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A Nano-Scaled Drug Delivery System for Olmesartan

Nisha Tiwari[1], Bhaskar Kasbekar[1], M. Joyce Nirmala[2], Andrew Ebenaezer[2], A.Sivakumar*[1], Amitava Mukherjee[2], N Chandrasekaran[2]

[1]Chemistry division, School of Advanced Science, VIT University Vellore,India.
[2]Centre for Nanobiotechnology, VIT University Vellore, India.

Abstract: Olmesartan is the recommended antihypertensive drug used in recent years. But due to its poor aqueous solubility and relatively low oral bioavailability, we intended to develop a clove oil based oil-in-water microemulsion system using conventional titration technique owing to its biocompatibility with minimal toxicity. This system showed good thermodynamic stability and reduced droplet size in the nanometer range and hence could reach blood capillaries and would serve as excellent drug delivery system for olmesartan.

1. Introduction

Microemulsions are clear stable isotropic mixtures of oil water and surfactant, commonly combined with a co-surfactant. They are defined as 'a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution'. Owing to their potential to act as drug delivery systems when incorporated into a wide range of drug molecules, great interest has been generated among pharmaceutical scientists. Main differences highlighting emulsions and microemulsions are that the former are thermodynamically unstable and results in the separation of the phases. Another difference being, emulsions appear cloudy while microemulsions appear clear or tranclucent. Other differences include methods of preparation, microemulsions require minimum energy when compared to emulsions. For a microemulsion to be formed, a well-defined boundary between the oil and water phases, at which the surfactant is located, is required. Surfactant molecules comprise of a polar head and an apolar tail, the latter having greater surface area.[1] Olmesartan an antihypertensive drug is administered orally and has bioavailability of only 26% due to low aqueous solubility (<7.75µg/ml). Olmesartan medoxomil(5-methyl-2-oxo-1,3-dioxolen-4-yl) methoxy-4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-{2-(tetrazol-5-yl) phenyl]phenyl}methyl immidazol 5 carboxylate) is a selective angiotensin II receptor blocker and serves as prodrug for olmesartan. Olmesartan is an active metabolite produced in gastrointestinal tract due to de-esterification of its prodrug.[2]

Olmesartan results in reduced blood pressure through arterial vasodilation and sodium retention which are found to be dose dependent. The present investigation helps in enhancing the bioavailability of olmesartan using microemulsion technique to improve its solubility and dissolution rate. The system is tried with oil in water (o/w) microemulsion along with a surfactant (tween 20) in varied ratio to get resultant small droplet size providing with larger surface area for drug release and absorbtion in gastrointestinal tract.

2.1 Materials and Methods

The drug olmesartan was provided by a bulk drug manufacturing company. Clove and cinnamon oils were obtained from SD fine. Tween 20 was obtained from Sigma- Aldrich.

2.1.1 Solubility

The solubility of olmesartan drug was carried out in clove oil by equilibration method, by adding excess amount of drug in 1 ml of oil in 2ml stopper vial. The sample was vortexed and kept for shaking for 72 hrs at 25˚C. The sample was then centrifuged at 3000 rpm for 15 mins and the supernatant from these sample were filtered using 0.45µm membrane filter. From the filtrate obtained we will determine the drug concentration using double beam UV visible spectrophotometer.

2.1.2 Preparation

The drug based on its good solubilising potential in clove oil was used for emulsion. For the microemulsion formulation the different concentrations 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9 were made using clove oil as constant and varying the concentration of tween 20 and water. This results in oil-in-water emulsion where the drug moves to the oil core which was basically aqueous insoluble and lyophillic in nature.

2.1.3 Construction of Phase Diagram and Formulation of Microemulsion

The construction of phase diagram is essential to obtain an optimum concentration range of components for use in identifying the existing region of microemulsions. The effect of various oils on the ternary phase diagram was constructed using conventional titration technique by titrating oil and surfactant mixture with water at room temperature. Oil and surfactant mixtures were prepared in various ratios ranging from 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9. Water was added drop by drop to the mixture under gentle magnetic stirring to allow equilibration. Visual changes in the sample from turbid to transparent were inspected to determine the endpoint of the compositions. An appearance of turbid mixtures that eventually phase separated was considered as the biphasic region. Clear, transparent and low-viscous mixtures that formed within few seconds were designated as monophasic area called the microemulsion region in the phase diagram. From the endpoint compositions of the titrated samples, various compositions of the components (oil, surfactant and water) were plotted as triangular co-ordinates, to construct the phase diagram. The area covered by the monophasic region was shaded and termed as the microemulsion existence region. The experiments were done in replicates, to ensure reproducibility. [3]

3.1 Thermodynamic Stability

SMEDDS are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and water, with no phase separation, creaming or cracking. The stability of microemulsions was examined at room and extreme condition for the formation of metastable systems. The following tests were performed:[4]

1) Centrifugation: The physical stability was checked by centrifuging at 3500 rpm for 30 minutes. The formulations having no phase separation were taken for heating and cooling cycle.

2) Heating cooling cycle: Between temperatures of 4 °C and 40 °C six cycles were performed for 48 h each. Those formulations having no phase separation were taken for freeze-thaw cycle.

3) Freeze thaw cycle: These were taken between -21°C and +25°C.

Those formulations which passed the thermodynamic stress tests were taken for study.

3.2 Physico-Chemical Characterization of Microemulsion

The conductivity measurements helped in determining whether the microemulsion system formed were oil-continuous or water-continuous. The conductivity of formulated sam- ples were measured using a conductivity meter. All the measurements were performed in triplicates.[5]

3.2.1 Measurement of pH

The pH values of the stable formulations were measured by immersing the electrode directly into the dispersion using a calibrated pH meter at 30 ± 1 °C. All measurements were done in triplicates.

3.2.2 Conductivity

The conductivity values of the formulations were measured using Pt electrode the values were taken at 30 °C (range 2mS, cell const. 1). All the measurements were done in triplicates.

3.2.3 Size Analysis

The droplet size and polydispersity were determined by the light scattering technique for the stable micro emulsion formulation. The size measurements were carried out in triplicates.

4. Result and discussion

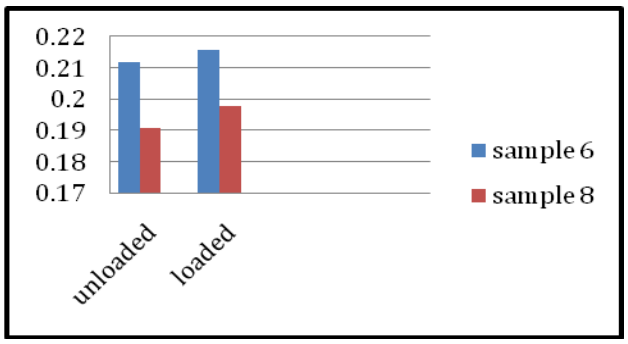
4.1 Solubility

Drug olmesartan was soluble in clove oil with a range of 10 mg/ml.

4.2 Thermodynamic stability

The sample A6 and A8 in case of unloaded and B6 and B8 in case of olmesartan were found to stable and no phase separation was seen after passing from all the stress condition.

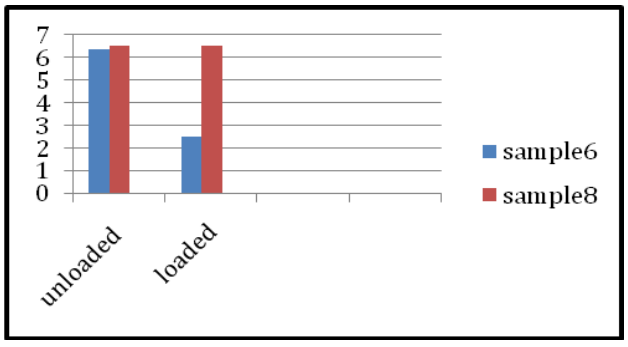
4.3 Conductometry



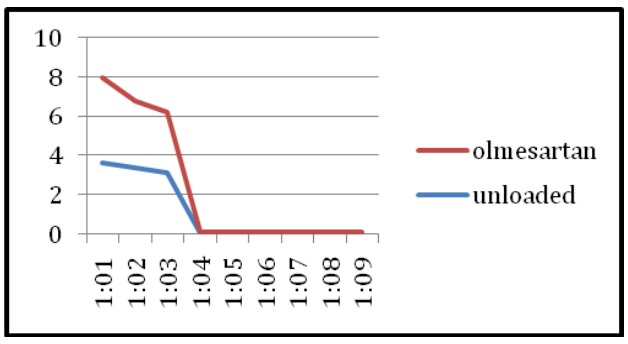
4.4 Size

The size was found to be 10-65 nm in range through light scattering and hence can be inferred that the shape of drug is spherical.

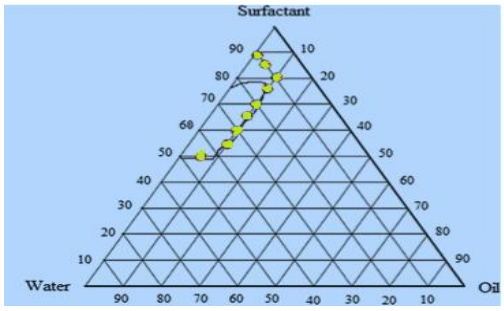
4.5 pH



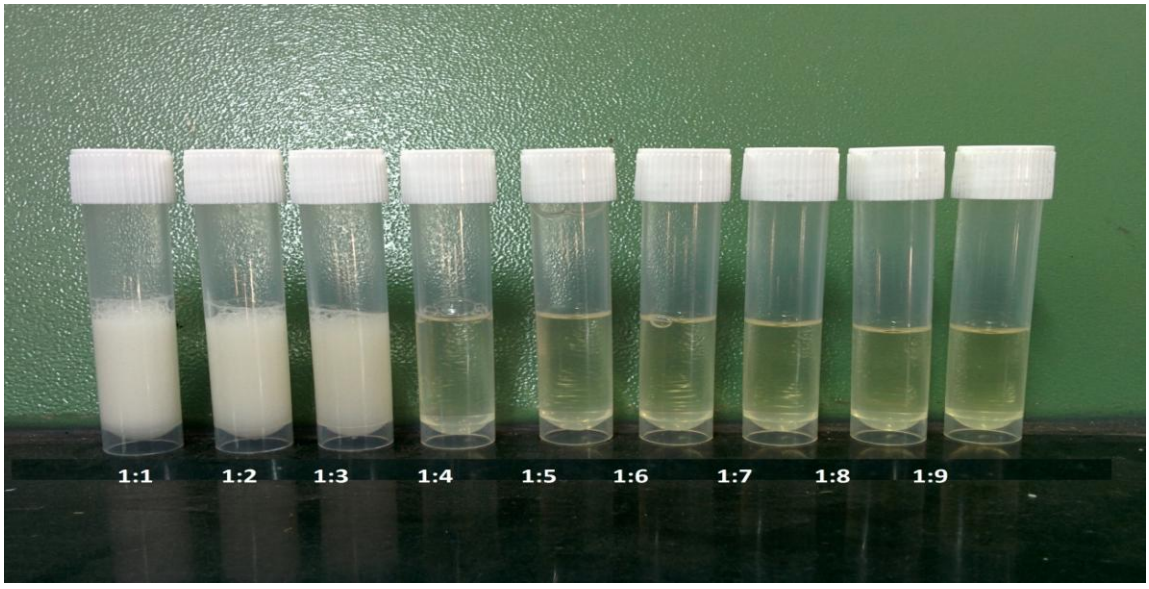
4.6 Turbidity



4.7 Ternary phase diagram



4.8 Visual Appearance and Turbidity



5. Conclusion

Olmesartan drug is found to be fairly soluble. Samples 1:6 and 1:8 were found to withstand the stress and hence the former is used due to the lower surfactant concentration.

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