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PREPARATION AND *IN-VITRO* EVALUATION OF MICRO EMULSION OF ANTI-HYPERTENSIVE DRUG: VALSARTAN

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ABSTRACT

Valsartan is an orally administered ACE inhibitor for the treatment of hypertension and cardiac failure, but its solubility and oral bioavailability are poor. The objective of investigation is to formulate a microemulsion drug delivery system of valsartan using minimum surfactant concentration that could improve its solubility and oral bioavailability. Valsartan microemulsion were prepared by Phase-titration method. The composition of optimized formulation consist of Capmul MCM(Oil), Tween 20 (Surfactant),PEG 400(Co-Surfactant) and it contains 40 mg of Valsartan.Pseudo-ternary phase diagrams were plotted to check for the micro-emulsification range. Prepared microemulsion formulations were tested for micro emulsifying properties and the resultant microemulsion were evaluated for robustness to dilution, viscosity, drug content, thermodynamic stability studies and in-vitrodissolution. The optimized microemulsion formulation further evaluated for thermodynamic stability studies, particle size distribution, and zeta potential to confirm the stability of the formed Microemulsion. Resultant microemulsion optimized formulation (F2) shows drug release (99.71%), droplet size (36 nm), viscosity (0. 8872 cP), Zetapotenial (-38.8 mV) and infinite dilution capability. The formulation was found to show a significant improvement in terms of the drug release with complete release of drug within 80 minutes. Thus, micro emulsifying formulation of valsartan was successfully developed with sustained release.

INTRODUCTION: Microemulsions are four component mixtures composing of an oil phase, a water phase surfactant/s and a co-surfactant. The tendency towards formation of w/o or o/w microemulsion is dependent on the properties of the oil and the surfactant, the water-to-oil-ratio and the temperature.

When a mixture of surfactant and cosurfactant is added to a biphasic oil-water system, a thermodynamically stable, optically transparent or translucent, low viscosity and isotropic mixture spontaneously forms [1]. The transparency of these systems arises from their small dropletsdiameter (10-200 nm).

Such small droplets produce only weak scattering of visible light when compared with that from the coarse droplets (0.5-100 µm) of traditional or standard macro-emulsions such as emollient liquids, cream, lotions, etc., structurally, micro-emulsions have normal micellar solutions, reverse micelles, cores or droplets of water or oil, and, for some systems, even bi-continuous structures could solubilizelarge amounts of both oil and water soluble drugs within micro-emulsions [2].

To triumph over these problems, various formulation strategies are exploited such as use of surfactants, lipids, permeation enhancers, micronisation, salt

formation, cyclodextrins, nanoparticles and solid dispersions. Each and every method for bioavailability enhancement is having its own merits and demerits. In salt formation, the salts that are formed may convert back to their original acid or base forms and lead to aggregation in the gastro-intestinal-tract (GIT). Particle size reduction may not be desirable in situations where handling difficulties and poor wettability are experienced for very fine powders.

For compounds in which the primary limitation to absorption is poor aqueous solubility and slow dissolution rate, where intestinal permeability is not a limiting factor, (e.g., BCS Type II drugs) and for which conventional formulation approaches (e.g. salt or crystal form selection, particle size reduction, solid dispersions or the addition of surfactants) have failed, a lipid-based formulation should be considered [3].

Micro-emulsion drug delivery system are the isotropic mixtures of oil, surfactant, co surfactant and drug that form oil in water microemulsion when introduced into aqueous phase under gentle agitation. Micro-emulsions are among the methods used to improve the oral bioavailability of poorly soluble drugs by presenting and maintaining the drug in a dissolved state, in small droplets of oil, all over its transit through the GIT [4].

These formulations spread readily in the GIT, and the digestive motility of the stomach and the intestine provide the agitation necessary for micro-emulsion. In a good micro-emulsion system, small emulsion droplets containing dissolved drug are formed on contact with gastrointestinal fluid. The drug in the fine emulsion droplets is exposed to a large interfacial area thus allowing for greater diffusion through the membrane to take place [5].

Valsartan is ACE inhibitor used as an adjuvant in treatment of hypertension. However, the low aqueous solubility and poor dissolution of this molecule in gastric fluid affects its rate of absorption, resulting in a low and variable oral bioavailability. It is absolute bioavailability of 19-25%, when 40 mg of oral valsartan is compared with the same dose 40 mg pure valsartan drug.

The dose of valsartan varies between 40-320 mg and frequently prescribed dose is 80 mg for the adult. Therefore, for the present study, 40 mg dose was selected for the development of microemulsion formulation. Primary objective is to enhance the solubility, dissolution rate and avoid intra and inter subject variability of valsartan by micro-emulsion drug delivery system. The main objective of the study was to develop and evaluated an optimal Micro-emulsion formulation containing valsartan.

MATERIAL AND METHODS:

Materials for Component Selection: Valsartan base was a gift sample from Torrent pharmaceutical limited, Ahmadabad (Gujarat, India). Capmul-MCM was gift sample from ABITEC Corporation, Janesville, WI and Tween-20 and PEG-400 were gift samples from Merck Specialities PLT. , Worli-Mumbai, India. All other chemicals were of analytical grade.

Solubility studies: The most important criterion for the screening of components for microemulsion is the solubility of poorly soluble drug in oils, surfactants and co surfactants. The solubility of valsartan in various oils was determined by adding an excess amount of drug in 5 ml of selected oils (Isopropyl Myristate (IPM), Capmul MCM, Olive oil, Coconut oil and Castor oil), surfactants (Tween-20, Tween-40, Tween-60, Tween-80, Captex-355, Accenon CC and Cremophor EL) and co-surfactants (Polyethylene Glycol 400 (PEG 400), Glycerol, Polyethylene Glycol 600 (PEG 600), Isopropyl alcohol, Isobutyl alcohol and Transcutol P) in 5 ml capacity stopper vials, and mixed using a vortex mixer (Spinix, Japan). The mixture vials were then kept at 25±1.0^{O}C on shaker (Pci, Japan) for 48 h to reach equilibrium.

After reaching equilibrium, each vial was centrifuged at 10000 rpm for 10 min and excess insoluble lovastatin was separated by filtration using Whatman filter. Both free drug as well as solubilized drug concentration was quantified by UV spectroscopy Spectrophotometer (Shimadzu 1700, Japan) at 251nm [6].

Pseudo-Ternary Phase Diagram: On the basis of the solubility study of drug, oil, surfactants, co-surfactants and aqueous phase were used for construction of phase diagram. Ternary phase diagrams of microemulsion were prepared by chemix software to decide the microemulsion zone in which at any point, microemulsion can be prepared.

For the ratios of surfactant and co-surfactant were at first selected. Here three ratios of surfactant Tween 20 and co-surfactant PEG-400 were selected (2:1, 3:1, 4:1). For each ratio, microemulsion were prepared by increasing the oil phase Capmul-MCM concentration from 10% to 90% with respect to decreasing the concentration of surfactant/co-surfactant from 90% to 10% to decide the maximum uptake of water by microemulsion up to which they remained transparent. The concentration of oil phase, surfactant and co-surfactant based on maximum uptake of water by microemulsion was optimized [7].

Different combination of oils and S/Co-S mix were made so those maximum ratios were covered for the study to delineate the boundaries of phase precisely formed in the phase diagrams. Pseudo-ternary phase diagram was developed using aqueous titration method. Slow titration with aqueous phase is done to each weight ratio of oil and S/Co-S mix and visual observation is carried out for transparent and easily flowable o/w micro-emulsion.

The physical state of the micro-emulsion was marked on a pseudo-three-component phase diagram with one axis representing water phase, the other representing oil and the third representing a mixture of surfactant and co-surfactant at fixed weight ratios (S/Co-Smix ratio) [8].

Formulation of Valsartan Microemulsion: The formulations were prepared by Phase titration method. Appropriate amount of surfactant and co-surfactant were mixed and then added oily part, mix the formulation until completely dispersion occurs at room temperature. Then drug was added and the final mixture was mixed by vortexing until a clear solution was obtained. The formulation was equilibrated at ambient temperature for at least 48 hrs, and examined for signs of turbidity or phase separation prior and particle size studies. In the formulation using Capmul-MCM as oil phase and Tween 20/PEG-400 as surfactant/co-surfactant were designed. Various concentrations of surfactant: co-surfactant (3:1, 2:1) respectively prepares and Capmul-MCM used as oil in formulation.

TABLE 1: FORMULATION OF MICRO-EMULSION

FORMULATION	KM (S:CO-S)	VAL. (mg)	CAPMUL MCM (%)	TWEEN 20(%)	PEG 400(%)
F1	3:1	40	10	67.5	22.5
F2	3:1	40	20	60	20
F3	3:1	40	30	52.5	17.5
F4	2:1	40	20	53.3	26.6
F5	2:1	40	30	46.6	23.3
F6	2:1	40	40	40	20

Evaluation of Valsartan Microemulsion [7]:

A. **Transmittance test:**The percentage of transmittance of the optimized microemulsion formulation, as well as its 100 times dilution with 0.1N HCl and distilled water.Stability of optimized lipid formulation with respect to dilution was checked by measuring transmittance through U.V. spectrophotometer (UV-1700 SHIMADZU) at 560 nm.

B. **Particle size Measurement and Zeta Potential Measurements:** The globule size and zeta potential of the microemulsion was determined by dynamic light scattering, using a Zetasizer HSA 3000 (Malvern Instruments Ltd., Malvern, UK).

C. **Viscosity Measurements:** Rheological behavior of the formulation was evaluated using a Brookfield LVDV III+ cone and plate (CP) viscometer (Brookfield, USA), using the Rheocal Software, at a temperature of 30 ± 1°C.

D. **Electrical Conductivity:** The water phase was added drop wise to a mixture of oil, surfactant and co-surfactant and the electrical conductivity of formulated samples was measured using a conductometer (CM 180 conductivity meter, Elico, India) at ambient temperature and at a constant frequency of 1 Hz.

E. **Thermodynamic Stability:**

1. **Heating cooling cycle:** Six cycles between refrigerator temperature 4˚C and 45˚C with storage at each temperature of not less than 48 hrs was studied. Those formulations, which were stable at these temperatures, were subjected to centrifugation test.

2. **Centrifugation:** Passed formulations were centrifuged at 3500 rpm for 30min. Those formulations that did not show any phase separation were taken for the freeze thaw stress test.

3. **Freeze thaw cycle:** Three freeze thaw cycles between - 21˚C and +25 ˚C with storage at each temperature for not less than 48h was done for the formulations. Those formulations, which passed these thermodynamic stress tests, were further taken for the dispersibility test for assessing the efficiency of self-emulsification. The formulations were observed visually for any phase separation or color change.

4. **Drug Solubility:** Drug was added in excess to the optimized microemulsion formulation as well as each individual ingredient of the formulation. After continuous stirring for 48 hrs at room temperature, samples were withdrawn and centrifuged at 6000 rpm for 10 min. The amount of soluble drug in the optimized formulation as well as each individual ingredient of the formulation was calculated by subtracting the drug present in the sediment from the total amount of drug added. The solubility of drug in microemulsion was compared with respect to its individual ingredients.

5. **Drug Content:** The drug content of valsasrtan Micro-emulsion formulation was measured using UV spectroscopic method. The 10 µg/ml of aliquot was prepared using Micro-emulsion formulation using methanol as a solvent. The samples were measured as 250 nm using UV spectroscopic method.

6. **Robustness to Dilution:** These systems when diluted with excess of water, standard phosphate buffer (pH 6.8) and 0.1N HCl (500-900 ml) and were stored for 12 hours give no precipitation or phase separation and are thus, said 'robust to dilution'.

7. **Drug and Surfactant Compatibility Study:** Physical compatibility of the water-insoluble drug with surfactants should be used in surfactant selection procedure. Physical compatibility may include precipitation/crystallization, phase separation and color change in the drug – surfactant solution during course study. Chemical compatibility is primarily regarded as the chemical stability of the drug in a surfactant solution. A surfactant was considered for further development only if it was physically and chemically compatible with drug.

F. ***In-vitro* drug release:** *In vitro* drug release of Valsartan Microemulsion from optimized formulation was performed by a conventional method. A hard gelatin capsule size "0" filled with percentage (equivalent to 40 mg Valsartan Microemulsion) and pure drug (40 mg) separately ware put into each of the 900 ml phosphate buffer pH 6.8 at 37±0.5 ^{0}C with 50 rpm rotating speed. Samples (5 ml) were withdrawn at regular time intervals (10, 20, 30, 40, 50, 60, 70, 80, and 90 min) and filtered using a 0.45µm filter. An equal volume of the respective dissolution medium was added to maintain the volume constant. The drug content of the samples was assayed using UV visible spectrophotometric method at 254 nm [9].

G. Stability studies: Stability studies of the Valsartan microemulsion samples were carried out by subjecting them to temperature stability and centrifugation. The temperature stability study was carried out by keeping the sample at two different temperatures (2-8 ^{0}C, Room temperature) for 45 days and visual inspection was carried out by drawing samples at intervals for the subsequent days.

In order to estimate metastable systems, the optimized formulation was diluted with purified distilled water. Then formulation was centrifuged (Remi Laboratories, Mumbai, India) at 1000 rpm for 15 minute at 0°C and observed for any change in homogeneity of Microemulsion formulation (Ghosh *et al*, 2004) [10].

RESULTS AND CONCLUSION:

1. **% Transmittance:** The clarity of micro-emulsions was checked by transparency, measured in terms of transmittance (%T). Formulation F2 has% transmittance value greater than 98%. These results indicate the high clarity of microemulsion. Due to higher particle size, oil globules may reduce the transparency of microemulsion and thereby values of %Transmittance.

TABLE 2: %TRANSMITTANCE

Formulation	100 times dilution with Water	100 times dilution with 0.1 N HCL
F1	98.02%	97.31%
F2	98.32%	96.58%
F3	97.18%	97.11%
F4	98.17%	98.07%
F5	97.92%	98.23%
F6	97.42%	97.12%

2. **Particle Size Distribution (PSD) and Zeta-Potential analysis:** Photon correlation spectroscopy (Malvern instrument, UK) using dynamic light scattering was employed to measure particles sizes of pre-concentrate generated microemulsion. The samples were loaded on to 1cm^2 cuvettes in a thermostated chamber. For microemulsion particles size ≤150. It has been reported that the smaller particle size of the emulsion droplets may lead to more rapid absorption and improve the bioavailability.

   It shows the particle size distribution of Valsartan Micro-emulsion diluted with water. The formulations F1-F5 were subjected for particle size measurement. The optimal batch is F2 (Valsartan + Capmul-MCM + Tween 20 + PEG 400) with mean particle size 38 nm in water. The magnitude of the zeta potential gives an indication of the potential stability of the colloidal system. A dividing line between stable and unstable aqueous dispersions is generally taken at either +30 or - 30 mV.

   Particles with zeta potentials more positive and negative +30 mV and -30 mV are normally considered stable. . The optimal batch is F1, F2 and F5 with -34.6, -38.8, -32.9 mV zeta potential respectively which are near to -30 mV which shows these are considerable as stable product.

TABLE 3: PARTICLE SIZE ANALYSIS

Formulation	Avg. Particle size
F 1	62
F 2	38
F 3	56.40
F 4	48
F 5	68

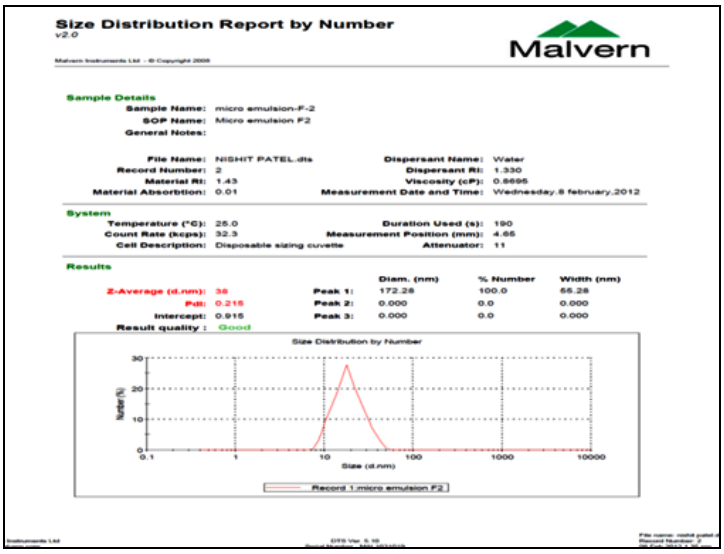


FIG. 1: DROPLET SIZE ANALYSIS OF F2 FORMULATION

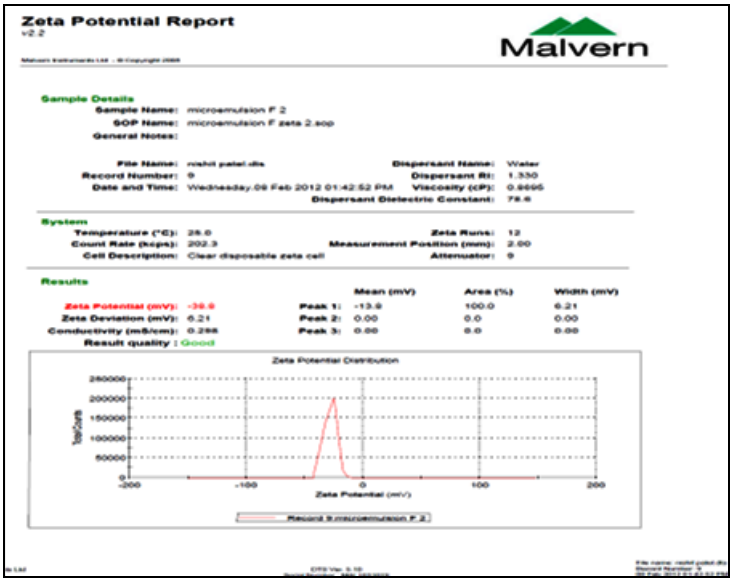


FIG. 2: ZETA POTENTIAL OF F2 FORMULATION

TABLE 4: ZETA-POTENTIAL ANALYSIS

Formulation	Zeta potential
F 1	-34.6
F 2	-38.8
F 3	-28.3
F 4	-29.5
F 5	-32.9

3. **Viscosity:** The viscosity of microemulsion systems can be monitored by standard rheological techniques. It depends on oils and surfactants used. It was observed that the viscosity of all the formulations is not less than 0.7012 cP. Formulation has the maximum viscosity 0.9010 cP which is highly similar to that of water i.e.1.0. Thus, it shows that o/w microemulsion. Water remains as external phase and viscosity of microemulsion is near to water. This reveals that formulation F2 and F 4 is very clear, transparent and low viscous liquid.

TABLE 5: VISCOSITY

Formulation	Viscosity (cP)
F 1	0.8863
F 2	0.8695
F 3	0.9010
F 4	0.7012
F 5	0.8890

4. **Electro-conductivity Measurement:** As the volume fraction of water increased the electrical conductivity increased. There is an increase in electrical conductivity till approximately 12% of water. This can be attributed to the occurrence of a percolation transition. The conductivity of water-in-oil microemulsion system showed quite a remarkable change. In the present study, with the increase in water content of the microemulsion system, the interactions between aqueous domains became increasingly important. Among the selected microemulsion samples F1-F6 (Table 16) F1 and F5 were found to be unfavorable because of high surfactant content and non-dilutability respectively whereas F2, F3, F4, F6showed electro conductive behavior inspite of nonionic nature of amphiphile. Among F2, F3, F4 and F6 is the best composition selected for further physicochemical studies and drug delivery.

5. **Thermodynamic Stability Studies:** Micro-emulsions are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and water, with no phase separation, creaming or cracking. It is the thermo stability which differentiates nano-or microemulsion from emulsions that have kinetic stability and will eventually phase separate.

Thus, the selected formulations were subjected to different thermodynamic stability by using heating cooling cycle, centrifugation and freeze thaw cycle stress tests. On the basis of the mentioned three studies five formulations were selected and results were shown in **Table 7**.

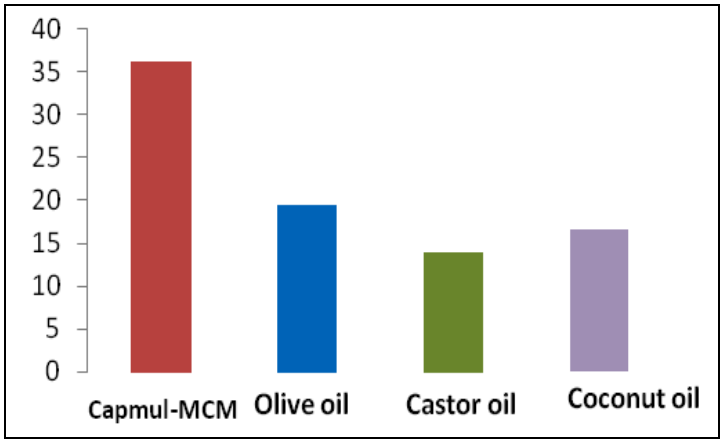
TABLE 7: THERMODYNAMIC STABILITY

Formulation	Heating/cooling cycle	Centrifugation	Freeze thaw cycle
F 1	√	√	√
F 2	√	√	√
F 3	√	√	x
F 4	√	x	x
F 5	√	√	√
F 6	√	√	x

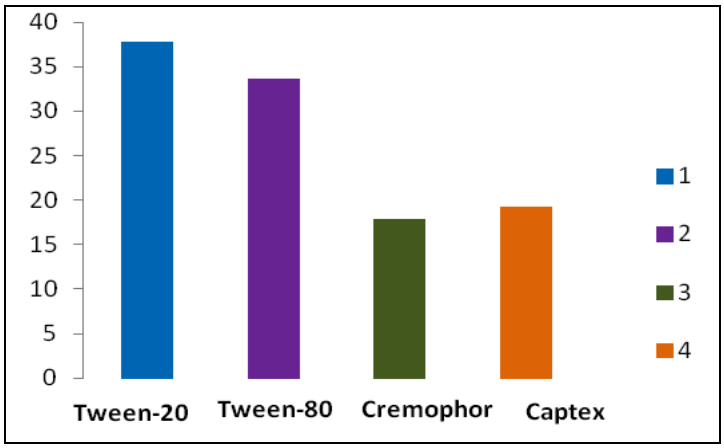
On the basis of the thermodynamic stability studies it was found that F1, F2 and F5 formulations were passed and selected for further characterization.

6. **Drug Solubility:**

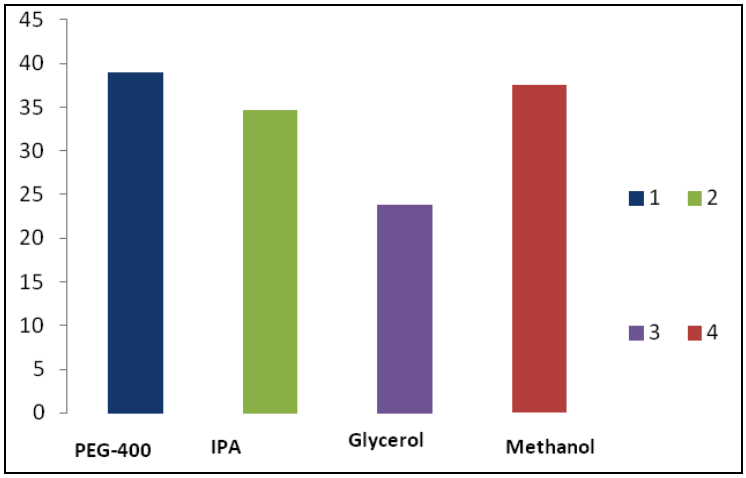
a. Solubility study with Oils: As per solubility data of Valsartan in different oils, maximum amount of drug dissolved in Capmul MCM (36.02±1.27 mg/ml). Therefore, this oil was selected for Microemulsion formulation.



b. Solubility study with Surfactant: As per solubility data of Valsartan in surfactant, maximum amount of drug dissolved in Tween-20 (37.82±1.10 mg/gm).Therefore this co-surfactant was selected for Microemulsion formulation.



c. **Solubility study with Co-Surfactant:** As per solubility data of Valsartan in co-surfactant, maximum amount of drug dissolved in PEG-400 (39.02±1.10 mg/gm). Therefore, this co-surfactant was selected for Microemulsion formulation.



7. **Drug Content:** Microemulsion of Valsartan with Capmul MCM, Tween 20 and PEG 400 were prepared by Phase Titration Method (Water titration) method. The percentage of drug content of all the formulations varied from 97.05% to 99.07% as shown in the **table 8**. This result indicates that there was uniform distribution of the drug throughout the batch.

TABLE 8: DRUG CONTENT

Sr. No.	Drug content (%)
1	97.5
2	99.1
3	98.4
4	98.1
5	99.7
6	97.6
Maximum	99.7
Minimum	97.5
Average	98.13

8. **Robustness to dilution:** Robustness to dilution was performed diluted with excess of water, standard phosphate buffer pH 6.8 and 0.1N HCl (500 ml) and was stored for 12 hours gives no precipitation or phase separation was found in F-1 to F-6 and result were shown in **Table 9**.

TABLE 9: ROBUSTNESS TO DILUTION

Formulation	Distilled Water	0.1NHCl	Phosphate buffer 6.8
F1	√	√	√
F2	√	√	√
F3	√	√	√
F4	√	√	√
F5	√	√	√
F6	√	√	√

Where, √-Passed and ×-Failed

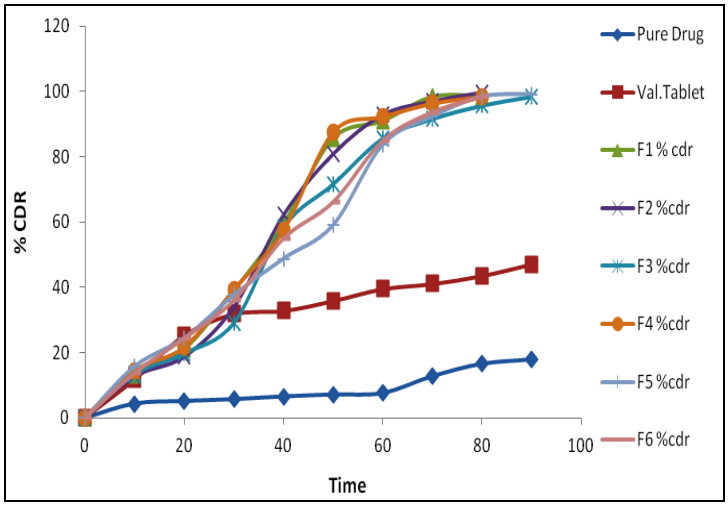
9. **Drug and Surfactant Compatibility Study:** Physical and chemical compatibility of the poorly water-soluble drug valsartan with various surfactants and co surfactants was carried out to check the physical as well as chemical compatibility. As shown in Table 20, the formulation F1-F6 contains Capmul-MCM as oil, Tween-20 as surfactant and PEG-400 as cosurfactant passed the physical as well as chemical compatibility tests. The results are as shown in **Table 10**. The formulation did not show any changes during the compatibility studies and were found to be stable.

TABLE 10: DRUG AND SURFACTANT COMPATIBILITY STUDY

Formulation	Precipitation	Crystallization	Phase separation	Color change
F 1	√	√	√	√
F 2	√	√	√	√
F 3	√	√	√	√
F 4	√	√	√	√
F 5	√	√	√	√
F 6	√	√	√	√

Where, √-Passed and ×-Failed

10. ***In-vitro* dissolution studies:** *In vitro* dissolution test results indicate complete dissolution of drug from all its microemulsion within 10 to 90 min which is depicted in table 21 and 22. The formulation F2 i.e., the microemulsion of Valsartan with Tween 20:PEG 400 (3:1 ratio) prepared by Phase titration method showed 99.70% release within 80 minutes, whereas the formulation F5 i.e., the microemulsion Valsartan with Tween 20:PEG 400 (2:1 ratio) prepared by Phase titration method 99.1086% release within 90 minutes. Drug release from the microemulsion formulation (F2) was found to be significantly higher as compared with that of pure valsartan drug and Valsartan marketed tablet. Thus, this greater availability of dissolved valsartan from the microemulsion formulation could lead to higher absorption and higher oral bioavailability. The maximum drug release was found to be F2formulation 99.7062%.



11. **Stability Study:** Stability studies of the Microemulsion samples were carried out by subjecting them to temperature stability and centrifugation. The temperature stability study was carried out by keeping the Microemulsion sample at temperatures (2-8^{o}C, Room temperature) for 45 days and visual assessment carried out. As per the results evidence of phase separation or any flocculation or precipitation was observed in Microemulsion formulation. A formulation shows no sign of phase separation when subjected to centrifugation at 10000 rpm for 30 minutes. Thus, it was concluded that the Microemulsion formulation was stable thermally as well as under stressful conditions.

CONCLUSION: In the present investigation, three polymers namely Capmul MCM, Tween 20 and PEG 400 were evaluated as Oil, Surfactant and Co-surfactant in Microemulsion systems for enhancing the dissolution rate of poorly soluble drug Valsartan. Microemulsion systems of the selected drug in Capmul MCM, Tween 20 and PEG 400 were prepared by Phase titration method. A microemulsion system was prepared in each case at 2:1, 3:1 and 4:1 ratios of surfactant: co-surfactant by phase titration method. Viscosity of all the formulations is not less than 0.7012 cp which shows that all Micro-emulsion forms o/w microemulsion.

Formulation F2 was found out to have minimum average particle size 36 nm. F1, F2 and F5 were found out to have zeta potential of around -30 mV which indicates its highest physical stability among all formulations. The maximum drug release was found to be F2 formulation 99.7062%. Stability study shows that all formulation are stable at two different temperature and they didn't have any phase-separation.

On the basis of Particle size, Viscosity, Robustness study and *in-vitro* drug release, it can be concluded that Microemulsion system is suitable for Oral administration.

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