

Formulation and Evaluation of Selfmicroemulsifying Drug Delivery System Ofhaloperidol

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ABSTRACT: The objective of the present research work was to formulate Self-microemulsifying drug delivery system of Haloperidol for the treatment of Schizophrenia. By using 3^2 full factorial design optimization of Haloperidol SMEDDS was done. Spectrometric analysis of Haloperidol was done by using a UV-Visible Spectrophotometer and Drug-Excipients compatibility study was conducted by Fourier Transform Infrared Spectroscopy. Oil, Surfactant, and Co-Surfactant were selected based on the results of a solubility study for the formulation of SMEDDS, while the ratio of Surfactant to Co-Surfactant (S-mix) was determined through a pseudo ternary phase diagram study. 3^2 full factorial design was applied using Design Expert 13.5 software. Concentration of Oil (X1) and Ratio of S-mix (X2) were chosen as an independent variable, while Globule size (Y1), Emulsification time (Y2) and % Drug release (Y3) were selected as dependent variables. All nine microemulsions were evaluated for different parameters such as pH, Viscosity, Cloud point, % Drug content, % Transmittance, Globule size and Polydispersity index (PDI), Emulsification time and % Drug release. A checkpoint was prepared and evaluated for the validation of the model. Optimized SMEDDS was subjected to a stability study under accelerated conditions for one month. Percentage drug release of optimized batch is higher as compared with the marketed formulation. So, it concluded that SMEDDS formulation is best to improve the solubility of poorly water-soluble drug like Haloperidol. Hence, a clear and stable Liquid SMEDDS of Haloperidol was formulated successfully.

KEYWORDS: Schizophrenia, Haloperidol, SMEDDS, 3^2 full factorial design, Liquid SMEDDS.

I. INTRODUCTION

Schizophrenia is a chronic several mental disorder that affects the way of person thinks, acts,

express emotions, observes reality and relates to other. It may result in a mix of hallucinations, delusions, and disorganized thinking and behavior. Hallucinations involve seeing things or hearing voices that aren't observed by others. Delusions involve firm beliefs about things that are not true. People with schizophrenia often have problems functioning in society, work, school, and relationships. People with schizophrenia can seem to lose touch with reality, which can make daily living very hard. so, they need lifelong treatment. This includes medicine, talk therapy and help in learning how to manage daily life activities. SMEDDS are isotropic mixtures of Oils, Surfactants and Co-Surfactants, which form Oil-in-water micro emulsion in aqueous media under gentle agitation. The finely divided Oily droplets, with a droplet size less than 50 nm, provide a large surface area for drug release and absorption. When such a system reaches in the lumen of the gastrointestinal (GI) tract, it disperses to form a fine emulsion (micro/nano) with the aid of GI fluid. This leads to in situ solubilization of drug that can subsequently be absorbed by lymphatic pathways, thus bypassing hepatic first-pass effect. Haloperidol is an antipsychotic agent used to treat schizophrenia and other psychoses, as well as symptoms of agitation, irritability, and delirium. Haloperidol is BCS Class-II drug having low water solubility (0.00446mg/ml). Haloperidol is extensively metabolized in the liver. Mechanism of action of haloperidol is blocks post-synaptic dopamine (D2) receptors in the brain, eliminating dopamine neurotransmission and leading to the relief of delusions and hallucinations that are commonly associated with psychosis.

Advantages of SMEDDS

- Improvement in solubility
- Improvement in oral bioavailability
- Stability
- Storage
- Patient Compliance

- No Effect of food
- Quick onset of action

Limitations of SMEDDS

Although SMEDDS formulation has several advantages, there are certain limitations associated with this system are given below:

- Drug precipitation on dilution
- Encapsulation in soft gelatin capsule
- Limited targeting to lymphatics

II. EXPERIMENTAL WORK

Method of formulation of SMEDDS^[7]

Preparation involves adding the drug to the mixture of Oil, Surfactant, and co-Surfactant, followed by vertexing. In some case the drug dissolve in one of the excipients and the remaining excipients are added to the drug solution. The solution must then be properly mixed and inspected for signs of cloudiness. After equilibrating for 48 hours at room temperature, the solution should be heated to a clear solution if necessary. Key considerations in SMEDDS formulation include assessing the drug's solubility in various Oils, Surfactants, and co-Surfactants, selecting excipients based on the drug's solubility, and preparing the formulation by dissolving the drug in a blend of Oil, Surfactant, and Co-Surfactant. The SMEDDS mixture can be filled in either soft or hard gelatin capsules.

Material:

Haloperidol was purchased from Yarrow Chem Products, India. Capryol 90, Gelucire 44/14, Transcutol HP, Labrasol, Maisine CC and Capmul MCM were gift samples from Gattefosse, France. Oleic acid, Tween 80, Propylene glycol and PEG 400 were provided by Astron Chemicals, India.

Preformulation study of Drug^{[8][9]}:

- 1) Characterization of organoleptic characteristics of drug: Haloperidol was evaluated for colour, odour, nature and appearance.
- 2) Determination of melting point of drug: The melting point of drug was measured using Veego melting point apparatus. A small amount of drug was put into a capillary tube, which was sealed at one end. This tube was then placed inside the apparatus. The temperature at which the drug started to melt was carefully noted and recorded.
- 3) FT-IR study: The IR spectral analysis of Haloperidol was performed using a Fourier Transform Infrared (FT-IR) spectrophotometer

(Shimadzu 8400s, Japan). The sample was scanned over a wavelength range of 600 to 3800 cm^{-1} , and the FT-IR spectrum of Haloperidol was recorded.

Spectroscopic analysis of Haloperidol^{[10][11]}:

Haloperidol was analyzed using UV-Visible spectrophotometry.

Preparation of Standard stock solution in methanol:

A precise amount of 10 mg of Haloperidol was weighed and added to a 10 ml volumetric flask containing methanol to prepare a primary stock solution with a concentration of 1000 $\mu\text{g/ml}$. From this solution, 1 ml was taken and transferred to another 10 ml volumetric flask. Methanol was added to make the total volume 10 ml, resulting in a secondary stock solution with a concentration of 100 $\mu\text{g/ml}$.

- Calibration curve of Haloperidol in methanol: 0.2, 0.4, 0.6, 0.8, 1, up to 1.6 ml of secondary stock solution were taken and diluted up to 10 ml with methanol to get 2 $\mu\text{g/ml}$, 4 $\mu\text{g/ml}$, 6 $\mu\text{g/ml}$, 8 $\mu\text{g/ml}$, 10 $\mu\text{g/ml}$, up to 16 $\mu\text{g/ml}$ respectively. The absorbance of each solution were measured at 247 nm against methanol as blank.

Preparation of standard stock solution in pH 1.2 acidic buffer:

A precise amount of 10 mg of Haloperidol was weighed and added to a 10 ml volumetric flask containing methanol to create primary stock solution with a concentration of 1000 $\mu\text{g/ml}$. From this solution, 1 ml was taken and transferred to another 10 ml volumetric flask. It was then diluted to 10 ml using a pH 1.2 buffer, resulting in a secondary stock solution with a concentration of 100 $\mu\text{g/ml}$.

- Calibration curve of Haloperidol in pH 1.2 acidic buffer: 0.2, 0.4, 0.6, 0.8, 1, up to 1.6 ml of secondary stock solution were taken and diluted up to 10 ml with pH 1.2 buffer to get 2 $\mu\text{g/ml}$, 4 $\mu\text{g/ml}$, 6 $\mu\text{g/ml}$, 8 $\mu\text{g/ml}$, 10 $\mu\text{g/ml}$, up to 16 $\mu\text{g/ml}$ respectively. The absorbance of each solution were measured at 249 nm against pH 1.2 acidic buffer as blank.

Solubility study^[12]:

To determine the solubility of Haloperidol in various Oils, Surfactants and Co-Surfactants, an excess amount of drug was added to 2 ml of selected oils, surfactants and co-surfactants. The mixture was blended using a vortex mixer and

centrifuged at 3000 rpm for 15 minutes. After centrifugation, the clear liquid (supernatant) was collected and filtered. The concentration of Haloperidol was measured using UV spectrophotometer at 247 nm and methanol was taken as blank.

Drug Excipient compatibility study:

The infrared spectra of Haloperidol with mixture of excipients was recorded on Fourier transformed infrared spectrophotometer (Shimadzu 8400s, Japan). Sample was scanned between the range of 600-3800 cm^{-1} .

Preparation of Liquid SMEDDS^[13]:

Based on the solubility studies, a series of SMEDDS formulations were developed using Capryol 90 as an Oil phase, Tween 80 as a Surfactant, and PEG 400 as a Co-Surfactant. Throughout all the formulations, the Haloperidol concentration remained constant at 20 mg. The procedure involved dissolving Haloperidol in the oily phase at 40°C under magnetic stirring until a clear solution archived. Then, a mixture of Surfactant and Co-Surfactant (Smix) was added to the oil phase, and the blend was carefully stirred, mixed using a vortex mixer, and heated to a temperature of 37±0.5°C. A total 9 different liquid formulations were prepared, each with varying concentrations of Oil and concentrations of Surfactant and Co-Surfactant.

Construction of pseudo ternary phase diagram^[14]:

Pseudo ternary phase diagram was used to confirm the microemulsion region. Pseudo ternary phase diagram was constructed using the phase titration method to confirm the microemulsion region. Based on solubility studies, Oil phase and the mixture of Surfactant and Co-Surfactant were used. Various weight ratios of Surfactant and Co-Surfactant (Smix), such as 1:1, 1:2, 1:3, 2:1, 3:1 were tested. Each Smix ratio was then combined with oil in different proportions, ranging from 1:9 to 9:1 (oil: Smix). Water was added dropwise to each mixture while stirring with a magnetic stirrer until the mixture became turbid, and the required amount of water was recorded. The concentrations of components were plotted on a pseudo ternary phase diagram using Chemix School software 13.5 to effectively illustrate the phase behavior.

Optimization of SMEDDS by using 3² full factorial design^[15]:

Once the responses have been measured, various models such as simple linear, interactive and quadratic can be developed using multiple regression analysis. F statistics are used to determine the significant terms in the model.

Linear equation: $Y = b_0 + b_1X_1 + b_2X_2$

Interactive equation: $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2$

Quadratic equation: $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$

Here, the dependent variable is represented by Y, the mean response over the 9 runs is indicated by b_0 , and the predicted coefficient for the factor X_i is indicated by b_i . The average result when changing one factor separately from its low to high level is shown by the main effects (X_1 & X_2). Interaction terms (X_1X_2) show how changing two factors at once changes the response. To find nonlinearity in the model, polynomial terms (X_1^2 & X_2^2) are added. In the present research work, a 3² factorial design was used for optimization of microemulsion.

Factorial design is a faster and more efficient way to create complex formulas with smaller batch sizes, compared to traditional methods. Additionally, it reveals the significance of selected factors and their relationships. In this design, 2 each factor was evaluated at 3 levels and experimental trials were conducted using all possible 9 combinations. Factors and levels for batches were determined based on pseudo ternary phase diagrams, which were made with varying ratios of Oil: S-mix and Surfactant: co-Surfactant. In the present study, Concentration of Oil (X_1) and Ratio of S-mix (X_2) were selected as independent variables. The Globule Size (Y_1), Emulsification time (Y_2) and % Drug release (Y_3) were selected as dependent variables.

Evaluation parameters^{[12][16][17][18]}:

- 1) Determination of self-emulsification time:** Emulsification time of SMEDDS formulations was evaluated using the USP type II dissolution apparatus. Each SMEDDS formulation was added to 300 ml of distilled water at 37°C. A stainless-steel dissolution paddle, rotating at 50 rpm, provided gentle stirring. The time taken for the mixture to form a clear dispersion was recorded as the emulsification time.
- 2) Percentage Transmittance measurement:** The transparency of the formulation was evaluated by determining the percent

transmittance by using UV spectrophotometer at a specific wavelength, with distilled water serving as a blank. The transmittance of samples were measured at 650 nm.

- 3) **Drug content of SMEDDS:** SMEDDS equivalent to 10 mg of active ingredient, was dissolved in 10 ml of pH 1.2 buffer. Different dilutions were made using pH 1.2 buffer as necessary. The resulting solution then went under filtration using Whatman-35 filter papers before analysis via UV-visible spectrophotometer.
- 4) **Phase separation study:** Approximately 1 ml of SMEDDS was combined with 5 ml of distilled water in a glass test tube at a temperature of 25°C. The mixture was then vortexed for 1 minute and stored at 25°C for a duration of 2 hours. Visual observation was performed to detect any signs of phase separations.
- 5) **Robustness to dilution:** SMEDDS were diluted to different dilutions (50,100,500 and 1000 times) using pH 1.2 acidic buffer. The mixtures of diluted SMEDDS were stored for 24 hours and visually inspected for indications of phase separation or precipitation.
- 6) **Globule size and PDI:** SMEDDS formulation was diluted 100 times with distilled water at 37±0.5°C. The resulting emulsions were prepared by gentle agitation for 10 minutes using a magnetic stirrer. The microemulsion globule size was determined using a Zetasizer (Malvern Zetasizer). This instrument works on the principle of laser light scattering to analyse fluctuations in light scattering. Light scattering measurements were conducted at 25°C, with detection performed at a 90° angle.
- 7) **Zeta potential analysis:** Zeta potential was evaluated using photon correlation spectroscopy with the Zetasizer (Malvern Zetasizer), capable of measuring potentials ranging from -120 to 120 mV. Clear disposable zeta cells were used for sample placement, and the results were observed accordingly. Prior to introducing each fresh sample, cuvettes went under washing with methanol and rinsing with the sample to be measured. Zeta potential measurements were conducted on all SMEDDS formulations taken after diluting 20 times with water.
- 8) **In vitro dissolution study:** In vitro drug release study of all prepared SMEDDS formulation were carried out by using the USP type II dissolution apparatus (paddle method)

and pH 1.2 acidic buffer as the dissolution media (900 mL) at 37°C and 50 rpm. The dialysis bag technique (8,000–14,000 Da) was used. The dialysis bags were cleaned with deionized water and immersed in pH 1.2 acidic buffer over night to equilibrate. A dialysis bag was filled with 10 ml SMEDDS containing 20mg API and 1 mL of the dissolution medium was withdrawn at regular interval 0,5,10,15,20,30,45,60 minutes. To keep sink conditions consistent, the removed samples were replaced with an identical volume of new medium (pH 1.2 acidic buffer). The samples were analysed for drug content using the UV-visible technique at a wavelength of 249 nm.

- 9) **pH measurement:** SMEDDS formulation was diluted with water in the ratio of 1:250. The pH of the formed microemulsion was determined by the digital pH meter.
- 10) **Measurement of viscosity:** SMEDDS formulation diluted with water in the ratio of 1:250 and the viscosity of formed microemulsion was determined using Brookfield Viscometer with spindle no. 61 at 25°C and 20 rpm.
- 11) **Cloud point determination:** Freshly formed SMEDDS formulation was placed in a water bath in the ratio of 1:250 (SMEDDS: Distilled water) and the temperature was increased gradually. The temperature at which the microemulsion become cloudy was observed.
- 12) **Stability study:** The most suitable formulation was placed in the stability chamber at 40 °C and 75% relative humidity for accelerated stability experiment. After one-month globule size, emulsification time and % transmittance were evaluated.

III. RESULT AND DISCUSSION

Preformulation study of drug:

Organoleptic characteristics of drug: Haloperidol was odourless, white to off white colour crystalline powder which is non hygroscopic in nature.

Melting point of drug: The melting point of Haloperidol was observed 149-154°C and it matches standard.

Spectroscopic analysis of drug:

Qualitative and Quantitative estimation of Haloperidol through UV spectroscopy in methanol and pH 1.2 acidic buffer. Maximum absorbance (λ max) was obtained at 247 nm in methanol and 249 nm in pH 1.2 acidic buffer. From calibration curve

in methanol, R square value observed was 0.9985 and slope of regression line 0.3938 with the intercept of regression line 0.1555. So, linearity was observed in the range between 2-16 µg/ml. From calibration curve in pH 1.2 acidic buffer, R square value observed was 0.9962 and slope of regression line 0.5428 with the intercept of regression line 0.0369. So, linearity was observed in the range between 2-16 µg/ml.

Solubility Study:

Solubility of Haloperidol in various oils, surfactants and co-surfactants were showed in given figure.

Drug Excipients compatibility study:

From FT-IR spectra, I was determined that there is no introduction of new peaks and removal of any peak in the functional group region of spectra. There for the drug and excipients are said to be compatible with each other.

Pseudo ternary phase diagram:

The Smix ratio of 1:1, 2:1 and 3:1 showed the larger microemulsion region in the pseudo ternary phase diagrams. Therefore, Smix 3:1, 2:1 and 1:1 was chosen as one of the dependent factors for optimization of self microemulsifying drug delivery system.

Formulation of factorial design batches: Formulation of factorial design batches were showed in given table.

Evaluation parameters:

- 1) **% Drug content:** The drug content of all nine formulation batches, H-1 to H-9 was calculated by UV spectrophotometric analysis and the result was in the range of 97.19% to 99.54%.
- 2) **Phase separation study:** To determine the phase separation study, all the formulation batches F-1 to F-9 were stored for 2 hours at 25°C and observed visually. The result showed that there was no visible phase separation.
- 3) **Robustness to dilution:** A dilution study was performed to determine the effect of dilution on SMEDDS pre-concentrates. The optimized formulation batches of SMEDDS were diluted 50, 100, 500, and 1000 times in pH 1.2 buffer. All the batches were stored for 24 hours and the result was observed that all the solutions were clear and there was no sign of phase separation.

- 4) **Self-emulsification time:** The emulsification time of SMEDDS formulations was determined using a USP Type II (paddle type) dissolution apparatus and the results are shown in the above table. The lowest emulsification time observed was 19.83 seconds.
- 5) **% Transmittance:** The % transmittance of all nine batches H-1 to H-9 was measured in UV spectrophotometer at a wavelength of 650 nm. The observed values are shown in the above table. The highest transmittance was observed in batch H-5 with 97.6% transmittance.
- 6) **Globule size and PDI:** Globule size and Polydispersity index of H-5 was measured in 20 times diluted sample with distilled water using Malvern Zetasizer and the results were recorded in nm.
- 7) **In vitro drug release:** The in vitro drug release study profile of all the nine batches (H-1 to H-9) is shown in table, it can be concluded that more than 50 % of the drug released within 20 minutes. Formulation H-5 shown higher drug release as compared to other formulations which was 94.50% at 60 minutes.
- 8) **pH measurement:** pH of all formulation (H-1 to H-9) batches were measured using digital pH meter and pH of all batches are in the range of 5.3 to 6.8.
- 9) **Viscosity:** Viscosity of all H-1 to H-9 batches were measured using Brookfield Viscometer. The results of these batches are in the range of 122.28 to 157.78 cps.
- 10) **Cloud point determination:** Cloud point of all nine batches were measured and the results are in the range of 58.45 to 71.14°C.

Optimization using factorial design:

Microemulsion was optimized by using 3² full factorial design. Responses of all the design batches are presented in table.

Effect of independent variables on Y1 (Globule size):

- The analysis of multiple regression for response Y1 (Globule size) was done by the linear model using Design Expert 13 and the data was interpreted as follows:
- The positive sign in X1 suggests that the amount of Oil has directly relation with Globule size. With the increase in the concentration of Oil, the globule size of SMEDDS will increase. The negative sign in X2 suggests that the ratio of S-mix has an inverse relation with Globule size. With the

increase in the concentration of S-mix ratio, the globule size of SMEDDS will decrease. Model p-value is 0.0329 which was less than 0.05 which indicates the model is significant. The equation was generated as following:

- **Full model:** $189.367 + 49.5333 X1 + (-29.9667) X2$
- **Reduced model:** $189.367 + 49.5333 X1$

Effect of independent variables on Y2 (Emulsification time):

- The analysis of multiple regression for response Y2 (Emulsification time) was done by the 2FI model using Design Expert 13 and the data was interpreted as follows:
- The positive sign in X1 suggests that the amount of Oil has directly relation with Emulsification time. With the increase in the concentration of Oil, the emulsification time of SMEDDS will increase. The negative sign in X2 suggests that the ratio of S-mix has an inverse relation with Emulsification time. With the increase in the concentration of S-mix ratio, the emulsification time of SMEDDS will decrease. Model p-value is 0.0415 which was less than 0.05 which indicates the model is significant. The equation was generated as following:
- **Full model:** $27.8911 + 6.82 X1 + (-1.585) X2 + (-2.795) (X1) (X2)$
- **Reduced model:** $27.8911 + 6.82 X1$

Effect of independent variables on Y3 (% Drug release):

- The analysis of multiple regression for response Y3 (% Drug release) was done by the quadratic model using Design Expert 13 and the data was interpreted as follows:
- The negative sign in X1 suggests that the amount of Oil has an inverse relation with Emulsification time. With the increase in the concentration of Oil, the emulsification time of SMEDDS will decrease. The positive sign in X2 suggests that the ratio of S-mix has a directly relation with Emulsification time. With the increase in the concentration of S-mix ratio, the emulsification time of SMEDDS will increase. Model p-value is 0.0449 which was less than 0.05 which indicates the model is significant. The equation was generated as following:

- **Full model:** $93.2611 + (-1.52) (X1) + 2.07 (X2) + 0.5175 (X1) (X2) + (-3.31667) (X1)^2 + (-0.826667) (X2)^2$
- **Reduced model:** $93.2611 + (-1.52) (X1) + 2.07 (X2) + (-3.31667) (X2)^2$
- Experimental responses were measured of check point batch H-10 and it was compared with predicted response and all experimental responses were near to predicted responses. So model was valid. Study concluded that factors like Oil and Surfactant: Co-Surfactant ratio played a significant role in the model.

Optimization of formulation:

H-5 was selected as optimized batch, as it showed minimum globule size of 139.8 nm and lowest emulsification time 19.83 seconds and highest % Drug release 94.50 %.

Stability study of optimized batch:

One-month stability study of Haloperidol SMEDDS was carried out under accelerated conditions, there was no major difference between the initial and after 30 days stability study data.

Comparison with marketed product:

In vitro drug release of optimized batch H-5 is higher 94.50% as compare to the marketed product.

IV. CONCLUSION

The present research work aimed to formulate SMEDDS of Haloperidol for the treatment of Schizophrenia. Self-Microemulsifying Drug Delivery Systems (SMEDDS) are a novel pharmaceutical formulation approach designed to enhance the solubility of poorly water-soluble drugs and increase oral bioavailability. These systems consist of a mixture of Oil, Surfactants, and Co-Surfactants. SMEDDS can provide rapid and enhanced absorption by increasing the lymphatic transport while bypassing first pass metabolism due to its nano sized particles. Spectrometric analysis of Haloperidol in methanol and phosphate buffer pH 1.2 acidic was done by using UV-Visible spectrophotometer and λ max was obtained at 247 and 249 nm respectively. Identification of drug was done by Fourier transform infrared spectroscopy. Solubility study was carried out to find suitable Oil, Surfactant and Co-Surfactant. In solubility study, Capryol 90 (113 mg/ml), Tween 80 (124 mg/ml) and Polyethylene glycol- 400(83mg/ml) demonstrated highest solubility of Haloperidol. So, they were further selected as Oil, Surfactant and Co-Surfactant respectively for the preparation of SMEDDS.

Drug-Excipients compatibility study was conducted by Fourier transform infrared spectroscopy, in which there was not any interaction observed. Pseudo Ternary Phase Diagrams for different S-mix ratios were constructed. In which, S-mix 1:1, 2:1 and 3:1 showed higher microemulsion region compared 1:2 and 1:3. So, it was further selected for optimization of SMEDDS. 3^2 full factorial design was applied for optimization of Haloperidol SMEDDS. Concentration of Oil (X1) and ratio of S-mix (X2) were chosen as independent variables, while Globule size (Y1), Emulsification time (Y2) and Drug release at 60 mins (Y3) were selected as dependent variables. 9 batches were formulated and evaluated for various parameters. H-5 batch was optimized because it showed 139.8 nm Globule size, 19.83 sec. Emulsification time and 94.50% Drug release. Check point batch (H-10) was formulated and evaluated. All experimental responses were near to predicted responses. Study concluded that factors like concentration of Oil and S-mix ratio played a significant role in the model. Stability study of SMEDDS was conducted for one month. All the parameters of SMEDDS were evaluated before and after the one month. They were almost similar. % drug release is higher as compared with the marketed formulation so, it concluded that SMEDDS formulation is best to improve the solubility of poorly water-soluble drug like Haloperidol. It is concluded that SMEDDS of Haloperidol can be effectively used for treatment of schizophrenia.

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TABLES & FIGURES

Table 1 - Formulation of factorial design batches

Ingredients	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9
Haloperidol (mg)	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg
Capryol 90 (%v/v)	10%	15%	20%	10%	15%	20%	10%	15%	20%
Tween 80 (%v/v)	45%	42.5%	40%	60%	56.67%	53.34%	67.5%	63.8%	60%
Polyethylene glycol 400 (%v/v)	45%	42.5%	40%	30%	28.33%	26.66%	22.5%	21.2%	20%

Table 2 – Evaluation parameters

Formulation Code	Globule Size (nm)	Self-emulsification time (sec)	% Drug release	% Transmittance	pH	Viscosity (cps)	Cloud point (°C)	% Drug content
H-1	142.1	20.26	89.12	96.3	5.6	125.37	66.37°C	99.21
H-2	221.7	33.42	89.95	86.7	6.3	122.28	61.64°C	98.64
H-3	294.5	38.53	85.39	78.5	5.7	118.38	58.45°C	97.25
H-4	147.1	20.36	91.19	95.1	6.5	150.55	60.35°C	99.22
H-5	139.8	19.83	94.50	97.6	6.8	146.33	71.14°C	99.54
H-6	280.4	35.92	87.46	92.8	5.3	138.65	61.24°C	97.19
H-7	154.1	23.38	92.43	94.2	6.4	157.78	67.14°C	99.36
H-8	158.8	28.85	93.68	89.4	6.2	151.87	66.46°C	97.38
H-9	165.7	30.47	90.77	84.7	6.3	139.41	64.61°C	97.23

Table 3 – In vitro drug release data

Time (Min.)	H-1 (%)	H-2 (%)	H-3 (%)	H-4 (%)	H-5 (%)	H-6 (%)	H-7 (%)	H-8 (%)	H-9 (%)
0	0	0	0	0	0	0	0	0	0
5	16.58	10.78	8.7	15.33	17.82	10.36	14.92	13.67	12.43
10	30.25	25.28	23.21	29.43	32.74	24.87	28.18	27.77	26.52
15	47.25	39.06	36.06	45.18	46.28	41.45	45.18	43.52	48.28
20	58.44	54.30	51.40	57.20	59.27	53.88	57.61	56.78	56.37
30	77.92	69.6	68.80	77.51	78.75	72.12	75.02	75.85	76.68
45	83.31	78.75	76.27	85.80	87.46	80.83	83.73	84.14	84.86
60	89.12	89.95	85.39	91.19	94.50	87.46	92.07	93.68	90.77

Table 4 - 3² factorial design batches of Haloperidol self- microemulsion

Formulation Code	Concentration of Oil (%) (X1)		Ratio of S-mix (%) (X2)	
	Coded Value	Actual Value	Coded Value	Actual Value
H-1	-1	10	-1	1:1
H-2	0	15	-1	1:1
H-3	+1	20	-1	1:1
H-4	-1	10	0	2:1
H-5	0	15	0	2:1
H-6	+1	20	0	2:1
H-7	-1	10	+1	3:1
H-8	0	15	+1	3:1
H-9	+1	20	+1	3:1

Table 5 - In vitro drug release comparison of marketed formulation and prepared formulation(H-5)

Sr. No.	Time (minutes)	% Drug release (Initial)	% Drug release (After 30 days)
1	0	0	0
2	5	18.75	17.54
3	10	30.64	29.35
4	15	44.36	43.06
5	20	59.46	57.97
6	30	76.38	74.82
7	45	86.90	85.13
8	60	94.68	93.18

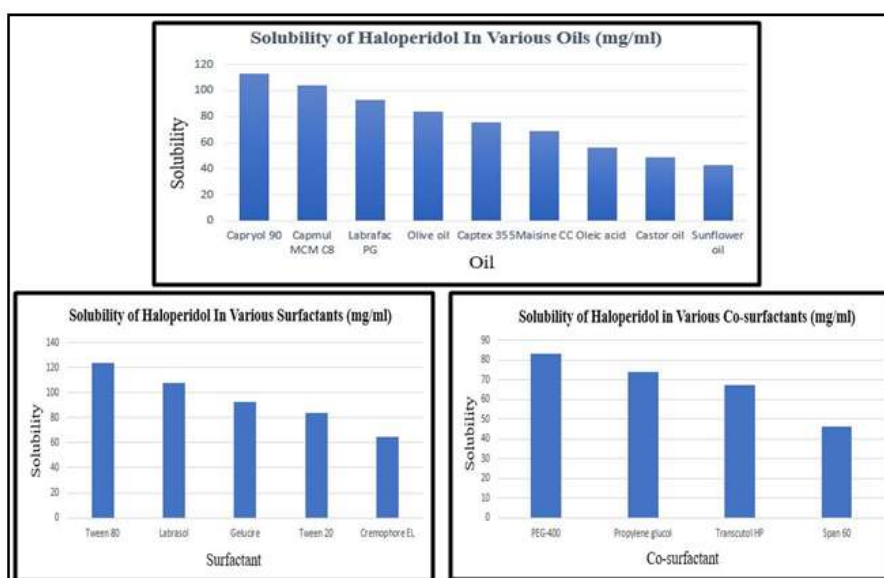


Figure 1 – Solubility of Haloperidol in various oils, surfactants and co- surfactants

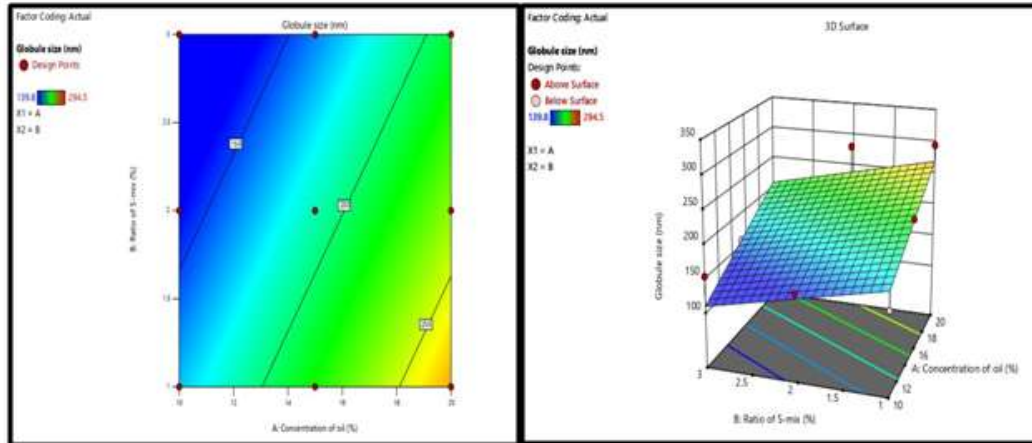


Figure 2 – Contour plot and response surface plot for response Y1 (Globule Size)

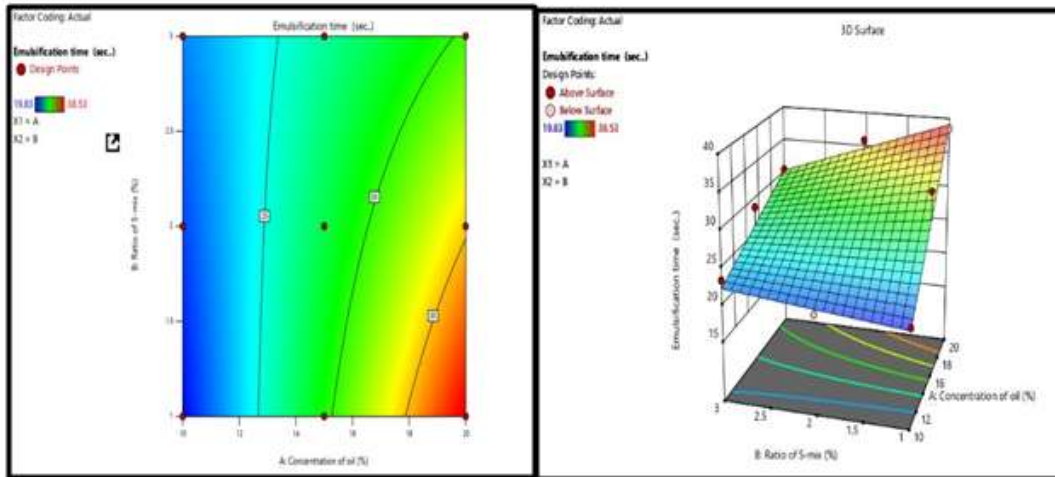


Figure 3 – Contour plot and response surface plot for response Y2 (Emulsification Time)

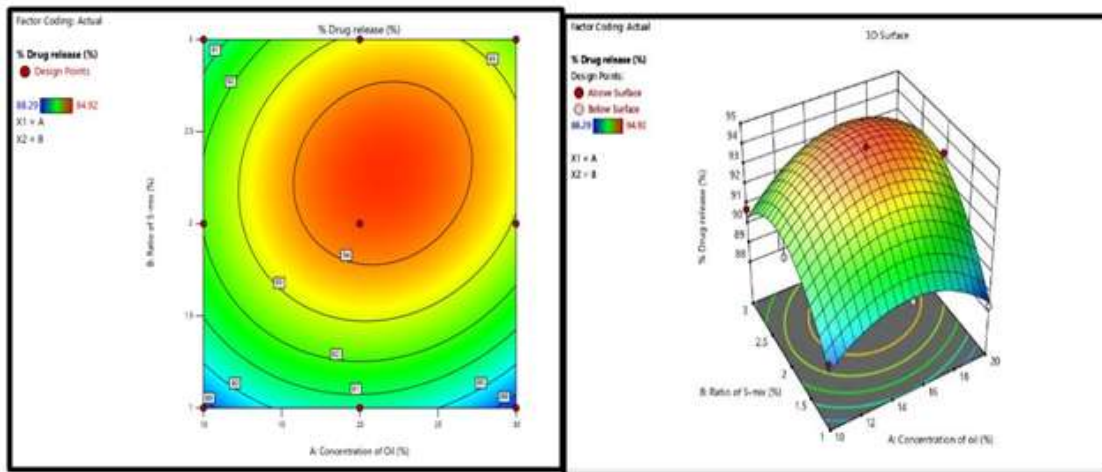


Figure 4 – Contour plot and response surface plot for response Y3 (% Drug Release)

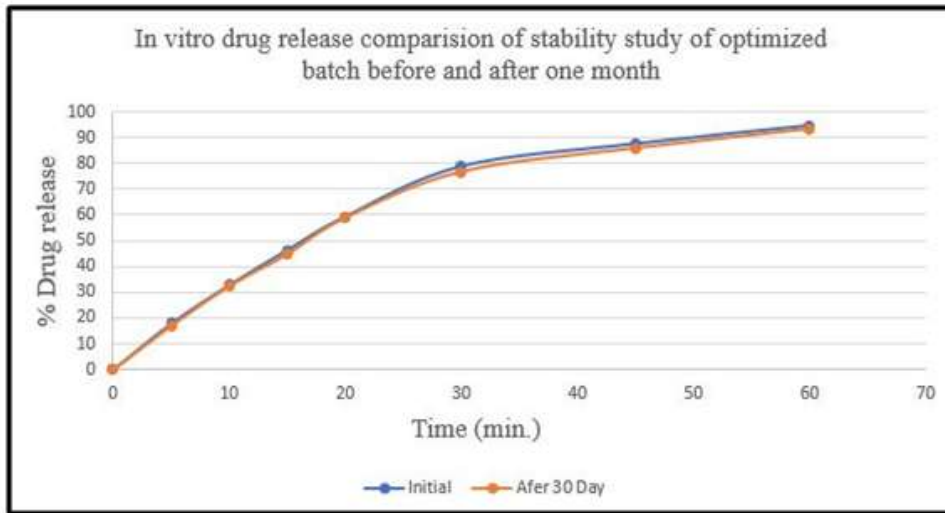


Figure 5 - In vitro drug release comparison of stability study (Batch: H-5)

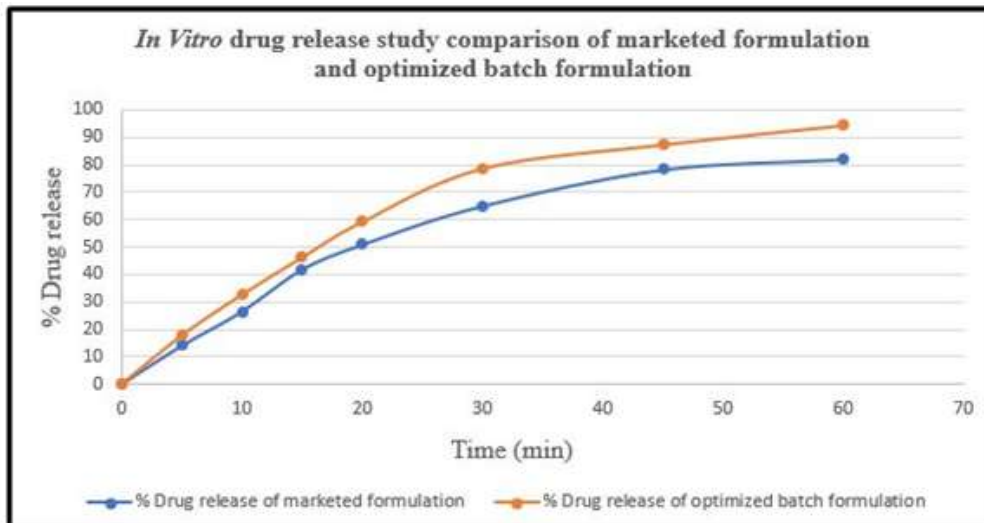


Figure 6 - In vitro drug release comparison of marketed formulation and optimized batch formulation