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Research Article

Development and characterization of Olmesartan Medoximil Self-Microemulsifying Fast Disintegrating Tablet

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Abstract

Olmesartan Medoxomil (OLM), is a BCS Class II hypertension drugs, with low solubility in water, leading to limited bioavailability. This study aimed to increase the dissolution rate of OLM using a Solid-Self Micro Emulsifying Drug Delivery System (S-SMEDDS). In the beginning, oils, surfactants, and co-surfactants were assessed for drugs solubility. Liquid SMEDDS was created by combining Capmul MCM (30-50%) as oil with Gelucire 44/14 and Transcutol HP (50-70%) as surfactants and co-surfactants. The method was tested for % transmittance, cloud point, reconstitution ability, stability, and drug content. Optimized SMEDDS, made up of Gelucire 44/14 (46.5%), Capmul MCM (40%), and Transcutol HP (23.5%), had good emulsification characteristics, including an adequate zeta potential, particle size, and polydispersity index (PDI). It was then adsorbed onto Neusilin U2 to obtain S-SMEDDS, which was further characterized by Differential Scanning Calorimetry (DSC) that confirmed no drug-excipient interactions, while Scanning Electron Microscopy (SEM) verified successful adsorption of liquid SMEDDS. The S-SMEDDS was formulated into a fast-dissolving tablet (FDT) using suitable excipients, exhibiting good flow properties and a disintegration time of 108 seconds. In vitro dissolution studies revealed 90% drug release in 60 minutes, significantly higher than the 35.4% release observed with pure drug. These results suggest that the S-SMEDDS-based fast-dissolving tablet of OLM could act as a novel drug delivery system for increasing solubility and bioavailability, offering a more effective oral treatment for hypertension.

Keywords: Olmesartan Medoximil, S-SMEDDS, Croscarmellose Sodium, Fast Disintegrating Tablet

INTRODUCTION

Hypertension is a public-health issue due to its high prevalence and accompanying issues, such as renal and cardiovascular disorders. It has been recognized as a main cause of death and the third-leading factor for DALY (disability-adjusted life-years) globally. The worldwide burden and incidence of hypertension are growing over time, owing to changes in lifestyle, population expansion, and ageing[1,2]. High blood pressure is closely associated to cardiovascular and renal events, which resulted in the deaths of about 10 million patients and over 200 million disability-affected life spans in 2015. Although this medical disease can be successfully treated by a change in lifestyle, medication therapy cannot be avoided[3,4]. Angiotensin II receptor blockers (ARBs) are nonpeptide antagonists that inhibit the angiotensin II type receptor, making them one of the most often used drugs for hypertension management[5].

OLM is used to treat hypertension. Decreasing the level of blood pressure can help to prevent heart attack, stroke, and kidney problems. Olmesartan is an angiotensin receptor blocker (ARB). It relaxes blood arteries, allowing blood to flow more readily[6]. According to the Biopharmaceutics Classification System (BCS), it is classed as a class II medication since it is nearly insoluble in water, resulting in low oral bioavailability (26%). Therefore, enhancing OLM's oral bioavailability can improve its effectiveness, lower the required oral dose to achieve the same therapeutic effect, and consequently minimize adverse effects[5].

Oral drug formulations are widely preferred in drug delivery systems due to their convenience, patient adherence, and flexible dosing. However, some drugs possess valuable pharmacological properties but have limited aqueous solubility, which hinders their absorption. To enhance solubility, several approaches are commonly utilized, including liposomal encapsulation, solid dispersions, macromolecular micelles, cyclodextrin inclusion complexes, nanoemulsions, and self-microemulsifying drug delivery systems (SMEDDS)[7].

SEDDS are an isotropic combination of oils, surfactants, and co-surfactants that produces fine o/w emulsions following dilution with the aqueous gastrointestinal

medium under moderate agitation[8,9]. When exposed to the aqueous phase following oral administration under gastrointestinal fluid and motility conditions, it forms a microsized emulsion with particle diameters less than 200 nm. These methods provide an advantage in delivering lipophilic drugs to the systemic circulation by skipping the dissolving phase[10].

SMEDDS are an effective carrier for hydrophobic, poor-absorbing, and quickly hydrolyzable drugs. SEDDS increase mucus permeability, rate, and amount of absorption by facilitating intestinal lymphatic transport of medicines, since they are known to protect against enzymatic hydrolysis and block P-gp efflux. Many studies have demonstrated that SMEDDS can enhance the oral bioavailability of poorly water-soluble drugs[11]. However, significant research attention has been given to SMEDDS due to its exceptional biocompatibility, biodegradability, stability, and ability to improve drug permeability as a carrier system[7,8].

Fast dissolving tablets are superior to standard tablets for medication administration due to their quick breakdown (≤3 minutes). Fast dissolving pills degrade swiftly and dissolve rapidly in a wet intestinal environment. Since the drug is incorporated into the lipid-based SMEDDS, which is an isotropic oil molecule with low fluidity, the formulation of fast-dissolving tablets requires appropriate adsorbent agents and excipients[12,13].

In the present study we have investigated the importance incorporating of self-micro emulsifying system into fast dissolving tablet to enhance the solubility of Olmesartan medoximil.

MATERIALS AND METHODS

MATERIALS

Olmesartan Medoximil (Yarrow chemPvt Ltd), Capmul MCM, Transcutol (Apotex Research Pvt Ltd), Gelucire 44/14 (Gattefose), Neusillin US2 (P D Navikar Bio ChemPvt Ltd), Croscarmellose sodium (Abitec corp), Magnesium Stearate, Talc (Fuji chemicals industry Pvt Ltd).

VEHICLE SCREENING FOR LIQUID SMEDDS PREPARATION

OLM was soluble in a range of oils, surfactants and co-surfactants. In 2ml capacity vials, an excess of the drug was added to 1ml of each of the chosen vehicles and vortexed using a vortex mixing. To aid in solubilization, the mixture was heated intermittently at 40-50°C. After a 24hr equilibration period at 30°C, the mixtures were centrifuged for 30 minutes at 10000 rpm in order to separate undissolved OLM. After pipetting aliquots of the supernatant, OLM was measured using spectrophotometry Shimadzu UV 1900i[14,15].

FORMULATION OF LIQUID SMEDDS

Different oil ratios of 30-50% and Smix (Surfactant and Co- Surfactant 1:1, 2:1 & 3:1) ratios 50-70% were used to develop SMEDDS formulations (OF1- OF9). A dose of 20 mg OLM was added in each formulation. The drug was dissolved in oil before being combined with Smix in glass vials to prepare the SMEDDS formulations. The resultant mixtures were constantly vortexed for a few minutes in order to achieve a uniform mixture. Until they were used, the SMEDDS were stored at room temperature. Compositions of 9 formulations are depicted in table1[16,17].

TABLE 1: Formulation of liquid SMEDDS

FORMULATION CODE		OF1	OF2	OF3	OF4	OF5	OF6	OF7	OF8	OF9
OLM (mg)		20	20	20	20	20	20	20	20	20
OIL (%)		30	40	50	30	40	50	30	40	50
Smix (%)	1:1	70	60	50	-	-	-	-	-	-
	2:1	-	-	-	70	60	50	-	-	-
	3:1	-	-	-	-	-	-	70	60	50

ASSESSMENT OF LIQUID SMEDDS

Percentage Transmittance (%T)

Dilute 100µl SMEDDS formulation with 100ml distilled water and measure the transmittance at 650 nm using Shimadzu UV-1700 spectrophotometer[18].

Cloud Point Measurement

A glass beaker containing 100µl of the formulation was diluted with 50ml of distilled water and heated gradually from a lower temperature to a higher one using a water bath. Note the temperature at which turbidity persists[19].

Drug content

In a 10 mL volumetric flask containing DMF, dissolve drug-loaded liquid SMEDDS and then sonicated for a period of 10 to 15 minutes. Dilute the mixture with Methanol and measure the absorbance using UV spectrophotometer set at 257 nm[20].

Robustness to Dilution

SMEDDS was diluted at ratios of 50, 100, and 1000 using distilled water, as well as solutions with pH 1.2, pH 4.5, and pH 6.8. The formulations were then observed for any phase separation or precipitation after being stored for 12 to 24 hours[21].

Determination of Globule Size, Polydispersity Index (PDI) & Zeta Potential

SMEDDS samples were dissolved in distilled aqueous solution and then gently sonicated to prevent clumping. Using Malvern particle size analyzer and Zetasizer ZSP, the particle size, particle distribution, Zeta potential and polydispersity index of SMEDDS particles were determined. Three mean values were determined after the homogenous dispersed solution was measured[22,23].

Stability studies

At room temperature, stability tests were carried out for a period of one month and UV spectroscopy was used to determine drug content[24].

Conversion of SMEDDS into S-SMEDDS

The liquid SMEDDS of OLM and Neusilin US2 were mixed together to produce the S-SMEDDS. Neusilin US2 was placed on a large porcelain dish and slowly drops of liquid SMEDDS of OLM was added and mixed. A glass rod was used to homogenize the mixture following each addition in order to obtain uniform dispersion of the formulation[25].

ASSESSMENT OF S-SMEDDS

Scanning Electron Microscopy (SEM)

The surface appearance of S-SMEDDS was investigated with a scanning electron microscope (SEM). To assure electrical conductivity, samples were adhered to a brass stub using double-sided adhesive tape and coated with a thin coating of gold. SEM pictures were then obtained using various accelerating voltages[26].

FORMULATION OF S-SMEDDS FAST DISSOLVING TABLETS

S-SMEDDS powder containing drug was compressed directly into tablet dosage form by adding suitable excipients (table 2). Before being mixed, each component was sieved. After that, a tablet press was used to compact the powder combination. Plain tablets containing the OLM were prepared by direct compression using same excipients for comparison study[27].

Table 2: Composition of S-SMEDDS fast dissolving tablet

Additives	OF4 S-SMEDDS tablets (mg for 10 tablets)
OLM (S-SMEDDS)	1200
Croscarmellose sodium	150
Magnesium Stearate	20
Mannitol	100
Talc	100

EVALUATION OF FAST DISSOLVING TABLET CONTAINING S-SMEDDS

Flow properties

Formulated S-SMEDDS granular particles were evaluated for a number of micromeritic characteristics, including compressibility index, angle of repose, Bulk density, Hausner's ratio and Tapped density.

Disintegration test

The USP Disintegration apparatus is used to measure the disintegration time. For the test, six formulated tablets were employed and the disintegration test is conducted at a rate of 30 cycles per minute in 900 milliliters of artificial saliva fluid with a pH of 6.8 at 37°C[28].

Differential scanning calorimetry

Dry samples of the pure drugs OLM, Neusilin US2, and S-SMEDDS fast dissolving tablets were subjected to DSC analysis using a Shimadzu DSC 60. After being accurately weighed, the samples are heated between 25 and 300°C underneath nitrogen flow on an aluminium pan and flow of heat was measured[29].

X-ray diffraction (XRD)

The pure drug (OLM) was subjected to X-ray diffraction analysis using a Philips X'Pert MPD diffractometer (Eindhoven, the Netherlands). In these XRD experiments, the samples were irradiated with Cu Kα radiation (λ = 1.5406 Å) and scanned across a 10° to 80° at 2θ, with each 0.04° step lasting 0.3 seconds. The resulting diffraction profiles were recorded for OLM, Neusilin and S-SMEDDS[30].

In Vitro Drug Release of fast dissolving tablet

Using a paddle-type dissolution apparatus, the dissolution properties of S-SMEEDS tablets and OLM tablets were examined in 900 ml of 0.05 M 6.8 pH PO4 buffer, at a temperature of 37± 0.5°C and 50 rpm. After pipetting out 1 ml samples at predetermined intervals and filtering the samples via a 0.45 membrane, the OLM content was determined using UV spectrometry at 257 nm for an hour at 10-minute intervals[31,32].

RESULT AND DISCUSSION

SCREENING OF VEHICLES FOR PREPARING LIQUID SMEDDS

An essential first step of producing SMEDDS is to find out how much soluble the drug is in different types of vehicles, such as oils, surfactants, and co-surfactants[33]. The drug solubility in the vehicles primarily determines SMEDDS's capacity to hold the drug in a solubilized form[34]. OLM's solubility in various oils, surfactants, and co-surfactants was assessed and is displayed in Figure 1. OLM was found to be most soluble in Capmul MCM (30±1), Gelucire 44/14 (18±1), and Trancutol HP (12±1) in that order[35,36].

For the preparation of the SMEDDS formulation, Capmul MCM, Gelucire 44/14 and Trancutol HP was selected based on drug solubility. The vehicles that were chosen also have other benefits, such as Capmul MCM's has good emulsifying qualities and it's generally recognized as safe (GRAS) classification and Gelucire 44/14, a non-ionic water dispersible surfactant was selected as it aids solubility of poorly water soluble drugs. Also literature reports roll of Transcutol HP in enhancing solubilization

properties in conjunction with surfactant Gelucire44/14[37,38].

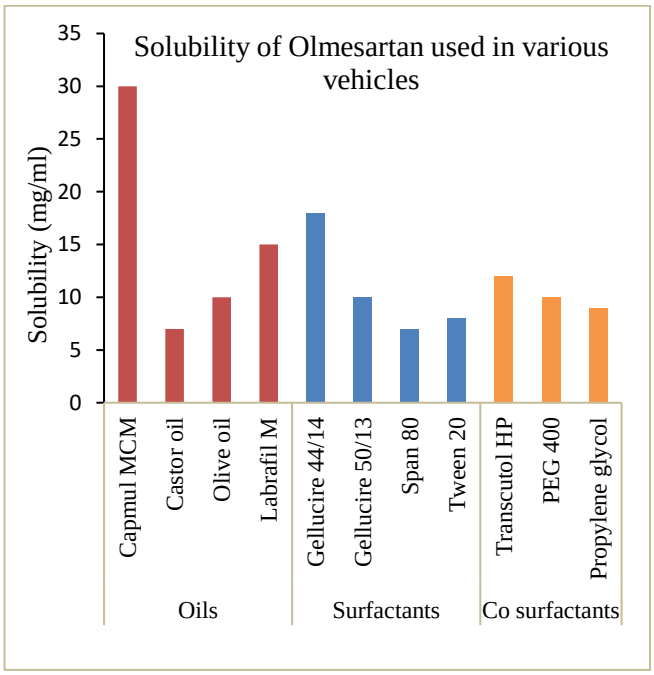


Figure 1: Solubility of OLM used in various vehicles

ASSESSMENT OF LIQUID SMEDDS

Table.1 shows the preparation of all nine SMEDDS formulations using different ratios of surfactant, oil and co-surfactant. Each formulation was assessed for its stability and emulsifying efficiency. Evaluations include percentage transmittance, stability testing, drug content analysis, cloud point measurement, robustness to dilution, particle size, polydispersity index, and Zeta potential were all assessed for each of the nine SMEDDS formulations.

Percentage Transmittance

SMEDDS's capacity to form micro-emulsion is assessed by calculating the % transmittance at 625 nm. Also the stability of SMEDDS with and without drug is assessed by determining percentage transmittance. As indicated in table 3, all of the SMEEDS ratios without drug demonstrated good transmittance. However, when the drug was present, the transmittance percentage dropped for all SMEEDS formulations (OF1- OF9). Out of the nine formulations, Formulation OF4 had the highest micro-emulsion clarity, with a higher transmittance score of 98%[39,40].

Cloud Point Measurement

In order to ensure emulsion stability at body temperature, cloud point analysis was performed. Cloud point of formulations OF1–OF9 were assessed in a water bath, and the cloud point is indicated by the temperature at which turbidity develops. Table 3 shows the cloud point temperature was between 40 and 80°C. Every formulation exhibited strong stability, showing that there is no chance of phase separation and the microemulsion will remain stable at physiological temperature[41,42].

Drug content

Using a UV spectrophotometer, the percentage drug content of each formulation was estimated. The % of drug content was computed by assessing the absorbance. All formulations percentage drug content fell between 52.87% and 78.21%. The drug content of the formulations, were observed to be between 52.87±0.38 and 78.21±0.42 and the OF4 formulation exhibited the highest drug content, with a value of 78.21%, showing uniform drug dispersion in the formulation, as shown in table 3[43,44].

Table 3: % Transmittance (without drug & with drug), % Drug content, Cloud Point Temperature ˚C for OF1-OF9 formulation

Formulation Code	% Transmittance (without drug)	% Transmittance (with drug)	% Drug Content	Cloud Point Temperature (°C)
OF1	99.7	94	61.94 ± 0.32	70
OF2	92.1	69	66.02 ± 0.14	65
OF3	80.2	78	52.87 ± 0.38	70
OF4	99.2	98	78.21 ± 0.42	80
OF5	86.8	78	65.86 ± 0.30	70
OF6	75.3	62	64.77 ± 0.50	60
OF7	98.4	93	71.95 ± 0.26	65
OF8	84.3	71	62.90 ± 0.38	50
OF9	62.3	45	55.82 ± 0.44	40

Robustness to Dilution

The formulated SMEDDS formulations were diluted 50, 100, and 1000 times with distilled water and Phosphate buffer at pH 1.2, pH 4.5, and pH 6.8 in order to figure out how dilutions affected the stability and clarity of the resulting micro emulsions. Visual observations were made for physical alterations in the micro emulsions including; droplet aggregation, phase separation, and drug or excipient precipitation. The results for distilled water, pH 1.2, pH 4.5, and pH 6.8 buffers are observed after 12-hour storage period and presented in table 4[45,46].

Table 4: Robustness to Dilution for OF1-OF9 formulation

Formulation code	Precipitation & Phase separation											
	pH 1.2			pH 4.5			pH 6.8			Distilled water		
	50 ml	100 ml	1000 ml	50 ml	100 ml	1000 ml	50 ml	100 ml	1000 ml	50 ml	100 ml	1000 ml
OF1	-	-	-	-	-	-	S	P	P	-	-	-
OF2	S	P	-	-	-	P	S	P	P	-	-	-
OF3	-	-	-	S	P	P	S	P	P	S	P	P
OF4	-	-	-	-	-	-	-	-	-	-	-	-
OF5	S	P	-	-	-	P	S	-	-	-	-	-
OF6	S	P	P	S	P	P	S	P	P	S	P	P
OF7	-	-	-	-	-	-	-	-	-	-	-	-
OF8	S	P		-	-	P	S	P	P	S	-	-
OF9	S	P	P	S	P	P	S	P	P	S	P	P

P-Precipitation & S-Phase separation

Based on all the evaluation of Liquid SMEDDS OF4 was selected as best formulation and subjected to further evaluation.

Globular Size, Polydispersity Index (PDI) & Zeta Potential Determination

The measurement of the particles size and the polydispersity index (PDI) indicates globule size and particle distribution of SMEDDS. The particle size was found to be 187.6 nm and PDI 0.007. The polydispersity value approaches zero as the droplets become more uniform. PDI of OF4 formulation (0.007) was observed to be in the range of 0.0 to 1.0 which confirms uniform distribution of the particles. The results are depicted in the (Fig. 2)[47,48].

The stability of the emulsion with the proper dilution is shown by the zeta potential value. A higher zeta potential denotes a formulation with good stability. The SMEDDS OF4 that was considered best showed Zeta potential value of -37.3mV(Fig.3) which indicated good stability of the formulation[47,48].

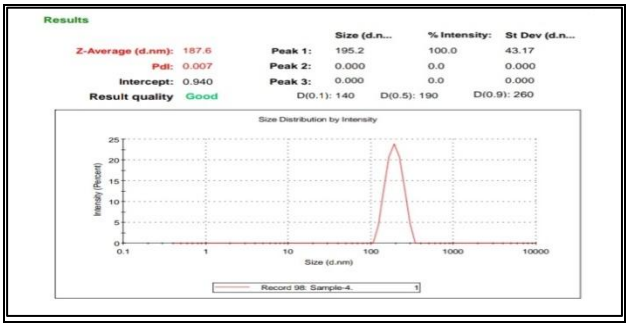


Figure 2: Average particle size & PDI of OF4

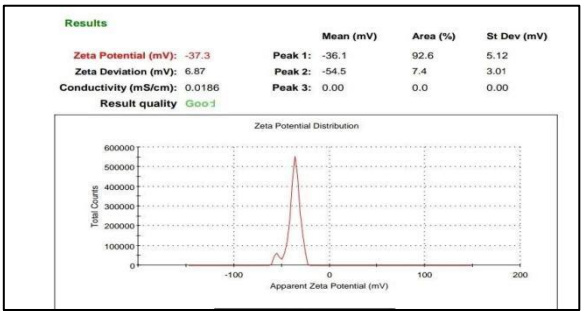


Figure 3: Zeta potential of the OF4

Stability studies

For a month, stability tests were conducted at room temperature. The purpose of stability testing is to illustrate how different environmental factors, like temperature, humidity, and light, affect the quality of medication formulation over time. When the formulation was examined for transmittance percentage after a month, the OF4 formulation revealed that neither the transmittance percentage (95.2%) nor the appearance of the micro emulsifying capacity had changed considerably[49,50].

EVALUATION OF S-SMEDDS

Scanning Electron Microscopy (SEM)

To examine the surface morphology of S-SMEDDS, microscopic images of Neusilin US2 and S-SMEDDS were captured using Scanning Electron Microscope (JEOL, JSM 5610 LV, Japan). As shown in Figure 4(a), Neusilin US2 exhibited a spherical and uniform surface. In contrast, the morphology of S-SMEDDS, as depicted in Figure 4(b), revealed the adsorption of liquid SMEDDS onto the Neusilin US2 powder[51,52].

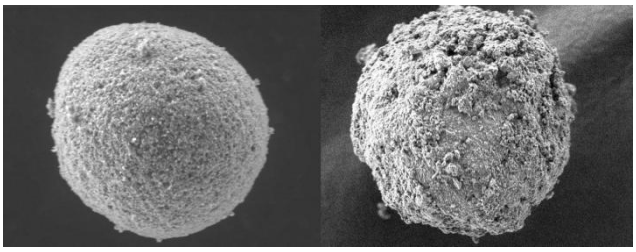


Figure 4: SEM image of (a) Neusilin US2 (b) S-SMEDDS

EVALUATION OF FAST DISSOLVING TABLET CONTAINING S- SMEDDS

Micromeritic properties

The developed S-SMEDDS showed excellent flow features with an angle of repose 27±0.02º, bulk density was 0.31±0.01(g/ml), the tapped density 0.39±0.03(g/ml), the Hausner's ratio was 1.12±0.0, and the Carr's index was less than 25%[53].

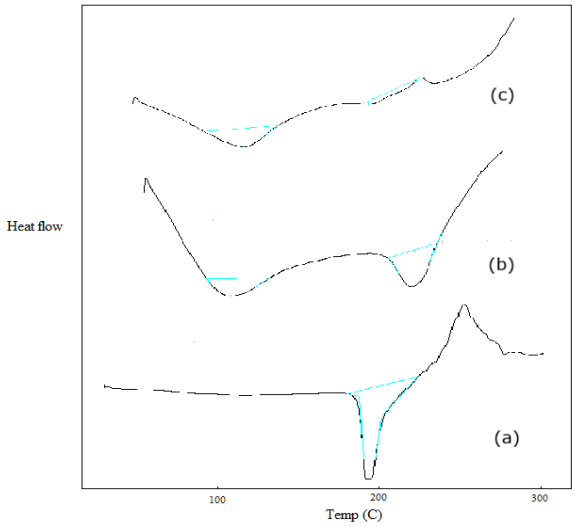
Disintegration test

A disintegration test was conducted using a USP disintegration apparatus to evaluate how rapidly the tablet breaks into smaller fragments, increasing its surface area.

The findings show that the S-SMEDD OF4 Tablet formulation disintegrates quickly, with the disintegration time being 108±0.02 seconds, which indicates rapid disintegration of the tablet[54].

Evaluation by Differential Scanning Calorimetry (DSC)

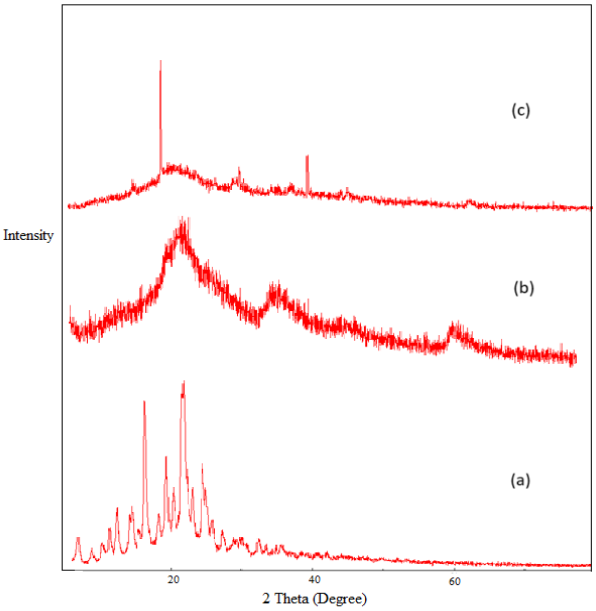
The drug-excipient interaction was studied using differential scanning calorimetry (DSC) Shimadzu DSC 60. Figure 5 displays the OLM, Neusilin, and S-SMEDDS DSC thermograms. A prominent endothermic peak at 194.62ºc, which matches to the melting point of OLM (Fig 5a) suggests the presence of OLM in crystalline form. A broad endothermic peak and the lack of a distinct OLM peak were visible in the DSC thermogram of the physical mixture of OLM and Neusilin (Fig 5b). This shows that OLM has completely dissolved in SMEDDS and changed from a crystalline to an amorphous state. In the self-emulsifying FDT endotherm (Fig 5c) the presence of a peak at 134ºc is may cause by additional excipients, such as mannitol, talc, magnesium stearate, and croscarmellose sodium, that were added during tablet preparation. Even after formulation to FDT, the drug maintained its amorphous state, as evidenced by the lack of an OLM endothermic peak[55].



DSC spectrum of OLM (a), Neusilin US2 (b) & S-SMEDDS (C)

X-ray diffraction analysis (XRD)

The diffractogram of the physical states of the OLM, neusilin, and S-SMEDDS that were examined using the X-ray diffraction method are depicted in Figure 6. The crystalline nature of OLM and the diffractogram were indicated by the different peaks in the OLM (fig 6a) XRD patterns that ranged from 0° to 25°. Neusilin US2 (fig 6b) pattern showed no distinct peaks, suggesting that it is amorphous in nature. OLM crystalline peaks are absent in S-SMEDDS (fig 6c), indicating that the drug's physical state has changed from crystalline to amorphous. This is explained by the formulation's higher internal energy, which causes a higher rate of dissolution[56].



XRD spectrum of OLM (a), Neusilin US2 (b) & S-SMEDDS (C)

In vitro drug release

A paddle type USP dissolution equipment was used to compare in-vitro drug release of S-SMEDDS OF4 tablets with plain OLM tablets. The S-SMEDDS OF4 tablet exhibits a 90.95% drug release in 60 minutes, while the plain OLM tablet showed a 35.4% drug release (fig 7). The increase in dissolution of S-SMEDDS formulation of OLM is attributed to the formation of microemulsions when comes in contact with dissolution medium the aqueous phase[55,56].

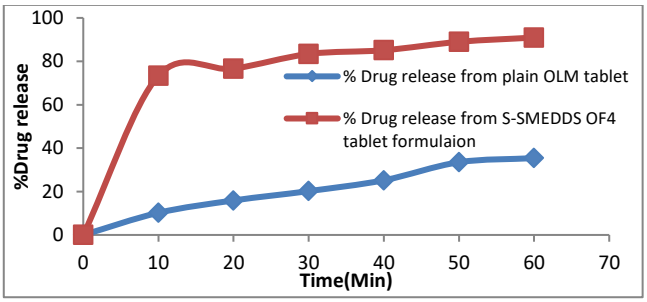


Figure 7: *In vitro* dissolution of solid SMEDDS OF-4 fast-dissolving tablets and plain drug OLM comparison

CONCLUSION

The study proved that the liquid OLM SMEDDS can be converted to SMEDDS fast dissolving tablet which combines the advantages fast disintegration and enhanced solubility. Further studies need to be carried out to assess its role in the management of Hypertension.

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Ethical approval: This study does not involve experiments on animals or human subjects.

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