

Original Article

SOLUBILITY ENHANCEMENT OF LURASIDONE HYDROCHLORIDE BY PREPARING SMEDDS

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ABSTRACT

Objective: The objective of the study was to enhance solubility of Lurasidone HCl, an atypical antipsychotic drug, by formulating self-micro emulsifying drug delivery system (SMEDDS) and its characterization.

Methods: Solubility study of Lurasidone hydrochloride (LH) was carried out in various surfactants, co surfactants and oils. Pseudo ternary phase diagrams were constructed to identify the self-micro emulsification region. Screening was done so as to determine the proper combination of components. Based on this, LH SMEDDS were prepared using Cremophor RH40 (surfactant), Soluphor P (co-surfactant) and Capmul MCM (oil). The pre-concentrate SMEDDS were evaluated for clarity (visual), precipitation, % transmittance, robustness to dilution, freeze thawing, particle size distribution and zeta potential and adsorbed SMEDDS were evaluated for drug content, flow properties, *in-vitro* dissolution and *ex-vivo* diffusion studies.

Results: The optimized LH SMEDDS composed of 14% Cremophor RH40, 68% Soluphor P, 18% Capmul MCM with a particle size of 3.95 μm and zeta potential of more than 50 mV showing 80% dissolution in 60 min.

Conclusion: The results of this study prove that SMEDDS help in improving the solubility, dissolution and bioavailability of lurasidone hydrochloride.

Keywords: Lurasidone Hydrochloride, Solubility enhancement, SMEDDS, *In-vitro* dissolution, *Ex-vivo* diffusion.

INTRODUCTION

Lurasidone Hydrochloride (Brand name: Latuda) was approved in 2010 by USFDA as the tenth atypical antipsychotic for the treatment of schizophrenia. It belongs to a class of drugs known as benzoisothiazol or azapirone derivatives, and is most similar to ziprasidone (Geodon) among the available atypical antipsychotics. It is a second generation antipsychotic, which may be better tolerated than the older antipsychotics. Atypical antipsychotics quickly replaced the older antipsychotics, such as chlorpromazine and haloperidol, as first-line treatment for schizophrenia and other psychotic disorders, because of their lower risks of extra pyramidal symptoms as well as better effectiveness in treating negative symptoms in schizophrenia [1].

LH has a poor bioavailability (<12% in all species tested) [2]. This is because of its poor solubility. It is found to be soluble in methanol and insoluble in acetone, ethanol and water. Till date solubility enhancement of LH has been tried by forming solid dispersions [3].

As compared to other enhancement techniques, SMEDDS help in increasing the absorption of lipophilic drugs taken orally. They spread readily in the GI tract, and the digestive motility of the stomach and the intestine provides the agitation necessary for self-emulsification. Also they can be encapsulated in hard or soft gelatin capsules or can be converted to solid state (Solid SEDDS/SMEDDS). Moreover they help in improving the efficacy of the drug allowing dose reduction and side effect minimization [4]. The potential of microemulsions or self-microemulsifying drug delivery systems (SMEDDS) in the improvement of the bioavailability and therapeutic performance of the hydrophobic agents has been very well-established for drugs like tacrolimus, glibenclamide, fenofibrate & furosemide [5-9]. The rationale of this project was to develop SMEDDS of Lurasidone HCl which will help in enhancing its solubility and thereby increase its bioavailability. Hence the present study was aimed to develop and evaluate an optimal SMEDDS formulation containing LH.

MATERIALS AND METHODS

LH was obtained as a gift sample from Glenmark Generics Limited (Gujarat, India). Capmul MCM, Captex 355 and Captex 200P were obtained as gift samples from Abitec (USA). Maisine, Peceol,

Labrasol and Transcutol HP were obtained as gift samples from Gattefosse India Pvt. Ltd. (Mumbai, India). Kolliphor RH40 (Cremophor RH40), Kolliphor EL (Cremophor EL) and Kollisolv P (Soluphor P) were obtained as gift samples from BASF South East Asia Pvt Ltd (India).

Span 20, Span 80, Tween 20, Tween 80 and Propylene Glycol (all AR grade) were obtained from SDFCL (Mumbai, India). Microcrystalline cellulose (MCC) was obtained from Research Lab-Fine Chemical Industries Pvt Ltd (Mumbai, India). Aeroperl 300 Pharma was purchased from Evonik (India). All other chemicals and reagents used were of AR grade.

Characterization of liquid SMEDDS

Solubility studies

The saturation solubility of LH was evaluated in various oils, surfactants, and cosurfactants as given in fig. 1. In this study, an excess amount of LH was added to 2 ml of each of the vehicle in eppendorf tubes and the mixture was mixed on a cyclomixer till it remained undissolved.

Then they were put in an orbital shaker for 24 h under ambient temperature to attain equilibrium. Aliquots of supernatant were diluted with methanol and analyzed for dissolved drug by the UV spectrophotometry (Lambda 25 UV/Visible spectrometer with UV Win lab software, Perkin Elmer, MA, USA) at λ_{max} 315 nm.

Water uptake studies

Using different combinations of surfactant: cosurfactant: oil, the amount of water uptake in each mixture was determined. The mixtures showing maximum water uptake were chosen and carried forward for drug loading.

Drug loading

Since LH has a poor solubility hence the mixtures showing maximum water uptake were loaded with 20 mg (dose) drug. From these batches, the mixture containing Cremophor RH40, Soluphor P and Capmul MCM was found to solubilize 20 mg drug. Hence this was selected and ternary phase diagrams were constructed for further optimization.

Pseudo ternary phase diagrams

Pseudo ternary phase diagrams of oil, surfactant/cosurfactant (S/CoS), and water were developed using the water titration method. The mixtures of oil and S/CoS at certain weight ratios were diluted with water in a drop wise manner. For each phase diagram (fig. 2) at a specific ratio of S/CoS (i.e. 1:1, 1:2wt./wt.), a transparent and homogenous mixture of oil and S/CoS was formed by vortexing for 5 min. Then each mixture was titrated with water and visually observed for phase clarity and flowability. The concentration of water at which turbidity-to-transparency and transparency to-turbidity transitions occurred was derived from the weight measurements. These values were then used to determine the boundaries of the microemulsion domain corresponding to the chosen value of oils, as well as the S/CoS mixing ratio. To determine the effect of drug addition on the microemulsion boundary, drug loading was carried out in the ratio which showed best microemulsion formation. Phase diagrams were then constructed using TriDraw Version 4.5 software.

Preparation of liquid SMEDDS

A series of SMEDDS formulations were prepared using Cremophor RH40, Soluphor P as the S/CoS combination and Capmul MCM as the oil. Different ratios of Cremophor RH40 and Soluphor P (1:1, 1:2, 1:3, 1:4 and 4:1) with Capmul MCM in ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 w/w were tried and maximum water incorporated was weighed. In all the formulations, drug (20 mg) was loaded. Briefly, accurately weighed LH was placed in a test tube, and oil, surfactant, and cosurfactant were added. Then the components were mixed by gentle stirring and vortex mixing and were heated on a magnetic stirrer, until LH was perfectly dissolved. The microemulsion thus formed was then stored at room temperature and evaluated [6, 7].

Evaluation of liquid SMEDDS

Drug excipient compatibility study

IR spectroscopy was conducted for drug and formulation using a FTIR spectrophotometer (Perkin Elmer, RXI, USA) and spectrum was recorded in the region of 4000 to 400 cm^{-1} .

Clarity test

0.5 ml of pre-concentrate SMEDDS was diluted with 250 ml distilled water. It was tested against white and black background and turbidity was checked for any visible particles [6].

Precipitation by visual inspection

0.5 ml of pre-concentrate SMEDDS was diluted with 100 ml of distilled water in a glass beaker at room temperature and the content was gently stirred. The tendency to form a transparent or clear emulsion was judged as good and bad when the formation was poor or milky in appearance. The prepared microemulsions were studied for this and observed for 24 h any sign of drug precipitation [7].

% Transmittance measurements

The percentage transmittance of pre-concentrate at 650 nm was determined using UV spectrophotometer keeping distilled water as a blank. Each measurement was carried out in triplicate.

Thermodynamic stability studies [8-10]

Microemulsions are thermodynamically stable formulation and are formed at a particular concentration of oil, surfactant and water, with no phase separation, creaming and cracking. The selected formulations were subjected to different thermodynamic stability by using freeze thaw cycle and centrifugation stress tests.

Centrifugation test

In this, the samples were centrifuged at 10,000 rpm for 10 min and then were examined for whether the system is monophasic or biphasic.

Freeze thawing

Freeze thawing was employed to evaluation the stability of the formulation. The microemulsion formulation was subjected to freeze

thaw cycle, which included freezing at 4°C for 24 h followed by thawing at 40 °C for 24 h. The various formulations were then subjected to centrifugation at 3000 rpm for 5 min. The formulations were then visually observed for phase separation.

Dispersibility studies

Pre concentrate SMEDDS were diluted to 100 times with various dissolution media viz. water, buffer pH 1.2 and buffer pH 6.8. The diluted micro-emulsions were stored for 24 h and observed for any sign of phase separation or drug precipitation thereby indicating its dispersibility.

Particle size distribution (PSD) and zeta potential

The optimized batch was outsourced for determination of particle size and zeta potential. A dispersion of pre-concentrate SMEDDS was prepared. After ensuring complete dispersion of the formulation the droplet size of resultant micro-emulsion was determined by photon correlation spectroscopy that analyze the fluctuation in light scattering due to the Brownian motion of the droplets as function of time using a Zetasizer Nano S 90 (Malvern Instruments, U. K).

Preparation of solid SMEDDS

Preconcentrate SMEDDS were adsorbed on solid carrier like MCC and Aeroperl® 300 Pharma (silicon dioxide). Flow properties and drug content were determined and based on the amount of solid carrier used; the final solid carrier was selected.

Evaluation of solid SMEDDS

Flow properties

The adsorbed SMEDDS were evaluated for the following flow properties:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Drug content

0.1 g of MCC adsorbed SMEDDS were taken and diluted with methanol. The concentration of drug in this was determined using UV spectrophotometer at 315 nm. Similar process was carried out for determining drug content in Aeroperl adsorbed SMEDDS.

In-vitro dissolution rate studies

For *in vitro* dissolution study, adsorbed SMEDDS equivalent to 20 mg of LH filled in hard gelatin capsules was carried out using USP dissolution Apparatus-type I (Basket) & II (Paddle) to check release pattern. The dissolution was maintained at 37 °C ± 0.5 °C and the paddle and basket speed was set at 50 rpm both. 5 ml aliquots were withdrawn at of 5, 10, 15, 20, 25, 30, 45, 60 min intervals. At the same time 5 ml of fresh media was replaced in the vessel. The samples were analyzed for drug content by spectrophotometric method at λ_{max} 315 nm using UV visible double beam spectrophotometer [11].

Ex-vivo studies

All experiments and protocols described in this animal study were approved by the Institutional Animal Ethics Committee (Approval no: CPCSEA/IAEC/SPTM/P-17/2015) and were in accordance with the guidelines of the Committee for Purpose of Control and Supervision of Experiments on Animals and Government of India. To check the intestinal permeability, small portion of small intestine of Albino wistar rats was isolated and used for the *ex vivo* permeability study. The tissue was thoroughly washed with pH 3.8 McIlvaine's buffer to remove any mucous and lumen contents and tied with a thread at one end. The pre-concentrate SMEDDS, 0.5 g (equivalent to 20 mg LH) was filled in the sac. Around 30 ml of McIlvaine's buffer pH 3.8 was used. The other end was again tied with a knot thereby forming a sac containing the microemulsion. Aliquots were taken from the medium at 5, 10, 15, 20, 25, 30, 45 and 60 min and suitably

diluted further. The absorbance was measured using a UV-Visible spectrophotometer at a wavelength of 315 nm.

The amount of drug diffused (%) was calculated against time and plotted on a graph as shown in fig. 6 [12].

RESULTS AND DISCUSSION

Solubility studies

The components used and their concentration have profound effects on the various characteristics of microemulsion, such as particle size, emulsification time and *in vitro* drug release. Hence, it is important to optimize the quantities of the SMEDDS components after initial selection. The initial selection of the components can be on the on the basis of their ability to solubilize the drug. [13]

LH is a poorly water soluble drug and the permeability efficiency of the drug is also not known. Hence initially, a saturation solubility study was performed in a preselected set of surfactants, co-surfactants and oils.

The results as given showed that LH showed good solubility in Peceol, Capmul MCM, Kollisolv P (Soluphor P), Cremophor RH40 and Propylene Glycol as seen in fig. 1. Batches prepared using Peceol as oil showed separation of the mixture into two layers. Hence Peceol was not taken for water uptake studies. Hence three batches containing Cremophor RH40: Transcutol HP: Capmul MCM; Cremophor RH40:

Propylene glycol: Capmul MCM and Cremophor RH 40: Soluphor P: Capmul MCM as surfactant, co-surfactant and oil were prepared and evaluated for their water uptake.

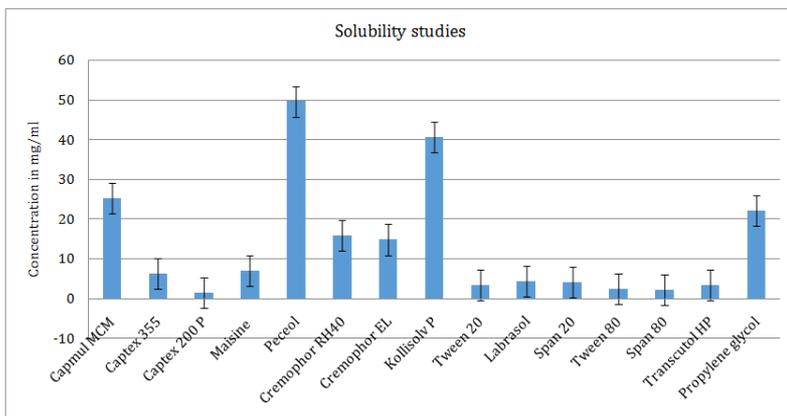


Fig. 1: Solubility of LH in different excipients

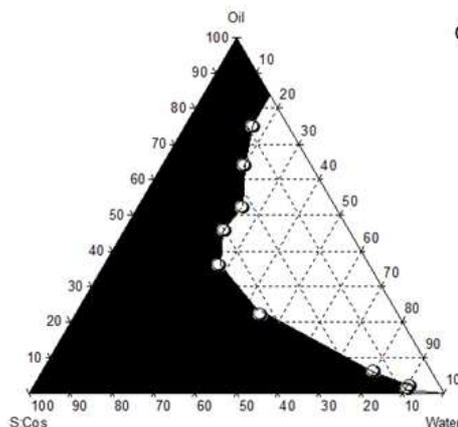
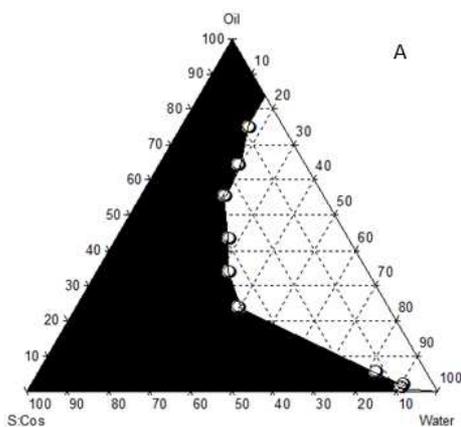
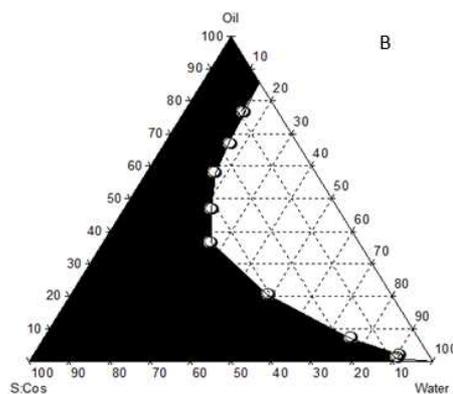
Water uptake studies

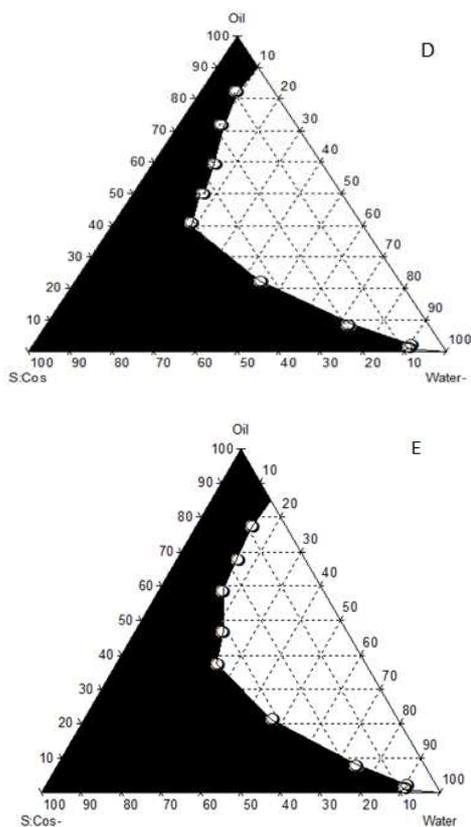
Of the various mixtures, four of them showed maximum water uptake. Hence these four batches were then tested for drug loading of 20 mg.

Drug loading

The mixture containing Cremophor RH40, Soluphor P and Capmul MCM could be incorporated with 20 mg of drug easily. Hence ternary diagrams were constructed using this mixture with the help of TriDraw software (Version 4.1a). From these diagrams (fig. 2) a microemulsion region was obtained. The shaded region indicates the microemulsion area. A wider microemulsion region indicates better microemulsifying ability [14]. A series of points from the microemulsion region was selected and drug loading was checked again at these points.

Following are the ternary phase diagrams for different ratios of surfactant: cosurfactant:





Ternary phase diagrams for the ratios	Fig. 2
1:1	(A)
1:2	(B)
1:3	(C)
1:4	(D)
4:1	(E)

Fig. 2: Ternary phase diagrams for the ratios

From each of the diagram different concentrations were taken from oil, cosurfactant and surfactant and drug loading was tried. It was found that Batch L3, L4, L5 and L6 showed a clear microemulsion even on adding 20 mg of drug.

Table 1: Results for evaluation tests performed

Tests performed	Batch L3	Batch L4	Batch L5	Batch L6
Clarity	√	√	√	√
Precipitation	√	X	X	X
% Transmittance	75.09	76.4	81.2	85
Freeze thawing	X	X	X	X
Dispersibility studies	X	X	X	X

Where, √-Passed and x-Failed, On the basis of evaluation tests Batch L6 was selected which consisted of a ratio of 1:4 of surfactant: co-surfactant. The complete mixture contained 14% Cremophor RH40, 68% Soluphor P, 18% Capmul MCM in the pre-concentrate SMEDDS formulation Batch(L6) was then taken forward for particle size analysis and zeta potential measurement since it satisfied all the evaluation tests.

Table 2: Evaluation of adsorbed SMEDDS on different solid carrier (n=3)

Solid Carrier	% Carr's Index (mean±SD)	Hausner's ratio (mean±SD)	% Drug content (mean±SD)
MCC	42.23±0.07	1.819±0.22	89.219±0.43
Aeroperl 300 Pharma(silicon dioxide)	17.6±0.21	1.22±0.12	93.753±2.60

Carr's index was found to be 17.6 % and Hausner's ratio was 1.22 for Aeroperl adsorbed SMEDDS which was within the acceptable limits. Hence Aeroperl was selected as a suitable adsorbant.

Hence these batches were subjected to evaluation

Drug excipient compatibility study

An FTIR spectrum is used to determine the interaction between the drug and the excipients used in the formulation. Lurasidone HCl shows peaks at 738±4, 776±4, 963±4, 1143±4, 1181±4, 1288±4, 1314±4, 1367±4, 381±4, 1423±4, 1493±4, 1687±4, 1761±4, 2848±4, 2879±4, 2929±4, and 3417±4 cm⁻¹. The formulation spectrum showed these drug peaks as well as additional peaks of the surfactant and cosurfactant used. However, the drug peaks were not affected by the presence of excipients, thus proving that the drug was compatible with the excipients used.

The results for test for clarity, precipitation, %transmittance and stability cycles (centrifugation, freeze thawing and dispersibility study) were found to be as given in table 1.

Particle size and zeta potential

The droplet size/particle size is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as absorption. The significance of emulsion droplet size in the *in vivo* performance of the formulation is not yet clear. Tarr and Yalkowsky have demonstrated enhancement of the rate of intestinal absorption of cyclosporine through the reduction of the emulsion droplet size [14].

One of the reasons for enhanced absorption observed with the small particle size is the larger surface area available for partitioning of the drug and for lipase activity. However, as per a recent statement by Pouton [15], the role of droplet size is less important than it was assumed by some authors due to the fact that digestion will take place directly after the lipid dispersion leaves the stomach and at this stage particle size will have no or little effect. The results for particle size and zeta potential obtained were as given in fig. 3.

These results showed particle size of 3.957 μm and zeta potential of above 50 mV which proved that the microemulsion formed was stable. The average diameter of microemulsion droplets is mainly due to cosurfactant molecules penetrating the surfactant film, lowering the fluidity and surface viscosity of the interfacial film, decreasing the radius of curvature of the microdroplets and forming a transparent system [13].

Preparation and evaluation of adsorbed SMEDDS

The pre concentrate microemulsion was adsorbed using suitable solid carriers-MCC (Microcrystalline cellulose) and Aeroperl (silicon dioxide) so as to form adsorbed SMEDDS to be filled in the capsule. On the basis of drug content and flow properties obtained the optimum solid carrier was selected as given in table 2

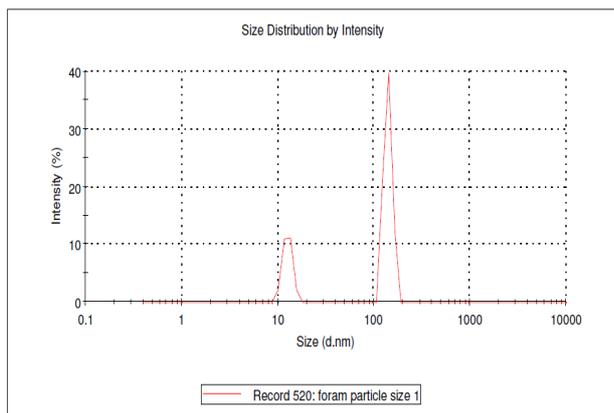


Fig. 3: Report of particle size distribution

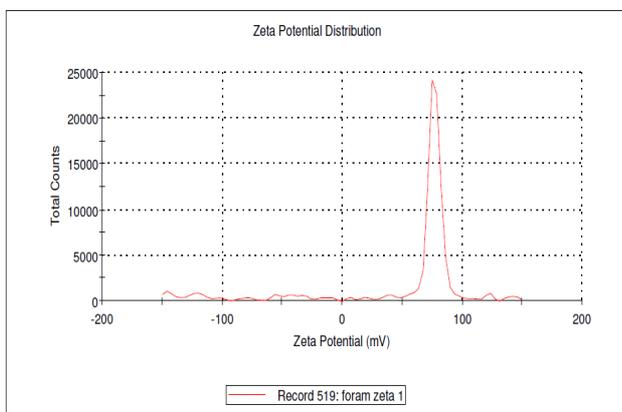


Fig. 4: Report of zeta potential

In-vitro dissolution rate studies

Next evaluation parameter was determining the release of drug from capsules *in-vitro*. Dissolution was carried out using USP Apparatus I & II.

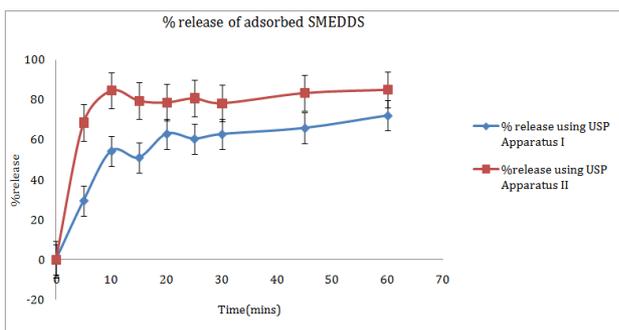


Fig. 5: Release pattern of adsorbed SMEDDS using USP Apparatus I and II (n=3)

Apparatus II showed 85 % release of the drug at the end of 60 min in comparison to 72 % release shown by Apparatus I as seen in fig. Hence apparatus II was selected as the preferred USP Apparatus to be used to carry out *in-vitro* dissolution of capsules.

Comparison of pure drug with formulation

A comparison of the drug release was done between pure drug in capsule and finished formulation in capsule. Fig. 6 shows that there was about 15 % release of pure drug from capsule at the end of 1 h

but a 5–6 folds increase was obtained at 5 min interval by capsule containing SMEDDS showing enhancement in solubility due to reduction in particle size by micro emulsification

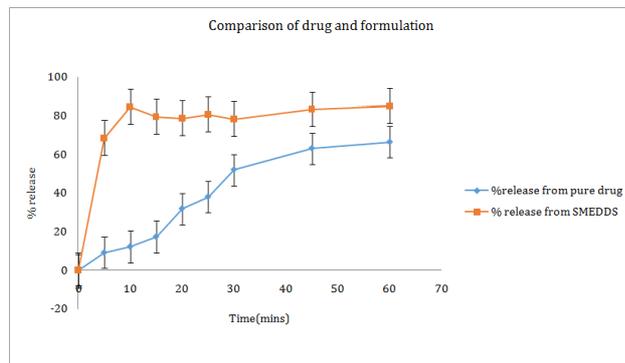


Fig. 6: A comparison of the % release of drug from capsule containing pure drug and SMEDDS respectively (n=3)

Diffusion profile

To understand the characteristics of drug permeation, *ex vivo* intestinal tissue permeation study was carried out across the small intestine of male Albino Wistar rats. The amount of LH permeated across rat intestinal tissue was determined by UV Spectrophotometer. The profile of drug permeation is shown in fig. 7. In the first half hour, the permeation of drug through the intestinal membrane from the pre-concentrate SMEDDS was 64.109±0.707. More than 50 % of the drug permeated across the intestine tissue within half an hour from.

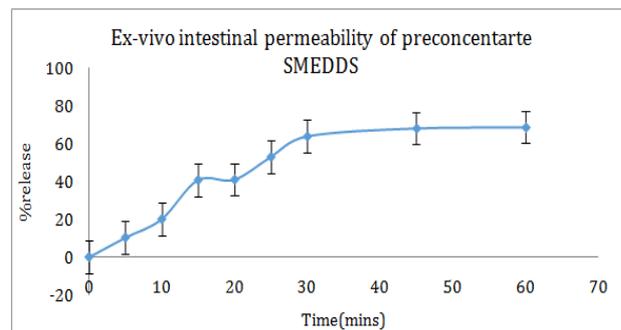


Fig. 7: Diffusion profile of LH in *ex-vivo* intestinal permeability study (n=3)

CONCLUSION

A SMEDDS formulation of poorly water soluble drug, LH was formulated by directly filling into hard gelatin capsules used for oral administration. The SMEDDS of lurasidone HCl were optimized by using parameters like clarity, precipitation, % transmittance, robustness to dilution, freeze thawing, particle size determination, zeta potential, drug content, flow properties and *in vitro* drug release. The optimized LH SMEDDS is composed of 14% Cremophor RH40, 68% Soluphor P, 18% Capmul MCM and complete drug release which showed limited dissolution rate. The results of the study show the ability of SMEDDS to enhance solubility and dissolution of poorly water soluble compounds like lurasidone hydrochloride.

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CONFLICTS OF INTERESTS

Declared None

REFERENCES

1. Yan J. Regulators and clinicians alike struggle with off-label use and safety risks of atypical antipsychotics in young patients. *The Tablet* 2011;12:1-7.
2. Loehr VR, Trueba AF, James D. Calvert. Lurasidone for the treatment of schizophrenia: new advance or nothing new? *The Tablet* 2011;12:7-14.
3. Mittal A, Yadav M, Choudhary D, Shrivastava B. Enhancement of solubility of lurasidone HCl using solid dispersion technique. *Int J Res Ayurveda Pharm* 2014;5:632-7.
4. Khan BA, Bakhsh S, Khan H, Mahmood T, Rasul A. Basics of self micro emulsifying drug delivery system. *J Pharm Alternative Med* 2012;1:13-20.
5. Mandal S, Mandal S. Microemulsion drug delivery system: a platform for improving dissolution rate of poorly water soluble drug. *Int J Pharm Sci Nanotechnol* 2011;3:1214-9.
6. Borhade V, Nair H, Hegde D. Design and evaluation of self-microemulsifying drug delivery system (SMEDDS) of tacrolimus. *AAPS PharmSciTech* 2008;9:13-21.
7. Nawale R, Mehta B. Glibenclamide loaded self-microemulsifying drug delivery (SMEDDS): Development and optimization. *Int J Pharm Pharm Sci* 2013;5:325-30.
8. Mahajan H, Shaikh T, Baviskar D, Wagh R. Design and development of solid self-microemulsifying drug delivery system (SMEDDS) of fenofibrate. *Int J Pharm Pharm Sci* 2011;3:163-5.
9. Deshmukh A, Nakhat P, Yeole P. Formulation and in-vitro evaluation of self-microemulsifying drug delivery system (SMEDDS) of furosemide. *Scholars Res Library* 2010;2:94-106.
10. Bali V, Ali M, Ali J. Nanocarrier for enhanced bioavailability of a cardiovascular agent: *In vitro*, pharmacodynamic, pharmacokinetic and stability assessment. *Int J Pharm* 2011;403:46-56.
11. DH Oh. Comparison of solid self-microemulsifying drug delivery system (solid SMEDDS) prepared with hydrophilic and hydrophobic solid carrier. *Int J Pharm* 2011;420:412-8.
12. Ghosh PK, Majithia RJ, Umrethia ML, Murthy RSR. Design and development of microemulsion drug delivery system of acyclovir for improvement of oral bioavailability. *AAPS PharmSciTech* 2006;7:77-85.
13. Reddy SM, Reddy MS, Reddy NS, Reddy OM. Formulation and evaluation of novel lipid based solid self nano emulsifying drug delivery system of repaglinide. *Int J Pharm Sci* 2014;6:106-10.
14. Ammar HO, Ghorab MM, Mostafa DM, Ghoneim AM. Self-nanoemulsifying drug delivery system for sertraline hydrochloride: Design, Preparation and Characterisation. *Int J Pharm Sci* 2014;6:589-95.
15. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. *Eur J Pharm Sci* 2000;11:S93-8.