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# Development & In Vivo Evaluation of Pomalidomide Super Saturable Self-Nanoemulsifying Drug Delivery System

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## Abstract:

Pomalidomide belongs to BCS class IV drug with low solubility and undergoes first-pass metabolism leads to reduced bioavailability of 15%.The current investigation was aimed to enhance the solubility and oral bioavailability of Pomalidomide by employing the supersaturable self-nanoemulsifying drug delivery system(S-SNEDDS). Akomed E oil, Caprol PGE 860, and PEG 600 were chosen as the oil, surfactant, and co-surfactant, respectively, based on the pseudo tertiary phase diagram. All the formulations were stable with no phase separation and maximum % transmittance. The formulation F11 selected as optimized one based on maximum drug release of 99.04% within 60 min. By adding PVP K17 as a precipitation inhibitor to conventional SNEDDS, a supersaturable system was prepared. First off, due to their nano-range size, the produced SNEDDS were significant in improving water solubility and, consequently, oral absorption. Second, the S-SNEDDS were found to be superior than SNEDDS due to their increased drug load and ability to prevent the pomalidomide dilute precipitation.Formulated S-SNEDDS (F11) showed drug release of 99.98%. The particle size, PDI and zeta potential of the optimized formulation F11 S-SNEDDS was 49.0 nm,0.318and -24.4 mV respectively. The FTIR and SEM studies did not indicate any drug excipient interaction and confirm nanosized which is stable.

*In vivo* pharmacokinetics study of S-SNEDDS showed a significant increase (4.4-fold) in the oral bioavailability of Pomalidomide in rats compared to pure drug. In summary, these observations illustrated the application prospects of S-SNEDDS technology in promoting solubility and oral bioavailability from poorly water-soluble drug Pomalidomide.

*Keywords* —Pomalidomide, S-SNEDDS, solubility, pseudo ternary phase diagram, anti-neoplastic agent.

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## I. INTRODUCTION

The application of a self-nanoemulsifying drug delivery system (SNEDDS) to increase the oral bioavailability of a hydrophobic drug is a technological advance in self-emulsifying drug delivery system. SNEDDS is defined as transparent, thermodynamically stable, isotropic mixture of oil, surfactants and cosurfactants. Under peristaltic movement upon contact with the aqueous medium in the gastrointestinal (GI) tract, the SNEDDS spontaneously forms a fine oil-in-water (o/w) emulsion with a droplet size of less than 100 nm . The merits of SNEDDS include ease of production and outstanding solubilizing capacity. In addition, self-nanoemulsion in the stomach produces large amount of small droplets and a large surface area, which facilitates the transport of the drug through the unstirred water layer to the intestinal epithelial cells, enhancing drug absorption. Moreover, other mechanisms can also enhance drug absorption, and these mechanisms include the improving gastrointestinal tract membrane permeability, inhibiting the activity of cytochrome P450, increasing the lymphatic transport of the drug and avoiding the first-pass effect.[1-3]

  

Nevertheless, precipitate frequently occurs after dilution in the stomach medium when SNEDDS loads medicines with low solubility and poor permeability, which decreases drug dissolution in vitro and absorption in vivo. To circumvent this limitation, the general approach was to increase the amount of surfactant. However, the SNEDDS formulation's several surfactants could cause hazardous effects including severe stomach poisoning. To overcome these difficulties and maximize the intestinal absorption of poorly soluble drugs, a supersaturable self-nanoemulsifying drug delivery system (S-SNEDDS) was proposed. To produce and keep the medication in a metastable supersaturated form in the digestive system, S-SNEDDS are typically SNEDDS that contain a water-soluble polymeric precipitation inhibitor. The concept of generation and maintenance of a supersaturated state is often referred to as "spring and parachute effect". Several hydrophilic polymers, such as polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus) and polyethylene glycol (PEG), have been shown to be useful precipitation inhibitors. Through hydrogen bonding, hydrophobic interactions, solution viscosity, the molecular weight of the polymer and steric hindrance, the precipitation inhibitor inhibits drug precipitation by delaying the rate of drug nucleation and crystal growth .[4]

Pomalidomide is a BCS class IV product, having low permeability and low solubility. The drug substance is practically insoluble in water. The present work described an innovative approach by designing a supersaturated self-emulsifying formulation (S-SNEDDS) to improve the dissolution and bioavailability of pomalidomide.

## II. MATERIALS AND METHODS

### *A.Materials*

Pomalidomide is gifted by Hetero Labs Limited, Hyderabad. Akomed E, Castor oil, Corn oil, Caprylic acid, Capryol 90, Imwitor, Miglyol 810, Neobee M5, Oleic acid, Triacetin, Brij35, tween20,Caprol PGE 860, Cremophor EL,CremophorHS15,Labrasol. Cremophor RH 40, Tween 85, D-alpha Tocopheryl Poly ethylene Glycol, PEG-400, PEG-600, Propylene glycol, lauro glycol FCC, HPMCK4M,PVPK30,EudragitL100 and Poloxamer 407purchased from Gattefosse, Mumbai.

### *B. Solubility of Pomalidomide In Vehicles*

An excess amount of pomalidomide was placed in screw-capped glass vials containing 1 g of vehicle (i.e., oil or surfactant or co-surfactant). To ensure thorough pomalidomide and vehicle mixing, glass vials were sealed with caps and vortexed for 10 min using a cyclomixer.. Then vials were shaken reciprocally using a mechanical rotary shaker for 48 hrs at 25° C and allowed for another 24 h to attain equilibrium conditions without shaking at the same temperature. The vials were centrifuged at 3000 rpm for 10 min using a centrifuge to obtain a clear supernatant liquid. Supernatant (100 mg) was collected extracted for pomalidomide and filtered through a millipore membrane filter (0.45µm) and diluted suitably with methanol and analyzed for pomalidomide using UV spectrophotometer at 251 nm**.** The amount of pomalidomide dissolved in various vehicles was calculated. [5,6]

### *C. Construction of Pseudo-Ternary Phase Diagrams*

From the solubility study oil, surfactant and co-surfactant were chosen based on the maximum solubility of the drug in it, the chosen vehicles were mixed in various ratios ranging from 1:9 to 9:1 (oil: $S_{mix}$). $S_{mix}$ is the mixture of surfactant and co-surfactant prepared in defined ratios of 1:1, 2:1, and 3:1. Ternary phase diagrams comprising surfactant, co-surfactant and oil were plotted, each of them, representing an apex of the triangle. Akomed E oil as oil phase Caprol PGE 860 as Surfactant and PEG 600 as co-surfactant were selected (based on the solubility studies). Varying ratios of oil: $S_{mix}$ were filled in 2ml eppendrof tubes shaken and kept aside. These mixtures were gently mixed with 100ml of water taken in beaker and checked for phase separation and turbidity. The ratios with no phase separation and clear appearance with no turbidity

  

were separated and checked for the transmittance using UV spectrophotometer[7].The transmittance value more than 90 indicated nano size droplets formation hence these ratios were noted and used for plotting pseudo-ternary phase diagram. Pseudo ternary phase diagram is constructed using CHEMIX software.[7,8]

***D. Effect of Pomalidomide Loading***

Nineteen compositions of varying ratios of Akomed E oil - Caprol PGE 860 - and PEG 600 were taken and in 1ml composition of each ratio were incorporated with 2 mg, 4 mg and 8 mg of pomalidomide (i.e. 19*3=57 formulations). Required amount of pomalidomide was added to the screw capped glass vials containing required amount of surfactant and co-surfactant. Drug was solubilized using a vortex mixer or by heating at 40°C in a water-bath wherever necessary. Finally required amount of oil was added to the vials and vortex mixed for 2 min for proper mixing. The transmittance of the resulting dispersions up on diluting 25 mg of the formulations with 50 mL distilled water was measured using UV spectrophotometer at 600nm. The area of nanoemulsification region was identified as described above by constructing pseudo-ternary phase diagrams.[9]

***E. Preparation of Pomalidomide SNEDDS***

A series of SNEDDS (F1- F15, the composition was shown in Table 1) which showed transmittance values more than 90) were selected from 4 mg loaded pomalidomide system and prepared as described above [8]. About 1ml of the formulation (equivalent to 4 mg of the Pomalidomide) was filled in size '00' hard gelatin capsules, sealed and stored at ambient temperature (25°C) until used. These SNEDDS were evaluated for visual observations, turbidity, effect of pH of the dispersion media on globule size and zeta potential, robustness to dilution and invitrodissolution study and were optimized.[10]

**TABLE 1**
**COMPOSITION OF POMALIDOMIDE SNEDDS**

| S. No | Formulation code | Pomalidomide drug (mg) | Ratios of Oil: Smix | Oil | Smix 3:1 | |
|---|---|---|---|---|---|---|
| | | | | (Akomed E oil) | Surfactant (Caprol PGE 860) | Co-surfactant (PEG 600) |
| 1 | F1 | 4 | 01:01 | 50 | 37.5 | 12.5 |
| 2 | F2 | 4 | 01:02 | 33 | 49.5 | 16.5 |
| 3 | F3 | 4 | 03:01 | 75 | 18.75 | 6.25 |
| 4 | F4 | 4 | 02:01 | 66 | 24.75 | 8.25 |
| 5 | F5 | 4 | 02:03 | 40 | 45 | 15 |
| 6 | F6 | 4 | 09:02 | 81.8 | 13.6 | 4.6 |
| 7 | F7 | 4 | 07:02 | 77.7 | 16.7 | 5.5 |
| 8 | F8 | 4 | 05:02 | 71 | 21.3 | 7.1 |
| 9 | F9 | 4 | 03:02 | 60 | 30 | 10 |
| 10 | F10 | 4 | 03:04 | 42.6 | 42.6 | 14.8 |
| 11 | F11 | 4 | 03:07 | 30 | 52.5 | 17.5 |
| 12 | F12 | 4 | 08:03 | 72.7 | 20.25 | 6.75 |
| 13 | F13 | 4 | 07:03 | 70 | 22.5 | 7.5 |
| 14 | F14 | 4 | 05:03 | 62.5 | 28.12 | 9.3 |
| 15 | F15 | 4 | 04:03 | 57.1 | 31.95 | 10.65 |

All the formulations are evaluated for visual observations [11], turbidity measurement[12], robustness to dilution[13],percentage drug content[14], entrapment efficiency[15] and in vitro dissolution studies as per the referred procedure[16,17].

***F. Screening for a precipitation inhibitor***

*In vitro* precipitation experiments were used to estimate the apparent drug concentration-time profile and the duration of the super-saturatedstate.PolymerssuchasHPMCK4M,PVPK30,Eudragit L100 and Poloxamer 407 were employedtostabilize the supersaturated pomalidomide solution. A 100 mL aliquot of simulated gastric fluid (SGF) was maintained at 37 °C with the stirring speed held at 100 rpm. One gram of optimized pomalidomide SNEDDS formulation with various polymers was added into the medium. One milliliter samples of the solution were taken without volume replacement at 5, 15, 30, 45, 60, 90, 120, 180 and 240 min, and the aliquots were centrifuged at 3000rpmfor 3 min. The supernatant was diluted with

  

methanol,andtheconcentrationofPomalidomidewasassayedbyUVanalysis at 251 nm.[18]

***G.Characterization of optimised pomalidomide SNEDDS formulation***

***Fourier Transform-Infrared Spectroscopy(FTIR)***

Pomalidomide and excipients were analyzed by FT-IR spectrophotometer with data acquisition system OPUS [18].The globule Size and zeta potential of optimised formulation was determined by a Zetasizer Nano ZS90 dynamic light scattering particle size analyzer (Malvern Instruments, Malvern, Worcestershire, UK).Scanning electron microscopy studies (JEOL JEM 2100 F, USA) were carried out for optimized formulation by diluting the same with distilled water to 1000 times and then plunging on a 2% uranyl acetate solution stained carbon grid.[19]

***H.AcceleratedStability Studies***

Optimised formulation was filled in hard gelatin capsules were packed in HDPE screw capped bottles and kept in humidity chambers maintained at 40 ± 2°C/ 75 ± 5% RH as per ICH guidelines for Zone III and stored for 6 months. Samples were evaluated for entrapment efficiency, drug content and drug release (ICH Harmonized Tripartite guideline on "Stability Testing of NewDrug Substances and Products Q1A (R2)", 6 February 2003).[20]

***I.Pharmacokinetic Studies of Pomalidomide***

***Animal preparation***

For this investigation, healthy male Wistar rats (weighing 200-220 g) were chosen, and all of the animals remained healthy throughout the treatment. All measures were put in place to keep the animals in a climate-controlled facility with temperature $25^0$C, 45% RH and 12 h alternate light and dark cycle along with 100 % fresh air exchange in animal rooms, and even some extended range power and water supply. Rats were given a regular pellet diet and water ad libitum after acquainting to the surroundings for at least three days. The protocol of animal study was approved by the institutional animal ethics committee (**IAEC NO :IAEC No.1447/PO/Re/S/11/CPCSEA-55/A).**

***Study Design***

The rats were divided into three groups at random (Group A, Group B and Group C). The rats were starved for 24 hours before to the testing. After 4 hours after dosing, foods were reoffered. The first group A received pure pomalidomide (as such) made into a suspension with 0.5 percent w/w HPMC 2.5 cps, while the second Group B received prepared Pomalidomideoptimizedsupersaturable SNEDDS via oral gavage followed by 1ml of water at a dose of 0.14 mg. Group C was kept as control.
For the determination of plasma drug concentration at different times, 200 µl of blood samples were collected into heparinized Microvette®100 centrifuge tubes. Using a 26-gauge needle, puncture the lateral tail vein at points (0, 0.5, 1, 2, 4, 8,12, and 24 hours). The local anesthetic (benzocaine cream) was injected to the surface of the tail 30 minutes before the experiment according to the NIH recommendations for survive bleeding of rats. The samples were centrifuged for 5 minutes at 10,000rpm at 4°C, with the supernatant plasma samples collected and stored at -80°C until further analysis.[21]

***PHARMACOKINETIC ANALYSIS***

The pharmacokinetic parameters employed to evaluate were maximum plasma concentration ($C_{max}$), time to attain $C_{max}$i.e., $T_{max}$ and $t_{½}$ values, area under plasma concentration–time curve from zero to the last sampling time ($AUC_{0\text{-}t}$), area under plasma concentration–time curve from zero to infinity ($AUC_{0\text{-}\infty}$).

## III. RESULTS AND DISCUSSION

***A. Determination of Pomalidomide Solubility In Various Excipients***

Akomed E oil was selected as oil phase due to its higher solubilization (190.54±0.94mg/ml) of Pomalidomide compared to other oils.SurfactantCaprol PGE 860 and co-surfactant PEG 600 were selected for further studies due to their higher solubilizing capacity towards Pomalidomide.

  

***B.ConstructionOf Ternary Phase Diagrams***

The region of nano emulsification was indicated as shadow area encircled by a solid line and the points indicate the compositions of the system explored. Akomed E oil - Caprol PGE 860 - and PEG 600 system with Smix ratio in 3:1 exhibited larger nanoemulsification region as compared to 1:1 and 2:1 Smix ratio (Figure 1)

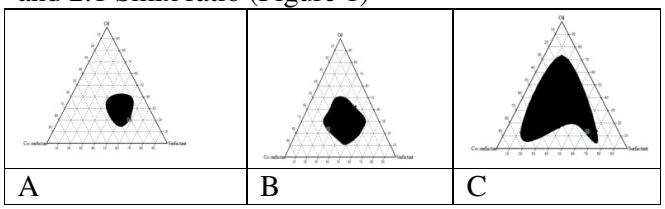


Figure 1: Ternary phase diagram for Akomed E oil - Caprol PGE 860 - and PEG 600 with Smix in 1:1 ratio(A); Smix in 2:1 ratio;Smix in 3:1 ratio
(Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)

The mean globule size was decreased with increase in surfactant concentration. Hence the systems containing Akomed E oil - Caprol PGE 860 - and PEG 600 with 3:1 Smix ratio were selected for further studies due to their larger nanoemulsifying area, greater capacity for incorporation of oily phase with uniformity of dispersion and high transmittance values.

***C. Effect of Pomalidomide Loading***

The area of nanoemulsification was considerably reduced with increase in pomalidomide loading from 4 to 8mg in to the Akomed E oil -Caprol PGE 860 - and PEG 600system with 3:1 Smixratio.Hence for the stability reasons of the SNEDDS, system containing 4 mg of pomalidomide was chosen (figure 2) for formulation of pomalidomide SNEDDS and further studies.

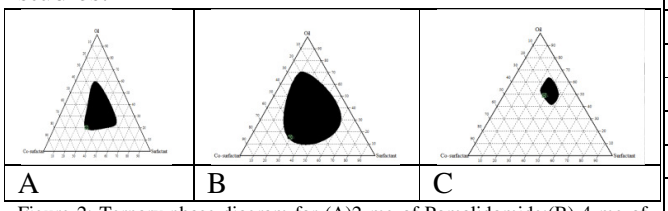


Figure 2: Ternary phase diagram for (A)2 mg of Pomalidomide;(B) 4 mg of Pomalidomide (C) 8mg ofPomalidomideloadedAkomed E oil - Caprol PGE 860 - and PEG 600 system with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)

***D.Preparation and Evaluation of Pomalidomide SNEDDS***

From the above results it was found that Akomed E oil concentration in the range of 30-82% w/w, Caprol PGE 860 in the range of 13-53% w/w and PEG 600 in the range of 4-18% w/w in 3:1 of oil:Smix ratio with 4mg of loaded Pomalidomide drug produced the SNEDDS having the transmittance greater than 90, with good stability. A series of SNEDDS were prepared in the above mentioned ranges of oil- surfactant-co-surfactant ratios and were evaluated for visual observations, turbidity measurements, robustness to dilution and in vitro dissolution study.

Visual observations showed that the self-emulsification process became more spontaneous at greater surfactant concentrations. Turbidity values show that the formulations that have low turbidity (<20) gave a transmittance values of more than 90 indicating rapid and spontaneous emulsification within 1min, hence it gives a good correlation between transmittance and turbidity values (table 3). Nanoemulsions resulting from the dispersion of pomalidomide SNEDDS (F1-F15) with distilled water, 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer were found to be robust to all dilutions and no separation or drug precipitation was observed even after 24 hs of storage.

**TABLE 3**
**Visual observation and turbidity measurement values**

| Formulation code | Visual Observation | Turbidity (NTU) |
|---|---|---|
| F1 | A | 17.65 |
| F2 | A | 16.87 |
| F3 | B | 21.24 |
| F4 | A | 18.32 |
| F5 | A | 17.05 |
| F6 | B | 21.85 |
| F7 | B | 21.56 |
| F8 | B | 20.02 |
| F9 | A | 17.95 |
| F10 | A | 17.42 |
| F11 | A | 15.24 |
| F12 | B | 20.64 |
| F13 | A | 19.03 |
| F14 | A | 18.08 |
| F15 | A | 17.77 |

  

***E .Percentage Drug Content and Entrapment Efficiency***

The drug content of all formulations ranged between 96.09±1.37 to 99.52±1.38 % with maximum value exhibited by F11 (table 4). The entrapment efficiency of all formulations varies between 96.19±1.48 to 99.85±1.63 % with maximum value displayed by F11.

**F.*InVitro Dissolution Studies***

Comparative dissolution profiles of Pomalidomide pure drug and pomalidomide SNEDDS formulations (F1-F15) are shown in (fig 11). Faster release rates were observed for pomalidomide SNEDDS than the pure drug. All Pomalidomide SNEDDS formulations (F1-F15) completed dissolution within 60 min and all formulation released more than 95% of drug, whereas, pure drug released 31.99 ±0.72 %. Formulation F11 exhibited highest drug release of 99.84±0.69 % within 60min. The release of the drug from SNEDDS formulation was increased proportionally with increase in surfactant concentration and hence F11 exhibited high drug release.

***G.InVitro Evaluation Of Precipitation***

As shown in figure 8, the precipitation profiles showed that the S-SNEDDS had better inhibition of pomalidomide precipitation than the SNEDDS (the same composition but without precipitation inhibitor) during the 60 min of the study. Upon mixing with the SGF, the SNEDDS formulation initially appeared as a nanoemulsion with a bluish reflection. After 30 min, solid precipitates of pomalidomide were observed, which suggested that the medium was in a supersaturated state. For theSNEDDS formulation, at t = 20 min, the concentration of pomalidomide declined to about 232.28µg/mL, and decreased rapidly to about 175.69µg/mL after 60 min due to the precipitation. In contrast, the S-SNEDDS formulation showed a consistently higher apparent pomalidomide concentration- time profile as compared to the SNEDDS formulation.

The pomalidomide concentration in the S-SNEDDS formulation decreased rapidly when soluplus were applied as the precipitation inhibitors. The concentration declined to < 350 µg/mL within 30 min (320.45µg/mL), indicating that soluplus was unable to sustain the apparent pomalidomide concentration. Although HPMC E5LV, PVP K17, Maltodextrin and Solupluscould all effectively inhibit pomalidomide precipitation, PVP K17performed better than HPMC E5LV and maltodextrin. Because the highest concentration of Pomalidomide(415.52µg/mL after 60 min) was observed with PVP K17; for comparison, the concentrations achieved with HPMC E5LV and maltodextrin were 345.82 and 390.94µg/mL, respectively.

Visual observations indicated that at higher levels of surfactant, the spontaneity of the self-emulsification process was increasedprominent characteristic peaks confirming the purity of pomalidomide as per the established standards.(figure 8,9)

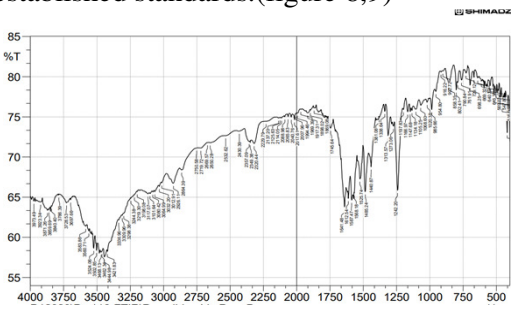

Figure 8: FTIR spectrum of pure drug Pomalidomide

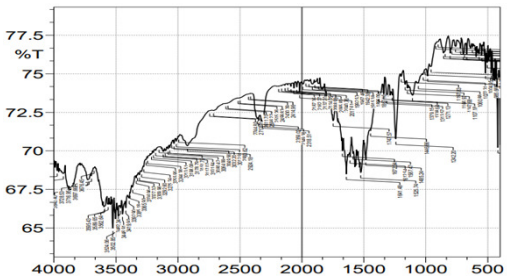

Figure 9:FTIR of optimised PomalidomideS-SNEDDS (F14)

**J.*SEM Studies***

Morphological and structural examination of the optimized batch F11 of Pomalidomide loaded SNEDDS was carried out using transmission electron microscope. These results were in accordance to that of globule size analysisand was observed that the size of all droplets of SNEDDS F11 was less than 200 nm as furnished in Figure 10 A,B,C. However, the shape of droplets was found to be spherical.

  

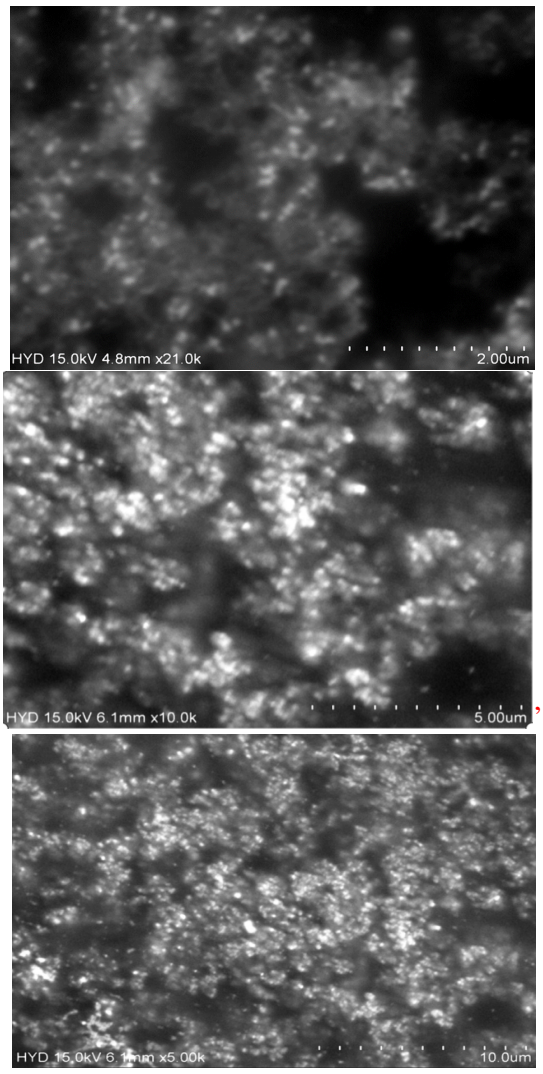

Figure 10: SEM images of optimised formulation of Pomalidomide SNEDDS F11 (A, B& C)

***K. Accelerated Stability Studies***

The purpose of stability testing is to demonstrate how a drug substance's or drug product's quality changes over time and in response to various environmental conditions, including as temperature, humidity and light and enables recommended storage conditions.

No visible physical changes were observed in F11 supersaturable SNEDDS formulation(F11 S-SNEDDS) withdrawn from the humidity chambers. The samples were assayed for %entrapment efficiency, % drug content and in-vitro drug release and the results are shown in Table 5. No significant difference was observed after storage at accelerated conditions at 40±2° C/75±5% RH for a period of six months.

**TABLE 5**
**Storage at 40±2° C/75±5% RH for 6 months**

| Retest time for optimized formulation F4 | %Drug content | % Entrapment efficiency | *In-vitro* drug release (%) |
|---|---|---|---|
| 0 days | 99.52±1.38 | 99.85±1.63 | 99.98±0.72 |
| 30 days | 99.25±0.53 | 99.64±0.68 | 99.67±0.37 |
| 60 days | 98.93±0.46 | 99.42±0.38 | 99.43±0.28 |
| 90 days | 98.82±0.74 | 99.18±0.94 | 98.95±0.64 |
| 180 days | 98.69±0.65 | 98.78±0.94 | 98.45±0.14 |

Above parameters are communicated as Average ± Standard Deviation; (n=3)

Figure 11 shows the plasma concentration–time curve in Wister rats after a single oral dose of Pomalidomide supersaturable SNEDDS formulation as compared toPomalidomidepure. At all the indicated time points, the Pomalidomide plasma concentrations in rats treated with supersaturable SNEDDS formulation was significantly higher than those treated with pure drug. Pharmacokinetic parameters of Pomalidomide after oral administration of the two formulations in Wister rats are shown in Table 6.

$C_{max}$ of the supersaturable SNEDDS61.54±1.55ng/ml was significant ($p<0.05$) as compared to the pure drug 18.05±1.66ng/ml. $T_{max}$ of both supersaturable SNEDDS formulation and pure drug was 2.0±0.06and3±0.05 h, respectively. AUC is an important parameter in evaluating bioavailability of drug from dosage form, as it represents the total integrated area under the blood time profile and represents the total the quantity of medication that, after oral delivery, enters the bloodstream. $AUC_{0-\infty}$ infinity for supersaturable SNEDDS formulation was higher (1928.1±2.62ng. h/ml) than the pure drug478.1±2.64 ngh/ml. Statistically, $AUC_{0-t}$ of the supersaturable SNEDDS formulation (1853.86±0.67ng h/ml) was significantly higher ($p<0.05$) as compared to pure drug (416.34±0.64ng h/ml). Higher amount of drug concentration in blood indicated better systemic

absorption of Pomalidomide from supersaturable SNEDDS formulation as compared to the pure drug.

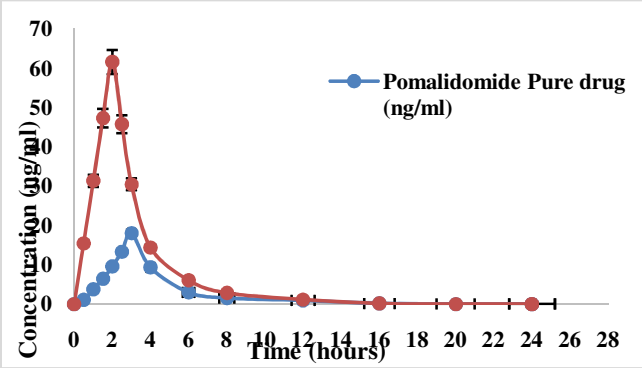


Figure 11: Mean plasma concentration-time profiles for Pomalidomide pure drug and Pomalidomide optimized supersaturable SNEDDS formulation in rats (n=6)

**TABLE 6**
**Mean pharmacokinetic parameters of Pomalidomide pure drug and Pomalidomide optimised supersaturable SNEDDS formulation**

| Pharmacokinetic parameters | Pomalidomide Pure drug | Pomalidomide optimised supersaturable SNEDDS |
|---|---|---|
| $C_{max}$ (ng/ml) | 18.05±1.66 | 61.54±1.55 |
| $AUC_{0-t}$ (ng. h/ml) | 416.34±0.64 | 1853.86±0.67 |
| $AUC_{0-inf}$ (ng. h/ml) | 478.1±2.64 | 1928.1±2.62 |
| $T_{max}$ (h) | 3±0.05 | 2.0±0.06 |
| $t_{1/2}$ (h) | 7.92±0.08 | 1.92±0.03 |
| $K_e$ | 0.080605 | 0.332553 |

The pharmacokinetic data was subjected to statistical analysis to test the significant differences between the pharmacokinetic parameters of two formulations. The data indicated that there was significant difference in $C_{max}$, $T_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, between Pomalidomide pure drug and Pomalidomidesupersaturable SNEDDS formulation.

## IV. CONCLUSION

The pomalidomide SNEDDS formulation prepared using Akomed E oil - Caprol PGE 860 - and PEG 600 aided by monophasic zone in pseudo tertiary phase diagram. The 15 developed formulations subjected to thermo dynamical physical stability studies, drug content, percentage entrapment efficiency and drug dissolution analysis. The formulation F11 chosen optimal with maximum drug content 99.52% with no phase separation during thermo dynamic stability study. The *in vitro* drug dissolution of 99.04% is indicative of reduced particle size and enhanced solubilizing capacity of F11 than pure drug. By adding PVP K17 as a precipitation inhibitor to conventional SNEDDS, a supersaturable system was prepared. First off, due to their nano-range size, the produced SNEDDS were significant in improving water solubility and, consequently, oral absorption. Second, the S-SNEDDS were found to be superior than SNEDDS due to their larger drug loads and ability to prevent the pomalidomide dilute precipitation.Formulated S-SNEDDS (F11) showed drug release of 99.98%. The FT-IR data assured the retention of the major peaks of pomalidomide in the F11 forecasting no interaction. The particle size, PDI and zeta potential of the optimized formulation F11 S-SNEDDS was 49.0 nm, 0.318 and -24.4 mV respectively. The SEM studied of F11 indicated narrow uniform distribution of drug in formulation. The stability studies carried out for 6 months indicate no significant variation in drug release and drug content of optimized formulation. Hence, these investigations advocated the suitability of supersaturable-SNEDDS loaded pomalidomide in enhancement of solubility and drug release.

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