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OPTIMIZATION OF AN ANTIDEPRESSANT DRUG LOADED SOLID LIPID NANOPARTICLES BY HOT HOMOGENIZATION TECHNIQUE WITH 3^2 FACTORIAL DESIGNS

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Abstract

A revolutionary type of colloidal pharmaceutical delivery system has been invented, and in comparison, to the conventional dosage forms, it provides a number of benefits that cannot be found with the other options. Solid lipid nanoparticles, also known as SLN, offer a number of benefits, one of which is the ability to administer medications in a controlled and location-specific manner because to their utilisation. It is made up of a solid core and possesses a substantial drug content in its phospholipid cover up both of which contribute to boost its bioavailability. Additionally, the shell contains phospholipids. It is estimated that more than 200 million people around the world are afflicted with depression, which makes it the most widespread form of mental and emotional illness in the world. The symptoms of this illness include reduced concentration, a depressed mood, a loss of excitement in things that were previously enjoyable, feelings of shame or inadequate worth, disruptions in sleep or eating, and an inability to focus. Antidepressant drug containing sertraline monohydrate has the ability to target particular regions of the brain. To look into the impact which the formulation of those solid lipid nanoparticles possessed, in addition to the impact that the process variables had, on the efficacy of such established solid lipid nanoparticles was the primary objective of this work. Additionally, the formulation of strong lipid nanoparticles which were loaded with sertraline hydrochloride was one of the process variables that was investigated. In order to manufacture the solid lipid nanoparticles, a hot homogenization method was used, and 3^2 distinct factorial designs were incorporated into the research. In this study, the effects of various independent parameters on the amount of poloxamer 188 and glyceryl monosterate, as well as the effects of these factors on viscosity and drug release, were investigated. In order to evaluate the efficacy of the SLNs that were manufactured, they were loaded with sertraline hydrochloride. According to the data, the formulation known as SNF6 was the one that was the most successful. It had an entire entrapment efficiency of 91.32 ±2.35% and a drug release of 89.45 ±2.35% respectively. Enrichment of sertraline was accomplished by HCl entrapment, resulting in an adequate particle size and controlled release, as a direct result of the exhaustive screening inquiry. The factorial design was able to illustrate either the significance of it and it influence in determining and grasping the formulation and execution of the factors that influence the quality of SLNs. This was accomplished via the use of factorial arrangements.

Keywords: Sertraline hydrochloride, Poloxamer 188, Glyceryl monosterate, Solid lipid nanoparticles, Depression

INTRODUCTION

Nanoparticles of solid lipids is solid particles with colloidal structure that have a size that varies from between 10 and 1000 nm. SLNs are an excellent alternative if you want to accomplish controlled and site-specific medication delivery [1]. SLNs have a number of benefits that set them apart from other conventional formulations, including improved drug stability, an elevated drug loading capacity, and the elimination of the need for a solvent that is organic. Due to the fact that these are also submicron colloid carriers, they have distinctive characteristics such as a tiny size, a large surface area, and a high drug loading. Additionally, they circumvent the restrictions that are associated with nanoparticles made of polymers, fat formulations, and liposomes that [2]. In the present investigation, lipid nanoparticles that were solid were produced by the heat homogenization method. The medicine sertraline hydrochloride served as a model for the substance. In order to create a formulation that is both reliable and stable, the formulation parameters, such as the concentration of the surfactant poloxamer 188, and the concentration of the lipid glyceryl monostearate (GMS), were optimised. Both of these characteristics have an influence on the process of formulating stable lipid nanoparticles that are solid [3]. Therefore, the purpose of this study was to develop solid lipid nanoparticles containing sertraline hydrochloride. In addition, an optimal system was planned to be designed on the basis of the size of the particles, entrapment efficiency, the viscosity and release of drugs using solid lipid nanoparticle [4].

A clinically depressed mood is the defining characteristic of the mental disease known as depression. Depression is a condition that is widespread throughout the world. Mood swings are not the same thing as this illness, which leads to a dangerous health problem. A person who is depressed is unable to make progress in his or her work and is more likely to consider ending their own lives. Each year, a significant number of people take their own lives [5]. There are three levels of depressive episodes that correspond to the severity of the underlying disorder: moderate, severe, and mild depressive episodes. Some of the drugs that is most successful for treating depression is called sertraline HCl, and there are many different types of pharmaceuticals that are used to treat depression. It belongs to the class of drugs known as selective reuptake inhibitors of serotonin (SSRIs), and in order for it to have an antidepressant effect, it must be able to pass through the blood-brain barrier, also known as the BBB [6]. In addition, it is utilised in the treatment of panic disorder, post-traumatic stress disorder, and social anxiety disorder. The blood-brain barrier (BBB) represents one of the most formidable barriers; it is responsible for preserving the equilibrium state of the cerebral cortex, and the management of brain diseases is difficult due to the obstacles that must be overcome in order for medications to be delivered to the cerebral cortex [7]. Nanocarriers are in the kind of lipid nanoparticles that are solid are now being investigated for their potential use for the management of depression. This is being done in an effort to mitigate the drawbacks of the standard treatment.

In its chemical form, sertraline hydrochloride can be written as (1S,4S)-4-(3,4-Dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine. Solubility of Sertraline HCl is that it is Soluble in DMSO (>25.0 mg/ml), ethanol (10.0 mg/ml), water (3 mg/ml), 0.1N HCl (0.5 mg/ml), isopropyl alcohol (4.3 mg/ml), chloroform (110.0 mg/ml), and dimethylsulfoxide (147.0 mg/ml) [8]. Sertraline has a half-life that ranges

from 24 to 32 hours in children, adolescents, and adults. Sertraline is slowly absorbed into the body, with its maximum concentration (Cmax) occurring between 4 and 10 hours after administration of the drug. The amount of sertraline that is in circulation has been calculated to be greater than 20 litres per kilogramme. It is widely dispersed. Clearance of a sertraline dose of 200 milligrammes per kilogramme of body weight ranged between 1.09 and 0.38 litres per hour per kilogramme of patient age in pharmacokinetic investigations [9]. These studies included individuals of varying ages.

MATERIALS AND METHODS

Materials

Hetero pharmaceuticals Ltd. in Hyderabad was the source of the sertraline HCl that was used. Poloxamer 188 and glyceryl monostearate were both procured through S D fine Chemicals in Mumbai, India. Loba Chemie Pvt. Ltd. in India provided us with the Tween 80 that we used as a surfactant. Triethanolamine was generously given by Loba Chemie Pvt. Ltd. in India, where it was utilised as a surface-active agent. We used HPLC Grade ethanol that was manufactured by S D fine Chemicals in Mumbai, India. The water that was distilled was acquired by a process that involved double distillation in the lab.

Methods

Selection of Solid Lipid

The drug's ability to dissolve in the liquid state of the lipid was taken into consideration when choosing the solid lipid. Glyceryl monostearate, stearic acids, and cetyl palmitate were the types of lipids that were utilised for this study. After measuring out the needed amount of the medication, it was poured into glass vials containing 10 millilitres of liquid lipid and melted in a water bath. It was determined whether or not the substance was water-soluble [10].

Method of preparation of Solid lipid Nanoparticles

The optimisation of the method was accomplished with the help of Fabrication of Solid Lipid Nanostructures Designs Expert Software. We decided to go with a 32-factorial design. The concentrations of the poloxamer 188 compound and tween 80, respectively, are examples of the independent variables that were tested to determine their influence overall the size of particles and drug release. The levels of the independent variables as well as the variables themselves are presented in Table 1.

In order to prepare the SLNs that were loaded with sertraline hydrochloride, the procedure of heat homogenization was utilised. In order to create the lipid phase, GMS and the medication were combined with ethanol and stirred. The aqueous phase was formed by adding the combination of Poloxamer 188 as well as Tween 80 to the water that had been distilled first. Both stages were brought to a temperature of 65 degrees Celsius. The lipid portion was incorporated to the water phase in a drop-by-drop fashion before being homogenised at a speed of 3000 rpm for a period of 30 minutes [11]. Triethanolamine was utilised in order to achieve the desired end pH. Tables 2 as well as 3 present the formula that should be used for the manufacture of every single solid nanoparticles of lipid loaded with sertraline HCl.

Table 1: For optimization studies, independent variables with their levels

Independent variables (mg)		Levels	
		-1	+1
Concentration of poloxamer 188	A	200	1000
Concentration of glyceryl monosterate (GMS)	B	400	1000

Table 2: Optimization design of Solid lipid nanoparticles formulations

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

Table 3: Formulation table for solid lipid nanoparticles

Ingredients	SNF_1	SNF_2	SNF_3	SNF_4	SNF_5	SNF_6	SNF_7	SNF_8	SNF_9
Sertraline HCl	100	100	100	100	100	100	100	100	100
Glyceryl Monosterate	400	400	400	1000	1000	1000	700	700	700
Poloxamer 188	200	600	1000	200	600	1000	200	600	1000
Triethanolamine	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Tween 80	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Ethanol	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml
Water	qs	qs	qs	qs	qs	qs	qs	qs	qs

Characterization of solid lipid nanoparticles (SLNs) pH measurement

In order to determine the pH for the formulation, a pH metre manufactured by Eutech Instruments in India was utilised. The SLNs, which weighed 1 g in total, were dispersed in one hundred millilitres of distilled water. Following the completion of the calibration, the transparent rod was placed within the SLN the solution, then the pH was then measured [9, 10].

Measurement of Viscosity

An Ostwald Viscometer was utilised in order to ascertain the formulation's level of viscosity. A measured quantity of water was poured into the larger bulge of the viscometer, and a pipette was used to draw the liquid out until the smaller bulge was completely filled. The viscometer was submerged in the water bath at a temperature ranging from 10 to 40 degrees Celsius in a vertical position. The water is allowed to

continue moving along the capillary tube unless it reaches the mark that indicates the bottom of the tube. The experiment was carried out multiple times, and each time, the outcomes were documented. The study was repeated with the other formulations, and the same process was followed in order to get an accurate reading of the viscosity [11, 12].

Table 4: Viscosity study by ANOVA analysis

Source	*Sum of squares*	*df*	*Mean square*	*F-value*	*p-value*	
Model	7.25	5	1.42	5.48	0.0225	
Concentration of Poloxamer 188 (A)	2.35	1	2.24	8.77	0.0214	
Concentration of glyceryl monosterate (B)	2.52	1	2.46	9.32	0.0188	**Significant**
AB	0.72	1	0.68	2.60	0.1516	
A²	1.54	1	1.45	5.52	0.0518	
B²	0.95	1	0.99	3.80	0.0942	
Residual	1.88	7	0.28	--	--	
Corrected Total Sum of Squares	9.26	12		--	--	

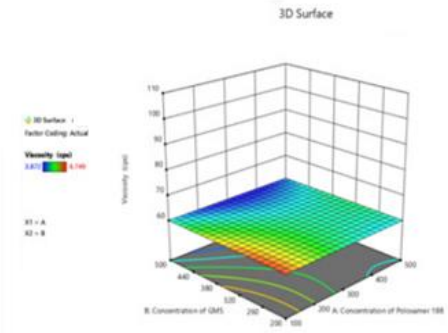

Figure 1: Three- dimensional response surface plot of formulations for viscosity

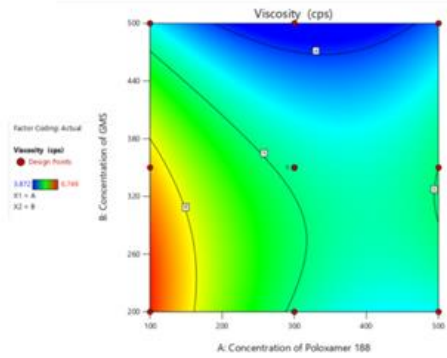

Figure 2: Contour plot of formulations for viscosity

Table 5: Drug release study by ANOVA analysis

Source	*Sum of squares*	*df*	*Mean square*	*F-value*	*p-value*	
Model	1238.45	5	247.65	4.26	0.047	
Concentration of Poloxamer 188 (A)	119.45	1	119.29	1.90	0.206	
Concentration of glyceryl monosterate (B)	40.68	1	40.51	0.59	0.445	**Significant**
AB	8.35	1	8.38	0.15	0.725	
A^2	187.76	1	187.50	3.26	0.124	
B^2	495.27	1	495.79	8.28	0.026	
Residual	429.78	7	61.37			
Corrected Total Sum of Squares	1667.39	12				

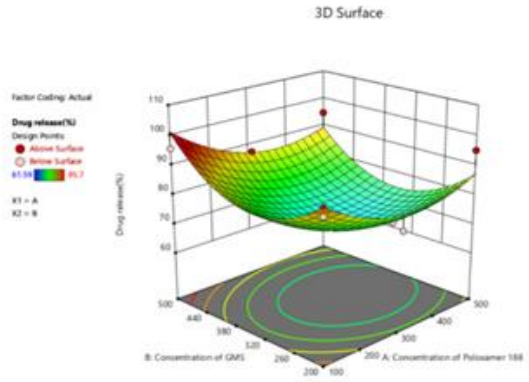

Figure 3: Three-dimensional response surface Plots of formulations for drug release

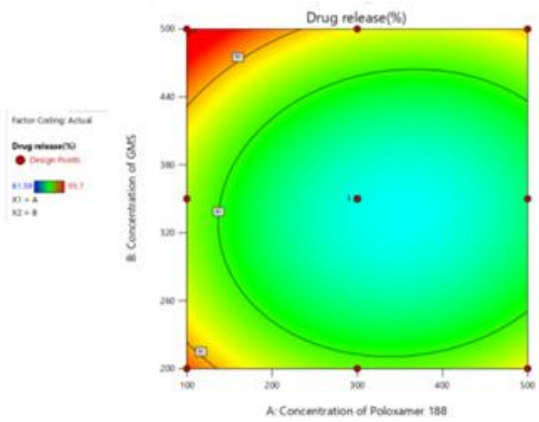

Figure 4: Contour plot of formulations for drug release

Table 6: Characterization responses with their factorial design variables

Formulation	*Factor 1 (A)*	*Factor 2 (B)*	*pH*	*Entrapment efficiency (%)*	*Particle size (nm)*	*Drug Release (%)*	*Viscosity (cps)*
SNF1	-1	-1	7.24	59.23 ± 1.45	167 ± 5.01	62.32 ± 1.46	3.23 ± 0.03
SNF2	0	-1	7.35	62.34 ± 1.53	154 ± 4.35	66.26 ± 1.25	3.34 ± 0.04
SNF3	+1	-1	7.42	61.41 ± 1.62	175 ± 3.37	68.45 ± 1.76	2.45 ± 0.05
SNF4	-1	+1	7.36	79.52 ± 1.32	365 ± 5.23	72.37 ± 1.28	4.36 ± 0.03
SNF5	0	+1	7.32	82.20 ± 1.52	336 ± 4.25	75.37 ± 2.46	4.65 ± 0.04
SNF6	+1	+1	7.31	91.32 ± 2.35	345 ± 6.41	89.45 ± 2.35	4.25 ± 0.09
SNF7	-1	0	7.25	72.47 ± 2.01	267 ± 4.65	71.21 ± 1.76	2.42 ± 0.10
SNF8	0	0	7.34	67.37 ± 2.23	253 ± 6.45	74.15 ± 1.67	3.15 ± 0.09
SNF9	+1	0	7.44	65.54 ± 2.21	236 ± 4.55	76.52 ± 1.86	4.32 ± 0.18

Particle Size measurement

A digital microscope was utilised in order to ascertain the SLN particle size distribution. A stage micrometre was utilised in the process of calibrating the microscope. A few

drops of SLN were dispersed across a slide made of glass with the assistance of a dropper, while the photos were acquired using the help of the programme known as Pixel Pro. [13, 14]

Drug Entrapment Efficiency

Assessing the quantity of drug that is free in the formulations was one of the methods that was used to determine the encapsulation efficiency of the medication in SLNs.

$$\text{Entrapment efficiency} = \frac{Mass\ of\ drug\ in\ submicron\ particles}{Mass\ of\ drug\ used\ in\ the\ formulation} \times 100$$

Ethanol containing five millilitres was used to dissolve ten milligrammes with freeze-dried sertraline HCl-loaded SLN. After diluting the solution to a volume of 10 millilitres with phosphate buffer having a pH of 7.4, it was filtered through membrane filters having a thickness of 0.45 micrometres. The absorbance for the filtered solution was measured with a UV spectrophotometer at a wavelength of 273 nm. [15, 16]

In vitro Drug Release Studies

An in vitro drug release test of optimal SLNs comprising sertraline HCl has been carried out by using cellophane membrane as the drug release medium. The inclined Franz diffusion cells were the primary point of emphasis. The device features not just a donor compartment but also a receptor compartment as one of its components. The phosphate buffer having a pH of 6.8 was utilised so that the receptor compartment could be totally stuffed up to the point where a cell would be marked. After being submerged in the boiling water for a short while, the cellophane membrane was removed. The donor compartment is located in the very topmost section of the cell. The temperature of the compartment containing the receptors, which has a phosphate buffer at a pH of 6.8 and is being swirled with a magnetic stirrer, was maintained at 37 degrees Celsius, give or take five degrees. The magnetic stirrer was used to stir the contents of the receptor compartment. After placing a dispersion containing 5 mg of SLN on top of the cellophane membrane and waiting the prescribed amount of time, a sample was removed from the cellophane membrane and placed within the receiver compartment. After single extraction, the water source within the compartment that houses the receptors was replenished with fresh water. This was done after each time the receptors were removed. Following the completion of each withdrawal, the material that was collected was subsequently diluted to a total amount of 10 millilitres. During the course of the analysis of the materials, a UV spectrophotometer with a 273 nm setting was utilised. After that, the computation of the medication release was then carried out, and the findings were presented [17, 18].

Results and Discussions

Selection of Lipid

In most cases, SLN will contain lipids that can be solidified at both room temperature and the temperature of the body. The increased permeability of the medication is demonstrated by the presence of lipids in SLN. When selecting the lipid, the ability to dissolve of the medication in the lipid was the primary factor to be considered. This is because the larger the solvent capacity, the more the potential there is for the drug loading. Because of this, the medication was shown to be most soluble in glyceryl

monostearate during the course of this research; hence, this particular formulation containing solid lipid nanoparticles was chosen for more investigation as a result.

pH measurement

The pH associated with the nanoparticles was found to be in a relatively narrow range, ranging from 7.24 to 7.44. That suggests something that is moderately fundamental and nearly consistent from one formulation to the next.

Particle Size measurement

The size of the particles analysis provides information on the dimensions the nanoparticles on a nanoscale. It was discovered that the quantity of lipid in the nanoparticles had an effect on the size of the particles of the nanoparticles. Particles had a tendency to gather together, and the size of the aggregated particles could be determined when the amount of lipid increased. This phenomenon may be attributable to the lipid's melting point. GMS having a melting point that is greater than other materials, which leads to delayed lipid crystallisation from the hot homogenised condition. This, in turn, causes a rise in the particle size. The size of the particles was measured to be anything from 154 ±4.35 to 365 ±5.23 nm.

Drug Entrapment Efficiency

According to the findings, the amount of lipid present has a significant bearing on the amount of sertraline HCl that is incorporated into the system. It was discovered that the entrapment efficiencies were satisfactory within the range of 59.23 ±1.45 to 91.32 ±2.35%. It demonstrated an improvement in the entrapment efficiency of sertraline loaded SLNs.

Experimental Design and Statistical Analysis

In order to analyse the impact of each of the variables that are not dependent on the response with the fewest possible number of experimental runs, it was decided that a 3^2-factorial design would be the most appropriate for the investigation.

Multiple Regression Analysis

It is important to develop a mathematical model which predicts the value of response and generates polynomial equations, which are helpful in the evaluation of the SLN results, in order to examine the impact of variables on response and to be able to forecast the value of the response. This can be accomplished by fitting the mathematical model which predicts the value of response.

Effect on Viscosity

Given that the model has an F-value of 5.48, it may be concluded that the model is noteworthy. An F-value of this magnitude occurring as a result of random noise has just a 2.28% chance of happening. If the p-value is lower than 0.05, this suggests that the model's terms are significant. In this particular instance, B is a significant model term. When looking at the model terms, values that are more than 0.1 imply that they are not significant. The signal-to-noise ratio is something that adequate Precision measures. It is preferable to have a ratio that is bigger than 4. A sufficient signal can be determined from the ratio of 8.425. Using this paradigm, one may move more easily through the design space. A concluding equation expressed in terms of factor coding.

Effect on *in vitro* Drug Release Studies

Given that the model has an F-value of 4.26, it may be concluded that the model is noteworthy. An F-value of this magnitude occurring as a result of random noise has just a 2.28% chance of happening. p-values below 0.05 suggest that the model parameters are significant. In this particular instance, B is a significant model term. When the variables in the model are not significant, the value must be bigger than 0.10 to show this. The signal-to-noise ratio is what is measured by adequate precision. It is preferable to have a ratio that is bigger than 4. Table 6 presents the results of an ANOVA study conducted on medication release. A sufficient signal can be determined from the ratio of 5.468. Using this paradigm, one may move more easily through the design space. Table 5 displayed the value of the R^2 factor for medication release.

The percentage of drug released for sertraline HCl ranged from 62.32 ±1.46 to 89.45 ±2.35 and was dependent on both lipid and surfactant concentrations. According to the findings, a rise in the amount of the surfactant improved the rate at which the medicine was released, but the converse was seen in the case of the lipid. Figure 3 provides a representation of the response plot of medication release. Because of their small size, nanoparticles formulated with surfactants may have improved wetting, solubilization, permeability, which is and dissolution of soluble surfactants, which may have contributed to the formation of pores in the matrix, which in turn contributed to the enhanced and consistent release of the medication.

The effect of chosen independent factors, such as the quantity of the Poloxamer 188 and the concentration of GMS, had a substantial influence on the responses that were observed for viscosity, size of particles, efficiency of entrapment EE (%), drug release, and drug loading (%), which are provided in Table 6.

Selection of Optimized Formula

Experiments were designed to maximise responses in order to determine whether or not there was a correlation among both independent and dependent variables. Following the completion of the evaluation tests, a formulation that is optimised for performance was chosen. Therefore, the formulation that was optimised was SNF6, that exhibited a viscosity of 4.25 ±0.09 cps and a drug release that was 89.45 ±2.35%. Figure 4 depicts the alternative plan for the distribution of the medicine.

Conclusion

By utilising lipid GMS with poloxamer 188, the researchers in this work were able to successfully produce solid lipid nanoparticles that contained sertraline HCl for the purpose of encapsulating the medicine. When it came to the production of solid lipid nanoparticles, the formulation as well as the method variables appeared to have a substantial effect. Studies conducted in vitro on drug release indicated that the formulation F6 allowed for an adequate amount of medication to be released. In addition to that, the SLNs that were prepared had a satisfactory particle size and entrapment effectiveness. It is possible to draw the inference that the SLNs received favourable reviews as a result of this observation. As a result of these observations, the researchers came to the conclusion that the produced SLN might be utilised as a possible conduit for longer drug delivery, which would result in less dosing and fewer adverse effects.

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