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Research Paper

Formulation And Comparative Evaluation of Liquid and Solid Self-Nano-Emulsifying Drug Delivery System of Clopidogrel Hydrogen Sulphate

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ABSTRACT

Main aim of this project is to formulate and to perform comparative evaluation of Clopidogrel hydrogen sulphate liquid and solid self -nano emulsifying drug delivery system (SNEDDS). Solubility studies were performed and excipients were selected. Pseudo ternary phase diagram was constructed by using aqueous titration method. Then, liquid Self nano emulsifying drug delivery system was formulated. Then, evaluated for particle size, self-emulsification time, subjected for freeze thaw cycle, centrifugation, drug content was determined and invitro drug release studies were performed. The optimized liquid SNEDDS is converted into solid SNEDDS by using adsorbent technique and further evaluation were performed and compared with the liquid SNEDDS.

INTRODUCTION

Drugs are mostly given through oral route. Around 40% of new chemical have entities shown low aqueous solubility, which results in low bioavailability, high intra and inter subject variability and lack of dose proportionality. Oral bioavailability also depends on many factors such as stability in gastrointestinal fluids, intestinal permeability, resistance to metabolism by

cytochrome p450 enzymes present in gut enterocytes and liver hepatocytes. Many strategies, like oral lipid – based drug delivery systems is one of the promising approaches to increase the bioavailability of the poorly soluble drugs. Self-emulsifying drug delivery systems (SEDDS) have been emerged as one of the greatest strategies for overcoming the issue of poor oral bioavailability of highly lipophilic drugs,

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especially the drugs which comes under BCS class II and Class IV. SEDDS, when they come contact with the gastrointestinal fluids, they rapidly form fine oil-in water emulsions. Thereby, overcome the problems of solubility and dissolution, then enhances drug solubilization and intestinal absorption. In addition, these systems provide formulation flexibility and enables the development of immediate and controlled release formulations.

1.1. WHAT ARE SEDDS: -SEDDS are isotropic of mixture of oil, surfactant and co-surfactant or co-solvents. The main principle is that, they form fine oil in water emulsion, when they come contact with the gastrointestinal fluids, they immediately form fine oil-in water emulsions.

1.2. TYPES OF SEDDS

Based on the droplet size of, these emulsions are divided as microemulsion or nano emulsion. Microemulsion drug delivery system (SMEDDS) is transparent microemulsion with droplet size ranging between 100 and 200 and self-nano emulsifying drug delivery system (SNEDDS) less than 100 nm.

1.3. SELF -NANO EMULSIFYING DRUG DELIVERY SYSTEMS⁹

Self-nano emulsifying drug delivery systems (SNEDDS) are anhydrous homogeneous liquid mixtures contains excipients like oil, surfactant, drug and co-surfactant which rapidly form oil-in-water nano-emulsion 100 nm or less in size upon dilution with water under gentle stirring.

1.5. MECHANISM OF SELF-EMULSIFICATION [2,3,13,14]

Self-emulsification occurs when the entropy change favoring dispersion is greater than the energy required to increase the surface area of the

dispersion. Free energy in the micro-emulsion formation is directly proportional to the energy required to create new surface between the two phases, and is given by the equation:

$$\Delta G = \Sigma N \pi^2 \sigma$$

Where,

ΔG -Free energy associated with the process.

Σ -Represents interfacial energy.

N-No. Of droplets of radius r.

In order to prevent the phase separation of emulsions, emulsifying agent is added. these emulsifying agents form a protective layer around the droplets and prevents the coalescence

2. MATERIALS

Clopidogrel hydrogen sulphate, Gelucire 44/14, Captex 200, capmul MCM, Kolliphor RH 40, Transcutol HP, ethanol, capsules, Neusilin us2.

3. METHODOLOGY

3.1. SOLUBILITY STUDIES:

- Solubility studies were performed by adding 10mg of drug in screw-capped vials, which contain 500mg of selected oils, surfactants, co-surfactants, and mixed using a vortex mixer.
- If the drug is soluble, then drug is added till saturation point and cyclomixed.
- The samples were kept in the shaking incubator for 72 hours at 37°C temperature.
- After 72 hours, the samples are transferred into the Eppendorf tubes and centrifuged at 3500rpm for 30 minutes. Pipette out supernatant and transfer it to a 10ml volumetric flask, and make up the solution with ethanol. The concentration of the active ingredient in each sample was determined.



3.2. PSEUDO TERNARY PHASE DIAGRAM:

- The phase diagram was constructed by using the aqueous titration method.
- It helps to identify the best emulsification region of oil, surfactant and co-surfactant composition.
- The Smix were taken in the ratio of 3:1, 2:1. The ratios of oil and S_{mix} [1:9,2:8,3:7,4:6,5:5,6:4,7:3,8:2,9:1] were taken into separate glass vials. Then, into each vial, water is added dropwise and cyclomixed for five minutes. The mixture is visually examined for any change, such as phase separation, transparent, bluish transparent, milky white, etc.

3.3. FORMULATION OF LIQUID SELF-EMULSIFYING DRUG DELIVERY SYSTEM

- weighed amount of API is added to the mixture of surfactant and co-surfactant. Then, the mixture was cyclomixed by using a cyclomixer to solubilise the drug. Then the selected oil and cyclomixed until a transparent preparation was obtained. The prepared formulation was stored at room temperature.

4.EVALUATION:

4.1. DETERMINATION OF PARTICLE SIZE, PDI AND ZETA POTENTIAL:

- L-SNEDDS were diluted with water, and droplet size, PDI, and zeta potential were determined by using Zetasizer nano ZS 90 version 7.1

4.2. SELF-EMULSIFICATION TIME:

- 100 mL of 0.1 N HCl of PH 1.5 and 100 mL of distilled water were taken into two separate beakers.

- 0.1ml of formulation was added to both beakers and slightly stirred with a glass rod.
- And then the length of time taken by the formulation to go from pre- concentrate state to a homogeneous mixture after dilution was noted.

4.3. FREEZE THAW CYCLE:

- Three cycles between 4°C and normal room temperature, with storage at each temperature for at least 48 hours.

4.4. DISPERSIBILITY TEST:

This test was performed by adding of 0.1ml formulation into 250ml of water with gentle agitation using, time taken to form formation of nano emulsion was observed, nano emulsion was evaluated using the grading system.

4.5. PERCENTAGE TRANSMITTANCE:

L-SNEDDS (0.1ml) were diluted to 10ml of water and observed for percentage transmittance in UV-visible spectroscopy in the range of 600-650nm.

4.6. ROBUSTNESS TO DILUTION:

L-SNEDDS were diluted with water, 0.1 N HCl, and phosphate buffer of ratio 1:1000 and observed for phase separation and precipitation.

4.7. DRUG CONTENT:

Drug content in formulation was determined by taking 0.1 ml L-SNEDDS and diluted upto 10ml with ethanol, analyzed by using UV visible spectroscopy.

4.8. IN VITRO DRUG RELEASE STUDIES:

The drug release was determined by using Franz diffusion cell by using egg membrane, the egg membrane was extracted and placed between the donar and receptor compartments. The receptor



compartment was filled with the media and continuously stirred using a magnetic bead. The formulation was added into donar compartment. Around 1ml was withdrawn at time intervals of 5, 10, 15, 20, 30, 45, 60- and fresh media was replaced in receptor compartment. The samples were analyzed by using UV visible spectroscopy.

5. FORMULATION OF L-SNEDDS INTO S-SNEDDS:

1. Adsorption technique: In this method, porous carriers are used to convert L-SNEDDS into solid, the formed free flowing powder was filled into capsules.

EX: Neusilin US2

5.1. ADSORPTION TECHNIQUE TO CONVERT L-SNEDDS INTO S-SNEDDS:

L-SNEDDS is converted to S-SNEDDS by using the adsorption technique by adding neusilin US2 to two grams of optimized L-SNEDDS until a free-flowing powder is formed, and the powder is filled into the capsules for future evaluation.

6. EVALUATION:

6.1. DROPLET SIZE, ZETA POTENTIAL AND PDI:

1mg of formulation diluted with 100ml of water, PDI, Zeta potential and droplet size was determined Zetasizer by using nano ZS 90 (Malvern Instruments)

6.2. SELF-EMULSIFICATION TIME:

- 100 mL of 0.1 N HCl and 100 mL of distilled water were taken into two separate beakers.
- 1 mg of formulation was added to both beakers and slightly stirred with a glass rod.
- And then the length of time taken by the formulation to a clear solution after dilution was noted.

6.3. ROBUSTNESS:

Solid formulations were dissolved at 1:100 ratios in water, 0.1N HCL and phosphate buffer and gently agitated by using a magnetic stirrer. Clear emulsion indicates Good, and less clear or dull emulsion indicates a bad emulsion appearance.

6.4. DISPERSIBILITY TEST:

- 100 mg of formulation was dissolved in 250ml of water and gently agitated using a magnetic stirrer. emulsion performance was assessed by a grading system

6.5. IN VITRO DRUG RELEASE STUDIES:

- In vitro drug release was determined by using USP II paddle dissolution apparatus by filling the powder equivalent to 75 mg of solid formulation filled into hard capsules and placed in the vessel containing 900ml of buffer, and aliquots (5ml) were withdrawn at 5, 10, 15, 20, 30, 45, 60-time intervals, respectively, and the buffer should be replaced to maintain sink conditions.

6.6. ACCELERATED STABILITY STUDIES:

- Stress study of S-SNEDDS were performed as per the ICH guidelines. Formulations were stored at the conditions 40-45°C and 70-75% RH for 1 month and later evaluated for robustness, zeta potential, PDI and particle size.

7. RESULTS

7.1. SOLUBILITY OF CLOPIDOGREL HYDROGEN SULPHATE IN DIFFERENT EXCIPIENTS:

- All values are expressed as Mean (n=3)



Table no:1 Solubility of Clopidogrel hydrogen sulphate in different excipients

S.no	Category	Excipient	Concentration
1	Oil	Captex 200	10.63+0.002
2	Oil	Gelucire 44/14	14.63+0.004
3	Oil	Capmul MCM	10.45+0.02
4	Surfactant	Kolliphor RH 40	6.78+0.002
5	Surfactant	Kolliphor HS 15	2.91+0.002
6	Surfactant	Cremophor EL	10.53+0.003
7	Co-surfactant	Lauro glycol 90	36.44+0.003
8	Co-surfactant	Transcutol HP	85.09+0.361
9	Co-surfactant	Labrafac lipophile	19.22+0.606

- Among Oils, Gelucire 44/14 showed good solubility.
- In Co-Surfactants, Transcutol HP has shown great solubility.
- In Surfactants, Cremophor EL has demonstrated good solubility.

7.2. PSEUDO TERNARY PHASE DIAGRAMS

Table no:3 Smix 3:1 ratio

Oil: Smix ratio [4:1]	Oil	Smix	Water	Total	%oil	%smix	%water	Remarks
1:9	50	450	3048	3548	12.68	1.40	85.90	Transparent
2:8	100	400	3672	4172	9.58	2.39	88.01	Transparent
3:7	150	350	2438	2936	11.91	5.10	82.98	Transparent
4:6	200	300	2888	3388	8.98	5.90	85.25	Transparent
5:5	250	250	2882	3382	7.39	7.39	85.21	Milky white
6:4	300	200	2152	2652	7.54	11.31	81.14	Milky white
7:3	350	150	3576	4072	3.68	8.59	87.81	Milky white
8:2	400	100	2208	2708	3.69	12.92	81.53	Milky white
9:1	450	50	3811	4311	1.15	12.43	88.90	Milky white

Table no:4 Smix 2:1 ratio

Oil: Smix ratio [4:1]	Oil	Smix	Water	Total	%oil	% Smix	%water	Remarks
1:9	50	450	3753	425	10.5	1.17	88.2	Milky white
2:8	100	400	4111	461	9.72	2.16	89.1	Milky white
3:7	150	350	3719	4219	8.2	3.5	88.1	Milky white
4:6	200	300	5149	5149	5.8	3.8	90.2	Milky white
5:5	250	250	3859	3859	6.4	6.4	87.04	Milky white
6:4	300	200	3768	4268	4.6	7.0	88.2	Transparent
7:3	350	150	4341	4841	3.09	7.2	89.6	Transparent
8:2	400	100	3534	4034	2.4	9.9	87.6	Transparent
9:1	450	50	2635	3135	1.5	14.3	84	Transparent



Table no:5 Formulation table

Formulation	Smix	Drug	Oil	Surfactant	Co-surfactant
G1C3T1[1:9]	3:1	75	200	1350	450
G1C3T1[2:8]	3:1	75	400	1200	400
G1C3T1[3:7]	3:1	75	600	1050	350
G1C3T1[4:6]	3:1	75	800	900	300
G1C2T1[1:9]	2:1	75	200	1200	600
G1C2T1[2:8]	2:1	75	400	1066.6	533.3
G1C2T1[3:7]	2:1	75	600	933.3	466.6
G1C2T1[4:6]	2:1	75	800	800	400

7.3. PARTICLE SIZE, PDI AND ZETA POTENTIAL:

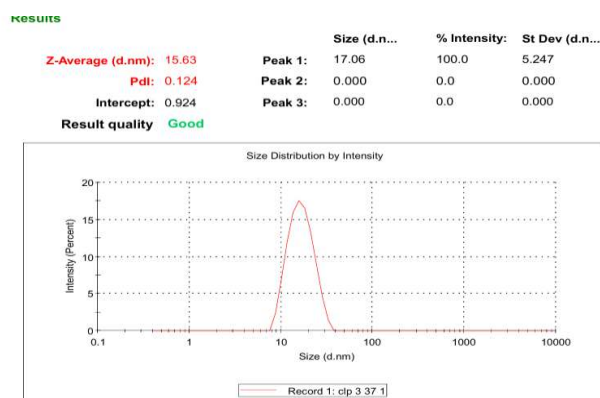


Fig no 1: particle size and PDI of G1C3T1 [3:7]

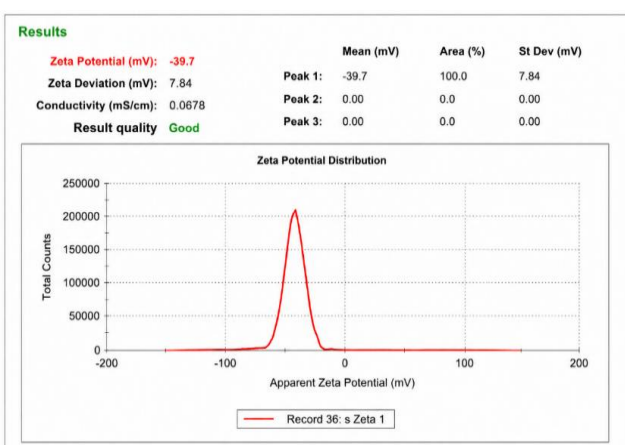


Fig no 2 : zeta potential of G1C3T1 [3:7]

7.4. DISPERSIBILITY TEST:

All the formulations comes under grade A, dispersed within 1 minute.

7.5. SELF-EMULSIFYING TIME:

Table no:6 Self-emulsification time values of L-SNEDDS

Formulation	Self-emulsification time in 0.1N HCL	Self-emulsification time in water
G1C3T1 [1:9]	16+1	29+5
G1C3T1 [2:8]	20+3	18+2
G1C3T1 [3:7]	10+2	15+6
G1C3T1 [4:6]	12+2	17+2
G1C2T1 [1:9]	25+3	20+4
G1C2T1 [2:8]	16+2	26+2
G1C2T1 [3:7]	29+5	18+3
G1C2T1 [4:6]	29+5	20+1

7.6. FREEZE THAW CYCLE:

There is no phase separation or cracking was seen after subjecting to the freeze thaw cycle.



7.7. PERCENTAGE TRANSMITTANCE: Two formulations show a % transmittance of more than 90%, indicating clear emulsions.

Table No 7: Percentage Transmittance Values of Clopidogrel L-SNEDDS

Formulation	% Transmittance
G1C3T1 [1:9]	91.25+0.29
G1C3T1 [2:8]	82.8+0.62
G1C3T1 [3:7]	97.5+0.35
G1C3T1 [4:6]	90.04+0.6
G1C2T1 [1:9]	87.37+0.15
G1C2T1 [2:8]	90.15+0.68
G1C2T1 [3:7]	83.04+0.32
G1C2T1 [4:6]	88.64+0.24

7.8. ROBUSTNESS TO DILUTION:

There is no phase separation of any formulation after diluting with water, 0.1N HCL, phosphate buffer.

7.9. DRUG CONTENT:

Table no 8: Drug content of Clopidogrel L-SNEDDS

Formulation	Drug content (%)
G1C3T1 [1:9]	88.34+0.44
G1C3T1 [2:8]	90.78+0.26
G1C3T1 [3:7]	98.33+0.56
G1C3T1 [4:6]	91.48+0.35
G1C2T1 [1:9]	88.02+0.67
G1C2T1 [2:8]	85.06+0.34
G1C2T1 [3:7]	90.45+0.45
G1C2T1 [4:6]	85.36+0.62

Formulation G1C3T1 [3:7] was found to be having more drug content of 98.33%

Based on evaluation results, G1C3T1[3:7] as the optimized formulation and performed an in vitro dissolution study.

7.10. IN VITRO DRUG RELEASE STUDIES:

Table no: 9 % Drug release of G1C3T1[3:7] formulation

Time	%Drug release
5	32.67
10	39.9
15	47.98
20	55.72
30	65.74
45	75.25
60	88.85



7.11. CONVERSION OF CLOPIDOGREL L-SNEDDS INTO S-SNEDDS:

Clopidogrel L-SNEDDS is converted to S-SNEDDS by using the adsorption technique by

adding neusilin US 2 to two grams of optimized L-SNEDDS until a free-flowing powder is formed, and the powder is filled into the capsules for further evaluation.

Table no10: composition of S-SNEDDS

Formulation	L-SNEDDS	Adsorbent [Neusilin US2]	Total
G1C3T1[3:7]	2ml	1gm	3gm

7.12. DROPLET SIZE, ZETA POTENTIAL AND PDI:

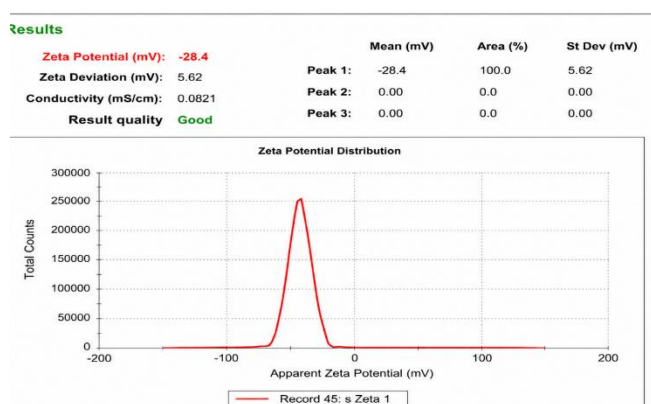
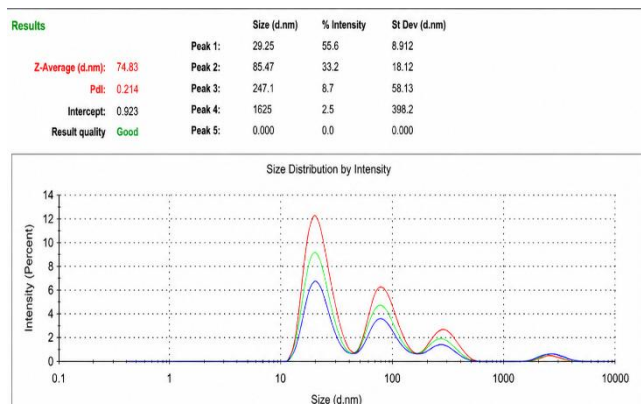


Fig. No 3: particle size and PDI of S- SNEDDS Fig no 4: zeta potential of S-SNEDDS

7.13. SELF-EMULSIFICATION TIME:

Table No 11: self-emulsification of S-SNEDDS

Formulation	water	0.1N HCL
G1C3T1[3:7]	28+2	23+4

7.14. DISPERSIBILITY TEST:

Visual observation of clopidogrel S-SNEDDS showed that the formulation is grade B, forming emulsions in 2 minutes

Table No 12: Dispersibility test of Clopidogrel S- SNEDDS in grading system

Formulation	Observation	Grade
G1C3T1[3:7]	Rapidly forming clear blue emulsion within 2 min	B

7.15. ROBUSTNESS TO DILUTION:

- There is no phase separation after dilution. So, the formulation is stable

7.16. IN VITRO DRUG RELEASE STUDIES

Table No 13: % drug release S-SNEDDS

Time [min]	%Drug release
5	36
10	59
15	72
20	80
30	87.5
45	94.7
60	98.8

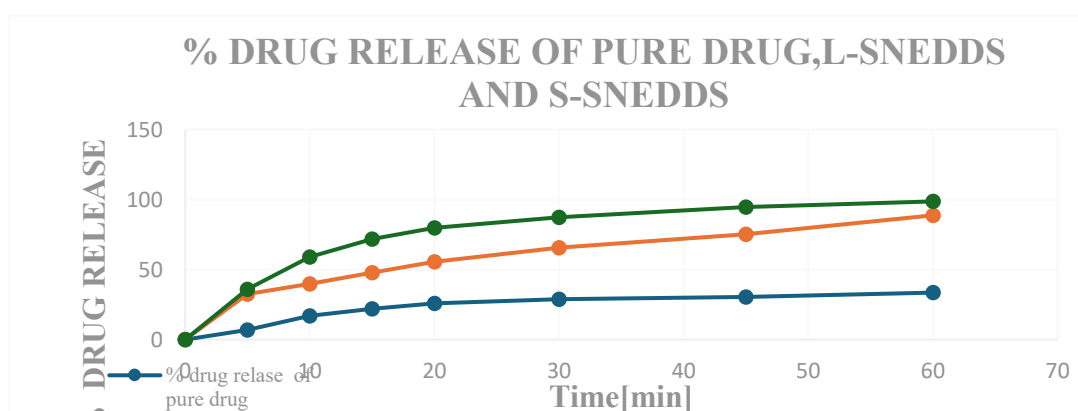


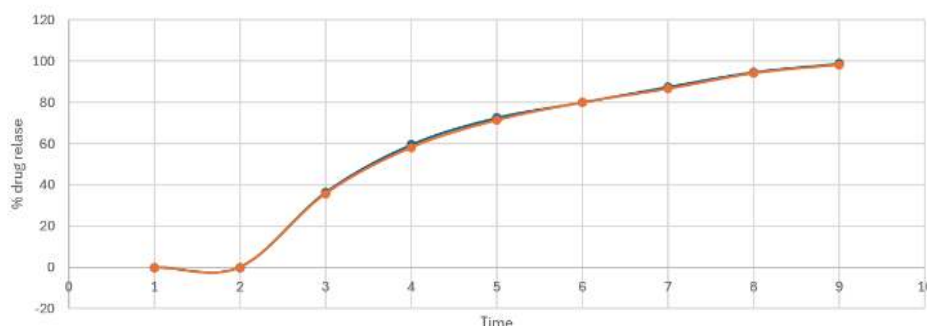
Fig no 5: Comparison of % drug release of pure drug, L- and S-SNEDDS

7.17. ACCELERATED STABILITY STUDIES:

Table No 14: % drug release S-SNEDDS after accelerated stability studies

Time	% Drug release S-SNEDDS on day one	% Drug release after three months of accelerated stability studies
0	0	0
5	36.23	35.7
10	59.43	58.13
15	72.5	71.37
20	80	79.98
30	87.5	86.6
45	94.7	94.2
60	98.8	98.3

comparison of dissolution profile of formulation after accelerated stability studies

**Fig no 6:comparative graph of dissolution after accelerated stability study**

SUMMARY AND CONCLUSION

Clopidogrel hydrogen sulphate is a less soluble drug that has been selected to formulate as an SNEDDS to increase its solubility and dissolution rate. Pseudo-ternary phase diagrams were constructed by using water titration method with the Smix ratio of 2:1 & 3:1, which gave clear nano emulsion, bluish clear emulsion and white emulsion. Eight formulations were formulated; among them, G1C3T1[3:7] was selected as the optimized formulation based on its size 15.63 nm, zeta potential mV -39.7 and PDI (0.124), drug release (88.85 %), self-emulsification time (16 sec), dispersibility test grade (A), % Transmittance ($98.587 \pm 0.67\%$). Optimized formulation was further converted into solid and evaluations was performed to solid formulation which has given better results: Robustness to dilution was passed, Dispersity grade (B), self-emulsification time (28 sec), Invitro drug release (98.8) and particle size (78.83), PDI (0.214), Zeta potential(28.7-mV) and accelerated stability studies was performed and compared with day 1 formulation, day drug release (98.8)and drug release compared after 1 month (98.3), Optimized formulation drug release compared with pure drug (33.2%). Hence, Clopidogrel hydrogen sulfate S-SNEDDS has the capability for enhancement of solubility and dissolution rate.

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