Review Article

# Preparation and *In Vitro* Evaluation of Self-Nanoemulsifying Drug Delivery System (SNEDDS) Containing Clopidogrel

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**ABSTRACT**

The oral delivery of lipophilic drugs presents a major challenge due to low aqueous solubility of such compounds. Clopidogrel is a BCS class II prodrug specifically and irreversibly inhibits the platelets aggregation by blocking activation of the glycoprotein IIb /IIIa pathway. The chief intention of this work is to develop an orally stable self Nano-emulsifying drug delivery system by evaluating its *in vitro* potential. Components of SNEDDS were assessed by solubility studies on various oils, surfactant, co-surfactants and co solvents. Ternary phase diagrams were constructed to identify area of nanoemulsification for the selected systems. Characterization of SNEDDS was done by Physical method, Droplet size, Zeta potential determination, drug loading capacity, Transmission test, Cloud point measurement and *in vitro* release study. The optimal Formulation consisted of mixture of Drug (13.05%), Acrysol K150 and PEG 400 (1:1) and Capmul MCM NF (17.39%). Droplet size of optimal batch was 22.91 nm with PdI 0.173.Drug loading capacity was 2 times the Actual dose of CLP (75 mg). Transmission values were above 99% in pH 1.2, Ph 6.8 and distilled water. Cloud point of formulations was above 65°C. *In vitro* release inspection of optimal formulation illustrated a complete release of Clopidogrel from SNEDDS within 15 min. Our study concludes that the SNEDDS shows potential approach for the poorly water soluble drugs including Clopidogrel.

**Keywords:** SNEDDS, Clopidogrel, Drug loading capacity.

## INTRODUCTION

Oral route prescribed as the ideal route for chronic drug therapy; yet 40% of new chemical entities exhibit low oral bioavailability and high intra- and inter subject variability due to their poor aqueous solubility.[1] Lipid-based formulations are of good interest in recent years. Lipid carriers such as oils, surfactant, emulsions, self-emulsifying formulations, self-nanoemulsifying systems, self-microemulsifying systems[2] are having potential to engulf lipophilic drug and most importantly remain inside until reaches to blood circulation. Self nanoemulsifying systems (SNS) are mixtures oil, surfactants, cosurfactants that form fine o/w nanoemulsion when introduced into aqueous phases under gentle agitation.[3] various formulation strategies to improve the dissolution and bioavailability have been subjected for BCS Class II drug but amongst them self-nanoemulsifying drug delivery systems (SNEDDS) have established particular interest as a means of enhancing oral bioavailability of poorly absorbed drugs.[4] SNEDDS spread into fine emulsion droplets inside the gut lumen where drug remains in solution state, evading the dissolution step that intermittently limits the rate of absorption of hydrophobic drugs from the crystalline state.

Clopidogrel is an oral, thienopyridine class antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease. Clopidogrel is a prodrug, which action may be related to an ADP receptor on platelet cell membranes. The drug specifically and irreversibly inhibits the P2Y12 subtype of ADP receptor, which is important in activation of platelets and eventual cross-linking by the protein fibrin.[5] The blockade of this receptor inhibits platelet aggregation by blocking activation of the glycoprotein IIb /IIIa pathway. The IIb/IIIa complex functions as a receptor mainly for fibrinogen. Activation of this receptor complex is the "final common pathway" for platelet aggregation and is important in the cross-linking of platelets by fibrin.

Present study shows preparation of various kind of SNEDDS formulation by performing trial batches of various oils (sunflower oil, soyabean oil, olive oil), surfactants (Acrysol derivatives and other Gattefosse surfactants, Tween 80, Tween 20), cosurfactants (captex 200,captex 300,labrafil M 2125) and cosolvents (PEG 400,Propylene Glycol, ethanol) with drug to assess the ability of drug in solubilized form and to form a transparent solution for better emulsification ratio of Surfactant:Cosurfactant:Cosolvents remains same. Non-ionic surfactants with high HLB (HLB = 10) and subsequent hydrophilicity is necessary for the instant creation of oil in water droplets and/or rapid spreading of the formulation in the aqueous environment providing a good dispersing/self-emulsifying performance. The surfactants are amphiphilic in nature have ability to dissolve and solubilize to some extent high quantities of the hydrophobic drug. In SNEDDS generally surfactant of HLB value 8-16 is used.

The prime objective of the investigation is to formulate, optimize and stabilize SNEDDS containing Clopidogrel with suitable surfactants and co-surfactants. To achieve High drug loading capacity with ability to retain drug in solubilized form. Solubility of drug plays a very important

role in dissolution and hence absorption of drug which hypothetically affects its bioavailability.

## MATERIALS AND METHODS

Clopidogrel was received as a gift sample from APOTEX Research Pvt. Ltd.(Bangalore, India) Gelucire 44/14,Labrasol, Labrafil M 2125, Capryol 90 were gift samples from Gattefosse (Mumbai, India), Capmul MCM NF, Acconon MC8-2, Captex 200 were kindly provided by Abitech Corporation (Columbus, OH, USA), Acrysol Derivatives ( K150, EL135) were generous gift from Coral Pharma (Ahmedabad, India), Tween 80, Tween 20 were kindly gifted by Indoco Pvt. Ltd (Aurangabad, India), PEG 400,Propylene Glycol, Methanol were purchased from S.D. fine chemicals (Mumbai, India) Double distilled water was prepared freshly whenever required. Various oils are purchased as received. All other chemicals were of analytical grade.

### Solubility studies

The solubility of Clopidogrel in various oils, surfactants, and cosurfactants was determined. Briefly, an excess amount of Clopidogrel (approximately 100 mg) was introduced into 1 gm of each vehicle, and mixture was kept in 20 ml beaker (covered with Aluminum foil).The mixture was stirred using mini magnetic stirrer (DBK Instruments) for up to the saturation point in beaker at 37°C. Samples were kept aside and allow standing for 48hr at ambient temperature to attain equilibrium. The equilibrated sample was centrifuged at 2,000 rpm for 10 min to remove the un-dissolved drug. Aliquot of 0.2ml was taken from clear supernatant. Filtered using membrane filter (0.45µm). The concentration of Clopidogrel was then quantified using U.V spectrophotometer (Systronics 2201). Table 1 shows the outcomes of the solubility studies.

**Table 1:** Solubility of Clopidogrel in Various Lipid Excipients

| Solubility of CLP in oils | | Solubility of CLP in Surfactants | |
|---|---|---|---|
| **Oil (1 gm)** | **Solubility (mg/gm)** | **Surfactant (1 gm)** | **Solubility (mg/gm)** |
| Gelucire 44/14 | 2.9185 | Labrafil M 2125 | 7.7927 |
| Capmul MCM NF | 0.4170 | Acrysol K 150 | 8.9970 |
| Sunflower oil | 0.5788 | Acrysol EL 135 | 14.6385 |
| Linseed oil | 0.2964 | Acconon MC8-2 | 42.2835 |
| Soyabean oil | 1.1498 | Tween 80 | 0.6170 |
| Olive oil | 0.0658 | Tween 20 | 14.902 |
| Solubility of CLP in co-surfactants (1gm) | | Solubility of CLP in co-solvents (1gm) | |
| Captex 200 | 0.0322 | Capryol 90 | 0.4438 |
| PEG 400 | 32.951 | PEG 400 | 32.9514 |
| Labrafac PG | 0.0157 | Propylene Glycol | 0.0294 |

### Construction of Pseudo Ternary Phase Diagram Study [7]

On the basis of the trial batches of excipients, the pseudoternary phase diagrams of oil (Capmul MCM NF), surfactant: co-surfactant (Acrysol K 150: PEG 400), and distilled water were developed using water titration method. The mixture of oil and surfactant/co-surfactant (Smix) at certain weight ratio were diluted with water in drop wise manner. For each phase diagrams at specific ratio of surfactant/co-surfactant (1:1, 1:2, 1:3, and 2:1 3:1) and oil ratio (1:9, 1:8.5, 1:8, 1:7.5, 1:7, 1:6.5, 1:6, 1:5.5, 1:5, 1:4.5, 1:4, 1:3.5, 1:3, 1:2.5, 1:2, 1:1.5, 1:1, 1.5:1 and 2:1) was taken and prepared transparent and homogeneous mixture by mini magnetic stirring. Then, each mixture was titrated with water and visually observed for phase clarity and flow ability. After the identification of nanoemulsion region in the phase diagrams, the nanoemulsion formulations were selected at desired component ratios. The physical state of the nanoemulsion was marked on a pseudo-three-component phase diagram with one axis representing aqueous phase, the other representing oil and the third representing a mixture of surfactant and cosurfactant at fixed weight ratios ($S_{mix}$ ratio). Figure 1 shows phase diagrams of various ratios.

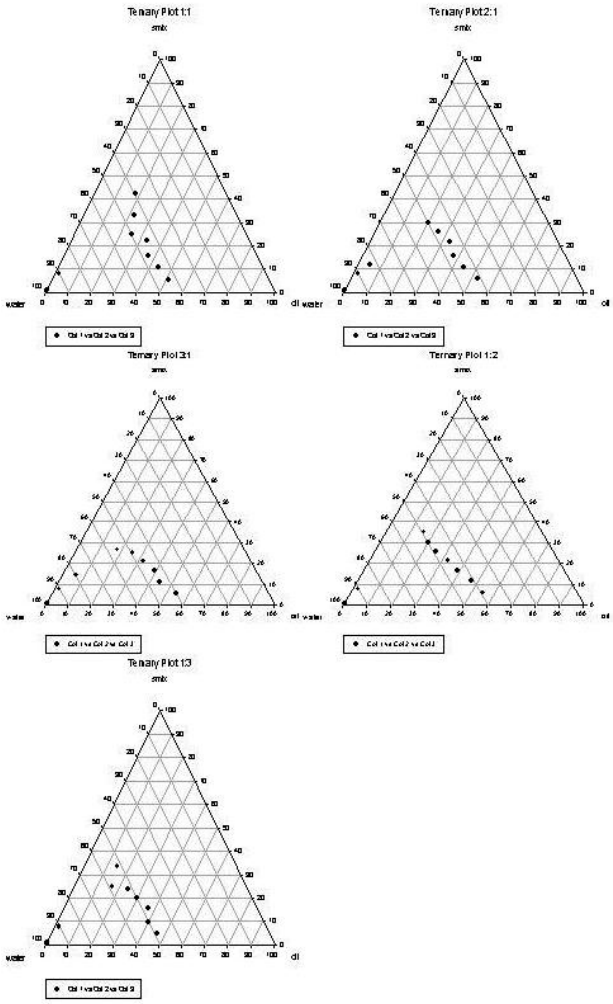


**Figure 1:** Ternary Phase Diagram Study on clopidogrel SNEDDS

### Drug loading capacity

This study was done with the purpose to achieve the highest drug loading capacity in the formulation specifically for high dose drug molecules. Make 1 gm

SMEDDS formulation as per 1:1 smix and 8:2 Smix: oil (in 3 beaker). In all three beakers add 50 mg,100mg and 150 mg drug respectively and after complete dissolution of the drug add slowly water in it (up to 100 ml) and cover it with aluminum foil. Keep it for 24 hrs to check the re-precipitation of drug.

**Table 2:** Different batches for Optimization

| Ingredient | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| | Qty. (mg) | | | | | | | |
| Drug : CLP | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| Acrysol K 150 | 400 | 450 | 540 | 600 | 600 | 680 | 220 | 300 |
| PEG 400 | 400 | 450 | 260 | 300 | 200 | 220 | 660 | 600 |
| Capmul MCM NF | 200 | 100 | 200 | 100 | 200 | 100 | 100 | 100 |
| Total | 1150 | 1150 | 1150 | 1150 | 1150 | 1150 | 1150 | 1150 |

### Preparation of liquid SNEDDS formulations

Sequences of SNEDDS were prepared in trial formulations with varying ratio of oil, surfactant, co-surfactant, and Clopidogrel. CLP concentration remains same in all formulations. All 8 formulations were prepared by taking accurate quantity of all excipients along with drug and stirred well till 10-15 min at 25°C in a small beaker. Heat the solution if drug don't get solubilize. Finally, the mixture was kept at room temperature quantities of various formulations were depicted in table 3.

**Table 3:** Dilution study of Clopidogrel SNEDDS

| Vehicles | I | II | III |
|---|---|---|---|
| Distilled water | Stable | Hazy within 2 Hrs | Hazy within 1 Hrs |
| pH 1.2 | Stable | Hazy within 6 Hrs | Hazy within 3 Hrs |
| pH 6.8 | Stable | Hazy within 3 Hrs | Hazy within 2 Hrs |

Formulation I: 75 mg Clopidogrel, 17.39 % Capmul MCM NF, 34.78 % Acrysol K 150, 34.78% PEG 400

Formulation II: 75 mg Clopidogrel, 17.39 % Capmul MCM NF, 46.96 % Acrysol K 150, 22.66% PEG 400

Formulation III: 75 mg Clopidogrel, 17.39 % Capmul MCM NF, 61.15 % Acrysol K 150, 17.39% PEG 400

### Dilution Study

Dilution may better mimic conditions in the stomach following oral administration of SMEDDS pre-concentrate. Dilution study was done to access the effect of dilution on SMEDDS pre-concentrates. An entire 75 mg of Clopidogrel integrated in SNEDDS formulation.1 part SNEDDS of each solution was diluted with 10 parts of distilled water, Phosphate buffer pH 1.2 and Phosphate buffer pH 6.8 and observed. Observation of dilution studies is shown in Table 4.

**Table 4:** Thermodynamic stability and Dispersibility test of different formulations

| Code | Effect of Temperature on Phase Separation, Flocculation, Precipitation | | | | | | Dispersibility study | Inference |
|---|---|---|---|---|---|---|---|---|
| | After 4 week | | After 8 week | | After 12 week | | | |
| | 2-8 °C | Room temperature | 2-8° C | Room temperature | 2-8 °C | Room temperature | | |
| F1-F8 | Not seen | Not seen | Not seen | Not seen | Not seen | Not seen | Grade A | Pass |
| | Centrifugation stability data (Phase Separation) | | | | | | | |
| | After 1 month | | After 2 month | | After 3 month | | | |
| F1-F8 | Not seen | | Not seen | | Not seen | | Grade A | Pass |
| | Heating and cooling cycle(Creaming or Cracking) | | | | | | | |
| | After 12 hr | | After 24 hr | | After 48 hr | | | |
| F1-F8 | Not seen | | Not seen | | Not seen | | Grade A | Pass |
| | Freeze thaw cycle (Phase Separation) | | | | | | | |
| | at -12 °C | | at 5 °C | | at 25°C | | | |
| F1-F8 | Not seen | | Not seen | | Not seen | | Grade A | Pass |

### SNEDDS characterization

### Thermodynamic stability studies [8]

- ✓ **Heating cooling cycle**: Six cycles between refrigerator temperature (4°C) and 45°C with storage at each temperature of not less than 48 h was studied. Stable formulations at these temperatures were subjected to centrifugation test.
- ✓ **Centrifugation**: Accepted formulations were centrifuged at 2500 rpm for 40 min. Those formulations having absence of any phase separation were taken for the freeze thaw stress test.
- ✓ **Freeze thaw cycle**: Three freeze thaw cycles amongst -21 °C and +25 °C with storage at each temperature for not less than 48 h was done for the formulations.

Formulations which passed these thermodynamic stress tests were further taken for the dispersibility test for assessing the efficiency of self-emulsification.

### Dispersibility test

The efficiency of self-emulsification of oral nanoemulsion was assessed using a standard USP dissolution apparatus type 2.[8] 1 ml of each formulation was added to 500 ml of water at 37 ± 0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The

*in vitro* performance of the formulations was visually assessed using the following grading system:

Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that will form within 2 min.

Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

**Percentage Transmittance (λ max 650 nm)**

The CLP SNEDDS were equipped by taking 100 times dilution of various media in 1 gm drug and the resulting nanoemulsion was observed visually for any turbidity. Subsequently, its % transmittance was measured at 650 nm using UV–vis spectrophotometer (systronics 2201). The studies were conducted by taking distilled water; phosphate buffer pH 1.2 and phosphate buffer pH 6.8.

**Cloud point measurement study**[12]

The cloud point is a crucial feature in the SNEDDS consisting of non-ionic surfactants, and it is responsible for the successful formation of a stable microemulsion. The SNEDDS were compared for cloud point value. Each formulation was diluted with distilled water in the ratio of 1:250 and placed in a water bath with gradual increase in temperature. The point at which cloudiness occur was noted as cloud point.

**Determination of droplet size/distribution and zeta-potential**

Clopidogrel SNEDDS concentration (approximately 100 mg) was diluted with purified water (100mL) and gently shaken in a volumetric flask at 25°C. The droplet size/distribution and zeta-potential were analyzed by dynamic light scattering technique using a Zetasizer (Nano ZS, Malvern Instruments, UK) equipped with a 4.0 mW He-Ne red laser (633nm).

**Drug diffusion studies**

SNEDDS of CLP was filled in dialysis bag. *In vitro* release profile of SNEDDS was studied using USP apparatus type II at 37±0.50 ◦C with a rotating speed of 100 rpm in dissolution media namely, pH 1.2 and 6.8 buffer so as to evaluate the effect of pH on *in vitro* dissolution. During the study, 3 ml of aliquots were removed at predetermined time intervals (5, 10, 15, 20, 25, 30, 40, 50 up to 90 min) from the dissolution medium and replaced with fresh buffer. The amount of CLP released in the dissolution medium (figure 3) was determined by UV spectrophotometer at λmax = 235 nm.

## RESULTS

**Pseudo-ternary phase diagrams study**

The pseudo-ternary phase diagrams were mapped with the water titration method to identify the area of microemulsion regions at 37°C. The distilled water was used as diluting medium and added into the formulation. The proper ratio of one excipient to another in the SNEDDS formulation was analysed. Several formulations with different oil and Smix values (the ratio of surfactant to cosurfactant) were dispersed with water at 37°C. The pseudo-ternary phase diagrams of the formulation composed of Acrysol K 150, Capmul MCM NF and PEG 400 are shown in Figure 1. From figure, it was concluded that emulsifying zone is observed in almost all the ratios applied and no significant effect on Smix: oil ratio. The shadow area represents the o/w microemulsion existence region. The size of the nanoemulsion region in the diagrams was compared as, larger the size the greater the self- nanoemulsification efficiency.

**Drug loading capacity**

Capacity of drug engulfment in nanoemulsion was observed by putting three different quantities and concludes that there is no precipitation of drug even after seven weeks and shows his maximum drug loading capacity by appealing the industrial use of SNEDDS.

**Preparation of liquid SNEDDS formulations**

In following experiment we undergo various trial batches so as to explore the perfect combination of excipients. After various trials prepared on the basis of solubility of drug, final batches were prepared through ternary phase diagram study shown in table 2.

**Dilution Study**

A right blend of emulsifier is necessary for the development of SNEDDS formulation; to form stable Nanoemulsion. When 1 part SNEDDS of each solution was diluted with 10 parts of distilled water, HCl buffer 1.2 pH and phosphate buffer 6.8 pH (Table 3). It implies that the formulation was more stable because there was no precipitation.

**SNEDDS Characterization**

***Thermodynamic stability studies***

Various thermodynamic stability studies were performed by evaluating its temperature, centrifugation and dispersibility potential. A study reveals that there is no effect of any of the parameter on the transparency of nanoemulsion and not show any precipitation, phase separation, creaming or cracking given in Table 4.

***Percentage Transmittance***

Percentage transmittance of nanoemulsion in distilled water, HCl buffer pH 1.2 and Phosphate buffer pH 6.8 was 99%, 98% and 99 %, respectively, which was nearer to 100%. It indicates clear nanoemulsion was formed from the SNEDDS up to 100 times dilution with distilled water.

***Cloud point measurement study***

The cloud point is the temperature above which a clear formulation turns cloudy. At temperatures higher than the cloud point, an irreversible phase separation occurs due to dehydration of its ingredients, which may affect drug absorption. Hence, to avoid this phenomenon, the cloud point for SNEDDS should be above body temperature (37 ◦C). The cloud point for CLP SNEDDS was much higher (60-65 ◦C) which indicates that it will form stable nanoemulsion at physiological temperature i.e. in vivo, without risk of phase separation.

**Determination of droplet size/distribution and zeta-potential**

Particle size after nanoemulsification was the most important property of SMEDDS. Mechanisms of particle size effect on drug absorption may include improved release and facilitated lymphatic transport. The CLP SNEDDS showed somewhat parallel mean globule size within range of 16-42 nm when diluted with distilled water. The time required for formation of nanoemulsion after dilution with distilled water was just 38 second. The resultant nanoemulsion were transparent in appearance and they didn't show any symptom of phase separation and drug precipitation even after 24 h .Droplet size of optimal formulation was given in figure 2.

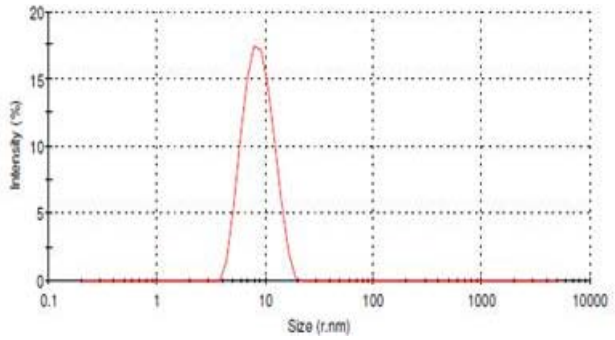


**Figure 2:** Globule size of optimized formulation

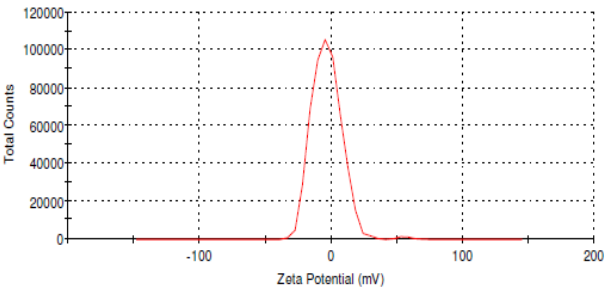


**Figure 3:** Zeta Potential of optimized formulation

Zeta potential of the SNEDDS is helpful to recognize the charge of oil globules in the emulsion. The increase in electrostatic repulsive forces between the globules averts the coalescence of nanoemulsion. In contrast, decrease in electrostatic repulsive forces can cause phase separation. Several studies have reported that the zeta potential played an important role in the interactions with mucus of the gastrointestinal tract. The zeta potential of all the batches lied between-0.366 to 4.51. The zeta potential of the optimized formulation obtained by diluting CLP SNEDDS with distilled water (100 times) was −3.25± 0.62 mV and results are shown in Fig.3. The charge on an oil globule may be negative due to surfactants and/or co-surfactant present in the formulation.

**Drug diffusion studies**

Diffusion patterns of CLP from plain drug, marketed tablet formulation and various batches after reconstitution with HCl buffer (pH 1.2) and phosphate buffer (pH 6.8) are depicted in Fig.4 The patterns disclose that release of CLP from various batches varied with change in pH. It was observed from optimized batch that more than 60% drug released within 5 min and complete release was obtained within 15 min in pH 1.2 buffers, while 92% drug was released in 15 min in phosphate buffer (pH 6.8). This difference may be due to the difference in solubility of CLP at different pH. On the other hand, the release of CLP from the marketed tablet (clopilet) was only 72% within 90 min in pH 1.2 and pH 6.8. These results were found to be more sliding with plain drug having release of 56% within 90 min. Thus, we can say that the formulated SNEDDS having much potential than the plain drug and even from marketed dosage form and shows uniform *in vitro* release throughout the GIT irrespective of pH variations.

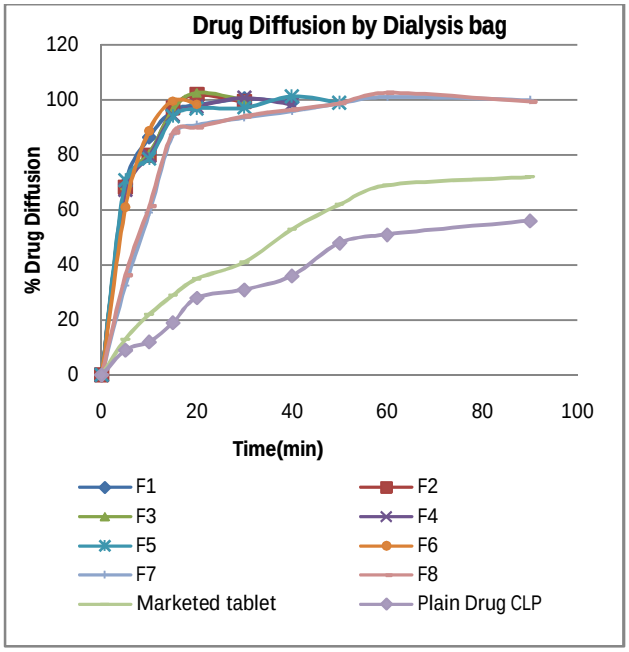


**Figure 4:** *In vitro* drug diffusion of formulation F1-F8 with plain drug and conventional tablet of CLP

## CONCLUSION

The present research work could be summarized as successful development of SNEDDS of Antiplatelet CLP using Acrysol K150 (surfactant), Capmul MCM NF (oil), PEG 400 (Cosurfactant/Cosolvent) which gives stable and transparent nanoemulsion. Based on higher solubility, ultimate nanoemulsifying zone, lesser globule size with minimum polydispersity index, acceptable globule charge, higher transmittance, lower viscosity, higher cloud point

and superior drug release illustrate the potential use of Clopidogrel SNEDDS orally. Formulation can also be given in liquid solution or in capsule dosage form deemed to be the efficacious and patient compliant delivery system. Studies also showed how nanoemulsion formulation can be supportive for the delivery of hydrophobic compounds with capacity to load higher drug concentration, minimum surfactant concentration and proper infinite dilution without attaining drug precipitation.

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