

## Formulation and Characterization of Isradipine as Oral Nanoemulsion

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### Abstract

Isradipine related to dihydropyridine (DHP) class of calcium channel blockers (CCBs). It is used to treat hypertension, angina pectoris, as well as Parkinson disease. It goes under the BCS class II drug (low solubility-high permeability). The drug will experience extensive first-pass metabolism in liver, thus, oral bio-availability will be approximately 15 to 24 %.

The aim of the study is preparing stable oral oil in water (o/w) nanoemulsion of isradipine to promote the colloidal dispersion of isradipine in the nano range, so that it may be absorbed by intestinal lymphatic transport in order to avoid hepatic first-pass metabolism (isradipine undergoes 15-24% first pass metabolism) and increase drug bioavailability.

The solubility study was carried out in various vehicles for selecting best solvent for dissolving isradipine. Pseudo-ternary phase diagrams is formed at (1:1, 1:2, 1:3, 1:4 and 2:1) ratios related to Smix (co-surfactant and surfactant). There are 11 nano-emulsion was prepared through the use of many concentrations of (Transcutol, Tween20, and Triacetin).

All formulations assessed for (in-vitro drug dissolution, pH measurement, viscosity, drug content, polydispersity index, particle size distribution, thermodynamic stability, dye test, and light transmittance). It is indicated that the extent as well as the rate of release regarding all the prepared formulations have considerably higher in comparison to that of crude drug powder. Results of characterization were explained that isradipine nano emulsion (NE9) with S mix(1:4) : oil : deionized water (40: 5: 55) ratio was the optimized formula that has droplet size range (177.1nm), the lowest value of polydispersity index (0.12), the highest percent of drug content (99.7%) typical pH value for oral administration (5.21), good percent of light transmittance (99.86 %), the range of viscosity (65.12 -25.2 m Pas. sec.) was suitable for oral administration, also the isradipine's in vitro release has been considerably higher. It can be concluded that nano emulsion drug delivery system (DDS) can be considered as an encouraging method for improving the stability, dissolution and solubility of formulation.

**Keywords:** Nanoemulsion, Isradipine, Pseudoternary phase diagrams.

### إعداد وتقييم أسراردين كمستحلب سائل نانوي دقيق يعطى عن طريق الفم نور عبد الله سعدون<sup>\*1</sup> و موفق محمد غريب<sup>\*\*</sup>

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### الخلاصة

اسراردين هو ٤,١ دايهايدروبايريدين مغلق لقتوات الكالسيوم يستخدم لعلاج الضغط، الذبحة الصدرية، الشلل الارتعاشي. ينتمي للأدوية المصنفة من الدرجة الثانية (الدوائية قليلة، النفاذية العالية) حسب نظام تصنيف الصيدلانيات البيولوجي، لذلك فانها غير قابلة للذوبان في الماء. التوافر البيولوجي الفموي هو يقارب ١٥-٢٤%. وبالتالي نهدف الى إعداد أسراردين بشكل نظام سائل الاستحلاب نانوي لتعزيز الذوبان، وهذا يؤدي إلى زيادة معدل الحل، لذلك سيتم الحصول على امتصاص جيد للدواء أجريت دراسة قابلية الذوبان في مركبات مختلفة لتحديد أفضل السواغات أسراردين. تم بناء المخططات الطورية الثلاثية الزائفة في (١ : ١ ، ١ : ٢ ، ١ : ٣ ، ١ : ٤ و ٢ : ١) من نسبة الفاعل بالسطح و المادة الخافضة للتوتر السطحي. تم تحضير إحدى عشر تركيبات باستخدام تراكيز مختلفة من زيت الترايستين، توين ٢٠ وترانسكيوتول. تم تقييم جميع التركيبات المعدة (توزيع حجم الجزيئات، مؤشر التشنت المتعدد، محتوى الدواء، الاستقرار التيرموديناميكي، اللزوجة، امتزاج الصبغة مع الماء، مقياس درجة الحموضة، نفاذية الضوء). نتائج دراسة الخواص توضح بان المستحلب النانوي الإسرارديين (NE9) الذي يتكون من (زيت الترايستين ٥%، خليط من المادة التي تقلل الشد السطحي والمادة المساعدة على تقليل الشد السطحي ٤٠% وماء منزوع الايونات ٥٥%) هي الصيغة الأمثل حيث تمتلك حجم كروي (١٧٧,١ نانومتر)، مؤشر التشنت (١,٢١)، قيمة الرقم الهيدروجيني للإعطاء عن طريق الفم (٥,٢) محتوى الدواء (٩٩,٧%)، نسبة منويه جيدة من نفاذية الضوء (٩٩,٨٦%)، نطاق اللزوجة (٦٥,١٢ - ٢٥,٢ م باس. ثانية) مناسباً للإعطاء عن طريق الفم وكان التحرر المختبري لدواء الاسراردين عالي التحرر، خلص إلى أن نظام توصيل الدواء بالمستحلب النانوي هو نهج واعد لتحسين قابلية الذوبان والانحلال واستقرار التركيبة.

الكلمات المفتاحية: مستحلب سائل نانوي، أسراردين مخطط المرحلة الزائفة الثلاثية

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## Introduction

Low Dissolution rate and partial absorption will be generally seen in drugs with low permeability and low water solubility<sup>(1)</sup>. Pharmaceutical researches focus on two fields to improve the oral bio-availability, which are: (i) enhance the dissolution rate as well as the solubility for drugs with low water-solubility, (ii) enhance the permeability related to drugs with low permeability<sup>(2)</sup>.

Solubility can be defined as a major parameter used for the purpose of achieving the required drug's concentration in a systemic circulation for pharmacological response<sup>(3)</sup>. Several methods were modified for resolving the drug's poor aqueous solubility<sup>(4)</sup>. There is high permeability and poor water solubility in the class II drugs according to BSC<sup>(5,6)</sup>. Distinctive approaches for the drug's solubilization are hydrotropy, complexation, pH adjustment, chemical modification, micronization, co-solvency, solid dispersion, and micellar solubilization.

Nano emulsions can be defined as new which might occur as oil-in-water (o/w) or water-in-oil (w/o) structure, in which the molecule's centre is oil or water, respectively with droplet diameters of range (50-1000nm), the average size of the droplet range between (100 and 500nm)<sup>(7)</sup>.

The nano-emulsions drug delivery are the best routes because of their capacity for dissolving large quantities of the low soluble drugs, also due to their common compatibility and ability for protecting drugs from hydrolysis and enzymatic degradation<sup>(8)</sup>.

The small size of the nano-emulsion's droplet are more clear transparent appearance which are definitely different from the milky-white color related to coarse emulsion (in which the micron-sized droplets are factors in the multiple light scattering)<sup>(9)</sup>.

Nano emulsions are kinetically stable but thermodynamically unstable, with Ostwald ripening being the main factor of their instability<sup>(10, 11, 12)</sup>.

Isradipine belongs to DHP class of CCBs, and it binds to the calcium channels with specificity and affinity to inhibit the calcium flux into cardiac and arterial smooth muscle cells<sup>(13)</sup>. It is used in prophylactic treatment of angina pectoris, treatment of hypertension, some currently studies have indicated that isradipine in the treatment of Parkinson's disease<sup>(14,15)</sup>.

Isradipine is considered to be freely soluble in methylene chloride, acetone, chloroform; soluble in ethanol; insoluble in water (<10 mg/L at 37°C)<sup>(16)</sup>. It is mainly absorbed from gastrointestinal tract following

oral administration, experiences some extensive first-pass metabolism; therefore bio-availability is (15 to 24%)<sup>(17)</sup>.

## Materials and Methods

Isradipine, triacetin, cremphore EL and transcutool were purchased from Hyper chem company, china, tween 80 and tween 20 have been bought from Thomas baker (chemicals) Pvt Ltd, India. Castor oil obtained from Evans medical Ltd, United Kingdom. Olive oil supplied by Pomace olive oil oilex, S.A. Spain, coconut oil, cinnamon oil obtained from Shaanxi Guanjie Technology CO, LTD, China. Liquid paraffin obtained from Merck, Germany. Poly ethylene glycol 400,200 supplied by M/s provizer pharma. India.. Methanol supplied by Avantor performance materials, Norway. Hydrochloric acid from Grin land chemical comp, United Kingdom. Na<sub>2</sub>HPO<sub>4</sub>, KH<sub>2</sub>PO<sub>4</sub> and deionized water were supplied by Janeen for chemical and laboratory materials, Baghdad, Iraq.

### Methods

#### Differential scanning calorimeter (DSC)

The thermal properties of drug powder samples were examined via the use of DSC /TA-60 thermal analysis controller with the intercooler-2 cooling system (DSC-60, Shimadzu, Japan). Sample heating was run for each sample set for 50-250°C at the rate of 10°C/min, using nitrogen as blank gas<sup>(18)</sup>.

#### Solubility study of isradipine

The solubility of isradipine measured in different oils which are coconut oil, liquid paraffin, cinnamon oil, castor oil, olive oil, Triacetin, the surfactants which are tween 80, tween 20 and cremphore EL and co-surfactants which are glycol polyethylene glycol 200,400 and transcutool. Excess amounts of the isradipine powder was added to 5ml of each oil, co-surfactants and surfactant in small plain tubes. Then, these tubes were tightly closed and placed in isothermal shaker water bath at 25 ± 0.5 °C for 48 hr. After this time, samples were centrifuged at 3000 rpm for 20 minutes, then the supernatant layer for each sample filtered by using filter membrane (0.45 μm). After filtration, samples were diluted with methanol, the solubility evaluated at λ max at 326nm through the use of UV-visible spectrophotometer and the measurement carried out in triplicate<sup>(19,20)</sup>.

#### Construction of pseudo- ternary phase diagrams

Components related to the pseudo-ternary phase diagrams consist of oil, mixture of surfactant and co-surfactant (S mix) as well as deionized water was prepared through the

use of aqueous titration approach<sup>(21)</sup>. Co-surfactant and surfactant were mixed in various ratios (1:1, 1:2, 1:3, 1:4, 2:1). With regard to each one of the phase diagrams, oil as well as the S mix were blended in various weight ratios until obtaining the maximum ratio of S mix and oil. There are 11 different combinations related to S mix and oil have been prepared, such combinations were slowly titrated with aqueous phase (deionized water), each mixture was titrated with deionized water under gentle magnetic stirrer without heating. The concentration of water at which transparent-to-turbid changes occurred was measured as the endpoint of the titration<sup>(22)</sup>.

#### **Thermodynamic stability studies<sup>(23)</sup>**

All formulations that were prepared were exposed to various thermodynamic stability tests (freeze-thaw cycle, heating-cooling cycle and centrifugation) for overcoming choosing metastable formulation.

#### **Centrifugation test**

All the prepared nanoemulsion formulations were centrifuged at 3500 rpm for (20-30minutes) and assessed for cracking, creaming, and phase separation.

#### **Heating-cooling cycle (H/C cycle)**

There are 6 cycles between (4-45 °C) with storage at each one of the temperatures for 48hr. Formulations, that are considered stable at such temperatures, were subjected to freeze-thaw cycle .

#### **Three freeze-thaw cycles**

between (-21 and +25 °C) with storage at each one of the temperatures for 48hr determined for all the prepared nano-emulsion formulations.

#### **Droplet size measurement**

An amount of 0.1 ml of each formula was dispersed in fifty milliliters of deionized water in volumetric flask, after that subjected to mixing process via inverting the flask. Globule size has been assessed via particle size analyzer which analyzed fluctuations in the light scattering because of particle's Brownian motion. Light scattering has been inspected at 25 °C at a 90° angle<sup>(24)</sup>.

#### **Polydispersity index (PDI)**

This assay is used to measures uniformity related to the globules size in nano-emulsion. It could be obtained by ABT-9000 nanolaser particle size analyzer. Higher polydispersity value indicates lower uniformity of globules size of nano-emulsion<sup>(25)</sup>.

#### **Measurement of pH**

The pH of all prepared nano-emulsion formulas was determined with the use of digital pH meter utilizing (20-30ml) sample placed in 50-ml capacity beaker<sup>(26)</sup>.

All the measurements have been repeated 3 times. The pH value is of high importance to determine the nano-emulsion's stability since the pH alteration mean the occurrence of the chemical reactions which could damage the final product's quality.

#### **Percent of light transmittance measurement (%T)**

Measurement of the %T was achieved for eleven control nano-emulsions at 650nm, while the distilled water kept as blank<sup>(27)</sup>.

#### **Viscosity determination**

The viscosity of sample was determined without dilution with the use of NDJ-5S digital viscometer and spindle number (2), the spindle has been inserted in (30-40ml) of the prepared NE sample in graduated beaker and revolved at distinctive speeds which have been (6, 12, 30 and 60 rpm)<sup>(28)</sup>.

#### **Dye test**

Water-soluble dye (methyl orange) was mixed with each one of the isradipine NE formulations. In the case when the dye is mixed with nano-emulsion homogenously without precipitation, this will indicate that the continuous phase is water and nano-emulsion structure is o/w<sup>(29)</sup>.

#### **Drug content**

Drug content was determined via UV visible spectrophotometer. Formulation diluted with methanol to the needed concentrations, and absorbance was determined at wave length against solvent blank. Drug content was calculated by employing the following equation<sup>(30)</sup>.

$$\text{Drug content} = \frac{\text{Analyzed content}}{\text{Theoretical content}} \times 100$$

#### **In vitro dissolution study**

In vitro drug release of all prepared nano-emulsion formulations were assessed via the use of USP dissolution apparatus-II (paddle approach). Dissolution medium, on the basis of monograph of isradipine in USP, is 0.1N HCl as dissolution media (500ml), at 37±0.5 °C and 50 rpm<sup>(31)</sup> through the use of dialysis bag technique (Molecular cut off 12000 Da)<sup>(31)</sup>, formula that contain isradipine equivalent to single dose has been placed in dialysis bag, also 5ml of the dissolution medium has been taken. The time intervals for drawing out aliquots have been 5, 10, 15, 30, 45, 60, 90 and 120 min<sup>(32)</sup>.

#### **Zeta potential measurement**

Zeta potential can be defined A parameter that is applied for measuring surface charge properties and as a sign of aphysical stability related to the nano-emulsions<sup>(33)</sup>.

### Fourier transform infrared spectroscopy (FTIR)

Compatibility of drug and formulation was determined by FTIR. The spectrum was obtained for (drug, tween 20, transcutool, triacetin, and selected formula).

It is used for identifying the functional groups with their means of attachment, and the fingerprint of the molecule. the sample can be prepared by employing a suitable method such as potassium bromide pellet method, Nujol mulls, and then the sample is scanned in FTIR at a moderate scanning speed between (4000-400 cm<sup>-1</sup>)<sup>(34)</sup>.

### Field Emission Scanning Electron Microscope (FESEM)

Isradipine nanoemulsions were also analyzed by field emission scanning electron microscope (FESEM). It is apparatus that used for an image surface roughness analysis, used to explain the shape, size droplets within formulated nanoemulsion of isradipine<sup>(35)</sup>.

### Statistical analysis

The results of the study indicate the average of triplicate readings for each sample. Analysis of variance test (ANOVA) were applied to investigate that the results of study considered as significant results when (P < 0.05) and the results were considered not significant when (P > 0.05).

## Results and Discussion

### Study of differential scanning calorimetry (DSC)

The measured melting point via DSC is used to confirm the purity of the drug used in the study. The sharp peak appeared in figure 1 referred to melting point of the drug and indicated the crystalline drug in nature<sup>(36)</sup>.

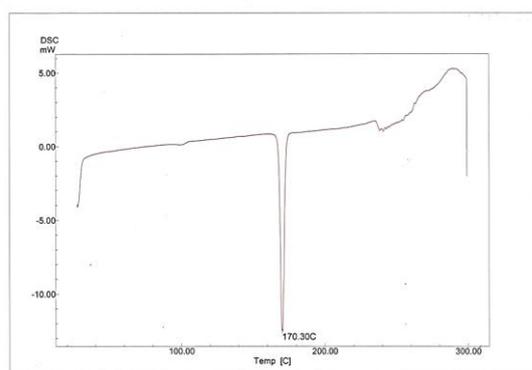


Figure 1. Differential scanning calorimetry of isradipine.

### Solubility study

Selection of the main constituents (co-surfactant, surfactant and oil) in preparation of nanoemulsion has been considered as an essential factor in formulation development,

since the nano-emulsion ability of maintaining drug in solubilized form has been considerably impacted via the drug's solubility in oil phase<sup>(37)</sup>. The isradipine's solubility was indicated to be highest in triacetin (81mg/ml) in comparison to other oils in table 1. With regard to the Smix part, high drug solubility in transcutool(75.1mg/ml) and tween20(20.101mg/ml) in table 2<sup>(38)</sup>. Although the drug solubility considered also high in PEG200,PEG400, transcutool was selected as a cosurfactant due to its higher solubility, better miscibility and give good nanoemulsion region in pseudo ternary phase diagram compared with PEG200,PEG400.

Table1.Saturation solubility of isradipine in different oils

Oil	Solubility (mg/ml) mean $\pm$ SD*
Castor oil	4.135 $\pm$ 0.15
Coconut oil	12.744 $\pm$ 0.04
Cinnamon oil	7.112 $\pm$ 0.03
Triacetin oil	81.000 $\pm$ 0.05
Olive oil	4.102 $\pm$ 0.01
Liquid paraffin	1.123 $\pm$ 0.12

Table2. Saturation solubility of isradipine in different surfactant/ cosurfactant

Surfactant/ cosurfactant	Solubility (mg/ml) mean $\pm$ SD*
Tween 20	20.101 $\pm$ 0.28
Tween 80	5.601 $\pm$ 0.02
Crempore EL	12.100 $\pm$ 0.03
PEG 200	40.10 $\pm$ 0.09
PEG 400	35.013 $\pm$ 0.05
Transcutool	75.101 $\pm$ 0.154

### Pseudo- ternary phase diagram construction

The components of the pseudo-ternary phase plot are (oil, deionized water and Smix surfactant/co-surfactant, which considered as a variable component due to that, it presents in various (surfactant /co-surfactant) ratio such as 1:1, 2:1, 1:2,1:3 and 1:4. In the pseudo-ternary phase plot, the shaded area represents the area of nanoemulsions while unshaded area represents the area of the emulsion.

Pseudo-ternary phase diagram plot for different S mix ratio Tween 20: Transcutool are shown in figure ( 2) . In Smix 2:1when concentration of surfactant was increased as related to cosurfactant, nano-emulsion area reduced in comparison to the Smix ratio1:2. co-surfactant concentration at Smix(1:2,1:3,1:4) rises in the nanoemulsion region more than in Smix ratio (2:1)<sup>(39)</sup>.

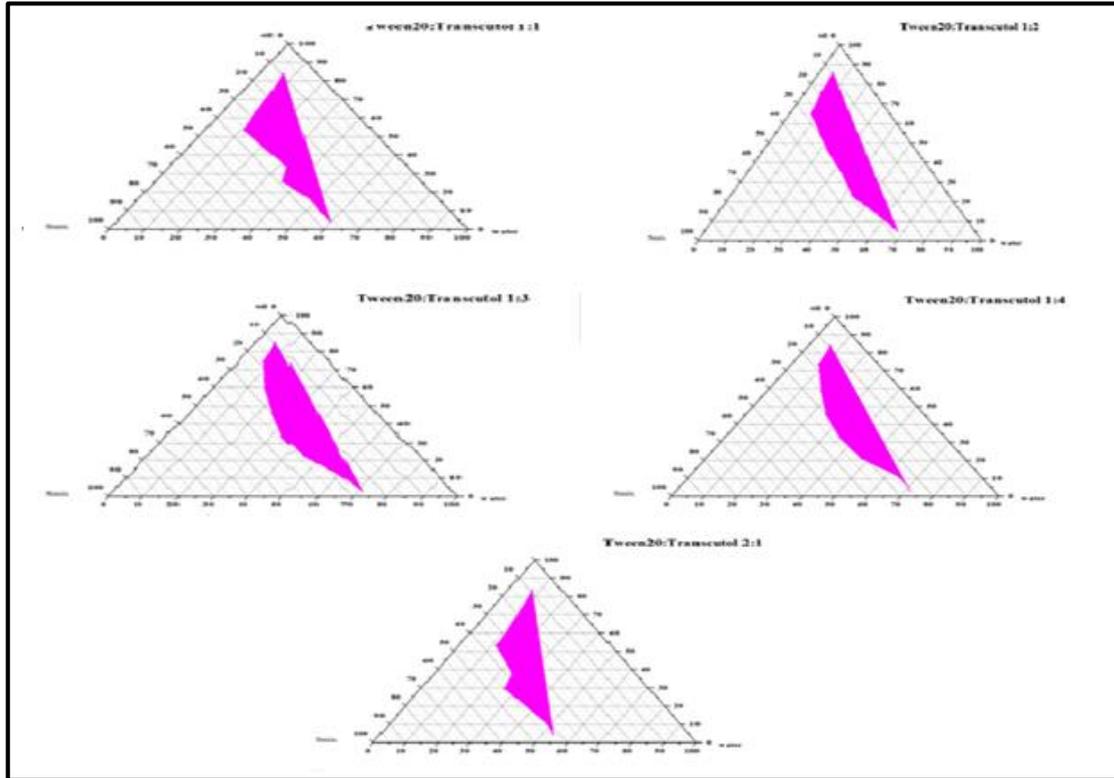


Figure 2. Pseudo ternary phase diagrams for different S mix ratio (tween 20: transcutol 1:1, 1:2, 1:3,1:4 and 2:1)

**Preparation of isradipine loaded nanoemulsion**

The quantity of isradipine(0.025) gram that required for preparation of (100) gram formula dissolved in the specialized quantity of triacetin, then S mix ratio was added to the oil and isradipine mixture and the whole

mixture mixed with the use of vortex mixer for 5 minutes , then deionized water titrated drop by drop up to 100 gm which is the final weight of the formula,so nine formulas of nanoemulsion (o/w) were produced .All of the nanoemulsion formulation were clear and transparent .

Table 3. Formulation of different isradipine loaded nanoemulsion

Formula No.	S mix ratio	% w/w of a component of nanoemulsions			
		Smix( Surfactant: Cosurtactant) S mix(Tween20,Transcutol)	Oil Tricetin	Water Deionzed water	Drug Isradipine
N1	1:1	40	10	50	0.025
N2		55	5	40	0.025
N3	1:2	40	5	55	0.025
N4		45	10	45	0.025
N5	1:3	40	5	55	0.025
N6		45	10	45	0.025
N7	1:4	35	5	60	0.025
N8		30	10	60	0.025
N9		40	5	55	0.025
N10		45	5	50	0.025
N11	2:1	35	5	60	0.025

**Thermodynamic stability studies**

All of the prepared nanoemulsions formulations passed the thermodynamic stability test, that is (freeze-thawing test, heating-cooling test, and centrifugation test) in order to get thermodynamic stable formulations of nanoemulsions that have no creaming, cracking and phase separation which may present in the macroemulsion<sup>(39)</sup>. The thermodynamic results of the prepared formulation were shown in table 4.

**Table 4 .Thermodynamic stability of isradipine loaded nanoemulsion**

Formul a code	Centrifugati on test	Heating - cooling cycle test	Freeze thawin g cycle test
NE1	pass	pass	pass
NE2	pass	pass	pass
NE3	pass	pass	pass
NE4	pass	pass	pass
NE5	pass	pass	pass
NE6	pass	pass	pass
NE7	pass	pass	pass
NE8	pass	pass	pass
NE9	pass	pass	pass

**Particle size measurement<sup>(40)</sup>**

It has been indicated that the systems which consist of 10 percent triacetin created nano-emulsion with larger particle size in comparison with the systems consisting of five percent triacetin. High surfactant ratios enabled interfacial film to stabilize and condense, while the film will increase with the increase in cosurfactant concentration.

Small mean droplet size might be related to penetration of the co-surfactant molecules into surfactant film. This might reduce the interfacial film's surface, which might lower radius of curvature of droplets and forming transparent systems. Therefore, relative proportion of surfactant to co-surfactant has different impact on droplet size.

**Polydispersity index (PDI)<sup>(40)</sup>**

Polydispersity of all the formulations has been not more than (0.5)), which indicates uniform and narrow globule size distribution, as can be seen in table(3)

**Determination of pH**

The pH related to all the formulations have been determined via pH meter in triplicate at  $25 \pm 1$  °C and indicated to be in range of ( 4.9-5.21 ) as can be seen in the table (3) . The higher pH value in the formulations of isradipine nanoemulsions was (5.21) for NE9 and this pH value is suitable for oral administration.<sup>(41,44)</sup>.

**Measurement of light transmittance**

Values of transmittance percentage shown in table 5 are close to 100% specified that all formulations were transparent, clear, and transmit light efficiently<sup>(42)</sup>.

**Table 5. Characterization of isradipine loaded nanoemulsion where,mean droplet size,polydispersity , pH and %T (mean  $\pm$  SD, n= 3)**

Formula code	Mean droplet size	Polydispersity	PH measurement	Light transmittance
NE1	297.7 $\pm$ 0.01	0.345 $\pm$ 0.00	5.120 $\pm$ 0.091	97.145 $\pm$ 0.1321
NE2	315.7 $\pm$ 0.01	0.363 $\pm$ 0.00	4.910 $\pm$ 0.0652	98.298 $\pm$ 0.0235
NE3	98.4 $\pm$ 0.011	0.217 $\pm$ 0.00	5.071 $\pm$ 0.008	98.512 $\pm$ 0.0041
NE4	358.2 $\pm$ 0.21	0.271 $\pm$ 0.00	4.811 $\pm$ 0.0026	97.223 $\pm$ 0.008
NE5	260.0 $\pm$ 0.01	0.333 $\pm$ 0.00	4.8143 $\pm$ 0.008	99.617 $\pm$ 0.0046
NE6	357.8 $\pm$ 0.01	0.005 $\pm$ 0.00	4.912 $\pm$ 0.0087	98.387 $\pm$ 0.0043
NE7	255.0 $\pm$ 0.01	0.215 $\pm$ 0.00	5.111 $\pm$ 0.003	98.411 $\pm$ 0.0076
NE8	186.2 $\pm$ 0.21	0.213 $\pm$ 0.00	4.517 $\pm$ 0.001	99.125 $\pm$ 0.15
NE9	177.1 $\pm$ 0.01	0.121 $\pm$ 0.00	5.214 $\pm$ 0.009	99.878 $\pm$ 0.035
NE10	287.1 $\pm$ 0.12	0.341 $\pm$ 0.00	5.140 $\pm$ 0.067	98.690 $\pm$ 0.034
NE11	413.0 $\pm$ 0.10	0.301 $\pm$ 0.00	4.910 $\pm$ 0.0013	97.121 $\pm$ 0.061

**Viscosity measurement**

The results of the viscosity of isradipine nanoemulsions were found to be in range (25.026 – 300.782 mPa.sec.). It was observed that all formulations have low viscosity and this important to ensure pourability, packing, especially if the nanoemulsion dedicated for oral use (43).When the rotation speed increased (velocity), the viscosity decreased indicating the pseudoplastic (shear thinning liquids) flow of the preparation (44).

**Dye test**

Methyl orange is an azo dye miscible with water. Following the addition of methyl orange dye, it has been shown that the dye miscible with all the isradipine NE formulations; no cumulative or cluster was formed(44).

**Drug content estimation**

The drug content related to all prepared isradipine nano-emulsions was more than 95% and there has been no considerable difference between different formulations (p >

0.05), which meet British pharmacopia requirement and were within an acceptable range (95.0%-105.0%), which indicates that there has been no precipitation of drug in any of prepared formulations(40).

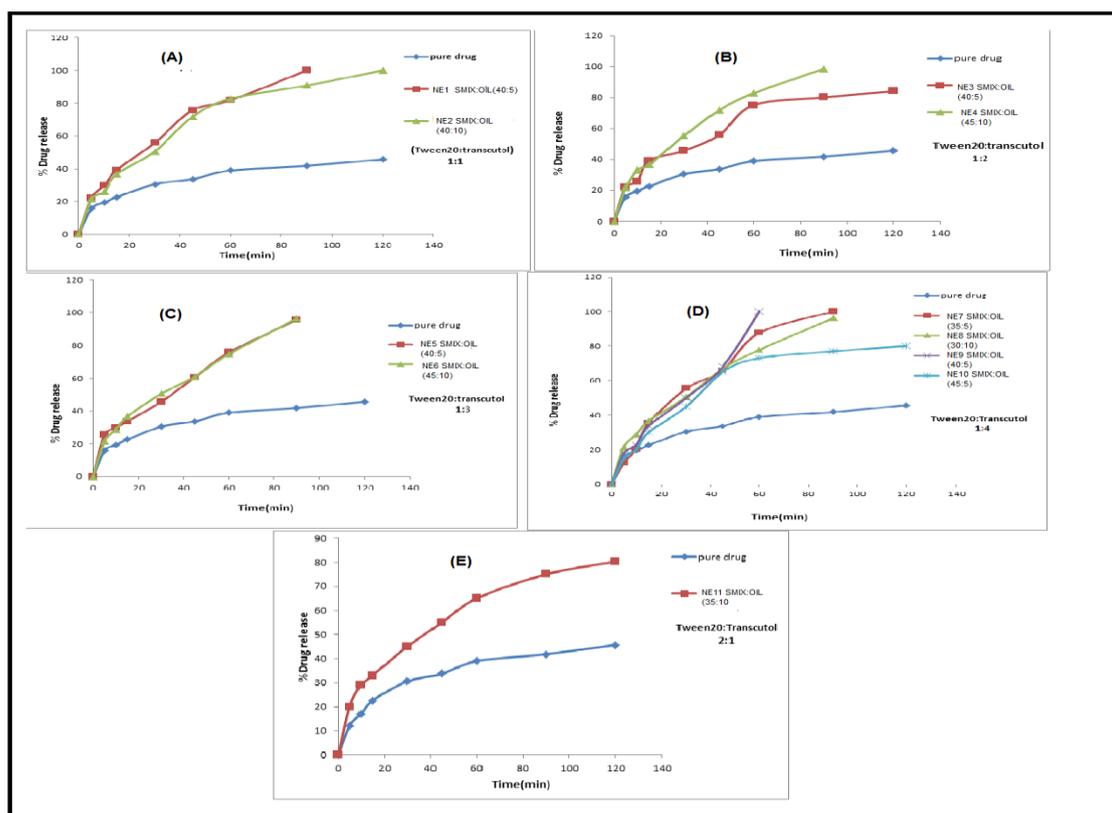
**In vitro drug release**

Pure drug showed (40.45%) drug release at end of sixty minute because of its low aqueous solubility.

With nanoemulsion formulation, it was noticed as the concentration of transcutool increase, the release is high reach 100% at the end of dissolution test, the reason behind this is due to the effect of co-surfactant which are good solubilizing and facilitating dissolution process of the pure drug (46, 47).

At the same time, NE9 showed highest release; end of sixty minutes, that could be the result high content of transcutool.

Co-surfactant role in nano-emulsion systems decrease interfacial tension and increases the interface's fluidity. Also, it increases the hydrocarbon tail's mobility and enable greater penetration of the oil in nanoemulsion region(48)



**Figure3. Effect of Smix:oil ratio on release profile where (A) release of NE1, NE2 and pure drug (B) release of NE3, NE4and pure drug (C) release of NE5, NE6 and pure drug, (D) release of NE7, NE8 NE9,NE10 and pure drug (E) release of NE11and pure drug**

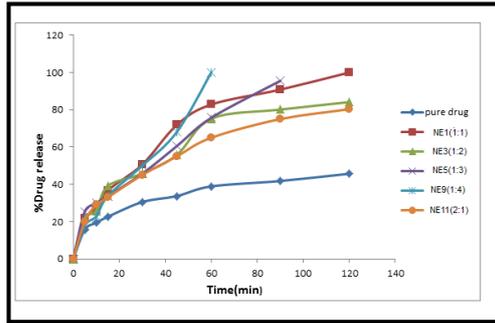


Figure 4. Effect surfactant:cosurfactant ratio on release profile of isradipine nanoemulsion (NE1,NE3,NE5,NE9,NE11) and pure isradipine .

**Selection of optimized formula of isradipine nanoemulsions**

According to the characterization study of the prepared nanoemulsions, there was an indication that the ( NE9) is the optimized formula, because it is characterized by good droplet size (177.1), low PDI (0.120), best pH value for oral use (5.214), good percent transmittance (99.96), percent of drug content was higher (98.9), accepted viscosity range for oral use (25.026 – 65.12 mPa.sec) and highest release of isradipine from the formula. The optimized formula would be subjected to further studies such as zeta potential, drug –

excipient compatibility, field emission scan electron microscope (FESEM).

**Zeta potential measurement**

The value of optimized formula was (-18.3) .

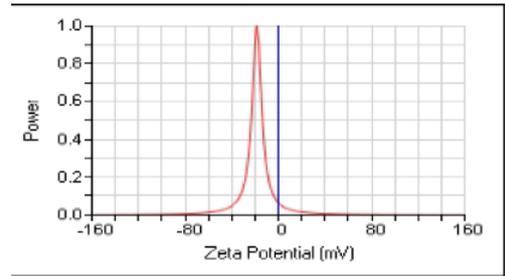


Figure 5. Zeta potential for NE9 formula

Studies of Dru – Excipient Compatibility study by Fourier Transformed Infrared Spectroscopy (FTIR) Pure isradipine exhibited characteristic peaks at 3,348 cm<sup>-1</sup>, (N-H stretching), 2,945cm<sup>-1</sup>, (C-H stretching), 2,358 cm<sup>-1</sup>, (O-H stretching), 1,701 cm<sup>-1</sup>, (C=O stretching), and 1,448 cm<sup>-1</sup> ,(C=C stretching) (Figure5). All these peaks had appeared in FTIR spectrum of nanoemulsion formulation .This indicates that there was drug – excipient compatibility between all components of prepared nanoemulsion.

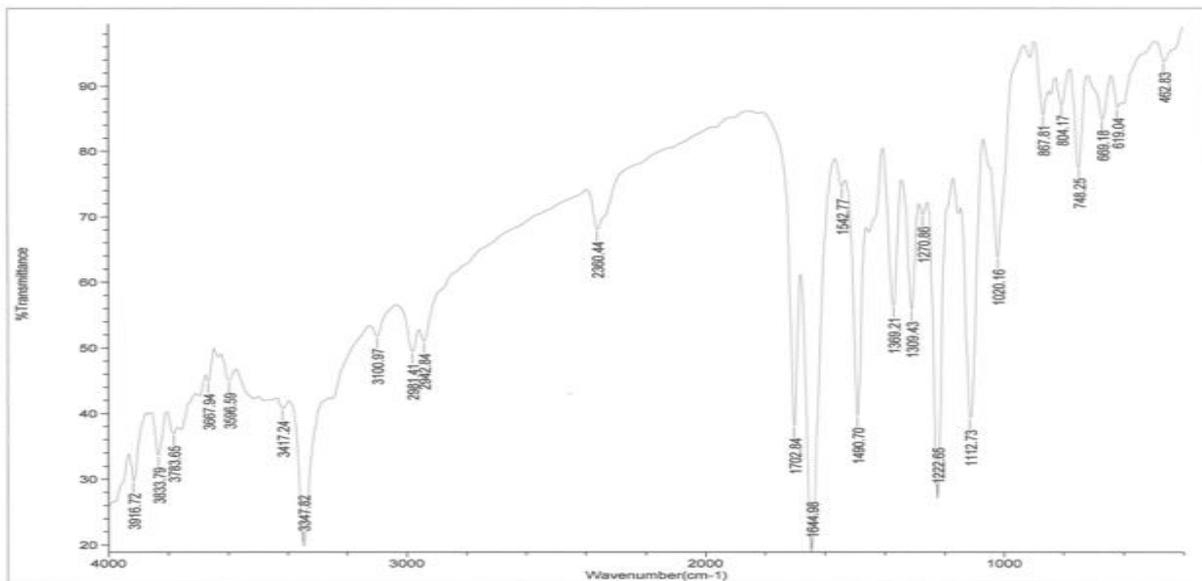


Figure 6. FTIR spectrum of isradipine powder.

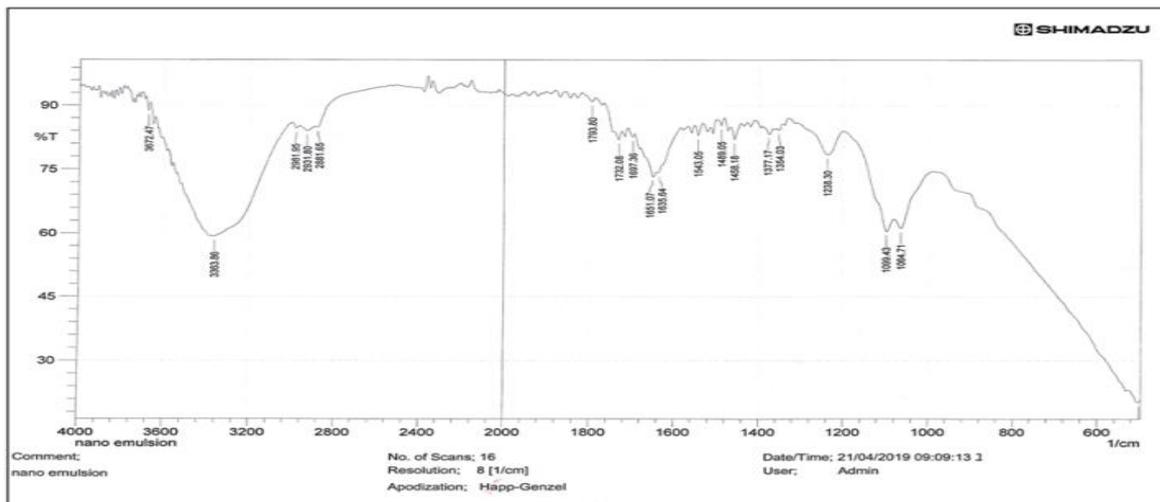


Figure7. FTIR spectrum of optimized formula (NE9)

#### Field emission scan electron microscope(FESEM)

Figure 7 shows that oil droplets of the optimized formula are spherical in shape and there are accumulation of smaller oil droplet, however, there was no main changes in shape and size of the oil droplets upon accumulation (35).

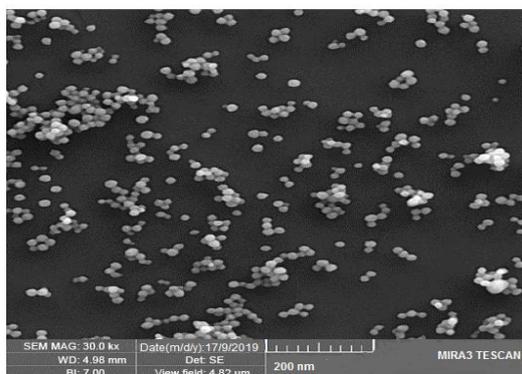


Figure 8. FESEM of optimized formula(NE9).

#### Conclusions

From this study, it is concluded that nanoemulsion provided an important dosage form for the oral water-insoluble drug. NE that was prepared from triacetin oil, tween 20 and transcitol was encouraging method for improving dissolution rate and solubility of isradipine. The present study may serve as a prototype approach for the formulation development of other hydrophobic drugs nanoemulsion drug delivery system.

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