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Original Article

FORMULATION AND CHARACTERIZATION OF CARVEDILOL NANOEMULSION ORAL LIQUID DOSAGE FORM

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ABSTRACT

Objective: Carvedilol is antihypertensive. It is practically water insoluble. Therefore, the objective of this investigation is a formulation and characterization of carvedilol nano emulsion (NE) employing orally to increase carvedilol solubility for enhancing of carvedilol bioavailability.

Methods: The formulation components were chosen according to the solubility study. The diagrams of pseudo-ternary phase were made using the aqueous phase titration method. The formulated nanoemulsions were subjected to various thermodynamic stability assays. We selected eight of formulas that have thermodynamic stability for further optimization for various characterizations in order to select the best formula.

Results: The carvedilol NE3 considered a selected formula. It composes of 1.25 mg carvedilol per g of the nanoemulsion, 10 % of peppermint oil, 20% of tween80, 10% ethanol and 60% of distilled water. It was characterized by a low globule size range, low poly dispersity index, higher zeta potential, good pH value, efficient electroconductivity, classy percent of light transmittance, higher % drug content, acceptable low viscosity and carvedilol release was significantly higher ($P<0.05$) in dissolution rate. The carvedilol NE3 subject for further investigations. Fourier transformed infrared spectroscopy confirm no incompatibility between the drug and excipients. The atomic force microscopy study shows that system in nanoscale and has high stability.

Conclusion: The selected formula (carvedilol NE3) was a promising nanoemulsion formula that increases the carvedilol solubility result in an increment of its bioavailability.

Keywords: Nanoemulsion, Carvedilol, Solubility studies, Peudoternary phase diagrams.

INTRODUCTION

The therapeutic level relies upon plasma drug concentration to attain pharmacological response. Solubility is one of the very important factors to achieve an aspired concentration of the drug in the blood circulation to remain above minimum effective concentration and within therapeutic range to reach pharmacological recriminate [1]. Dissolution of poorly soluble drug meets a great confrontation in the assaying of new chemical existence also in preparation, design and sophisticating [2]. There are many of systematics exploited to enhance the drug dissolution of poorly soluble in water and more to raise its bioavailability. The micellar solubilisation, micronization, solid dispersion, chemical modification, complexation, pH adjustment, co-solvency, hydrotropy, etc. are conventional approaches to the dissolution of the drug and bioavailability enhancement [3]. The drug solubility in an aqueous media and drug permeability through hydrophobic membranes are important parameters in improving bioavailability. In fact, the drug molecules should be present in a solubilized form in order to absorb by the cell membrane and arrive the site of drug action [4]. The practically insoluble compounds in aqueous media represent more than 40% of new chemical existence in the pharmaceutical industry and make a coalition to slow absorption of drug that cause insufficient and changeable bioavailability and toxicity of the gastrointestinal tract [5]. Carvedilol is An antihypertensive that has non selective β-blocking, α-adrenergic blocking activity and antioxidant properties, is practically water insoluble [6]. Nan emulsions defined as a drug delivery system composing of emulsified oil and the aqueous phase with an average globule diameters rating about 50 to 1000 nm. Normally, the mean globule size is about 100 to 500 nm and present mainly as water-in-oil (w/o) and oil-in-water (o/w) design, where the essence of the globule is either water or lipid, respectively. Srilatha *et al.* Formulate glipizide nano emulsion. The results of pharmacodynamic assay found that the selected preparation (F9) decreased blood glucose level up to 12 h [7]. Preeti K Suresh and Sudhanshu Sharma, develop cinnarizine self-nano emulsifying drug delivery system (SNEDDS). They found that SNEDDS with a surfactant: co-surfactant (Smix) ratio (2:1) and (Smix)-oil ratio (6:1) has the highest release of the drug [8]. Thus, the aim of this investigation is a formulation and characterization of carvedilol nano emulsion employing orally for enhancement of carvedilol solubility result consequently in an increased bioavailability.

MATERIALS AND METHODS

Materials

Carvedilol supplied by Wadi Al-Rafidian factory for pharmaceutical products, Baghdad, Iraq. Ginger oil, cyperus oil and black seed oil from AI-Emad for plant oil product, Iraq. Anise oil and peppermint oil from BAR-SUR-loup Grasse A. M Franc. Garlic oil from ATI laboratory, Holland. Tween 80 from SD fine Chemlimited (SDFCL) Mumbai, India. Propylene glycol from AOBA Chemie India. Tween 20, methanol and ethanol from grin land chemical comp, United Kingdom.

Method

Components screening by solubility determination

The carvedilol solubility was determined in various soils which are ginger oil, black seed oil, anise oil, peppermint oil, cyperus oil and garlic oil, surfactants (tween 80 and tween 20) and co-surfactants (methanol, ethanol and propylene glycol). The excess quantity of the carvedilol was added to 2 ml of various oils, surfactants and co-surfactant that contained in the small plain tube. The plain tube was tightly closed and was continuously shaked on an isothermal shaker water bath for 72 h at 37+/-0.05 °Cand then specimens were centrifuged 15 min at 3000 rpm. The afloat was filtered through a microfilter paper (0.45 µm) and after adequate methanol dilution, solubility was measured through a UV spectrophotometer at the λ_{max} 285 nm [9]. The measurements were performed in triplicate.

Construction of pseudo ternary phase diagrams

The components of the pseudo ternary phase plot, including of oil, Smix and aqueous phase and it is developed by employing the aqueous phase titration technique [10]. Surfactant and co-surfactant that meld

in various weight ratios (1:1, 2:1, 3:1, 4:1) was chosen on the basis of increment the concentration of surfactant at a constant concentration of co-surfactant. Oil and a particular Smix ratio were blended appropriately in various weight ratios for each phase graphing, so that maximum ratio were obtained.

In order to know the borderline of phases specifically con fig. in each phase graphing, slow titration of each weight ratio of Smix and oil was achieved with distilled water and visual searches were made for evaluating transparency where the distilled water was added drop by drop until the nano emulsified blend is clear to the eyes, after that further addition of distilled water was stopped and various o/w nano emulsion formed. The pseudo ternary phase diagram was constructed by using triplot V4 software (4.1.2. Version). The plotted area of nano emulsion represented by the shaded area and the wider region indicated better nano emulsifying activity. No heating was conducted during the preparation.

Screening of carvedilol nano emulsion formulations on the basis of thermodynamic stability studies [11]

The thermodynamic stability assays were achieved depending on the following tests.

Centrifugation assay

The chosen preparations were centrifuged for 30 min at the 5000 rpm and noticed the phase separation, creaming and cracking. The chose formulations should have the maximum stability that is no phase separation, creaming and cracking can be seen. The succeeded formulations exposed to other thermodynamic stability tests. The measurements were performed in triplicate**.**

Heating-cooling test

It is utilized to show the racking effect of heating and cooling on the nanoemulsions stability where the preparations should kept at 45 °C and at 0 °C temperature for not less than 48 h for each temperature test. The measurements were performed in triplicate.

Freezing–thawing test

This test was achieved for accelerated stability assaying of nanoemulsion formulations. The formulations were subjected at two different temperatures, which are (-21°C and 21°C) for each temperature test not less than 24 h. The measurements were performed in triplicate.

Characterization of the prepared carvedilol nanoemulsion

Globule size assay

The specimens of nanoemulsion were put in a 5 ml cell of ABT-9000 nanolaser particle size analyzer after sonication at the 37 °C for 30 min, globule size distribution plots were received and the mean globule size can be obtained. The measurements were performed in triplicate.

Poly dispersity index (PDI) assay

It measures the uniformity of globules size in nanoemulsion and can be obtained by ABT-9000 nanolaser particle size analyzer. The measurements were performed in triplicate. The higher the poly dispersity value refers to the lower uniformity of globules size of nanoemulsion [12].

Zeta potential (ZP) assay

Zeta potential for nanoemulsion was determined by brook heaven instrument USA zeta sizer. Samples were placed in clean disposable zeta cells then recording the results. Before putting the new sample, cuvettes were rinsed with the methanol and the sample to be measured before each test [13]. Zeta potential values were determined in triplicate for all nanoemulsions.

Determination of pH

The pH is one of the major parameters in nanoemulsion. Observation the pH value is consequential for determining the stability of the nanoemulsion due to the pH alteration mean occurrence of chemical reactions that can impair the quality of the final product. The digital pH meter utilizes to determine the pH of the formulations. Results were being taken in triplicate [14].

Electrical conductivity assay

The electrical conductivity definition is highly important to determine the type of the continuous phase and to find out the phenomena of phase inversion. Conductivity measurements were executed by a conductivity meter [15]. The measurements were performed in triplicate.

Percent of light transmittance assay

The nano emulsion percent transmittance was measured by UV-Visible spectrophotometer keeping distilled water as blank at 600 nm [16]. The measurements were performed in triplicate.

Drug content estimation [17]

The drug content was determined using a UV-visible spectrophotometer. The formula was diluted to desirable concentration through employing methanol as solvent. The measurements were performed in triplicate. The absorbance was determined at 285 nm and the drug content was obtained by the following equation:

Drug content = (Analyzed content/Theoretical content) x 100 (Eq 1)

Viscosity measurement

By NDJ-55 digital Viscometer using a spindle no. 1 at 25 °C, the viscosity of the formulations was measured as it is without dilution. The measurements were performed in triplicate.

***In vitro* release study**

By USP dissolving apparatus II (Copley dissolution tester DIS 8000, UK) using the dialysis bag technique, the *in vitro* carvedilol release from the optimized nanoemulsions was performed. The dissolving medium for *in vitro* release analysis was phosphate buffer pH 6.8 with 1% tween 80. The quantity of carvedilol in nanoemulsion and the pure carvedilol solution was 1.5 mg of carvedilol and put in the dialysis bag, and then the dialysis bag submerges in 500 ml of dissolution medium and set at 37±0.5 °C and rotating velocity is at 50 rpm. An aliquot of 5 ml were siphoned at regular intervals of time (10, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180 min) and filtered using microfilter paper with pore size is 0.45 µm. An equal volume of the dissolving medium was added to obtain constant total volume. The drug content of the specimens was assayed by a UV-visible spectrophotometer at 285 nm wavelength. All analogies were done in triplicate [18].

Kinetic analysis of drug release [19]

The *in vitro* release data were corresponded into differential equations and release kinetic models to excuse the release kinetics of carvedilol from nanoemulsions. The kinetic models exploited were zero-order (cumulative % drug dissolved against time), first-order (log cumulative % of drug undissolved against time), Higuchi (cumulative % amount of drug dissolved against the square root of time) and Korsemeyer-Peppas (log cumulative % of drug dissolved against log time) models.

Drug-excipient compatibility study

Fourier transformed infrared spectroscopy (FTIR)

The study of interactions between drug and excipients achieved by FTIR Spectroscopy. IR spectrum of pure drug and the physical mixture at a ratio (1:1) of carvedilol with all components of nanoemulsion was carried out where the range was selected from 400 cm^{-1} to 4000 cm^{-1} [20].

Atomic force microscopy (AFM) study

The shape and size of carvedilol nanoemulsion were detected by AFM angstrom advanced inc. AA3000 USA. AFM analysis was achieved by putting drops of the nanoemulsion onto a glass slide and then measure [21].

Statistical analysis

Agreeing to the analysis of variance (ANOVA) assay. The results of the investigation were given as an average of triplicate specimens were studied at level (P<0.05) [22].

RESULTS AND DISCUSSION

Components screening by solubility determination

One of the important factors to formulate a stable nanoemulsion system is choosing components of nanoemulsion which are oil, surface active agent and co-surfactant. The more imperative for the nanoemulsion formulation is a higher solubility of carvedilol in the oily phase rather than solubilization of drug in the surfactant or co-surfactant due to the gastrointestinal tract dilution of nanoemulsion will yield to a lower solvability of surfactant or co-surfactant that leading to risk of drug precipitation [23]. The outcomes of solubility of carvedilol in the components of nanoemulsion indicate that the solubility in various oils was in the following descending order; peppermint oil>anise oil>ginger oil>black seed oil>garlic oil>cyperus oil as shown in table 1. However, carvedilol has a higher solubility in peppermint oil, thus peppermint oil was chosen as oil phase for the formulation of nanoemulsions. The solubility of carvedilol in surfactants was in the following descending order; tween 80>tween 20 as presented in table 1. The solubility of carvedilol in co-surfactants was in the following descending order methanol>ethanol>propylene glycol as shown in table 1thus, co-surfactant ethanol was selected for the study as it showed high drug solubility due to shorter chain length and less viscosity than propylene glycol and less toxicity than methanol [24]. Thus, depending on solubility studies the nanoemulsion components which are the peppermint oil as oil, tween80 as a surfactant, and ethanol as co-surfactant was selected for the preparation of the nomination system.

Table 1: Solubility studies

S. No.	Oils, surfactants and co-surfactants	Solubility (mg/ml)
1	Ginger oil	15.841
2	Black seed oil	3.662
3	Anise oil	17.959
4	Peppermint oil	31.937
5	Cyperus oil	2.497
6	Garlic oil	3.026
7	Tween 20	11.816
8	Tween 80	16.492
9	Propylene glycol	9.148
10	Methanol	17.175
11	Ethanol	12.436

Construction of pseudo-ternary phase diagrams

Pseudoternary phase plots were made by variable Smix ratios as 1:1, 2:1, 3:1, and 4:1 as shown in figs. 1–4. The shaded regions of phase plots display the areas of nanoemulsion, whereas the region that is non-shaded displays the area of emulsion.

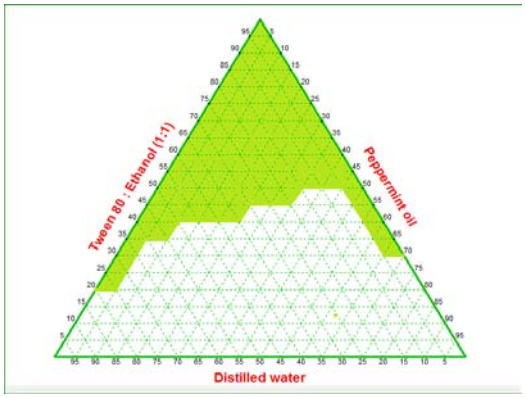


Fig. 1: Pseudoternary phase diagram of peppermint oil, tween 80, ethanol and distilled water (Smix 1:1)

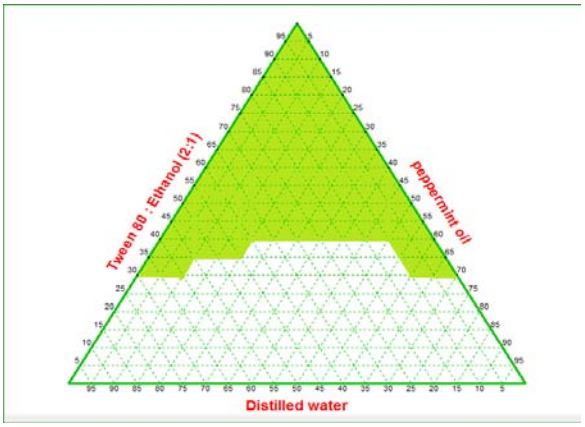


Fig. 2: Pseudoternary phase diagram of peppermint oil, tween 80, ethanol and distilled water (Smix 2:1)

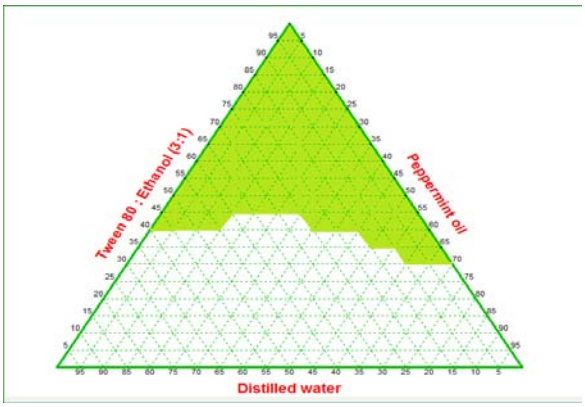


Fig. 3: Pseudoternary phase diagram of peppermint oil, tween 80, ethanol and distilled water (Smix 3:1)

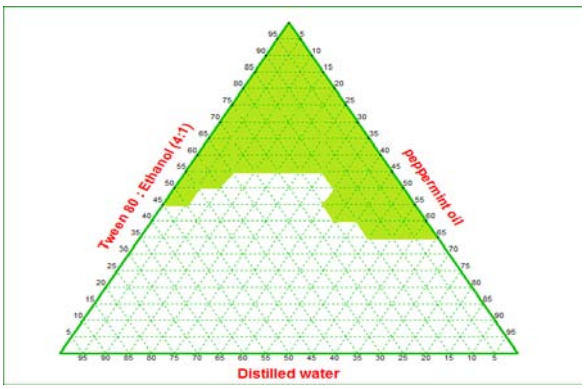
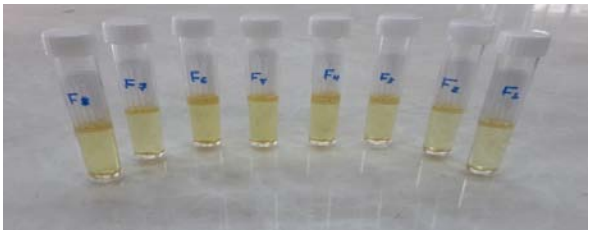


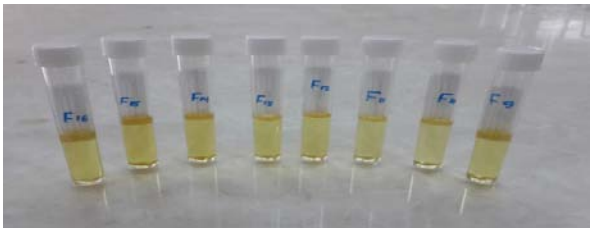
Fig. 4: Pseudoternary phase diagram of peppermint oil, tween 80, ethanol and distilled water (Smix 4:1)

Screening of carvedilol nanoemulsion formulations on the basis of thermodynamic stability studies [25]

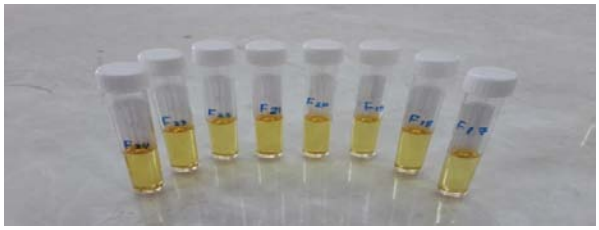
The outcomes of the thermodynamic study, which is centrifugation, heating-cooling cycles and freeze-thaw cycles. The outcomes indicate that all the preparations had an excellent physical stability as shown infig.5. Depend on thermodynamic stability results and criteria exploited for the choice of various formulations from the phase diagrams, we select the eight formulas which are F4 (NE1), F6 (NE2), F10 (NE3), F12 (NE4), F16 (NE5), F18 (NE6), F22 (NE7), F24 (NE8) for characterization of globule size, PDI, zeta potential, pH, electrical conductivity, percent of light transmittance, viscosity and *in vitro* release study.



Photographic picture (A)



Photographic picture (B)



Photographic picture (C)

Fig. 5: Inferential photographic pictures (A), (B) and (C) where it represented the carvedilol nanoemulsion formulations of F1-F8, F9-F16 and F17-F24 respectively

Characterization of the prepared carvedilol nanoemulsion

Globulesize assay

The results globule size range was NE1 (50-70.6 nm); NE2 (25-31.5); NE3 (11.1-158 nm); NE4 (5-125 nm); NE5 (9.97-199 nm); NE6 (5-140 nm); NE7 (56.1-70.6) and NE8 (111-140) that have tween 80: ethanol (%w/w) concentrations 40, 50, 30, 40, 40, 50, 50, 60 respectively. All the preparations had droplets in the nano scale [26]. Analysis of variance indicated significant correlativity between globule size values and independent variables (%w/w of Smix) where ($p<0.05$).

Polydispersity index (PDI) assay

PDI was from (0.007 to 0.135). The results of PDI indicated that nanoemulsion formulations had a high homogeneous and constrict size distribution.

Zeta potential assay

Zeta potential is an index of the nanoparticle dispersion stability. The results of the mean zeta potential scale (-10.45 to-22.56 mV) which indicate the stability of nanoemulsions. There should be a higher electrical charge on the NEs surface in order to preclude aggregation of the nanoemulsions in the solutions due to the strong resistance violence among particle. Zeta potential absolute values according to thumb rule are: the range-5 mV to+5 mV show fast aggregation, about 20 mV supply only short term stability, above 30 mV offers good stability and above 60 mV excellent stability[27]. The thumb rule can apply for perfect electric stabilization and stabilizers of small molecular weight, but not for large or great molecular weight surfactants such as tween 80 which is nonionic stabilizers that has a steric stability for conserving the NE stability [28].

Determination of pH

The carvedilol nanoemulsion formulations had suitable noticed pH value in the range of (7.04-7.25) that is better for oral administration

Electrical conductivity assay

The carvedilol nanoemulsions formulations had the average conductivity in the range of (0.16-0.30 ms/cm) that is shown o/w structure of nanoemulsions [29].

Percent of light transmittance assay

The percent transmittance of the all preparations was computed at (600 nm) where the blank was distilled water. The percent transmittance of the optimized preparations was found in a range from (96.161 % to 98.174%). The results of percent transmittance illustrate that all the formulations were closely transparent [30].

Drug content estimation

The outcome of drug content was in a range of (90.972-99.445%). The drug content deviated for up to 8.473 % between formulations NE1 to NE8.

Viscosity measurement

It was mostly noticed a very low viscosity of the carvedilol nanoemulsion preparations where the range was (41.937-241.603 mPa. sec). This was expected, due to one of the characteristic parameters of nanoemulsion preparations is of lower viscosity and this ensures comfortable handling, packing and smoothen formulations administration of preparations. Agreeing to analysis of variance, there is a significant difference ($P<0.05$) between carvedilol nanoemulsions.

***In vitro* release studies**

Drug release analysis was done for the pure drug and carvedilol nanoemulsions by employing the dialysis bag technique. Outcomes of carvedilol release from pure drug and carvedilol nanoemulsions that hold peppermint oil, tween 80 (surfactant) and ethanol (co-surfactant) which are{NE1,NE2 have oil: Smix (1:1): distilled water (10:40:50) and (10:50:40) ratio respectively}, {NE3,NE4 have oil: Smix (2:1): distilled water (10:30:60) and (10:40:50) ratio respectively}, {NE5,NE6 have oil: Smix (3:1): distilled water (10:40:50) and (10:50:40) ratio respectively} and {NE7,NE8 have oil: Smix (4:1): distilled water (10:50:40) and (10:60:30) ratio respectively} in phosphate buffer pH (6.8) with tween 80 1% (w/w) is presented in fig. 6. The profile of carvedilol release was significantly higher ($P<0.05$) in dissolution rate for the carvedilolNE3 with oil: Smix (2:1): distilled water (10:30:60) ratio while carvedilol release profile was significantly lower ($P<0.05$) in dissolution rate of the pure drug. The comparability profile of the drug release of pure drug and nanoemulsions NE1, NE2, NE3, NE4, NE5, NE6, NE7andNE8 reveal that the profile of drug release of nanoemulsions confirms the order: NE3>NE1>NE4> NE2>NE5> NE6>NE7>NE8>pure drug and the profile of drug release of nanoemulsions with Smix (1:1), Smix (2:1), Smix (3:1), Smix (4:1) confirm the order: NE1>NE2, NE3>NE4, NE5>NE6 and NE7>NE8 respectively. The release profile of all nanoemulsions in phosphate buffer pH (6.8) reflects the effect of surfactant concentration on the carvedilol release in each Smix ratio at a constant concentration of oil. As tween 80 concentration increase, the carvedilol release decrease due to that carvedilol molecules encounter retarding effect from tween 80 molecules also increase diffusional pathway for carvedilol molecules to reach dissolution medium after passing from dialysis bag and therefore we found that the profile of drug release of the nanoemulsions with Smix (1:1), Smix (2:1), Smix (3:1) and Smix (4:1) follow the order: NE1>NE2, NE3>NE4, NE5>NE6 and NE7>NE8 respectively. It was found that carvedilol release was more for the NE3 with oil: Smix (2:1): Distilled water (10:30:60) ratio due to the least tween 80 concentration and this gives the less retarding effect from tween 80 molecules and shorter diffusional pathways for carvedilol molecules to reach dissolution medium. Also, it is observed that carvedilol release was lower from nanoemulsions NE8 compared to other nanoemulsion formulations have oil: Smix (4:1): distilled water (10:60:30) ratio because higher tween 80 concentrations and this gives more retarding effect from tween 80 molecules and longer diffusional pathways for carvedilol molecules to reach dissolution medium. It was observed that the pure drug gives a lower dissolution rate of carvedilol profile in comparison to all nanoemulsion

formulations because that the reduction of drug particle size in nanoemulsion caused an increase in the surface area and permits a higher interaction with the solvent that result in an increase in dissolution rate [31].

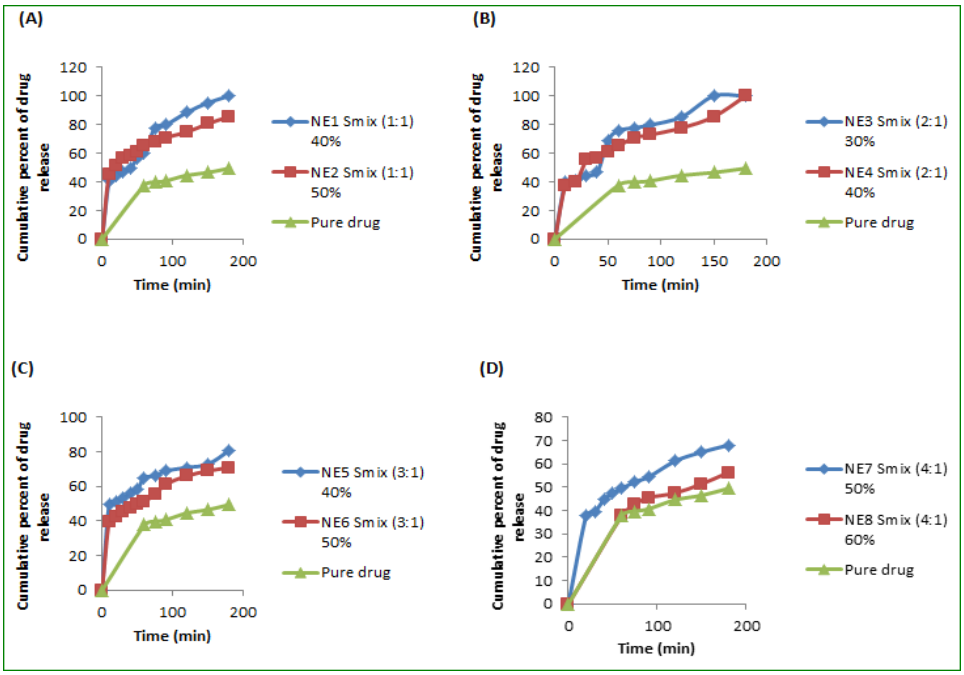


Fig. 6: Dissolution comparison of pure drug and nanoemulsion formulations where (A)Release profile of pure drug, NE1 and NE2 (B)Release profile of pure drug, NE3 and NE4 (C) Release profile of pure drug, NE5 and NE6 (D)Release profile of pure drug, NE7 and NE8

Kinetic analysis of drug release

The kinetic data of various nanoemulsion formulations were summarized in tables2. The data analysis illustrates that excellent regression coefficient (R^2) was received for Higuchi's equation, which suggested that the released of a drug in the idealistic matrix in all preparations was Higuchi's diffusion. The 'n' values (release exponent), of all nanoemulsion formulations, were significantly lower ($P<0.05$) than 0.45 indicating that the release of carvedilol from formulations following fickian transport i. e diffusion.

Table 2: The correlation coefficient (R^2) and release exponent (n) of different kinetic models of prepared nanoemulsions (NE1-NE8) and the pure drug released in phosphate buffer pH (6.8)+1 % (w/w) tween 80 solution

Formulation Code	Zero Order model	First Order model	Higuchi model	Korsemeyer-peppas model	
	R^2	R^2	R^2	R^2	n
NE1	0.9432	0.9304	0.9587	0.8864	0.1797
NE2	0.9553	0.9925	0.9963	0.9947	0.1825
NE3	0.8758	0.8912	0.9259	0.8811	0.1173
NE4	0.9352	0.7611	0.9695	0.8253	0.3212
NE5	0.9343	0.9564	0.9653	0.934	0.1005
NE6	0.9622	0.9808	0.9816	0.9663	0.1593
NE7	0.9844	0.9944	0.9952	0.9833	0.2594
NE8	0.9616	0.9683	0.9698	0.969	0.3295
Pure drug	0.9918	0.9931	0.9939	0.9906	0.2457

Where R=regression coefficient, n= diffusion exponent

Selection of the optimized formula

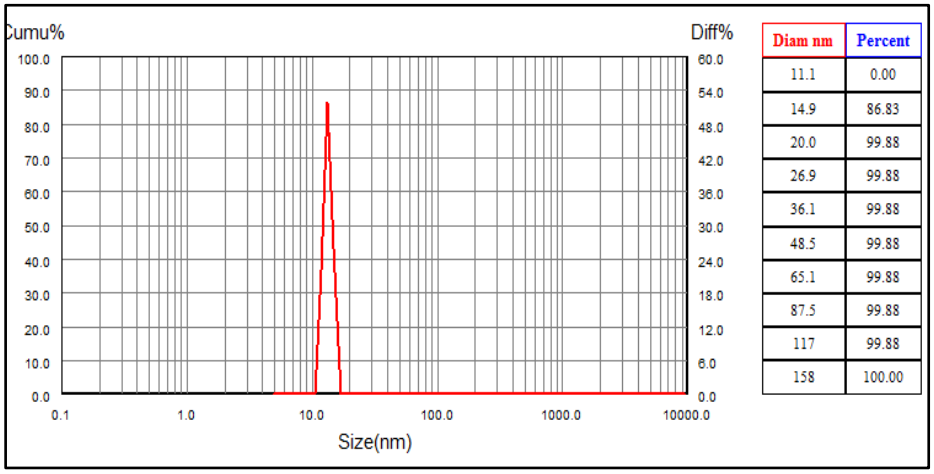
From study of the globule size analysis, PDI, zeta potential measurements, pH, electrical conductivity, percent of light transmittance, drug content, viscosity and *in vitro* release studies behavior of the nanoemulsion formulations (NE1-NE8) it was found that NE3 is selected formula that characterized by a low particle size range (11.1-158 nm) as shown in fig. 7, low PDI (0.030), higher zeta potential (-22.56 mV), good pH value (7.12), efficient electrical conductivity (0.30 ms/cm), classy percent of light transmittance (97.274), higher % drug content (99.445), acceptable low viscosity (0.00105 Pa. s) and higher dissolution rate. The selected formula (carvedilol NE3) subject for further investigations of drug-excipient compatibility and atomic force microscopy (AFM) study.

Drug-excipient compatibility studies

Fourier transformed infrared spectroscopy (FTIR)

The result of the FTIR spectrum of pure carvedilol showed the peaks as described in fig.8 was 3342.75 (Aliphatic Secondary amine, NH stretch), 1629.9 (Secondary amine NH bend), 1174.69 (Secondary amine, CN stretch), 1346.36(Aromatic Secondary amine, CN stretch), 3450 (Aromatic Secondary amine, NH stretch), 3203.87(Hydroxy group, H-bonded OH stretch), 1097.53 (Secondary alcohol, C-O stretch), 1303.92 (Primary or secondary, OH in-plane bend), 617.24(Alcohol, OH out-of-plane bend), 2820 (Methoxy (CH3-O-), C-H stretch), 1253.77 (Aromatic ethers, Aryl-O stretch), 2922.25 (Methylene C-H asymmetric stretch), 2847.03(Methylene C-H symmetric stretch),1448.66 (Methylene C-H bend),1606.76, 1587.47 and1502.6 (Aromatic ring stretch(C=C)), 3090 (Aromatic C-H stretch), 1213.27 (Aromatic C-H in-plane bend),

748.41(Aromatic C-H out-of-plane bend, these peaks were corresponding with the described one which suggests the drug purity. Also the spectrum of physical mixture (1:1) of carvedilol with all nanoemulsion components which are tween 80, ethanol and peppermint oilas shown in fig. 9were studied by FTIR spectroscopy using KBR disc. The results show that the characteristic peaks of carvedilol not affected and prominently observed in all described IR spectra, this indicated that there is no incompatibility between the drug and excipients and no interaction between carvedilol and nanoemulsion components.



Diam nm	Percent
11.1	0.00
14.9	86.83
20.0	99.88
26.9	99.88
36.1	99.88
48.5	99.88
65.1	99.88
87.5	99.88
117	99.88
158	100.00

Fig. 7: The particle size distribution for NE3

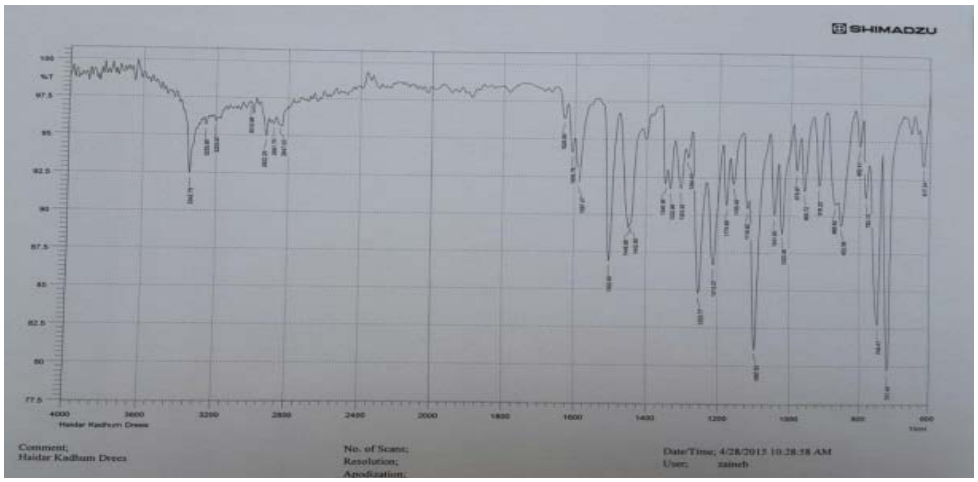


Fig. 8: FTIR spectra of pure carvedilol

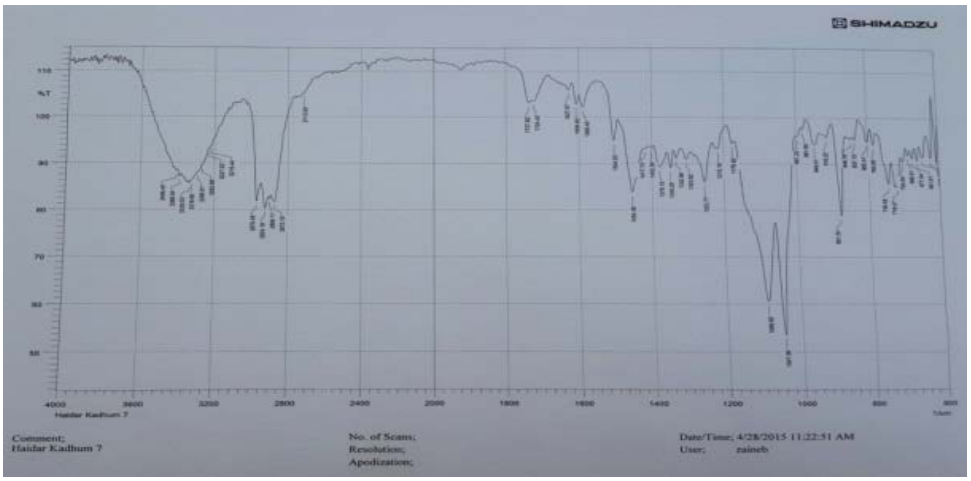


Fig. 9: FTIR spectra of physical mixture (1:1) of carvedilol, tween 80, ethanol and peppermint oil

Atomic force microscopy study [32]

The AFM study that described in fig. 10, confirm that the system in nanoscale and has high stability against aggregations of particles within carvedilol NE.

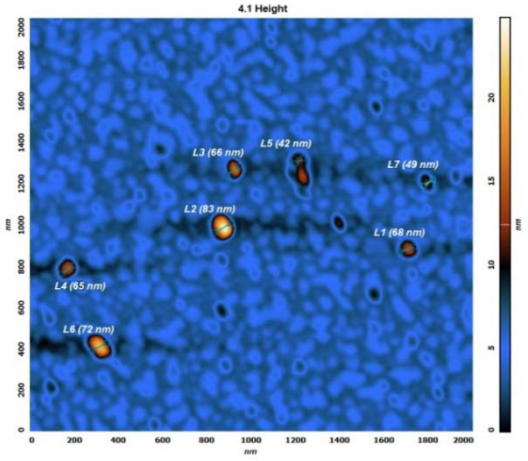


Fig. 10: AFM image of carvedilol nanoemulsion (NE3) where scanning area is 2 µm * 2 µm

CONCLUSION

1. An aqueous phase titration method which is low energy emulsification methods employ low energy that consolidate the nanoemulsions manufacture by decrease the cost and increase stability.

2. *In-vitro* dissolution study provided a significant increase in the solubility of carvedilol for NE3 compared to pure drug and other nanoemulsion formulations thus; NE3 can be regarded as commercially feasible alternative to formulate a carvedilol preparation to be employed orally.

3. Nanoemulsion NE3 which is a fat base formulation has accepted to meliorate the bioavailability potential of the hydrophobic drugs by increment their dissolution and permeation therefore the NE3 can be used for oral delivery of the biopharmaceutics classification system (BCS) class II and IV drugs.

CONFLICTS OF INTERESTS

All authors have none to declare.

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