the oil phase and the nature of the surfactant layer were found to have a considerable impact on nanoemulsion formation and stabilization. The optimization of surfactant architecture, and differential viscosity, has led to the formation of remarkably small nanoemulsions. In this work, we study emulsions consisting of water, in oil (eucalyptus oil and oleic acid in 1:1 ratio forms the oil component) and a mixture of surfactants (tween80 and ethanol). It is done by the formulation of placebo nanoemulsion. The placebo which is clear and thermodynamically stable is used for drug loading. Analysis is done by TEM.

INTRODUCTION

Nanoemulsions (NE) have received a growing attention as colloidal drug carriers for pharmaceutical applications. Typically, NE consists of oil, surfactant, co surfactant and aqueous phase, which are transparent, thermodynamically stable with a droplet diameter usually within the range of 10–100 nm and does not have the tendency to coalesce [1,2]. **Dutasteride Fig (1)**, reduces the risk of incident prostate cancer, approved for the treatment of benign prostatic hyperplasia (BPH); colloquially and Male pattern baldness (MBP). Signs of allergic reactions are difficulty breathing; swelling of your face, lips, tongue, or throat.Thus, alternative routes of administration for these drugs are being currently investigated. Recently, more attention has focused on nanoemulsions for transdermal delivery of drugs [3, 4, 5, 6]

Emulsions with sizes between those of conventional emulsions and microemulsions, i.e. with a typical size range of 20–500 nm are termed mini-emulsions [7], ultrafine emulsions [8], submicron emulsions [9], translucent emulsions and nano-emulsions [10]. Due to their small size, nano-emulsions may appear transparent, and Brownian motion prevents sedimentation or creaming, hence offering increased stability. In contrast to microemulsions, nanoemulsions are metastable and can be diluted with water without changing the droplet size distribution [11]. Emulsion stability refers to the ability of an emulsion to resist change in its properties over time [12]. These emulsions may be called creams, ointments, liniments (balms), pastes, films, or liquids, depending mostly on their oil-to-water ratios, other additives, and their intended route of administration[13,14]. Microemulsions are used to deliver vaccines and kill microbes.

A nanoemulsion is a mixture of two or more liquids that are normally immiscible (nonmixable or unblendable). Two liquids can form different types of emulsions. As an example, oil and water can form, firstly, an oil-in-water emulsion, where the oil is the dispersed phase, and water is the dispersion medium. Secondly, they can form a water-in-oil emulsion, where water is the dispersed phase and oil is the external phase. Multiple emulsions are also possible, including a "water-in-oil-in-water" emulsion and an "oil-in-water-in-oil" emulsion.

Emulsifiers are surfactants play a major role in the formation of stable nanoemulsions in aqueous solutions. The interfacial tension between the oil and water phases was reduced. Low amount of surfactant required to form nanoemulsion. Essential oils has a rich source of bioactive compounds and have been shown to possess antibacterial, antifungal, antiviral, insecticidal and antioxidant properties [15,16,17]. Tween80 is a non-ionic surfactant that readily miscible at the oil-water interface, and moreover less sensitive to pH and ionic strength, it is used for various applications [18] including nanoemulsions [19,20].

2. MATERIALS AND METHOD

2.1. Materials

In the present study, eucalyptus oil and oleic acid in 1:1 ratio forms the oil component of placebo, Tween80, as the surfactant, ethanol as the co-surfactant and water as the aqueous phase were used.

2.2. Method

Steps in the formation of nanoemulsion of dutasteride are:

- Thermodynamic stability of placebo and drug loaded formulation.
- Formation of dutasteride loaded nanoemulsions.
- Evaluation of nanoemulsion of dutasteride.
- Particle size analysis by TEM (transmission electron microscopy).

It is done by the formulation of placebo nanoemulsion. Placebo is formed by mixing the oil and Smix in various ratios 1:1, 1:2, 2:1, 1:3 eucalyptus oil and oleic acid in 1:1 ratio forms the oil component of placebo, surfactant (Smix) –tween80 and ethanol both are used as surfactant and water is added to the point that the solution remains clear sometimes further addition of slight amount of water will make the solution turbid, hence discarded. The placebo which is clear and thermodynamically stable is used for drug loading. Analysis is done by TEM.

3. COMPONENTS OF DUTASTERIDE NANOEMULSION

The components of nanoemulsion formation are, oils (eucalyptus oil and oleic acid), surfactants (tween80 and ethanol) and water used as a solvent (double distilled water).

3.1 Oil phase

The selection of oil is based on the nature of the drug as well as the route of administration. The screened oil should have solubilization potential for the drug. The oil influences the curvature and has the capability to swell the tail group of surfactant. Saturated and unsaturated fatty acids have penetration enhancing activity of their own. The fatty acids increase the permeability of by disrupting densely packed lipids and filled up in extracellular spaces of stratum corneum. Amongst unsaturated fatty acids, oleic acid is an effective skin penetration enhancer. Also penetrating effect of fatty acids is selective of individual drug.

3.2 Surfactant

The actual purpose of surfactant is to lower the interfacial tension to negligible value facilitating the process of dispersion during preparation of nanoemulsion. Tween80 have been investigated for their minimal toxicity.

3.3 Co-surfactant

In most of the cases, single chain surfactants alone are incapable to reduce o/w interfacial tension sufficiently to form nanoemulsion, a co-surfactant accumulates substantially at interface layer, increasing the fluidity of interfacial film by penetrating into surfactant layer. Short to medium chain length alcohols are generally added as co-surfactants helping in to increase the fluidity of interface [21]. Amongst short chain alkanols, ethanol is used as permeation enhancer.

3.4 Aqueous phase

Most commonly, water is used as aqueous phase. The pH of aqueous phase always needs to be adjusted due to its considerable impact on phase behavior of nanoemulsions

4. ADVANTAGES OF DUTASTERIDE NANOEMULSION

Nanoemulsions offer several advantages over the conventional topical drug delivery sources

- Thermodynamically stable hence leading to longer shelf life.
- Act as solvents, improving the solubility and thermodynamic activity of the drug.
- Enhances the percutaneous uptake of drug.
- Small particle size so large interfacial area hence quickly released.
- Hydrophobic and lipophilic domains.

5. RESULT AND DISCUSSION

The formulation of nanoemulsions usually involves: the formulation composition should be simple, safe and compatible; it should possess good solubility; a large efficient region which should be found in the pseudo ternary phase diagram, and have efficient droplet size after forming nanoemulsion [22]. In order to screen appropriate solvents for the preparation of nanoemulsions, the solubility of dutasteride in various oil and surfactants were measured and the results were shown in figures. **Table 5** is the list of selected ratios of placebo for drug loading. The results demonstrated that in **Fig.2** (212.95-180.12) nm size drug were obtained where the ratio of oil and Smix was 1:1. In 1:2 ratios maximam size reduction takes place. **Fig.3** shows the best result in this fig1 drug size ranges from (17.83-42.13) nm in which we achieve the best result i.e smallest particles in 1:2 ratio, where the concentration of Smix was higher than that of oil content. Gelling occurs in 2:1 ratio in which oil content is more than that of Smix and at this ratio particle size is 570.53 nm (**Fig.6**). The right blend of low and high hydrophilic lipophilic balance (HLB) surfactants leads to the formation of stable nanoemulsion formulations [23].

6. IN VIVO STUDY

All animal procedures were conducted in accordance with approved institutional protocols. The rat model was adopted to monitor the skin delivery of a variety of drugs including lipophilic ones similar to our drug [24]. The extent and rate of skin permeation of dutasteride from nanoemulsions of various compositions were determined, as expected; the drug penetration rate through rat skin was faster in 1:2 ratio where the concentration of Smix was higher than that of oil content in comparison to the 2:1 ratio in which oil content is more than that of Smix.

7. CONCLUSION

Dutasteride-Nanoemulsions prepared by this method, it appears that the higher the surfactant concentration, smaller size drug can be obtained. We demonstrate that a surfactant concentration is necessary for emulsification and size reduction. Size distribution mainly depends on the surfactant-to-oil ratio.

Table 1 - 1:1 Ratio

Oil (oleic acid:Eucalptus oil) (1:1) (µl)	S_{mix} (Tween80+Ethanol) (µl)	Water (DDW) (µl)
200	600	600
200	800	650
300	700	800
300	800	800
400	800	600

Table 2 - 1:2 Ratio

Oil (oleic acid:Eucalptus oil) (1:1) (µl)	S_{mix} (Tween80+Ethanol) (µl)	Water (DDW) (µl)
200	600	600
200	800	650
300	700	800
300	800	600
400	800	600

Table 3 - 2:1 Ratio

Oil (oleic acid:Eucalptus oil) (1:1) (µl)	S_{mix} (Tween80+Ethanol) (µl)	Water (DDW) (µl)
200	800	600
300	900	600

Table 4 - 1:3 Ratio

Oil (oleic acid:Eucalptus oil) (1:1) (µl)	S_{mix} (Tween80+Ethanol) (µl)	Water (DDW) (µl)
200	700	800
200	800	1000
300	900	800
300	1000	1000
400	900	800

Table 5 – list of selected ratios of placebo for drug loading

Ratio of oil and S_{mix}	Oil (oleicacid: Eucalptus oil) (1:1) (µl)	S_{mix} (Tween80+ Ethanol) (µl)	Water (DDW) (µl)
1:1	400	800	600
1:2	200	700	1000
1:2	300	800	1200
1:2	300	900	1400
2:1	300	900	600

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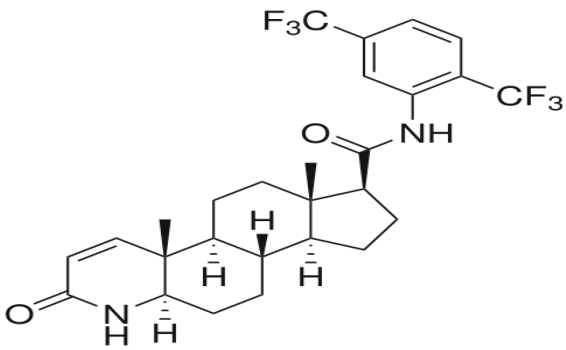
Fig – 1 - Structure of dutasteride



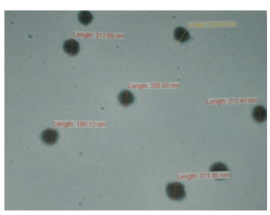


Fig.2 - 1:1 Ratio

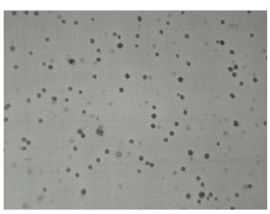


Fig. 4 - 1:2 Ratio

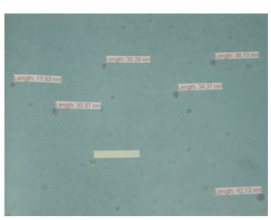


Fig. 3 - 1:2 Ratio

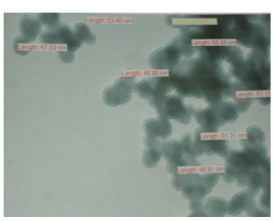


Fig .5 - 1:2 Ratio

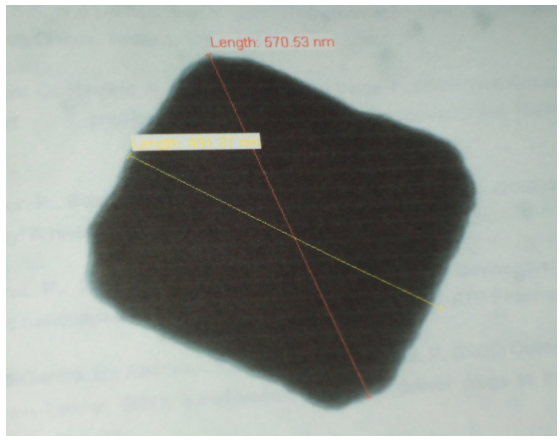


Fig .6 - 2:1Ratio

Fig. Shows different size of drug at different ratio of oil and surfactant

REFERENCE

[1] Kreilgaard M (2002) Influence of microemulsions on cutaneous drug delivery. Adv Drug Deliv Rev 54, 77–98. | [2] Tenjarla S (1999) Microemulsions: an overview and pharmaceutical applications. Crit Rev Ther Drug Carrier Syst 16: 461–521. | [3] Cevc G, Vierl U (2010) Nanotechnology and the transdermal route: A state of the art review and critical appraisal. J Control Release 141: 277-299. | [4] Djordjevic L, Primorac M, Stupar M, Krajisnik D (2004) Characterization of caprylocaproyl macrogolglycerides based microemulsion drug delivery vehicles for an amphiphilic drug. Int J Pharm 271, 11–19. | [5] Lee J, Lee Y, Kim J, Yoon M, Choi YW (2005) Formulation of microemulsion systems for transdermal delivery of aceclofenac. Arch Pharm Res 28: 1097–1102. | [6] Madhusudhan B, Rambhau, D, Apte S S, Gopinath D (2007) 1-O-alkylglycerol stabilized carbamazepine intravenous o/w nanoemulsions for drug targeting in mice. J Drug Target 15: 154–161. | [7] M. El-Aasser, C. Lack, J. Vanderhoff, F. Fowkes,(1988) nano-emulsions: formation, propertises and applications 29, 103-118 | [8] C. Solans, Hironobu Kunieda, (1997) Industrial Applications of Microemulsions. Food Science and Technology 66. | [9] S. Benita, M.Y. Levy, (1993) Submicron emulsions as colloidal drug carriers for intravenous administration: comprehensive physicochemical characterization. J. Pharm. Sci. 82, 69-79. | [10]C. Solans, J. Esquena, A.M. Forgiarini, N. Ulson, D. Morales, P. Izquierdo, N. Azemar, M.J. Garcia-Celma, (2003) Absorption and Aggregation of Surfactants in Solution, 109, 525-554. | [11]D. Morales, J.M. Guti´errez, M.J. Garc´ıa-Celma, C. Solans, (2003) Oil/water droplet formation by temperature change in the water/c(16)e(6)/mineral oil system, Langmuir: the ACS J. surfaces colloids, 22, 14-20. | [12] Satoshi Ogawa , Eric A. Decker , and D. Julian McClements (2003) Influence of Environmental Conditions on the Stability of Oil in Water Emulsions Containing Droplets Stabilized by Lecithin–Chitosan Membranes J. Agric. Food Chem., 51 (18), 5522–5527. | [13] Aulton, Michael E., ed. (2007). Aulton's Pharmaceutics: The Design and Manufacture of Medicines (3rd ed.). Churchill Livingstone. 92–97. | [14] Troy, David A.; Remington, Joseph P.; Beringer, Paul (2006). Remington: The Science and Practice of Pharmacy (21st ed.). Philadelphia: Lippincott Williams & Wilkins 325–336. | [15] Burt SA, (2004) Essential oils: their antibacterial properties and potential applications in foods: a review. Inter J Food Microbiol. 94, 223–253. | [16] Kordali S, Kotan R, Mavi A, Cakir A, Ala A, Yildirim A, (2005) Determination of the chemical composition and antioxidant activity of the essential oil of Artemisia dracunculus and of the antifungal and antibacterial activities of Turkish Artemisia absinthium, A.dracunculus, Artemisia santonicum, and Artemisia spiciger a essential oils. J Agric Food Chem 53, 9452–9458. | [17] Milhau G, Valentin A, Benoit F, Mallie M, Bastide J, Pelissier Y, Bessiere J, (1997) In vitro antimicrobial activity of eight essential oils.J Essent Oil Res. 9, 329–333. | [18] Cheong JN, Tan CP, Man YBC,Misran, (2008) M.α-Tocopherol nanodispersions: Preparation, characterization and stability evaluation. J Food Eng. 89, 204–209. | [19]Yuan Y, Gao Y, Mao L, ZhaoJ, (2008) Optimization of conditions for the preparation of β-carotene nanoemulsions using response surface methodology. Food Chem. 107,1300–1306. | [20]YuanY, Gao Y, Zhao J, MaoL, (2008) Characterization and stability evaluation of β-carotene nanoemulsions prepared by high pressure homogenization under various emulsifying conditions. Food Res Int. 41, 6–68 | [21]Graf A, Ablinger E, Peters S, Zimmerb A, Hooka S, Rades T, (2008) Microemulsion containing lecithin and sugar based surfactants: Nanoparticles templates for delivery of protein and peptides, International Journal of Pharmaceutics, 350, 351-360. | [22]Subramanian N, Ray S, Ghosal SK, Bhadra R, Moulik SP. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur J Pharm Biopharm 66, 227-243. | [23]Craig DQM, Barker SA, Banning D, Booth SW (1995) An investigation into the mechanism of self-emulsification using particle size analysis and low frequency dielectric spectroscopy. Int J Pharm 114, 103-110. | [24] Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M (2000) Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release 65, 403–418.