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IMPROVEMENT OF RUTIN BIOAVAILABILITY BY NANOEMULSION TECHNOLOGY

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ABSTRACT

Poor bioavailability by the oral route can be due to poor solubility, degradation in GI lumen and poor membrane permeation. Any of the approaches, which can alter these characteristics, should help in improving the bioavailability of the drugs. Rutin is a flavonoid most widely and abundantly present in herbs and plant foods; but possesses poor bioavailability. The objective of the present study was to develop and characterize an optimal stable nanoemulsion formulation of rutin with an aim to increase its bioavailability. Nanoemulsion was prepared with isopropyl myristate, eugenol, Tween80, ethanol and water. Eugenol was used as an oil phase in the formulation; an average particle size of this nanoemulsion was 43.2 ± 6.1 nm. Formulations were characterized by means of globule size, refractive index and viscosity etc. *In vitro* drug release was carried out using a dialysis bag and the selected formulations were compared for the drug release with plain drug. The release of drug from nanoemulsion formulations was high when compared to plain drug. Thus nanoemulsions could be used effectively to improve the solubility of poorly water soluble drugs thus improving their bioavailability.

KEYWORDS: Nanoemulsion, bioavailability, flavonoids, rutin.

INTRODUCTION

Nanoemulsions being colloidal nanodispersions of oil in water or water in oil, thermodynamically stabilized by an interfacial film of surfactant and cosurfactant [1]. Droplet size in thermodynamically stable nanoemulsions is usually 10-100 nm [2]. Nanoemulsions have a higher solubilization capacity than simple micellar solutions and their thermodynamic stability offers advantages over unstable dispersions, such as emulsions and suspensions, because they can be manufactured with little energy input and has a long shelf life. The nanosized droplets leading to enormous interfacial areas associated with nanoemulsions would influence the transport properties of the drug, an important factor in sustained and targeted drug delivery [3-4].

Nanoemulsions have been reported to make the plasma concentration profiles and bioavailability of drugs more reproducible [5-6]. Rutin widely and abundantly present in herbs and plant foods.Rutin was recognized to decrease the permeability of capillaries [7]. It has been reported to scavenge free radical, to lower hepatic and blood cholesterol levels, and showed antiplatelet activity [8, 9]. The objective of the present study was to prepare nanoemulsion of rutin to improve its solubility and bioavailability.

MATERIAL AND METHODS

Rutin hydrate (purity 95%) and Eugenol were purchased from Sigma aldrich (USA). All other reagents were of analytical grade.

Development of nanoemulsion formulation

The nanoemulsion of Rutin was prepared by solubilization of Rutin in ethanol, which was used as co-surfactant. The oil phase (isopropyl myristate), eugenol, and surfactant (Tween80) were added slowly under gentle stirring until a homogeneous mixture formed. Then water was added dropwise at 37^{0}C under stirring at 600 rpm.

Characterization of the nanoemulsion

Viscosity measurements

The viscosity of the prepared nanoemulsion formulations were determined as such without dilution by Brookfield DV III ultra V6.0 RV cone and plate rheometer (Brookfield Engineering Laboratories, Inc, Middleboro, MA) using spindle # CPE40 at 25 ±0.5°C. The software used for the viscosity calculations was Rheocalc V2.6.

Refractive index

Refractive index of selected formulations was determined using an Abbe type refractrometer. It was standardized using castor oil.

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Interfacial tension measurement

The formation and properties of nanoemulsion can be studied by measuring the interfacial tension. Spinning drop apparatus was used to measure the ultra-low interfacial tension.

Droplet size distribution

Droplet size of the prepared nanoemulsion was determined by using photon correlation spectroscopy, which analyzes the fluctuations in light scattering due to Brownian movement of the particles [10]. The formulation (0.1 mL) was dispersed in 50 mL of distilled water in a volumetric flask and gently mixed by inverting the flask and measurement done using a Zetasizer (Nano ZS-90, UK). Light scattering was monitored at 25°C at 90° angle.

Morphology observation by Transmission Electron microscope (TEM)

The morphology of the droplet was observed using transmission electron microscopy(JEM-2010; JEOL, Tokyo Japan). One drop of dilutedsamples was deposited on a film-coated 200-mesh copperspecimen grid and allowed to stand for 10 minutes afterwhich any excess fluid was removed with filter paper. Thegrid was then stained with one drop of 3% phosphotungsticacid and allowed to dry for 5 minutes before examinationwith an electron microscope.

In-vitro drug release performance

The study was performed by using dialysis bag Method [11]. The dialysis membrane used in the study was Cellulose membrane. In vitro release test was performed in 250 ml of distilled water, 1 ml of nanoemulsion formulation was placed in treated dialysis bag and 1 mL samples was withdrawn at regular time intervals up to 24 hrs and same amount of distilled water was replaced [12]. The withdrawn 1 ml samples were diluted with 3 ml methanol and analyzed spectrophotometricallyat 258 nm. The release of drug from different selected nanoemulsion formulations was compared with plain drugs.

RESULTS AND CONCLUSION

In the present study, isopropyl myristate, eugenol, Tween80, ethanol and water were selected for the nanosuspension formulations (Table 1). The morphology of rutinnanoemulsion was characterized using TEM (Figure 1). It showed a spherical shape and uniform droplet size of nanoemulsion. Droplet size analysis of the selected formulations was carried out. The difference in the droplet size between the formulations was not statistically significant an average particle size of this nanoemulsion was 43.2 ± 6.1 nm.

It was observed that the viscosity of all the formulations is less than 45 mP. The formulation (N3) having optimum globule size (43.1 nm) and lower viscosity (26.41 ± 1.01 mP). *In vitro* drug release was carried out using a dialysis bag and the selected formulations were compared for the drug release with plain drug. The release of drug from nanoemulsion formulations was high when compared to plain drug. The drug release of

optimum formulation (N3) was found to be highest (73.63±0.65 %) compared to the plain drug (53.37±0.22 %) in 10 hrs (Fig. 2). Thus the results of study revail that nanoemulsions can be used effectively to improve the solubility and bioavailability of poorly soluble drugs.

Table 1. Different formulations of rutinnanoemulsion

Formulations	Ingredients				
	Rutin	Eugenol %	Tween80 %	Ethanol(ml) %	Water(ml) %
N1	10 (mg)	20	0.01	1	40
N2		40	0.01	1	40
N3		20	0.02	1	40
N4		40	0.02	1	40

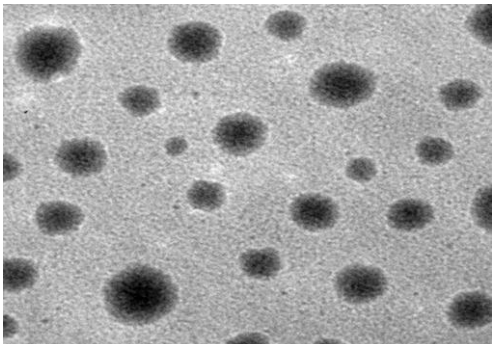

Figure 1. Transmission electron microphotograph of rutinnanoemulsion.

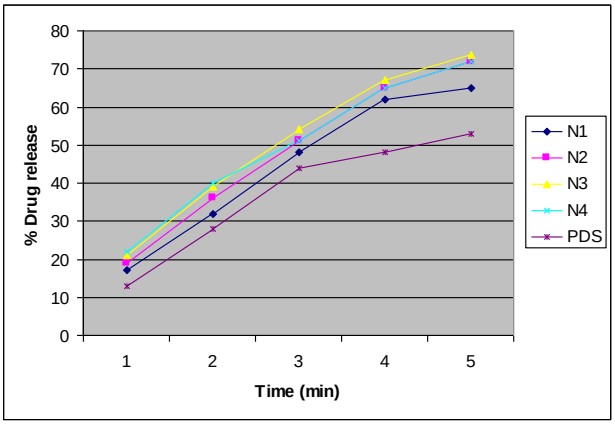

Figure 2. Comparative dissolution profile of formulations and plain drug solution (PDS).

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