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Research Article

Formulation and Optimization of Liquisolid Compact for Enhancing Dissolution Properties of Polyphenol Stilbenoid- Resveratrol

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Abstract

Resveratrol is a class II drug in the Biopharmaceutics Classification System (BCS) with poor water solubility (0.03 mg/ml) and high permeability. Liquisolid system is an innovative technique used for enhancing dissolution rate and bioavailability of poorly soluble drugs. The present study demonstrated that Resveratrol loaded SNEDDS and Liquisolid compacts were successfully developed. Ten SNEDDS formulation were formulated with different ratio oil, surfactant and co-surfactant. Out of ten formulations four were selected based on dilution and self-emulsification time. Out of four formulations F4 formulation showed smaller particle size than compared with other formulations. Characterization was done for particle size, polydispersity index and zeta potential was found to be 22.03nm, 0.281 and -1.20Mv respectively. Morphology was found to in spherical shape with the size range of 10-40 nm. *In-vitro* studies showed that formulation F4 has better release of 90.09% compared to drug in solution of 39.62%. F4, F5, F6 and F9 formulations were selected and converted into Liquisolid compacts using adsorbents Neuslin and Fuji calin and total eight formulations were formulated and Liquisolid compacts made of formulation F4 of Neuslin was found to be better release of 93.53% compared to formulation F4 of Fuji calin. Hence from our study it showed that Neuslin showed better drug release than Fuji Calin and Neuslin can be used to improve solubility and dissolution of poorly water soluble drugs.

Keywords: Resveratrol, Self-nanoemulsifying drug delivery systems, Liquisolid compacts, Characterization, Neuslin, Fuji calin.

INTRODUCTION

Bioavailability of a drug depends on its solubility in gastrointestinal fluids and its permeation across biological membranes. For a drug to be absorbed it must be in solution. So, solubility is the most important parameter for orally administered drugs. The improvement of drug solubility remains one of the most challenging aspects of drug development process. About 40 % of the newly developed drugs are insoluble in water[1]. Numerous conventional and modern approaches like solid dispersions, use of surfactants, inclusion complexes and nanonization are used to improve the solubility of these drugs. Liquisolid technique is one of the most promising approaches for solubility enhancement of poorly soluble drugs. Resveratrol, a natural polyphenol derived from plants, such as Polygonum cuspidatum, grape, peanut and mulberry[2], has a wide range of pharmacological activities, including anticancer, antioxidant, anti-inflammatory and antineuralgic[3-7], thus, it has attracted the attention of researchers. However, Resveratrol is a class II drug in the Biopharmaceutics Classification System (BCS) with poor water solubility (0.03 mg/ml) and high permeability[2]. Accordingly, improving the solubility of Resveratrol is a top priority. Self-nanoemulsifying drug delivery systems (SNEDDS) are isotropic mixtures of oils, hydrophilic emulsifiers and co-emulsifiers. SNEDDS possess thermodynamic stability and are spontaneously emulsified into droplets of size in the range of 10-100 nm under slight stirring[8]. The SNEDDS is used for the improvement of the bioavailability of poorly soluble drugs based on high stability, low viscosity and simple preparation[9-11]. There are many studies on the use of SNEDDS as carrier of poorly soluble drugs. Compared with the total flavones of Hippophae rhamnoides L. (TFH), the TFH SNEDDS significantly enhances the solubility of the TFH up to 530 times in water, and its relative bioavailability is dramatically improved 3.09 times[12]. Wu X et al. also reported that the SNEDDS improved the water solubility of curcumin, increasing the relative oral bioavailability of the SNEDDS by 12.13 times compared with pure curcumin[13]. Compared with pure Resveratrol, the Resveratrol SNEDDS exhibited excellent antioxidant activity and less toxicity[10]. One of the most promising strategies for release enhancement is the Liquisolid compacts (LSC) [14]. Liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. Liquisolid technology is also referred to as powder solution technology[15]. The term Liquisolid medication implies oily liquid drugs and solutions or suspensions of water-insoluble solid drugs carried in suitable nonvolatile solvent systems. Using this new formulation technique, a liquid medication may be converted into a dry-looking, non-adherent, free flowing and compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials[16]. Particles that possess porous surfaces with high absorption properties may be used as the carrier material. The increasing moisture content of carriers results in decreased powder flowability. The coating material must cover the surface and maintain powder flowability[17]. The liquisolid

tablets that contain water-insoluble drugs are expected to enhance drug dissolution because of the increased wetting properties of the drug particles and the large surface area available for dissolution. The liquisolid tablets are suitable to formulate low-dose water-insoluble drugs[18].

MATERIALS AND METHODS

Materials

Resveratrol was gifted by Sami labs, Bangalore, India. Castor oil, eucalyptus oil, cod liver oil and sesame oil were purchased from Sigma Aldrich, Mumbai, India. Kolliphor EL, Kolliphor HS, Kolliphor RH 40 was purchased from BASF chemicals Pvt Ltd, Mumbai, India. Capmul PG 2 L, Captex 300, Caprol PGE 860, Capmul MCM and Propylene glycol was purchased from Abitec Corporation Ltd, Mumbai. Neuslin US 2, Fuji Calin SG were purchased from Gangwal Chemicals Pvt Ltd, Mumbai. Chloroform and methanol were purchased from Fisher Scientific, India. Deionization (DI) water from the Milli-Q purification system (Millipore Corp., USA) was used throughout the studies. All other chemicals and solvents were used without further purification and were of analytical grades.

Methods

Solubility studies

Solubility of resveratrol was determined by pouring an excess of drug into 1 ml of each vehicles. The mixture was mixed continuously for 2min and then shaken at 100 rpm for 15min. The obtained mixture was centrifuged at 10000 rpm for 10 min. The supernatant was removed and diluted with methanol. The drug content was analysed using UV spectrophotometer.

Construction of ternary phase diagram

Ternary phase diagrams were constructed using essential oils, surfactants and cosurfactants. The selection of these excipients was based on the solubility study of Resveratrol. Series of self-emulsifying systems was prepared in the formula with varying concentrations of oil surfactant), co-surfactant at room temperature (25 ◦ C). For any mixture, the total of surfactant, co-surfactant and oil concentration added was always 100%. Ten of such mixtures with varying concentrations were prepared in this investigation. Ternary phase diagrams were constructed in the absence of Resveratrol calcium to identify the self-emulsifying regions. The phase diagram was plotted using CHEMIX ternary plot software.

Determination of λmax

Determination of absorption maxima

A solution of Resveratrol containing the concentration 40µg/ml was prepared in 7.4 pH phosphate buffer. UV spectrum was taken using double beam UV/VIS spectrophotometer (Shimadzu UV-1800). The solution was scanned in the range of 200-400nm[19, 20].

Preparation of standard calibration curve

100mg of drug was accurately weighed and dissolved in 100ml phosphate buffer pH 7.4 in 100 ml volumetric flask, to make (1000µg/ml) standard stock solution and then final concentrations were prepared 5-100µg/ml with phosphate buffer pH 7.4. The absorbance of standard solution was determined using UV/VIS spectrophotometer (Shimadzu UV-1800) at 306nm. Linearity of standard curve was assessed from the square of correlation coefficient (r^2) which determined by least-square linear regression analysis.

FT-IR Spectroscopy

FTIR spectra are recorded with JASCO 4100 model spectrophotometer equipped with ATR. Infrared spectroscopic analysis was performed to check out the compatibility between the selected carriers, drug and mixtures IR spectrum of the pure drug and the physical mixtures of drug with polymers of optimized formulation were studied.IR spectra was compared and checked for any shifting in functional peaks and non-involvement of functional group. The samples were studied using FTIR JASCO 4100 in the wave number range from 500 to 4,000 cm^{-1}.

Formulation of SNEDDS

The desired component ratios of SNEDDS were selected for drug incorporation. Twenty five milligram of drug and mixed surfactant and co-surfactant were incorporated in their determined ratios into oil phase containing drug. Finally homogeneous mixture was obtained by vortex mixing. The prepared SNEDDS was kept in a tightly closed bottle at 25°C and from these the stable formulations were subjected to further study i.e. dilution studies, droplet size analysis, self-emulsification time, particle size analysis and zeta potential analysis.

Optimization of SNEDDS

Formulation was optimized using Quality by design (QbD) and the design chosen was 2^3 full factorial designs with 2 intermediate points and the ratio of oil, surfactant and cosurfactant was set.

Table 1: Different ratios of oil, surfactant and co-surfactant used in the formulation

S. NO	Drug(mg)	Oil%	Surfactant %	Co-surfactant %
1.	10	30	60	10
2.	10	40	40	20
3.	10	50	30	20
4.	10	25	55	20
5.	10	30	50	20
6.	10	50	45	5
7.	10	60	35	5
8.	10	60	30	10
9.	10	45	45	10
10.	10	40	50	10

Characterization of formulations

Self-emulsification time

Self-emulsification time is the time required by the pre concentrate to form a homogeneous mixture upon dilution, when disappearance of SNEDDS is observed visually. The efficiency of self-emulsification of SNEDDS was assessed by using a standard USP XXII dissolution apparatus. One ml of each formulation was added drop wise to the medium (900 ml of water with a paddle speed of 100 rpm at 37.0 ± 0.5 ◦ C) by a dropping pipette and the time required for the disappearance of the SNEDDS was recorded. The efficiency of self emulsification was visually assessed.

Dilution test

It was studied by diluting 100, 150 and 200 times with water. The diluted samples were stored for 24 h and observed for any signs of phase separation or precipitation.

Particle size analysis

The particle size of the selected formulation was determined by Malvern Zeta Sizer Nano Series ZS90. The polydispersity index reflects the uniformity of particle diameter and it can be used to depict the size distribution of nanoemulsion. The sensitivity range was 10 nm to 5 m and the data shown by computer calculation using the Mie equations of light scattering. The measurements were performed at 25 ◦ C at a fixed angle of 90 ◦ C.

Zeta potential analysis

The nano emulsion stability is directly related to the magnitude of the surface charge. The zeta potential of the selected formulations was determined by laser diffraction analysis using particle size analyser. The samples were diluted with a ratio of 1:100 (v/v) with distilled water and mixed for 1 min using a magnetic stirrer. All studies were repeated in triplicate.

In vitro drug release study

The release profile study of Resveratrol SNEDDS was performed using the dialysis bag method according to dissolution apparatus II in USP 24. Resveratrol SNEDDS was instilled in to the dialysis bag (Dialysis Membrane-110 (Mol. Weight12, 000–14,000)). This was firmly sealed with dialysis clamp and was placed in 250 ml, pH 7.4 of phosphate saline buffer as the dissolution medium at 37oC. The revolution speed of the paddle was maintained at 100 rpm. The samples (5 ml) were drawn at predetermined time intervals, and replenished with the same volume of fresh dissolution medium. The release of Resveratrol from SNEDDS formulation was noted and percentage release was calculated. . The drug content in the samples was assayed using UV-spectrophotometer.

Transmission electron microscopy (TEM)

The morphology of SNEDDS was observed by transmission electron microscopy. SNEDDS was diluted with distilled water and sonicated and mixed by slightly shaking. One drop of diluted samples was deposited on a film-coated 200 mesh copper specimen grid and allowed to stand for 4 to 5 days, after which any excess fluid was removed with the filter paper and was examined with the transmission electron microscope.

Conversion of liquid SNEDDS to Liquisolid compacts using adsorbents

The prepared formulation was converted into Liquisolid compacts by using adsorbents namely Neuslin US2 and Fuji Calin SG 2.1ml of formulation each (F4, F5, F6 and F9) was added separately to 1.0g of Neuslin US 2 and mixed and 0.5 g of microcrystalline cellulose, 0.5 g of lactose was added to get solid powder. 1ml of formulation each (F4, F5, F6 and F9) was added separately to 1.5g Fuji Calin SG 2 and mixed.0.7 g of microcrystalline cellulose and 0.7 g of lactose was added and mixed to get solid powder. Obtained powders four from Neusilin US 2 and 4 from Fuji Calin SG 2 was converted into Liquisolid solid by punching it into tablets.

Evaluation of Liquisolid compacts[21, 22]

Weight variation

Tablets were randomly selected and individually weighed. The average weights of tablets were calculated. Then tablets were individually weighed. Average weight and individual weight of tablets were compared and percentage weight variation of individual tablet should fall within specified limits in terms of percentage deviation from mean.

Hardness

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Tablets from each formulation were tested for hardness.

Disintegration time

The disintegration time of the tablets was measured in distilled water (°C) using disintegration test apparatus with disk. Five tablets from each formulation were tested for the disintegration time calculations.

In-Vitro drug release study

The in vitro drug release study of the tablets was performed using USP type II apparatus paddle at 37°C ± 0.5°C using phosphate saline buffer pH 7.4 (900 ml) as a dissolution medium and 50 rpm. At the predetermined time intervals, 10 ml samples were withdrawn and replaced with fresh dissolution media. Withdrawn samples diluted, and assayed at 306 nm using a Shimadzu UV- spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a calibration curve.

RESULTS AND DISCUSSIONS

The solubility of RES was determined in various essential oils, surfactants and cosurfactants by pouring an excess of drug into1 ml of each vehicles. The obtained mixtures were mixed continuously for 2 min using cyclo mixer. The mixtures were shaken (100 rpm) for 24 h at 25 ◦ C in a thermostatically controlled shaking water bath followed by equilibrium for12 h. The equilibrated samples were removed and centrifuged at10, 000 rpm for 5 min. The supernatant solution was taken and filtered through a Millipore membrane filter and then suitably diluted with methanol. The concentration of Resveratrol was determined using UV Spectrophotometer. Solubility studies on various oils, surfactants, co-surfactants revealed that Resveratrol was more soluble in Kolliphor RH 40 in surfactant, propylene glycol in co-surfactants and eucalyptus oil in oils as shown in the Tables 2. Based on the data obtained from the solubility study, eucalyptus oil was used as oil phase. Kolliphor RH 40 was used as surfactants and propylene glycol was used as co-surfactants for constructing different phase diagram in order to identify the best self emulsifying region. It was found that increase in surfactant increases the emulsion forming capacity and particle size was found to be less in it. Surfactant concentration with 45-55%, oil with 30-50% and co-surfactant with 5 -20% an ideal emulsion and particle size for this ratio was found to be between 20-1000 nm as shown in the Figure 1. λ_{max} of Resveratrol was found to be 306 nm by using U.V. spectrophotometer (Shimadzu UV-1800). The calibration curve of Resveratrol was found to be linear in the

concentration range of 5-100 µg/ml at 306nm Figure 2. FT-IR spectra of drug, selected excipients, and mixtures were analyzed to check the interactions between them. The spectra and major peaks of individual compounds and their combinations are given in the Figures 3 and 4. The spectra showed that there is no interaction between the drug, selected excipients and combinations. Hence, the selected stabilizer was found to be compatible with drug and other components without any mutual interactions. The rate of emulsification was a major index for assessment of the efficiency of self emulsification. The SNEDDS should disperse completely and quickly when subjected to dilution under mild agitation. From the results it was found that formulations F3, F4, F5, and F9 have less emulsification time when compared to other formulations as shown in Table 3. Uniform emulsion formation from SNEDDS is very important at different dilutions because drugs may precipitate at higher dilution in vivo which affects the drug absorption significantly. Different fold dilutions of selected formulations were exposed to different media to mimic the in vivo conditions where the formulation would encounter gradual dilution. Hence, each formulation was subjected to 50, 100,250 times dilution in distilled water. Even after 24 h, formulations F4, F5, F6 and F9 showed no signs of precipitation, cloudiness or separation which ensured the stability of the reconstituted emulsion and the rest of the formulations showed phase separation and turbidity as shown in Table 4. The selected SNEDDS formulations taken for particle size distribution were F4, F5, F6 and F9. Smaller particle size of the emulsion droplets may lead to more rapid absorption and improve bioavailability. The particle size distribution of the selected formulations was 22.03 nm, 939.50 nm, 99.16 nm, and 33.58 nm respectively. The polydispersity index (PDI) of F4, F5, F6 and F9 was found to be 0.281, 1.00, 0.973 and 0.354 respectively. Selected SNEDDS formulations F4, F5, F6 and F9 were taken for zeta potential analysis. Formulations having high zeta potential will confer stability, i.e. the solution or dispersion will oppose aggregation and charge interactions are governed by zeta potential. Zeta potential of the selected formulations F4, F5, F6 and F9 were -1.20 mV,-0.632 mV, - 0.0674m V and-1.10 mV respectively. Out of four formulations, F4 formulation showed smaller particle size than compared with other formulations. Particle size, polydispersity index and zeta potential of F4 was found to be 22.03 nm, 0.281 and -1.20Mv respectively Figure 5&6. The in vitro drug release studies of the formulations were performed in 250 ml, pH 7.4 phosphate saline buffer. The release pattern of SNEDDS reveals that the maximum drug release was observed with F4 formulation with 90.09% and least for the formulation F10 with 60.76.other formulation which showed better release after formulation F4 was formulations F6, F5 with 80.18% and 80.16% respectively and resveratrol which has low solubility in water and buffer gave percentage release of 33.61% and 39.62% percentages respectively which was compared with formulation F4 having highest release 90.09% of as shown in the tables and Figure 7. F4 formulation of SNEDDS was viewed under Transmission electron microscopy. The formulation F4 was mixed with distilled water in the ratio of 1:4 and mixed and dried for 3 days and viewed under transmission electron microscopy and are in the range of 10-50nm and the optimized formulation F4 was found to be nanosized. TEM images of resveratrol loaded SNEDDS at 100 nm are shown in the Figures 8. Hardness of all the formulations 4 using Neuslin and 4 using Fuji Calin as adsorbents was in the range of 3.5±0.71 to 4.5±0.71 (kg/cm^2) which is well within the limit. Disintegration time of Liquisolid compacts using Neuslin as adsorbent was found to be in the range of 3.4±to 5.8±0.14 which is well within the limit. Disintegration time of formulation F9N was greater among formulations using Neuslin as adsorbents and for formulations using adsorbents Fuji Calin disintegration time was in the range of 1.2±0.14 to 4.1±0.35. Weight variation was in the range of 99.5±0.71 to 103±4.24 which was well inside the limit as shown in the Table 5. In-vitro dissolution study was done for both Liquisolid compacts with Neuslin and Fuji Calin adsorbents for formulations F4, F5, F6 and F9. As shown in the table, in-vitro dissolution study of liquisoild compacts with Neuslin showed that F4 formulation showed more release compared to other formulations with about 93.53 % release. F5, F9, F6 formulations showed 79.62%, 54.53%, 74.09 % release respectively. F6 formulation showed less percentage release then others as shown in the Table 6. In-vitro dissolution study of Resveratrol loaded liquisolid using Fuji Calin as adsorbent was done for formulation F4, F5, F6 and F9. It was found that formulation F4 was having more release than other formulations with 80.30%. Least release was recorded for formulation F6 with 64.62%. Other formulations F5 and F6 showed intermediate release as shown in the Table 7.

Table 2: Solubility of resveratrol in oils, surfactants, co-surfactants

Oil	Concentration (mg/ml)
Olive oil	40
Castor oil	40
Cod liver oil	40
Lin seed oil	40
Sesame oil	40
Eucalyptus oil	60
Surfactants	
Captex300	40
CaprolPGE860	40
Capmul PG2L	40
Kolliphor EL	190
KolliphorRH40	190
KolliphorHS15	190
Co-surfactant	
Propylene Glycol	80
Capmul MCM	40

Table 3: Self emulsification time of resveratrol loaded SNEDDS for different formulations

S .No.	Formulations	Time (secs)
1	F1	57
2	F2	45
3	F3	42
4	F4	31
5	F5	43
6	F6	98
7	F7	46
8	F8	44
9	F9	40
10	F10	46

Table 4: Dilution studies of Resveratrol loaded SNEDDS for different formulation

S .No.	Formulations	Appearance
1	F1	Turbid
2	F2	Turbid
3	F3	Turbid
4	F4	Clear
5	F5	Clear
6	F6	Clear
7	F7	Turbid
8	F8	Turbid
9	F9	Clear
10	F10	Turbid

Table 5: Hardness, disintegration and weight variation of liquisolid compacts

Formulation code	Hardness (kg/cm^2)	Disintegration (min)	Weight variation (mg)
F4N	4.5±0.71	3.4±0.15	101.5±2.12
F5N	4.5±0.70	5.8±0.14	99.5±0.71
F6N	4.5±0.71	4.15±0.07	103±4.24
F9N	4.5±0.71	5.6±0.21	102±2.82
F4F	3.5±0.71	4.1±0.35	101±1.42
F5F	3.5±0.71	1.5±0.21	110.5±2.12
F6F	3.5 ±0.71	1.2±0.14	100.5±3.54
F9F	3.5± 0.71	2.4±0.28	103±2.80

Table 6: in-vitro dissolution of resveratrol loaded liquisolid compacts using neuslin as adsorbent

TIME (min)	F4N %	F5N %	F6N %	F9N %
0	0	0	0	0
5	19.72±1.80	15.39±0.57	11.84±0.79	17.06±3.38
10	30.88±0.86	23.54±1.63	17.59±1.61	26.47±1.80
15	45.11±1.10	37.26±1.46	28.91±6.08	40.3±1.32
30	68.39±1.51	61.84±0.35	43.54±8.64	57.79±0.99
45	85.04±1.32	79.62±1.22	54.53±3.19	63.89±2.35
60	93.53±1.64	86.12±2.64	71.25±5.35	74.09±3.15

Table 7: in-vitro dissolution of resveratrol loaded liquisolid compacts using Fuji Calin as adsorbent

TIME (min)	F4F %	F5F %	F6F %	F9F %
0	0	0	0	0
5	10.835±0.72	10.32±1.25	7.615±1.19	11.57±1.12
10	20.44±1.24	19.95±2.43	15.19±1.56	23.575±1.74
15	33.67±1.05	27.39±0.71	24.08±2.04	25.78±1.79
30	46.555±0.97	46.615±1.76	33.97±0.42	38.36±2.43
45	62.36±1.43	59.955±0.45	43.835±1.49	57.9±1.85
60	80.305±0.88	74.265±0.73	64.62±1.64	71.03±2.55

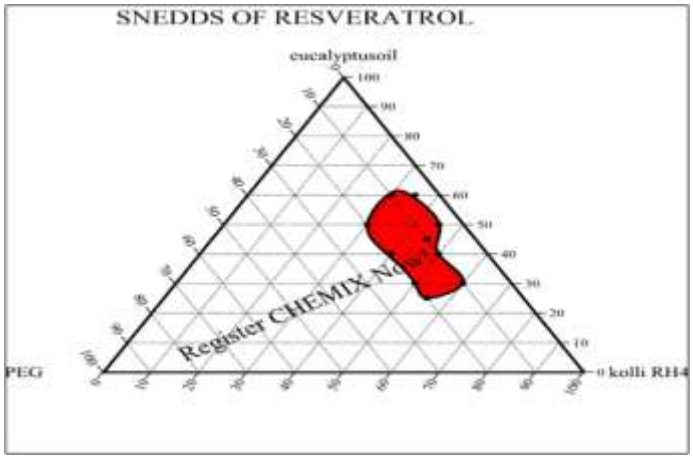

Figure 1: Ternary phase diagram of SNEDDS of resveratrol

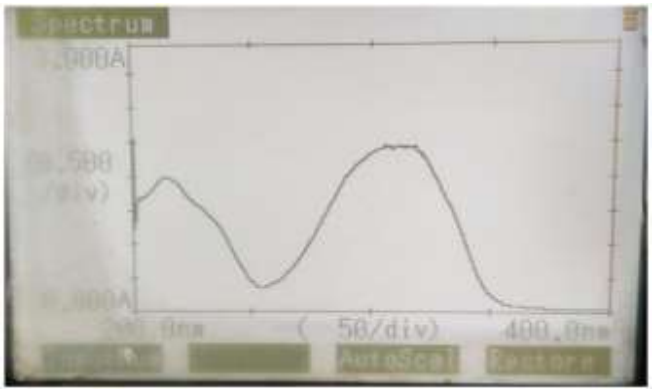

Figure 2: Lambda maxima of Resveratrol

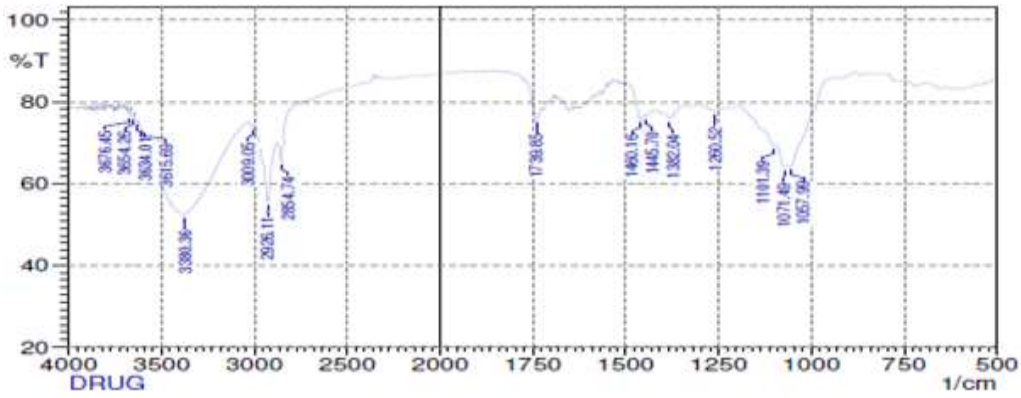

Figure 3: FT-IR spectra of drug

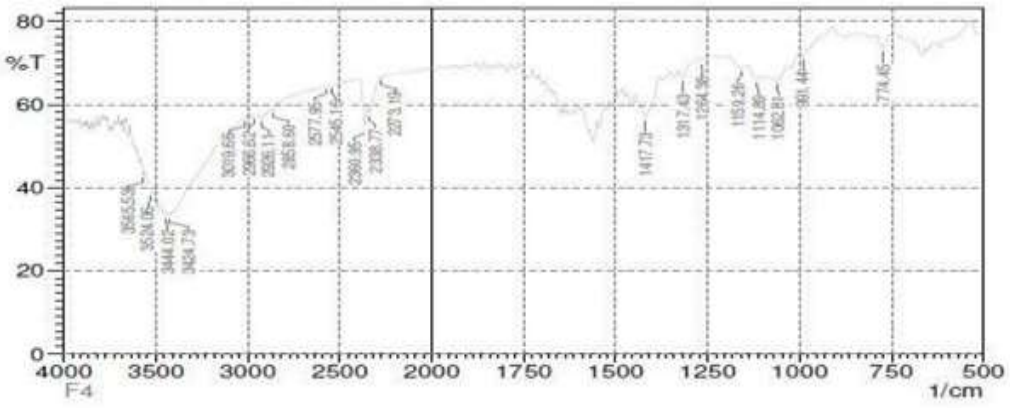

Figure 4: FT-IR spectra of formulation F4

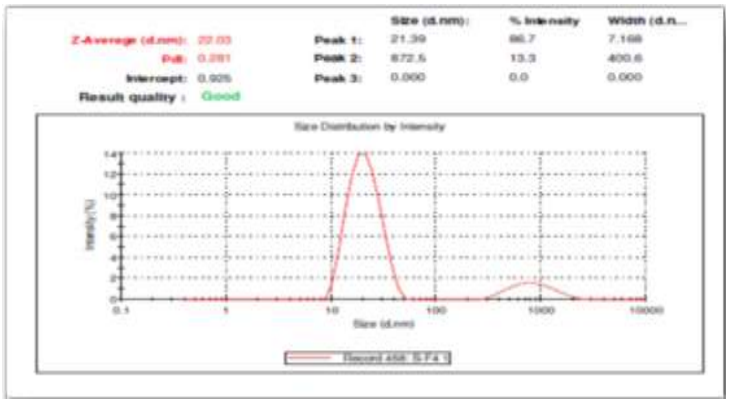

Figure 5: Particle size distribution of formulation F4

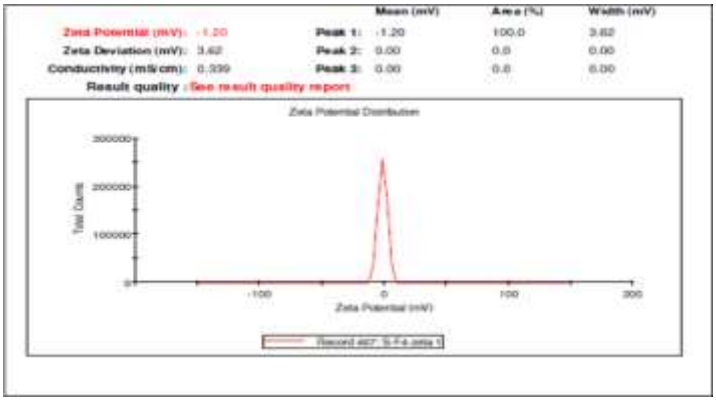

Figure 6: Zeta potential of formulation F4

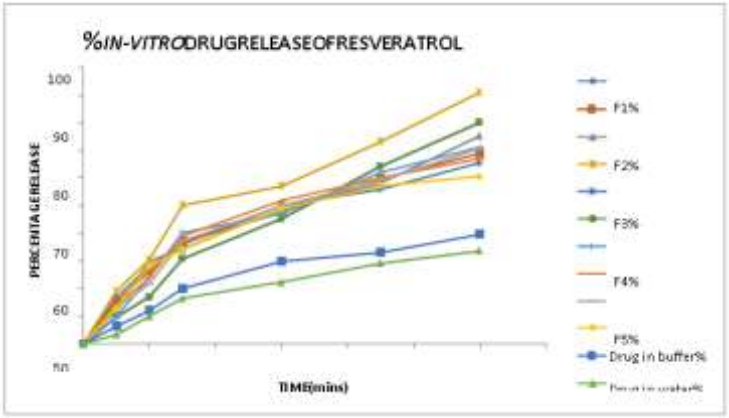

Figure 7: In-vitro drug release of resveratrol loaded SNEDDS for different formulations

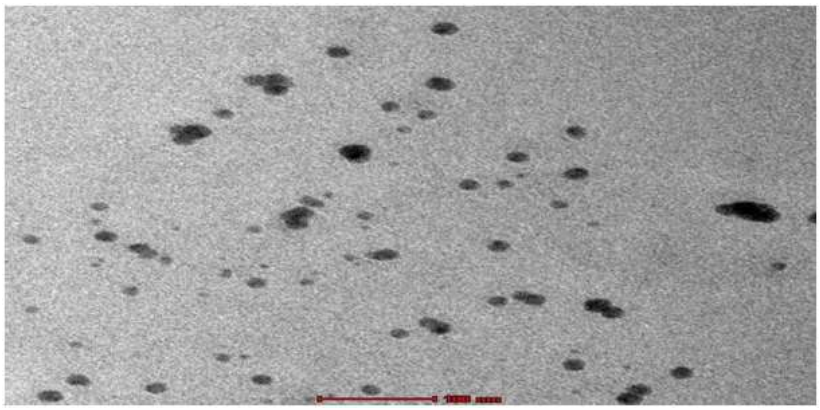

Figure 8: Transmission electron microscopy of resveratrol loaded SNEDDS at 100 nm

CONCLUSION

The results showed that the Liquisolid technique could be adopted as a new tool to produce promising resveratrol compacts containing Neuslin. Out of four formulations F4 formulation showed smaller particle size than compared with other formulations. Characterization was done for particle size, polydispersity index and zeta potential was found to be 22.03 nm, 0.281 and -1.20Mv respectively. Morphology was found to in spherical shape with the size range of 10-40 nm. In-vitro studies showed that formulation F4 has better release of 90.09 % compared to drug in solution of 39.62 and Liquisolid compacts made of formulation F4 of Neuslin was found to be better release of 93.53% compared to formulation F4 of Fuji Calin. Hence from our study it showed that Neuslin showed better drug release than Fuji Calin and Neuslin can be used to improve solubility and dissolution of poorly water soluble drugs.

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