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PREPARATION AND EVALUATION OF ETOPOSIDE AND CURCUMIN BASED NANOEMULSION

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ABSTRACT

Sustained or controlled release of drug, genetic material and biologically active ingredient are achieved through nanoemulsion which is the novel drug delivery system. Nanoemulsion is an anisotropically clear and kinetically or thermo-dynamically stable liquid solution, consisting of oil, surfactant and an aqueous phase, generally droplet diameter of 10-500 nm. Preparation of Etoposide and Curcumin containing lipidic nanoemulsion was proposed. Optimization of formulation was done using various oils, surfactant ratios and stabilizers. Two formulations using vitamin E acetate as oil, tween 80 and labrasol as surfactant and phosphatidylcholine as stabilizer were prepared using ultrasonication method, by varying volume ratio of vitamin E acetate 1% v/v and 2% v/v. These o/w nanoemulsions were prepared and checked for their particle size, zeta potential. Particle size obtained was 162.7 nm and 137.1 nm, and polydispercity index obtained was 0.224 and 0.226 respectively, which showed uniform distribution of globules in the nanoemulsion. The Zeta Potential curve of optimized nanoemulsion implies that the nanoemulsion were in the satiability region between -25 to -35 mV. The amount of released etoposide and curcumin gradually decreases with respect to time. *In vitro* drug release profile showed biphasic release behavior with an initial burst effect followed by slow and sustained release. This obviously results in a lower release of drug from nanoemulsion. Thus it may be concluded that nanoemulsion could be a better option for the parenteral (i.p.) delivery of etoposide and curcumin.

KEYWORDS: Nanoemulsion, Etoposide, Curcumin, Ultrasonication method, *In vitro* drug release.

INTRODUCTION

The term “nanoemulsion” refers to a thermodynamically stable, isotopically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules.[1,2] A nanoemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant. The dispersed phase typically comprises small particles or droplets, with a size range of 50 nm-500 nm, and has very low oil/water interfacial tension. Because the droplet size is <25% of the wavelength of visible light, nanoemulsions are transparent. The nanoemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases, a cosurfactant or co-solvent is used in addition to the surfactant, oil phase, and the water phase.[3] Etoposide (ETP) is the inhibitor of deoxyribonucleic acid (DNA) topoisomerase II. Its main effect appears to be at the G2 phase of the cell cycle in mammalian cells. ETP has been one of the treatment options for gastric carcinoma but ETP is challenging to administer because of solubility, and undergoes short biological half-life as well as drug resistance.[4,5] This necessitates repetitive high dosages and severe side effects. Moreover, deficiencies such as metabolic inactivation, drug resistance, myelosuppression, poor bioavailability and secondary acute myelocytic leukemia, which occur in a several percentage of patients have limited their scopes of applications.[6,7] On the other hand, curcumin (CUR) is a natural remedy, and has been shown to enhance the antitumor efficacy of ETP for prostate cancer.[8] Curcumin can be used extensively to treat a variety of solid tumors, including stomach, breast and colorectal carcinoma. In gastric cancer cell lines, CUR protects against chemoresistance in human gastric cancer cell lines (SGC7901 cells) by down-regulating NF-kB and subsequent NF-kB-mediated anti-apoptotic genes, such as Bcl-2 and Bcl-xL.[9] It has been also reported that CUR suppresses the expression of epidermal growth factor receptor (EGFR) and was

capable of suppressing cell proliferation and migration through inhibition of STAT3 phosphorylation, which contributes to gastric carcinogenesis.[10,11] In spite of excellent therapeutic potential, low-aqueous solubility and rapid systemic elimination limit its application in medicine. Recently, the development in the field of nanotechnology has made excellent progresses toward administrative lipophilic drug. So, the objective of the present research work was to formulate Nanoemulsion of Etoposide and Curcumin for improving the solubility and bioavailability of drug.

MATERIALS AND METHODS

Materials

ETP was generously provided as a gift sample by Getwell Pharmaceuticals (Gurgaon India), CUR (95% purity) was provided as a gift sample Sanat Products Ltd., (New Delhi India). Soya phosphotidylcholine and Tween-80 was purchased from Sigma Chemicals (St. Louis, MO). Labrasol was kindly provided as a gift sample by Gattefosse India (Mumbai, India). Vitamin E Acetate and Oleic acid was purchased from Merck India ltd (Mumbai, India). Isopropyl palmitate was purchased from Aldrich Chemical Company Inc. (Milwaukee, USA). All other chemicals and solvents were of reagent grade.

Preformulation studies

Before development of any formulation it is mandatory to carry out pre-formulation studies to find any changes in the drug characteristics and suitability of a drug candidate for formulation development.

Physical appearance

Drug samples were noted for its organoleptic properties. Etoposide was white powder, available in press sealed polyethylene envelope pack as gift sample from Getwell Pharmaceuticals, Gurgaon and curcumin was bright yellow orange powder obtained from Sanath Product Ltd, New Delhi.

Melting point

Melting point of etoposide and curcumin were determined using scientific melting point apparatus (Gallenkamp). By filling the drug sample in three separate capillaries.

Fourier transform infrared spectrum (FTIR)

Infrared spectrum of any compound or drug gives information about the groups present in that particular compound. Fourier transform infrared (FT-IR) spectra were obtained on a Perkin-Elmer RXI FT-IR spectrometer. Potassium bromide was mixed with GG and Drug samples (etoposide and curcumin) in the specified ratio and the pellet was made. The scanning range was 450–4000 cm^{-1} and the resolution was 2 cm^{-1}. The IR spectrums of drugs were examined and were found to be concordant with the reference spectrum of the drugs.

UV Spectroscopy

A double beam UV Spectrophotometer (1700 Shimadzu Inc., USA) was used to scan drug samples of known dilution and λmax was noted. The UV spectrum of etoposide and curcumin were examined.

DSC thermogram (DSC)

Approximately 2 mg of samples were sealed in an aluminum pan with an empty encapsulated pan as a reference. The samples were scanned at a heating rate of 10 °C/min from 50-350°C (Perkin-Elmer Model 1-DSC). The instrument was calibrated with Indium.

Partition coefficient

Partition coefficient is the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium. The partition coefficient of drug was determined by log P determination i.e. the Shake-flask method at room temperature (30 ^{o}C). Ten ml of n-octanol and 10 ml of distilled water was taken in a glass stopper graduated tube and 5 mg of accurately weighed drug was added, the mixture was then shaken with the help of mechanical shaker for 24 h at room temperature and transferred to a separating funnel and allowed to equilibrate for 6 h. The aqueous and n-octanol phase were separated and filtered through membrane filter and drug content in aqueous phase was analyzed by UV-Visible spectrophotometer. The partition coefficient was calculated by following formula

Partition coefficient, PC = Ct-Ca/Ca

Where, Ct is the concentration of the total drug taken (5 mg), Ca is the concentration of the drug in aqueous phase.

Quantitative estimation of Etoposide and Curcumin with HPLC and Validation

To estimate the drug content in nanoemulsion, an HPLC method was developed and validated.

Equipment

The HPLC system was equipped with LC 10 ATVP isocratic pumps (Shimadzu). A Rheodyne (Cotati, CA, USA) model 7125 injector with a 20 µl loop and SPD-M10 AVP UV detector (Shimadzu) was used. HPLC separation was achieved on a LiChrospher LichroCART RP−C8 (5µm) column. Column effluent was monitored at 262 and 285 nm. Data was acquired and processed using Shimadzu LC Solution software.

Preparation of mobile phase

The mobile phase was a mixture of acetonitrile: triple distilled water: glacial acetic acid (40:59:1) v/v. The solution were filtered and degassed before use via bath sonicator. Chromatography was performed at 30 °C at a flow rate of 1.5 ml/minute.

Preparation of Stock and Working standard solution

Stock solution of etoposide and curcumin was prepared by dissolving 10 mg of drugs in a 10 ml of volumetric flask. Volume was made up to 10 ml with triple distilled water. Working solutions were prepared from stock solution in the range of 0.25-8.0 µg/ml by serial dilution method. Sample (20 µl) was injected into the column. Chromatographic conditions used in the analysis are depicted below.

Chromatographic conditions of HPLC

HPLC Pump	Shimadzu LC-10AT
Detector	UV−VIS detector
Column	MERCK 50995, LiChrospher LichroCART RP-C18)
Mobile phase	Acetonitrile: TDW:GAA (40:59:1)
Flow rate	1.5 ml/min
Flow	Isocratic
Wavelength	262 and 285 nm
Sample injection volume	20µl
Pressure	200 to 400 kgf /cm^2
Temperature	30 °C

Analysis of drug in formulation

Analysis of drug in formulation was done in a manner for the standard curve and concentration of sample is calculated by the following formula

Concentration of the sample, Cs = {€Asample / €Astd.}* Cstd. D

Cstd is the concentration of the standard, D is the dilution factor, Astd is the area under the curve of standard concentration, A sample is the area under the curve of the sample.

Experimental work

Selection of oil

The selection of oil was done by using various oils to formulate nanoemulsion and the result is presented in tables.

Table 1: Selection of oil (0.5%) v/v.

Formulation code	Oil (0.5%) v/v	Z-Average Size (nm)	PDI	Zeta Potential (mV)
F-1	Soya oil	576.9	0.845	-8.75
F-2	Oleic acid	386.3	0.474	-19.8
F-3	Isopropyl palmitate	284.1	0.332	-28.6
F-4	Vitamin E acetate	139.9	0.334	-31.3

Table 2: Selection of oil (1%) v/v.

Formulation code	Oil (1%) v/v	Z-Average Size (nm)	PDI	Zeta Potential (mV)
F-11	Soya oil	1088	0.988	-11.8
F-22	Oleic acid	568.3	0.857	-23.5
F-33	Isopropyl palmitate	528.6	0.746	-31.7
F-44	Vitamin E acetate	282.0	0.332	-48.9

Table 3: Selection of oil (2%) v/v.

Formulation code	Oil (2%) v/v	Z-Average Size (nm)	PDI	Zeta Potential (mV)
F-111	Soya oil	2167	0.837	-17.4
F-222	Oleic acid	523.6	0689	-28.3
F-333	Isopropyl palmitate	371.8	0.477	-25.8
F-444	Vitamin E acetate	251.0	0.358	-30.7

Table 4: Selection of oil (3%) v/v.

Formulation code	Oil (3%) v/v	Z-Average Size (nm)	PDI	Zeta Potential (mV)
F-1111	Soya oil	1963	0.967	-15.7
F-2222	Oleic acid	673.3	0.804	-21.8
F-3333	Isopropyl palmitate	451.9	0.954	-23.4
F-4444	Vitamin E acetate	367.6	0.432	-37.2

Selection of Surfactant and Excipient

Tween 80, being a hydrophilic nonionic surfactant, is widely used for oil in water nanoemulsions. Tween 80 is an excipient that is used to stabilize aqueous formulations of medications for parenteral administration. It has a strong permeation enhancing effect and increases drug solubility. Due to its interfacial tension lowering capacity, it helps to form stable nanoemulsion.

Labrasol, caprylocaproyl macrogolglycerides (Polyoxylglycerides) non-ionic water dispersible surfactant composed of well characterised polyethylene glycol (PEG) esters, a small glyceride fraction and free PEG. Surfactive power improves the solubility and wettability of active pharmaceutical ingredients in vitro and in vivo. Increased bioavailability is reported to be associated with strong inhibition of the enterocytic efflux transporter (known as P-gP inhibition). Phosphatidylcholine, which has two long hydrocarbon chains, is a major component of lipid bilayers of cell membranes and a natural, biological amphiphile. Furthermore, it is in many respects regarded as an ideal biological surfactant because it is biodegradable. It may be used for various purposes. Careful selection of additives can help adjust appropriately the hydrophilic–lipophilic balance (HLB). Recent study has indicated that phosphatidylcholine embedded microemulsion systems improved the transmembrane bioavailability in both rat skin and Caco2 cells.

The effect of surfactant concentrations

The effect of surfactant concentrations was observed by using various different concentrations of surfactants to formulate nanoemulsion.

Table 5: Optimization of Tween-80 concentration.

Formulation code	Vitamin E Acetate % (v/v)	Tween-80 %(v/v)	Z-Average Size (nm)	PDI	Zeta Potential (mV)
P-1	2	0.5	231.3	0.437	-21.9
P-2	2	1	275.4	0.344	-23.5
P-3	2	2	284.9	0.542	-27.7
P-4	2	3	208.9	0.323	-30.4
P-5	2	4	243.6	0.456	-19.8

Table 6: Optimization of concentration of tween-80 and Labrasol mixture.

Formulation code	Vitamin E Acetate % (v/v)	Tween-80 %(v/v)	Labrasol %(v/v)	Z-average size (nm)	PDI	Zeta Potential (mV)
P-11	2	1	1	345.8	0.562	-25.8
P-22	2	2	1	410.2	0.392	-23.4
P-33	2	3	1	251.0	0.358	-37.2

Table 7: Optimization of concentration of Phosphatidylcholine.

Formulation code	Vitamin E Acetate % (v/v)	Phosphatidylcholine (mg)	Z-average size (nm)	PDI	Zeta Potential (mV)
P-111	2	20	210.8	0.392	-28.9
P-222	2	25	287.6	0.467	-36.4
P-333	2	30	115.3	0.383	-41.1
P-444	2	35	243.7	0.354	-38.6

Optimization of concentration of Curcumin and Etoposide in formulation

The selection of concentration of Curcumin and Etoposide in formulation was done by using various different concentrations of both drugs and the result is presented in table.

Table 8: Optimization of concentration of Curcumin and Etoposide in formulation.

Formulation code	Concentration of curcumin (mg/ml)	Concentration of etoposide (mg/ml)	Drug precipitation
V-1	-	0.3	No
V-2	-	0.4	No
V-3	-	0.5	No
V-4	-	0.6	No
V-5	-	0.7	Yes
V-6	0.5	-	No
V-7	1	-	No
V-8	1.5	-	No

V-9	2	-	Yes
V-10	1.75	-	Yes
V-11	1.5	0.6	Yes
V-12	1.5	0.5	No

Overview of the composition of optimized nanoemulsion

The selected composition of nanoemulsion from above data has following optimized parameters.

Table 9: Overview of the composition of optimized nanoemulsion.

S. No.	Parameter	Optimized quantity
1	Vit-E Acetate	1 (%v/v) and 2 (%v/v)
2	Tween 80: Labrasol	3:1 (%v/v)
3	Phosphatidylcholine	30 mg
4	Curcumin	1.5 mg/ml
5	Etoposide	0.5 mg/ml

Method of nanoemulsion preparation

The high energy emulsification method was used to prepare o/w nanoemulsions from mixture of various oils and surfactants. Accurate quantity of tween-80 was taken and poured into the water and then curcumin solution and etoposide solution (Solution prepared in acetone) was added into the oil and vortexes for 10 min. Then phosphatidylcholine was weighed accurately and put into the oil mixture. Then the mixture was sonicated for 30 seconds (At 25% amplitude) according to the formulation and acetone was evaporated. Oil mixture was poured into aqueous phase (Triple distilled water, 10 ml) and then was sonicated (At 25 % amplitude) for 3 min to form a lipidic o/w nanoemulsion.[12]

Characterization of nanoemulsion[13]

Finally optimized formulations of o/w lipidic nanoemulsion were characterized for various parameters.

Particle size

Particle size and zeta potential was measured by Dynamic Light Scattering and Laser Doppler Anemometry, respectively (Zetasizer Nano-ZS, Malvern Instruments, UK). The nanoemulsion formulations were diluted with triple distilled water for the dynamic lighter scattering analysis. Measurements were made in triplicate at 25 ± 1 °C. Optical properties of the sample were defined as follows: refractive index 1.48 and absorption 0.01. The samples were diluted until they were transparent so as to ensure free diffusion and unhindered Brownian motion of the nanoemulsion.

Particle stability- zeta potential measurement

Electrophoretic mobilities of the nanoemulsion were measured using a Zetasizer Nano ZS (Malvern 3000 HS). The mobility (u) was converted into zeta potential (ξ) values using the Smoluchowski relation, according to which

Zeta potential, $\xi = u\eta/\in$

Where η and ∈ are the viscosity and permittivity of the solution, respectively. All ξ-potential measurements were performed without added electrolyte. Finally the data of optimized formulations are recorded.

Drug entrapment efficiency

Drug entrapment in nanoemulsion was determined by centrifugation method. The mass of curcumin and etoposide entrapped in nanoemulsion was determined by dissolving formulation in ACN and measuring the mass of un-entrapped drug recovered from the supernatant. After ultracentrifugation of nanoparticles at 13000 rpm for 20 minutes the concentration of curcumin and etoposide in the supernatant was determined using HPLC (Shimadzu) at 285 nm. The mass of drug in nanoemulsion, percent drug entrapment were calculated using the following equations.

Mass of drug in nanoemulsion = mass of drug used in formulation − drug mass at supernatant

Drug entrapment efficiency (%) = (mass of drug in nanoemulsion / mass of drug used in formulation) × 100

***In vitro* drug release studies**

The release of etoposide and curcumin from nanoemulsion was determined by dialysis membrane method. Drug loaded nanoemulsion corresponding to 1mg loaded etoposide and 3 mg loaded curcumin were distributed in dialysis bag of 12 kDa molecular weight cut off. The bags were suspended in 250 ml of TDW and Ethanol $(50:50)^{90}$ at 37 ±1 °C in the dissolution apparatus (DISSO 2000, LABINDIA) at 100 rpm to simulate the *in vivo* conditions. At the predetermined intervals (0.25, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 25,and 48 hours) aliquots of 1 ml samples were withdrawn, filtered through 0.22 µm filter and the medium was replaced with fresh TDW and ethanol (50:50). The concentrations of drugs were estimated by measuring the absorbance at 262 and 285 nm with reverse phase HPLC using C_8 column.

Physical stability of nanoemulsion

The physical stability of the nanoemulsion was evaluated by examining changes in mean particle size and zeta

potential during storage at 4 °C, and at room temperature (25 °C) for two months.

RESULTS AND DISCUSSION

The melting points of etoposide and curcumin were found to be 252 ± 2 °C and 183 ± 2 °C respectively. The UV spectrum of etoposide and curcumin were examined and λmax was found to be at 431 nm and 232 nm for etoposide and 401 nm and 213 nm for curcumin Figure 1& 2. The drug purity was identified by IR spectroscopy and characteristic peaks obtained were compared with standard spectra of pure drug reported in official monograph. The IR spectrum of drug sample is in agreement with the standard IR spectra of pure etoposide and curcumin Figure 3& 4. DSC scan of etoposide and curcumin shows a single melting endotherm at 245 °C for etoposide and 183°C for curcumin Figure 5& 6. The partition coefficient of etoposide and curcumin were found as log PC {n-octanol/water) and were found to be 9.92 and 3.21 respectively. In the present study, a simultaneous HPLC method was developed for the estimation of etoposide and curcumin. The calibration curves of etoposide and curcumin were prepared in the mobile phase acetonitrile: triple distilled water: glacial acetic acid (40:59:1) v/v. The data were regressed to obtain the straight lines. The correlation coefficients were found to be 0.9996 for etoposide and 0.9993 for curcumin, indicating good linearity. The HPLC of the drugs etoposide and curcumin showed retention time of 3min and 15.3 min respectively. Calibration curve of etoposide and curcumin will be helpful for future *in vivo* and bioavailability study Figure 7. Preparation of Etoposide and Curcumin containing lipidic nanoemulsion was proposed. Optimization of formulation was done using various oils, surfactant ratios and stabilizers. Two formulations using vit. E acetate as oil, tween 80 and labrasol as surfactant and phosphatidylcholine as stabilizer were prepared using ultrasonication method, by varying volume ratio of vitamin E acetate 1% v/v and 2% v/v. These o/w nanoemulsions were prepared and checked for their particle size, zeta potential. Particle size obtained was 162.7 nm and 137.1 nm, and polydispercity index obtained was 0.224 and 0.226 respectively, which showed uniform distribution of globules in the nanoemulsion. The Zeta Potential curve of optimized nanoemulsion implies that the nanoemulsion were in the staibility region between -25 to -35 mV Table 10. Drug entrapment is the fraction of the total drug incorporated in the nanoemulsion. Percentage entrapment efficiency of the formulation was calculated Table 11. The *in vitro* drug release profile of entrapped etoposide and curcumin from the formulation and free etoposide and curcumin dispersed in TDW and ethanol (50:50) was studied using sink condition. As the encapsulation of both drugs has been demonstrated and quantified, the question arises whether the encapsulated drugs can be released afterwards, which is apparently crucial for practical applications. Drugs released from the nanoemulsion and free drug dispersed in TDW and Ethanol (50:50) were monitored with RP-HPLC of the release medium and Figure 8 & 9 depicts the release profiles of the formulations at 37 ± 1 °C. The formulation NE-2 showed rapid release of both etoposide and curcumin i.e., 83.049 % of etoposide was released in 48 h (compared to NE-1 which released 80.335%), and 63.391% of curcumin was released in 48 h (compared to NE-1 which released 59.499%). The amount of released etoposide and curcumin gradually decreases with respect to time. *In vitro* drug release profile showed biphasic release behaviour with an initial burst effect followed by slow and sustained release. This obviously results in a lower release of drug from nanoemulsion. Thus it may be concluded that nanoemulsion could be a better option for the parenteral (i.p.) delivery of etoposide and curcumin. On applying various release kinetics models for evaluating the release mechanism it was concluded from the results that Higuchi model showed maximum linearity. No phase separation or turbidity was observed in optimized formulations at room temperature (25 °C) and 4 °C. The size changing at 4 °C is minor as compared to the size changing at 25 °C so as there is minor increase in the size of the formulation at 4 °C, it could be assumed the best storage temperature for the formulated nanoemulsion.

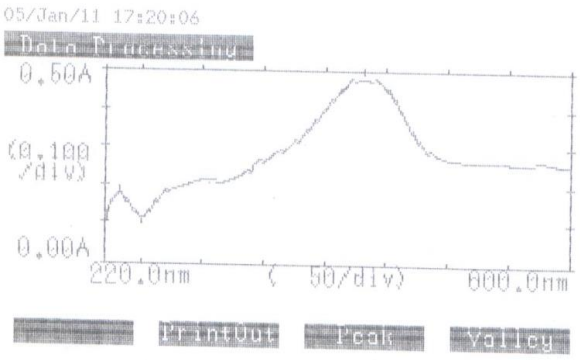

Figure 1: UV spectrum of etoposide.

Figure 2: UV spectrum of curcumin.

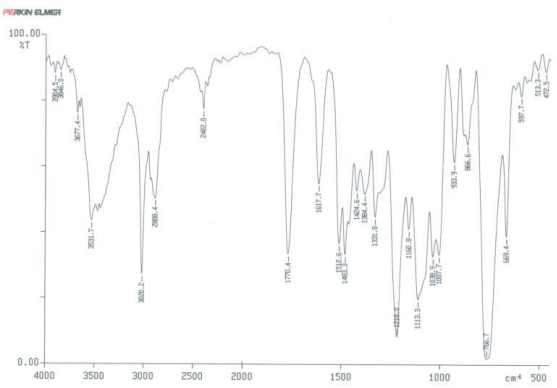

Figure 3: Infrared spectrum of etoposide.

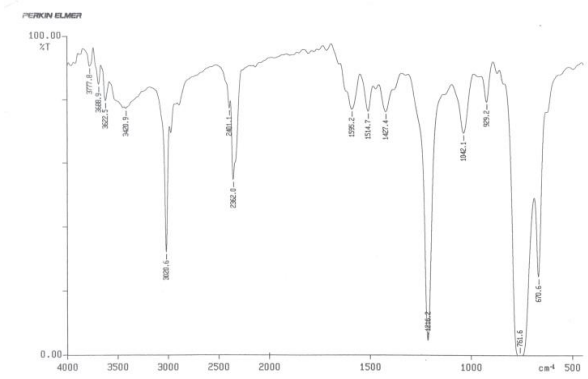

Figure 4: Infrared spectrum of curcumin.

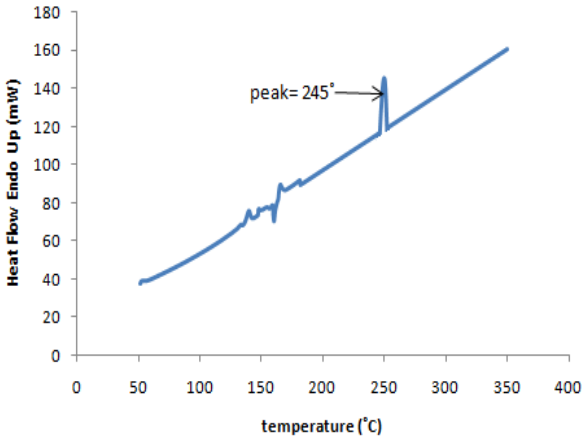

Figure 5: DSC thermogram of etoposide.

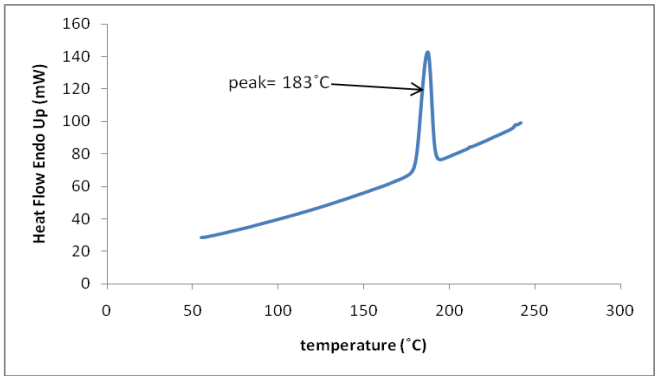

Figure 6: DSC thermogram of curcumin.

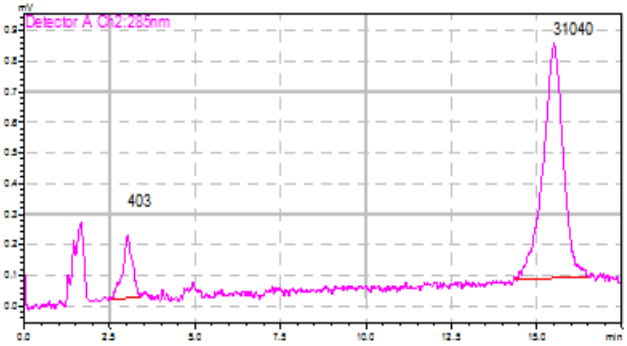

Figure 7: HPLC chromatogram showing retention time of Etoposide and Curcumin.

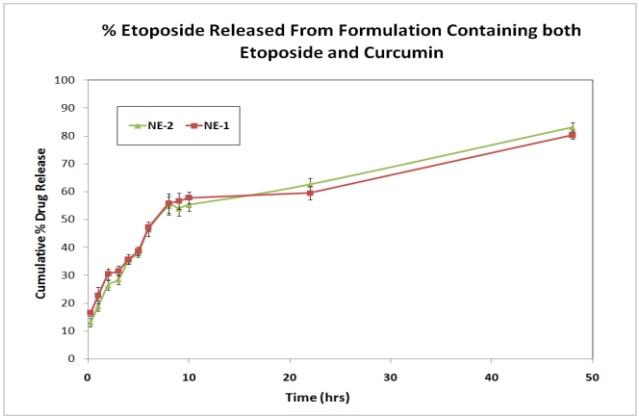

Figure 8: Drug release profile of etoposide in NE-1 and NE-2.

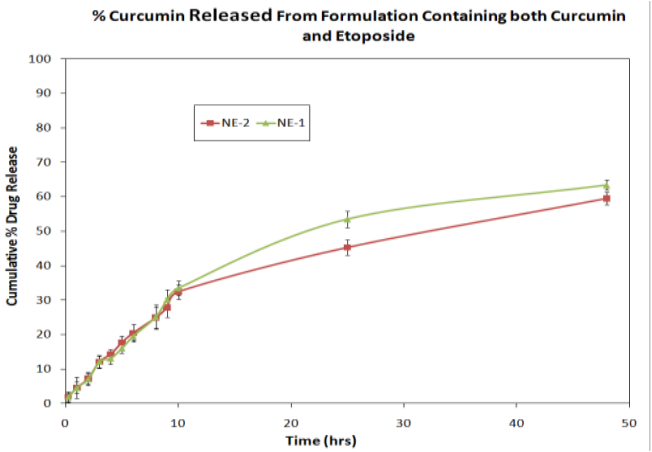

Figure 9:Drug release profile of curcumin in NE-1 and NE-2.

Table 10: Final optimized Size and Charge of the nanoemulsion.

Formulation code	Vit. E Acetate %(v/v)	Tween 80 %(v/v)	Labrasol %(v/v)	Phosphatidyl -choline (mg)	Z-avg (nm)	PDI	Zeta Potential (mV)
NE-1	1	3	1	30	162.9	0.244	-29.8
NE-2	2	3	1	30	137.1	0.226	-30.7

Table 11: Percent entrapment efficiency of Etoposide and Curcumin.

Formulation	% EE	
	Etoposide	Curcumin
NE-1	86± 2	94± 3
NE-2	89± 3	97± 2

CONCLUSION

When cancer cells develop a MDR phenotype either due to intrinsic factors, such as microenvironmental selection pressures, or after first exposure to a chemotherapeutic agent, the ensuing clinical outcomes are always very poor. Strategies that allow for enhancement of systemic delivery efficiency as well as augmentation of therapeutic response by lowering tumor apoptotic threshold can have a profound impact in the management of cancer. In this study, we have examined co-administration of etoposide and curcumin using nanoemulsion formulations that can aid in enhancing delivery efficiency to the tumor mass. The oil-in-water nanoemulsion can also solubilize hydrophobic compounds, such as etoposide and curcumin, and allow for efficient intracellular delivery.

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