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DESIGN, CHARACTERIZATION AND PHARMACOKINETIC STUDIES OF SOLID LIPID NANOPARTICLES OF ANTIHYPERTENSIVE DRUG TELMISARTAN

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ABSTRACT: In the present study, we explored the potential of Telmisartan loaded solid lipid nanoparticle (SLN), as a new formulation in improving the oral bioavailability of antihypertensive drug Telmisartan which otherwise reported with poor bioavailability. The "modified emulsification-ultrasonication method" was adopted for preparation of SLN, and Design of Experiments (DOE) was applied to optimize the lipid and surfactant composition. The formulations were lyophilized to get free flowing powder. The mean particle size of SLN measured to be 391.7nm with PDI value of 0.324, and zeta potential value of 21.5±0.4 mV was observed. The entrapment efficiency was estimated to be 97.58 % for the optimized formulation. Single dose (10 mg/kg) oral pharmacokinetic studies were performed in Albino Wistar rats to determine the drug delivery potential of SLN. The pharmacokinetic results indicated that the oral bioavailability of Telmisartan was significantly improved after its incorporation into SLN as total AUC obtained with SLN was 28 folds higher than that of AUC of drug suspension. The *in vitro* release from SLN demonstrated a sustained release with 85.13 % drug released compared to 15.34 % drug released from drug suspension in a period of 24 hours. In addition, DSC, PXRD and FTIR results also confirmed the molecular encapsulation of drug in the lipid matrix. During stability studies, the formulations were found more stable at temperature 5±3°C. These finding explore the potential of proposed SLN formulation as an alternative drug delivery system in improving oral bioavailability Telmisartan.

INTRODUCTION: Telmisartan is an angiotensin II receptor antagonist (ARB) widely used to treat hypertension, increasingly prescribed because of its good tolerability [1, 2]. Telmisartan is a BCS Class II lipophilic drug (log P=7.7), reported with very poor solubility in aqueous systems at physiological pH range and low oral bioavailability [3, 4]. Moreover, the solubility of Telmisartan is strongly pH depended due to which varied plasma profile is obtained.

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Hence there is need of alternative solid oral formulations of Telmisartan, which can improve its bioavailability. Due to low bioavailability with existing tablets, efforts are done from time to time by various scientists for improvements [3-6], but search is continued to develop an effective formulation. The lipophilic drug Telmisartan can easily incorporated into lipids to form a lipid based drug delivery system like SLN.

The lipids are known to improve the oral absorption of drugs by modulating the absorption through the lymphatic route. The lymphatic route is recommended for highly lipophilic drugs as an alternative to avoid first pass metabolism in liver. The lipophilic drugs are incorporated into lipid micelle and absorbed into lymphatic circulation, and then systemic circulation.

Thus, this study sheds light on the development of a new oral lipid formulation of Telmisartan which can be employed for superior bioavailability. SLNs are lipid nanoparticles of size 10-1000 nm, reported to be a suitable carrier system for pharmaceuticals with various benefits including the lymphatic absorption [7], the potential of controlled/sustained release of incorporated compounds due to solid matrix which helps in maintaining therapeutic concentration for a longer period of time [8].

They are also recommended for the protection of labile drugs against chemical degradation [9, 10]. Due to their nano size, SLN possesses unique properties and reported to have features like improvement in absorption and bioavailability [11, 12]. SLNs have received considerable interest due to their ability to overcome the limitations of previous colloidal carriers [13-16] and offer an alternative to the polymeric nanoparticles as polymers are reported with some toxic effects [17].

The SLN are supposed to be identical to oil/water emulsion for parenteral nutrition, only the liquid lipid has been replaced by the solid lipid [18]. SLNs are prepared using physiologically safe, biodegradable and non toxic lipid components like fatty acids, mono, di and triglycerides and phospholipids, which are known to be normal constituents of the human body and are thus biocompatible [19]. These lipids are solid at room and body temperature. SLNs can efficiently incorporate lipophilic drugs due to their lipid matrix and are safe in terms of GRAS (Generally recommended as safe) status lipids [20 - 22].

MATERIALS AND METHODS:

Materials: Telmisartan was obtained as a gift sample from Amoli Organics Pvt. Ltd., Vadodara, India. Stearic acid was purchased from Lipidchem Sendirian Berhad, Malayasia. Poloxamer188 (BASF, Germany) was supplied by Signet Chemical Corporation Pvt. Ltd., Dialysis membranes - 70 were purchased from HIMEDIA. All other chemicals and solvents used were of analytical or HPLC grade.

Method of preparation of SLN: SLNs were prepared by "modified emulsification–ultrasonication" method [23-25]. Briefly, the lipid phase was prepared by dissolving Stearic acid and Telmisartan in 10 ml of methanol and heating at 75 ºC (temperature above melting point of the lipid). An aqueous solution of poloxamer 188 heated up to the same temperature of lipid phase, was added slowly to the lipid phase along with continuous stirring to form a pre-emulsion. The pre-emulsion formed was stirred at 10,000 rpm for 10 minutes using high speed homogenizer (REMI). Then the dispersion was ultrasonicated for 10 minutes to reduce the size to nanoscale using Probe Sonicator (PCi 750 F). Further this dispersion was poured into cold water (1–4 ºC) and stirred with a magnetic stirrer to re-crystallize the lipid particles. The formulations were freeze dried and stored under refrigerator conditions for further analysis.

In this study, the design of experiments (DOE) was applied to optimize the lipid and surfactant concentration, and to select the best formulation. The thirteen batches of SLN were prepared by varying the lipid concentration(X_1) and surfactant concentration(X_2), using central composite design as shown in **Table 1** and **Table 2**, and the best formulation was optimized in terms of entrapment efficiency. The following regression equation was obtained.

$$Y= 92.82+3.90X_1+2.82X_2 + 1.76\ X_1X_2- 3.58X_1^2 - 0.62X_2^1$$

Statistical validity of the polynomials was established on the basis of ANOVA as shown in **Table 3** and **Table 4**. Three-dimensional (3D) response surface plots and two dimensional Counter plots were constructed based on the modal polynomial functions by using Design Expert software as shown in **Fig. 1a** and **1b** respectively. These plots are very useful to see interaction effects of the factors on the responses. The positive value before a factor in the regression equation indicates that the response increases with the factor and vice-versa.

The effect of lipid and surfactant concentration on the entrapment efficiency was studied with the help of these plots. The calculated entrapment efficiency data were compared with that of predicted response data. On the basis of these results, SLN 9 was optimized as the best formulation as it showed maximum entrapment efficiency of 97.58%.

3D surface plot **Contour plot**

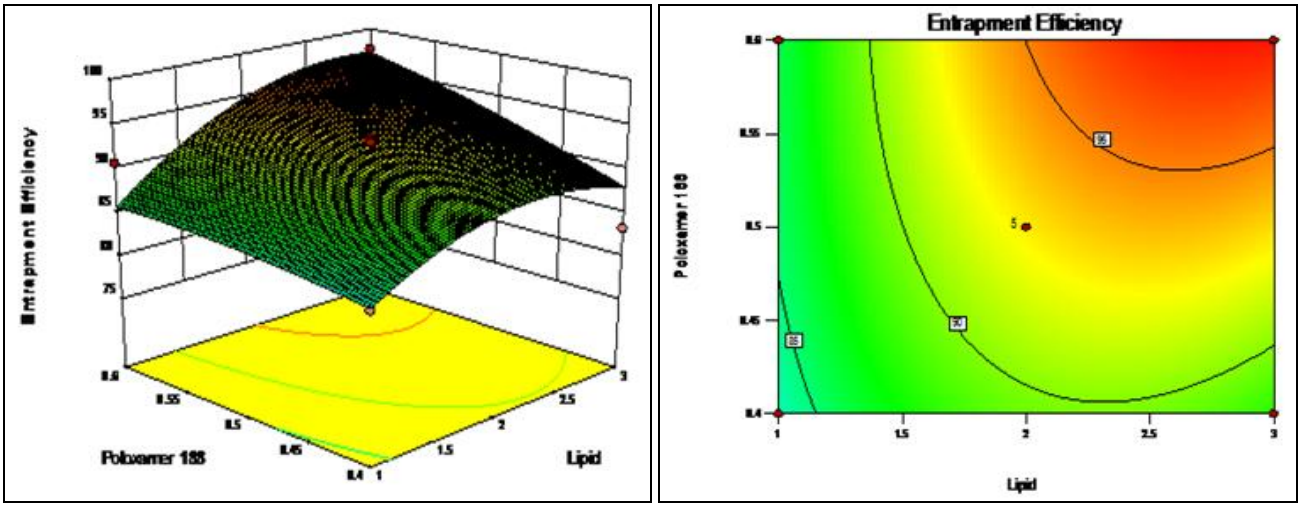


FIG. 1: (a) 3D SURFACE PLOT **(b) CONTOUR PLOT**

TABLE1: COMPOSITION OF SOLID LIPID NANOPARTICLES USING CENTRAL COMPOSITE DESIGN

Factor	Level				
	-1	**0**	**1**	**-1.41**	**1.41**
X_1 (Lipid)	1% (w/v)	2% (w/v)	3% (w/v)	0.59% (w/v)	3.41% (w/v)
X_2 (Poloxamer 188)	0.4 % (w/v)	0.5% (w/v)	0.6% (w/v)	0.359% (w/v)	0.641% (w/v)

TABLE 2: COMBINATION LEVELS OF INDEPENDENT VARIABLES AND THE OUTCOMES OF RESPONSE ENCAPSULATION EFFICIENCY

	Independent variable		Dependent variable	
Formulation code	**X_1**	**X_2**	**Observed value**	**Predicated value**
SLN 1	0	0	93.7	92.82
SLN 2	0	1.41	91.81	95.57
SLN 3	-1	1	90.7	85.77
SLN 4	0	0	93.36	92.82
SLN 5	-1.41	0	76.87	80.15
SLN 6	0	-1.41	91.12	87.60
SLN 7	0	0	91.7	92.82
SLN 8	1.41	0	94.22	91.18
SLN 9	1	1	97.58	97.11
SLN 10	0	0	92.33	92.82
SLN 11	1	-1	83.27	87.60
SLN 12	0	0	93.02	92.82
SLN 13	-1	-1	83.47	83.67

TABLE 3: SUMMARY OF EACH FACTOR EFFECT AND ITS P-VALUES FOR RESPONSE

Factor	Entrapment Efficiency	
	Factor	**P value**
Intercept	92.82	
X_1	3.90	0.0202
X_2	2.82	0.0678
X_1X_2	1.76	0.3709
X_1^2	-3.52	0.0378
X_2^2	-0.62	0.6726

TABLE 4: ANOVA SUMMARY OF MEASURED RESPONSE

	Degree of freedom	**Sum of square**	**Mean square**	**F Value**	**F-Significance**
Regression	5	287.09	57.42	4.21	0.04360*
Residual	7	95.45	13.64	-	-
Total	12	382.54	-	-	-

Characterization of SLN:

FTIR Analysis: FTIR Analysis of the drug, mixture and SLN powder were done using FTIR spectrophotometer (PERKIN- ELMER) with KBr pellet method. The middle region (4000-200 cm^{-1}) of IR range is an absorption region which gives structural information about a compound, and any interaction between drug and excipients can be interpreted in this region from FTIR results.

Particle Size and Zeta Potential measurement: The optimized SLN were subjected for measurement of average particle size and polydispersity index (PDI) values with the help of Zetasizer Nano ZS (Malvern, UK) based upon photon correlation spectroscopy (PCS). Distilled water was used as a dispersion medium. The Zeta potential values of the formulations were also determined at same concentration.

TEM (Transmission Electron Microscopy) of SLN: The shape and surface morphology of prepared SLN was examined by TEM (Morgagni 268; Phillips, Holland). Samples were stained with phosphotungstic acid (PTA, 2%), spread on a gold grid and examined for shape and size.

Drug entrapment efficiency: The percentage of drug entrapped was calculated by centrifugation method. A fixed volume (1ml) of SLN was dissolved in methanol and centrifuged at 18000 rpm at temperature 4 °C using cooling centrifuge (REMI) for 30 minutes, and supernatant was decanted without disturbing the SLN pellets. The samples were filtered and analysed after suitable dilution, at λ_{max} 298 nm using UV-1800 spectrophotometer for free drug. The percentage drug entrapment was calculated using following formula:

Entrapment efficiency = (Total drug - Free drug)/Total Drug*100

Release studies: The *in-vitro* release studies of optimized SLN formulations were carried using a dialysis bag method and compared with the drug suspension at equivalent amounts. The samples were taken in the dialysis membrane (HIMEDIA) and placed in a beaker containing 100 ml of simulated intestinal fluid (without enzymes) which acted as receptor compartment. Previously, the dialysis membrane was soaked in distilled water for about 12 hrs. The beaker was placed over a magnetic stirrer (100 rpm) and maintained at 37±2 ^{0}C. An aliquot of 1 ml of the receptor fluid were withdrawn at predetermined time intervals and replaced with fresh volumes. The samples were filtered and analysed after suitable dilution at λmax 298 nm against simulated intestinal fluid as blank using Shimadzu UV-1800 spectrophotometer. The obtained data were fitted into Zero order, first order, Higuchi and Korsmeyer-Peppas mathematical models for evaluation of kinetics of drug release of drug from the lipid matrix.

DSC Studies: DSC thermograms of pure drug, mixture and drug loaded SLNs were recorded on a Q20 Differential Scanning Calorimeter (TA Systems, USA). Samples were weighed accurately (5 mg) in aluminium pans and heated at a predefined rate of 10 ºC/min over the temperature range of 20 and 30 ºC in nitrogen atmosphere. Thermal data analyses of DSC thermograms were conducted using TA instruments universal analysis 2000 software (version: 4.5A). The scans were recorded and plots between heat flow (w/g) and temperature (ºC) were obtained.

PXRD Studies: Powder X-ray diffractometer (Bruker D8) was used to get diffraction patterns and to find out crystalline/amorphous nature of SLNs. PXRD studies were performed for the drug and SLN powder by exposing them to CuKα radiation (50 kv, 34 mA) and scanned from 3 to 45º 2θ values at a scan step of 0.02 º and step time of 3º/min.

***In vivo* Pharmacokinetic Studies in rats:** The experimental protocol was approved by the Institutional Animal Ethical Committee (IAEC) and conducted according to the guidelines of ‘‘Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA)”. A single dose *in vivo* study was designed and adult male Wistar rats (150-200 grams) were used for the study. The animals were divided into two groups (n=6). Group I was administered Telmisartan suspension and Group II was given SLN at an equivalent dose of 10mg/Kg of drug, orally using an oral feeding canula [1, 26]. The animals were anesthetized and blood samples (0.5 ml) were withdrawn at different time intervals from retro orbital sinus into heparinised

microcentrifuge tubes containing 50 µl of heparin per ml of blood [12]. Plasma was separated by centrifuging the blood samples at 15000 rpm for 10 min at 4 ºC and stored at -20 ºC until further analysis. To 150 µl of plasma, 300 µl of acetonitrile (deproteinizing agent) was added and the dispersion was vortexed for 5 minutes.

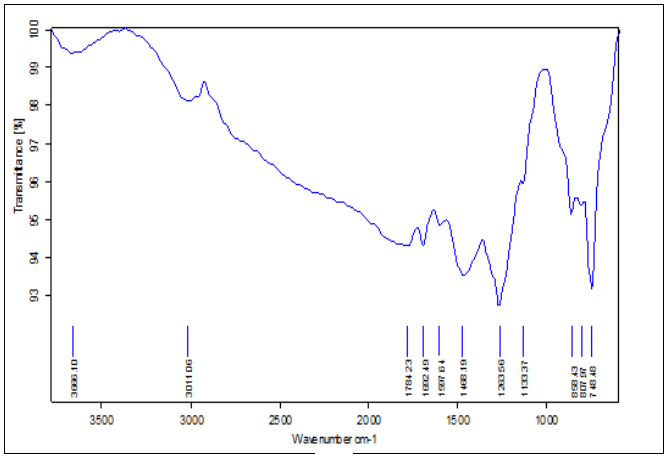
The samples were then centrifuged at 15,000 rpm for 60 min at 4 ºC. The supernatant was decanted, filtered (0.2 µm membrane filters) and 20 µl of each sample was injected into HPLC column. Simultaneously calibration curve was plotted by spiking known concentration of Telmisartan into the rat plasma over the concentration range of 1–5 µg/ml. A simple and precise RP-HPLC method using HPLC (Shimadzu) equipped with C18 column was developed for analysis of drug content present in plasma.

Stability Studies: The optimized SLN formulations (n=3) were subjected to stability testing at refrigerator temperature (5±3 ºC) and at 25±2 ºC/ 60±5% RH conditions in a stability chamber (REMI) for a period of 3 months. The parameters used to access the stability of SLNs were: variations in pH of formulation, particle size and PDI values, zeta potential and drug entrapment efficiency.

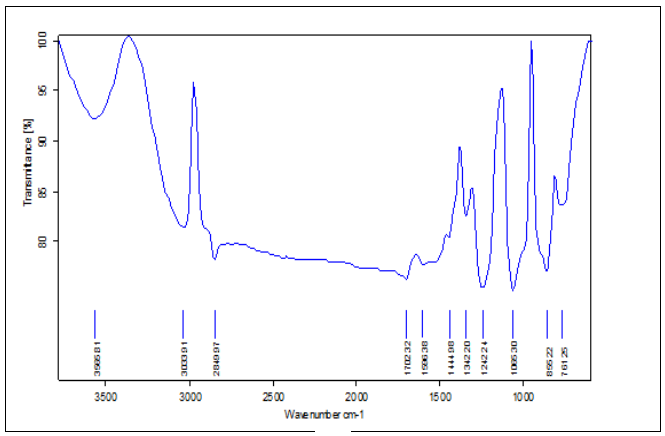
RESULTS AND DISCUSSIONS:

FTIR Analysis: No significant changes were found in the FTIR spectra of drug, mixture and SLN **(Fig. 2)**. All the characteristic peaks were maintained. IR (KBr, cm^{-1}): OH stretch 3421.78, aromatic stretch 3057, CH_3 stretch 2917.02, C=O stretch 1696.55, C=C stretch 1650, C-O bend 1245, CH_3 bend 1295, C=N stretch 1612.98, C-N stretch 1381.84, aromatic system bend 740-862, C=C bend 1000-650 cm^{-1}. These all peaks were present in mixture and drug loaded SLN, hence confirmed that no interactions occurred between drug and excipients and the drug was successfully encapsulated in the matrix of lipid.

Particle size and zeta potential: The nanometer size range and low PDI values obtained confirmed good quality nanosized SLNs produced which can provide many advantages in drug delivery. The results of particle size of optimized formulation along with PDI value, and zeta potential values are shown in **Fig. 3** and **Fig. 4** respectively. The globule size and PDI of optimized SLN measured to be 391.7nm and 0.324 respectively. Zeta potential is used to predict long term stability of the prepared dispersions. The zeta potential value was observed to be -23.1±4.73, the negative values of zeta potential are due to the carboxyl group of stearic acid.



(A)



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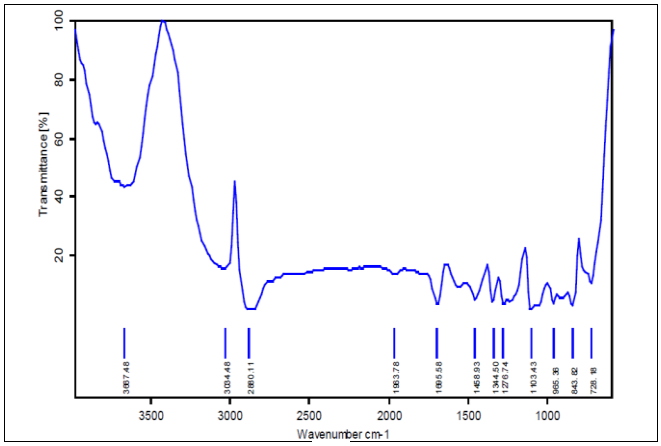


(C)

FIG. 2: FTIR SPECTRA OF (A) DRUG TELMISARTAN (B) PHYSICAL MIXTURE (C) SLN

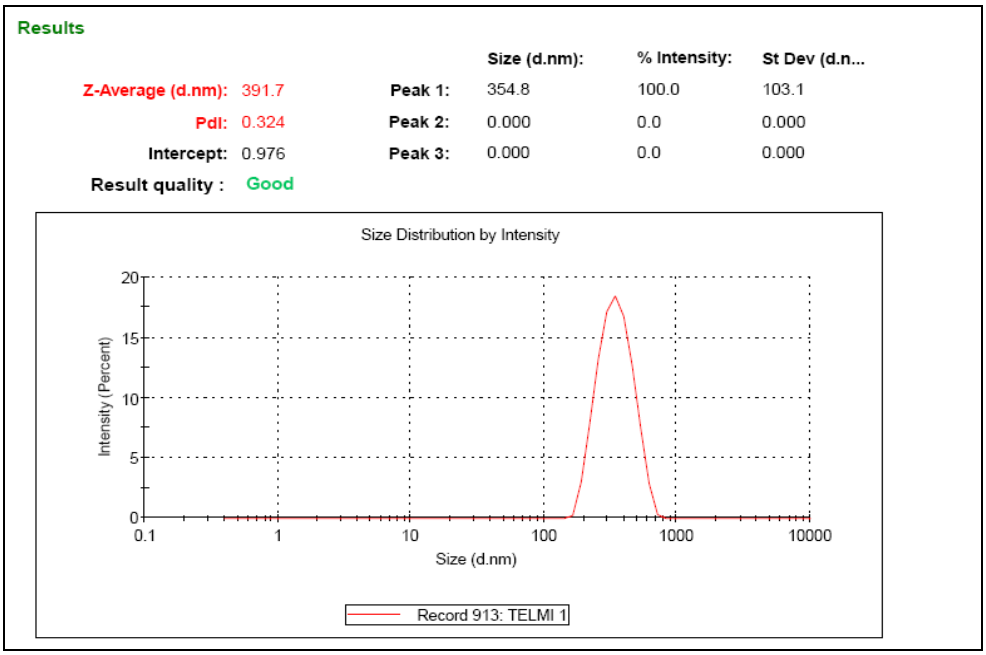


FIG. 3: PARTICLE SIZE DISTRIBUTION

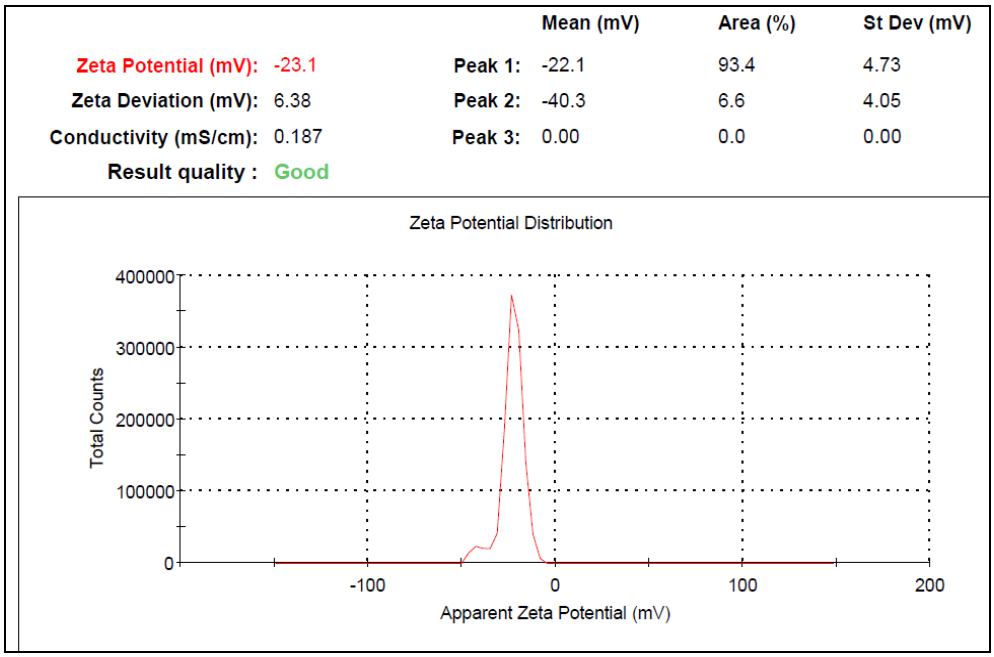


FIG. 4: ZETA POTENTIAL VALUE

TEM Analysis: The SLNs prepared are spherical in shape as shown in TEM images at various resolutions, small nanosized SLNs with sizes like 11.7, 14.1, 18.0, 18.4 and 29.8 nm are shown in the images **(Fig. 5)**. The sizes of SLNs measured by TEM analysis are smaller than that measured by PCS method using Zetasizer. This discrepancy could be due to difference in principles of measurements, measuring conditions and technology applied in this technique. This may be explained in terms of a unique arrangement of these small particles as observed under TEM. The size measurements with a Zetasizer are expected to be biased in such cases wherein a particle appearing to be single is actually a cluster of much smaller particles [12]. Thus it is recommended that electron microscopy at high magnification (TEM/SEM) should be considered more reliable for determining the size of such particulate systems.

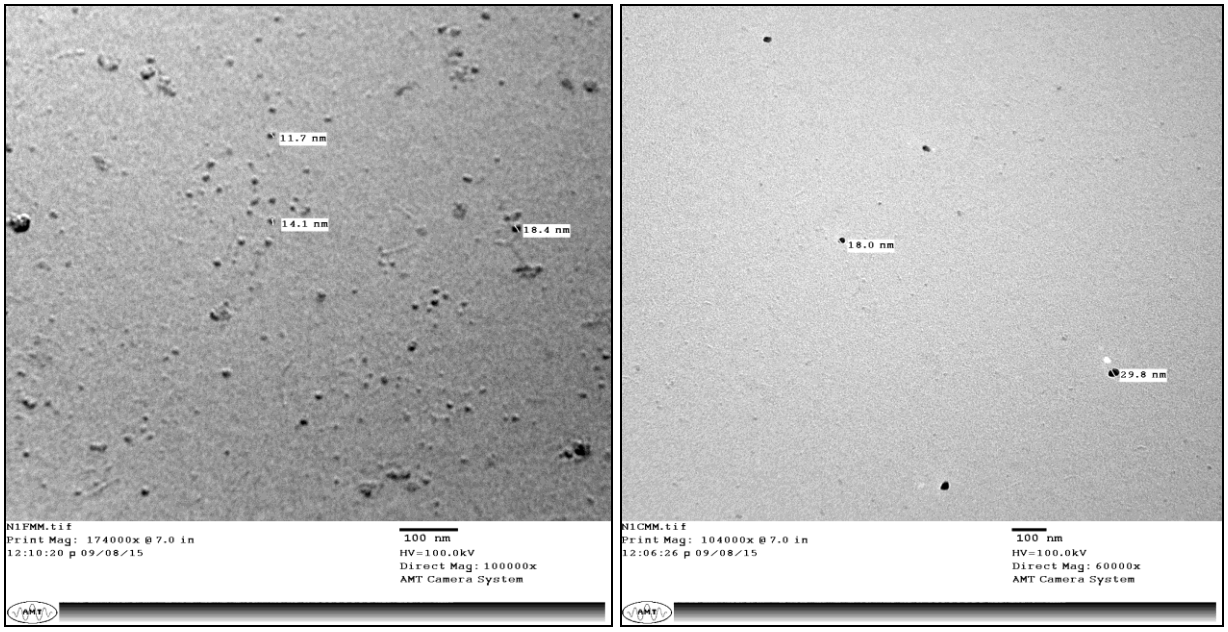


FIG. 5: TEM IMAGE (100NM SCALE)

Drug entrapment efficiency: The entrapment efficiency which is ratio of the drug encapsulated to that of total drug loaded was calculated for all the thirteen SLN formulations, and the values are as shown in the **Table 2**, these values were also compared with the predicted values depicted from DOE. The formulation SLN 9 has shown highest entrapment of the drug. The high entrapment efficiency is attributed to high affinity of lipophilic drug Telmisartan toward the lipoidal matrix of stearic acid, and the maximum stabilization provided by the surfactant Poloxamer 188 to the lipid core.

Release Studies: The cumulative percentage release of drug from the optimized SLN formulation and the drug suspension at equivalent amounts are as shown in the **Fig. 6**. The drug release from the SLN was higher than drug suspension and more sustained up to 24 hours. The SLN formulation showed initial fast release followed by comparatively slower release up to 85.13 % lasting up to 24 hours **(Fig. 6)**. The initial fast release may be explained in terms of free drug present on the surface of SLN molecules. The further slow release is due to diffusion of the entrapped drug from the solid matrix of the lipids.

The results of mathematical models for kinetics of drug release from the SLN matrix are shown in **Table 5**, zero order release, first order release, Korsmeyer-Peppas release and Higuchi release are shown. From regression analysis, the drug release from the SLN was most appropriately described by Korsmeyer-Peppas fit mathematical model with highest value of regression coefficient (r^2 =0.994). Hence, drug release from SLN followed Korsmeyer-Peppas release.

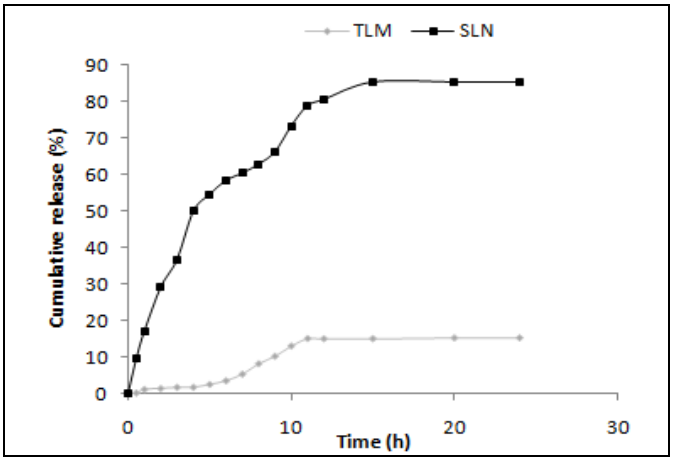
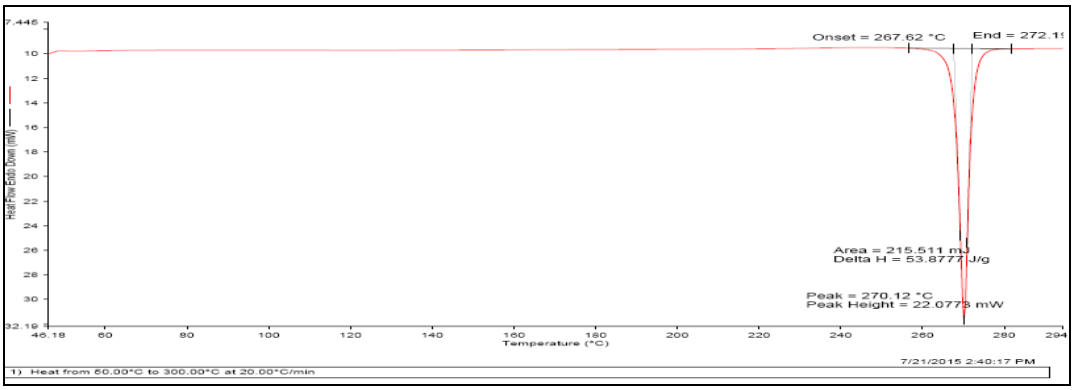


FIG. 6: *IN VITRO* DRUG RELEASE OF TELMISARTAN FROM SLN, COMPARED WITH PURE DRUG

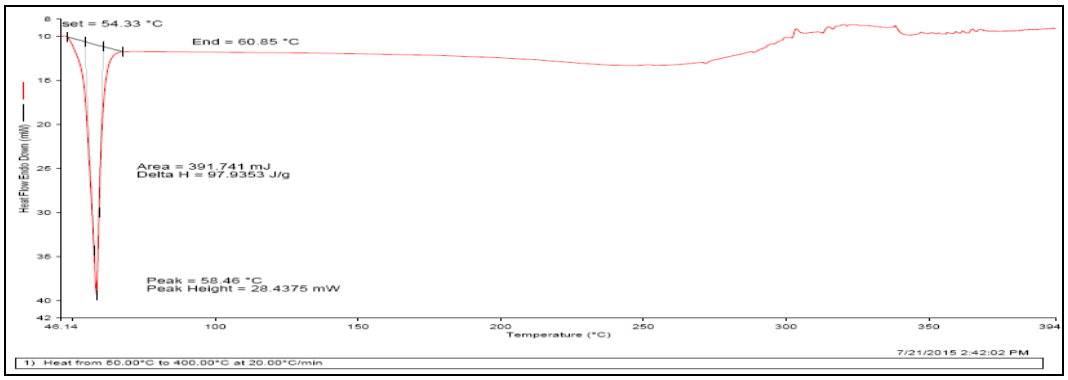
TABLE 5: RESULTS OF MATHEMATICAL MODELS FOR DATA FITTING OF DRUG RELEASE STUDIES

Formulation name	Zero order		First order		Higuchi		Korsmeyer-Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
SLN 9 Formulation	0.826	2.759	0.990	-0.031	0.964	21.22	0.994	1.144

Differential scanning calorimetry (DSC) studies: A sharp endothermic peak at 270 ºC was observed for pure Telmisartan **(Fig.7a)**. The endothermic peak for the excipient was observed at 58.46 ºC **(Fig. 7b)**. The physical mixture only exhibited the peaks of individual components. The DSC of optimized SLN showed a very small endothermic peak at 270 ºC corresponding to free drug, but a sharp single peak at 54.37 ºC indicated the molecular dispersion of drug in SLN and successful encapsulation of drug in lipid matrix. Reduction of peak height and disappearance of peaks pointed toward a positive interaction. The decrease in enthalpy change pointed toward a reduction in crystallinity indicating successful entrapment of the respective drugs in SLNs which in turn ensure a decreased drug expulsion and a better controlled release from the SLNs with a minimal burst effect.



(A)



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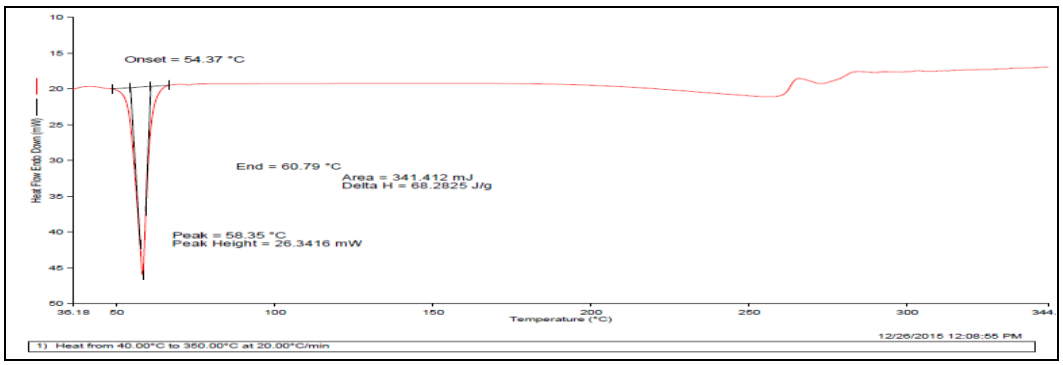
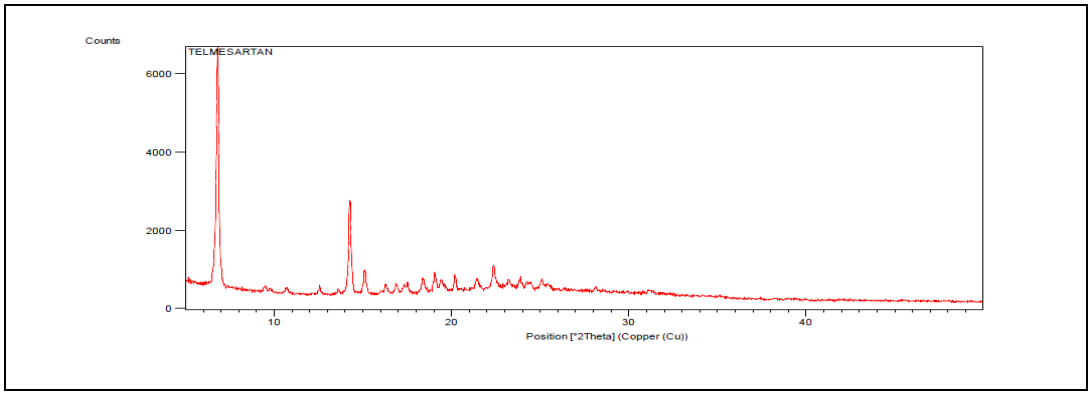


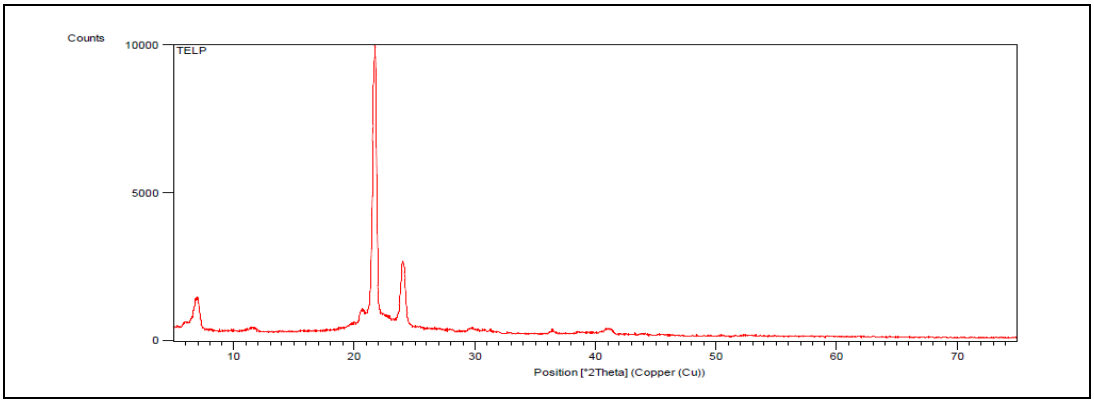
(C)

FIG. 7: DSC CHROMATOGRAM OF (A) DRUG TELMISARTAN (B) PHYSICAL MIXTURE (C) SLN

PXRD Studies: PXRD patterns of Telmisartan exhibit sharp peaks at 2θ scattered angles indicating highly crystalline nature of Telmisartan. The characteristics sharp peaks of Telmisartan in XRD patterns are 6.8,12, 15.7, 18.2, 21, 23.2, 24.5 (2° Theta) values. The PXRD spectra of pure Telmisartan and lyophilised SLN formulations are almost same are shown in the **Fig. 8(a)** and **8(b)** respectively, indicating that there were no noticeable changes in crystallinity of Telmisartan.



(A)



(B)

FIG. 8: PXRD PATTERNS OF (A) TELMISARTAN (B) SLN

***In vivo* Pharmacokinetic Studies in rats:** HPLC chromatogram was recorded at 230 nm and the corresponding plasma drug concentration versus time profile is as presented in the **Fig. 9**. The pharmacokinetic parameters were calculated using non-compartmental analysis and are as shown in the **Table 6**. Plasma levels achieved with SLNs were higher than that of drug Telmisartan as shown in **Fig. 7** and also prolonged up to 24 hours. The pharmacokinetic parameters were calculated with the software NCSS11.0.4 and the results showed 28 folds increase in total AUC compared to the free drug suspension. The C_{max} was much higher for SLN formulation and was achieved in 4 hours.

The increase in AUC of Telmisartan with SLN formulation may be attributed to intrinsic nano nature of prepared SLNs and lymphatic absorption through oral lymphatic region, hence avoiding the first pass metabolism of the drug [12, 27-29]. The mean residence time (MRT) for drug from SLN formulation was significantly higher than that of free drug depicting sustained release over a long period. Hence, these *in vivo* results confirmed that SLN formulation could be successful in improving the oral bioavailability of poorly soluble drug Telmisartan [30-32] and controlled release over an extended period of time is achieved.

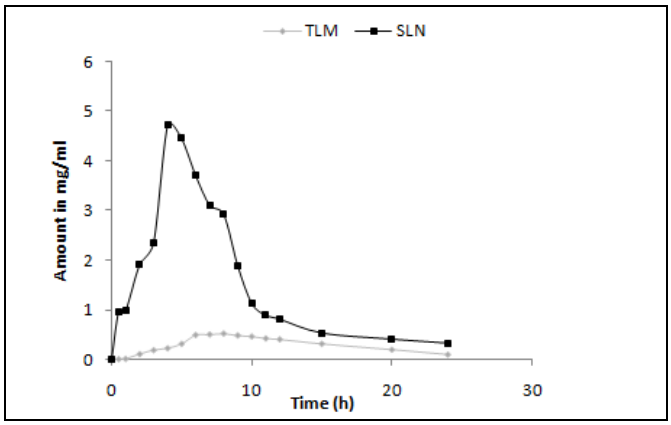


FIG. 9: PLOT OF RAT PLASMA CONCENTRATION VERSUS TIME FOR SLN AND DRUG IN RATS [THE ORDINATE IS Y INDICATING PLASMA CONCENTRATION (mg/ml) AND ABSCISSA INDICATING TIME (HOURS)]

TABLE 6: PHARMACOKINETICS PARAMETERS AFTER ORAL ADMINISTRATION OF FREE DRUG AND SLN TO RATS

Pharmacokinetic parameters	Telmisartan	SLN
AUC (mg/ml.hrs)	1.26	28.45
C_{max}(mg/ml)	0.53	4.721
T_{max} (hours)	8	4

Stability Studies: The stability estimation results are shown in **Table 7**, **Table 8** and **Table 9**. The results showed that changes found in any of assessed parameters at low temperature conditions were less than that observed at room temperature. The increase in particle sizes and small changes in zeta potential values observed at room temperature conditions may be attributed to aggregation of particles. The reduction in percentage drug entrapment values at different time intervals at 25 ± 2 °C is explained in terms of some drug expulsion from solid lipid matrix upon aging. Hence, it is recommended that SLN formulation should be stored under refrigerator conditions (5 ± 3 °C).

TABLE 7: pH VALUES OF SLN AT DIFFERENT TEMPERATURE

S. No.	Formulation	Initial pH	pH		
			30 days	60 days	90 days
1	SLN at refrigerator temperature(5±3 °C)	7.3±0.25	7.2±0.26	6.9±0.21	6.8±0.11
2	SLN at room temperature (25±2 °C)	7.4±0.054	7.2±0.39	7.0±0.46	6.9 ±0.35

TABLE 8: PARTICLE SIZE AND ZETA POTENTIAL VALUES AT DIFFERENT TEMPERATURE

S. No.	Formulation code	Particle size			Zeta potential values		
		0 day	30 Days	90 Days	0 day	30 Days	90Days
1	SLN at refrigerator temperature(5±3°C)	391.7	388	537.4	-23.1	-20.0	-19.5
2	SLN at room temperature (25±2°C)	391.7	628	642	-23.1	-20.5	-13.6

TABLE 9: PERCENTAGE DRUG ENTRAPMENT OF SLN AT DIFFERENT TEMPERATURE

S. No	Formulation	Initial drug content	% Drug Content		
			30 days	60 days	90 days
1	SLN at refrigerator temperature (5±3°C)	100%	96.26±0.85	94.45±0.57	93.21±0.44
2	SLN at room temperature (25±2°C)	100%	92.21±0.14	91.25±0.26	90.26±0.85

CONCLUSION: Good quality nanosized Telmisartan loaded SLN were prepared using stearic acid as matrix forming lipid and Poloxamer 188 as stabilizing emulsifier. The "Modified emulsification–ultrasonication technique" was successfully employed to prepare SLN. The SLN dispersions were freeze dried. The drug was successfully incorporated with high entrapment efficiency of 97.58% for the optimized formulation. The *in vivo* and *in vitro* results have assured that SLN of Telmisartan could be successful drug delivery option to enhance its efficacy to treat hypertension. Further, the pharmacodynamic studies are proposed for these formulations. Hence, these systems offer the possibility to develop well tolerated oral drug delivery systems.

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