International Journal of Pharmacy and Biological Sciences-IJPBS™ (2019) 9 (3): 587-598
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved
UGC Approved Journal

Formulation and Evaluation of Vitamin D_3 (Cholecalciferol) Self-Nanoemulsifying Drug Delivery Systems for Enhancing Solubility

Syed Umar Farooq[1*], D Sudheer Kumar [1] and Abdul Azeez Shahid[2]
[1*]Research scholar. Department of Pharmaceutics Singhania University pacheri bari, Jhun Jhunu, Rajasthan.
[1]Professor Department of Pharmaceutics Care College of Pharmacy
[2]Research scholar Department of Pharmacy Singhania University, jhun jhunu, Rajasthan.

Received: 10 Mar 2019 / Accepted: 9 Apr 2019 / Published online: 1 Jul 2019
***Corresponding Author Email:** suf.pharmacist@gmail.com

Abstract
A self-nanoemulsifying drug-delivery system (SNEDDS) improves the solubility and dissolution profile of poorly soluble drugs. Different formulations were prepared using different oils, surfactants and co-surfactants. A pseudo ternary phase diagram was constructed to identify the self-micro emulsification region. Further, the resultant formulations were investigated for clarity, phase separation, drug content, % transmittance, globule size, freeze-thaw, in vitro dissolution studies, particle size analysis and zeta potential. On the basis of particle size, zeta potential and dissolution profile and other studies, (D29) was found to be the best formulation of Vitamin D_3SNEDDS. The particle size of the emulsion is a crucial factor in self emulsification performance because it determines the rate and extent of drug release as well as absorption. The average particle size of Vitamin D_3SNEDDS for transparent micro-emulsions should be less than 100nm. The particle size of the optimized SNEDDS formulation was found to be 51.2 nm and zeta potential was found to be -12.6 mV which comply with the requirement of the zeta potential for stability. The faster dissolution from SNEDDS may be attributed to the fact that in this formulation, the drug is a solubilized form and upon exposure to dissolution medium results in small droplet that can dissolve rapidly. The % release from optimized SNEDDS formulation D29 was highest (99.72%) and faster than Vitamin D_3 Capsule (63.29%) and other SNEDDS formulations indicating influence of droplet size on the rate of drug dissolution. Thus, Vitamin D_3 with SNEDDS formulation may be used for the improvement of solubility and dissolution rate.
Keywords
self-nanoemulsifying drug-delivery system, SNEDDS

*****

INTRODUCTION
Drugs with poor solubility are difficult to formulate by applying conventional approaches as they pose problems such as slow onset of action, poor oral bioavailability, lack of dose proportionality, failure to achieve steady state plasma concentration, and undesirable side effects, thus resulting in over or under medication and poor patient compliance (Patwekar et al., 2012). These challenges can be overcome by applying self-nanoemulsifying systems

that offer benefits like reduction in dose frequency, lowering of dose size, site specific targeting, enhanced permeability, and improvement in oral bioavailability. Nanotechnology is a promising strategy in the development of drug delivery systems especially for those potent drugs whose clinical development failed due to their poor solubility, low permeability, inadequate bioavailability, and other poor biopharmaceutical properties (Sharma et al., 2016). SNEDDS formulations for poorly water-soluble drugs have shown considerable increase in solubility and bioavailability (Rajanikanth et al., 2012).

Vitamin D_3 plays an important role in human nutrition. It regulates the absorption, metabolism and excretion of calcium and phosphorus from the intestine and kidneys. Further it controls the incorporation of calcium and phosphorus in the skeleton. It is common a fat-soluble agent that, in its pure form, it is oxidation-sensitive substance. Furthermore, a fine dispersion of the agent is advantageous for optimal absorbability and thus bioavailability. These substances are therefore often supplied in the form of emulsions or in the dry powders or as solution in physiologically tolerated oil or embedded in fine dispersion in a protective colloid. All of these methods have common drawbacks such as rapid deformation and disintegration due to heat or physical force and also due to aqueous solution employed. Recently soft gelatin capsules containing vegetable oil solution of active vitamin D_3 also developed. But soft capsules have their drawbacks.

So an attempt will be made to produce an efficient formulation of SNEDDS which will be stable throughout its shelf life, dispersible in aqueous solutions in GIT and overcomes the above mentioned drawbacks.

MATERIALS AND METHODS

Vitamin D_3 was obtained as a gift sample from Aurobindo Pharma Limited, Hyderabad. Tween 40, Tween 80 were procured from Oxford lab chemicals Pvt. Ltd, Mumbai, India. Span 60 and Span 80 were obtained from Qualikems Chemicals Pvt. Ltd, Gujarat, India. PEG 400 and PEG 600 were obtained from Oxford lab chemicals Pvt. Ltd, Mumbai, India. Sunflower oil, Clove oil, Castor oil, Olive oil, Eucalyptus oil, cotton seed oil, Emu oil, Sesame oil, Sunflower oil and Coconut oil were procured from Research lab fine chemicals.

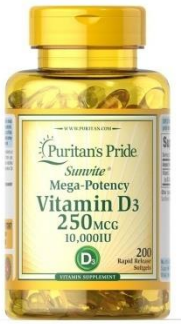

Figure 1: Marketed Vitamin D_3 Soft gelatin Capsules used for comparative studies

METHODS

SOLUBILITY STUDIES

The solubility study was used to find out the suitable oil, surfactant and co-surfactant that possess good solubilizing capacity for Vit D. An excess amount (500mcg) of Vitamin $D_3$was added into 2 ml of each excipient (clove oil, emu oil, castor oil, olive oil, eucalyptus oil, sesame oil and cotton seed oil). Surfactants – (Span 60, Span 80, Tween 40, and Tween 80). Co-surfactants (PEG 400 and PEG 600) and kept in mechanical shaker for 24hrs and centrifuged at 10,000 rpm for 20 min using a centrifuge. Supernatant was filtered through membrane filter using 0.45µm filter disk. Filtered solution was appropriately diluted with methanol, and UV absorbance was measured at 320 nm. Concentration of dissolved drug was determined spectrophotometrically (Patel et al., 2011).

PSEUDOTERNARY PHASE DIAGRAM

To determine the concentration of components for the existing range of SNEDDS, pseudo ternary phase diagram was constructed using water titration method at ambient temperature (25^0C). Surfactant and co-surfactant (Smix) in each group were mixed in different volume ratio (1:1, 2:1, 3:1). Oil and surfactant/co-surfactant mixture (Smix) were mixed thoroughly in different volume ratios 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1) w/w for all the three Smix ratios 1:1,2:1, 3:1. The mixture of oil, surfactant and co-surfactant at certain ratios were titrated with water by drop wise addition under gentle agitation. Deionized water was used as diluting medium and added into the formulation. The proper ratio of one excipient to another in the SNEDDS formulation was analyzed. Pseudo ternary plots were constructed using Chemix software (Sermkaew et al., 2013).

VISUAL OBSERVATION

A visual test to assess the self-emulsification properties was modified and used in the present study. With the use of this method, a predetermined

volume of mixture (0.2 ml) was added to 300 ml of water in a glass beaker under stirring and temperature was maintained at 37^{0}C using a magnetic stirrer. The tendency of formation of emulsion was observed. If the droplet spreads easily in water was judged as 'good' and judged as 'bad' when there was milky or no emulsion or presence of oil droplets (Gurjeet et al., 2013).

DEVELOPMENT OF SNEDDS FORMULATION

A series of SNEDDS formulations for Vitamin D_3were prepared based on solubility studies, pseudo ternary phase diagram and visual observation. Here, Olive oil was used as oil phase. Tween 40 and PEG 600 were used as surfactant and co-surfactant respectively. 500mcg of Vitamin $D_3$was added in accurately weighed amount of oil into screw-capped glass vial and heated in a water bath at 40ºC. The surfactant and co-surfactant were added to the oily mixture using positive displacement pipette and stirred with magnetic bar. The formulation was further sonicated for 15mins and stored at room temperature until its use in subsequent studies (Table 1).

Table 1: Formulation of Vitamin D_3liquid SNEDDS

Smix (Surfactant: Co-surfactant)	Oil:Smix	Formulation code	Vit D (mcg) Or 10k IU	Oils (ml)	Surfactants (ml)	Co-surfactant (ml)
1:1	1:9	D1	250	0.2	0.9	0.9
	2:8	D2	250	0.4	0.8	0.8
	3:7	D3	250	0.6	0.7	0.7
	4:6	D4	250	0.8	0.6	0.6
	5:5	D5	250	1	0.5	0.5
	6:4	D6	250	1.2	0.4	0.4
	7:3	D7	250	1.4	0.3	0.3
	8:2	D8	250	1.6	0.2	0.2
	9:1	D9	250	1.8	0.1	0.1
2:1	1:9	D10	250	0.2	1.2	0.6
	2:8	D11	250	0.4	1.06	0.53
	3:7	D12	250	0.6	0.92	0.46
	4:6	D13	250	0.8	0.8	0.4
	5:5	D14	250	1	0.66	0.33
	6:4	D15	250	1.2	0.52	0.26
	7:3	D16	250	1.4	0.4	0.2
	8:2	D17	250	1.6	0.26	0.13
	9:1	D18	250	1.8	0.12	0.06
3:1	1:9	D19	250	0.2	1.35	0.45
	2:8	D20	250	0.4	1.2	0.4
	3:7	D21	250	0.6	1.05	0.35
	4:6	D22	250	0.8	0.9	0.3
	5:5	D23	250	1	0.75	0.25
	6:4	D24	250	1.2	0.6	0.2
	7:3	D25	250	1.4	0.45	0.15
	8:2	D26	250	1.6	0.3	0.1
	9:1	D27	250	1.8	0.15	0.05
4:1	1:9	D28	250	0.2	1.44	0.36
	2:8	D29	250	0.4	1.28	0.32
	3:7	D30	250	0.6	1.12	0.28
	4:6	D31	250	0.8	0.96	0.24
	5:5	D32	250	1	0.8	0.2
	6:4	D33	250	1.2	0.64	0.16
	7:3	D34	250	1.4	0.48	0.12
	8:2	D35	250	1.6	0.32	0.08
	9:1	D36	250	1.8	0.16	0.04

FREEZE THAWING (THERMODYNAMIC STABILITY STUDIES)

The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature variations on SNEDDS formulations.

FREEZE THAWING

The main objective of this study was to evaluate the phase separation and effect of temperature variations on SNEDDS formulations. Formulations were subjected to freeze cycle (-20°c for 2days followed by 40°C for 2days) and stable formulations were further studied. (Gupta et al 2011).

CENTRIFUGATION

Centrifugation was performed at 3000 rpm for 5 minutes. The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies.

% TRANSMITTANCE MEASUREMENT

The percent transmittance of various SNEDDS formulations was measured at 320nm using UV spectrophotometer keeping water as a blank (Chirag et al., 2011).

DETERMINATION OF DRUG CONTENT

SNEDDS equivalent to 200mcg of Vitamin D_3were weighed accurately and dissolved in 100 ml 0.1N Hcl. The solution was filtered, diluted suitable and drug content was analyzed at λ_{max} 235 nm against blank by UV spectrophotometer. The actual drug content was calculated using the following equation as follows:

$$\% \text{ Drug content} = \frac{\text{Actual amount of drug in SNEDDS}}{\text{Theoretical amount of drug in SNEDDS}} \times 100$$

***IN – VITRO* DISSOLUTION STUDIES**

The release of drug from liquid SNEDDS formulations and pure drug was determined using a US Pharmacopoeia Type II dissolution apparatus. SNEDDS of Vitamin D_3 (equivalent to 75 mg of Drug) was filled in size "0" hard gelatin capsules. The dissolution media is 0.1N Hcl and temperature of the dissolution medium was maintained at 37^0C operated at 50 rpm. An aliquot of 5 ml was withdrawn at predetermined intervals 2, 5, 10, 15, 20, 25, 30, 45, and 60 min and filtered through 0.45-µm pore size membrane filters. The removed volume was replaced each time with 5 ml of fresh medium. The concentrations were assayed spectrophotometrically at 320nm.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

The Drug Excipient Compatibility Studies were carried out by Fourier Transform infrared spectroscopy (FTIR) method.

FTIR STUDIES

An FTIR-8400S Spectrophotometer (Shimadzu, Japan) equipped with attenuated total reflectance (ATR) accessory was used to obtain the infrared spectra of drug in the isotropic mixtures of excipients. Analysis of pure drug i.e., Vitamin $D_3$and physical mixtures of the drug with the excipients were carried out using diffuse reflectance spectroscopy (DRS)-FTIR with KBr disc. All the samples were dried under vacuum prior to obtaining any spectra to remove the influence of residual moisture. For each the spectrum, 8 scans were obtained at a resolution of 4 cm^{-1} from a frequency range of 400–4000 cm^{-1}.

DETERMINATION OF DROPLET SIZE

The average droplet size of Vitamin D_3SNEDDS formulations were determined by Photon correlation spectroscopy (Malvern Instrument UK) able to measure sizes between 10 and 5000 nm. The selected formulations were diluted with deionized water and placed in an electrophoretic cell for measurement (Vanitha et al., 2013).

DETERMINATION OF ZETA POTENTIAL

The emulsion stability is directly related to the magnitude of the surface charge. In conventional SNEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids. The zeta potential of the diluted SNEDDS formulation was measured using a zeta meter system. The SNEDDS were diluted with a ratio 1:2500 (v/v) with distilled water and mixed with magnetic stirrer. Zeta-potential of the resulting micro emulsion was determined using a Zetasizer. (Vijaykumar et al., 2016)

SCANNING ELECTRON MICROSCOPY

Shape and surface morphology of microspheres was studied using scanning electron microscopy (SEM). The SNEDDS after converting to emulsion were mounted on metal stubs and the stub was then coated with conductive gold with sputter coater attached to the instrument HITACHI, S-3700N.

PERCENT ENTRAPMENT EFFICIENCY

The contents of free drug were separated from nanoemulsion by ultrafiltration at 3500 Da with centrifugation at 3000rpm for 5 to 10 minutes, followed by quantification using HPLC method (Zhongcheng et al., 2016). The Entrapment Efficiency was calculated as follows.

$$\text{Entrapment Efficiency} = \frac{\text{Total amount of drug in SNEDDS}}{\text{Total weight of ingredients in nanoemulsion}} \times 100$$

RESULTS AND DISCUSSION

Table 2: Characterization of Vit D

Characterization of Vitamin D_3						
Density	**Appearance**	**Taste**	**Melting point**	**pH**	**Solubility**	**Loss on drying**
138.5 g/ml	Yellow to Orange liquid or crystals	Bitter	83-86ºC	6	Insoluble in water, Freely Soluble in ethanol, methanol, chloroform, and vegetable oils	4.7 – 6%

Standard graph of Vitamin D_3

Standard graph of Vitamin D_3 in phosphate buffer pH 6.8

Vitamin D_3 (100 mg) was dissolved in small amount of methanol, and make the volume up to 100 mL with buffer pH 6.8, from this primary stock (1mg/ml), 10 ml solution was transferred to another volumetric flask made up to 100 mL with Phosphate buffer pH 6.8. From this secondary stock 0.2, 0.4, 0.6, 0.8 and 1.0 mL was taken separately and made up to 10 mL with phosphate buffer pH 6.8 to produce 2, 4, 6, 8 and 10 respectively. The absorbance was measured at 320 nm using a UV spectrophotometer.

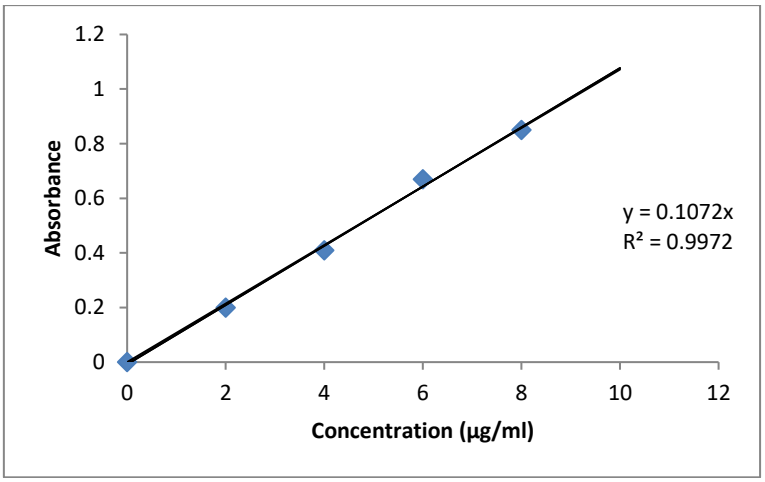

Figure 2: Standard graph of Vitamin D_3 in phosphate buffer pH 6.8

SOLUBILITY STUDIES

Preliminary solubility analysis was carried out to select the appropriate excipient from various (Oils – Clove oil, Cotton seed oil, Olive oil, Sunflower oil, Coconut oil, Castor oil, Eucalyptus oil, Emu oil, Sesame oil and Oleic acid), Surfactants – (Tween 40, Tween 80, Span 60, Span 80), Co-surfactants (PEG 400, 600). Based on drug solubility, Olive oil was used as oil phase Tween 40and PEG 600 were used as surfactant and co-surfactant respectively (Table 3, 4, 5 and Figure 1, 2, 3).

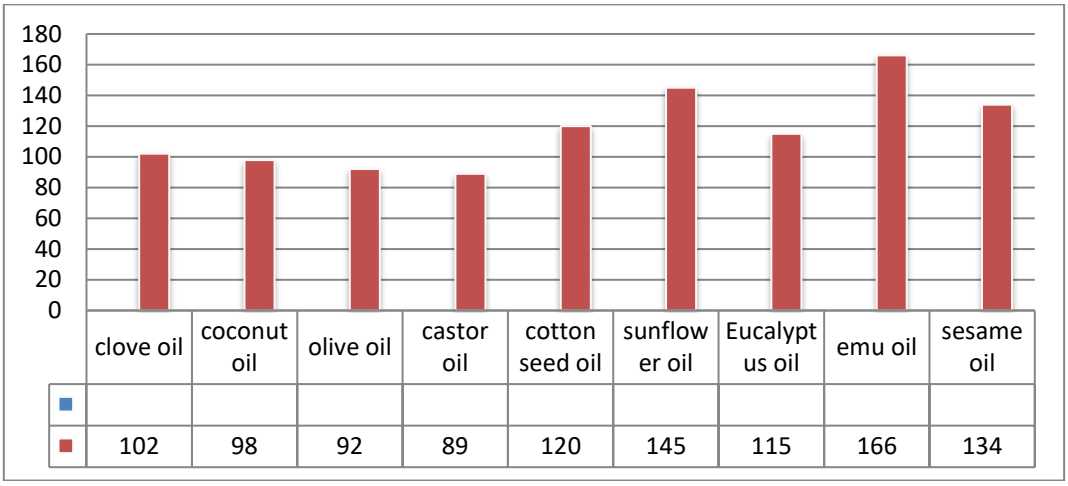

Figure 3: Solubility studies of Vitamin D_3 in oils

Table 4: Solubility studies of Vitamin D_3 in various surfactants

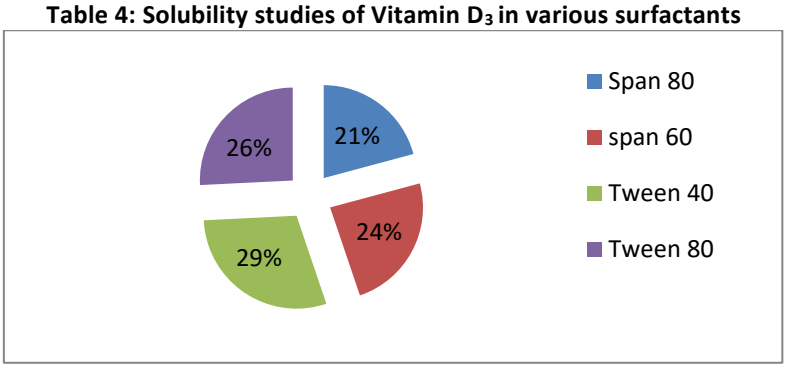

Table 5: Solubility studies of Vitamin D_3 in various co-surfactants

CO-SURFACTANTS	SOLUBILITY (mg/ml)
PEG 400	10.54±1.37
PEG 600	**18.92±2.48**

PSEUDO TERNARY PHASE DIAGRAM

From the solubility studies, olive oil was used as oil phase, Tween 40and PEG 600 were selected as oil, surfactant and co-surfactant respectively. From the phase diagram (Figure 5) it was observed that self emulsifying region was enhanced with increasing concentrations of surfactant and co-surfactant with oil. Efficiency of self-emulsification was good when the surfactant concentration increased.

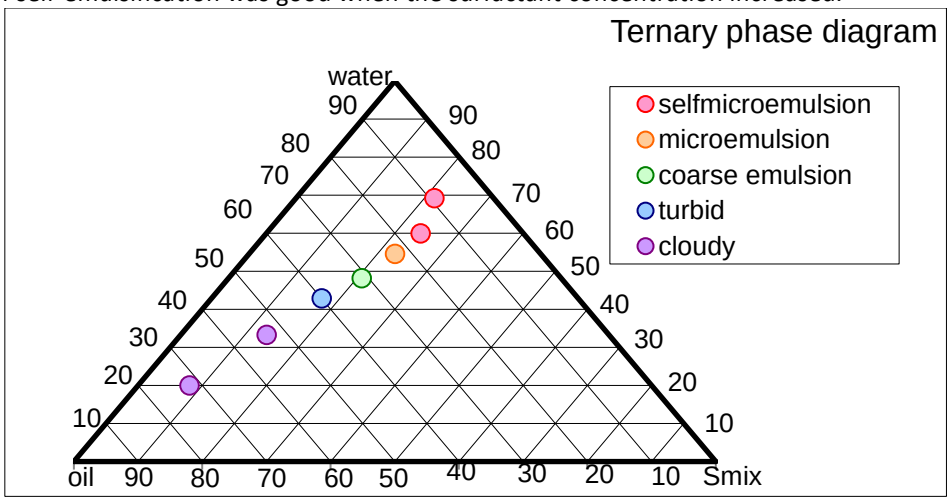

Figure 6: Ternary phase diagram of Olive oil, Tween 40and PEG 600 (D29)

VISUAL OBSERVATION

With the use of visual observation method, the tendency of formation of emulsion was observed. Visual observation test was performed for different ratios by keeping the surfactant and co-surfactant ratio (Smix) as 1:1, 2:1, 3:1 and 4:1. Grades were given to the ratios based on the tendency of formation of micro-emulsion. Ratios 1:9, 2:8, 3:7 and 4:6 of Smix 1:1 and 1:9, 2:8, 3:7 and 4:6 of Smix 2:1 and 1:9, 2:8, 3:7, 4:6 and 5:5 of Smix 3:1 and1:9, 2:8, 3:7, 4:6, 5:5 and 6:4 of Smix 4:1 showed rapid formation of micro emulsion within a minute having a clear appearance. Therefore, these ratios were selected for the formulation of SNEDDS. (Tables 6, 7, 8 and Figures 5, 6)

Figure 7: Visual observation test of optimized formulation (D29)

Table 6: Visual observation test for Smix (Surfactant: Co-surfactant) ratio 1:1

Smix (Surfactant: Co-surfactant) ratio 1:1			Smix (Surfactant: Co-surfactant) ratio 2;1			Smix (Surfactant: Co-surfactant) ratio 3;1			Smix (Surfactant: Co-surfactant) ratio 4;1		
O:S mix	Time of self emuls'n (min)	Grade	O:S mix	Time of self emuls'n (min)	Grade	O:S mix	Time of self emuls'n (min)	Grade	O:S mix	Time of self emuls'n (min)	Grade
1:9	<1	I	1:9	<1	I	1:9	<1	I	1:9	<1	I
2:8	<1	I	2:8	<1	I	2:8	<1	I/ II	2:8	<1	I
3:7	<1	I/ II	3:7	<1	I	3:7	<1	I	3:7	<1	I/ II
4:6	<1	I	4:6	<2	III	4:6	<2	I	4:6	<1	I
5:5	<1	I/ II	5:5	<2	III	5:5	<2	III	5:5	<2	III
6:4	<1	I	6:4	<1	I/ II	6:4	<1	III	6:4	<2	III
7:3	<2	III	7:3	<2	III	7:3	<1	I	7:3	<1	I/ II
8:2	<2	I/ II	8:2	<2	III	8:2	<1	I	8:2	<1	I
9:1	<2	III	9:1	<1	I	9:1	<1	I/ II	9:1	<1	I

THERMODYNAMIC STABILITY STUDIES

No phase separation and effect of temperature variations on prepared formulations were observed during thermodynamic stability studies. There was no change in the visual description of samples after centrifugation freeze-thaw cycles. Formulations which are thermodynamically stable only those were selected for further characterization (Table.9).

Table 10: Thermodynamic stability studies of the formulations

Formulation code	Centrifugation	Freeze thaw method	
		-20°C for 2 days	+40°C for 2 days
D1-D36	No phase separation	No change	No change

% TRANSMITTANCE MEASUREMENT

The clarity of microemulsion was checked by transparency, measured in terms of transmittance (%T). SNEDDS forms o/w microemulsion since water is external phase Formulation (D29) has % transmittance value greater than 99%. These results indicate the high clarity of microemulsion. In case of other systems %T values were less than 99% suggesting less clarity of microemulsion. This may be due to greater particle size of the formulation. Due to higher particle size, oil globules may reduce the transparency of microemulsion and thereby values of %T (Table11).

DRUG CONTENT OF SNEDDS

The drug content of the prepared SNEDDS Maximum % drug content was found to be i.e. 99.21% was found in the formulation D29 (Table 11).

Table 11: Visual observation, % Transmittance and %drug content of different formulations

Code	Visual observation	Transmittance	% Drug content	Code	Visual observation	Transmittance	%Drug content
D1	Transparent	86.28	85.49	D19	Transparent	93.45	90.57
D2	Transparent	90.57	87.54	D20	Transparent	90.21	94.28
D3	Slightly clear	89.26	84.21	D21	Transparent	88.27	91.22
D4	Transparent	91.43	86.70	D22	Slightlyclear	82.16	89.15
D5	Slightly clear	88.41	85.22	D23	Transparent	92.39	94.86
D6	Turbid	75.10	85.36	D24	Turbid	83.11	86.27
D7	Slightly clear	92.22	74.39	D25	Slightly clear	91.26	93.15
D8	Turbid	93.74	81.23	D26	Slightly clear	89.47	87.18
D9	Turbid	81.55	77.21	D27	Turbid	79.53	85.29
D10	Transparent	82.51	96.24	D28	Transparent	97.92	98.23
D11	Transparent	79.26	94.22	D29	Transparent	**99.61**	**99.21**
D12	Transparent	90.56	90.85	D30	Transparent	96.59	97.17
D13	Slightly clear	97.52	91.28	D31	Slightly clear	94.22	97.28
D14	Transparent	96.89	92.33	D32	Transparent	92.31	94.20
D15	Turbid	93.41	89.27	D33	Slightly clear	84.28	86.71
D16	Slightly clear	91.84	90.42	D34	Slightly clear	85.79	91.67
D17	Slightly clear	92.71	91.49	D35	Turbid	80.25	82.03
D18	Turbid	72.18	81.56	D36	Slightly clear	85.69	90.21

***IN-VITRO* DISSOLUTION STUDIES OF SNEDDS**

The faster dissolution from SNEDDS may be attributed to the fact that in this formulation, the drug is a solubilized form and upon exposure to dissolution medium results in small droplet that can dissolve rapidly in the dissolution medium. The release from liquid SNEDDS formulation (D29) was faster and higher than other SNEDDS formulations indicating influence of droplet size on the rate of drug dissolution. (Figure 7, 8, 9 and 10

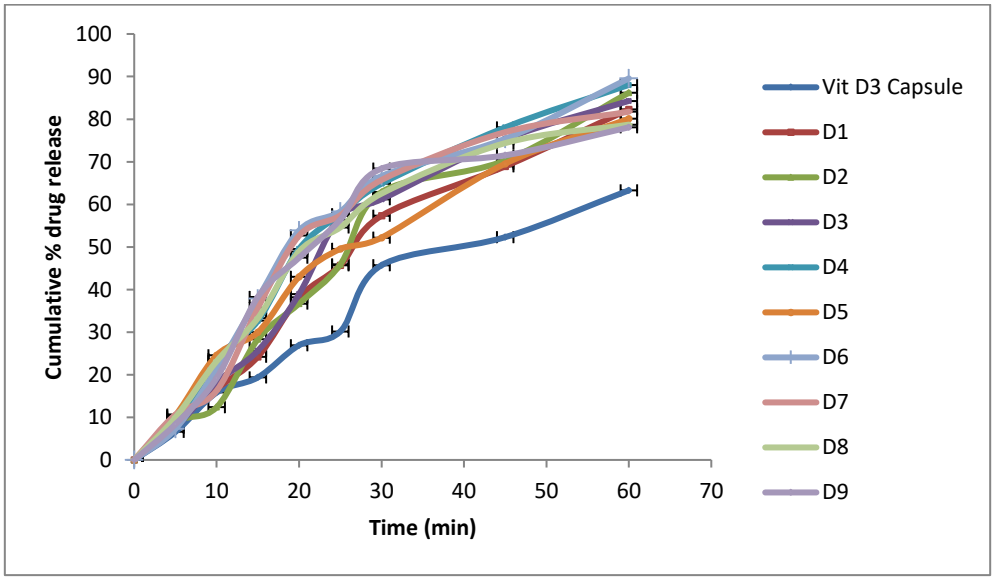

Figure 8: Dissolution profiles of Vitamin D_3formulations (D1 to D9)

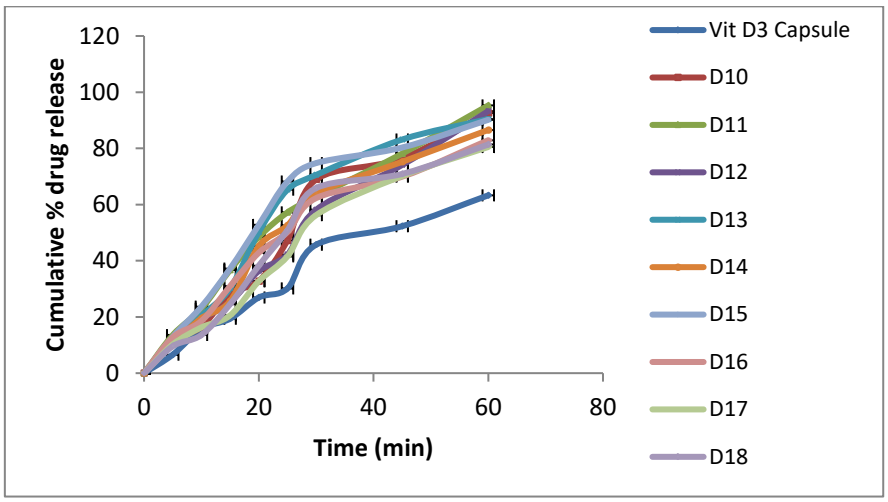

Figure 9: Dissolution profiles of Vitamin D_3 formulations (D10 to D18)

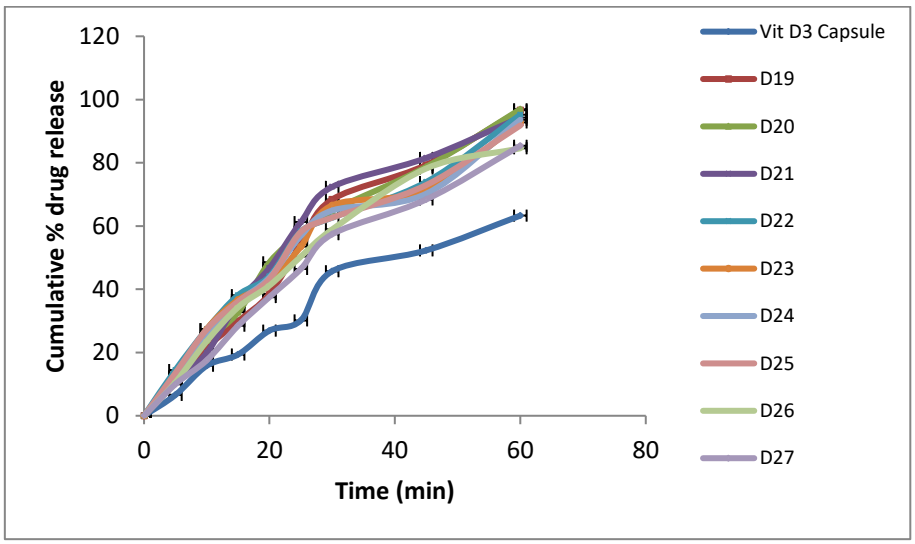

Figure 10: Dissolution profiles of Vitamin D_3 formulations (D19 to D27)

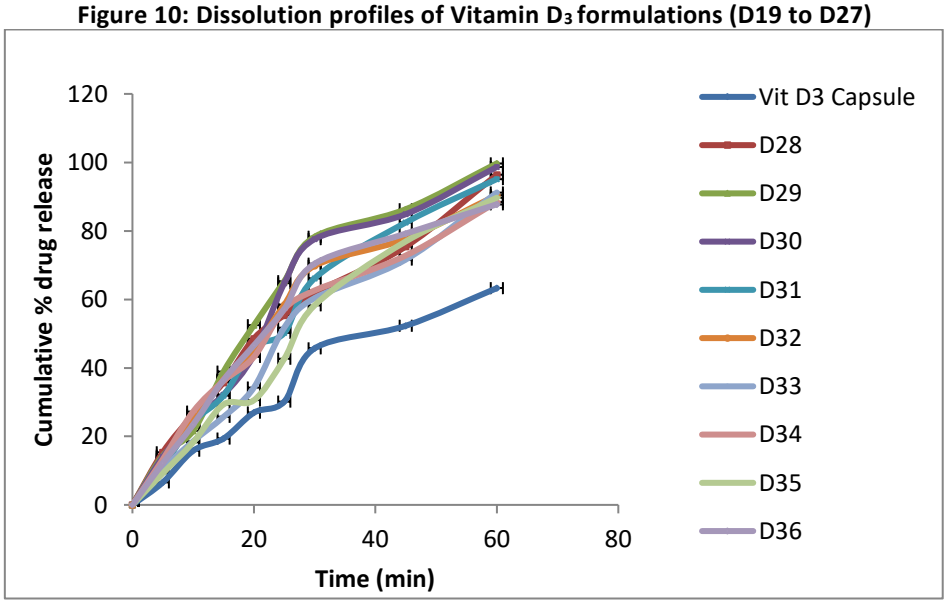

Figure 11: Dissolution profiles of Vitamin D_3formulations (D28 to D36)

PARTICLE SIZE ANALYSIS OF SNEDDS

Droplet size determines the rate and extent of drug release as well as drug absorption. Smaller the particle size, larger the interfacial surface area which may lead to more rapid absorption and improved bioavailability. SNEDDS with a mean droplet size below 200 nm exhibit excellent bioavailability. The particle size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption. The particle size of the optimized SNEDDS formulation (D29) was found to be 51.2 nm & Z-Average of 89.3 nm indicating all the particles were in the nanometer range. (Figure 11).

HORIBA Scientific

HORIBA SZ-100 for Windows [Z Type] Ver2.10

SZ-100

201906111244020.nsz

Measurement Results

Date	: Tuesday, June 11, 2019 12:44:04 PM
Measurement Type	: Particle Size
Sample Name	: LID 3
Scattering Angle	: 90
Temperature of the Holder	: 24.8 °C
Dispersion Medium Viscosity	: 0.898 mPa·s
Transmission Intensity before Meas.	: 16110
Distribution Form	: Standard
Distribution Form(Dispersity)	: Monodisperse
Representation of Result	: Scattering Light Intensity
Count Rate	: 1790 kCPS

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	53.0 nm	2.7 nm	51.2 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	53.0 nm	2.7 nm	51.2nm

Cumulant Operations

Z-Average	:89.3 --- nm
PI	: 5.819---

Molecular Weight Measurement

Molecular Weight	: ---
Parameters for Molecular Weight Calculation	: ---

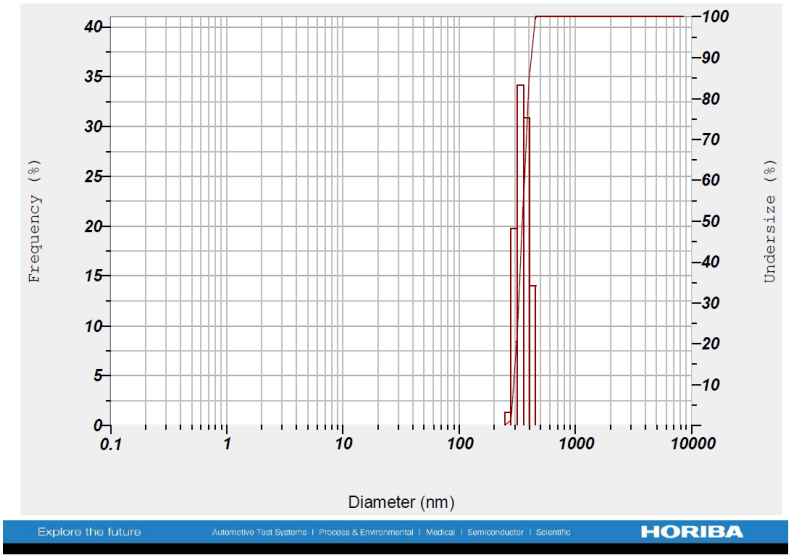

Figure 12: Particle size analysis of optimized formulation D29

ZETA POTENTIAL OF SNEDDS

Zeta potential is responsible for the degree of repulsion between adjacent, similarly charged, dispersed droplets. A zeta potential value of ±30 mV is sufficient for the stability of a micro emulsion. The zeta potential of the optimized SNEDDS formulation (D29) was found to be -12.6mV which comply with the requirement of the zeta potential for stability. (Figure 12)

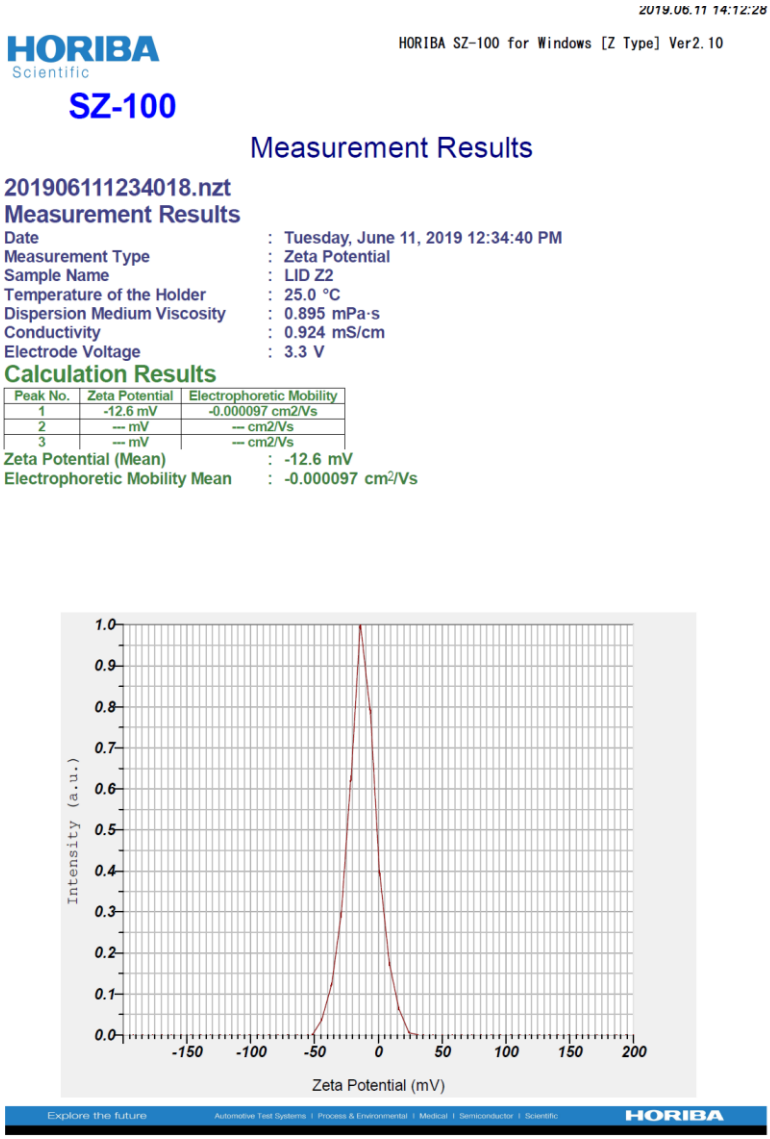

Figure 13: Zeta potential of the optimized formulation D29

CONCLUSION

Vitamin D_3 SNEDDS comprising of Olive oil, Tween 40, PEG 600 were prepared for enhancing the dissolution and bioavailability. SNEDDS were optimized based on the optimum globule size, increased dissolution and drug release. Close to complete drug release was achieved from the formulation (D26) which is significantly higher as compared to that of Marketed Vitamin D_3 capsules. Thus, the developed SNEDDS can be used as an effective approach for enhancement of solubility and bioavailability.

REFERENCES

Bang LM, Chapman TM, Goa KL (2003). Clopidogrel: A review of its efficacy in the management of hypertension. Drugs, 63:2449-72.

Marjorie J Haskell (2012), The challenge to reach nutritional adequacy for vitamin A: β- carotene bioavailability and conversion – evidence in humans. The American Journal of Clinical Nutrition, 96:1193-1203.

Chirag R, Neha J, Jitendra P, Upadhyay UM (2012). Enhanced oral bioavailability of olmesartan by using novel solid SEDDS. International journal of advanced pharmaceutics, 2:82-92.

Bhikshapathi DVRN, Madhukar P, Dilip KB, Aravind KG (2015). Formulation and characterization of Pioglitazone HCl self-emulsifying drug delivery system. Scholars Research Library, 5 (2):292-305.

Gupta AK, Mishra DK, Mahajan SC (2011). Preparation and in-vitro evaluation of self-emulsifying drug delivery system of antihypertensive drug Valsartan. International Journal of Pharmacy and Life Sciences, 2 (3): 633-639.

Gurjeet K, Pankaj C, Harikumar SL (2013). Formulation Development of Self Nanoemulsifying Drug Delivery System (SNEDDS) of Celecoxib for

Improvement of Oral Bioavailability. Pharmacophore, 4(4):120-133.

Herbette LG, Vecchiarelli M, Sartani A (1998). Clopidogrel: short plasma half-life, long duration of action and high cholesterol tolerance updated molecular model to rationalize its pharmacokinetic properties. Blood Press Suppl. 2:10–17.

Lalit KT, Mohan LK (2014). Stability Study and In-vivo Evaluation of Lornoxicam Loaded Ethyl Cellulose Microspheres. International Journal of Pharmaceutical Sciences and Drug Research, 6(1): 26-30.

Patel J, Kevin G, Anjali P, Mihir R, Navin S (2011). Design and development of a self-nanoemulsifying drug delivery system for Telmisartan for oral drug delivery. International Journal of Pharmaceutical Investigation. 1(2):112-118.

Patwekar SL and Baramade MK (2012). Controlled release approach to novel multiparticulate drug delivery system, International Journal of Pharmacy and Pharmaceutical Sciences, 4(3):757–763.

Rajinikanth PS, Neo WK, Sanjay G (2012). Self-nanoemulsifying drug delivery systems of Valsartan: preparation and in-vitro characterization, International Journal of Drug Delivery, 4(2):153–163.

Sermkaew N, Ketjinda W, Boonme P, Phadoongsombut N, Wiwattanapatapee R (2013). Liquid and solid self-microemulsifying drug delivery systems for improving the oral bioavailability of andrographolide from crude extract of Andrographis paniculata. European Journal of Pharmaceutical Sciences. 50(3–4):459–66.

Sharma M, Sharma R, Jain DK (2016). Nanotechnology based approaches for enhancing oral bioavailability of poorly water-soluble antihypertensive drugs. Scientifica, 1:1-11.

Vanita SS, Subhashini NJP (2013). Novel self-nanoemulsion drug delivery system of fenofibrate with improved bioavailability. Int J Pharm Bio Sci. 4(2): 511-521.

Vijaykumar N, Zhijun W, Guru VB (2016). Pharmacokinetic Evaluation of Improved Oral Bioavailability of Valsartan: Proliposomes versus Self-nanoemulsifying drug delivery systems. AAPS Pharm Sci Tech, 17 (4): 851-862.

Zhongcheng K, Xuefeng H, Xiao-bin J (2016). Design and optimization of self-nanoemulsifying drug delivery systems for improved bioavailability of cyclovirobuxine D. Drug Design Development and Therapy. 10: 2049-2060.