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FORMULATION AND CHARACTERIZATION OF NOVEL MICROEMULSIONS OF TELMISARTAN

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ABSTRACT

The objective of the present study was to develop a novel microemulsion drug delivery system of a poorly water soluble drug, Telimisartan. Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with implications of low bio availability,high intra and inter subject variability and lack of dose proportionality. Hydrophobic drugs can often be dissolved in microemulsion allowing them to be encapsulated in the form of fine globules, so that drug remains undissolved in the gut avoiding the dissolution step, which frequently limit the rate of absorption of hydrophobic drugs. Phase solubility studies were conducted for the maximum solubility of Telimisartan. Highest solubility was found in tween 20 (surfactant), carbital (co surfactant) and meglyol (oil). Ternary phase diagrams were constructed to evaluate microemulsion regions. FTIR analysis was done for investigating the drug-excipient interactions. The mean globule size of both microemulsion was observed to be below 200nm for the optimized formulations and the zeta potential was negative. The dissolution of emulsion formulations was compared with commercial tablets; the results indicated that the rate of dissolution of developed formulations containing Telimisartan was 2 to 3 folds increased compared with that of commercial tablets. SEM studies were done for the shape and morphology of the globules. Stability studies were conducted according to the Q1 ICH guidelines and formulations were stable at different conditions. Thus, microemulsions can be regarded as novel and commercially feasible alternative to the current Telmisartan formulations.

KEY WORDS

Tween20, Carbitol, Meglyol, Ternary phase diagrams, Zeta potential.

INTRODUCTION

Selection of an appropriate salt form or for liquid dosage forms and adjustment of pH of the solution is the basic fundamental step involved in the solubilisation of the drug products. Majority of newer solubilisation techniques like nanosuspensions and microemulsions utilize co-solvents when applied to polar compound which becomes an important selection [1]. Particle size reduction via comminution, spray drying, addition of surfactants, inclusion in cyclodextrin-drug complexes and the use of more novel mechanisms such as self-emulsifying systems, micronisation via nanoparticles, pH adjustment and salting in processes are the solubility enhancement of both traditional methods which are included by these technologies[2,3]. The reactivity of triglycerides and surfactants with the walls of the gastrointestinal tract is the thought of solubilising and absorption promoting effect of potential solubility enhancing technologies which is emerged by micro emulsions. To incorporate drugs into self-emulsifying systems, long and medium chain triglycerides (LCT's and MCT's, respectively) have been employed with surfactants, traditionally [4, 5].

To ensure immediate formation of oil-in-water (O/W) droplets during production, non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high

hydrophile-lipophile balances (HLB) are often used. Drug solubilisation in higher degrees and precipitation of the drug may be prevented out of microemulsion in-vivo is allowed by amphiphilic, non-ionic surfactants. To increase the amount of drug capacity of being dissolved into the lipid base, frequently co-surfactants are employed, this is because the concentration of surfactant should be excess of 30% W/W in most of self emulsifying systems. Co-surfactants (such as ethanol, propylene glycol and poly ethylene glycol) used should be suitable for oral administration, hence co-surfactants are often organic solvents. Alike to the effect of introducing these organic solvents in manufacturing of drug product, complexity is processed during improving the potential drug load of the emulsion as the use of co-solvents increased [6]. Due to the liquid nature of the product, most of these self-emulsifying systems are limited to administer in lipid-filled soft or hard-shelled gelatin capsules. To prevent the hydroscopic contents from dehydrating or migrating into the capsule shell, the interaction between the capsule shell and the emulsion should be considered. Telmisartan is an oral anti-hypertensive agent drugs used by the patients to avoid heart failure, kidney failure and acute stroke induced by hypertension and delay the development of atherosclerosis by controlling blood pressure. Telmisartan comes under angiotensin receptor blockers, used to treat hypertension; it is a bcs class II drug with low solubility hence in this study a novel microemulsion preparation of telmisartan was investigated for improvement of drug solubility and bioavailability.

MATERIALS AND METHODS

Materials:

Telmisartan was procured from Yarrow chemicals, Mumbai. cremophor RH40, sun flower oil, migloyol, Span 20, span 80, PEG 400, brij 30, carbitol, olive oil, cotton seed oil were purchased from Sd-Fine chemicals limited, Mumbai; Tween 20, tween 60, tween 80, oleic acid, castor oil were purchased from Merck specialties pvt limited, Mumbai.

METHODS:

1. Solubility study of Telmisartan in various excipients:

The solubility of Telmisartan in various oil, surfactant, and co-surfactant was determined. Solubility studies were conducted by placing an excess amount of drug in each vehicle in a 2ml Microtube (Axygen MCT 200) containing 1.5ml of the vehicle. Then the mixture was vortexed and kept for 48hrs at 25ºC in a Orbital shaking incubator (Remi electrotechnik ltd.) to facilitate the solubilization. The samples were centrifuged at 3000rpm for 15min to remove the undissolved drug. The supernatant was taken and the concentration of drug in each vehicle was quantified by U.V-spectrophotometer.

2. Construction of Pseudo-ternary phase diagrams:

The pseudo-ternary phase diagrams of oil, surfactant: co-surfactant and water were developed using surfactant titration method: The mixtures of oil and water at certain weight ratios were titrated with surfactant: co-surfactant mix in a drop wise manner. Three types of surfactant phases were prepared: Tween 20+ carbitol(1:1, 2:1, 3:1). For each phase diagram at a specific ratio of surfactant/co-surfactant transparent and homogenous mixture of oil and water was formed under the mixing by cyclomixer. Then, visually observed for phase clarity and flow ability. After the identification of microemulsion region in the phase diagrams, the microemulsion formulations were selected at desired component ratios, in order to form the microemulsion.

3. Formulation design of microemulsion containing Telmisartan:

A series of micro emulsions were prepared in each of fifteen formulations with varying ratio of oil, surfactant, co-surfactant and telmisartan. In all the formulations, the amount of telmisartan was constant (20mg/ml). Briefly, telmisartan was dissolved by co-surfactant (carbitol) in glass vials. Oils and surfactants were accurately weighed and incorporated into glass vials, then water is added and components were mixed by gentle stirring and vortex mixing and heated at 37^0C in incubator, until telmisartan perfectly has dissolved. The mixture was stored at room temperature until used.

Table 1: Formulation table of Telmisartan microemulsions

F		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
% w/w of different components in formulation	Oil	6.9	8.6	3.2	5.3	2.3	5.9	8.4	4.7	8.2	2.3	14.5	18.6	14.5	4.7	4.1
	Smix	76.7	78.2	67.7	74.6	65.1	77.6	78.8	76.1	80	65.1	75	74.4	75	76.1	75
	Water	16.2	13	29	20	32.5	16.4	12.6	19	11.7	32.5	10.4	6.9	10.4	19	20.8

4. Characterization:

4.1. Drug excipient compatibility studies: FTIR spectrums of telmisartan and drug-micro emulsion formulation were obtained by means of a FTIR spectrophotometer (bruker-alpha T). The samples were prepared by the potassium bromide disk method and measurements were attempted with the accumulations of 20 scans and a resolution of 4 cm^{-1} over the range of 400-4000 cm^{-1} . After running the spectra, significant peaks relating to major functional groups were identified; spectra of the subsequent samples of the same compound were compared with the original [7].

4.2. Droplet size measurement: The mean droplet size of emulsion globules was determined by using photon correlation spectroscopy (which analysis the fluctuations in light scattering due to Brownian motion of the particles) using nano zeta sizer able to measure sizes between 10-3000nm. Light scattering was monitored at 25ºC at a 90º angle. The dispersed formulations were measured after dilution (1:100) to produce the required count rate (50-200) to enable the accurate measurement [8, 9, 10)]

4.3. Zeta potential: The zeta potential of micro emulsion was determined using nano zeta sizer. Charge on emulsion droplets and their mean zeta potential value (± SD) were obtained from the instruments [8, 10].

4.4. Viscosity determined: The viscosity of microemulsion formulation generally was very low. This was expected, because one of the characteristics of microemulsion formulation is lower viscosity. The viscosity of formulations was determined without dilution using BROOKFIELD-DV-11 + pro viscometer using spindle00 UV adapter at 25±0.5^{0}C [11)]

4.5. Conductivity determination: A conductometer (lab india pico +) was used in non-linear temperature compensation mode, according to EN 27888 conductivity was determined between 45 and 90ºC under magnetic stirring at an agitation of 250rpm. This temperature ranges permit a steady state to be achieved, either as an emulsion O/W (high steady state) or as an emulsion W/O (low steady state) in different conditions tested. The recording of conductivity relative to temperature permits the determination of phase inversion temperature. Conductivity values lower than 10 micro cm^{-1} means that the continuous phase is oil, where as a higher steady state shows that water is the continuous phase [11, 12].

4.6. Drug content: A measured quantity of microemulsion were added to 100ml of pH 1.2 buffer. The resulting mixture was kept at 24hrs at a drak place. Then the solution was filteres through membrane filter of 0.45µm pore size and 1ml of this solution was diluted to 10ml using 1.2 pH buffer. After further dilutions with mobile phase, the samples were analysed by UV spectrophotometer for drug content at 297nm. The drug content was determined using the relationship [13]

$$\frac{\boldsymbol{experimental\ drug\ content}}{\boldsymbol{theoretical\ drug\ content}} \times \mathbf{100} = \boldsymbol{Drug\ content}$$

4.7. Thermodynamic stability studies:

Freeze thaw cycle: Freeze thawing was employed to evaluate the stability of the formulations. The formulations were subjected to 3-4 freeze thaw cycles, which included freezing at -4ºC for 48hrs followed by thawing at 40ºC for 48hrs. Centrifugation was performed at 3000rpm for 5min. the formulations were then observed for phase

separation. Only formulations that were stable to phase separation were selected for further studies.

Stability studies: The microemulsion formulations were put into empty hard gelatin capsules (size 0) and subjected to stability studies 25ºC and 60% relative humidity (RH), 30ºC/65%RH and 45ºC/75% RH. Samples were charged in stability chambers with humidity and temperature control. They were withdrawn at specified intervals for analysis over a period of 3 months for intermediate and accelerated conditions and 6 months for long-term conditions. Drug content of the capsules was analyzed using a previously developed and validated stability indicating UV method [14]

4.8. In vitro dissolution studies: The release of telmisartan from the microemulsion formulations was determined according to USP dissolution apparatus type II. To permit the quantitative drug release from microemulsion formulation, 900ml of pH 1.2 buffer was placed in the dissolution vessel and then the microemulsion formulation filled ion hard gelatin capsule was placed in the dissolution medium and was agitated at 500rpm at 37ºC. At pre-determined time intervals of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 minutes, 5ml of the samples were withdrawn and the drug concentration was determined by UV spectrophotometer at wavelength 296nm. The volume withdrawn was replaced each time with fresh dissolution medium. Cumulated released amounts were plotted as a function of time.

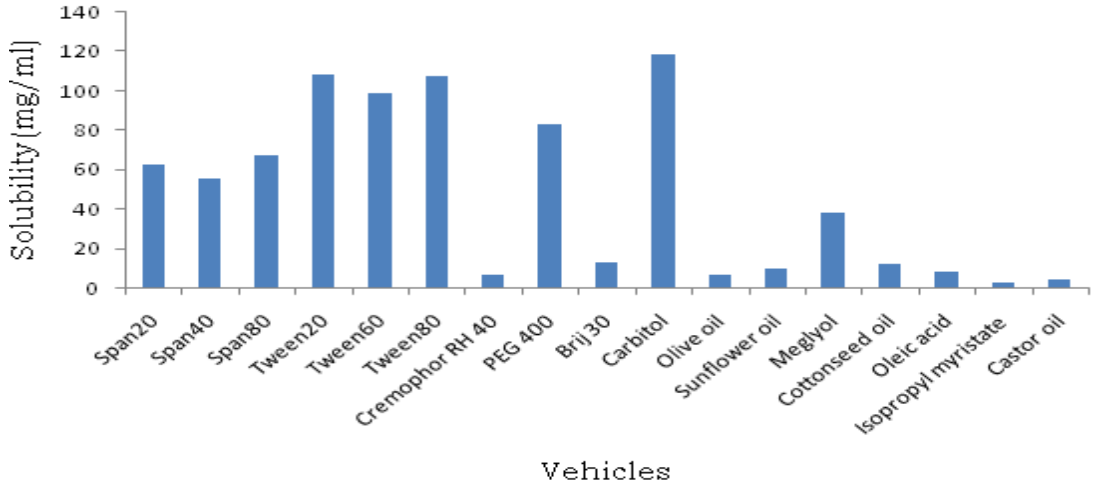
RESULTS AND DISCUSSION

1. Solubility study of Telmisartan in various excipients: Selection of right component is important prerequisite for formulation of stable SMEDDS. The drug should have good solubility in components of microemulsion so as the precipitation of drug during shelf life of formulation and after dilution in GI lumen can be avoided. The solubility of Telmisartan in various vehicles is presented in table 2 &fig 1. Tween20 and carbitol provided higher solubility than other vehicles and meglyol as oil was selected for the optimal novel emulsion formulation resulting in improved drug loading capabilities. 20mg dose of Telmisartan was selected to prepare formulations.

Table 2: solubility studies of telmisartan in various vehicles.

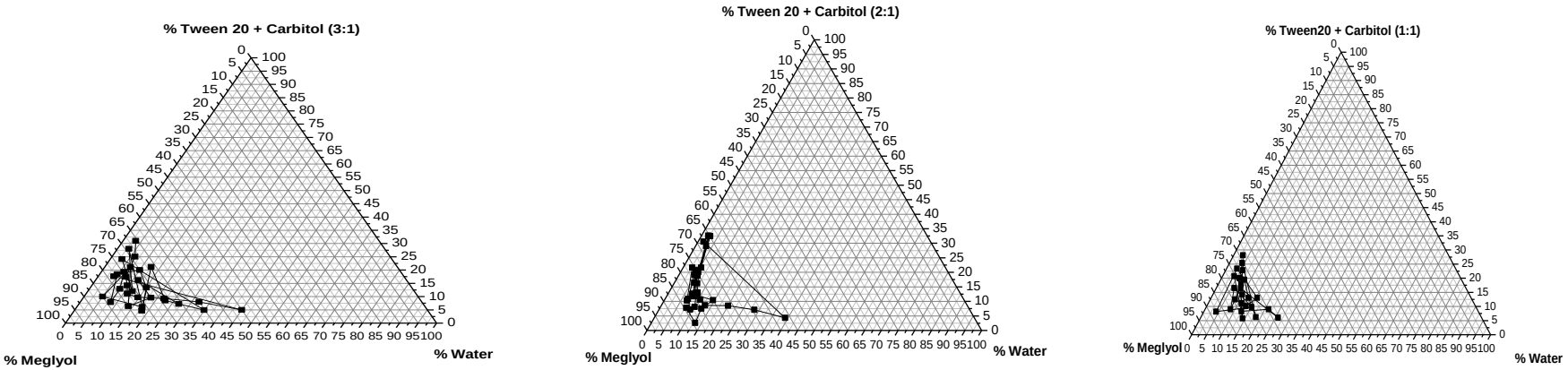
Vehicle	Span 20	Span 40	Span 80	Tween 20	Tween 60	Tween 80	Cremophor RH40	PEG 400	Brij 30	carbitol	Olive oil	Sun flower oil	Meglyol	Cotton seed oil	Oleic acid	Iso propyl myristate	Castor oil
Solubility (mg/ml)	62.68	55.21	67.55	108.01	99.21	107.63	5.96	82.76	12.69	118.69	6.61	9.62	38.13	12.15	8.02	2.16	4.19

Fig 1: Graph showing solubility of Telmisartan in various oils and surfactants, the solubility of Telmisartan was determined in various vehicles by UV spectroscopic method. The solubility of Telmisartan was found to be high in Tween20 (surfactant) and Carbitol (cosurfactant), meglyol (oil)



2. Ternary phase diagrams: Phase diagrams were constructed in the presence of Telmisartan to obtain the optimum concentrations of oil, surfactants and co-surfactants and to identify the self emulsifying regions. A pseudo ternary phase diagram of investigated quaternary system Water/Meglyol/Tween20/Carbitol is

presented in fig2(a). Formation of microemulsion was found at room temperature. The phase study revealed that the maximum proportion of oil was incorporated in microemulsion system when the surfactant/co-surfactant ratio was 2:1 as shown in **Fig 2(b).**



a) **b)** **c)**

Fig 2: Pseudo ternary phase diagrams indicating the efficient microemulsion region containing (Tween20 / Carbitol) = (a) 3:1 (w/w) (b) 2:1 (w/w) (c) 1:1 (w/w). The shaded area represents O/W microemulsion existence range.

3. FTIR studies: FTIR spectrums of formulations were obtained by means of a FTIR spectrophotometer (Bruker-AlphaT). The FTIR spectrum of pure Telmisartan has three characteristic peaks at 3442cm^{-1}, 2958cm^{-1}, 1268cm^{-1} for O-H stretching vibration,C-H vibration and Carboxylic acid functional group respectively as shown in fig3. The FTIR spectrum of Telmisartan microemulsion formulation has three characteristic peaks at 3418cm^{-1}, 2925cm^{-1}, 1105cm^{-1} and the as shown in fig3 and fig4. It is indicated that there was no interaction between Telmisartan and excipients used in the formulation as the functional groups obtained for three spectrums are almost similar.

Fig 3: FTIR spectra of Telmisartan

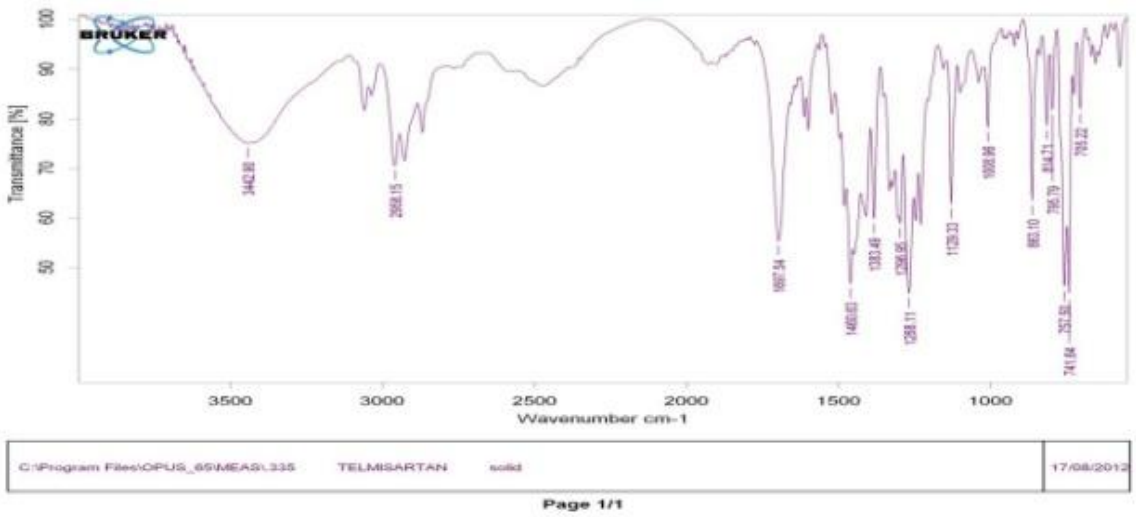
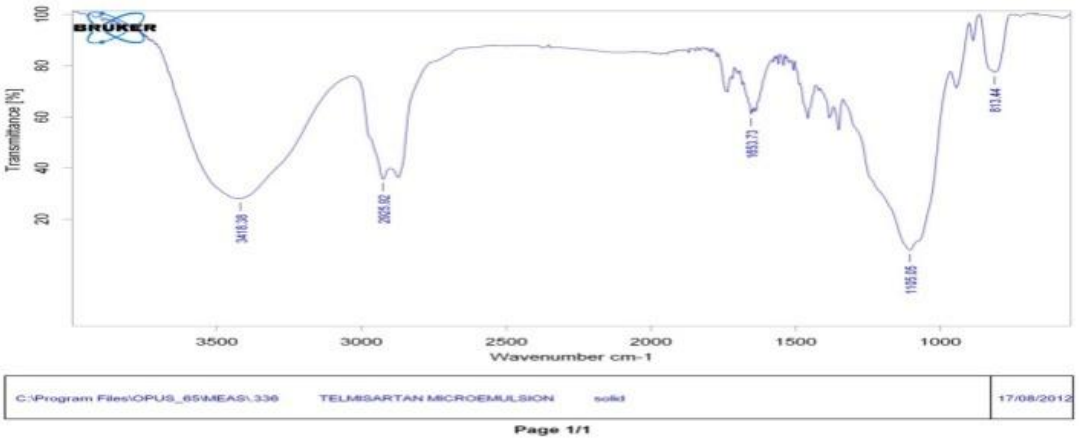


Fig 4: FTIR spectra of Telmisartan microemulsion



4. Droplet size measurement and Zeta potential study: Droplet size measurement determines the rate and extent of drug release as well as absorption. The reduction of droplet size to values below 100nm leads to formation of ME, which are stable, isotropic and clear o/w dispersions. The least droplet size was observed in the formulation F7, in which the percent of surfactant and co-surfactant concentrations are

taken in the ratio of 1:1(Tween20: carbitol) because of low concentration of surfactantas shown in **Table 3**.

Table 3: droplet size and zeta potential values of telmisartan microemulsions.

Formulation	Droplet size, nm	Zeta potential, mv
F7	190nm	-1.2
F13	100nm	-2.5

5. Viscosity and Conductivity: The viscosity of the optimized formulations was determined and the values are shown in table 6. It was observed that the viscosity of all the formulations is less than 25cP. F7 has the minimum viscosity (20.525cP) which is highly significant as compared to the other formulations. Electrical conductivity of the formulations was determined to check the stability and assert the nature of formulations. It was found that the conductivity was the lowest in F12 and highest in F7formulation. The higher conductivity of F7 is attributed to a larger percentage of water which allows more freedom for mobility of ions as shown in **Table 4**.

Table 4: viscosity and conductivity values of microemulsions

Formulation	Mean viscosity (cP)	Mean conductivity ($s.m^{-1}$)
F2	23.1	17.035± 0.5
F7	20.525	32.011 ± 0.5
F9	24.8	20.235± 0.5
F12	22.5	16.035 ± 0.5
F13	21.8	22.554± 0.5

6. Drug Content: Percentage drug content was quantified by dissolving Microemulsion formulations equivalent to 20mg in methanol and made concentration equivalent to 100µg/ml with pH 1.2 buffer and analysed by UV method. Percent drug was calculated using the formula given in methodology and results are shown in **Table5**.

Table 5: Drug content of microemulsion formulations

Formulation code	F2	F7	F9	F12	F13
% of drug	97.18	99.67	98.43	97.82	99.33

7. Stability Studies: The developed formulations are subjected to stability studies to evaluate its stability and the integrity of the dosage form. **Tables 6, 7, 8** gives the results of the evaluation test conducted on stability samples. The formulation was found to be stable for 3 months at intermediate and accelerated conditions and 6 months at long-term conditions. The formulation was compatible with hard gelatin capsule shells, as there was no phase separation, drug precipitation or capsule leaks.

Table 6: Evaluation data of formulation subjected to stability studies at 25˚C/60% RH

Formulation code	Sampling point	Droplet size(nm)	% drug content
F7	0 days	192.2	99.67
	45 days	190.1	98.65
	3 months	191.1	97.87
F13	0 days	100.2	99.33
	45 days	101.1	98.77
	3 months	102.1	96.10

Table 7: Evaluation data of formulations subjected to stability studies at 30˚C/65% RH

Formulation code	Sampling point	Droplet size (nm)	% drug content
F7	0 days	192.1	99.67
	45 days	190.2	98.20
	3 months	199.9	97.13
F13	0 days	100.1	99.33
	45 days	101.2	98.18
	3 months	102.1	96.23

Table 8: Evaluation data of formulations subjected to stability studies at 40˚C/75%RH

Formulation code	Sampling point	Droplet size(nm)	% drug content
F7	0 days	190.1	99.67
	45 days	192.1	98.56
	3 months	191.2	98.12
F13	0 days	100.2	99.33
	45 days	102.4	98.27
	3 months	101.2	97.63

8. Invitro dissolution studies: The results of dissolution studies are shown in fig 5, at the end of one hour, the dissolution of F7 microemulsion formulation was significantly greater(98.62%) than that of other formulations. It suggests that Telmisartan dissolved perfectly in microemulsion formulation, and could be released due to its small droplet size which permits a faster rate of drug release into the aqueous phase.

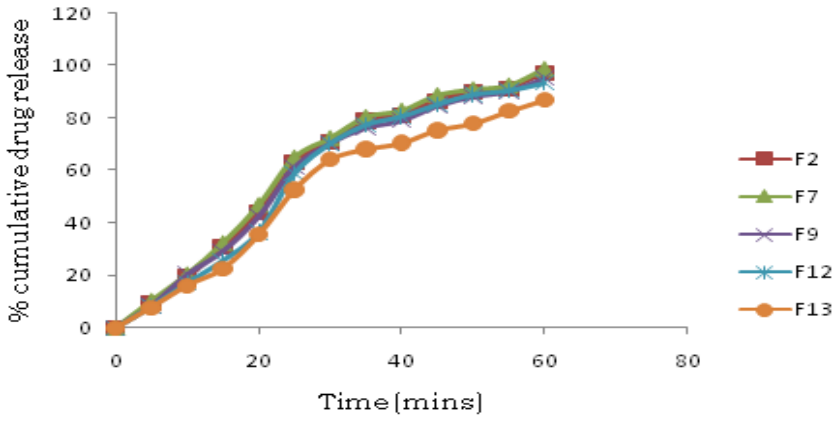


Fig 5:% cumulative drug release from various formulations

CONCLUSION

Telmisartan microemulsions were prepared as a novel technique to improve the solubility of poorly soluble drug. The preformulation studies done clearly indicate good compatibility of the drug with the various excipients used. The reduction of particle size was clearly depicted in the droplet size measurements where the size is reduced to nanometer range, which has led to increase in dissolution rates as shown in the dissolution studies and graph. Stability studies conducted has given a valid proof of good stability of the otherwise instable microemulsions. Thus it can be concluded that microemulsion formulation can be used as a successful tool to enhance the bioavailability of the drug, and there formulations can be further tested in vivo by using animal models.

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