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FORMULATION AND EVALUATION OF NANOEMULSION CONTAINING GEFITINIB

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ABSTRACT

Gefitinib (GFT) was a tyrosine kinase inhibitor (TKI), also known as a cancer growth inhibitor. The aim of this research work was to develop in Nanoemulsion (NE) loaded with Gefitinib (GFT), for anticancer EGFR inhibitor activity. Nanoemulsion (NE) were fabricated by Vortexing technique. Oleic acid was used as oil phase. Tween 80 was employed as surfactant and Polyethylene glycol 400 was employed as co-surfactant phase. Optimised Nanoemulsion (NE) (M 12) had droplet size 55.25 ± 0.45 nm and drug content of gefitinib (GFT) was 99.88 ± 0.12 % respectively.

KEYWORDS

Nanoemulsion (NE), Vortexing process, Gefitinib (GFT), Anticancer activity and EGFR.

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INTRODUCTION

Gefitinib (GFT) was a tyrosine kinase inhibitor (TKI), also known as a cancer growth inhibitor. Kinases are proteins in the body that regulate uncontrolled cell growth. GFT inhibits the protein from sending signals to the cancer cells that make them grow and divide. GFT inhibits the activity of EGFR by competing with adenosine triphosphate (ATP) for its binding site on the intracellular tyrosine kinase domain of the receptor. This inhibits autophosphorylation of EGFR and blocks downstream signaling. The mean oral bioavailability of GFT is minimum due mainly to hepatic first pass metabolism. GFT plasma protein binding is 90 %. GFT inhibits the intracellular

phosphorylation of numerous tyrosine kinases (TK) associated with transmembrane cell surface receptors, including the TK associated with the EGFR-TK. EGFR was expressed in the cell surface of many normal cells and cancer cells. The goal of this research work was to formulate Nanoemulsion (NE) containing GFT for cancer growth inhibitor activity (EGFR-TK)[1-2].

MATERIAL AND METHODS

MATERIAL

Gefitinib (GFT) was a gift from Khandelwal industries Ltd. (Mumbai, India). Oleic acid, Tween 80 and polyethylene glycol 400 (PEG 400) were gift from Loba Chemie Ltd. (Mumbai, India).

FORMULATION OF NANOEMULSION (NE)

Selection of Excipients for formulation

The solubility of Gefitinib (GFT) in various oils (soya oil, oleic acid, ethyl oleate, castor oil, coconut oil and clove oil), surfactants (Tween 20, Tween 80 and Span 60) and co-surfactant (polyethylene glycol 200 and polyethylene glycol 400) was determined by using Screening technique[3].

Preparation of Nanoemulsion (NE)

Gefitinib-Nanoemulsion (GFT-NE) were prepared by Vortexing technique (Low energy spontaneous emulsification technique)[4] by slowly pouring the oil, surfactant and co-surfactant mixture using Vortex mixer (Sphinix Ltd, India) into aqueous phase. GFT (200 mg) was dissolved in mixture of Oleic acid (mL), Tween 80(mL) and PEG 400(mL) was slowly added with stirring at 800rpm using magnetic stirrer and formulation composition was reported in Table No.1.

PHYSICOCHEMICAL CHARACTERIZATION OF GEFITINIBLOADED NANOEMULSION (GFT-NE)

Droplet size analysis

The droplet size (DS) 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˚cangle[5].

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[6].

Drug Content

The drug content of formulation was determined by UV spectrophotometric method. GFT from NE formulations (M 12) was extracted by dissolving 1 ml of NE in methanol. GFT content in the Methanolic extract was analyzed spectrophotometrically (UV 1700, Shimadzu, Japan) at 254 nm, against the standard Methanolic solution of GFT.

***In vitro* Drug permeation studies**

In vitro diffusion study of optimized NE (M 12) 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 k Da 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 NE equivalent to 20 µg of GFT (M 12) 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 254 nm.

RESULTS AND DISCUSSION

Preparation and characterization of Nanoemulsion (NE)

The GFT-loaded NE 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 GFT-loaded NE (M 12) was found to be 55.25 ± 0.45 nm and -38.18 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 (M 12) was found to be 99.88 ± 0.12 %.

In vitro Drug permeation studies

The release profile of GFT-loaded NE(M 12) through the dialysis membrane in PBS (pH 6.4) was found to be 99.89 ± 0.10 %.The release pattern of optimized NE(M 12) appears to be fast release with negligible burst effect.

Table No.1: Compositions of GFT-Ne 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)
M 10	6	19	12	119.12
M 11	8	16	15	103.28
M 12 (op)	5	13	9	55.25
M 13	10	18	16	156.1
M 14	8	22	20	69.2
M 15	10	19	11	98.20

CONCLUSION

GFT 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 GFT-NE for its cancer growth inhibitor activity (EGFR-TK).

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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