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FORMULATION AND EVALUATION OF W/O/W MULTIPLE EMULSION OF ENALAPRIL MALEATE

M. Vani[*1], S. Jaisri[1], S. Aarthi[1], K. Karthick[1], A. Meena[1], A. Shanthi[1]

[1*]Department of Pharmaceutics, The Tamil Nadu Dr. M.G.R. Medical University Chennai, Tamil Nadu, India.

ABSTRACT

Enalapril is a prodrug belonging to the angiotensin - converting enzyme (ACE) inhibitor drug that works on the renin- angiotensin aldosterone system, which is responsible for the regulation of blood pressure and electrolyte homeostasis. Enalapril is an orally active and long acting non sulphydryl antihypertensive agent that suppresses the renin- angiotensin aldosterone system to cover blood pressure. Enalapril maleate of W/O/W multiple emulsion was prepared by 2 step emulsification technique using different non-ionic surfactants (span 40, span 60, span 80, tween 80). Fourier transform infrared compliance as showed the good results in all formulations. The formulation F3 showed that best result from the study conducted and was found that no interaction between drug and surfactants. It is concluded that as the increase in droplet size and decrease in the percentage entrapment efficiency. The formulation F3 showed the highest percentage of cumulative drug release and optimized to be the best formulation.

KEYWORDS

ACE Inhibitor, Nonionicsurfactant, Enalapril maleate and Renin-angiotensin aldosterone system.

Author for Correspondence:

M. Vani,
Department of Pharmaceutics,
K.K. College of Pharmacy,
Gerugambakkam, Chennai-600128,
Tamilnadu, India.

Email: mandrummoorthy@gmail.com

INTRODUCTION

Multiple emulsions, additionally referred to as w/o/w and o/w/o emulsions, area unit innovative carrier systems that area unit advanced, polydispersed, polyphase systems created of a minimum of 2 immiscible liquids. These 2 emulsions area unit stabilized victimization lipotropic and hydrophilic surfactants. The droplets of phase contain even smaller spread droplets themselves, therefore additionally referred to as "emulsions of emulsions"[1]. The inner spread droplets in multiple emulsions area unit separated

from outer liquid section by a layer of another section. Since the substance should move from the inner to the outer miscible sections via the center unmixable organic phase before being discharged at the absorption website, this method is usually stated because the liquid membrane system[2]. Partition and diffusion constant of drug and strength of middle membrane section, that may be a multi-molecular layer of oil, water and wetting agent at each the interfaces of multiple emulsion, controls the drug unharness from these systems. These area unit heterogeneous preparation composed of 2 immiscible liquids, i.e., oil and water, one in all that is spread as fine droplets uniformly throughout the opposite[3]. Drop diameter in multiple emulsions could vary from 0.1 to 100μm. By emulsifying associate degree existing emulsion to make 2 spread phases, several emulsions fabricated from oil and water area unit created. These emulsions are researched as controlled-release drug delivery systems and have promising uses in an exceedingly form of industries, together with chemistry, medical specialty, cosmetics, etc. (DDS)[4]. High pressure level is treated with ACE inhibitor. Conveyance down high pressure level reduces the danger of heart attacks, excretory organ problems, and strokes. ACE inhibitor may be a member of the ACE inhibitor medication taxonomic category. So as to facilitate easier blood flow, it acts by reposeful blood vessels[5]. Concerning hour of the absorbed dose is extensively hydrolyzed to Enalapril via de-esterification mediate by viscous esterase. In humans, metabolism on the far side bio activation to Enalapril isn't discovered[6].

MATERIAL AND METHODS

Enalapril, antidepressant drug is the sample obtained from Intermed Laboratories, Chennai, Span 40, Span 60, Span 80, Tween 80 were obtained from scientific research lab, Chennai, Liquid paraffin, Phosphate buffer (6.8) were additionally used.

Pre-formulation studies

Physical appearance

The drug (Enalapril) powder was examined for its organoleptic properties like color and odor.

Solubility study

The sample underwent qualitative testing to determine its solubility in different solvents. It was determined by taking 10mg of drug sample in 10ml of solvent as water, methanol, ethanol, acetonitrile, pH buffer 6.8 in small test tubes and well solubilized by shaking[7].

Melting point determination

The Melting point was determined by the Capillary tubes were fused, filled, and packed by gently pressing the open end into pure drug sample and tapping the capillary's bottom against a hard surface to force the drug down into the tube's bottom. The tube was positioned once the medicine was stuffed into the tube's bottom into the slot of the apparatus, the apparatus was started and the temperature was noted at which the drug melt[8].

Determination of Wavelength of Maximum Absorbance (λmax)

Accurately weighing 10mg of the drug, 10ml of volumetric flask were then filled with it. After that, phosphate buffer 6.8 (a suitable solvent) was added to completely dissolve the drug. With solvent, the volume was increased to 10ml. At 1000g/ml, the prepared sample. Then, 1ml of the proceding solution was transferred to a different 100ml volumetric flask and diluted to the desired concentration using phosphate buffer 6.8. This sample was 10μg/ml[9].

Preparation of Calibration Curve of Enalapril:

The calibration curve was drawn between the concentration and absorbance. The calibration curve of 2-20μg/ml was carried out and Enalapril solution was scanned in the UV range of 290-365nm by using systronic double beam UV spectrometer[10].

Determination of partition coefficient

25mg of drug and 25ml of distilled water and 25ml of methanol was taken in the separating funnel the separating funnel were shaken for 2 hours in a wrist action shaker for equilibration. And was allowed to stand for 1hrs, then the two phases were separated

and the amount of the drug in aqueous phase as well as in lipophilic phase was analyzed spectrophotometrically. Using a formula, the drug's partition coefficient in both phases was obtained:

K = amount of drug in organic layer/ amount of drug in aqueous layer[11]

Fourier-Transform Infra-Red spectroscopy (FTIR)

Using IR spectroscopy, the IR spectrum of the drug ingredient was verified. The presence of characteristic peaks associated with specific structural characteristics of the drug molecule was noted. Compatibility study for drug and surfactant was performed by using FTIR spectroscopy[12].

Preparation of multiple emulsion

Multiple emulsions were prepared by 2 step emulsification process a) Preparation of primary emulsification b) Secondary emulsification.

Primary emulsification

10ml of water containing 25mg of drug was drop wise added to 14ml of oil section containing primary wetting agent (Span40, Span60, and Span 80) and 25mg of drug with continuous stirring at 5000 rate for 5 mins. It provides the primary emulsion.

Secondary emulsification

With constant stirring at 1000rpm for 10 minutes, 20ml of a viscous primary emulsion were further emulsified with an external aqueous phase containing secondary emulsifier (Tween 80) and 50mg of drug. The same process was used to prepare all of the formulations. By analysing various formulations, the principle emulsifier's impact was discovered[13].

EVALUATION OF MULTIPLE EMULSION

Macroscopic and microscopic evaluation

Macroscopic evaluation was performed in order to judge the homogeneity of the EE and ME formulations. Formulations were visually observed for homogeneity, color, consistency and appearance. Optical microscope was used for microscopic evaluation and observations were made at 40x magnification after suitable dilutions with distilled water[14].

Globule size determination

In this study, globule sizes of the multiple emulsions prepared were determined using light microscope for the freshly prepared emulsions and for the emulsions kept at different conditions for 30 days[15].

Entrapment efficiency

Freshly manufactured W/O/W multiple emulsions were immediately centrifuged at 4000rpm for 10 minutes to calculate the percentage entrapment efficiency (% EE). The bottom layer, the aqueous phase, was then accurately removed and diluted with phosphate buffer 6.8 to 1 ml. The solution was filtered and drug content was analyzed on UV spectrophotometer at 247.6nm.

The Encapsulation Efficiency was determined by following equation:

%EE = [Total drug incorporated - Free Drug] x 100 /Total drug[16]

Rheological analysis

Rheological analysis was performed employing Brookfield viscometer (DV-I Prime, Brookfield, USA) using S61 spindle at 20rpm at room temperature. All the measurements were carried out in triplicate. The rheological behavior of each EE and ME was evaluated by plotting the viscosity versus shear rate[17].

Zeta Potential

The colloidal systems potential stability is indicated by the zeta potential. The tendency for the particles to attract each other and come together will be absent if all the particles in suspension have a strong negative or positive zeta potential. However, if the zeta potential of the particles is low, there won't be any force to stop the particles from aggregating and flocculating. It is customary to draw the border between stable and unstable suspensions at either +30 or -30mV. Generally, stable particles are those with zeta potentials greater than or equal to +30mV or greater than -30mV. The particles will eventually settle and create a densely packed bed if their density is different from that of the dispersant[18].

***In vitro* drug release study**

Cellophane membrane with a thickness of 200mm and a breaking strength of 2.7kg/cm was used for the in vitro drug release research on a basic dissolving cell. The cellophane membrane was immersed in a 5% v/v glycerol solution for at least 60 minutes before being used in release studies. It was then cleaned five times with distilled water before being used in the studies. 15ml freshly prepared multiple emulsion was added to donor chamber, made up of a hollow glass tube (2.5cm in diameter and 10cm in length) and membrane was tied on bottom end of the tube with anylon string. This tube was dipped into 250ml vessel containing 100ml of PBS pH 6.8 and was stirred at 100rpm on a magnetic stirrer and maintained at 37°C which acted as receiving chamber. Aliquots of 1ml were collected from receiving chamber at predetermined time interval sand the drug content was determined on UV spectrophotometer at 247.6nm after suitable dilution[16].

pH determination

A digital pH-meter was used to measure the pH of freshly created emulsions as well as emulsions stored under various conditions. pH measurements were repeated for multiple emulsions after 1, 3, 7, 14, 21 and 30 days of preparation.

Stability test

Centrifugation Test

Freshly prepared multiple emulsion formulations and formulations stored at different conditions were centrifuged at 3000rpm for 15 minutes by placing 10mg of samples in the centrifugal tubes. The same test was repeated for multiple emulsion after 24hour, 3 days, 7days, 18 days and 30days of preparation.

Thermal Stability Test

Multiple emulsion samples were stored in tightly closed glass vessels at 8 ±1^{o}C (refrigerator), 25 ±0.5^{o}C (room temperature) and 40 ±0.1^{o}C(oven) and examined periodically to test the physical characteristics[18].

RESULTS AND DISCUSSION

Pre-formulation studies

Physical appearance

The drug powder was examined for its organoleptic properties like color and odor and it was observed that Enalapril maleate is a white to off-white, crystalline powder.

Solubility study

The sample's solubility in various solvents was qualitatively examined.

Melting point determination

Melting point of Enalapril maleate was found at 142±2ºC.

Partition coefficient determination

25mg of drug and 25ml of distilled water and 25ml of methanol was taken in separating funnel the separating funnel were shaken for 2hrs in a wrist action shaker for equilibration. And was allowed to stand for 1hrs, then the 2 phases were separated and the amount of the drug in aqueous phase as well spectrophotometrically. In both phases, the drug's partition coefficient was estimated using the following formula:

$$\text{Partition coefficient, } K = \frac{\text{Amount of drug in organic layer}}{\text{Amount of drug in aqueous layer}}$$

Calibration curve of Enalapril maleate

Accurately weighing 10mg of the medication, it was then transferred to a 10ml volumetric flask. To completely dissolve the medication, phosphate buffer 6.8 (a suitable solvent) was then added. Solvent was used to increase the volume to 10ml. A 1000g/ml prepared sample was used. Then, 1ml of the aforementioned solution was transferred to a different 100ml volumetric flask and diluted with phosphate buffer 6.8 to the appropriate concentration. This sample was 10µg/ml. The absorbance of these drug solutions were estimated at 212nm. This procedure was performed in triplicate to valid the calibration curve.

Compatibility studies

Utilizing FTIR, compatibility investigations were carried out (Fourier transform infrared spectrophotometer). The spectrum of pure drug, surfactants and mixture of drug and excipients were studied. The peaks obtained in the spectra of each

formulation correlates with peak of drug spectrum. This shows that the medicine and the formulation's ingredients got along well.

EVALUATION

Microscopic evaluation

Microscopic analysis shows that many droplets were presented in the internal phase of multiple globule indicating type B w/o/w multiple emulsion.

Globule size determination

Globule size of optimized batches were found to be in the range of 15.65 ± 1.97µm to 25.21 ± 2.23µm. Multiple emulsion had narrow size distribution as PDI was in the range of 0.2-0.3. From the results obtained, it was found that multiple emulsion prepared with Span 80 had slightly larger size as compared to multiple emulsion prepared with Span 40 and span 60. The possible reason could be the difference in HLB values of Span 80 and Span 40 and 60. The lower particle size obtained with Span 40. Greater surfactant buildup at the interface may have caused a thicker interfacial film, which in turn increased the size of the globules.

Zeta potential

A larger zeta potential value ensures that there is no phase separation, whereas a value closer to zero increases the likelihood of coalescence and denotes instability. The zeta potential is a measure of the charge on the surface of the particles.

The zeta potential decreased as the surfactant concentration increased. This may be as a result of the surfactant's nonionic nature and rising concentration. Negative values of the zeta potential indicate that the electrostatic repulsion between globules will prevent their aggregation and thereby stabilize the multiple emulsion.

Entrapment efficiency

The result shows the multiple emulsion prepared with Span 80 had higher EE and ME as compared to multiple emulsion prepared with Span 60. Lower EE and ME could be attributed to higher solubilization effect produced by higher concentration of Span 80. At higher concentration of surfactant, solubility of Enalapril maleate in the external phase may increase due to diffusion of drug from lipid into aqueous phase leading to reduced EE and ME.

In vitro drug release

The result indicates more release of F3 formulation will be higher release profile as compare to other formulation and data was shown in the figure given below.

Discussion

The release profiles of Enalapril maleate from multiple emulsion and plain drug solution through dialysis bag are presented. About 60% of drug was released in 2 hours and 94% of drug released in 6 hours from plain drug solution. Multiple emulsion exhibited biphasic release with an initial rapid release phase (40-45%) in 1st two hours and then a slower release (65-85%) between 2 to 8hours. Initial release of Enalapril maleate might be due to presence of Enalapril maleate in the external aqueous phase while the second prolonged release phase can be attributed to the slow release from the inner aqueous phase governed by the interfacial barrier of the oil phase. The drug in the internal phase of w/o/w EE and ME is compelled to partition through two phases before being released into the sink solution. Several release models were fitted with the data from in vitro drug release experiments. The regression coefficient value was found to be highest (r^2 =0.9733) for Higuchi model. Hence, it can be concluded that the release of Enalapril maleate from multiple emulsion was by Higuchi diffusion-based mechanism.

Stability studies

The stability of multiple emulsion was observed in different storage conditions and analyzed them microscopically and visually for particle size, zeta potential and entrapment efficiency.

Table No.1: Solubility of Enalapril maleate in different solvent

S.No	Solvent	Solubility
1	Phosphate buffer 6.8	Soluble
2	Methanol	Freely soluble
3	Ethanol	Freely soluble
4	Acetonitrile	Soluble
5	Water	Sparingly soluble

Table No.2: Partition coefficient values of enalapril

S.No	Solvent System	Partition Coefficient
1	n-Octanol /Distilled water	4.6

Table No.3: Standard graph of Enalapril maleate (6.8 pH phosphate buffer)

S.No	Concentration(µg/ml)	Absorbance (nm)
1	0	0
2	2	0.313
3	4	0.456
4	6	0.612
5	8	0.805
6	10	0.980

Table No.4: FTIR values of pure drug

S.No	Characteristic peak	Pure drug
1	C=O Stretching (ester)	1733.05
2	C=O Stretching (amide)	1643.23
3	C=O Stretching (carboxylic acid)	1770.42
4	N-H stretching (amide)	3780.20

Table No.5: Zeta potential values

S.No	Formulation	Zeta Potential (mV)
1	F1(span 40)	-15±1.14
2	F2(span 60)	-16.09±0.99
3	F3(span 80)	-18.49±2.11

Table No.6: Showing *In-vitro* release study

Time (hour)	Percentage drug release		
	F1	F2	F3
1	13.65	13.93	15.09
2	20.17	19.74	23.99
3	26.5	28.74	33.5
4	35.33	37.33	43.97
5	46.07	45.4	53.22
6	55.74	58.19	63.96
7	69.16	70.16	70.18
8	72.28	75.28	85.83

Table No.7: Values of linear correlation coefficient of enalapril

In-vitro release study	Linear correlation coefficient (r2) value			
	Zero order	First order	Higuchi	Korsemeyer peppas
	0.9364	0.9705	0.9733	0.8568

Table No.8: Organoleptic characteristics

Time	Liquefaction			Color			Phase separation			Centrifugation		
	A	B	C	A	B	C	A	B	C	A	B	C
0 hour	-	-	-	W	W	W	-	-	-	-	-	-
1 hour	-	-	-	W	W	W	-	-	-	-	-	-
24 hour	-	-	-	W	W	W	-	-	-	-	-	-
72 hour	-	-	-	W	W	W	-	-	-	-	-	-
7 days	-	-	-	W	W	W	-	-	-	-	-	-
14 days	-	-	-	W	W	W	-	+	-	+	+	+
21 days	-	-	-	W	YW	YW	-	+	+	+	+	+
28 days	-	+	+	YW	YW	YW	-	+	+	+	+	+
30 days	-	+	+	YW	YW	YW	-	+	+	+	+	+

(-) = NO changes, (+) = slight changes, W=white, YW= yellowish-white, (++) = more changes, A=8ºC, B=25ºC, C=40ºC (in oven) (n=3)

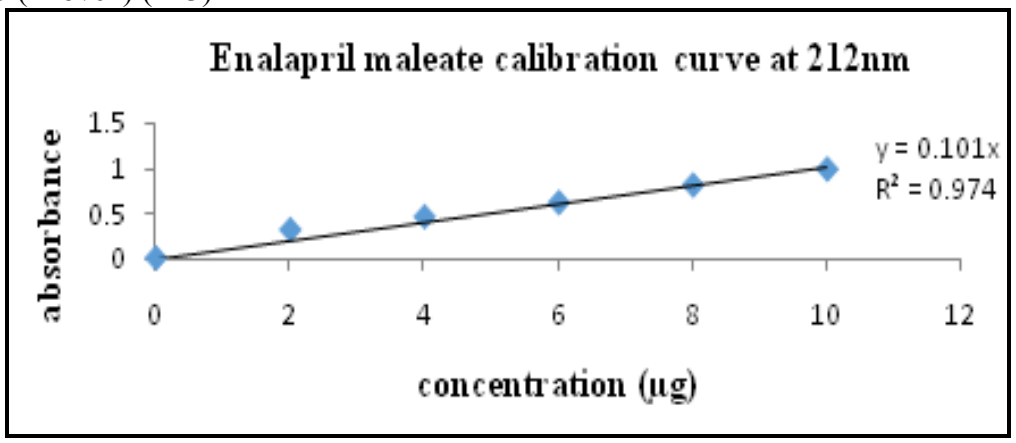

Figure No.1: Calibration curve of Enalapril maleate in phosphate buffer 6.8

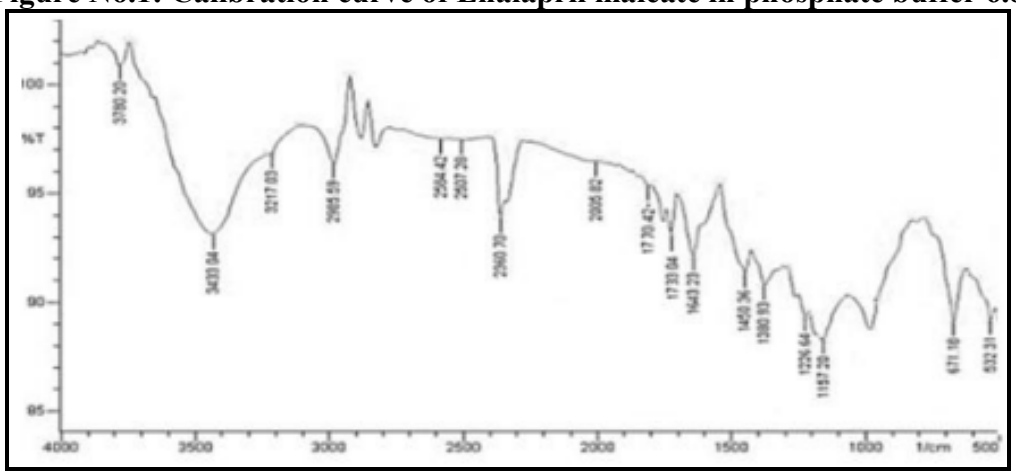

Figure No.2: FTIR of pure drug Enalapril maleate

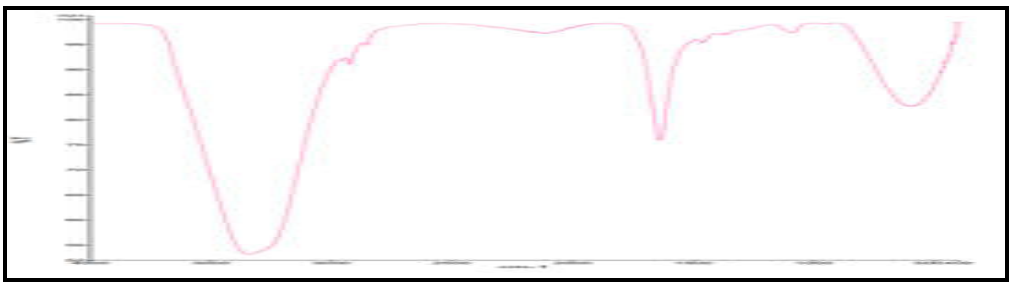

Figure No.3: FTIR of W/O/W multiple emulsion of Enalapril maleate (F3)

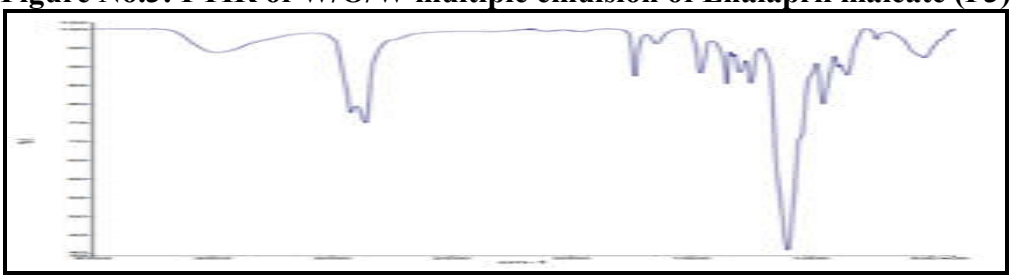

Figure No.4: FTIR of SPAN 80

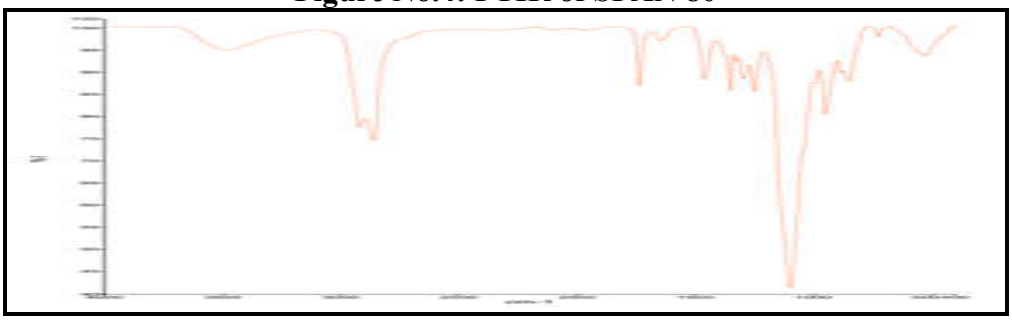

Figure No.5: FTIR of TWEEN 80

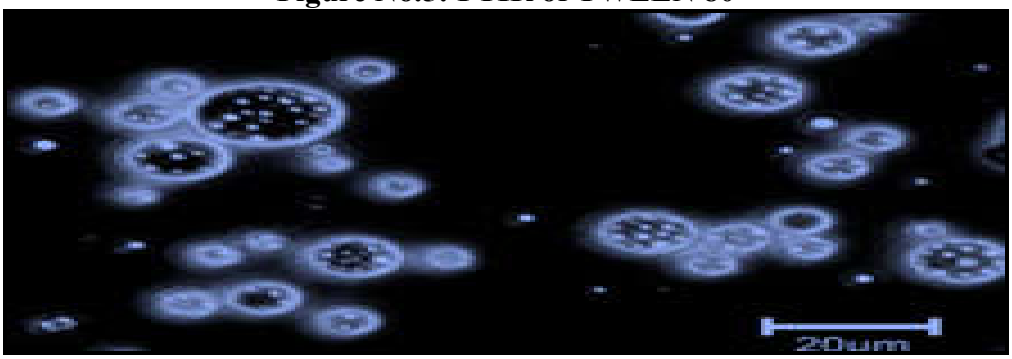

Figure No.6: Optical photograph of w/o/w of ME (under 40x)

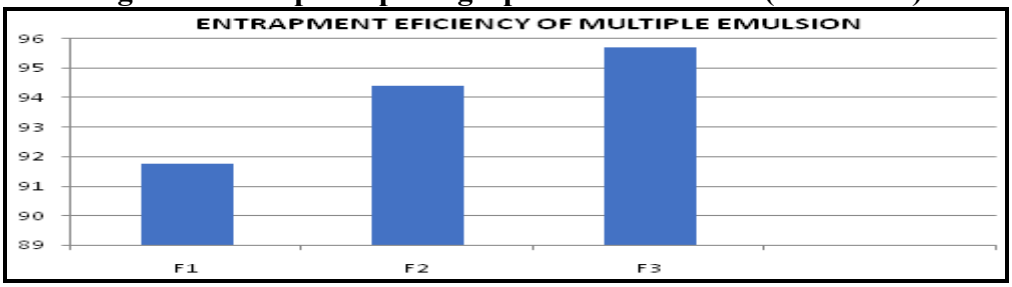

Figure No.7: Entrapment efficiency of multiple emulsion

Figure No.8: *In vitro* drug release of multiple emulsions

Figure No.9: Showing zero order release kinetics of F1, F2, F3

Figure No.10: Showing first order release kinetics of F1, F2, F3

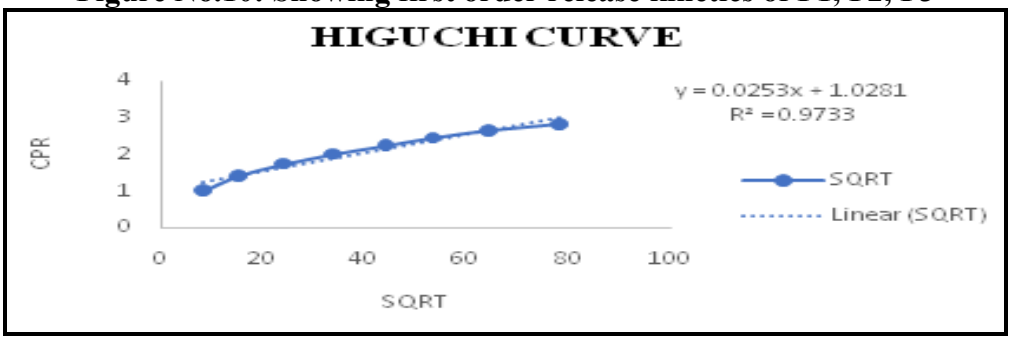

Figure No.11: Showing higuchi curve of F3

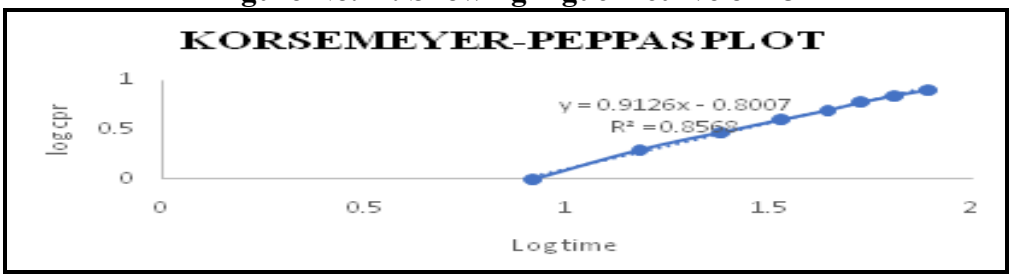

Figure No.12: Showing korsemeyer peppas curve of F3

CONCLUSION

W/O/W Multiple emulsion containing Enalapril maleate were developed by two step emulsification technique using different surfactants (Span 40/Span 60/Span 80/Tween 80). The drug pre-formulation studies were carried out like FTIR to find various functional group are same as the standard drug and found that was no interaction between drug and surfactant. Good correlation was obtained between actual and predicted values for the optimized formulation. Drug release across the dialysis bag started very quickly and then slowed down over the course of 8 hours. A study on permeability revealed that multiple emulsion had a greater penetration rate than ordinary drug solution. Stability studies indicated that refrigeration condition was desirable for the storage of developed multiple emulsion. The objective of present work is to development and evaluation of multiple emulsion of Enalapril maleate. The FTIR studies were carried out to find out the various functional group are same as the standard drug and it was found that was no interaction between drug and surfactant. Freshly prepared primary emulsion was creamy white in color, liquefaction, phase separation are presented in Table No.11. It can be concluded that as the increase in droplet size, the percentage entrapment efficiency decrease. The percentage cumulative amount of drug released at the end of 8 hours was 85.83 % for formulation F3 which was optimized to be the best formulation.

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CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

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