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Enhancing the Solubility of Telmisartan by the Employment of Egg Yolk

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ABSTRACT

Telmisartan is Angiotensin II Receptor blocker, which is used in the treatment of hypertension. The main issue with Telmisartan is its solubility in aqueous medium which is very low resulting in poor bioavailability after oral administration, hence; it is important to improve its dissolution and solubility. The egg yolk (EY) is one of the common surfactants which can be formulated with Telmisartan to improve its water solubility. Access quantity of the drug added to EY and Telmisartan amount in the prepared formulations of increasing quantity of the EY measured using UV-spectrophotometer. The results showed that the solubility of Telmisartan was improved by the employment of EY. The solubility of the drug directly related to the amount of EY since it acted as surfactant that form strong layer around the hydrophobic drug drops.

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1. INTRODUCTION

Telmisartan is Angiotensin II Receptor blocker, which is utilised in the prevention and treatment of hypertension. The solubility of Telmisartan in aqueous medium was very low i.e. Water Solubility Estimate from Log Kow: Water Solubility at 25ºC: 2.8 µg/mL in water (1). The drug belongs to class II drug in biopharmaceutical classification system (BCS) that has low solubility and high permeability. Low solubility in biological fluids is one of the major problems with this drug, which results into poor bioavailability after administration orally. The biological half-life of the drug is only 24 hours and absolute bioavailability is 42-58% that results into poor bioavailability after oral administration. Poor solubility of the drug leads to poor dissolution and therefore variation in bioavailability. Thus, increasing aqueous solubility and dissolution of the drug is of therapeutic importance (2-8). Telmisartan is 2-(4-{[4-methyl-6-(1-methyl-1H-1, 3-benzodiazol-2-yl)-2-propyl-1H-1, 3-benzodiazol-1-yl]methyl} phenyl) benzoic acid, as explained in Figure 1 (9). Telmisartan solubility in aqueous solutions is pH-dependent, with maximum solubility observed at low and high pH. Within the pH range of 3–9, it is only poorly soluble. The Telmisartan molecule is unusually stable. It is active as such it is not a prodrug (10).

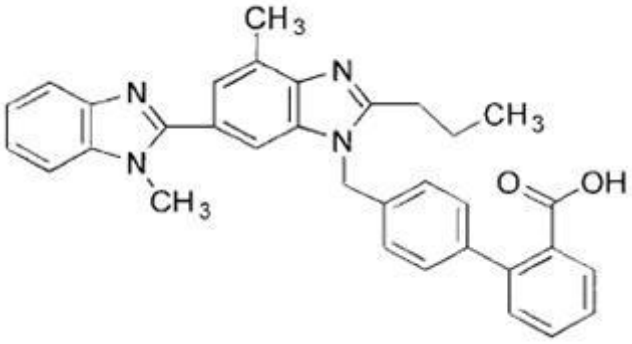

Figure 1. Chemical Structure of Telmisartan.

The pharmacodynamic and pharmacokinetic parameters are strong predictors of the drug therapeutic response. Pharmacodynamics is a link of relation between drug dosage forms and its pharmacological effects, especially how solid dosage forms are absorbed *in vivo*. In this process, many complicated factors are included such as disintegration and dissolution of the drug are very important ones (11). Accordingly, Telmisartan oral bioavailability depends on its solubility and dissolution rate. The dissolution is the rate determining step for appearance of the drug medicinal

effect, hence; increasing the drug dissolution, which has limited water solubility, is often needed. Many strategies to improve these characteristics are available, including micronization, addition of surface active agents or solvent and salt formation (12).

The egg yolk (EY) is the most commonly used surface active agent in the Food Industry due to its characteristics and sensorial properties. The phospholipids (lecithin) and lipoproteins combination of EY provide suitable mixture to produce excellent emulsifying properties. The EY produces a cohesive and strong film around the oil drops in the oil/water interface which avoids the coalescence (13). EY contains total dry matter of about 48-50%, in which 20% is present in the form of insoluble granules and 80% is the water-soluble plasma fraction. Plasma contains mainly globular glycoproteins and low-density lipoproteins (LDLs). Granules contain 70% high-density lipoprotein (HDL) and 16% phosvitin, a phosphoprotein. LDL is apoproteins called lipovitellins, which is the main constituent of EY. In addition, 12% of LDL can be found in insoluble granule aggregates. The emulsifying properties of the two main egg yolk fractions, egg yolk LDL micelles and granules, are highly dependent on environmental conditions. Changes in salt concentration or pH influence the structural and chemical characteristics for each fraction in a different way (14, 15).

Lecithin of EY is a mixture of zwitterionic phospholipids which contain two fatty acid chains, as illustrated in Figure 2. It is described as a natural multi-functional surfactant. Lecithin as a typical surface active agent greatly speeds up dispersion of aqueous and fatty components in many emulsion types. In addition, it accelerates moisture distribution, makes mixing easier and improves texture (16). Positional distribution of unsaturated and saturated fatty acids on EY lecithin is known and the nature of these fatty acids varies with diet composition of chicken (17). The number of carbons of the fatty acid chains range from 14 to 22 and 0 to 6 double bonds can be present in each fatty acid (18, 19, 20). The aim of this research is to enhance the solubility profile of Telmisartan using EY as potential surfactant to improve overall bioavailability of the drug.

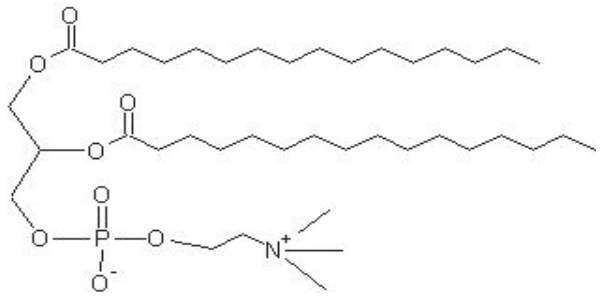

Figure 2. Molecular structure of 1,2-dipalmitoyl-sn-glycero-3-phsphatidylcholine.

2. MATERIALS AND METHODS

2. 1. Materials

Telmisartan was purchased from Hetero drugs limited, India. Chickens eggs were purchased from local store of Alkafeel (http://www.alkafeel.com/), Kerbala, Iraq). NYLON Syringe Filters Polypropylene housing diameter: 25 mm pore size: 0.22um non-sterilized purchased from Giorgio11185's store Jiangsu, Mainland, China. HPLC-grade Methanol was purchased from, Himedia Laboratories Pvt. Ltd, Mumbai, India.

2. 2. Methods

2. 2. 1. Calibration curve preparation:

A stock solution of Telmisartan was prepared by dissolving 10 mg in 10 ml of methanol then 1 ml of this stock was diluted up to 10 ml to get 100µg/ml solution. The resultant solution was utilized to prepare different concentrations of Telmisartan ((4, 8, 12, 16, and 20) µg/ml). The maximum absorption was scanned in the UV- Instrument, SPUV-26 UV-Spectrophotometer from Sco Tech (Germany) and the lambda max was recorded. The UV-absorptions of the prepared concentrations were observed and the calibration curve was plotted.

2. 2. 2. Samples preparations:

Three egg yolks were elicited from chickens' eggs and carefully isolated from egg whites. These egg yolks were homogenized and immediately utilized in preparing egg yolk solutions. One hindered ml of freshly prepared 1% (v/v) egg yolk solution was used to prepare triplicates of 10-ml of each of the six following concentrations (0.0, 0.1, 0.2, 0.3, 0.4, and 0.5) % v/v. Then

excess of Telmisartan powder was inserted in each of the eighteen test tubes. The tubes were sonicated for 10 minutes using SRI sonicator from Scientific Labo (Italy) and submitted to agitation for 1 hour utilizing SV 1422 agitator from Memmert (Germany). Afterward, these eighteen tubes were centrifuged at 1000 rpm for 10 minutes using Hettich zentrifugen D-78532 from Tuttlingen (Germany). The resultant samples (i.e. (0.0, 0.1, 0.2, 0.3, 0.4, and 0.5) % v/v) were filtered. Then the diluted samples were assayed utilizing UV instrument.

3. RESULTS AND DISCUSSION

3. 1. Telmisartan calibration curve:

The Telmisartan solution in methanol was scanned to obtain the maximum absorbance wavelength (lambda max). The lambda max was found to be 296nm, as shown in Figure 3. The observed lambda max for Telmisartan depends on the cutoff values of the solvent system. UV-cutoff for methanol was 205nm and the preferred value to be chosen was as far as possible from that for methanol due to solvent effect. The assay demonstrated a linear relationship between the absorbance of the UV radiation and concentration of Telmisartan (4, 8, 12, 16, and 20) µg/ml in methanol solutions with coefficient of determination (R^2) equals to 0.999 as shown in Figure 4 according to the Beer-Lambert Law. The calibration curve was plotted as explained in Figure 4.

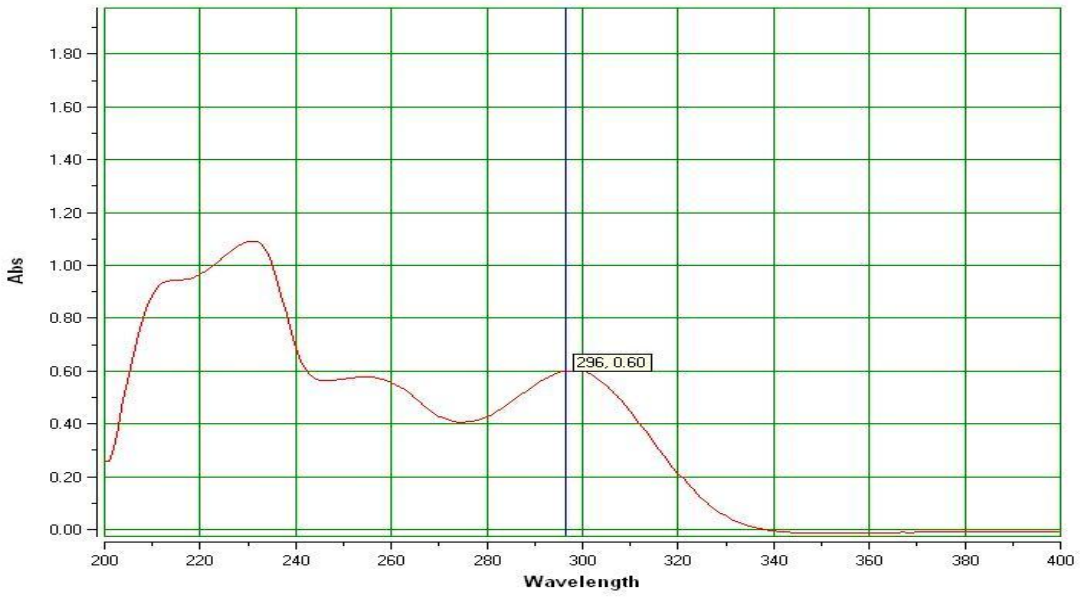

Figure 3. Reveals the observed lambda max for Telmisartan that was dissolved in HPLC grade methanol employing UV-instrument. The wavelength of 296nm was accredited.

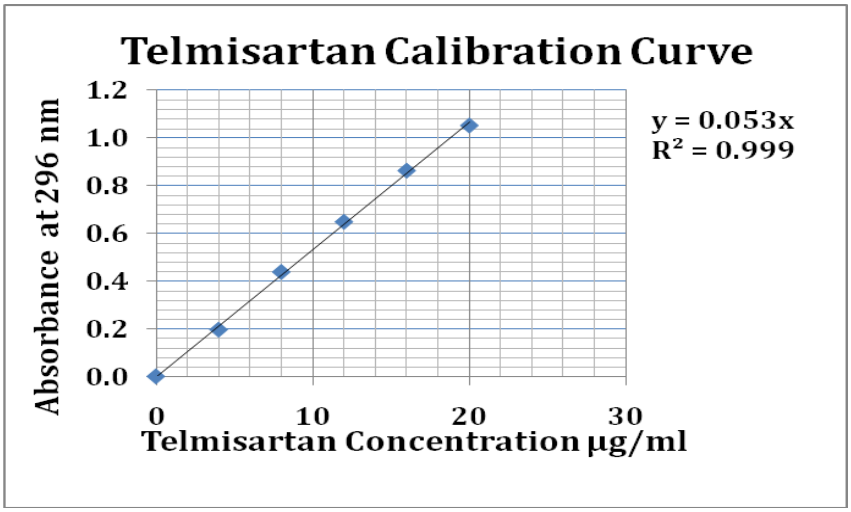

Figure 4. The calibration curve of Telmisartan (4, 8, 12, 16, and 20) µg/ml dissolved in HPLC grade methanol using UV-Spectrophotometer. The Coefficient of determination (R^2) equals to 0.999 while the slope equals to 0.0534.

B. The observed saturated solubility of Telmisartan:

The concentration of Telmisartan in each formula was carefully calculated as revealed in Table 1. The solubility of Telmisartan was significantly (p= 0.00072) increased with increase the concentration of egg yolk since EY as a strong surfactant over the hydrophobic phase of the medication enhancing its dissolution and solubility and that can potentially improve the bioavailability of the drug (21, 22, 23).

Table 1. The saturated solubility of Telmisartan in different percentages of EY.

EY % v/v	Dilution factor	Observed absorption*	(Telmisartan conc. µg/ml) y = 0.0534x	(Telmisartan conc. µg/ml) × (Dilution factor)
0.0	0	0.246 ± 0.0015	4.607	4.607
0.1	10	0.071 ± 0.0015	1.324	13.240
0.2	20	0.071 ± 0.0031	1.335	26.704
0.3	30	0.071 ± 0.0031	1.324	39.719
0.4	40	0.071 ± 0.0059	1.324	52.959
0.5	50	0.069 ± 0.0010	1.292	64.607

***Mean ± SD, n=3, p= 0.00072**

Consequently, by the utilization of the data in Table 1, the observed saturated solubility of Telmisartan was plotted against the EY%, as shown in Figure 3.3. All plots showed linear relationships with R^2 of 0.99 that demonstrated linear relationship and significant (p= 0.00072) enhancing in the drug solubility.

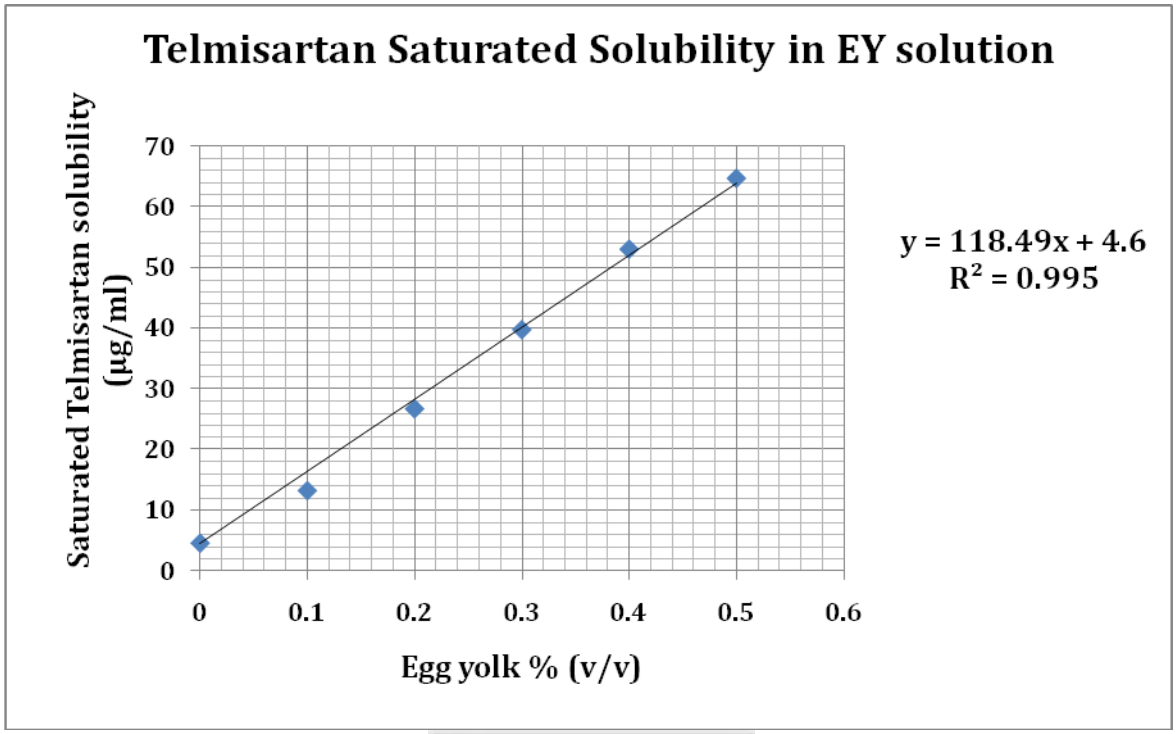

Figure 5. Shows a linear relationship of the saturated solubility of Telmisartan with different concentrations of EY. The slope was 118.49, the intercept 4.6, The Coefficient of determination (R^2) equals to 0.99.

5. CONCLUSION

Telmisartan has poor water solubility; therefore, enhancing the solubility is required. Many drug formulation strategies can be used to overcome this difficulty including the utilization of surfactant. EY is one of the most commonly used emulsifiers in food industry which added to the antihypertensive agent. The results demonstrated a significant enhancement in Telmisartan solubility. Hence, for future work, a drug formulation (e.g. tablet) would be highly demanded to analyze the effect of EY on drug dissolution.

6. REFERENCES

1. National Center for Biotechnology Information. PubChem Compound Database; CID=65999, https://pubchem.ncbi.nlm.nih.gov/compound/65999 (accessed Sept. 25, 2015)
2. Brahmankar .D.M., Sunil Jaiswal.B.,- Biopharmaceutics and Pharmakokinetics A Treatise. 1st edition:2005: 27-30,5-6.
3. Christian Leuner., Jennifer Dressmann., Improving drug solubility for oral delivery using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics. 2000; 50: 47-48.
4. Gare Kani. H.A., Sadeghi. F., Badiee. A., Mostafa S.A., Rajabisiahboomi. A.R., Crystal habit modifications of Ibuprofen and their Physicochemical Characteristics. Drug Development and Industrial Pharmacy. 2001; 27 (8): 803-809.
5. Nandita Das G.and Sudip Das.K., Formulation of Poorly Soluble Drugs. Drug Delivery Report Spring/Summer. 2006; 52-55.
6. James Swarbrick., James C. Boylan., Encyclopedia of Pharmaceutical Technology, 2nd ed, Vol: 1:641-647.
7. Christian Leuner., Jennifer Dressman., Improving Drug solubility for oral delivery using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics. 2000; 50:48-51
8. Modi A., Tayade P., Enhancement of dissolution profile of solid dispersion (Kneading) technique. AAPS Pharm Sci Tech. 2006;7 (3):1-13.
9. British Pharmacopoeia .The Department of Health, The stationary office on behalf of the Medicines and Healthcare Products Regulatory Agency (MHRA), London, Vol I, 2009, electronic edition
10. W. Wienen, M. Entzeroth, A. Jacobus, J. Stangier, U. Busch, T. Ebner, J. Schmid, H. Lehmann, K. Matzek, J. Kempthorne-Rawson, V Gladigau, and N. Hauel ; A Review on Telmisartan : A Novel, Long-Acting Angiotensin II-Receptor Antagonist ; Cardiovascular Drug Reviews, 2000, 18(2): 127–154
11. M. Lee, C. Huang, S. Huang, Y. Chen, C. Chen and K. Wen, A Comparative Study on the Dissolution Profiles of Commercial Hydrochlorothiazide Tablets., Journal of Food and Drug Analysis., 2002,10(1):18-24.
12. Kothawade S. N. Kadam N. R. Aragade P. D. and Baheti D. G. (2010). Formulation andCharacterization of telmisatan solid dispersions. *Int J of PharmTech Research*, 2(1):341-347
13. Kiosseoglou, V.D., 2003, Egg yolk protein gels and emulsions. Current Opinion in Colloid and Interface Science, 8, 365-370.
14. Le Denmat, M., Anton, M., Beaumal, V. (2000). Characterisation of emulsion properties and of interface composition in oil-in-water emulsions prepared with hen egg yolk, plasma and granules. Food Hydrocolloids, 14,539–549.
15. Anton, M., Gandemer, G. (1997). Composition, solubility and emulsifying properties of granules and plasma of henegg yolk. Journal of Food Science, 62(3), 484–487.
16. Misenti, L., Tappero, T., & Ganji V. (1998). Lecithin, an emulsifier, replaces the fat and reduces energy content. *J American Dietetic Association, 98*, 102.
17. Navarro, J. G.; Saavedra, J. C.; Borie, F. B.; Caiozzi, M. M.; *J. Sci. Food Agric.* 1972, *23*, 1287.
18. Tattrie, N. H.; *J. Lipid Res*. 1959, *1*, 60.
19. Kai, M.; Joshita, T.; Saga, M.; *J. Biochem.* 1963, *54*, 403.
20. Kuksis, A.; Marai, L.; *Lipids* 1967, *2*, 217.
21. Y. Mine, Emulsifying characterization of hens egg yolk proteins in oil-in-water emulsions, Food Hydrocolloids, 1998, 12(4):409–415.
22. V. Kiosseoglou, Egg yolk protein gels and emulsions, Current Opinion in Colloid & Interface Science, 2003, 8(4–5):365–370.
23. O. Castellania, C. Belhommea, E. David-Brianda, C. Guérin-Dubiardb, M. Antona, Oil-in-water emulsion properties and interfacial characteristics of hen egg yolk phosvitin, Food Hydrocolloids, 2006, 20(1): 35–43.