**Asian Journal of Biomaterial Research 2017; 3(6):25-27**

*Research Article*

# Formulation and Evaluation of Intranasal Microemulsion containing Rutin

***Sagar Kishor Savale**

*Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, MS, India

Received: 08 Dec 2017 Revised: 13 Dec 2017 Accepted: 17 Dec 2017

## Abstract

**Objective:** Rutin-flavonoid-polyphenolic has gained attention in prevention of brain cancer. The low permeability of Rutin (RU) across the blood-brain-barrier (BBB) leads to its insufficient delivery which in turns result in low therapeutic index. Therefore, developing a novel approaches enhancing the CNS delivery of RU are required for the treatment of Cancer. The aim of this research work was to develop in Microemulsion (ME) loaded with RU, for CNS targeting. **Method:** Rutin (RU) is a poorly water soluble anticancer drug, with oral bioavailability is about 2 %. Microemulsion (ME) were fabricated by Vortexing technique. Oleic acid was used as oil. Tween 80 was employed as surfactant and Polyethylene glycol 400 was employed as co-surfactant. **Conclusion:** RU loaded ME for intranasal delivery are considered as promising vehicle for its targeting to CNS to treat the brain cancer.

**Keywords:** Intranasal delivery, Microemulsion, Brain targeting, Vortexing technique**.**

## 1.Introduction

The uncontrolled growth of cells and tissue can arises cancer, cancer was a one of the most distressing and life threading disease that serves date worldwide. Cancer like Brain tumors were an abnormal and uncontrolled growth of cells in brain. Modern colloidal nanoparticulate system was novel approach to overcome the problems of chemotherapy.

***Author for correspondence:**
**Mr. Sagar Kishor Savale,**
Department of Pharmaceutics,
R. C. Patel Institute of Pharmaceutical Education & Research, Shirpur, 425405,
Dist. Dhule, Maharashtra State, India.
Mobile No: +91 9960885333.
Email ID: avengersagar16@gmail.com

Intranasal drug delivery was the promising strategies for direct deliver drug in nose to brain by passing the BBB via olfactory and trigeminal nerve pathways. Rutin (RU) (polyphenolic compound) has potent antimetastatic and antiproliferative activity against brain tumors. It was important to suppression of nuclear factor-kB is responsible for tumor proliferation. RU having a promising ability to inhibit angiogenesis, it is process for formation of new blood cell in blood vessel for tumor growth, RU having ability to stop the new blood cell formation in blood vessels responsible for tumor growth and shows antiangiogenic activity. The goal of this study was formulate Microemulsion (ME) containing RU for intranasal (nose to brain) delivery to central nervous system (CNS) for the treatment of brain tumor (Savale et al., 2015; Savale et al., 2017).

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## Materials and methods

### Materials

Rutin (RU) was a gift from Loba Chemie Ltd. (Mumbai, India). Oleic acid, Tween 80 and polyethylene glycol 400 (PEG 400) were purchased from Loba Chemie Ltd. (Mumbai, India).

### Methods

### Formulation of Microemulsion (ME)

### Selection of Excipients for formulation

The solubility of Rutin (RU) in various oils (castor oil, oleic acid, ethyl oleate, soya oil, coconut oil, oleic acid and clove oil), surfactants (Tween 20 and Tween 80) and co-surfactant (polyethylene glycol 400, polyethylene glycol 200 and propylene glycol) was determined by using Screening technique (Savale et al., 2017).

### Preparation of Microemulsion (ME)

Rutin-Microemulsion (RU-ME) were prepared by Vortexing technique (Low energy emulsification technique) by slowly pouring the oil, surfactant and co-surfactant mixture using Vortex mixer (Sphinix Ltd, India) into aqueous phase. RU (100 mg) was dissolved in mixture of Oleic acid (mL), Tween 80 (mL) and PEG 400 (mL) was slowly added with stirring at 500 rpm using magnetic stirrer and formulation composition was reported in Table 1.

**Table 1. Compositions of RU-ME formulations**

| Formulation batches | Con. of Oil (Oleic acid) (mL) | Con. of Surfactant (Tween 80) (mL) | Con. of Co-surfactant (PEG 400) (mL) | Droplet size in (nm) |
|---|---|---|---|---|
| M1 | 4 | 10 | 5 | 225.22 |
| M2 | 4 | 8 | 7 | 177.58 |
| M3 | 3.5 | 9 | 5 | 195.15 |
| **M4 (op)** | **3** | **6** | **4** | **106.25** |
| M5 | 5 | 7 | 8 | 158.26 |
| M6 | 4.5 | 9 | 6 | 167.48 |

### Physicochemical characterization of Rutin loaded Microemulsion (RU-ME)

### Droplet size analysis

The mean droplet size (MDS) were determined by photon correlation spectroscopy (PCS) using a Malvern Zetasizer (Nano ZS 90, Malvern Ltd., Malvern, UK). The measurement using PCS is based on the light-scattering phenomena in which the statistical intensity fluctuations of the scattered light from the particles in the measuring cells are measured. Prior to the measurements, all samples were diluted with double-distilled water to produce a suitable scattering intensity the light scattering was monitored at 25˚c at a 90˚c angle (Yang et al., 2004).

### Zeta Potential

The ZP, reflecting the electric charge on the droplet surface and indicating the physical stability of colloidal systems, was measured by determining the electrophoretic mobility using the Malvern Zetasizer (Nano ZS 90, Malvern Ltd., and Malvern, UK). The measurements were performed following dilution in double-distilled water. It was measured using the Dip cell by applying a field strength of 20 V/cm and the average of the ZP was given from 30 runs (Vanitasagar et al., 2013).

### Drug Content

The drug content of formulation was determined by UV spectrophotometric method. RU from ME formulations (M4) was extracted by dissolving 1 ml of ME in methanol. RU content in the Methanolic extract was analyzed spectrophotometrically (UV 1700, Shimadzu, Japan) at 257 nm, against the standard Methanolic solution of RU (Savale et al., 2017).

### *In vitro* Drug permeation studies

*In vitro* diffusion study of optimized ME was carried out by Franz diffusion cell having 2.0 cm diameter and 25 ml capacity. Dialysis membrane (Himedia) having molecular weight cut off range 12000-214000 kDa was used as diffusion membrane. Pieces of dialysis membrane were soaked in phosphate buffer saline (PBS) pH 6.4 for 24 h prior to experiment. Diffusion cell was filled with PBS pH 6.4 and dialysis membrane was mounted on cell. The temperature was maintained at 37°c. After a pre-incubation time of 20 minutes, the ME equivalent to 10 µg of RU (M4) was placed in the donor chamber. Samples were periodically withdrawn from the receptor compartment for 4 hours and replaced with the same amount of fresh PBS, and assayed by a UV spectrophotometer at 257 nm (Savale et al., 2017).

**Results and discussion**

**Preparation and characterization of Microemulsion (ME)**

The RU-loaded ME were prepared using Vortexing technique. For the preparation of oleic acid as a liquid lipid. Tween 80 were selected as a surfactant and Polyethylene glycol 400 as a co-surfactant a stabilizer, respectively.

**Droplet size analysis and Zeta Potential**

The droplet size (nm) and zeta potential (mV) of RU-loaded ME (M4) was found to be 106.25 nm and -32.48 mV respectively.

**Drug Content**

The concentration of oil and surfactant: co-surfactant was important effect on drug content. The oil content (oleic acid) was increases, to increase drug content and the surfactant and co surfactant concentration (tween 80 + PEG 400) decreases to increase drug content. Because drug having maximum solubility in oil phase and drug content of optimized formulation (M4) was found to be 98.38 %.

***In vitro* Drug permeation studies**

The release profile of RU-loaded ME (M4) through the dialysis membrane in PBS (pH 6.4) was found to be 99.77 %. The release pattern of optimized ME (M4) appears to be fast release with negligible burst effect.

**Conclusion**

RU have various activities as it may be anticancer, antioxidant, anti-inflammatory drug lipophilic in nature having low oral Bioavaibility, is selected as candidate for the development of RU-ME for its intranasal delivery to target the CNS via olfactory and trigeminal nerve pathway for the treatment of brain tumor.

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