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Research Paper

Formulation and Evaluation of Valsartan Solid Lipid Nanoparticles

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Abstract

Valsartan is a potent and specific competitive angiotensin II antagonist which is used in the management of hypertension. It is well absorbed following oral administration, with rather poor bioavailability of about 25 %. Peak plasma concentration of valsartan occurs 2-4 hours after ingestion. Optimized VAL_SLNS are prepared by hot homogenization method and spray dried to improve handling processing and stability. Solid state studies such as FTIR indicated absence of any chemical interaction between valsartan and the lipid.

The mean particles size, Polydispersity index (PDI) and entrapment efficiency of optimized formulation (F-05) was found to be 136.5 nm, 0.424, 80.98% respectively. The drug release study from the nano formulation was studied in Phosphate buffer 6.8 for all the formulations F1 F2 F3 F4 and F5. The results demonstrated that V-SLN formulation (F-5) showed biphasic behaviour with an initial burst release followed by a sustained release maximum up to 72-79% till 12 hours. The release curve was found to follow Korsmeyer Peppas model (R^2=0.98).

Keywords: hot homogenization, hydrogenated soya phosphatidyl choline, sustained release

INTRODUCTION

Solid lipid nanoparticles (SLNs) and nano-structured lipid carriers (NLCs) SLNs are colloidal carriers having size range between 50 and 1000 nm with a lipid-forming core at both body and room temperatures. This system allows for high entrapment for hydrophobic drugs with controlled release profile.it is a replacement carrier system to traditional colloidal carriers such as emulsions, liposomes, and polymeric micro and nanoparticles. Recently, about 40% of molecules being developed by the pharmaceutical industry have been reported to be poorly water soluble, which limits their absorption in the gastrointestinal tract and reduces the overall bioavailability. mostly many molecules have been rejected due to their low aqueous solubility. A drug's therapeutic efficacy depends on four fundamental pathways of drug transport and modification within the body, absorption, distribution, metabolism, and elimination. Failure in therapy includes insufficient drug concentration due to poor absorption, rapid metabolism and elimination, poor drug solubility, and high fluctuation of plasma levels due to unpredictable bioavailability. A promising strategy to overcome these problems involves the development of a suitable drug colloidal carrier system. Among the colloidal carrier systems solid lipid nanoparticles have many advantages and limited disadvantages as compared to other colloidal carrier systems. [1]

Their small size and relatively narrow size distribution permits sire specific drug delivery. Controlled and sustained release of active drug can be achieved. Improved bioavailability, protection of sensitive drug molecules from the outer environment (water, light) Controlled release by incorporation of poorly water-soluble drugs in the solid lipid matrix. Easy to scale up and sterilize. Better control over release kinetics of encapsulated compounds. Enhanced bioavailability of entrapped bioactive compounds. Chemical protection of labile incorporated compounds. Much easier to manufacture than biopolymeric nanoparticles. No special solvent required. Conventional emulsion manufacturing methods applicable. Raw materials essential are the same as in emulsions. Very high long-term stability. Application versatility. Can be subjected to commercial sterilization procedures. [2, 3]

Valsartan is a potent and specific competitive angiotensin II antagonist which is used in the management of hypertension. Valsartan is a novel and orally active Ang II antagonist that does not require hepatic metabolism. It is highly selective antagonist of Ang II at the AT1-receptor subtype and does not possess agonist properties.[4, 5] It belongs to BCS class II in biopharmaceutical classification as it is having low solubility in this study we have made an attempt to improve solubility by formulating in solid lipid nanoparticle formulation with drug content 99.05 and possessing entrapment efficiency of 80.98

MATERIALS AND METHODS

Chemicals

Valsartan was obtained as gift sample from Hetero Chemicals, Hyderabad. Hydrogenated phosphatidyl choline was provided as gift sample from IPCA Laboratories, Silvasa, Dadra and Nagar Haveli. Tween 20 and 80 was obtained as gift sample from BASF, Turbhe, Navi Mumbai. All chemicals were analytical grades and used as received.

Formulation table

Hydrogenated soya phosphatidyl choline (HSPC) Tween 80 tween 20

Table 1: formulation code

Formulations	Concentration of Drug (mg)	Concentration of HSPC (mg)	Concentration of Tween 80 (ml)	Concentration of Tween 20 (ml)
F1	40	20	5ml	5ml
F2	40	30	5ml	5ml
F3	40	60	5ml	5ml
F4	40	60	5ml	5ml
F5	40	80	5ml	5ml

Method of preparation of SLNs

VAL-loaded SLNs were prepared by *hot homogenization method*. The lipid was melted at 74-76 ° C (10 ° C) above the melting point of the HSPC used as lipid), and VAL was dissolved in lipid to obtain a drug–lipid mixture. The clear lipid melt containing VAL was added to the hot aqueous surfactant solution (tween 20, Tween 80) preheated to 69 _C above the lipid's melting point under high-shear homogenization at 5000 rpm for 6 min to yield a crude emulsion. The hot nano emulsion obtained was then cooled in ice cool water to recrystallize the lipid back to the solid state in the form of an aqueous SLN dispersion.[6]

Characterizations

UV method for the analysis of drug sample

Preparation of standard stock solution:

Standard drug solution of Valsartan was prepared by dissolving 10mg pure Valsartan in phosphate buffer 6.8 and transferred into 100ml volumetric flask to obtain 10µg/ml of stock solution from which desired concentrations 5, 10,15, 20, 25, 30 µg/ml of solution were prepared.

Preparation of sample solution:

Twenty tablets were weighed; average weight was determined and finely powdered. An accurately weighed quantity of tablet powder equivalent to 10mg of Valsartan was transferred to 100 ml volumetric flask and dissolved by sonication with sufficient quantity of phosphate buffer 6.8, volume was made up to mark. The solution was then filtered through Whatman filter paper no.41. A 1 ml portion of the filtrate was further diluted with phosphate buffer 6.8 in a 10 ml volumetric flask up to mark (10µg/ml) on label claim basis. The absorbance of the resulting solution was measured at 250 nm (method I) and 220 nm (method II) against solvent blank. The results of estimation by proposed method.[7]

Determination of percentage of drug content

1 mL of SLN suspension was pipetted out and dissolved in the methanol. The final volume was made up with methanol and ritonavir content was determined by HPLC at 210 nm (Sudhakar *et al.,* 2016; Raju *et al*., 2014).[8]

Determination of zeta potential, particle size distribution and polydispersity index (PDI) and of SLN

The valsartan loaded SLNs after dilution (1:100) with 0.1 sodium chloride solution was taken in a cuvette and size was measured using HORIBA Nano Z S100, Malvern, UK. The observations of vesicle size were recorded at 90° light scattering angle and 25°C. The ζ was measured based on the mobility of particles (Sudhakar *et al.,* 2016; Raju *et al*., 2014).[9]

Determination of % EE

The percentage of drug entrapped in the lipid is determined by ultrafiltration method using sartorius centrist devices which are equipped with a mem- brane filter at the base of the sample recovery chamber. The unit is centrifuged at 20000 rpm for 15-20 min. The solid lipid nanoparticles along with the encapsulated drug remain in the outer chamber and the aqueous phase is moved into the sample recovery chamber through the membrane. The amount of drug in the aqueous phase is estimated by HPLC at 210 nm using the below equation (Raju *et al*., 2014; Patravale *et al.,* 2003 ; Arjun *et al*., 2013).[10]

Entrapment efficiency = Wt. of drug incorporated/Wt. of drug initially taken × 100

Invitro release studies by dialysis and release kinetics

Cellulose membrane (DM 60 from HI Media, Mum- bai, India, with 12000D) was soaked in pH 7.4 phosphate buffer overnight and 2 mL of SLN sus- pension (equivalent to 4 mg of ritonavir) has taken into dialysis membrane and hanged into a beaker containing pH 7.4 phosphate buffer (500 mL at 37±0.5°C) on magnetic stirrer with 100 rpm using Teflon coated bead. 5 mL of sample was collected at different time intervals from the beaker and the samples were analyzed through HPLC (Sudhakar *et al.,* 2016; Raju *et al*., 2014). The results were fitted to different release kinetic models, i.e., zero order and first order. The drug release mechanism was confirmed with the help of Higuchi's model and Korsmeyer Peppas models.[11]

Preparation of stealth solid lipid nanoparticles

The optimized SLNs formulation subjected for PEGylation to modify into stealth SLN using 10, 20 and 30 mg of DSPE-mPEG-2000 (Sudhakar *et al.,* 2016; Fundaro *et al.,* 2000). The physicochemical evaluation of SLNs was followed same as

above mentioned characterization from section 2.3 to 2.9.[12]

Visualization by field emission scanning electron microscopy (FESEM)

The size of the stealth SLNs was studied by FESEM. Before going to study, the formulations were sputtered with gold for 2 min to make them conducting (Rosa *et al*., 2008).

Drug and excipients compatibility studies FTIR, DSC and XRD studies

The FTIR spectra of compounds were recorded on a Bruker FTIR spectrophotometer using Opus software. Thermal analysis was carried out for ritonavir, triglycerides (tristearin) and SLNs formulations using Pyrus DSC Perkin Elmer with 10°C/min heating rate between 20–240ºC.

Sterilization by two-step technique: lyophilization followed 0.22µm filtration

Two-step sterilization technique was applied for sterilization of tested products before *the in-vivo* study (Raju *et al*., 2014). Lyophilization was carried out for selected conventional SLN, stealth SLNs and pure ritonavir solution using Christ Alpha 1-2 LD Freeze Dryer. 10% w/v sucrose was used as a cryoprotecting agent for selected products. The samples were filtered through 0.22µm EDF filter into a 10 CC vials (PALL life sciences PVT LTD) and closed with half sealed stoppers under aseptic conditions. This process involves three steps. The first sample was cooled to -50°C by adjusting condenser temperature for 3 hrs. This primary drying process was taken for 15hrs whereas the secondary drying process was taken for 6hrs at 20 to 30°C temperature. While running lyophilization cycle, the pressure was maintained around in the range of 200 to 300Torr. After the lyophilization process, the tested lyophilized products were analyzed again reconstitution time, percent drug content, zeta potential, particle size and pH etc.

Stability studies

Stability studies on the optimized formulated patches (F-4) were carried out as per ICH guidelines. Drug content were used to check the stability of the formulation after predetermined time. Samples were withdrawn at the end of 0, 30, 60 and 90 days and evaluated for Drug content.

RESULTS AND DISCUSSION

Selection of lipid

Selection of lipid was done on the basis of maximum solubility of valsartan in different lipids and also on melting point of lipid as the type of drug-lipid matrix and drug release pattern will depend on it. Out of different lipids used, valsartan showed maximum solubility in Hydrogenated soya phosphatidyl choline.

Evaluation of VAL-SLN:

Table 2: entrapment efficiency

Formulations	Concentration of drug (mg)	Concentration of HSPC (mg)	Concentration of tween 80(ml)	Concentration of tween 20 (ml)	Entrapment efficiency
F1	40	20	5ml	5ml	55.1
F2	40	30	5ml	5ml	66.3
F3	40	60	5ml	5ml	71.3
F4	40	60	5ml	5ml	75.8
F5	40	80	5ml	5ml	80.98

Particle size determination

The particle size analysis of the nanoparticulate dispersion by laser diffraction using Horiba nano partica nano particle analyzer SZ-100 showed particle size in the range between 136.5 nm to 267.5 nm. Particle size distribution curve of optimized sample O4 was 136.5nm is shown below

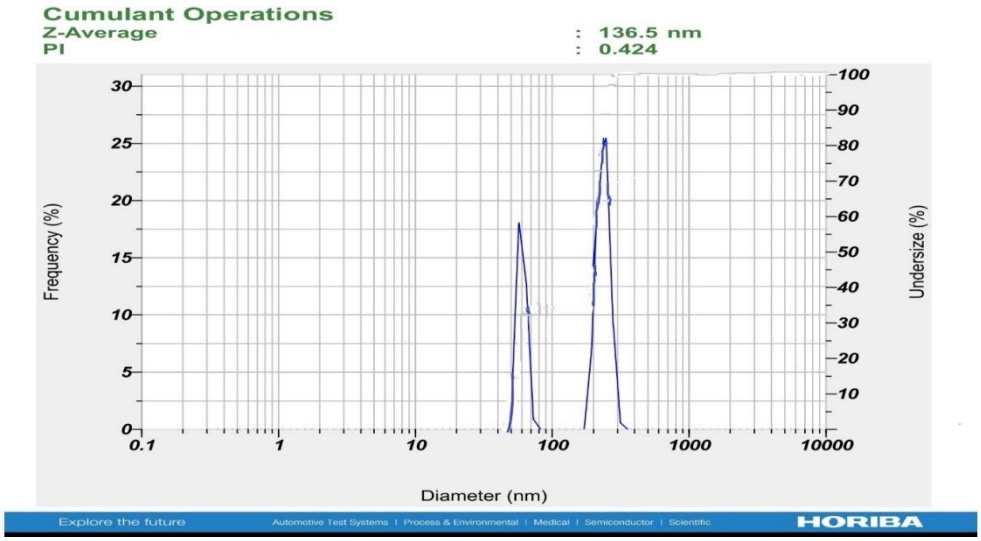

Figure 1: particle size determination graph of formulation F5

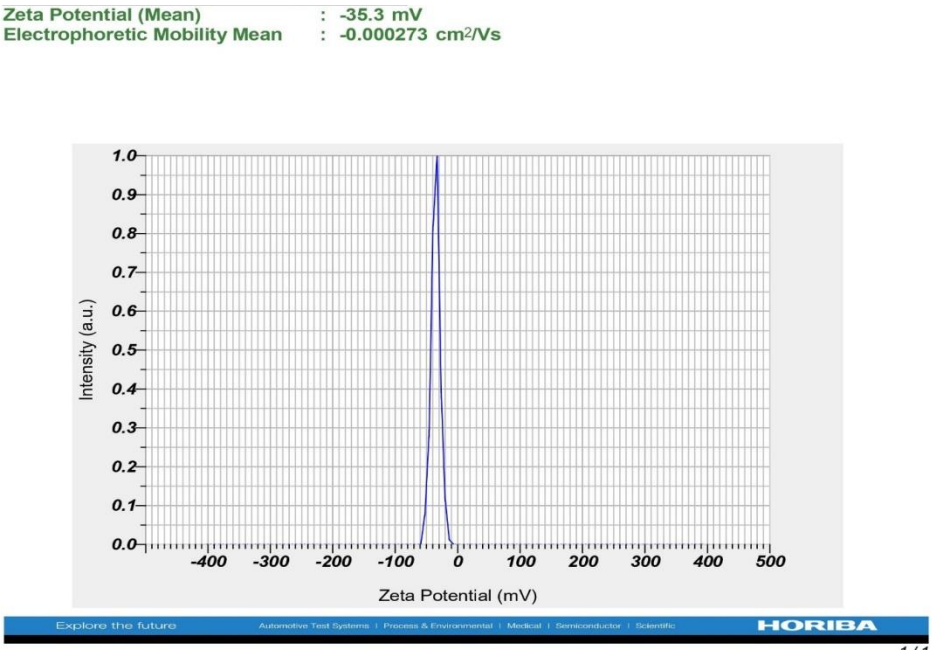

Figure 2: zeta potential determination of formulation F5

Solid state study

Drug content determination

Table 3: drug content determination of the formulations

Formulation	Drug content (%)
F-1	95.0 ± 0.7
F-2	97.0 ± 1.2
F-3	98 .12 ± 0.2
F-4	98.16 ± 1.2
F-5	99.01 ± 0.5

FTIR study

From FTIR study, the characteristic peak of drug such as ketonic C=O stretch (1602 cm-1), acid C=O stretch (1726 cm–1), carboxylic group (-COOH stretch) 3000-3300 cm-1, aromatic and aliphatic (C-H stretch) 2900-3000 cm-1 disappeared and were replaced by the peak of Hydrogenated soya phosphatidyl choline as shown in figure This established drug entrapment in lipid matrix.

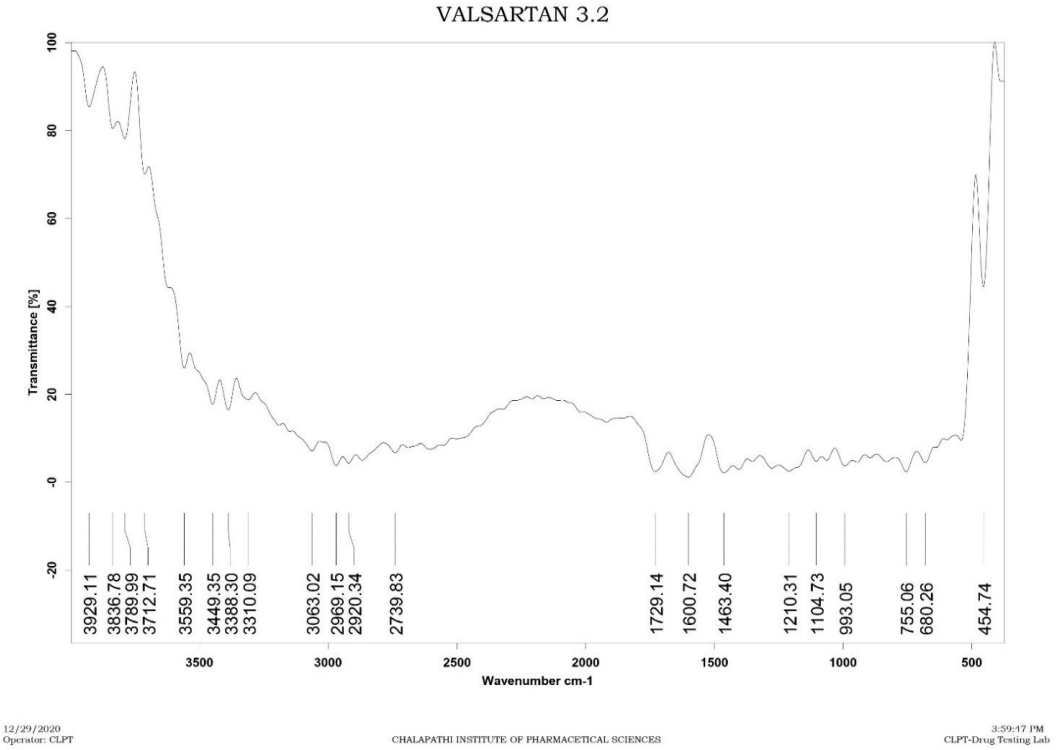

Figure 3: FTIR study of pure drug valsartan

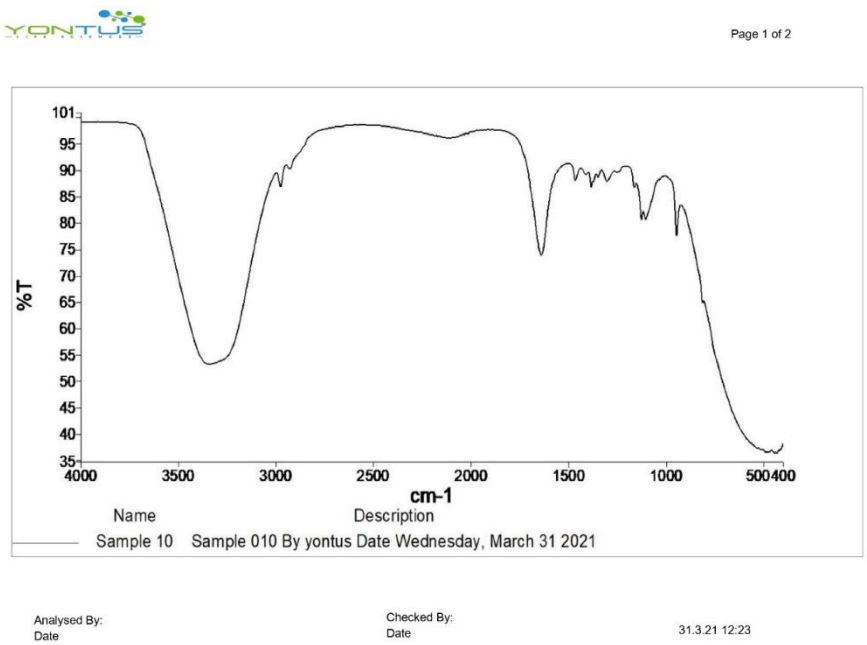

Figure 4: FTIR study of optimized formulation

***In-vitro* drug release of valsartan from SLN**

Release rate study in Phosphate buffer 6.8

Plain drug: Valsartan

The drug release of Valsartan was studied using dialysis bag diffusion technique. The release of Valsartan was studied across the dialysis membrane-50 (Himedia) which was used as synthetic barrier and hydrated with receiver medium before experiments. The drug equivalent to 8mg was transferred to a dialysis bag and sealed. Samples (2ml) were collected at fixed intervals for up to 60min (10, 20, 30, 40, 50 and 60min) and replaced with solvent (2ml). The drug concentrations in the samples were determined by UV Spectrophotometry.

Drug release from V-SLN

The *in vitro* release of Valsartan from different SLN dispersions was determined using the dialysis bag diffusion technique. An accurately weighed amount of Valsartan-loaded SLN dispersions containing the drug equivalent to 8mg was transferred to a dialysis bag and sealed. The sealed bag was then suspended in a beaker containing 250 ml of Phosphate buffer 6.8 and stirred at a constant speed of 50 rpm at 37°C ± 0.5°C. Aliquots were withdrawn at predetermined intervals from the receptor compartment up to 24 hours and the same was replaced with fresh buffer. Then the drug content was determined spectrophotometrically by measuring the absorbance at 250 nm using the respective receptor medium as a blank, to calculate the amount of drug release from nanoparticles.

Table 4: Percent Cumulative Release of plain Valsartan

Time (min)	Cumulative % drug release
10	10.6 ± 1.72
20	18.6 ± 1.59
30	29.9 ± 1.05
40	33.6 ± 2.72
50	39.8 ± 1.76
60	45.2 ± 1.72

Table 5: Percent drug release of Valsartan from nanoparticles in phosphate buffer 6.8 pH

Time (hours)	Cumulative percentage of drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	5.6±0.11	6.7±1.32	7.9±2.57	8.6±1.41	10.28±1.17
2	12.02±0.6	13.7±1.9	14.2±1.36	15.23±2.17	17.71±2.62
3	26.31±0.9	27.6±3.24	28.02±1.13	33.02±1.69	35.01±2.14
6	46±0.1	44.03±2.12	49.03±2.96	49.3±1.63	50.0±1.96
9	50.0±0.1	56.3±2.21	55.03±1.68	59.30±1.21	66.56±1.85
12	53.3±0.22	58.30±1.35	62.8±1.26	65±1.71	71.29±1.46

Percent Cumulative Release curves:

Drug release studies of Valsartan in its pure form and from nano formulation were done in Phosphate buffer 6.8.

The release of V-F 5 SLN was found to be sustained when compared with the plain Valsartan. The formulation showed sustained release maximum up to 72-79% till 12 hours. When compared the release of plain Valsartan and that from the nano formulation at 60 min the nano formulation showed a sustained type of drug release. For application of kinetics to the release study, the release curve was divided in two parts as it showed biphasic behavior. The initial burst release showed zero order kinetics (R^2= 0.76) while the second half of release curve was found to follow a Korsmeyer Peppas model(R^2=0.98).

SEM analysis

The shape and surface morphology of the best formulation was studied by using scanning electron microscopy. The SEM micrograph revealed that the particles were found to be spherical shaped with smooth surface.

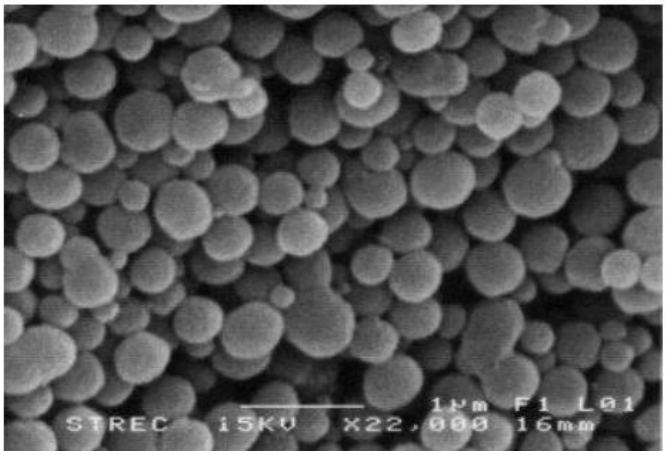

Figure 5: SEM graph of optimized formulation

CONCLUSION

It was found that increase in concentration of lipids in combination with surfactant in formulation shows increase in entrapment efficiency and lower particles size. The initial burst release shown by these nano formulations was due to the drug present on the surface of nanoparticles. When compared the release of plain Valsartan and that from the SLN (F-5) at 60 min the SLN showed a sustained type of drug release compared to plain Valsartan. From the above study it could be concluded that the Valsartan was an ideal candidate for formulating SLN as well as it was compatible with the excipients used. Thus V-SLN prove to be a good drug delivery system to overcome the previously mentioned problems.

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