ISSN No:-2456-2165

Bioavailability Enhancement of Poorly Soluble Olmesartan medoxomil using Solid-Self-Micro Emulsifying Drug Delivery System (S-SMEDDS)

Devendrakumar Jain, Karunakar Shukla, Ragini Bundela
Dr. A.P.J. Abdul Kalam University, Indore, India

Abstract:- Olmesartan medoxomil (OLM) is a frequently prescribed drug for the management of hypertension that works by blocking the angiotensin II receptor. OLM is classified as a class II medicine by the Biopharmaceutical Classification System (BCS) due to its weak solubility and bioavailability. The current work aims to create a self-micro-emulsifying drug delivery system (S-SMEDDS) to improve the solubility and availability of OLM. In this experiment, the liquid SMEDDS was formulated using the optimized mixture of carbitol, tween 20 and castor oil. The solid-SMEDDS formulation was developed by lyophilizing L-SMEDDS in the presence of mannitol in 2% w/v amount as a cryoprotectant. Evaluation and characterization of the generated freeze-dried powder was carried out using various techniques. The powder has excellent flow qualities, according to the results. Furthermore, the freeze-dried powder in vitro dissolution study was compared to the marketed drug and plain drug. The freeze-dried powder exhibited 98.55±0.015% drug release within 45 minutes, whereas the marketed formulation and plain drug displayed only 57.35±0.085 % and 39.42±0.051 % release respectively after 45 minutes. Results of in vitro dissolution investigation conclude that the freeze-dried powder form of S-SMEDDS of OLM boosts the solubility profile.

Keywords:- *Olmesartan medoxomil, Bioavailability, S-SMEDDS, Lipid-based formulation.*

I. INTRODUCTION

For oral drug administration, a variety of lipid-based formulations offer various benefits, including improved permeability, decreased pre-systemic metabolism, and greater drug apparent solubility. OLM, a medication that blocks the angiotensin II receptor, is frequently used to treat hypertension. Because of its low solubility and bioavailability OLM has been designated under a class II drug by the Biopharmaceutical Classification System (BCS).[1-2] The self-micro emulsifying drug delivery system (SMEDDS) is a potential innovation that elevates the pace and volume of absorption of drugs like OLM that are poorly water-soluble. SMEDDS is an isotropic blend of co-surfactants, oils and surfactants which emulsify in mildly agitated circumstances comparable to those seen in the digestive system. This has the significant benefit that hydrophobic medications are frequently dissolved in SMEDDS, enclosing them as single-dose forms for oral delivery. [2-3]

The liquid formulation of SMEDDS (L-SMEDDS), on the contrary, requires the use of cost-effective soft gelatin capsules and as a result, the oily content may leak out of the capsules. Furthermore, L-SMEDDS can be unstable chemically and produce medication precipitation. As an alternative to L-

SMEDDS technologies in this situation, it has been proposed that the application of solid SMEDDS (S-SMEDDS) is a better tactic since it reduces production costs while promoting stability, patient acceptance, and dosage consistency. Safety is also improved using S-SMEDDS as they tend to be more bearable to the gut mucosa.[4] Techniques that are often utilized to transform typical L-SMEDDS to S-SMEDDS include melt extrusion, supercritical fluid-based processes, spray drying, melt granulation, spray cooling adsorptions to solid carriers, and high-pressure homogenization. The resultant powder can then be compressed into tablets or combined with appropriate excipients before being added to hard gelatin capsules. [5-6].

The spray drying creates tiny droplets by pushing a liquid feed through an atomization system and spraying it into a heated air stream. This promotes quick drying and yields a fine powdered result.[22] Spray cooling method includes spraying a molten substance into a chamber that is being chilled, molten droplets come into contact with the cooling air, they congeal and re-crystallize to form rounded solid particles that drop to the bottom of the chamber as a fine powder used to create solid dosage forms like tablets or capsules.[22] Freeze drying involves removal of water from the composition by sublimation under vacuums. It offers a variety of advantages, including the ability to manage the finished product's moisture content and drying at low temperatures reduces the deterioration of heat-sensitive materials.[23] The present study aims to formulate reliable solid SMEDDS to enhance OLM's oral absorption, solubility, and dissolution via freeze drying powder using lyophilization method.

ISSN No:-2456-2165

II. MATERIAL AND METHODS

A. Material:

Olmesartan medoxomil was purchased from Zydus Cadila Healthcare, Ahmadabad (Gujarat, India). Castor oil and Tween 20 were purchased from Chiti-Chem Corporation. Carbitol was purchased from Aatur Instru-chem. Mannitol was purchased from Balaji Drugs, Surat.

A pre-formulation study (solubility studies) of SMEDDS was done with several co-surfactants, oils and surfactants. Using certain volume ratios of surfactant and co-surfactant (Smix) (2:1, 1:1, 1:2) with oil in several volume ratios (9:1 to 1:9), a pseudo ternary phase diagram was created by using CHEMIX software. [7-8]

B. Liquid SMEDDS production

Various proportions of co-surfactant (carbitol), oil (castor oil), and surfactant (Tween 20) were incorporated to create a variety of SMEDDS formulations. Box Behnken Design (BBD) was utilized for formulation parameter optimization in order to analyse the second-order model, construct the experiment, and generate the response surface and contour plots. There were 17 experimental runs total in the entire design, comprising 5 replications and 12 single runs at the centre point. Olmesartan Medoxomil (OLM) at a consistent dose of 20 mg was used throughout every formulation. Components were combined using careful mixing and stirring while being heated to 40 °C. Until it was utilised, the mixture was kept at room temperature. [7-8-9]

C. Evaluation of liquid SMEDDS formulations

Parameters include Dispersibility Test, Robustness on dilution, Emulsification time, Percentage Transmittance, Drug Content, In-vitro Dissolution Study, Thermodynamic stability studies, Viscosity, Globule size measurement, Poly Disparity Index (PDI), and Zeta Potential. [10-11-12]

D. Production of S-SMEDDS formulation

The lyophilization technique is used to prepare S-SMEDDS. Mannitol is utilized as a cryo-protectant in variable ratios. The 2.5%, 1.5%, 1% & 2% w/v mannitol blended in L-SMEDDS. The blend was solidified at -50° C in a lyophilizer. After the mixture had solidified, it was lyophilized at a temperature of -75° C with a vacuum pressure of 50 mm Hg. The prepared lyophilized powder underwent evaluation and testing as described below. [13-14-15]

E. S-SMEDDS Formulation Evaluation

Tapped Density, Carr's Index (%), Bulk Density and Hausner's ratio were evaluated for S-SMEDDS.

F. Hausner's ratio and Carr's Index

This is evaluated as per the below-mentioned Table 1.

Table 1. Hausner's ratio and Carr's Index as indicators of powderflow and compressibility index

Type of flow	Excellent	Good	Fair	Passible	Poor	Very Poor	Extremely Poor
Hausner's Ratio	1.00 – 1.11	1.12 – 1.18	1.19 – 1.25	1.26 – 1.34	1.35 – 1.45	1.46 – 1.59	>1.60
Carr's Index (%)	≤ 10	11-15	16 – 20	21 – 25	26 – 31	32 – 37	>38

G. Angle of Repose

Calculation of the radius of a pile of self-emulsified freeze-dried powder using the following formula gives the angle of repose

Angle of repose = tan-1 (h/r)
Repose

Table 2. Correlations between flow property and angle

Predicted flow property	Excellent	Good	Fair	Passible	Poor	Very Poor	Extremely Poor
Angle of repose (Θ)	5 – 15	12 – 16	18 – 21	23 – 28	28 – 35	35 – 38	>40

H. Characterization of Solid SMEDDS Formulation [16-17-18]

- Drug Content

Methanol was used to dilute the required amount of freeze-dried powder of Olmesartan Medoxomil (corresponding to 20 mg) to 100 ml. Take out 1 mL of the aforementioned solution and dilute it with methanol up to 10 mL before measuring absorbance at 257 nm with a UV spectrophotometer.

- Zeta Potential

Malvern Zetasizer NS90 was used to calculate zeta potential. The zeta potential indicates the presence of an electric charge on the oil globule. Zeta potential allows us to determine the stability of the emulsion. An emulsion separates if the zeta potential is unreliable.

- Globule Size

The Malvern Zetasizer NS90 was used to gauge the emulsion's globule size. With the use of a plastic syringe or micropipette, the emulsion (1–1.5 ml) was introduced to a disposable polystyrene cuvette, and the globule size of the emulsion was evaluated using a combination of phase analysis light scattering (PALS) and laser doppler velocimetry at an angle of 90° at 25° C.

- Poly Dispersity Index

Oil globules are more uniformly distributed when the PDI value is between 0.0 and 0.5. The emulsion is more

uniform as a result. Malvern NS90 was used to determine the poly dispersity index.

- Powder Self-emulsification time

It was investigated by the addition of water slowly in self-emulsified freeze-dried powder and measuring the time (sec) until the emulsion was formed.

- Fourier Transform Infrared spectroscopic studies (FTIR)

To explore the compatibility of excipients and drugs, FTIR spectra for the drug alone and with excipients were taken using an FTIR spectrophotometer with KBR pellets. The interaction of drugs and excipients was investigated utilizing FTIR (Bruker, Mumbai).

I. In-Vitro Dissolution Study

In vitro, drug release studies from Solid SMEDDS were performed by means of a USP Type I dissolution apparatus with a number of paddle rotations set to 50 rpm. The dissolution medium consisted of 900 ml of 0.1N HCL maintained at 37 ±0.5°C. The freeze-dried powder containing 20 mg of Olmesartan Medoxomil was put it in a capsule and introduced into the dissolution medium. At predetermined time intervals, 5ml of aliquot was withdrawn and filtered using a 0.45µm syringe filter, and an equivalent volume of fresh dissolution medium was immediately added. The amount of drug released was estimated by measuring absorbance at 257 nm using a UV spectrophotometer. The dissolution reading was carried out with a similar procedure as mentioned above for plain drugs and marketed tablets with aim of a comparison study. [19-20-21]

III. RESULT AND DISCUSSION

A. Pre-formulation study

Castor oil is shown to have a maximal dissolution ability 19.63±0.08 mg/ml of OLM. Tween 20 was chosen as a surfactant because it had the highest OLM solubilizing capacity of 80.58±0.120 mg/ml. The co-surfactant phase for the SMEDDS composition was determined as carbitol since it had the highest OLM solubilizing capacity of 83.62±0.165 mg/ml.

B. Pseudo ternary phase diagram

Pseudo ternary phase diagram was constructed using 2:1, 1:1 and 1:2 ratio of Smix with distilled water and castor oil to identify the efficient self-microemulsification area. The development of pseudo-ternary phase diagrams yielded better results from a stability standpoint when Smix was used in a 1:1 ratio, according to the results.

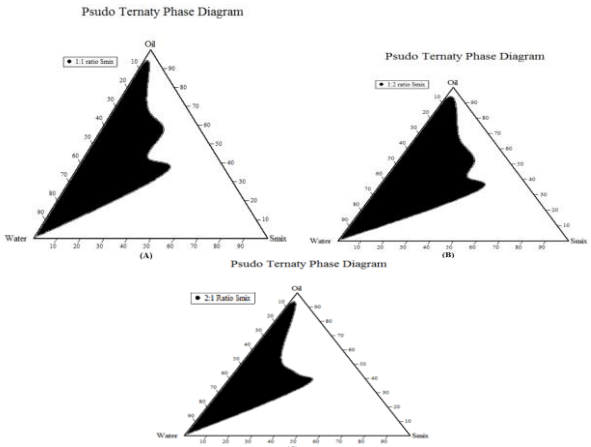

Fig 1. Pseudo ternary phase diagram (Tween 20, Castor oil : Water and Carbitol)

(A) 1:1 - Surfactant:co-surfactant
(B) 1:2 - Surfactant:co-surfactant
(C) 2:1 - Surfactant:co-surfactant

C. Liquid SMEDDS Formulation and Evaluation

Optimized L-SMEDDS and its evaluation are mentioned in Table 3.

Table 3. Optimized L-SMEDDS and Evaluation

No	**Optimized Formulation**	**1ml Castor oil 2.5 ml Tween 20 4.5 ml Carbitol OLM: 20 mg**
	Parameters	***Evaluation value***
1	Emulsification Time	17±2.62 sec
2	Transmittance %	98.05±0.14%
3	Cumulative Drug Release	99.15±0.27%
4	Dispersibility Test	Stable formulation
5	Robustness on dilution	stable without any precipitation
6	Drug Content	99±0.009 % at 257 nm UV
7	Thermodynamic stability studies	Stable formulation
8	Viscosity	0.8872 cp
9	Globule size measurement	92.28 nm
10	Poly Disparity Index (PDI)	0.243
11	Zeta Potential	-27.5 mv

D. Production of S-SMEDDS formulation

The 2% w/v of mannitol in freeze-dried powder, when compared to other ratios of mannitol, has an excellent efficiency for transforming L-SMEDDS into S-SMEDDS. So, the 2% w/v mannitol ratio will be investigated further.

E. S-SMEDDS Formulation Evaluation

The findings of solid-state characterization are mentioned below.

F. Bulk Density

Direct loading of self-emulsified freeze-dried powder into a measuring cylinder was used to determine the bulk density of the optimised freeze-dried powder. Bulk density was found to be 0.58±0.016. The freeze-dried powder's bulk density is shown in Table 4.

Table 4.Freeze-dried powder Bulk Density

Sr. No.	Powder Weight (mg)	Powder Volume (ml)	Bulk Density(mg/ml)	Avg±SD
1	15	26	0.59	0.58±0.016
2	15	25	0.58	
3	15	25	0.58	

G. Tapped Density

By mechanically tapping the optimised freeze-dried powder 100 times, the tapped density of the self-emulsified freeze-dried powder's was determined. Tapped density was found to be 0.68±003. A result of freeze-dried powder tapped density is shown in Table 5

Table 5. Freeze-dried powder Tapped Density

Sr No.	Weight of Powder (mg)	Volume of TappedPowder (ml)	Tapped Density(mg/ml)	Avg±SD
1	15	20	0.65	0.68±0.03
2	15	22	0.68	
3	15	21	0.71	

H. Hausner's ratio and Carr's Index

The optimized freeze-dried powder's Hausner's ratio and Carr's Index were determined to be 1.15±0.04 and 16.04±2.69 respectively. A result of Hausner's ratio and Carr's Index of freeze-dried powder is shown in Table 6

Table 6.Hausner's ratio and Carr's Index of freeze dried powder

SrNo	TappedDensity (mg/ml)	Bulk Density (mg/ml)	Carr'sIndex	Avg±SD	Hausner'sratio	Avg±SD
1	0.65	0.58	18.12	16.04±2.69	1.11	1.15±0.04
2	0.68	0.60	13.56		1.15	
3	0.71	0.60	16.43		1.19	

I. Angle of Repose

Optimized freeze-dried powder's angle of repose was found to be 24.91±1.25°. Result of angle of repose of freeze-dried powder was shown in Table 7.

Table 7. Angle of Repose of freeze dried powder

Sr No.	Height of Pile(cm)	Radius of Pile(cm)	Angle of Repose(θ)	Avg±SD
1	1.7	4.2	25.47	25.31±2.16°
2	1.5	3.8	22.83	
3	1.8	4.1	27.63	

J. Characterization of Solid SMEDDS Formulation:

- Drug Content

  The drug content of the self-emulsified freeze-dried powder was determined to be 94.27±0.15% of the optimised batch.

- Zeta Potential

  Freeze-dried powder's zeta potential was estimated to be -23.5 mv. Refer Figure 2 for the zeta potential.

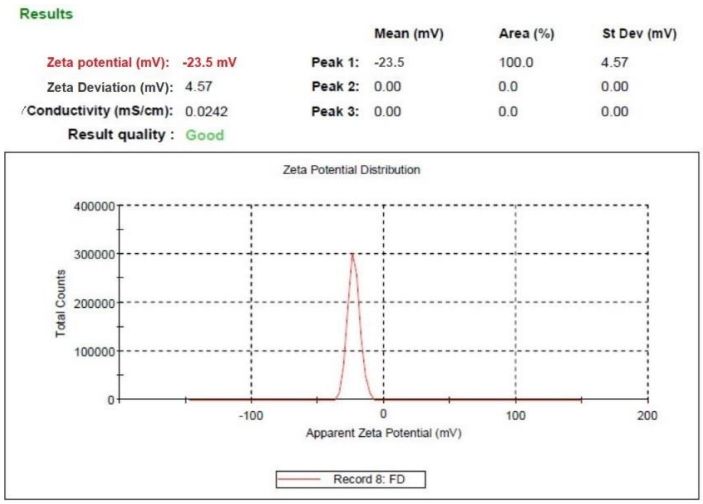

Fig 2. Freeze-dried powder's zeta potential

- Globule Size and Poly Disperbility Index

Optimized Freeze-dried powder's globule size and poly disperbility index were determined as 98.24 nm and 0.304 respectively. Results are shown Figure 3.

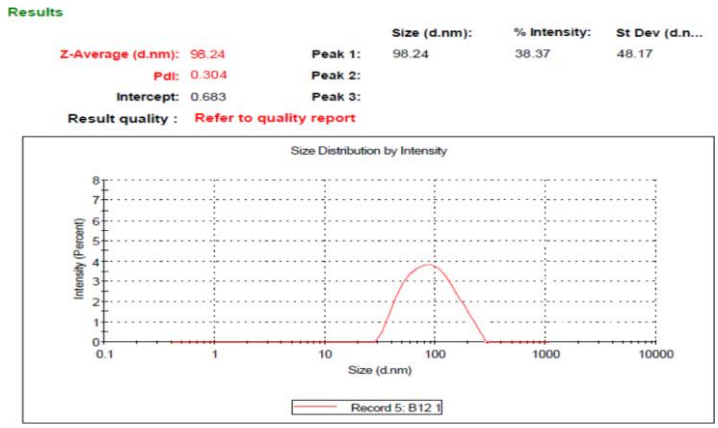

Fig 3.Globule size and Poly Disperbility Index

- Powder Self-emulsification time

The time required to form self-emulsification was evaluated utilising a stop watch and it was found to be 21±2.73 seconds.

- Fourier Transform Infrared spectroscopic studies (FTIR)

Figures 4 and 5 show the FTIR spectra of the drug and the final freeze-dried powder combination. Table.6 shows the spectral elucidations for the medication alone and with the freeze-dried powder combination.

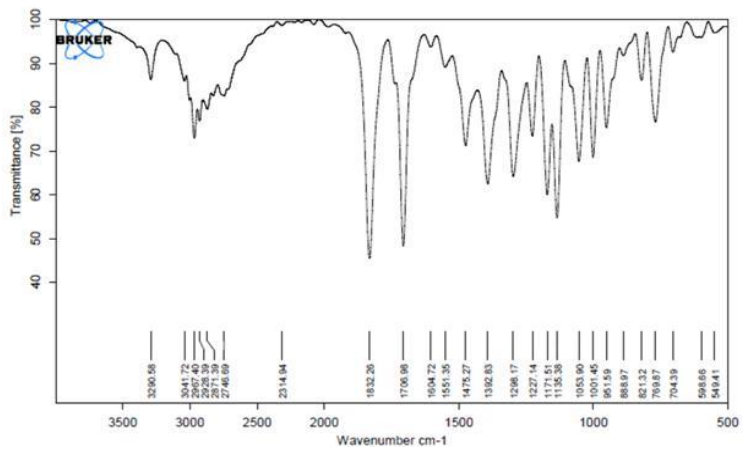

Fig 4: FTIR Spectra of Olmesartan medoxomi

ISSN No:-2456-2165

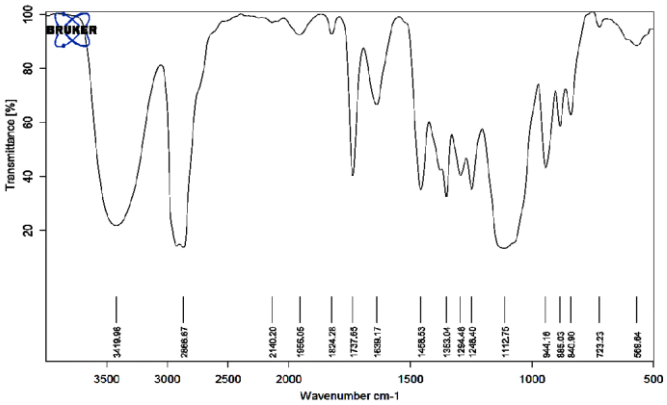

Fig 5. FTIR Spectra of Final freeze-dried powder of OLM

Table 8.FTIR peaks of Olmesartan Medoxomil

Functional group stretching	Olmesartan medoxomil (Pure Drug)	Freeze-dried powder of OLM
C-H Aliphatic	2967,2928	2866
C=C (Aromatic)	1475 and 1604	1458 and 1639
C=O of ESTER (CYCLIC)	1832	1737
C-O	1053	1112
C-N	1298	1294
NH Amine	3290	3419
C-H Aromatic	3041	

In a mixture of other excipients and the drug, the frequency of the primary peaks in the FTIR spectra was almost identical to the frequency of the principal peaks in the FTIR spectra of the pure drug. These findings, therefore, exhibited that the drug was excipient-compatible and that there were no drug breakdown or drug-excipient or excipient-excipient interactions in the formulation.

- In vitro Drug release

Results showed that within 45 mins, 98.55±0.015% drug was released in freeze-dried Solid-SMEDDS, while marketed formulation and plain drug showed only 39.42±0.051 % and 57.35±0.085 % drug release within 45 mins. According to in vitro dissolving experiments, OLM's formulation as freeze-dried SMEDDS powder improves its solubility characteristics.

Table 9: In vitro drug release of freeze-dried power

Sr. No	Time (Min)	Plain Drug	Marketed Formulation	% CDR of 2% w/v mannitol freeze-dried powder
1	0	0	0	0
2	5	1.31±0.009	3.38±0.017	12.73±0.021
3	10	5.06±0.014	7.50±0.016	27.22±0.017
4	15	14.06±0.026	14.06±0.019	41.71±0.027
5	20	21.19±0.024	21.94±0.019	54.24±0.011
6	25	25.13±0.012	27.75±0.011	71.08±0.024
7	30	28.69±0.015	35.25±0.018	79.90±0.024
8	35	31.88±0.022	44.63±0.012	90.08±0.020
9	40	34.69±0.030	51.00±0.017	97.72±0.014
10	45	39.42±0.051	57.35±0.085	98.55±0.015

- Summary of Optimized freeze-dried powder Formulation and its Evaluation

Table.10 shows the composition of the freeze-dried powder and results mentioning its evaluation.

ISSN No:-2456-2165

Table 10. Optimized freeze-dried powder formulation and its evaluation results

S. No	Parameters		Inference
1	Batch Composition		20 mg OLM + 1 ml Castor oil + 2.5 ml Tween 20 + 4.5 ml Carbitol + 2 % w/v Mannitol
2	Bulk Density (mg/ml)		0.58±0.016
3	Tapped Density (mg/ml)		0.68±003
4	Hausner's ratio		1.15±0.04
5	Carr's Index (%)		16.04±2.69
6	Angle of Repose (θ)		24.91±1.25°
7	Zeta Potential (mv)		-22.5
8	Globule Size (nm)		98.24
9	Poly Disperbility Index (PDI)		0.304
10	Emulsification Time (Sec)		21±2.73
11	Drug Content (%)		94.27±0.15%
12	In vitro drug release(%)	Freeze Dried Powder	98.55±0.015
		Plain Drug	39.42±0.051
		Marketed Tablet	57.35±0.085

IV. CONCLUSION

The formulation of S-SMEDDS was attained successfully using castor oil, carbitol, tween 20 and 2% mannitol. From the above evaluation, it can be concluded and declared that S-SMEDDS is a more beneficial and easily recognized technique than L-SMEDDS comparatively. This freeze-dried powder has good flow property and showed more impactful in vitro dissolution study compared to market tablet and plain drug. In vitro dissolution study indicates that S-SMEDDS of OLM shows better drug solubility properties. So, this developed S-SMEDDS can be a reliable and safe oral drug delivery approach for the treatment of patients with hypertension.

ACKNOWLEDGMENT

The author extends thanks to PRYXA Healthcare for providing analytical assistance in this research work.

REFERENCES

[1]. L. D. Silvaa , S. L. Almeidaa , C.P. Ellen, Preparation of a solid self-microemulsifying drug delivery system by hotmelt extrusion, International Journal of Pharmaceutics 541 (2018) 1–10.
[2]. S. S. Bakhle and J. G. Avari, formulation and evaluation of solid self-microemulsifying drug delivery system for improved oral delivery of olmesartan medoxomil, IJPSR, 2015; Vol. 6(8): 3285-3298.
[3]. G. Mette, M. Anette, L.N. Jeanet, G. Pommergaard. Bioavailability of seocalcitol II: development and characterisation of self-microemulsifying drug delivery systems (SMEDDS) for oral administration containing medium and long chain triglycerides. Eur J Pharm Sci 2006;28(3):233-42.
[4]. J. Yua , M.C. Romeo , A. Cavallarob , H.Chana, Protective effect of sodium stearate on the moisture-induced deterioration of hygroscopic spray-dried powders, International Journal of Pharmaceutics 541 (2018) 11–18.
[5]. A. Nasr, A. Gardouh, and M. Ghorab , Novel Solid Self-Nanoemulsifying Drug Delivery System (S-SNEDDS) for Oral Delivery of Olmesartan Medoxomil: Design, Formulation, Pharmacokinetic and Bioavailability Evaluation, Pharmaceutics 2016, 8, 20; doi:10.3390/pharmaceutics8030020.
[6]. S. Dokania and A.K. Joshi, Self-microemulsifying drug delivery system (SMEDDS) – challenges and road ahead, Drug Delivery, Early Online: 1–16 ! 2014 Informa UK Ltd. DOI: 10.3109/10717544.2014.896058.
[7]. S. Mehetre, V. Kadam, Dr. Karpe, Dr. Kadam, S. Mehetre, V. Kadam, International Journal of Research and Scientific Innovation (IJRSI) | Volume VI, Issue IX, September 2019 | ISSN 2321–2705.
[8]. H. Shen and M. Zhong, Preparation and evaluation of self-microemulsifying drug delivery systems (SMEDDS) containing atorvastatin, 1183-1191, journal of pharmacy and pharmacology, ISSN 0022-3573.
[9]. S. Prajapati, H. Joshi, and C.N. Patel, Preparation and Characterization of Self-Microemulsifying Drug Delivery System of Olmesartan Medoxomil for Bioavailability Improvement, Hindawi Publishing Corporation Journal of Pharmaceutics Volume 2013, Article ID 728425, 9 pages.
[10]. Zhongcheng Ke, Xuefeng Hou, Xiao-bin Ji, Design and optimization of self-nanoemulsifying drug delivery systems for improved bioavailability of cyclovirobuxine

D, Drug Design, Development and Therapy 2016:10 2049–2060.
[11]. N. Hanh , A. Mitrevej, K. Sathirakul, P. Peungvicha, N. Sinchaipanid, Development of phyllanthin-loaded self-microemulsifying drug delivery system for oral bioavailability enhancement, Drug Dev Ind Pharm,2015 Feb;41(2):207-17
[12]. A.Nasr , A. Gardouh, and M. Ghorab Novel Solid Self-Nanoemulsifying Drug Delivery System (S-SNEDDS) for Oral Delivery of Olmesartan Medoxomil: Design, Formulation, Pharmacokinetic and Bioavailability Evaluation, Pharmaceutics 2016, 8, 20; doi:10.3390/pharmaceutics8030020.
[13]. S. Savale, S. Chalikwar, Self Micro Emulsifying Drug Delivery System (SMEDDS): A Review, Asian Journal of Biomaterial Research 2017; 3(2):12-17.
[14]. M. Viswaja, D.V.R.N. Bhikshapathi, R.K. Sadasivam, A. Goje, S. Cheruku, Formulation and Evaluation of Liquid based Supersaturable Selfnanoemulsifying Drug Delivery System of Manidipine, International Journal of Pharmaceutical Sciences and Drug Research, 2023;15(1):80-87.
[15]. V. D. Kurmi, Dr.S.Shah and A. Jain, comparison of complexation, solid dispersion and solid smedds for dissolution enhancement of olmesartan medoxomil, World Journal of Pharmacy and Pharmaceutical Sciences, Vol 4, Issue 07, 2015.
[16]. C. Sun, Y. Gui, R. Hu, J. Chen, B.Wang, Preparation and Pharmacokinetics Evaluation of Solid Self-Microemulsifying Drug Delivery System (S-SMEDDS) of Osthole, AAPS PharmSciTech (# 2018) DOI: 10.1208/s12249-018-1067-3.
[17]. J. Madan, K. Patil, R. Awasthi & K. Dua, Formulation and evaluation of solid selfmicroemulsifying drug delivery system for azilsartan medoxomil, International Journal of Polymeric Materials and Polymeric Biomaterials, Volume 70, 2021 - Issue 2
[18]. M. Cirri, A. Roghi, M. Valleri , P. Mura, development and characterization of fast-dissolving tablet formulations of glyburide based on solid selfmicroemulsifying systems, European Journal of Pharmaceutics and Biophar maceutics, Volume 104, July 2016, Pages 19-29.
[19]. W. Cho, MS. Kim, JS. Kim, J. Park , H.J. Park, Optimized formulation of solid self-microemulsifying sirolimus delivery systems. Int J Nanomedicine 2013;8:1673-82.20. Wonkyung Cho, Min-Soo Kim, Jeong-Soo Kim,Junsung, Optimized formulation of solid selfmicroemulsifying sirolimus delivery systems, International Journal of Nanomedicine 2013:8 1673–1682.
[20]. Y. Cho, Y. Park, In vitro and in vivo evaluation of a self-microemulsifying drug delivery system for the poorly soluble drug fenofibrate, Arch. Pharm. Res. DOI 10.1007/s12272-013-0169-4.
[21]. D. Parakh, M. Patil, N. Dashputre & S. Jayprakash Kshirsagar, Development of Self Microemulsifying Drug Delivery System of Mebendazole by Spray Drying Technology: Characterization, in-Vitro and in-Vivo Evaluation, Drying Technology An International Journal ISSN: 0737-3937-1532-2300
[22]. S.K. Singh, P.R. Vuddanda, S.Singh, A.K.Srivastava . A Comparison between Use of Spray and Freeze Drying Techniq ues for Preparation of Solid Self-Microemulsifying Formulation of Valsartan and In Vitro and In Vivo Evaluation. BioMed Research International. 2013 Jul 18;2013