IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Development of Solid Self-Emulsifying Formulation for Improving the Oral Bioavailability of Artemether

Hanmant S. Mali[*1], Safiya R. Shaikh[2], Akshay R. Yadav[3]

[1]Department of Pharmaceutics, Rajarambapu College of Pharmacy, Kasegaon, Dist-Sangli, Maharashtra, India-415404

[2,3]Department of Pharmaceutical Chemistry, Rajarambapu College of Pharmacy, Kasegaon, Dist-Sangli, Maharashtra, India-415404

Abstract: The oral route is the most preferred drug administration path because to its ease of administration, convenience, high patient compliance, flexibility in dosage form design, fewer sterility constraints, and cost effectiveness. Lipid emulsions, lipid solutions, micro emulsions, and dry emulsions are examples of lipid drug delivery systems. Artemether (ARM), a poorly water soluble chemical, presents difficulties in developing pharmaceutical formulations with adequate bioavailability. Capmul MCM was used as the oil, Tween 80 as the surfactant, and PEG 400 as the co-surfactant in various ratios to create four self micro-emulsifying formulations. Using an adsorption method, optimised liquid SMEDDS formulations were converted into free-flowing powder and evaluated for drug content, FTIR, DSC, Globule size analysis, SEM, and in-vitro dissolution study. The results show that decreased crystallinity, altered surface morphology, and smaller globules were responsible for a significant increase in drug dissolving rate from the modified S-SMEDDS formulation.

Keywords: Artemether, Poor water solubility, Solid self micro-emulsifying Drug delivery system.

INTRODUCTION

Oral formulations are preferred in drug delivery systems because of high patient convenience, good compliance and flexibility in regimen. Nevertheless, some drugs have good pharmacological activities, but their poor aqueous solubility limits their absorption. At present, the methods of enhancing drug solubility mainly include liposomal encapsulation, solid dispersion, macromolecule micelles, cyclodextrin inclusion complexes, nanoemulsion, and self-microemulsifying drug delivery system (SMEDDS) [1]. However, much more attention has been focused on SMEDDS, because SMEDDS, as a carrier system, exhibit splendid biocompatibility, biodegradability, stability, and enhanced permeability [2]. SMEDDS is an isotropic mixture consisting of an oil, surfactant, co-surfactant and the drug [3], which can form fine oil-in-water microemulsion with a droplet size less than 100 nm in aqueous phases by gentle agitation [4,5]. The microemulsion droplets dispersed in the gastrointestinal tract provide a large surface area and promote rapid release of the drug, which is beneficial to improve the absorption and bioavailability of the drug. Overall, SMEDDS, as an effcient drug delivery system, not only protects unstable drugs but allows these drugs to quickly exert their effects [6]. SMEDDS can be used as an excellent carrier for hydrophobic, poor absorbing and easily hydrolyzable drugs [7,8]. In recent years, SMEDDS has been extensively investigated for improving the oral bioavailability of unstable and water insoluble drugs, such as Ligusticumchuanxiong oil [9], curcumin [10], resveratrol [11] and simvastatin [12]. To the best of our knowledge, the formulation of Artemether -loaded self-microemulsifying drug delivery system (ARM-SMEDDS) has not been developed. Therefore, the objective of the current research was to optimize and prepare ARM-SMEDDS. In addition, the physicochemical characterizations of ARM-SMEDDS were conducted.

MATERIALS AND METHODS

Materials

Artemether was obtained as a gift sample from Ipca Laboratories, Mumbai., India. The Capmul MCM was gifted by Abitec Corp., USA. Other materials such as Cotton seed oil, Linseed oil, Olive oil, Castor oil, Tween 80, Span 80, Polyethylene Glycol 400, Propylene Glycol, Silicon dioxide, Magnesium sterate, Magnesium hydroxide, Talc, Ethanol purchased from the LobaChemie Pvt. Ltd., Mumbai., India.

Preparation of liquid self micro-emulsifying drug delivery system (SMEDDS) [13,14, 17,18,19]

At various Km values, phase diagrams were created. The Km value at high microemulsion obtained region was selected for further studies. Four formulations were selected from this microemulsion region and used for further evaluation studies. % content of water, oil and surfactant/co-surfactant in each selected formulation was determined. Oil, co-surfactant and surfactants were accurately weighed and mixed by gentle stirring. Based on solubility, formulation amount of Artemether (40 mg) was dispersed into mixture of oil and surfactants. Components were mixed by gentle stirring on magnetic stirrer until Artemether was completely dissolved. Mixture was sealed in glass vial and stored at room temperature for further studies.

Preparation of solid self micro-emulsifying drug delivery system (SSMEDDS) *[13, 14, 21, 24]*

S-SMEDDS was prepared by mixing liquid SMEDDS containing Artemether with suitable carrier like silicon dioxide, talc, magnesium hydroxide, aluminium hydroxide and starch. SMEDDS liquid was added dropwise over the carrier in a large porcelain dish. To ensure uniform distribution of the formulation, the mixture was homogenized after each addition using a glass rod.

Table no. 1: Formulation table of SMEDDs

Sr. no.	Formulation	Drug (mg)	% composition (w/w)	
			Oil	S_{mix}
1	ME1	40	10	20
2	ME2	40	10	30
3	ME3	40	10	40
4	ME4	40	10	50

Characterization Of Solid Self Micro-Emulsifying Drug Delivery System (S-SMEDDS)

a. Physical Characterization:

The organoleptic properties of the S-SMEDDS, like color, odor and physical appearance were checked by visual observation.

b. Micromeritic properties of S-SMEDDS[13,16,19]

A. Angle of repose

Angle of repose was a measure to determine the flowability of the powder or granules. Angle of repose was determined by fixed funnel free standing cone method. Powder waspassed freely through fixed funnel to make a heap of predetermined height and angle made by hypotenuse with that of base was determined, from which, the flow type of the sample was found out as per given in Table no.3

The angle of repose of the powder was determined by using the formula:

$$\theta = \tan^{-1} h/r$$

Where,

h - Height between the lower tip of funnel and the base of heap of granules,

r- Radius of the base of heap formed.

Table no. 2: Relationship between Angle of Repose (θ) and Flowability

Angle of repose (θ)	Flowability
<20	Excellent
20-30	Good
30-40	Passable
>40	Very poor

C. Drug Content Determination[19,20,21]

Amount of drug present in the S-SMEDDS powder formed was determined by sampling10mg of solid micro-emulsion and carrying out assay method for Artemether as follows:

Powder was taken in the 100mL volumetric flask. To this sufficient quantity of ethanol wasadded and the flask was shaken for 10min, final volume was made upto 100 ml with ethanol.Was sonicated for 10-15 min and filtered. From that solution 1ml was transferred to anothervolumetric flask of 10 ml and volume was made with ethanol. The amount of drug present was analyzed spectrophotometrically (Shimadzu UV-1800, Japan) at 215 nm.

D. Reconstitution properties of S-SMEDDS:

1) Dilution Study by Visual Observation[13,22]

Dilution study was done to study the effect of dilution on S-SMEDDS, since dilution can more closely resemble the state of the stomach after oral administration. In this process, 100 mg of S-SMEDDS was added to 100 ml of distilled water in a glass beaker held at 37 °C, and the contents were gently mixed with a magnetic stirrer. With respect to time, the propensity to emulsify spontaneously and the progression of emulsion droplets were observed. After stopping stirring, the emulsification capacity of S-SMEDDS was graded as "good" when a clear micro emulsion developed and "bad" when a turbid or milky white emulsion formed.

2) Emulsification study[15,23]

Characterization of the self-emulsifying properties of SMEDDS formulations were tested visually, as previously stated. In a nutshell, different compositions were classified based on emulsification speed, clarity, and apparent emulsion stability. Dropwise addition of the preconcentrate (SMEDDS) into 250 ml of distilled water was used for visual evaluation. Grading method for visual evaluation of self-microemulsification efficiency was used in a glass beaker at room temperature.

A+ - Within 1 minute, the formulation dispersed rapidly in water, creating a smooth and transparent micro-emulsion.

A - Prior to dispersing entirely, the formulation formed a transparent, gel-like intermediate structure, but it could form a micro-emulsion in 3–5 minutes.

B –Within 5 minutes, the formulation droplets disperse in water to form a turbid emulsion.

C - The formulation had low emulsification and oil coalescence.

3) Globule Size and polydispersity index Determination[13,22]

Solid S-SMEDDS formulations (10 mg) were diluted in a beaker with 10 ml double distilled water and continuously stirred with a magnetic stirrer. Lesser light scattering technique with Malvern Zetasizer was used to calculate the average droplet size, size distribution, and polydispersity index of micro-emulsion from solid S-SMEDDS.

4) Thermodynamic stability studies[22,23]

The stability of formulations was tested using freeze thawing. Three to four freeze-thaw cycles were performed on the formulations, which involved freezing at –4 °C for 24 hours and then thawing at 40 °C for 24 hours. For 5 minutes, centrifugation was carried out at 3000 rpm. After that, the formulations were analyzed for phase separation.

5) Solid state characterization of S- SMEDDS

FTIR study

SMEDDS FTIR study FTIR experiments were carried out to see whether there was any contact between the drug, the oil, the surfactant, the co-surfactant, and the silicon dioxide. This was done by FTIR Spectrophotometer (Jasco-410,Japan) Infrared spectrums of pure drug, and in the wavelength range of 4000 to 400 cm^{-1}, formulated batches were reported.The procedure consist of a sample in excess wasdispersed in potassium bromide closely at ratio 1:100, mix well and then mixture keptinto sample holder for analysis.

6) Differential scanning calorimetry (DSC) [21-30]

Thermograms of pure drug and solid SMEDDS batches was obtained using DifferentialScanning Calorimetry (TA Instruments SDT-Q-600 V-209) equipped with an intracooler.The Enthalpy scales and DSC temperature were calibrated using an indium standard. Samples were heated in hermetically sealed aluminum pans under nitrogen flow rate100 mL/min at a scanning rate of 10◦C/min from 30◦C to 300◦C. Empty aluminum panwas used as reference.

7) Morphological analysis of S-SMEDDS [14,22]

SMEDDS were studied by SEM (JEOL, JSM 50A, Tokyo, Japan) at 2000x. The samples were analyzed after being mounted on double-sided adhesive tape that had previously been secured on copper stubs. 15kV was used as the accelerating voltage.

8) In-vitro dissolution study[31-36]

Dissolution study of prepared solid–SMEDDS was carried out using dissolutionapparatus (USP type II). Dissolution study was carried out using 900 ml buffer pH1.2 at 37± 0.5 °C at 100rpm. 40 mg of pure Artemether and its equivalent amount solid SMEDDS wereadded to 900 ml buffer pH1.2. 5 ml samples were withdrawn after 5, 10, 15,30,45,60 minand replaced each time with 5 ml fresh buffer solution. The solution was immediately filteredthrough Whatmanfilter paper. From the filtered sample, 1mL sample was withdrawn anddiluted upto 10mL with buffer solution pH1.2. Concentration of Artemether was determined spectrophotometrically at 215nm.

Table no. 3: *In-vitro* Dissolution Condition employed in the Dissolution Study

Sr. No.	Parameters	Specification
1	Dissolution medium	900 ml buffer pH 1.2
2	Temperature	37°± 0.5 °C
3	Rotation speed	100 rpm
4	λmax	215nm

RESULTS AND DISCUSSION

A. General Description

The sample of Artemether was found to be white, odourless, slightly bitter, crystallinesolid.

B. Melting Point

The melting point determined by close capillary method (melting point determination apparatus) was found to be 86-90°C.

C. Spectroscopy Study

i. UV Spectroscopy:

Preparation of Standard Calibration Curve of ARM in Ethanol

Table no. 4: Standard calibration curve of ARM in ethanol

Sr. no.	Concentration (µg/ml)	Absorbance at 215 nm
1	0	0
2	2	0.2112
3	4	0.3996
4	6	0.5974
5	8	0.7853
6	10	0.9564

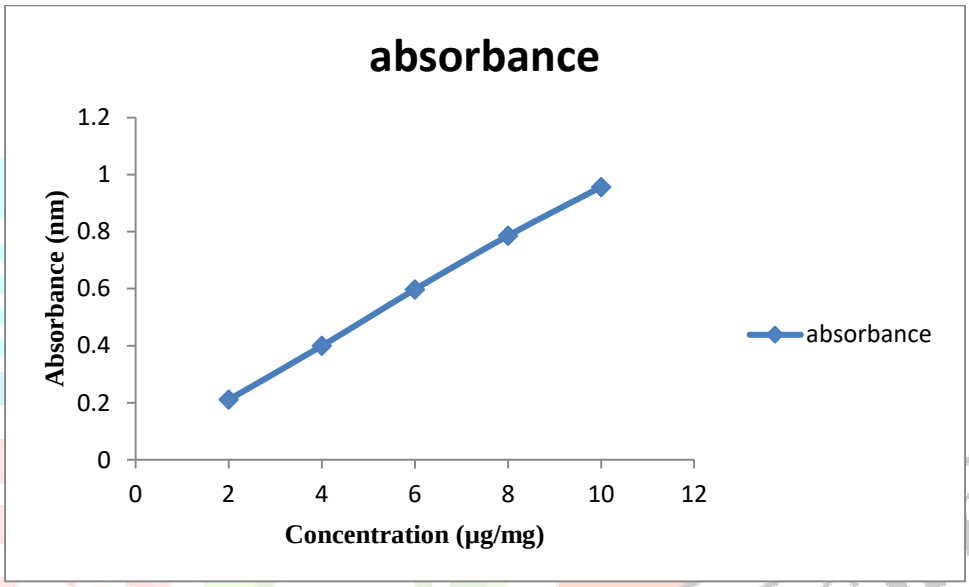


Fig. no 1.: Standard calibration curve of ARM in ethanol

Slope	0.098
Intercept	0.012
R^2	0.998

ii.Infrared (IR) Spectroscopy

The IR spectrum of pure Artemether was shown in Fig. No.2. The observed peaks of artemether were shown in Table no 6

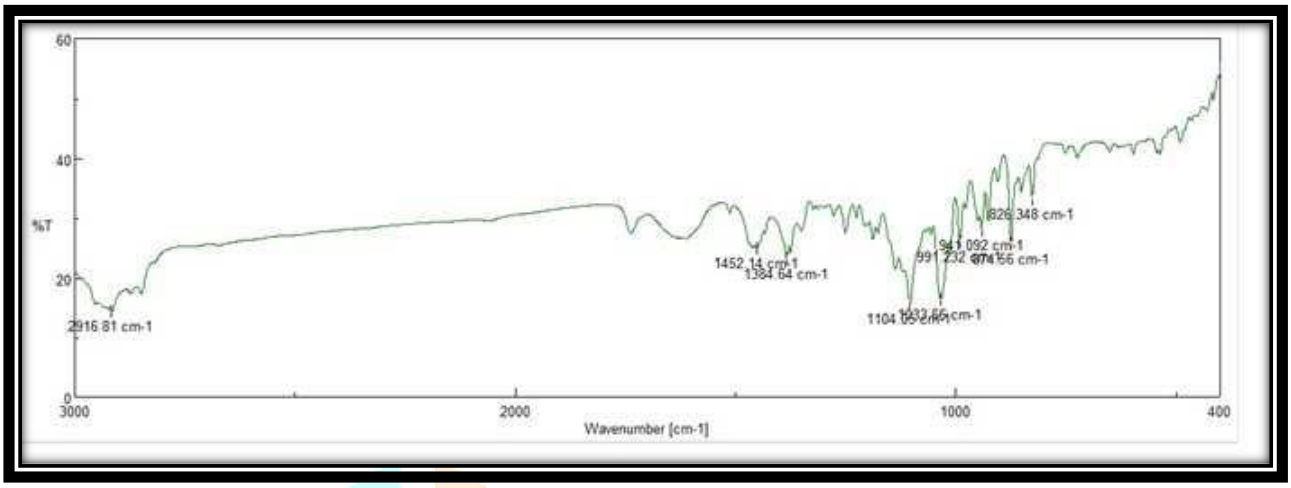


Fig no 2: FTIR Spectra of Artemether.

Table no. 5: FTIR values of Artemether

Sr. No.	Value	Exact value	Bond	Functional Group
1	3000-2850	2916	C-H Strech	Alkanes
2	1500-1400	1452	C-C Strech(in ring)	Aromatic
3	1320-1000	1104	C-0 Strech	Ether
4	900-675	826	C-H Bend	Aromatic

It shows all characteristics peaks of Artemether

D. Determination of Saturation Solubility of Artemether in Oils, Surfactants and cosurfactants:

The self micro-emulsifying formulation consists of one or more surfactant/ cosurfactants and drug dissolved in oil. To allow the drug to be presented in solution, the pre-concentrate mixture should be a clear, monophasic liquid with good solvent properties at room temperature. The aim of the solubility analysis was to find oils and surfactants that were effective at solubilizing Artemether. The concentration of Artemether within different excipients was determined by UV spectrophotometer at room temperature andresults are shown in following tables.

Table no. 6: Solubility study of Artemether in oils

Sr. No.	Oils	Solubility (mg/mL)
1	Capmul MCM	75.78 ±0.42
2	Oleic acid	41.05 ±0.87
3	Cotton seed	50.52 ±0.93
4	Linseed	44.21 ±0.52
5	Olive	57.89 ±0.30
6	Castor	36.84 ±0.24

Table no. 7: Solubility of Artemether in surfactants and co-surfactant, Co-solvent

Sr. No.	Co-surfactant/ co-solvent	Solubility mg/ml
1	Tween 80	156.84 ±0.85
2	Span 80	66.31 ±0.78
3	Polyethylene Glycol 400	81.05 ±0.64
4	Propylene Glycol	12.320.25

E. Characterization of Solid self micro-emulsifying drug delivery system (S-SMEDDS)

i. Physical Characterization:-

The solid SMEDDS of Artemether prepared by adsorption technique was found to bewhite in colour, odorless powder. The product obtained was cohesive to flow smoothly.

ii. Flow Property of Solid SMEDDS:-

1. Angle of repose

The angle of repose (θ) for all S-SMEDDS batches is shown in Table No. 9. The θ value for all batches was found to be in the range of 20-30. There is no significance difference in the flowability of all batches. Thus all S-SMEDDS batches show passableflow properties.

Table no.8: Flow Property of Solid SMEDDS Batches

Sr. no.	Batch code	Angle of repose (θ)
1	ME1	23.90±0.32
2	ME2	22.45±0.47
3	ME3	22.37±0.24
4	ME4	23.41±0.83

2. Drug Content Determination:-

Drug content of Artemether solid SMEDDS batches were determined by UV spectroscopy method to evaluate uniformity of formulation. The drug content of different Artemether solid SMEDDS batches is given in following Table No. 10

Table no.9: Drug Content of Solid SMEDDS Batches

Batch	Drug Content (%)
ME1	94.94±0.96
ME2	95.27±0.88
ME3	94.43±0.85
ME4	96.62±0.98

*Each value is average ±SD (n=3)

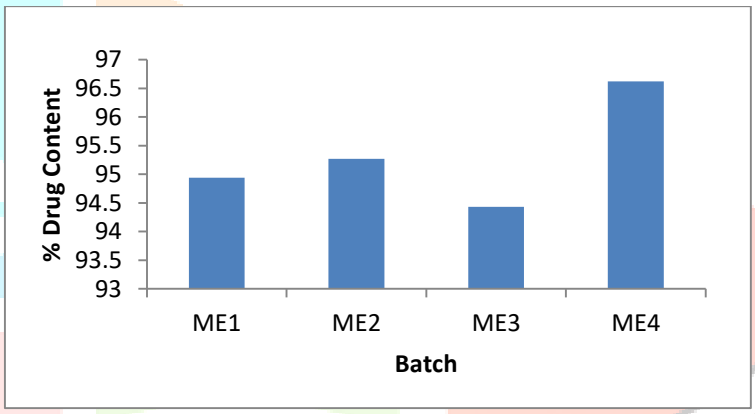


Fig. no. 3: Drug Content of Solid SMEDDS Batches

3. Reconstitution Properties of Solid SMEDDS:

a) Dilution Study by Visual Observation

Visual Observation Dilution Analysis a visual test was performed to determine whether solid SMEDDS could self-emulsify in 100 mL distilled water at 37°C with gentle agitation. After 2 hours of storage, all solid SMEDDS batches display spontaneous emulsification and no signs of phase inversion or phase separation of the emulsion.

b) Emulsification Study

The rate of emulsification, which is an very essential index for evaluating emulsification efficiency, can be used to estimate the efficiency of self-emulsification.When kept for aqueous dilution under agitation, S-SMEDDS formulations should disperse fully and rapidly. The formulations showed emulsification time as follows.

Table no. 10: Emulsification Time of the Formulations

Sr. No.	Batch	Time (sec)
1	ME1	23
2	ME2	25
3	ME3	30
4	ME4	19

c) Globule Size Determination

There is a relationship between the droplet size and the concentration of the surfactantbeing used. Increasing the surfactant concentration can result in droplets with smaller mean droplet sizes in some cases. In this case it could be explained by stabilization of oil droplets asa result of localization of the surfactant molecules at the oil–water interface. On another side, in some cases, the mean droplet size may increase with increasing surfactant concentrations.

This phenomenon may be explained by the interfacial disruption caused by increased water penetration into oil droplets, which is induced by increased surfactant concentration and results in oil droplet ejection into the aqueous phase.Since it defines the rate and extent of drug release as well as drug absorption, the droplet size of the emulsion is a critical factor in self-emulsification results. Also according to studies, the smaller the particle size, the greater the interfacial surface region, which may contribute to faster absorption and improved bioavailability.Polydispersity index (PDI) for all formulations have been summarized in Table No. 12. These results shows that globule size of S-SMEDDS ME1, ME2, ME3, ME4 were lessthan 100 nm and with less PDI.The ratio of standard deviation to mean droplet size is known as polydispersity. This denotes droplet size uniformity within the formulation. The lower the uniformity of droplet size in the formulation, the higher the polydispersity value.Here the PDI values of S-SMEDDS ME1, ME2, ME3 and ME4 are 0.100, 0.182, 0.125 and 0.175 respectively, which indicate droplet size uniformity within the formulation. If PDI value more than 1 it indicates that non-uniformity of particles inemulsion. This may be due to the drug's poor solubility in solvents. This triggers drug precipitation and, as a result, a rise in globule size. S-SMEDDS with larger globules cause agglomeration of globules, resulting in system instability. Which show thatlow uniformity in globule size of formulation to have remarkable effect on globule size andself-emulsification nature of liquid SMEDDS.Formulations were having globule size between 50-100 nm which fulfill criteria of SMEDDS and low PDI shows uniformity of globules. Therefore formulation batchesconsidered for further *in-vitro* studies.

Table no. 11: Globule Size Data of the Reconstituted S-SMEDDS

Sr. no	Batch code	Globule size (nm)	PDI
1	ME1	97.03±0.31	0.100
2	ME2	96.1±0.42	0.182
3	ME3	94.6± 0.54	0.125
4	ME4	93.02±0.32	0.175

Table no. 12: Stability of Formulations at 4°C and 40°C

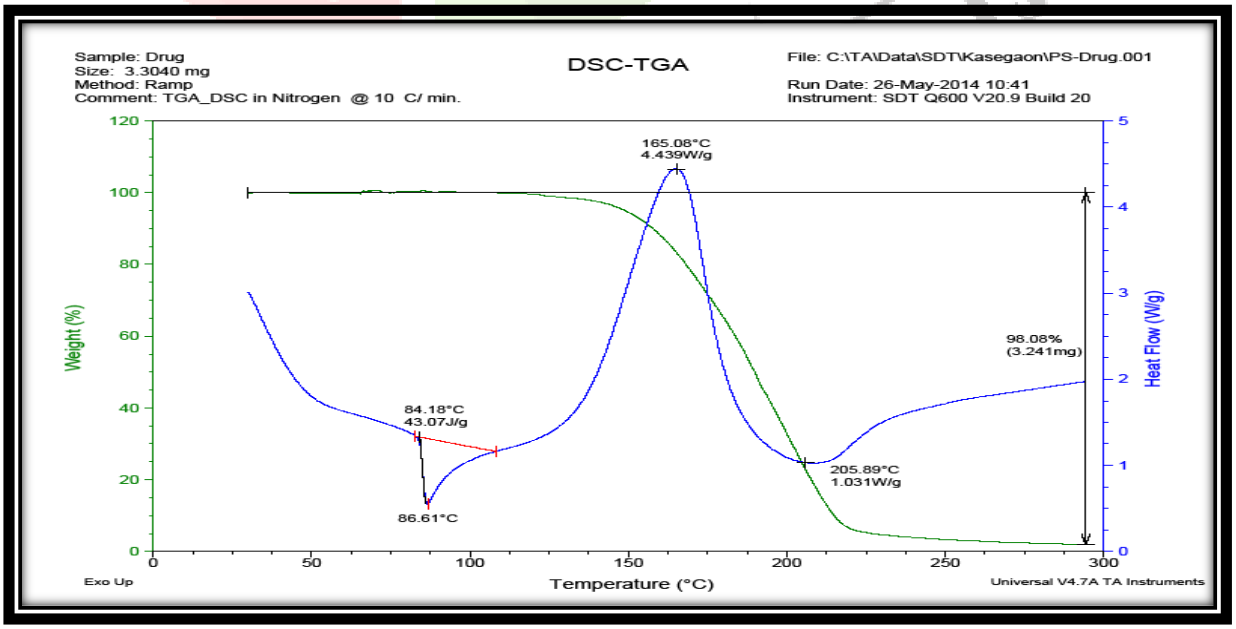
Formulation	Storage stability at 4°C and 40°C for 24 hrs
ME1	-
ME2	-
ME3	-
ME4	-

(+ Phase separation, - No phase separation.)

d) Solid state characterization of S- SMEDDS

i. Differential scanning calorimetry (DSC)

DSC curves of pure drug and formulation batches are shown in Fig no. 3 Pure ARM shows sharp endothermic peak at about 86 ºC. The peak of formulation was broad,less sharp than drug.



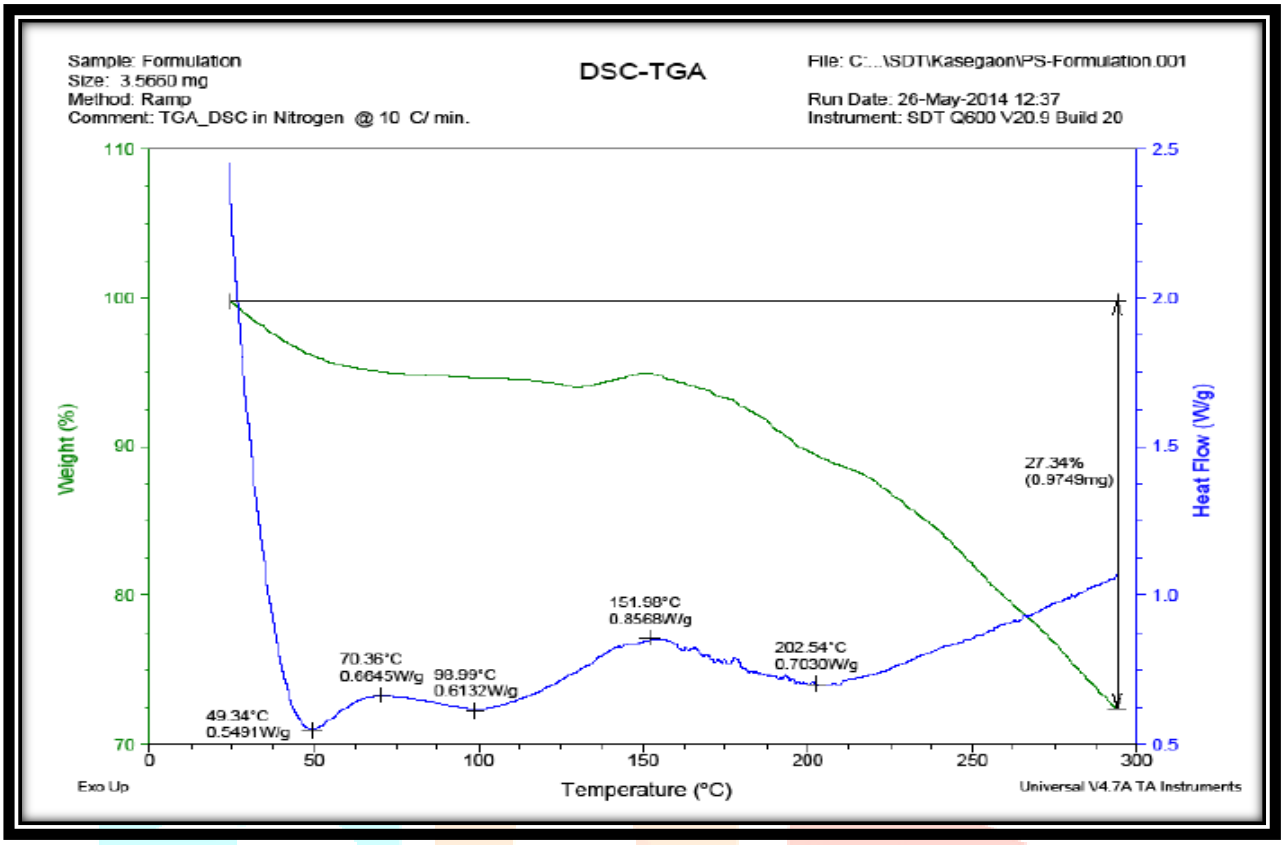


Fig. no. 3: DSC Curves of Pure ARM and ME4

By DSC results, the sharpness of peaks as well as number of sharp peak presentin ARM was found to be significantly diminished in case of S-SMEDDS formulations.Decrease in melting point than pure ARM which may due to existence of drug informulation was totally different form other than crystalline form.

e) Morphological analysis of S-SMEDDS: (By SEM)

Scanning Electron Microscopy

SEM images of and solid SMEDDS of batch ME4 are shown in Fig. no. 4. The pure Artemether was characterized by crystals of larger size irregular shape. According to SEM images, the solid SMEDDS formulation surface was found to be smooth regular. Theseparticles were found almost in spherical shape.

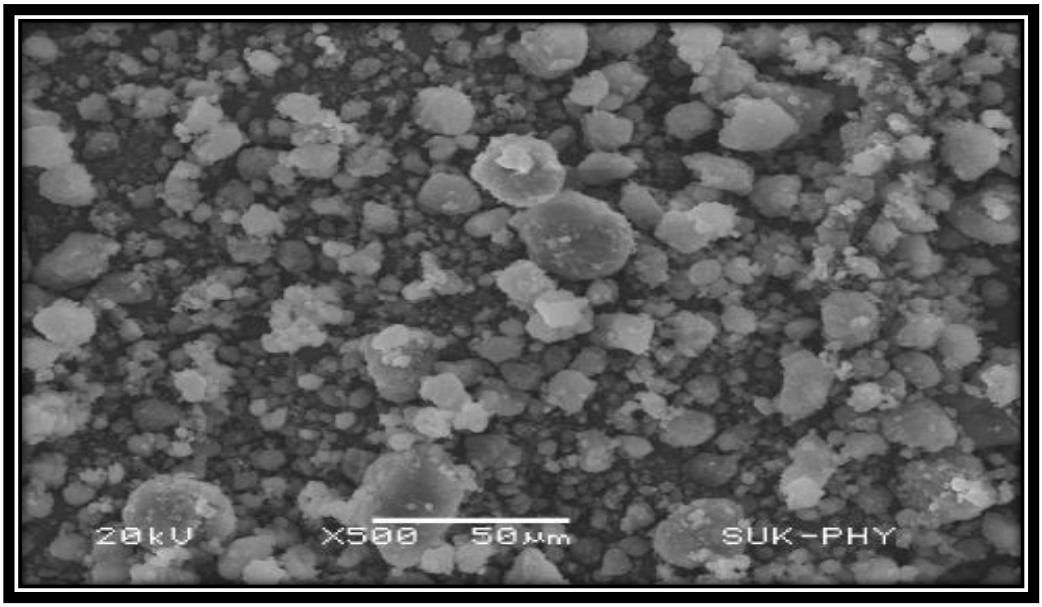


Fig. no.4: SEM Solid S-SMEDDS Formulation ME4

f) *In-vitro* Dissolution study:

In the solid self-micro emulsifying system, since the free energy needed to form an emulsion was so tiny, an interface between oil droplets and water formed spontaneously. The oil/surfactant/co surfactant and water phases are thought to effectively swell, decreasing the oil droplet size and ultimately increasing the release rate. The *in –vitro*dissolution of solid SMEDDS formulation in dissolution media buffer pH 1.2.

Result revealed that S-SMEDDS showed more than 90% release in 60 min. It's likely that the solid SMEDDS formulation triggered the spontaneous development of a micro-emulsion with small droplet size, allowing for faster drug release into the aqueous phase. As a consequence, the increased availability of dissolved ARM from solid SMEDDS formulations can result in increased absorption and oral bioavailability. FromFig. No. 5It clearly observed that solid SMEDDS formulations shows more than 90% drug release in 60min in buffer pH 1.2.

Table no.13: *In-vitro* drug release study

Sr. no.	Time (min)	% Cumulative Drug Release of formulation batches			
		ME1	ME2	ME3	ME4
1	0	0	0	0	0
2	5	19.00 ±0.85	27.63 ±0.56	35.25 ±0.33	38.37 ±0.77
3	10	25.97 ±0.25	34.60 ±0.29	47.53 ±0.12	50.98 ±0.53
4	15	1.20 ±0.27	41.31 ±0.44	62.46 ±0.39	63.41 ±0.36
5	30	40.50 ±0.35	57.76 ±0.75	71.31 ±0.55	76.55 ±0.96
6	45	56.72 ±0.40	70.38 ±0.75	80.01±0.95	88.21 ±0.13
7	60	72.03 ±0.40	81.11 ±0.88	90.22 ±0.23	95.43 ±0.33

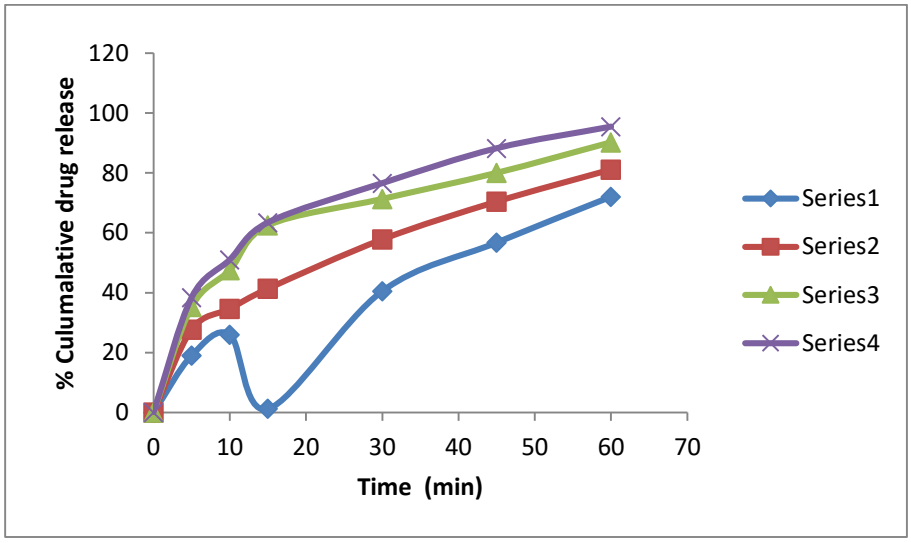


Fig. no. 5: % Cumulative Drug Release of formulation batches

CONCLUSION

The observations lead us to the conclusion that SMEDDS seems to be a promising drug delivery system, which can provide an effective and practical solution to the problem of formulating drugs with low aqueous solubility and poor systemic bioavailability.

REFERENCES

1. Wu, L.; Qiao, Y.; Wang, L.; Guo, J.; Wang, G.; He, W.; Yin, L.; Zhao, J. A Self-microemulsifying Drug Delivery System (SMEDDS) for a Novel Medicative Compound Against Depression: A Preparation and Bioavailability Study in Rats. AAPS PharmSciTech2015, 16, 1051–1058.
2. Chen, L.; Liu, C.; Chen, Q.; Wang, S.; Xiong, Y.; Jing, J.; Lv, J. Characterization, pharmacokinetics and tissue distribution of chlorogenic acid-loaded self-microemulsifying drug delivery system. Eur. J. Pharm. Sci. 2017,100, 102–108.
3. Yi, T.; Zhang, J. Effects of Hydrophilic Carriers on Structural Transitions and In Vitro Properties of Solid Self-Microemulsifying Drug Delivery Systems. Pharmaceutics 2019, 11, 267.
4. Mahmoud, D.B.; Shukr, M.H.; Bendas, E.R. In vitro and in vivo evaluation of self nanoemulsifying drug delivery systems of cilostazol for oral and parenteral administration. Int. J. Pharm. 2014, 476, 60–69.
5. Sermkaew, N.; Ketjinda, W.; Boonme, P.; Phadoongsombut, N.; Wiwattanapatapee, R. Liquid and solid self-microemulsifying drug delivery systems for improving the oral bioavailability of andrographolide from a crude extract of Andrographispaniculata. Eur. J. Pharm. Sci. 2013, 50, 459–466.
6. Dhadde Gurunath S., Mali Hanmant S., RautIndrayani D., Nitalikar Manoj M., An Overview on Multiple Emulsions, Asian Journal of Pharmacy and Technology, 2021; 11(2): 156-158.
7. Dokania, S.; Joshi, A.K. Self-microemulsifying drug delivery system (SMEDDS)-challenges and road ahead. Drug Deliv. 2014, 22, 675–690.

8. Yadav A, Mohite S. Aquasomes as a Self Assembling Nanobiopharmaceutical Carrier System for Bio-Active Molecules. Research J. Topical and Cosmetic Sci. 2020; 11(2): 66-70.
9. Yadav A, Mohite S. Potential Role of Peptides for Development of Cosmeceutical skin Product. Research J. Topical and Cosmetic Sci. 2020; 11(2): 77-82.
10. Yadav A, Mohite S. Applications of Nanotechnology in Cosmeceuticals. Research J. Topical and Cosmetic Sci. 2020; 11(2): 83-88.
11. Zhu, Y.; Xu, W.; Zhang, J.; Liao, Y.; Firempong, C.K.; Adu-Frimpong, M.; Deng, W.; Zang, H.; Yu, J.; Xu, X. Self-microemulsifying Drug Delivery System for Improved Oral Delivery of Limonene: Preparation, Characterization, in vitro and in vivo Evaluation. AAPS PharmaSciTech2019, 20, 153.
12. Dhadde G.S, Yadav J.P , Sapate R.B, Mali H.S, Raut I.D, In vitro Anthelmintic Activity of crude extract of flowers of Bougainvillea Spectabilis Wild against Pheretima Posthuma, International Journal of Pharmacy and Pharmaceutical Research, 2020; 17: 1-18.
13. Yadav A, Mohite S. Recent advances in protein and peptide drug delivery. Res. J. Pharma. Dosage Forms and Tech. 2020; 12(3): 205-212.
14. Honmane P, Yadav A, Singh S, Mohite S. 3D printing technology in pharmaceuticals and biomedical. World J Pharm Pharm Sci. 2020; 9(9): 598-609.
15. Salunkhe K, Yadav A. Recent Advances in Manufacturing Technologies and Future Prospects of Mouth Dissolving Tablets (FDTs). International Journal of Scientific Research in Chemistry. 2020; 5(2): 26-32.
16. Suryawanshi V, Yadav A, Birajdar R. Optimization of Ayurvedic Herbal Medicine by Nanoformulation. Asian Journal of Research in Pharmaceutical Sciences. 2019; 9(1): 55-56.
17. Yao, G.; Li, Y. Preparation, characterization and evaluation of self-microemulsifying drug delivery systems (SMEDDSs) of Ligusticumchuanxiong oil. Biomed. Preventive Nutr. 2011, 1, 36–42.
18. Cui, J.; Yu, B.; Zhao, Y.; Zhu,W.; Li, H.; Lou, H.; Zhai, G. Enhancement of oral absorption of curcumin by self-microemulsifying drug delivery systems. Int. J. Pharm 2009, 371, 148–155.
19. Vasconcelos, T.; Araújo, F.; Lopes, C.; Loureiro, A.; Neves, J.; Marques, S.; Sarmento, B. Multicomponent self nano emulsifying delivery systems of resveratrol with enhanced pharmacokinetics profile. Eur. J. Pharm. Sci. 2019, 137, 105011.
20. Sharma, P.; Singh, S.K.; Pandey, N.K.; Rajesh, S.Y.; Bawa, P.; Kumar, B.; Gulati, M.; Singh, S.; Verma, S.; Yadav, A.K.; et al. Impact of solid carriers and spray drying on pre/post-compression properties, dissolution rate and bioavailability of solid self-nanoemulsifying drug delivery system loaded with simvastatin. PowderTechnol. 2018, 338, 836–846.
21. Dhadde Gurunath S., Mali Hanmant S., Raut Indrayani D., Nitalikar Manoj M.,Bhutkar Mangesh M., A Review on Microsphere: Types, Method of Preparation, Characterization and Application, Asian Journal of Pharmacy and Technology, 2021; 11(2):149-155.
22. Ashish Deshmukh, Premchand Nakhat. Formulation and in-vitro evaluation of self- microemulsifying drug delivery system of furosemide.Scho Res Lib 2010; 2(2):94-106Karim A, Gokhale R, Cole M, Sherman J,

Yeramian P. HIV protease inhibitor SC-52151: a novel method of optimizing bioavailability profile via micro-emulsion drug deliverysystem. Pharm Res. 1994; 11: 368.

23. Mahajanharshal. Design and development of solid self-micro-emulsifying drug deliverysystem (SMEDDSs) of fenofibrate.Int J Pharm Pharm Sci. 2011; 3(4):163-166.
24. Medha Joshi. Solid microemulsionpreconcentrate (Nanosorb) of artemether for effectivetreatment of malaria.Int J Pharm. 2008; 362:172-178.
25. Sagar D. Mandawgade. Development of SMEDDS using natural lipophile: Application to-Artemether delivery.Int J Pharm. 2008;362:179–183.
26. Yadav A, Mohite S. Formulation and Evaluation of Antidandruff Shampoo. Research Journal of Topical and Cosmetic Sciences. 2020; 11(2): 55-58.
27. Yadav A. Preparation and Evaluation of Herbal Mouthwash containing Psidium guajava Leaf Extract. International Journal of Pharmaceutical Research and Development. 2020; 2(1): 24-26.
28. Yadav A, Raut I, Vakhariya R. Formulation & Evaluation of Herbal Lipstick using Morus alba Linn. International Journal of Pharmacy and Pharmaceutical Science. 2020; 2(1): 04-05.
29. Patil S, Yadav A, Chopade A, Mohite S. Design, Development and Evaluation of Herbal Mouthwash for Antibacterial Potency against Oral Bacteria. Journal of University of Shanghai for Science and Technology. 2020; 22(11): 881-898.1137-1148.
30. Myers R. A, Stella V. J. Systemic bioavailability of penclomedine (NSC-338720) fromoil-in-water emulsions administered intraduodenally to rats. Int J Pharm. 1992; 78:217-226.
31. DhaddeGurunath S., Mali Hanmant S., RautIndrayani D., NitalikarManoj M., An Overview on Multiple Emulsions, Asian Journal of Pharmacy and Technology, 2021; 11(2): 156-158.
32. Grovea M, Mullertzb A. Bioavailability of seocalcitol II: development andcharacterization of self-microemulsifying drug delivery systems (SMEDDS) for oraladministration containing medium and long chain triglycerides. Euro J Pharm Sci. 2006;28:233-242.
33. Dhadde Gurunath S., Mali Hanmant S., Raut Indrayani D., Nitalikar Manoj M.,Bhutkar Mangesh M., A Review on Microsphere: Types, Method of Preparation, Characterization and Application, Asian Journal of Pharmacy and Technology, 2021; 11(2):149-155.
34. Honmane P, Mali V, Mali A, Mahadik P, Yadav A, Mohite S. Formulation and Evaluation of Herbal Ointment Containing *Eclipta Alba (L.)* Extract. Journal of Seybold Report. 2020; 25(10): 569-577.
35. Dange V, Dinde S, Doiphode A, Dhavane S, Dudhal B, Shid S, Yadav A. Formulation and Evaluation of Herbal gel Containing *Lantana Camara* for Management of Acne Vulgaris. Journal of University of Shanghai for Science and Technology. 2020; 22(11): 799-809.
36. Shah N.H, Carvagal M.T, Patel C.I, Infild M.H and Malick A.W. Self-emulsifying drugdelivery system (SEDDS) with polyglycolyzed glycerides for improving *in vitro* dissolutionand oral absorption of lipophilic drugs. Int J Pharm. 1994; 106:15-23.