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Formulation and evaluation of OlmesartanMedoxomil solid lipid nanoparticles for solubility enhancement

B G Waghmare[1*]; P P Karle; A P Potulwar
School of Pharmacy, SRTM University, Nanded (MH), India.
Corresponding Author: Mr. B G Waghmare

Abstract:*Poor aqueous solubility is a major obstacle in the development of highly effective formulation of many drugs which affect the stability and bioavailability of drug formulation. A novel technique, solid lipid nanoparticles has been developed as a strategy to overcome poor water solubility of drugs. The reduction of drug particle to the nano-level increases the surface area and improves solubility and dissolution of drug and proportionate increase in the bioavailability of poorly water soluble drugs. OlmesartanMedoxomil, antihypertensive drug used as model drug to improve its aqueous solubility, dissolution rate & ultimately bioavailability by preparing solid lipid nanoparticles using solvent emulsification-evaporation method. The prepared solid lipid nanoparticles were characterized by SEM, FTIR, DSC and XRD. The solubility profile was compared with pureOlmesartanMedoxomiland found that more than three-fold increase in solubility of OlmesartanMedoxomil SLNs. In vitro release of OLMSLNs formulation was shown to be improved as compared to pure drug.*

Keywords:*OlmesartanMedoxomil solid lipid nanoparticles (OLMSLNs), Solubility, Entrapment efficiency, FTIR analysis, In-Vitro release.*

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I. Introduction

Poor water solubility of drugs is the major obstacle and a big challenging task facing by formulators in the industry. The therapeutic effectiveness of a drug directly relates to the blood plasma drug concentration, i.e. bioavailability, which comes upon the solubility parameter of the drug. Aqueous solubility of an active pharmaceutical substance is a most important parameter concern with dissolution, absorption and in bioavailability of oral drug formulations [1, 2].

Solid lipid nanoparticle is tiny colloidal carriers with submicron range in between 50-1000nm encompasses drug with solid lipid matrix. The lipid used should be biocompatible or biodegradable, solid at body temperature, e.g. complex glyceride mixtures, highly purified triglycerides or waxes. Additionally, contains surfactants as stabilizers. Internally, solid hydrophobic core having a monolayer of phospholipids coating. They are able to carry lipophilic or hydrophilic drugs [5].

OlmesartanMedoxomil comes under anti-hypertensive category, possess low aqueous solubility and low bioavailability of 26%. Considering essentiality of formulation approaches, the main objective is to prepare OLMSLNs(OlmesartanMedoxomil loaded solid lipid nanoparticles)and make such poorly soluble drugs into soluble with more extent. The present study is undertaken to provide enhanced solubility of a drugby formulating and evaluating SLNs which will overcome the inherent drawbacks of existing dosage form [3, 4].

II. Material and method

OlmesartanMedoxomilused to be a gift sample fromUmedica Pharmaceuticals (P)Ltd.Potassium Dihydrogen Phosphate from Merck Specialties Pvt. Ltd. Polyvinyl alcohol (PVA), Stearic acid (analytical grade), Microcrystalline Cellulose, Magnesium Stearate fromRankem Pvt. Ltd. Mumbai. Polyvinyl alcohol (PVA), Microcrystalline Cellulose, Magnesium Stearate, Tween 80 Were obtained from S D Fine Chemicals. And all other chemicals used were of lab research grade.

2.1. Preparation of OLMSLNs

After performing a preformulation study of pure drug, the OLMSLNs were prepared by the solvent evaporation method. OlmesartanMedoxomil and lipid i.e. stearic acid were dissolved in methanol at temperature 70 ^{0}C i.e. above 10^{0}C of steric acid melting point. Under constant stirring at 1000 RPM the prepared drug solution was injected drop wise into water containing PVA, PEG400, and tween 80; particle's precipitated from the solvent evaporation and a milk like suspension formed which was then filtered and dried[6, 7].

Table 1: Formulation design of SLNs using PVA (Polyvinyl alcohol)

Formulation Code	Drug: Lipid Ratio	PVA (%w/v)	PEG 400 (%w/w)	Tween 80(%w/w)
F_1	1:1	1	1	1
F_2	1:2	1	1	1
F_3	1:3	1	1	1
F_4	1:4	1	1	1
F_5	1:1	1.5	1	1
F_6	1:2	1.5	1	1
F_7	1:3	1.5	1	1
F_8	1:4	1.5	1	1
F_9	1:1	2	1	1
F_{10}	1:2	2	1	1
F_{11}	1:3	2	1	1
F_{12}	1:4	2	1	1

(All ingredients are taken in mg per batch)

2.2. Characterization of prepared nanoparticles

2.2.1. Excipients Compatibility Study

Compatibility study was carried out by the use ofIR spectroscopy and Differential Scanning Calorimetry (DSC) for the confirmation of, no any chemical alteration of the Olmesartan was happening[8].

2.2.2. Fourier transform infra-red spectroscopy (FT-IR)Analysis

The FTIR spectral measurements were carried out at ambient temperature using a Shimadzu, IR affinity. About 2 mg of pure drug, solid lipid nanoparticles samples were used separately. The pure drug (OlmesartanMedoxomil) and solid lipid nanoparticle samples were dispersed in potassium bromide (KBr) powder and the pellets were preparedby 6000 kg/cm^{2}applied pressure. FTIR spectral graph were obtained on FTIR spectrometer and observed for drug excipients compatibility[10].

2.2.3. Differential scanning calorimeter

To understand the possible polymorphic transition of the compound during crystallization, DSC study was carried out. Samples were heated in an atmosphere of nitrogen and thermograms were obtained at a constant heating rate of 10^0 C/min in the range of 40-200 ^{0}C. And DSC measurements of OlmesartanMedoxomil and solid lipid nanoparticles sample were recorded.

2.2.4. X-ray Diffraction Analysis (XRD)

Compound polymorphic transition also checked by X-ray powder diffraction pattern technique during the process solid lipid nanoparticles formation. X-ray diffraction patterns were obtained at room temperature using Bruker D8 diffractometer and Cu-kα radiation with scanning angle ranged from 1° to 40° of 2θ [10].

2.2.5. Scanning Electron Microscopy (SEM)

Solid lipid nanoparticles formulation was examined using scanning electron microscope. The surface morphology of OLMSLNsformulation was examined with Gold ion coating for 5-6 min.

2.2.6. Drug entrapment efficiency SLNs[9]

Entrapment efficiency (EE), which corresponds to the percentage of OlmesartanMedoxomil encapsulated within and adsorbed onto the nanoparticles, was determined by measuring the concentration of free OlmesartanMedoxomil in the dispersion medium[10].

$$\% \text{ EE} = \frac{[M_{\text{initial drug}} - M_{\text{Free drug}}] \times 100}{[M_{\text{initial drug}}]}$$

Where, $M_{\text{initial drug}}$ is the mass of drug initially used for the assay $M_{\text{Free drug}}$ is the mass of free drug in the supernatant.

2.2.7. Solubility study of solid lipid nanoparticle

Determination of solubility measurements was done by recording absorbance using a UV spectrophotometer (SHIMADZU Corporation, Japan) at 257 nm wavelength. The aqueous supersaturate solution of OLMSLNs was stirred by a magnetic stirrer for 24 hours at a room temperature. Then solution filtration was carried throughWhatmann filter paper and the drug concentration was determined spectrophotometrically at257nm[11].

2.2.8. In vitro release studies

Prepared OlmesartanMedoxomil SLNs dispersion is placed in a prewashed dialysis tube with artificial membrane which immersed in pH 6.8 Phosphate buffer solution (dissolution medium). This operation, under continuous agitation with magnetic stirrer at room temperature. 5 ml sample was collected at different time

interval over 24 hours with the maintenance of sink condition. The extent of drug released was determined spectrometrically at 257 nm[15].

III. Result and Discussion

3.1. FT- IR Spectrum Interpretation

Compatibility with OlmesartanMedoxomilof excipients was studied by Fourier Transform Infrared Spectroscopy (SHIMADZU). The FT-IR Spectrum of OLMSLNs formulation shows that no any significant shift in the peaks or no significant difference in the spectra and characteristic peaks of formulations is similaras of pure drug. Hence, there is no any interaction in nanoparticles formulation indicating the compatibility between OlmesartanMedoxomil and stearic acid. The FT-IR spectrum of all formulations shows same peak values when compared with the characteristic peak values of pure drug shown in the table

Table 2: IR Interpretation of OlmesartanMedoxomil

Peak cm^{-1}	Group	Stretching/ deformation
3290	O – H	Stretching
2956	Aliphatic C - H	Stretching
1830	Aliphatic C – H	Stretching
1707	C =O	Stretching
1473	C - N	Stretching
783	C – N	Stretching

3.1.1. IR Spectrum ofOlmesartanMedoxomil.

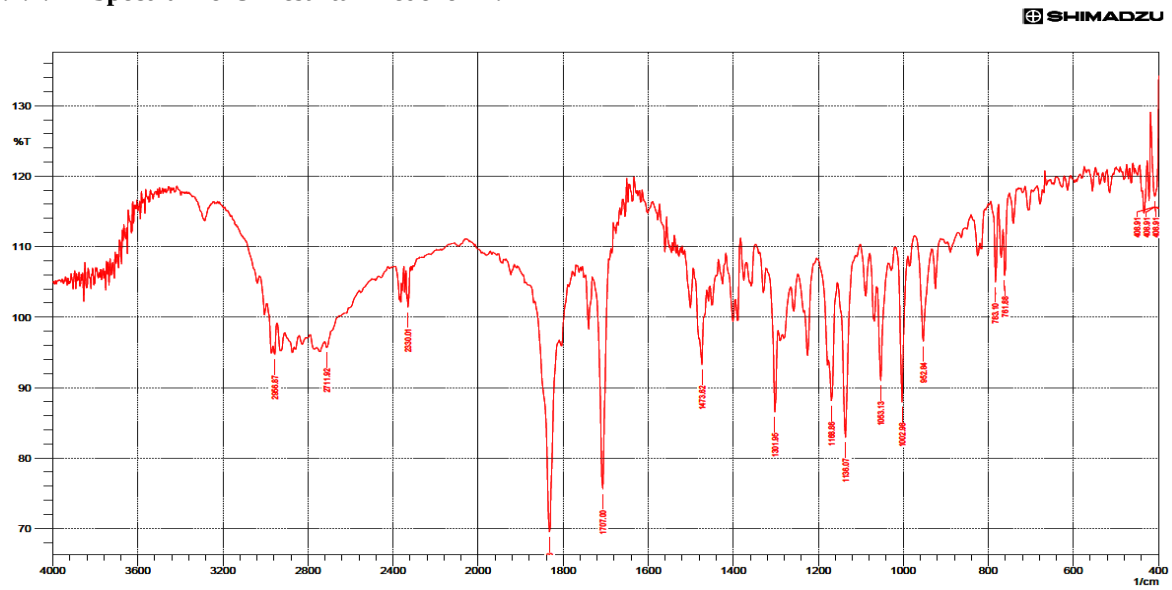

Figure- 1IR Spectrum of OlmesartanMedoxomil.

3.1.2. IR Spectrum of SLNs Formulation.

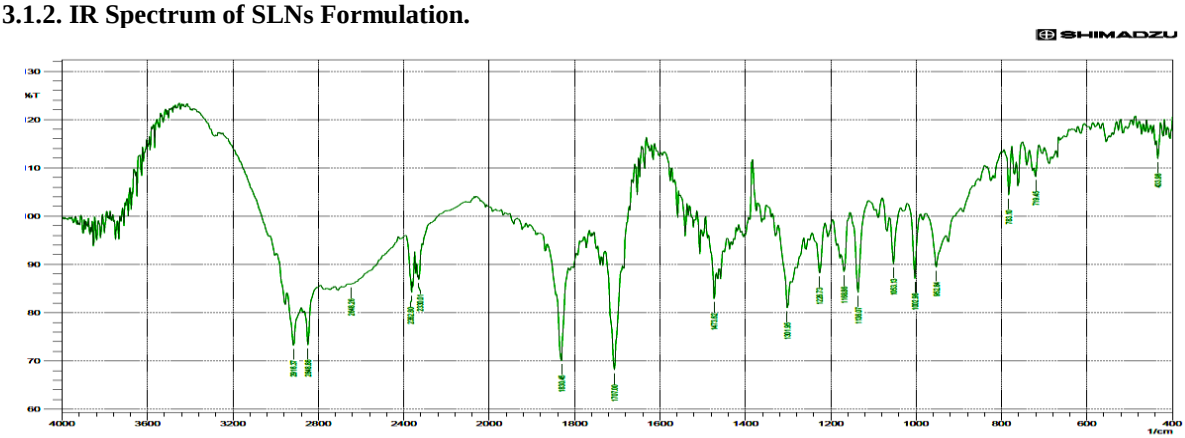

Figure- 2 IR Spectrum of SLNs Formulation.

3.2. Differential Scanning Calorimetry (DSC)

Differential scanning calorimetric analysis was carried out to examine the thermal behavior of the components used in the OLMSLNsformulations. The DSC thermograms of the OlmesartanMedoxomil drug and OLMSLNsformulations are given in Figure no. 3 & 4.Drug candidate showed a small and sharp characteristic endothermic peak at 182.5 ^{0}C whereas DSC thermograms of SLNs formulation showed an endothermic peak at 68.9 ^{0}C and 179 ^{0}C respectively. In DSC thermograms, the characteristic endothermic peaks of pure drug and lipid (stearic acid) reveal there is no appearance of any new peak or disappearance of peak corresponding to those of pure drug, indicating that crystalline nature remains with negligible change in crystallinity due to change in melting point.

3.2.1. DSC of Pure Drug

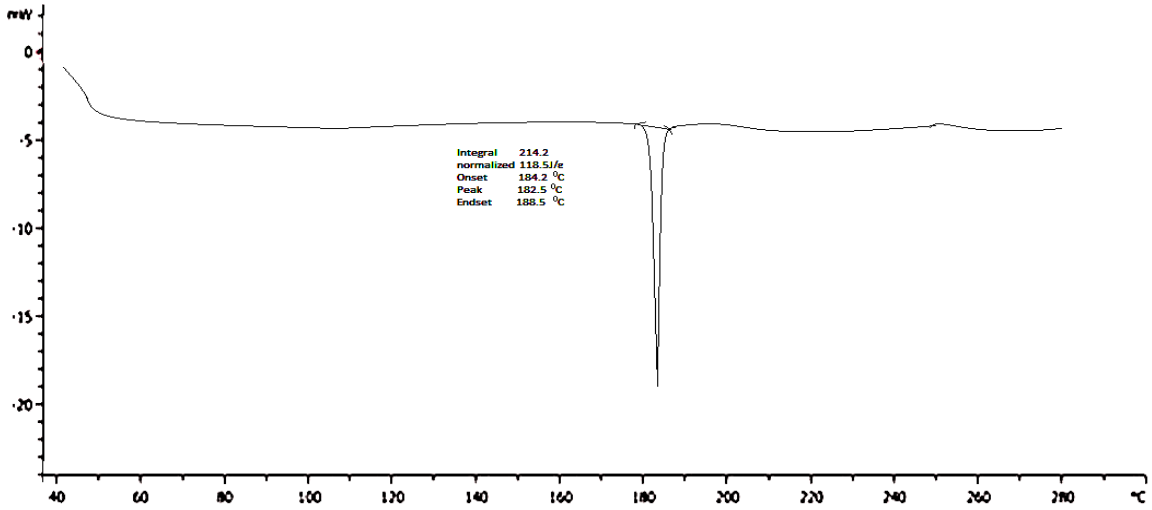

Figure- 3 DSC of Pure Drug.

3.2.2. DSC of OlmesartanMedoxomilSLNs Formulation

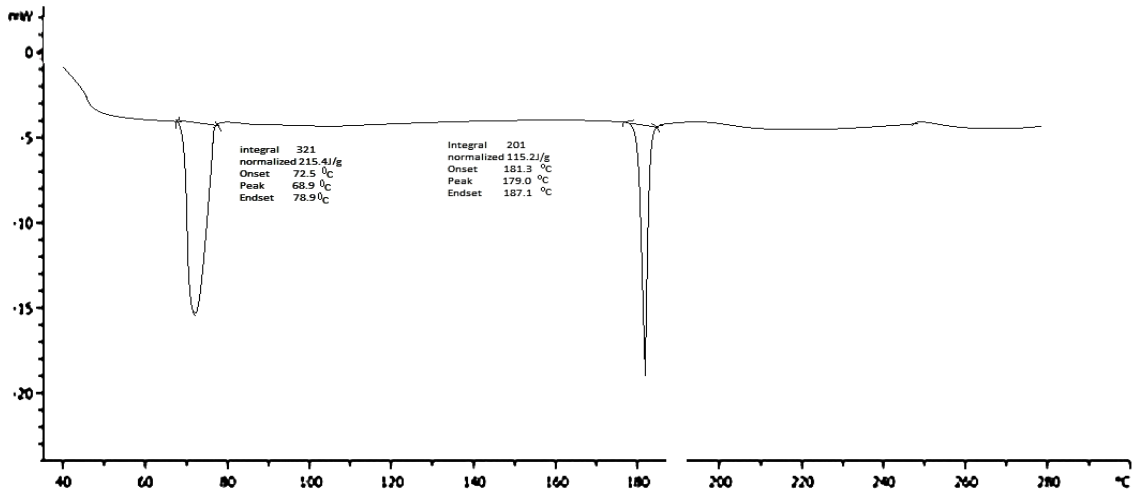

Figure- 4DSC of SLNs Formulation.

3.2. X-ray Diffractograms

The X-ray diffraction analysis was carried out for pure drug and SLNs formulation and the plots are shown in Figure no. 5& 6. After overlapping on a single scale to study the difference in the crystallinity of OlmesartanMedoxomil andoptimized OLMSLNs.The X-ray diffraction of pure OlmesartanMedoxomil shows characteristic peaks at 16.0397 º, 22.7471 º, 45.0414 º & 76.5542 º at (2Ɵ). These peaks were to compare the X-ray diffraction pattern of optimized SLNs of OlmsesartanMedoxomil at the end of 10h interval. And observed that the intensity of the peaks reduces indicating that stearic acid interferes with the OlmesartanMedoxomil by forming H-bonding and thus reduces the crystallinity of the drug and indicates complete amorphization of the drug. Hence X-ray diffraction data reveal conversion of OlmesartanMedoxomil crystalline form to its amorphous form.

3.3.1. XRD of OlmesartanMedoxomil.

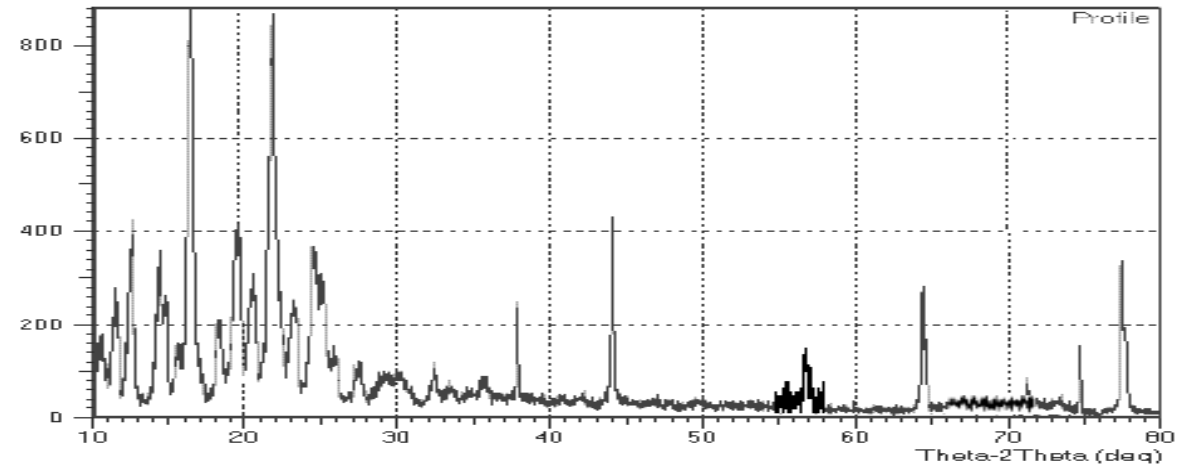

Figure- 5 XRD of OlmesartanMedoxomil**.**

3.3.2. XRD of SLNs Formulation.

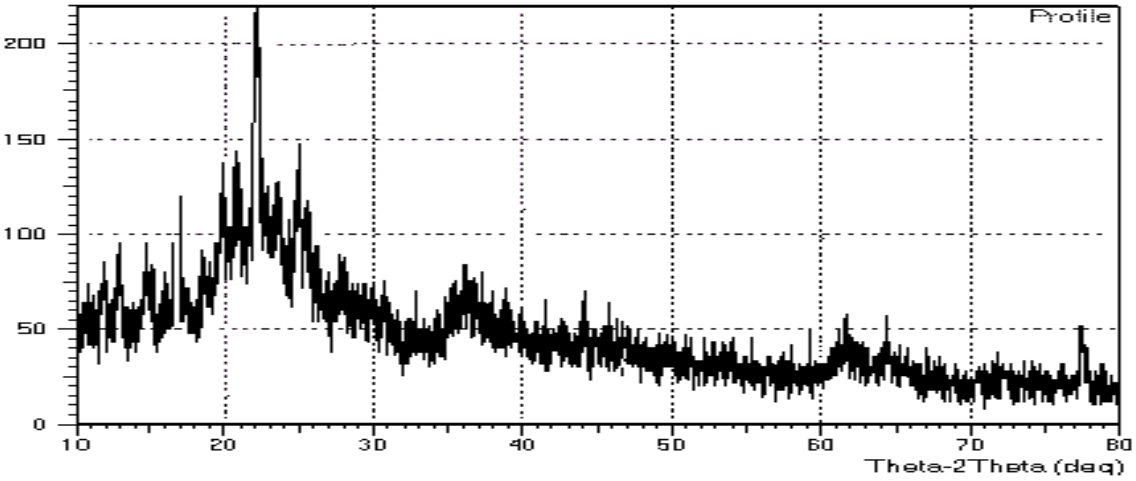

Figure- 6 XRD of SLNs Formulation.

3.4. Scanning Electron Microscopy (SEM)

The surface morphology of OLMSLNs formulation was determined by using SEM and it was found that the particle size of OLMSLNsbelow 1000 nm as compared to pure OlmesartanMedoxomil. The shape of forming OLMSLNs was found spherical and amorphous nature of all the formulations remains with slight change in crystallinity. The SEM images of pure OlmesartanMedoxomilandOLMSLNs formulation are shown in Figure.

3.4.1. SEM of Pure Drug

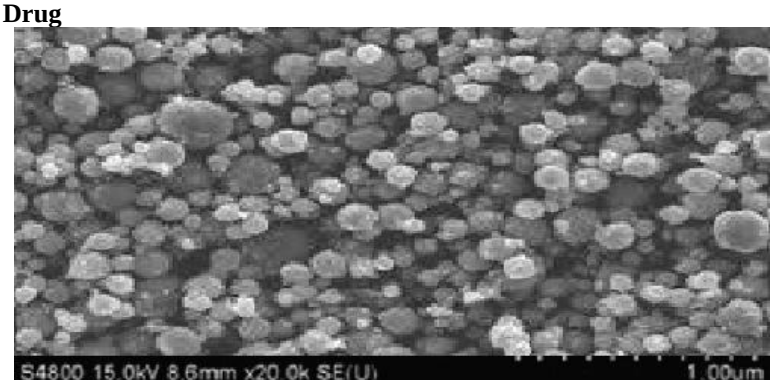

Figure- 7SEM of Pure Drug

3.4.2. SEM of SLNs Formulation

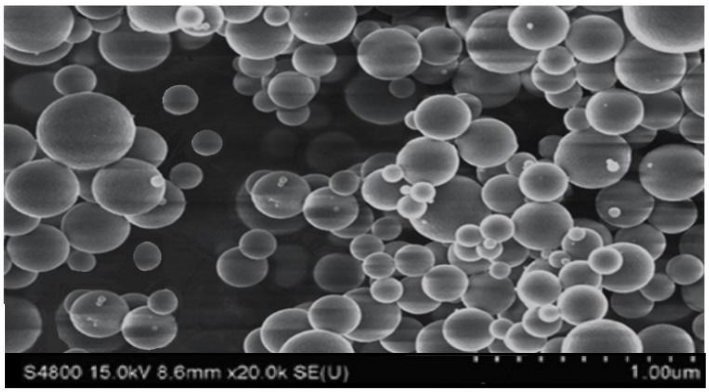

Figure- 8SEM of SLNs Formulation.

3.5. Drug entrapment efficiency SLNs

Percentage entrapment efficiency of F_4, F_8 and F_{12} SLN was found satisfactorily high that is 91.00, 91.09 and 90.70 % respectively. As observing table numerical value indicating lipid concentration increases % entrapment efficiency also gets increases. That is, entrapment efficiency is proportional to the increase in the lipid content as evidenced by lipid. Entrapmentefficiency of F_8 was found to be with maximum % entrapment efficiency that is 91.06 %.

Table 3: Entrapment efficiency of various formulations.

Formulation Code	% Entrapment efficiency
F_1	87.68
F_2	88.26
F_3	90.09
F_4	91.00
F_5	86.61
F_6	88.06
F_7	89.72
F_8	91.06
F_9	86.73
F_{10}	88.62
F_{11}	89.96
F_{12}	90.70

3.6. Solubility study

Prepared OLMSLNssamples showed increased solubility than the pure drug in the water and increased more than threefold higher (21.92 µg /ml) than pure OlmesartanMedoxomil(6.29 µg /ml). The high solubility of OlmesartanMedoxomilfrom prepared OLMSLNsmay be due to the reduction in particle size.

Table 4: Solubility study of OlmesartanMedoxomil SLNs.

Formulation Code	Water solubility	
	In (µg /ml)	***Increased (in fold)***
Pure drug	6.29	1.000
F_1	10.60	1.635
F_2	3.512	0.559
F_3	20.95	3.330
F_4	14.78	2.349
F_5	5.14	0.817
F_6	3.92	0.623
F_7	20.19	3.209
F_8	21.92	3.484
F_9	10.97	1.744
F_{10}	19.00	3.020
F_{11}	19.34	3.074
F_{12}	5.29	0.841

3.7. In vitro release studies

Percentage cumulative drug releaseof pure drug and optimized formulation of OLMSLNs(F_8)were found to be released 41.25 % and 86.41 % in 60 min respectively. And results reveal that there is improved drug release behavior ofOLMSLNs (F_8) formulationthan a pure sample of OlmesartanMedoxomil. The reason for this faster release behavior could be linked to the reduction in particle size of formulation than pure sample.

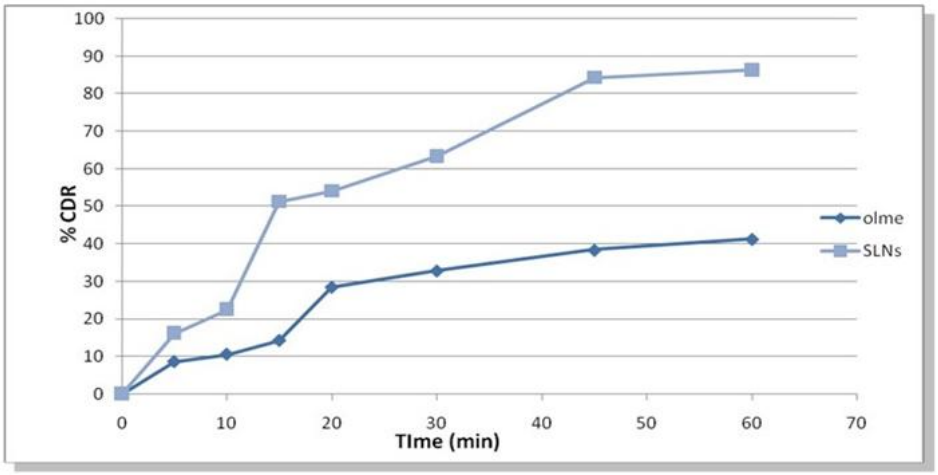

Figure- 9 Comparative release profile of SLNs formulation.

IV. Conclusion

Based on drug entrapment efficiency, solubility and *in vitro* release, formulation F_8 were selected as an optimal formulation of prepared OLMSLNs. The results of the above study revealed thatthe present work was a satisfactory for improved solubility and also showsan ability to release drug effectively. Hence it was concluded that prepared SLNs ofOlmesartanMedoxomil meeting of predetermined objectives.

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