CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com Research Article

DESIGN AND DEVELOPMENT OF VORICONAZOLE LOADED SOLID LIPID NANOPARTICLES BY QUALITY-BY-DESIGN

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Abstract:

The purpose of this study was to design and development of Voriconazole loaded solid lipid nanoparticles by quality-by-design. Voriconazole loaded solid lipid nanoparticles, was prepared by High pressure homogenization technique, Cold homogenization technique and Solvent emulsification-evaporation technique. Results: Fourier Transform Infra-Red (FTIR) Spectroscopy and differential scanning colorimetry (DSC) reveals there is interaction between drug and formulation excipients. % Entrapment efficiency was found to be 87.5 +2.19. Zeta potential value of more than ±30 is considered the reference value to derive a physical stable dispersion system. The mean particle size of optimized formulation of SLNs showed particle size below 200 nm. Transmission electron microscopy (TEM) particles showed spherical and uniform shape

Key words: Solid lipid nanoparticles, High pressure homogenization technique, Cold homogenization technique and Solvent emulsification-evaporation technique.

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Please cite this article in press Y. Sarah Sujitha et al., Design And Development Of Voriconazole Loaded Solid Lipid Nanoparticles By Quality-By-Design., Indo Am. J. P. Sci, 2026; 13(04).

INTRODUCTION:

SLNs originated in the late 20th century. They were used as a substitute for traditional drug colloidal carriers such as emulsions, liposomes, microemulsions, and other similar formulations containing polymers. Solid lipid nanoparticles were first developed for oral administration28. They lack the toxicity issues associated with lipids and have an industrial-scale production process. They are nanosized drug carriers in lipid form that remain solid at room and body temperature. They can be fabricated in very small sizes, ranging from 50 nm to 500 nm. Due to their smaller size, they have an increased surface area and exhibit high drug loading capacity[1-3].

Solid lipid nanoparticles prepared from biodegradable lipids offers numerous advantages like controlled release, high drug loading, low toxicity and ease of large scale production. The ingredients utilized commonly are solid lipids, surfactants and purified water. The lipids include fatty acids, triglycerides, waxes and steroids4-8.

Nanostructured lipid carriers (NLC), the modified form of solid lipid nanoparticles in which drug in the form of liquid form is encapsulated in lipid matrix are also very popular for brain targeted delivery of drug[9-10].

The potential for a paradigm shift in ocular treatments occurs with the combination of colloidal and in-situ delivery systems which overcome physiological and anatomical limitations of ocular delivery. In terms of improving solubility, stability, targeting, prolonged release, and adaptability, colloidal drug delivery methods are a promising new direction for the pharmaceutical industry. This current review provides an overview of combining in situ gel with niosomes for ocular delivery of many therapeutic agents. An in-depth review has been made focusing on various formulation, characterization, safety, and development prospects of in situ gels loaded with niosomes for ocular administration[11-14].

MATERIALS AND METHODS:

Materials

Voriconazole was received from GSK Pharmaceuticals Ltd., Mumbai, Other chemicals used were of analytical grade.

Methods

High pressure homogenization technique

High pressure homogenization or hot homogenization is a technique in which homogenization of sample takes place at a temperature higher than the melting point of lipid used. In this method first the lipid was melted at a temperature above its melting point. The drug being lipophilic in nature was dissolved in the melted lipid. Another phase containing purified water mixed with surfactant was prepared and heated to the same temperature as that of drug loaded lipid phase. The melted phase was dispersed in hot aqueous surfactant mixture drop wise and homogenised at high speed to make primary o/w type emulsion. This type of primary emulsion has coarse size of particles. This emulsion was again homogenized at high pressure above the temperature of melting point of lipid to convert the coarse emulsion of drug loaded lipid in nanoemulsion form. This hot nanoemulsion was kept a side for some time to cool at room temperature where lipid solidify at room temperature and resultant mixture was filtered through membrane filter to get solid lipid nanoparticles. High temperature during the process decreases the viscosity and produces the smaller size particles but this may also cause the degradation of heat liable drugs. Here, high pressure homogenization increases the sample temperature, approximately by 10 °C at 5 ×107Pa. In most cases, 3–5 homogenization cycles at 5 ×107 Pa to 5 ×109 Pa pressure is sufficient to have better products in hands[15-16].

Cold homogenization technique

The cold homogenization technique is employed in the formulation of solid lipid nanoparticles with an object to overcome the problems associated with the use of hot homogenization method. The hot homogenization methods leads to drug degradation of thermolabile drugs, unwanted lipid transitions states during recrystallization step and loss of drug in aqueous phase232. The first step in the cold homogenization process was same as that of hot homogenization. In this process, lipid was fist melted to a temperature higher than its melting point and drug was dissolved into the melted lipid. The drug loaded lipid phase was cooled and solidified by using dry ice or liquid nitrogen. The precipitated drug loaded solidified particles were coarse in size. The comminution of these particles was performed by using grinding mill to a size range of 50 to 100 µm. The surfactant was dispersed in aqueous phase and the powdered solid particles were dispersed in the surfactant mixture. The mixture was homogenized at high pressure at room temperature or below of that to get solid lipid nanoparticles[17].

Solvent emulsification-evaporation technique

In this method the lipid was first melted above its melting point and drug was dissolved into the melted lipid. The drug-lipid mixture was dissolved completely in an organic solvent by using sonication technique. The surfactant was dissolved in purified water to make an aqueous phase and the water phase was heated to the same temperature as that of lipid phase. The lipid phase was added slowly into hot aqueous phase using high speed mechanical stirring. As the high speed stirring takes pale, the temperature was increased due to the heat generated. Because of increased temperature, the volatile organic solvent gets evaporated and lipid nanoparticles start to precipitate due to low concentration of dispersion medium. These lipid nanoparticles were solidified through cooling at room temperature and filtered through membrane filter. Washed nanoparticles were lyophilized for stable formulation[18]

Determination of entrapment efficiency and drug loading

Entrapment efficiency is the study of drug amount that is encapsulated in the lipid matrix and quantity of drug present in supernatant layer received after the process of centrifugation at very high speed of 16000 rpm for half an hour. The entrapment efficiency is the ratio of actual amount of drug loaded and theoretical amount of drug loaded in lipid nanoparticles. The loading of drug can be measured by subtracting the free drug amount from the total quantity of drug used in the formulation. The entrapment efficiency and drug loading can be calculated using the formulas given below235:

%EE = free drug amount / total weight of drug *100

% Drug loading= drug entrapped in SLNs/ weight of vehicle *100

Dissolution study

The in-vitro release of drug from Voriconazole loaded SLNs was performed using treated dialysis membrane. The SLNs suspension in 1 mL quantity was poured to dialysis tube and sealed. The tube was transferred to a vial having 10 mL of phosphate buffer solution pH 6.4 mixed with 2% tween 80. The sample was subjected to a shaker apparatus maintained at 37±1°C. The speed of strokes was fixed at 5o min-1. The samples in 2 mL quantity from the vial were taken out at time hour of 0, 0.5, 1, 2, 4, 8, 12, 16, 20 &24h. The sink conditions were maintained by replacing the amount of sample with fresh media236. The samples were analyzed by UV spectroscopy method at 291 nm. The release of drug from SLNs was compared with the release of drug from pure drug suspension[18].

X-ray Diffraction (XRD) study

X-Ray diffraction is the measurement of diffraction angle and spacing of lattice in the crystalline sample. Theses diffracted X-Rays were detected and counted. The study was investigated using Panalytical XpertPro Diffractometer. The sample of drug loaded solid lipid nanoparticles were analyzed.

DSC analysis of sample

DSC is a thermal analysis to measure the amount of heat required to increase the temperature of processed sample. This study was performed using DSC instrument. The sample of pure drug, lipid and drug loaded SLNs were analyzed in the temperature range of 0-300°C.

Determination of zeta potential

The zeta potential studies for prepared formulations were carried out utilizing Zeta sizer instrument. For the preparation of sample, the drug loaded solid lipid nanoparticles were diluted with purified water in the ratio of 1:2. The sample were analysed three times and average mean was taken into consideration.

Surface study by Transmission electron microscopy (TEM)

Transmission electron microscopy (TEM) was utilized to evaluate surface characteristics of developed solid lipid nanoparticles. The prepared SLNs dispersion was first diluted with purified water in the ratio of 1:100. The diluted dispersion was filtered through membrane filter of 0.45 µm. The filtered sample was kept on a copper grid coated with carbon. The sample was put on the dried grid mixed with diluted solution of phospho-tungstic acid. The slide was fixed by a cover slip and observed under light microscope[19].

RESULTS & DISCUSSION:

Entrapment efficiency and drug loading

Entrapment efficiency is the study of drug amount that is encapsulated in the lipid matrix and quantity of drug present in supernatant layer received after the process of centrifugation at very high speed of 16000 rpm for half an hour. The entrapment efficiency is the ratio of actual amount of drug loaded and theoretical amount of drug loaded in lipid nanoparticles. The loading of drug can be measured by subtracting the free drug amount from the total quantity of drug used in the formulation. Drug loading end entrapment efficiency of solid lipid nanoparticles were dependent of drug lipid matrix and physico-chemical properties of drug and lipid used in the formulation,

Yield

Yield of the formulation indicates the quantity of solid lipid nanoparticles achieved after the preparation. The yield is expressed as the ratio of lipid present after drying and used initially. The yield was calculated in percentage .

Table 1: % Entrapment efficiency, % drug loading and % yield for optimized Formulation (n=3)

Optimized formulation	%Entrapment efficiency	Drug loading	% Yield
VC-SLNs (**GMS-9**)	87.5 ±2.19	17.50 ±0.43	95.20 ±2.3

Analysis of particle size distribution

The study of particle size and its distribution in the developed formulation is an important tool to give information of existing size range of the particles formed in the formulation. A no. of techniques was employed in the determination of particle size analysis. In current study, the particle analysis in solid lipid nanoparticles was investigated by photon correlation spectroscopy method. Photon correlation spectroscopy reports the data on the basis of intensity using Z average with PDI. The PDI is the representation of "broadness" of particle size distribution. The mean particle size of optimized formulation of SLNs showed particle size below 200 nm. The PDI is also mentioned in the table given below:

Table 2: Particle size, PDI and zeta potential of optimized formulation (n=3)

Optimized formulation	n Particle size (nm)	Polydispersity Index (PDI)	Zetapotential (mV)
VC-SLN(GMS-9)	151.1±10.7	0.172 ±0.07	-40.3±0.8

The optimized batch of Voriconazole loaded solid lipid nanoparticles showed low value of PDI which indicates uniform size distribution in the formulation (Table 17).PDI represents the standard deviation ratio to the particles size and denotes the uniform distribution of particle size through-out the formulation.
The stability of dispersed system depends upon the charge exist on particles. The surface charges of particles are well described with the values obtained of zeta potential (ζ).This parameter is an important one to study the physical stability of the formulation during storage. Zeta potential value of more than ±30 is considered the reference value to derive a physical stable dispersion system. If zeta potential value is less than given value then particles tends to aggregate and cause physical instability. However high zeta potential prevents the aggregation of particles because of repulsion.

Surface morphological studies by Transmission electron microscopy (TEM)

The TEM image of VC-SLN prepared by hot homogenization method using glyceryl monostearate as a lipid was taken. The image is having light background whereas particles seen black against bright background. TEM image of particles showed spherical and uniform shape.

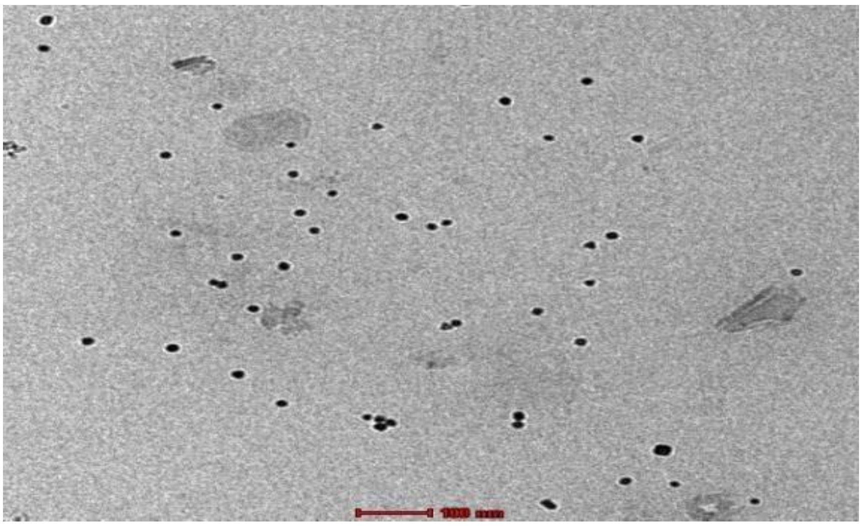

Fig.1: Transmission Electron Microscopy (TEM) image of VC-SLN

Surface topography studies by Scanning electron microscopy (SEM)

This technique involves focused beam of electrons through the surface of sample. These electrons interact with the particles present in the sample and generate signals. The signals produced gave information regarding topography of surface .

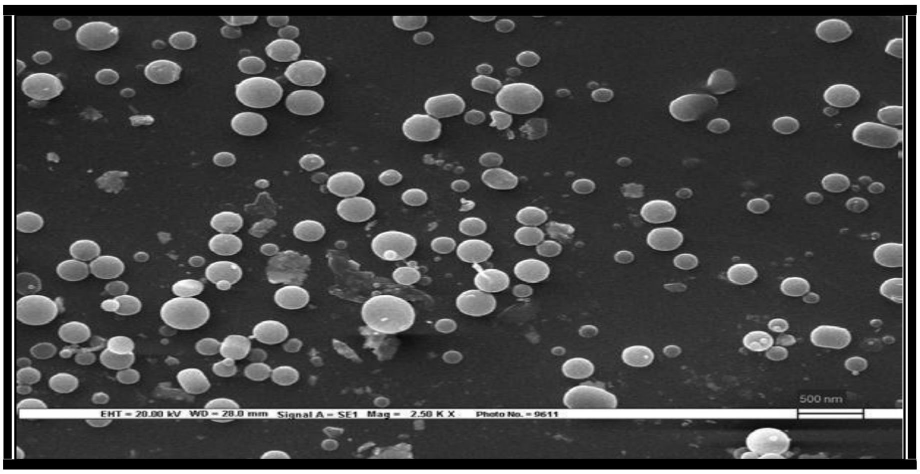

Fig.2: Scanning Electron Microscopy (SEM) image of VC-SLN

Thermal analysis of drug loaded SLNs by DSC and XRD

The polymorphism is an important point of consideration in the characterization of solid lipid nanoparticles. The different polymorphic forms of SLN consider the changes in the physico-chemical properties of drug and lipids like changes in melting point, thermal behaviour etc. It is commonly observed that formulation of solid lipid nanoparticles sometimes lead to such changes which are necessary to identify[260-262]. The thermal analytical technique (DSC) measures the amount of heat required to change the temperature of any material. DSC thermogram gives useful information regarding thermal changes in drug and polymers during formulation development. The DSC thermogram of Voriconazole, glyceryl monostearate taken for blank SLNs and VC- SLNs**.** In thermogram a sharp peak of Voriconazole was observed at 220 °C at its melting point and GMS peak was also observed. The peaks were also indicated in the physical mixture of lipid. The blank SLNs prepared with the lipid alone showed a peak of GMS only. The DSC thermogram of the Voriconazole loaded solid lipid nanoparticles showed that endothermic melting point of drug was almost dispersed which indicate that drug was completely dispersed in lipid matrix of SLNs.

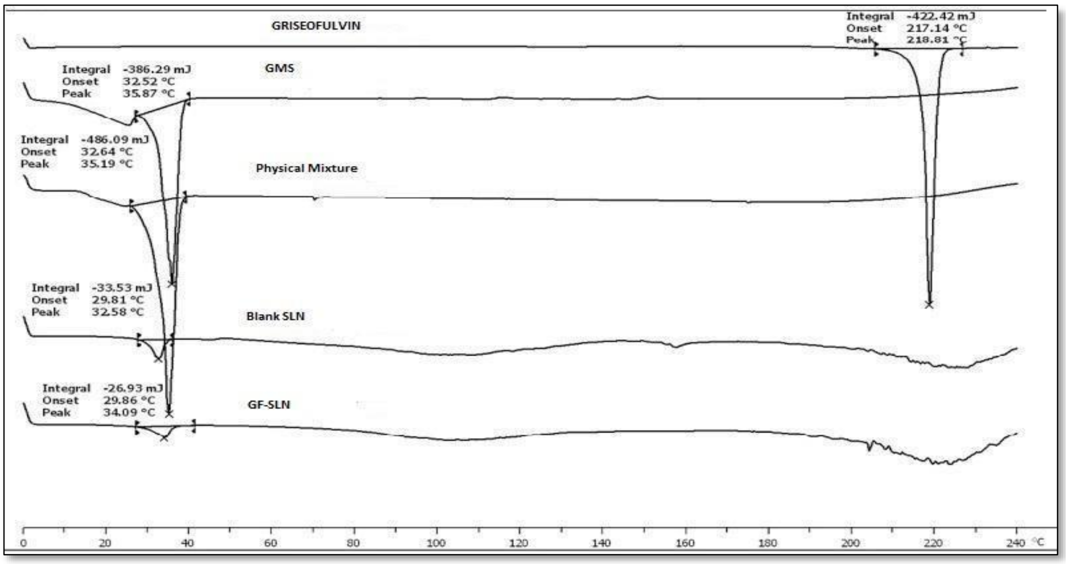

Fig.3: DSC Thermograms showing drug, lipid, blank SLN, VC-SLN

X-ray diffraction (XRD) has been used for the phase identification studies of sample in SLNs formulation[263]. The sharp peak of Voriconazole and glyceryl monostearate shown in XRD pattern of sample proved the crystalline nature of the drug and lipid. The crystalline peak of drug and lipid almost disappeared in developed Voriconazole containing solid lipid nanoparticles. This proved the encapsulation of drug in the lipid matrix which was quite difficult to explore in the pattern at molecular level. Hence no separate crystals of drug and lipid were found besides drug lipid matrix.

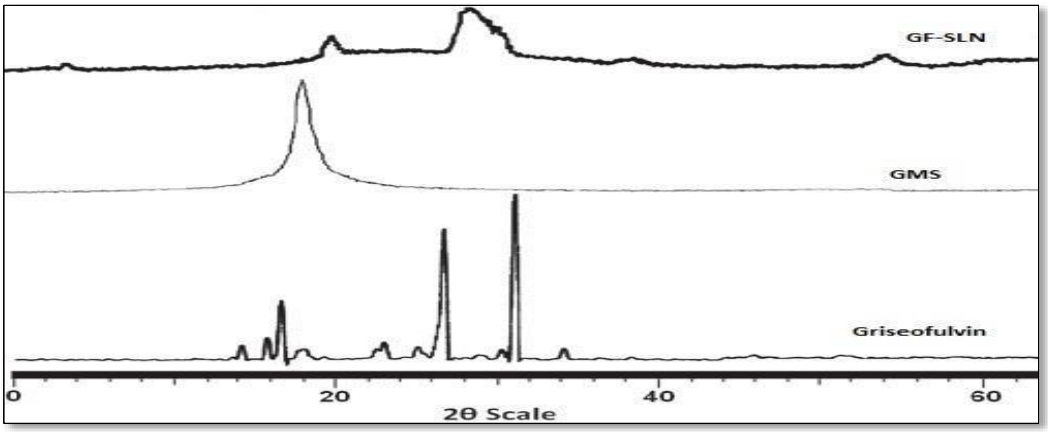

Fig.4: XRD pattern showing drug, lipid and VC-SLN

In-vitro dissolution study for VC-SLNs

The in-vitro release of drug from Voriconazole loaded SLNs was performed using treated dialysis membrane. The in-vitro dissolution studies were investigated using phosphate buffer pH 6.4 mixed 2% tween 80 as surfactant. The SLNs suspension in 1 mL quantity was poured to dialysis tube and sealed. The tube was transferred to a vial having 10 mL of phosphate buffer solution pH 6.4 mixed with 2% tween 80. The sample was subjected to a shaker apparatus maintained at 37±1°C. The speed of strokes was fixed at 50 min^{-1}. The samples in 2 mL quantity from the vial were taken out at time hour of 0, 0.5, 1, 2, 4, 8, 12, 16, 20 &24 h. The sink conditions were maintained by replacing the amount of sample with fresh media[236]. The samples were analyzed by UV spectroscopy method at 291 nm. The release of drug from SLNs was compared with the release of drug from pure drug suspension. The concentration of drug was calculated by extrapolating of curve and by making a graph between times

versus % cumulative release.

The in-vitro studies concluded that the maximum release (98.23%)for pure drug suspension was obtained in 4 hrs. the solid lipid nanoparticles exhibited the extended release of drug and release 33.64% of drug in 4 hrs. The initial burst release of drug loaded solid lipid nanoparticles was observed which may be due to deposition of certain amount of drug at the surface of developed SLNs. On subsequent studies, the drug loaded solid lipid nanoparticles showed a sustained release of drug. The cumulative percentage of drug released was 89.47% for a time period of 24 hrs. In the later stage of dissolution profile of SLNs showed slow release of drug from lipid matrix through the mechanism of diffusion and dissolution. The result obtained from the drug loaded SLNs was found to be matched with the reported data of drug release of a lipophilic drug encapsulated in lipid matrix from SLNs.

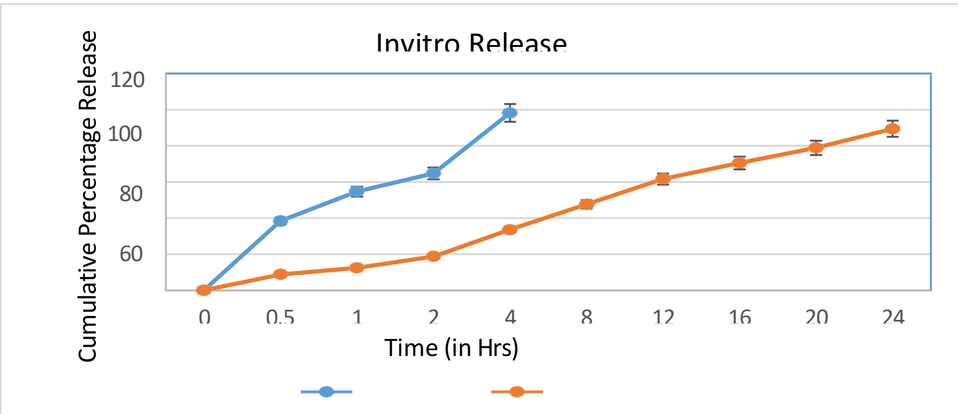

Fig.5: In-vitro release pattern showing release profile of pure drug suspension and Voriconazole loaded SLNs

CONCLUSION:

The current research proved that solid lipid nanoparticles are an adaptable technology that has the potential to enhance the solubility of poorly water-soluble drugs listed in BCS class II. Voriconazole is a lipophilic drug whose oral bioavailability is limited due to poor aqueous solubility. Solid lipid nanoparticles are nano lipid carriers that encapsulate lipophilic drugs in the lipid matrix. The SLN approach was used to increase the solubility and oral bioavailability of Voriconazole. The solid lipid nanoparticles containing Voriconazole were prepared by the hot homogenization method after method optimization. Glyceryl monostearate was used as a lipid, Tween 80 as a surfactant, and PVA as a stabilizer in the formulation. The prepared formulation batches were analyzed for particle size, polydispersity index, drug entrapment efficiency, drug loading, zeta potential, and yield. The drug-to-lipid ratio was set at 1:5, with surfactant concentration at 4% and stabilizer at 1% after optimizing the formulation variables. The optimized batch of VC-SLNs was found to be stable in accelerated stability studies at room temperature. In-vitro release studies showed extended drug release from drug-loaded SLNs over 24 hours.

ACKNOWLEDGEMENT
The corresponding author desires to explicit utmost gratitude to the Management and Prof. Dr. D. Ranganayakulu, M. Pharm., Ph. D., Principal, Sri Padmavati school of pharmacy, Tiruchanoor, Andhra Pradesh, India, for presenting all the necessary laboratory demands of the review and constant support.

Conflict of Interest
The authors declare no conflict of interest, financial or otherwise.

Funding Support
The authors declare that they have no funding for this study

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