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International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Formulation and Evaluation of Solid Lipid Nanoparticles of Sertraline Hydrochloride

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ARTICLE INFO

Article history:

Received: 01 October, 2020

Revised: 19 February, 2021

Accepted: 27 February, 2021

Published: 30 March, 2021

Keywords:

Blood-brain Barrier,
Depression,
Sertraline hydrochloride,
Solid lipid nanoparticles.

DOI:

10.25004/IJPSDR.2021.130206

ABSTRACT

Depression is a global affective and common mental disorder, with over 264 million people experiencing it. It is characterized by depressed mood, loss of interest, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. A new class of colloidal delivery system has been introduced that encompasses a number of advantages over the conventional dosage forms and one of it includes the solid lipid nanoparticles (SLN) with the major advantage of been controlled and site-specific drug delivery. It is made up of a solid core and phospholipid shell having high drug loading to enhance bioavailability. Sertraline hydrochloride is an antidepressant drug used for brain targeting. The main objective of the work was to formulate Sertraline hydrochloride-loaded solid lipid nanoparticles and to screen the effect of formulation with process variables on the performance of these formulated solid lipid nanoparticles. Hot homogenization technique was used to formulate the solid lipid nanoparticles using of 3^2 factorial designs. The effect of independent variables on the concentration of Poloxamer 188 and Glyceryl monosterate on viscosity and drug release was studied. SLNs containing sertraline hydrochloride were prepared and evaluated. The results depicted F6 as an optimized formulation with an entrapment efficiency of 87.36 ± 1.45% and a drug release of 84.26 ± 1.10%. With the thorough screening study, the enrichment of Sertraline hydrochloride entrapment was attained with good particle size and controlled release. The factorial design confirmed its influence and significance in determining and understanding both formulation and process variables affecting the quality of SLNs.

Introduction

Depression is a mental illness characterized by a pathologically depressed mood. Depression is a common illness worldwide.[1] It is different from mood swings and leads to the serious health condition. A person who is affected by depression shows poor progress in his work and exhibits a suicidal tendency. Many people die annually due to suicide. Depressive episodes are of three types: mild, moderate, and severe depressive episodes based on the severity of disorder.[2] There are varieties of drugs that are used for the treatment of depression, and Sertraline HCl is one of the drug of choice for it. It is in the selective serotonin reuptake inhibitors (SSRIs) class and could cross the blood-brain barrier (BBB) to achieve its antidepressant effect. It is also used to treat panic disorder, social anxiety disorder, post-traumatic disorder.[3] The BBB is one of the toughest barriers, maintains the homeostasis of the brain, and the treatment of the brain disease possesses a challenge due to the hurdles involving the transport of the drugs to the brain. To overcome disadvantages of the conventional treatment, nanocarriers in the form of SLN are being explored for the treatment of depression.[4]

Solid lipid nanoparticles are solid colloidal particles that range from 10 to 1000 nm. To achieve controlled and site-specific drug delivery SLNs are a great choice. SLNs show advantages over the other conventional formulations, such as better drug stability, high drug loading capacity, and the use of organic solvent are avoided.[5] As these are submicron colloidal carriers, they

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

possess unique properties as small size, large surface area, high drug loading and avoids the limitations of polymeric nanoparticles, fat emulsions, and liposomes.[6] In this study, SLN has been prepared by the hot homogenization method using sertraline hydrochloride as a model drug. The formulation parameters like surfactant concentration of poloxamer 188 and lipid glyceryl monostearate (GMS) concentration were optimized to formulate a robust and stable formulation. These two parameters have an impact on the formulation of stable SLN formulation. Thus, the aim of the present study was to develop sertraline hydrochloride solid lipid nanoparticles and based on particle size, entrapment efficiency, viscosity, and drug release of SLN, an optimum system was intended.

Materials and Methods

Materials

Sertraline HCl was obtained from Wockhardt, Aurangabad, India. Glyceryl monostearate was obtained from Research Labs Fine Chem Industries, Mumbai. Poloxamer 188 was purchased from Ana Lab Fine Chemicals, Mumbai, India. Tween 80 was obtained from Loba Chemie Pvt. Ltd, India as a surfactant. Loba Chemie Pvt kindly supplied triethanolamine. Ltd, India. HPLC Grade ethanol (S D fine Chemicals, Mumbai, India) was used.

Table 1: Independent variables with their levels for optimization studies

		Levels	
Independent variables (mg)		*-1*	*+1*
Concentration of poloxamer 188	A	100	500
Concentration of glyceryl monosterate (GMS)	B	200	500

Table 2: Optimization design for the formulation of Solid lipid nanoparticles

Batch No.	*Factor 1 (A)*	*Factor 2 (B)*
1	-1	-1
2	0	-1
3	+1	-1
4	-1	+1
5	0	+1
6	+1	+1
7	-1	0
8	0	0
9	+1	0

Methods

Selection of Solid Lipid

The solid lipid was selected based on the solubility of the drug in melted lipid. Lipids used for this study were glyceryl monostearate, stearic acid, cetyl palmitate. The required quantity of the drug was taken and added to the melted lipid in a water bath in 10mL glass vials. The solubility of the drug was determined.

Formulation of Solid lipid Nanoparticles

Preparation of SLN Design Expert Software was used for the optimization of the formula. A 3^2 Factorial design was selected. The independent variables include the concentration of poloxamer 188 and tween 80 to check the effect on particle size and drug release. Independent variables and their corresponding levels are shown in Table 1.

The hot homogenization method was used for the preparation of sertraline hydrochloride-loaded SLNs. GMS and the drug were mixed with ethanol to form the lipid phase. In distilled water Poloxamer 188 and Tween 80 were added to form the aqueous phase. Both phases were heated up to 65°C. The lipid phase was added drop-wise into the aqueous phase and was subjected to homogenization at 3000 rpm for 30 minutes. The final pH was adjusted by using triethanolamine.[7,8] formula for the preparation of all SLN loaded with sertraline HCl formulation is shown in Table 2 and Table 3.

Characterization of SLN

pH measurement

The pH of the formulation was measured by using a pH meter CyberScan pH 510 Eutech Instruments, India. A 1 g of SLNs was dissolved in 100 mL of distilled water. After the calibration was done, the glass rod was inserted into the SLN solution, and the pH was recorded.

Viscosity

Table 3: Formulation table for solid lipid nanoparticles

Ingredients	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
Sertraline Hcl	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Poloxamer 188	100mg	300 mg	500 mg	100 mg	300 mg	500 mg	100 mg	300 mg	500 mg
Glyceryl monosterate	200 mg	200 mg	200 mg	500 mg	500 mg	500 mg	350 mg	350 mg	350 mg
Tween 80	0.05gm	0.05gm	0.05gm	0.05gm	0.05gm	0.05gm	0.05gm	0.05gm	0.05gm
Triethanolamine	0.2mL	0.2mL	0.2mL	0.2mL	0.2mL	0.2mL	0.2mL	0.2mL	0.2mL
Ethanol	5mL	5mL	5mL	5mL	5mL	5mL	5mL	5mL	5mL
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

The viscosity of the formulation was determined with an Ostwald Viscometer. A certain amount of water was introduced into the large bulge of the viscometer and pulled by pipette until the slight bulge was full. The viscometer was placed vertically in a water bath at a 10–40°C temperature.[9] Water is allowed to flow through the capillary tube until it reaches the bottom mark. The experiment was repeated, and then results were recorded. The experiment was repeated for the other formulations by using the same procedure, and viscosity was determined.

Particle Size

The particle size of SLN was determined using a digital microscope. The microscope was calibrated using a stage micrometer. A drop of SLN was spread on a glass slide with the help of a dropper, and images were captured using Pixel Pro software.[10]

Drug Entrapment Efficiency

The entrapment efficiency of the drug in SLNs was determined by quantifying the amount of free drug in the

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Mass of drug in submicron particles}}{\text{Mass of drug used in formulation}} \times 100 \quad \text{...(eq-1)}$$

A 10mg of freeze-dried sertraline HCl-loaded SLN was dissolved in 5 mL of ethanol. A 1mL of the above solution was diluted to 10 mL with phosphate buffer of pH 7.4 and filtered using 0.45 µm membrane filters. A UV spectrophotometer recorded the absorbance of the filtered solution at 273 nm.[11]

In vitro Drug Release Studies

In vitro drug release study of the optimized sertraline, HCl loaded SLNs was carried out by using cellophane membrane. Vertical Franz diffusion cells were used. Apparatus consists of receptor compartment and donor compartment. The receptor compartment was filled with phosphate buffer of pH 6.8 to the mark of a cell. The cellophane membrane was dipped into hot water. The donor compartment is the upper part of the cell. The receptor compartment containing phosphate buffer of pH 6.8 was maintained at a temperature of 37 ± 5° C., and it is subjected to magnetic stirrer. A 5 mg of SLN dispersion was placed on the cellophane membrane, and a sample was withdrawn from the receiver compartment at a pre-determined time interval. The receptor compartment was replenished with fresh water after every withdrawal. After every withdrawal sample was diluted to 10 mL. Samples were analyzed by using UV Spectrophotometer at 273 nm. Drug release was then calculated and stated.[12]

Results and Discussions

Selection of Lipid

Generally, SLN contains lipids that remain solid at room temperature and body temperature. The lipid content in SLN shows the improved permeability of the drug. The choice of the lipid was mainly based on the solubility of the drug in lipid as the higher the solvent capacity is, the higher potential will be for the drug loading.[13] Thus, in this study, the drug showed the highest solubility in glyceryl monostearate; hence it was selected for further study, which is a formulation of solid lipid nanoparticles.

pH

The pH of the nanoparticles was in the range of 7.3 ± 7.5.

Particle Size

The particle size analysis reveals the size of nanoparticles on a nano scale. It was found that the concentration of lipid affected the particle size of the nanoparticles. As the concentration of lipid increased, the particles tended to aggregate, and the particle size was observed. This experience might be due to the melting point of the lipid, as GMS has a higher melting point that results in slower lipid crystallization from the hot homogenized condition that results in an increase in the particle size. The particle size was found in between 183 ± 8 to 402 ± 17 nm.[14]

Entrapment Efficiency

The results indicated that the lipid concentration has a critical effect on the sertraline HCl incorporation efficacy. The entrapment efficiencies were found be good in the range of 41.6 ± 6.72 to 84.3 ± 4.02 %. It showed better entrapment efficiency of sertraline Hcl loaded SLN's.[15]

Experimental Design and Statistical Analysis

A 3^2 factorial design was preferred for the study to evaluate the effect of the independent variables on the response, with the least number of experimental runs.

Multiple Regression Analysis

To predict the value of the response and study the effect of variables on response, it is necessary to fit a mathematical model that predicts the value of response that generates polynomial equations, that is useful for evaluation of the SLN results

$$Y = k + b\,1A + b\,2B + b\,12AB + b\,11A2 + b\,22B2 \quad \text{...(EQ-2)}$$

Where Y is the response evaluated, k is the intercept; b_1 to b_{22} is the five coefficients of independent variables.

Effect on Viscosity

The model F-value of 5.47 implies the model is significant. There is only a 2.29% chance that an F-value this large could occur due to noise. A *p*-value less than 0.0500 indicates model terms are significant. In this case, B is a considerable model term. Values greater than 0.1000 indicate the model terms are not significant. Adeq Precision measures the signal-to-noise ratio. A ratio greater than 4 is desirable. The ratio of 8.698 indicates an adequate signal. This model can be used to navigate the design space. A final equation in terms of coded factors

Table 4: ANOVA analysis on viscosity

Source	*Sum of squares*	*df*	*Mean square*	*F-value*	*p-value*	
Model	7.17	5	1.43	5.47	0.0229	significant
A-CON OF POLOXAMER 188	2.28	1	2.28	8.72	0.0213	
B-CONC OF GMS	2.44	1	2.44	9.30	0.0186	
AB	0.67	1	0.67	2.59	0.1515	
A^2	1.44	1	1.44	5.49	0.0517	
B^2	0.98	1	0.98	3.75	0.0940	
Residual	1.83	7	0.26			
Cor Total	9.01	12				

Table 5 : Value of R^2 for viscosity

Std. Dev.	0.51	R^2	0.7963
Mean	4.95	Adjusted R^2	0.6508
C.V. %	10.33	Predicted R^2	0.8690
		Adeq Precision	8.6981

Expressed as mean ± SD, *n*=3.

$$\text{Viscosity} = +4.90 - 0.6170\,A - 0.6373\,B + 0.4120 + 0.72157A^2 - 0.5965B^2 \ldots\ldots\ldots(EQ\text{-}3)$$

Final equation in terms of actual factors

Viscosity = +7.12665-0.018714 CON OF POLOXAMER 188 +0.0101CONC OF GMS +0.00014 CON OF POLOXAMER* CONC OF GMS +0.00018 CON OF POLOXAMER 188^2-0.000027 CONC OF GMS^2

The positive sign before a factor in the regression equation indicates that the response increases with the factor and vice versa. ANOVA Analysis on viscosity is shown in Table 4. Table 5 shows the value of R^2 for viscosity. Figs. 1 and 2 indicate the surface plot and counter-plot for viscosity.

Effect on *in vitro* Drug Release Studies

The model F-value of 5.47 implies the model is significant. There is only a 2.29% chance that an F-value this large could occur due to noise. *p*-values less than 0.0500 indicate model terms are significant. In this case, B is a considerable model term. Values greater than 0.1000 indicate the model terms are not significant. Adeq Precision measures the signal-to-noise ratio. A ratio greater than 4 is desirable. ANOVA analysis on drug release is shown in Table 6.

The ratio of 5.665 indicates an adequate signal. This model can be used to navigate the design space. The value of R2 factor for drug release was shown in Table 7. A final equation in terms of coded factors,

$$\text{Drug release} = +71.14 - 4.47\,A + 2.60\,B - 1.43 + 8.247A^2 + 13.39B^2 \ldots\ldots\ldots (EQ\text{-}4)$$

Final Equation in Terms of Actual Factors

Drug release = +158.206-0.0129 CON OF POLOXAMER 188 -0.3849 CONC OF GMS -0.00048 CON OF POLOXAMER* CONC OF GMS +0.00020 CON OF POLOXAMER 188^2-0.000595 CONC OF GMS^2

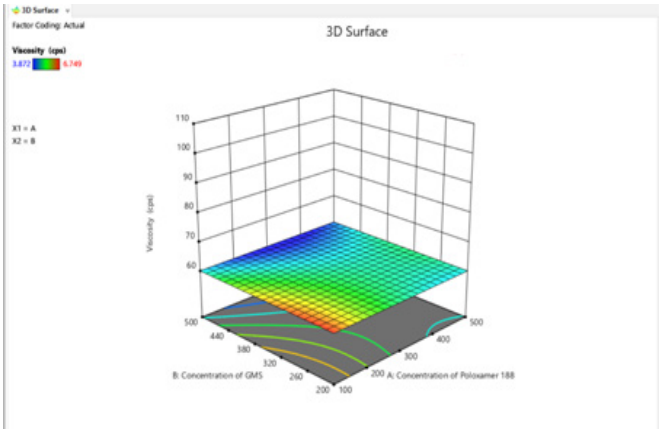

Fig. 1 : Three- dimensional response surface plot for viscosity

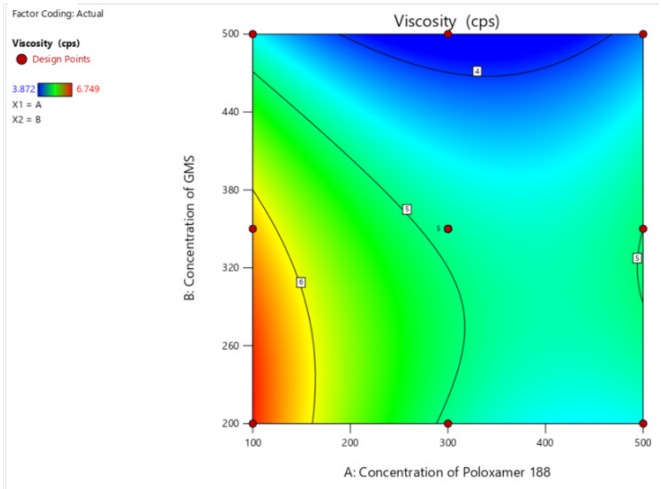

Fig. 2: Contour plot for viscosity

The percent drug release for sertraline HCl was between 80.41 ± 5.2 to 96.09 ± 0.06 that depended on the concentration of the lipid and surfactant. The results depicted that increase in the concentration of surfactant enhanced the release of the drug, while the opposite was observed for lipid. The response plot for drug release is shown in Fig. 3. The small size of nanoparticles with surfactant formulation might have enhanced the wetting, solubilization, permeability, and dissolution of soluble surfactants to form pores in the matrix might have played a role for consistent and enhanced release of the drug.[16]

Table 6: ANOVA analysis on drug release

Source	*Sum of squares*	*df*	*Mean square*	*F-value*	*p-value*	
Model	1238.79	5	247.76	4.04	0.0480	significant
A-CON OF Poloxamer 188	119.62	1	119.62	1.95	0.2051	
B-CONC OF GMS	40.56	1	40.56	0.66	0.4427	
AB	8.24	1	8.24	0.13	0.7248	
A^2	187.44	1	187.44	3.06	0.1238	
B^2	495.42	1	495.42	8.08	0.0249	
Residual	429.05	7	61.29			
Cor Total	1667.83	12				

Table 7: Value of R^2 for Drug release

Std. Dev.	7.83	R^2	0.7428
Mean	81.13	Adjusted R^2	0.5590
C.V. %	9.65	Predicted R^2	1.4611
		Adeq precision	5.6651

Table 8: Factorial design variables with their responses

Formulation	*Factor 1 (A)*	*Factor 2 (B)*	*pH*	*Viscosity (cps)*	*Particle size (nm)*	*Entrapment efficiency (%)*	*Drug Release (%)*
F1	-1	-1	7.4	4.01 ± 0.01	183 ± 8	56.16 ± 2.21	52.4 ± 0.91
F2	0	-1	7.52	4.30 ± 0.09	186 ± 10	60.26 ± 2.28	55.43 ± 2.21
F3	+1	-1	7.39	3.87 ± 0.04	185 ± 5	59.26 ± 0.45	57.16 ± 1.37
F4	-1	+1	7.51	6.79 ± 0.06	402 ± 17	78.60 ± 1.54	71.8 ± 0.62
F5	0	+1	7.55	6.74 ± 0.09	394 ± 14	81.98 ± 3.9	73.46 ± 1.25
F6	+1	+1	7.43	6.86 ± 0.13	394 ± 19	87.36 ± 1.45	84.26 ± 1.10
F7	-1	0	7.53	4.95 ± 0.32	303 ± 16	70.33 ± 1.76	62.4 ± 2.43
F8	0	0	7.51	5.24 ± 0.05	297 ± 13	65.23 ± 1.61	63.03 ± 0.86
F9	+1	0	7.59	5.07 ± 0.19	315 ± 13	68.86 ± 1.88	64.96 ± 2.04

Data are expressed as mean ± SD, *n* = 3.

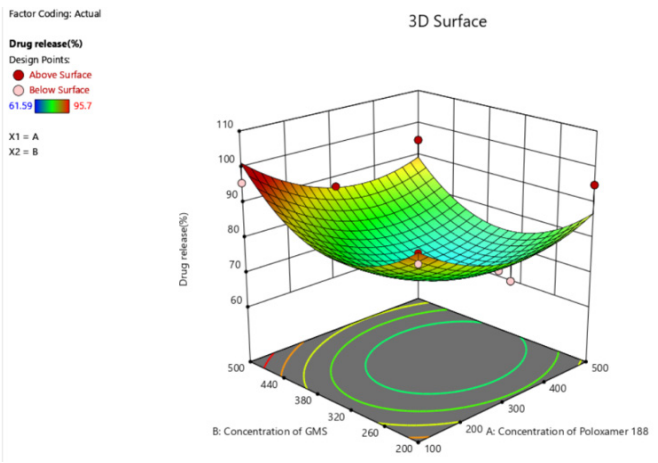

Fig. 3: Three-dimensional response surface Plots For drug release

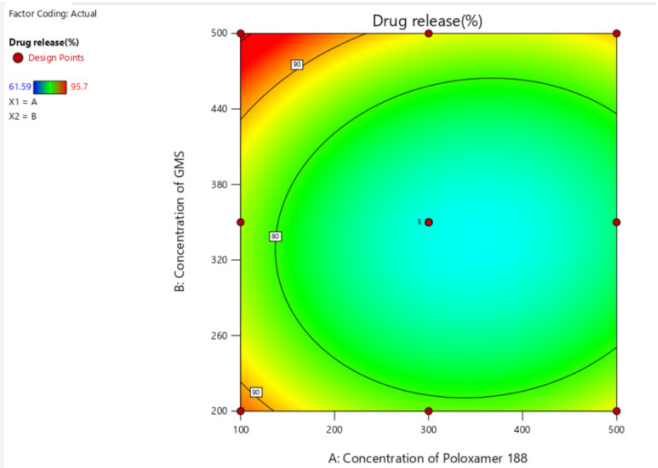

Fig. 4: Contour plot for drug release

The effect of selected independent variables concentration of Poloxamer 188 and concentration of GMS significantly influenced the observed responses for viscosity, particle size, entrapment efficiency EE (%), drug release DL (%) that are presented in Table 8.

Selection of Optimized Formula

To obtain correlation between the independent and dependent variables, experiments were optimized for the responses. An optimized formulation was selected based on the results of the evaluation tests. Thus, the optimized

formulation was F6 which had a viscosity of 6.86 ± 0.13cps and drug release of 84.26 ± 1.10%. The counter-plot for drug release is shown in Fig. 4.

Conclusion

In this, study, solid lipid nanoparticles containing sertraline HCl were prepared successfully for encapsulation of the drug by using lipid GMS and poloxamer 188. The formulation and process variables showed a significant effect on the fabrication of solid lipid nanoparticles. The i*n vitro* release studies confirmed a suitable percentage of drug release from the formulation F6. Besides, the prepared SLNs had good particle size, entrapment efficiency. From this observation, it can be concluded that the SLNs were widely accepted. Thus, the findings concluded that the developed SLN could be used as a potential carrier for prolonged drug delivery, leading to reduced dosing and side effects.

Acknowledgment

The authors are thankful to the Wockhardt Pharmaceuticals, Aurangabad, Research lab Fine Chem Industries, Mumbai, AnaLab Fine Chemicals, Loba Chemie Pvt.Ltd.The authors are also thankful to LNCT, University Bhopal for providing facility to carry out research work.

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HOW TO CITE THIS ARTICLE: Hangargekar SR, Mohanty PK, Jain A. Formulation and Evaluation of Solid Lipid Nanoparticles of Sertraline Hydrochloride. Int. J. Pharm. Sci. Drug Res. 2021;13(2):152-157. **DOI:** 10.25004/IJPSDR.2021.130206