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Research Article

DEVELOPMENT AND CHARACTERIZATION OF A SELF-EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS) OF RILPIVIRINE HCL

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ABSTRACT

The present study was aimed towards to formulate and characterize self-emulsifying drug delivery system containing Rilpivirine HCl (RIL). Exhaustive Solubility study of the model drug, RIL was performed in different edible and GRAS listed oils to select oil component. Similarly, a supportive mixture of surfactants and Co-surfactants (S_{mix}) of was selected. Pseudo-ternary diagram was plotted to judge micro emulsification existence area. The d-optimal design was employed to optimize SMEDDS composition using the amount of oil, surfactant, and Co-surfactant as independent variables and globule size and emulsification time as dependent variables. Developed SMEDDS formulations tested for self-micro emulsifying properties and the resultant formulation loaded with RIL measured for clarity, phase separation, % transmittance, globule size, and zeta potential. TEM study was performed to check the morphology of developed microemulsion globules. *In vitro* drug release study was undertaken and comparison was done with market formulation (Edurant®). Out of different trials, Capryol (Oil), Labrasol (Surfactant) and Transcutol-P (Co surfactant) were selected SMEDDS components. Highest microemulsion region was found in 1:1 Smix ratio. Significant impact of selected independent variables was found on responses, which was confirmed by regression equations (Y_1 and Y_2) and contour plots (2D). Significant improvement in the dissolution of RIL was observed by SMEDDS as compared to pure drug and marketed formulation. Short term stability study revealed stable characteristics of developed SMEDDS.

KEYWORDS: Rilpivirine HCl, SMEDDS, D-optimal Design, Dissolution, Stability study

INTRODUCTION

Drug discovery and development is the continuous process for better health profile of human being. Approximately, 40% of new chemical entities belong to BCS class II or IV (poor solubility in water). These results in poor oral bioavailability with high intra and inter-subject variability. It a great challenge for formulation scientists to improve bio-availability of such drugs (1).

Use of lipidic materials has been increased in the design of drug delivery systems due to its accepted nature and improving biopharmaceutical profile of the drug. Self-micro emulsifying drug delivery system (SMEDDS) is one of the most famous and commercially viable approaches. Comparative to emulsion similar products, the scale up to SMEDDS is easy with less manufacturing issues (2).

SMEDDS are isotropic mixtures of oils, solid or liquid surfactants, or instead, one or more hydrophilic solvents and cosolvents/surfactants which leads into microemulsion (ME) upon modest stirring and proper dilution in aqueous media. The resultant globules have a size almost less than 100 nm, which increases stability (3, 4).

SMEDDS also help to reduce dosing size, better and steady absorption profile with selectivity in specific absorption window. It protects the drug from gastric conditions with less variability, high drug entrapment. It also can be sterilized easily (5). Oral absorption may be increased by SMEDDS, by delaying GI transit time, improving drug solubility in the lumen, increase lymphatic and enterocyte mediated permeation and enhance membrane transport (6).

Development of pharmaceutical products through trial and error method is complex, tedious and risk involving approach (7). Recently, due to the mutual involvement of information technology and statistical principles, various software and tools are available as aids in the design of pharmaceutical formulation.

Rilpivirine HCl is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) and chemically it is Benzonitrile, with molecular formula $C_{22}H_{18}N_6$•HCl (8). It shows *in vitro* activity against wild-type HIV-1 and NNRTI-resistant mutants. It has better safe and tolerable as compared to other NNRTIs (e.g. nevirapine, efavirenz, etravirine). It is a poorly soluble drug with intermediate *in vitro* permeability. The maximum plasma concentration (Cmax) of RIL is generally achieved within 4-5 hours after oral administration, (9, 10). Thus, in view of this, the present study was aimed towards development of SMEDDS for the RIL, poorly water-soluble anti-viral drug.

MATERIALS AND METHODS

Rilpivirine HCl was kindly gifted by Mylan laboratories Hyderabad, India. Capryol 90, Labrasol and Transcutol P were gifted by Gattefosse, France. Hydrochloric acid, potassium dihydrogen phosphate (all AR grade), and acetonitrile (HPLC grade) were purchased from s.d. Fine Chemicals (Mumbai, India). Trifluoroacetic acid was procured from Sigma Aldrich (India). Double distilled water was used throughout the experiments. The marketed product of RIL (Edurant®) was purchased from a local pharmacy (Ahmedabad, India)

Quantification of RIL

The quantification of RIL was done by RP HPLC method employing column Acquity UPLC BEH shield RP18 column with the specification of 100mm x 2.1mm, i.d., 1.7µm. The mobile phase was a mixture of A (water: Acetonitrile: Tri fluoro acetic acid (90:10:0.05% v/v) and B (Acetonitrile: Methanol (95:5:0.05% v/v). Other parameters were column temperature (40°C), Injection Volume (2 µL), Flow Rate (0.4 mL/min), the run time was 15 mins and UV detection were done at 285 nm.

Solubility studies

The solubility of RIL in different oils, surfactants, and co-surfactants was tested using the technique given by Basalious et al. (2010). Excess amount of RIL was added in selected in ME components. The mixture was heated at 40 °C and mixed well. The mixing was continued upto 48 hrs on shaker bath (30±0.5 °C). The resultant mixture was centrifuged (Remi, C 24 BL, 3000 rpm for 15 mi). A supernatant (0.5 mL) was taken and properly diluted to quantify the amount of RIL by UV Spectrophotometer at 285 nm. (11).

Construction of pseudo-ternary phase diagram

Building pseudo-ternary phase diagrams are the first step towards the formulation of SMEDDS which indicates the capacity of microemulsion formation once the compatibility between different components is confirmed. Water titration method was employed to plot the pseudo-ternary phase diagram of SMEDDS components (oil, Smix and doubled distilled water). Different trials were done at 1:1, 2:1 and 3:1 (weight ratio of surfactant to co-surfactant).

Optimization of SMEDDS (RIL)

The mixture design (D-optimal) was employed for optimization SMEDDS formulation compositions. Based on the results of solubility study and pseudo-ternary phase diagram, amount concentrations of Oil (Capryol 90; X_1), Surfactant (Labrasol; X_2), and Cosurfactant (Transcutol-P; X_3) were finalized within ranges of 5%–20%, 20%–60%, and 30%–70%, respectively. The summative concentrations of X_1, X_2, and X_3 were kept constant at 100%. Globule size (Y_1) and emulsification time (Sec) (Y_2) were fixed as responses to optimize SMEDDS formulation with excellent physiochemical characteristics. Appropriate design space (DS) and multiple linear regression (MLR) equations were evolved by Design-Expert Software version 7 (12, 13).

Preparation of SMEDDS

A drug (RIL) was dissolved in selected oil component oil. Demanded amount of Smix (surfactant and co-surfactant) were added. Further, it was mixed employing vortex mixer and was warmed (40°C) on the water with sporadic shaking. The developed SMEDDS was evaluated for different parameters.

Evaluation of SMEDDS (14-16)

Self-emulsification and dispersibility test

A ternary mixture of oil, surfactant, and co-surfactant was added glass beaker containing 250 ml of water (37°C) and mixed well. After equilibrium, the system was inspected visually for the efficiency of self-emulsification, dispersibility, and appearance and grade was assigned. Grade A region was considered as desirable as it was thermodynamically stable.

Droplet size measurement and zeta potential

The droplet size RIL SMEDDS (resultant emulsion) and zeta potential were checked employing a Malvern Zeta Sizer Nano ZS 90 (Malvern Instruments, Malvern, UK) after 100 times dilution with double distilled water to get appropriate scattering intensity. The globule size distribution was ascertained by PDI value. All experiments were done performed in triplicate and results are conveyed as mean size ± SD.

Conductance

This test was carried out to confirm the nature (type) of the microemulsion. The electro conductivity of the resultant system was measured by an electro conductometer (Pico conductivity meter, Lab India, Mumbai, India).

% Transmittance

One ml of RIL SMEDDS was diluted with double distilled water (100 times). UV spectrophotometer (UV 1700, Shimadzu, Japan) was employed to find %T of diluted SMEDDS at 650 nm (Blank: Double distilled water)

Morphology of RIL SMEDDS

The morphology of resultant ME from RIL SMEDDS was investigated by TEM (Tecnai 20 Philips). For the same, RILSMEDDS was diluted with double distilled water and a drop of it was mounted on a carbon-coated copper grid (300 mesh, 3mm) and was further air dried.

In vitro dissolution study

Drug release study of RIL SMEDDS and MF was done in dissolution apparatus (USP II) per the United States Pharmacopeia (USP)(17). HPMC capsules (size "00") comprising RIL SEMDDS (25 mg of RIL) was used for this study. This study was performed in dissolution medium (0.5% Polysorbate 20 in 0.01N HCl; pH=2.0; 900mL) at 37 ± 0.5 °C and 75rpm. Five ml sample was withdrawn at different time intervals (5, 10, 15, 30, 45, and 60 min). Samples were filtered through membrane filters (0.45 µm). The amount of RIL was quantified by checked by UV spectrophotometer after proper dilution at 285 nm. The comparison was done within dissolution profiles of RIL SMEDDS, pure drug and MF.

Stability studies(18)

Robustness to dilution

RIL SMEDDS were diluted with various media including water, 0.1N HCl and pH 7.4 phosphate buffers (10, 100 and 1000 times). The resultant MEs were preserved for 24 hours and observed for instability (for a sign of precipitation or separation).

Thermodynamic stability studies

This study was to evaluate the phase separation and effect of temperature variation on RIL SMEDDS. The RIL SMEDDS were diluted to 100 times with double distilled water (Centrifugation at 10,000 rpm; 20minutes). Freeze-thaw condition applied on samples to check the effect of temperature (-20°C for 2 days followed by 25°C for 2 days). Appropriate dilution was done and samples were centrifuged at the end of the cycle. Phase separation and the variation in droplet size were checked.

Physicochemical stability

The samples were stored at 25°C/60%RH and 40°C/75%RH for up to 3 months. Periodically samples were taken at predetermined time intervals after 1, 2, and 3 months. Various physical parameters including clarity, phase separation, pH, droplet size and Zeta potential were measured after proper dilution. Additionally, chemical stability was confirmed by assay, related impurities, and dissolution study.

RESULT AND DISCUSSION

Screening of excipients

Construction of pseudoternary phase diagram

Based on the results of solubility studies, Capryol 90 was selected as oil phase. Labrasol and Transcutol-P were used as a surfactant and co-surfactant, respectively. The mixing of surfactant and co-surfactant was done in different ratios (1:1, 1:2 and 1:3). Corresponding pseudoternary phase diagram of each combination are presented in Figure 1.

On the basis of pseudoternary phase diagrams, Surfactant, and co-surfactant in the ratio of 1:1 was selected due to the highest area of microemulsion region.

Optimization of SMEDDS

D optimal design with 3 factors and 13 runs along with 6 center point was selected for the optimization study. Formulation composition and responses are listed in Table 3.

To generate multiple linear regression equations and to find a suitable fitting model, various ANOVA parameters were selected and are mentioned in Table 3.

Effect of factors on the responses

Globule Size

Multiple linear regression equation relating selected independent variables and globule size (Y_1) was generated from the results of ANOVA.

$$Y_1 = -32074.38161\ X_1 - 85.03506X_2 + 220.02954\ X_3 + 50401.73972\ X_1X_2 + 56734.26562\ X_1X_3 - 81.84857\ X_2X_3 - 44515.05419\ X_1X_2X_3 + 17762.65627\ X_1X_2(X_1-X_2) + 28798.02555\ X_1X3(X_1-X_3) + 197.62245\ X_2X_3(X_2-X_3)$$

The factor X_1 was a critical factor for determining globule size due to the strong magnitude to coefficients of X_1 alone and interaction terms with. Other coefficients such as X_1X_2, X_1X_3, X_1X_2 (X_1-X_2), and X_1X_3 (X_1-X_3) were positive. The positive relation confirms remarkable positive effect of X_1 on Y_1. This relationship is illustrated by a 2D contour plot (Figure 2).

Emulsification time

Based on the ANOVA results, the following multiple linear regression equation was equated Y_2.

$$Y_2 = +45161.36X_1 - 392.02X_2 + 21.07X_3 - 76192.61X_1X_2 - 73891.74X_1X_3 + 400.81\ X_2X_3 + 65461.53\ X_1X_2X_3 - 36327.44X_1X_2(X_1-X_2) + -31024.09X_1X3(X_1-X_3) + 519.43\ X_2X_3(X_2-X_3)$$

The model fitting data revealed the linear relation between selected independent variables and emulsification time. As the magnitude of the coefficient of variable X_1 indicates that as the amount of oil in SMEDSS composition increases, emulsification time is increased due to more interfacial tension. Oppositely, this effect can be balanced by using a surfactant and as the number of surfactant increases, emulsification time decreases which can be proved by coefficient value of X_2. Further, this relation was studied by plotting a 2D contour plot (Figure 3).

Further to define design space, two contour plots were overlapped and overlaid plot was constructed (Figure 4). An optimized batch was selected from the design space and the combination was further applied for the experiment to know the prediction power of the selected model. The percentage prediction error (PPE) was used to determine the accuracy of prediction. The predicted value of globule size and emulsification time for selected optimized batch (X_1: 8.47, X_2:51.83, X_3:39.70 combination was 18.72 and 43.79 respectively. The experimental values of the same were 17.58 and 41.35 respectively. The PPE (%) for Y1 and Y2 were 6.09 and 5.57. Thus, the evolved models are highly predictive and can be used further.

Characterization of RIL SMEDDS

The globule size distribution curve and zeta potential curve is shown in Figure 5. This indicates uniform size distribution of globules and acceptable range of zeta potential

Due to the presence of free fatty acids, the charge of the oil globules in conventional SMEDDS is negative. As non-ionic surfactants have minimum toxicity, they are widely used. Moreover, the nonionic microemulsions are insensitive to pH and electrolyte concentration comparative to their ionic counterparts, which is an added advantage.

Physico-chemical characterization

The type of emulsion can be confirmed based on the conductivity. The conductivity value of RIL SMEDSS was 97.63 ± 0.23 µS. This reveals that developed SMEDDS formulations were water continuous and there were no chances of phase inversion. The pH value of SMEDDS was found to be 5.9. The pH value is based on the presence of excipients used and may alter the zeta potential which further affects the stability of the formulation. The assay (n=3) of the drug was found to be 99.47%±0.61. The % Transmittance (%T) value of SMEDDS (n=3) was found to be 99.34 ±0.09, revealing monophasic system.

Dissolution study

Dissolution profiles of RIL, Marketed formulation (Edurant 25mg tablets, B.No.610709A) and L-SMEDDS are presented in Figure 6. The drug dissolution rate is markedly enhanced in the L-SMEDDS as 89% of the drug was dissolved in 5 min, as compared to only 4% and 44% from RIL API and marketed drug product tablets respectively. Due to existence in solubilized form and upon dilution increment into surface area (micronization), the dissolution from SMEDDS was relatively faster. The RIL API did not achieve complete dissolution during the 60 minute test period and only 52% of the drug dissolved over 60 minutes, owing to large crystal size, while L-SMEDDS showed a significantly enhanced dissolution rate with 100% of drug dissolved over 60 minutes.

Stability Studies

The results of the stability study of RIL SMEDDS are presented in Table 4. The results indicate the stable characteristics of the developed formulation. There was the non-significant difference ($p<0.05$) between drug content after said months stating chemical stability of SMEDDS. The zeta potential and globule size of the formulation remained unaltered, confirming the physical stability of microemulsion structure. Optimized formulation SMEDDS

formulations exhibited similar pH values (5.5 to 6.0), confirming stability. So it can be anticipated that drug remains in oil phase only and since water is in external phase entire system showed pH of water.

CONCLUSION

The SMEDDS formulation for the poorly water-soluble drug (RIL) suitable for oral administration was successfully developed. The role of Oil (Capryol 90), Surfactant (Labrasol), and Cosurfactant (Transcutol-P) were found critical in the stable conversion of solid SMEDDS into microemulsion. D optimal design has also assisted in the optimization of the design. Pseudoternary phase diagram helped in deciding amount of Smix. The result of short-term stability study exhibited stable characteristics of SMEDDS. In a nutshell, this design can be a promising design for achieving better oral bioavailability from poorly water-soluble drugs.

Table 1: Efficiency of emulsification, dispersibility, and appearance

Magnitude	Nature of dispersibility and appearance
A	Clear and transparent in appearance Rapid forming emulsion, which is
B	Bluish white appearance
C	Bright white emulsion or grayish white emulsion (Minor oily the appearance)
D	Large oils droplets present on the surface

Table 2: Formulation composition and responses of D-optimal mixture design batches

Run	Capryol 90 (X_1)	Labrasol (X_2)	Transcutol-P (X_3)	Globule size (nm)	Emulsification time (Sec)
1	17.26	37.24	45.5	40.25	95
2	11.64	25.67	62.69	26.54	71
3	14.25	55.41	30.34	30.14	69
4	19.56	43.16	37.28	28.34	105
5	5.12	25.41	69.47	25.15	36
6	6.34	59.14	34.52	11.25	32
7	5.06	34.12	60.82	20.18	32
8	6.97	59.14	33.89	12.47	37
9	7.13	49.37	43.5	15.23	44
10	18.67	21.05	60.28	53.67	101
11	12.67	55.34	31.99	34.26	62
12	5.52	25.01	69.47	21.03	39
13	19.87	20.13	59.99	52.14	145
14	19.57	43.15	37.28	22.37	107
15	19.94	29.83	50.23	45.32	115
16	10.64	28.34	61.02	15.37	65

Table 3: ANOVA parameters for selected responses (Globule size and Emulsification time)

Models	SD	R^2	Adjusted R^2	PredictedR^2	PRESS	Remark
Globule size (nm; Y_1)						
Linear	8.13	0.685	0.636	0.543	1247.07	–
Quadratic	8.10	0.759	0.639	0.432	1551.38	–
Special cubic	8.22	0.777	0.628	0.412	1606.45	–
Cubic	3.66	0.971	0.926	0.693	837.72	Suggested
Emulsification time (Sec; Y_2)						
Linear	8.31	0.952	0.944	0.919	1492.35	Suggested
Quadratic	8.11	0.964	0.947	0.891	2038.94	–
Special cubic	8.40	0.966	0.943	0.861	2593.82	–
Cubic	8.52	0.977	0.942	0.645	6609.98	–

Table 4: Result of stability study of RIL SMEDDS

Month	25°C/60% RH			40°C/75%RH			
	GS (nm)	ZP (mV)	% Assay	GS (nm)	ZP (mV)	% Assay	MDS (nm)
1	16.25 ± 0.48	-22.44	99.1%	17.12 ± 0.55	-23.10	98.1%	16.25 ± 0.48
2	15.29 ± 0.42	-22.37	98.8%	16.72 ± 0.55	-21.28	98.6%	15.29 ± 0.42
3	15.47 ± 0.44	-22.58	98.7%	17.11 ± 0.55	-23.45	98.3%	15.47 ± 0.44

(GS: Globule size, ZP: Zeta potential)

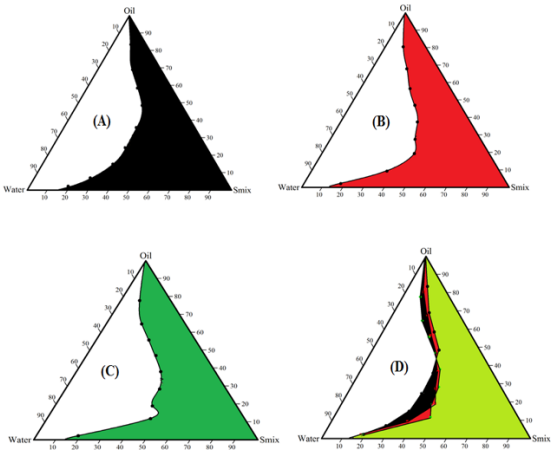

Figure 1: Pseudoternary phase diagrams with different ratio of Smix, (A) 1:1 (B) 2:1 (C) 3:1 and (D) Overlay

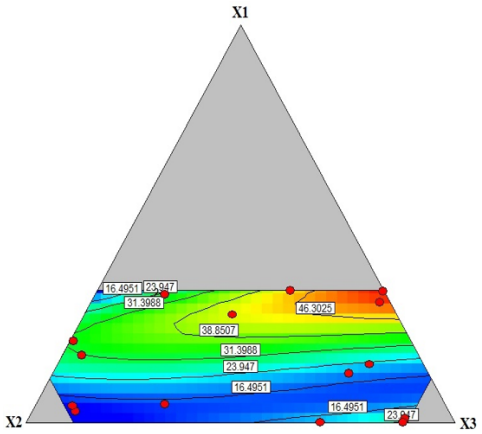

Figure 2: Contour plot (2D) relating effect of independent variables on Y_1

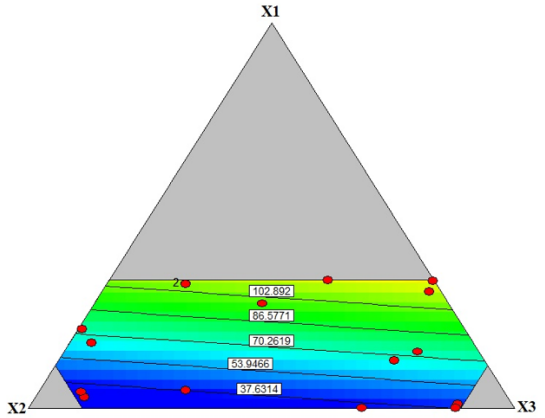

Figure 3: Contour plot (2D) relating effect of independent variables on Y_2

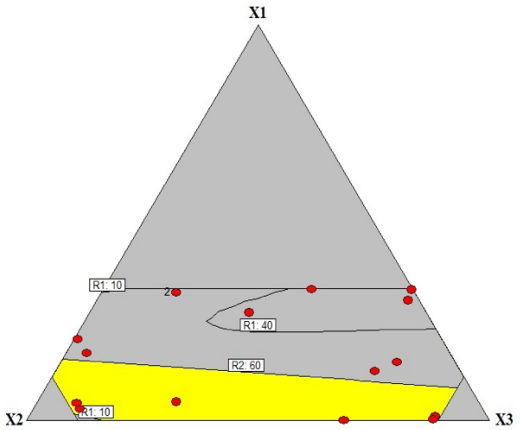

Figure 4: Overlay plot of Y_1 and Y_2

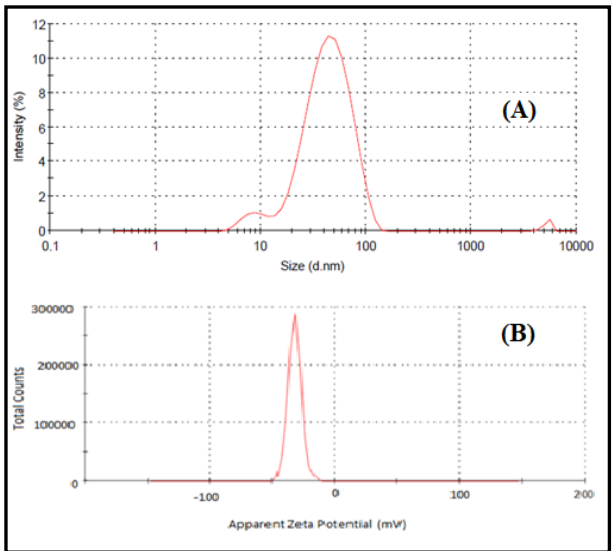

Figure 5: Globule size distribution (A) and zeta potential (B)

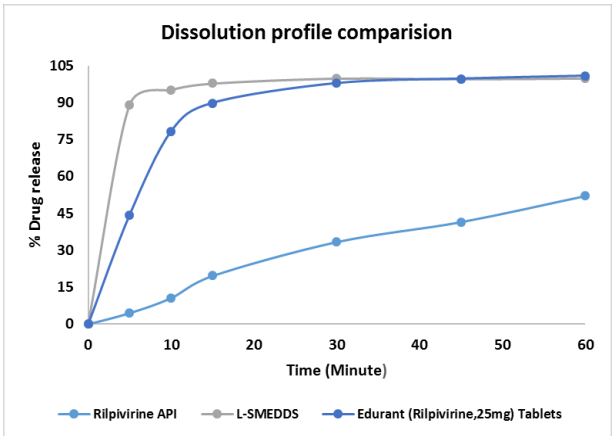

Figure 6: The comparative dissolution profile of RIL SMEDDS, RIL API, and marketed formulation

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