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DEVELOPMENT OF MICROEMULSION BASED INTRANASAL DRUG DELIVERY SYSTEM FOR AN ANTI-PSYCHOTIC DRUG

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Abstract:

Purpose: The present study was intended to develop lurasidone micro emulsion for intranasal delivery in the treatment of psychosis.

Methods: Sesame oil, tween-20(surfactant) and plurol oleique(co-surfactant) were selected based on the solubility of lurasidone. Pseudo ternary phase diagram was constructed to know the surfactant: co surfactant ratio which can form microemulsion. The prepared micro emulsion was characterized for FTIR, thermodynamic stability, droplet size and zeta potential, drug content, in-vitro diffusion study, stability study and release kinetics.

Results & Conclusion: The ratio of surfactant to co surfactant 1:2 and 1:3 were selected from the pseudo ternary phase diagrams. Among all the formulations LA1 showed higher diffusion rate (99.11%) with a particle size of 3.957µm and zeta potential above 50mv. The optimised formulation was stable for a period of 3 months. Thus Lurasidone intranasal micro emulsion was developed which improved solubility and hence in-vitro diffusion of the drug.

KEY WORDS: *Micro emulsion, intranasal drug delivery, pseudo ternary phase diagram, zeta potential.*

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INTRODUCTION:

Intranasal drug delivery is one of the intense delivery options for brain targeting. In intranasal route of administration the drug is insufflated through the nose. It could be additionally topical administration or systemic administration. Attentiveness in nasal route for therapeutic purpose arises from the anatomical, physiological and histological characteristics of the nasal cavity which provide rapid systemic drug absorption and quick onset of action. The nasal route contains vascularized epithelium with larger surface area for drug absorption, lower enzymatic activity compared to GIT and it is a non-invasive route, ease of application and self-administration is possible [1-3].

Micro emulsion drug delivery system is an isotropic mixture of oil, surfactant and co-surfactant and drugs which emulsify spontaneously to produce fine water-in-oil emulsion when introduced in to aqueous phase under gentle agitation. Microemulsion based alternative drug delivery system will result in rapid nose to brain transport of drug and distribution in to and within the brain. This can help to maximize the therapeutic index of the drug, reduce the side effect, decrease the dose and frequency of dosing [4].

Lurasidone is an anti-psychotic drug with a poor oral bioavailability of (9-19%) and 99% protein binding and a half-life of 18-40hrs. Micro emulsion formulation was selected to enhance the solubility and bioavailability of lurasidone.

MATERIALS:

Lurasidone was obtained from Nicholas Piramal, Hyderabad, sesame oil, sunflower oil, peanut oil, castor oil, olive oil were obtained from Aclamar oils and fats. Ltd. Hyderabad, labrafil, plurol oleique were gifted by Gattefosse India Pvt ltd, Mumbai, all other chemicals were obtained from S.D Fine chemicals Ltd. Hyderabad.

METHODS:

SOLUBILITY STUDIES:

The solubility of lurasidone in selected oils, surfactants and co-surfactants was carried y adding 100mg of drug into each vial containing 5ml of selected vehicle (oils, surfactants and co-surfactants). The above mixture was placed in a vortex apparatus for half an hour and then kept in a shaker for 48 hours at 25ºC. It was then centrifuged at 5000 rpm for 10min. The concentration of solubilized lurasidone was determined using UV visible spectrophotometer[5].

CONSTRUCTION OF TERNARY PHASE DIAGRAM:

Phase diagram is constructed to determine optimum concentration of oil, surfactant and co-surfactant. micro emulsion is formed when titrated with water under agitation condition and it is a thermodynamically spontaneous process. This process is facilitated by presence of surfactant which forms a layer around oil globule in such a way that polar head lies towards aqueous and non polar tail pull out oil thereby reduces surface tension between oil phase and aqueous phase. Also the formation of micro emulsion is greatly influenced by the ratio of surfactant and co-surfactant.

Sesame oil, tween-20 and plurololelque were mixed in nine different S_{mix} ratios of 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9 and titrated with water at intervals and then mixed on a vortex mixer. The solutions were observed visually and categorized in to different phases:

1. Transparent with good flow (c)
2. Slightly clear with medium flow (sc)
3. Turbid with medium flow (t)
4. Slightly turbid with good flow (st)

Based on the observation, phase diagram was constructed using CHEMIX school v3.51 software with point A as oil, point B as Smix and point C as water and the area of micro emulsion was shaded.

PREPARATION OF LURASIDONE MICRO EMULSION:

Based on the area of micro emulsification from the phase diagram, Smix ratio of 1:2 and 1:3 was selected for the formulation development. Micro emulsion formulation was prepared using tween-20 as surfactant and plurol oleique as co-surfactant. The weight of the formulation was kept approx. 500mg. Quantity of lurasidone in all the formulation was 40mg. Lurasidone was accurately weighed and placed in a glass vial with required quantity of sesame oil. The components were mixed by gentle stirring and vortex mixer. Respective quantity of surfactant and co-surfactant were added to glass vial and mixed by vortex mixer. The mixture was then stored at room temperature [6].

Table no.1 Developed lurasidone micro emulsion with their composition

Formulation codes	LA1	LA2	LA3	LA4	LA5	LB1	LB2	LB3	LB4	LB5
Lurasidone(mg)	40	40	40	40	40	40	40	40	40	40
Smix Ratio	1:2					1:3				
Oil:Smix	1:1	1:2	1:3	1:4	1:5	1:1	1:2	1:3	1:4	1:5
Sesame oil (mg)	130	90	80	70	60	130	90	80	70	60
Tween-20 (mg)	110	123.3	126.6	130	133.3	107.5	117.5	120	122.5	125
Plurololeique (mg)	220	246.7	253.4	260	266.7	222.5	252.5	260	267.5	275

CHARACTERIZATION OF MICRO EMULSION:

Thermodynamic stability[7-13]:

Thermodynamic stability study of micro emulsion was carried out in order to determine physical stability of the formulation.

Centrifugation study:

Formulation were subjected to centrifugation at 5000 rpm for 30min and observed for phase separation, creaming and cracking. The formulation which showed maximum stability were selected and studied for heating-cooling cycle and freeze-thaw cycle.

Heating – cooling cycle:

In this cycle the formulation were subjected to 45ºC and 0ºC temperature for 48hr's, for each temperature cycle using stability chamber. Formulation that does not show any phase separation are subjected to freeze-thaw cycle.

Freeze – thaw cycle:

Micro emulsions were stored at 25ºC for 2hrs followed by 24hrs at -5ºC the cycle was repeated 3times and the change in stability of micro emulsion was noted.

Determination of droplet size and zeta potential:

Zeta potential of formulation was measured by using Malvern Zeta sizer equipped with a 4.0mW He-Ne red laser. Zeta sizer measures the potential range from -30-30v. For measurement of zeta potential 1 ml of each formulation were diluted with 100ml of water.

Drug content:

Micro emulsion equivalent to 10mg of lurasidone was dissolved in suitable quantity of buffer(6.4pH). The sample was mixed continuously to dissolve the drug in the buffer and analyzed using UV-Spectrophotometer at 315nm[14-15].

***In-vitro* diffusion studies:**

In-vitro diffusion study of lurasidone micro emulsion was compared to pure lurasidone using Franz diffusion cell using phosphate buffer6.4pH. The formulation was subjected to stirring at 300rpm over a magnetic stirrer at 37ºC. 1ml samples were withdrawn and diluted suitably for a period of 3hours. The concentration of lurasidone was then estimated using UV-Spectrophotometer.

Release kinetics of drug:

The optimised formulation was subjected to release kinetic study. Drug release profile was fitted to zero order kinetics, first order kinetics, Higuchi matrix model and Korsmeyer-peppas model.

Stability studies:

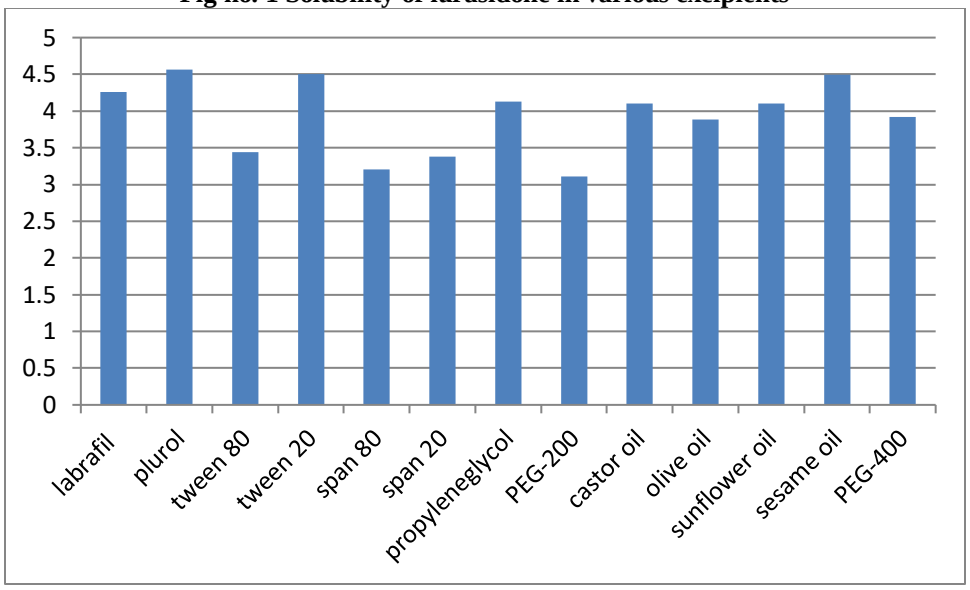
The stability study was performed as per ICH guidelines for a period of 3 months for the optimized formulation at accelerated conditions of 40ºC/75% RH. Based on the stability of the formulation under these conditions shelf life of the formulation can be decided. The formulations were examined periodically after 1, 2 and 3 months for physical stability by means of creaming, phase separation or flocculation [16].

RESULTS AND DISCUSSION:

Solubility studies:

Solubility of lurasidone was found to be higher in sesame oil, tween-20 and plurol oleique. The results of solubility studies are shown in fig no.1.

Fig no. 1 Solubility of lurasidone in various excipients

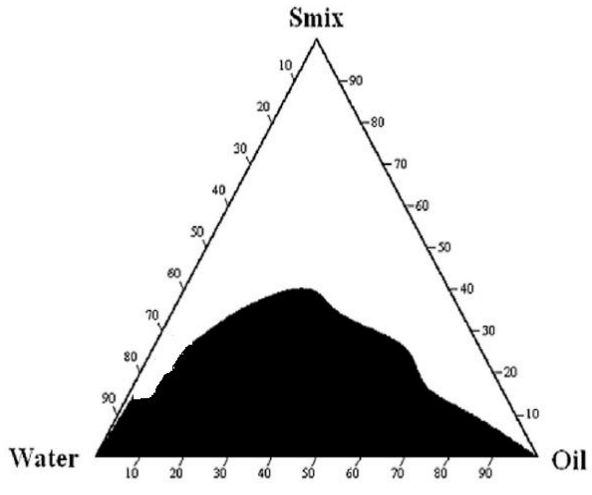


Construction of pseudo-ternary phase diagram:

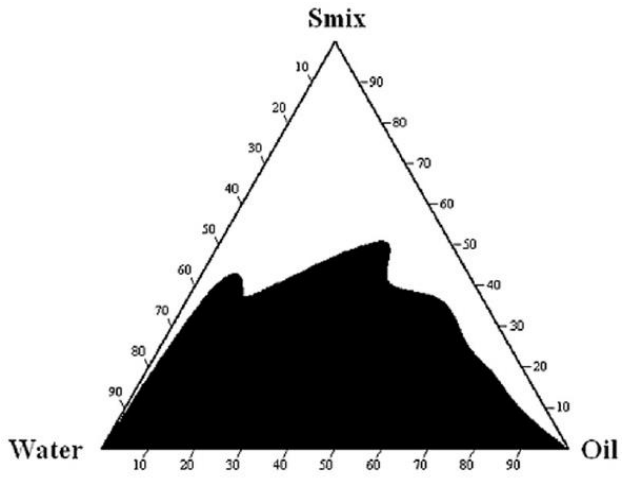
Among all the ratios of surfactant and co-surfactant 1:2 and 1:3 has larger micro emulsion region. size of micro emulsion indicates the greater self-emulsification efficiency. Increase in co surfactant may Depending upon the results 1:2 and 1:3 formulations are selected for further study.

Fig no.2. pseudo –ternary phase diagram with ratios (A. 1:1, B. 1:2, C. 1:3, D. 1:4, E. 1:5, F. 1:6, G. 1:7, H. 1:8, I. 1:9)

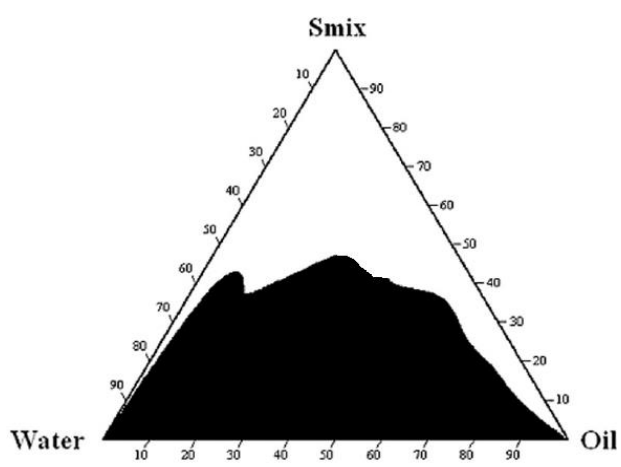
A

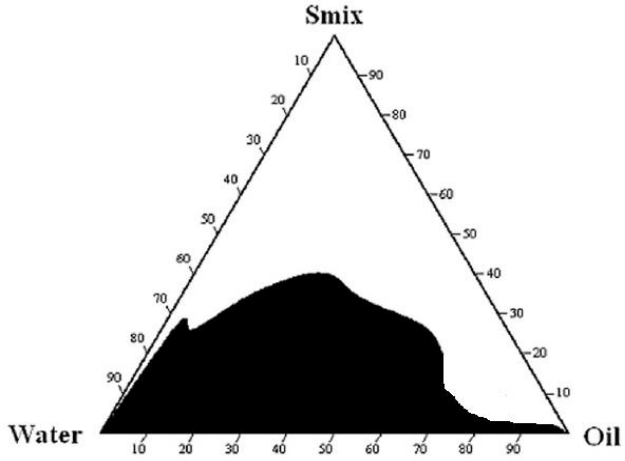


B

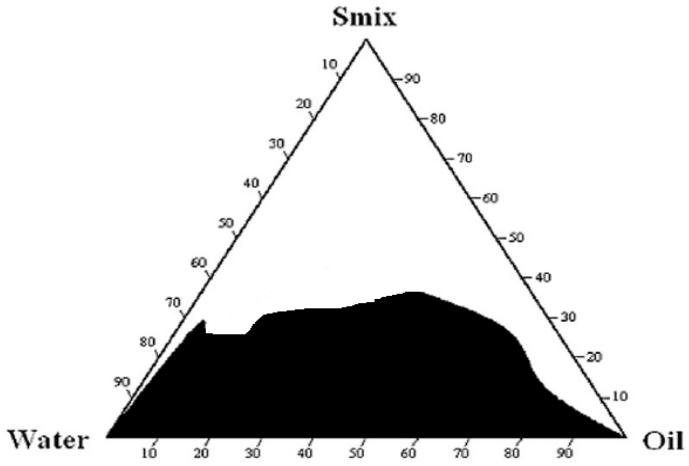


C D

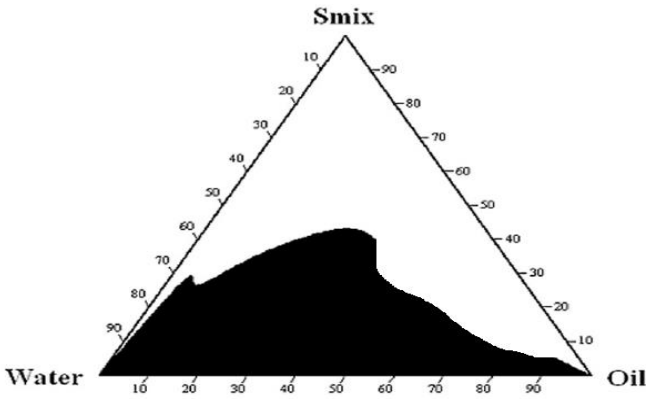




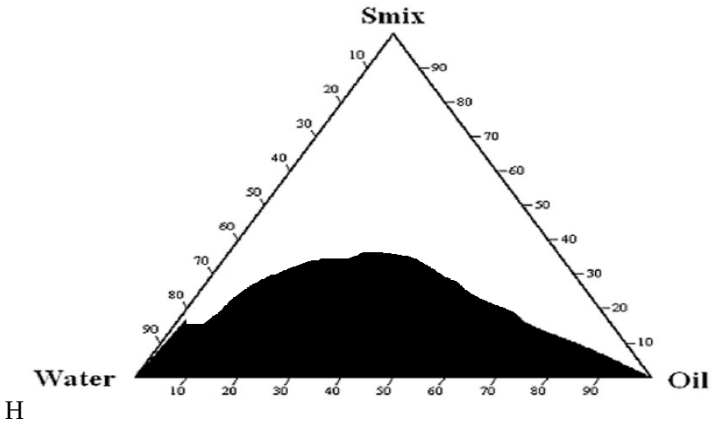
E



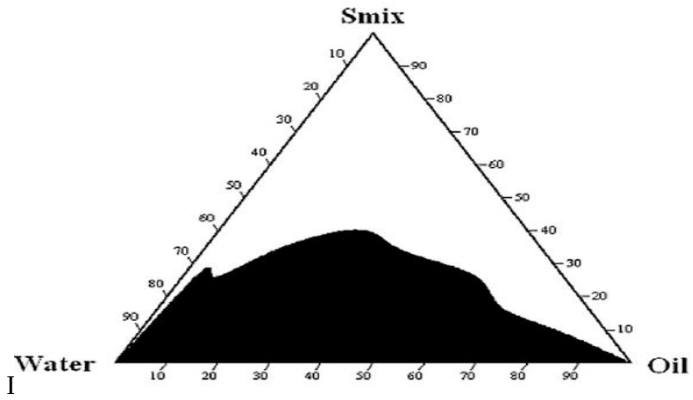
F



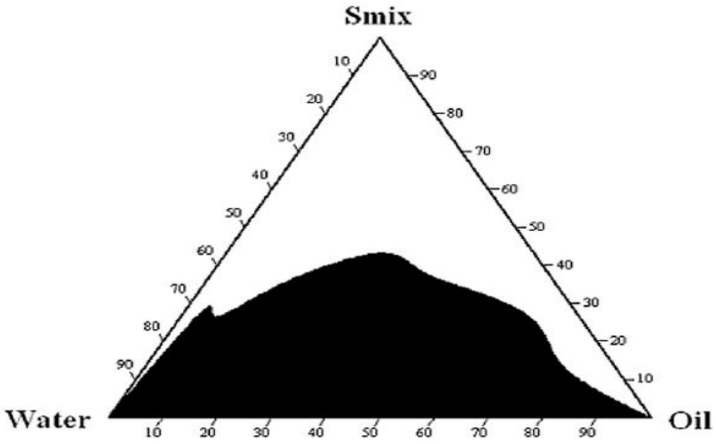
G



H



I



Thermodynamic stability studies:
Formulations were subjected to different stress test such as heating-cooling, centrifugation and freeze-thaw cycle.

Heating-cooling cycle:
All the formulations were subjected to 45ºC and 0ºC temperature for 48hours. LB1, LB4, and LB5 were unstable.LA1-LA5 and LB2, LB3 formulations were stable and further subjected to centrifugation.

Centrifugation:
Stable formulations (LA1-LA5) were subjected to centrifugation at 5000rpm for 30mins. LB2 and LB3 formulations was separated into two phases.

Freeze-thaw cycle:
Formulations with good stability were subjected to freeze-thaw cycle at 25ºC for 2hrs followed by 24hrs at -5ºC the cycle was repeated for 3 times.

Table no.3 Thermodynamic stability and precipitation assessment data

Formulation (1:2)	LA1	LA2	LA3	LA4	LA5
Clarity	Clear	clear	Turbid	Turbid	turbid
Drug precipitation	Absent	absent	Present	Present	present
Stability	Stable	stable	Unstable	Unstable	unstable
Formulation (1:3)	**LB1**	**LB2**	**LB3**	**LB4**	**LB5**
Clarity	Slightly turbid	turbid	Slightly clear	Turbid	turbid
Drug precipitation	Absent	present	Present	Present	present
Stability	Stable	unstable	Unstable	Unstable	unstable

Determination of droplet size and zeta potential:

The results showed particle size of 3.957µm and zeta potential of above 50mv, which proved that the micro emulsion formed was stable.

Fig no.3. Droplet size of lurasidone optimized formulation

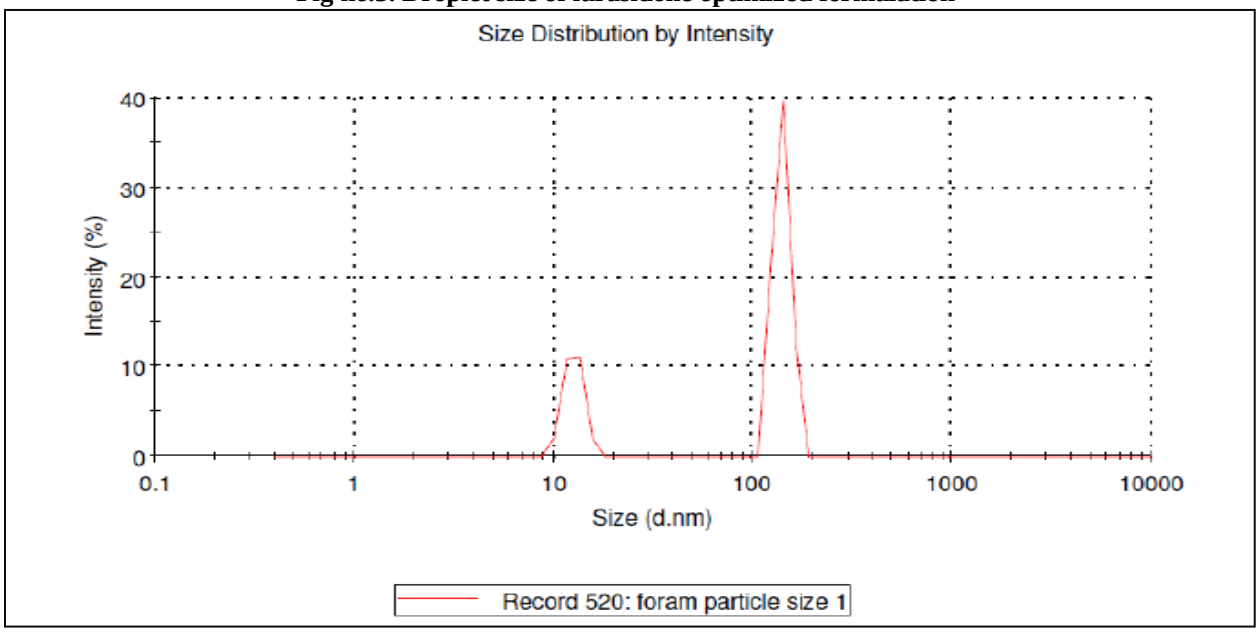
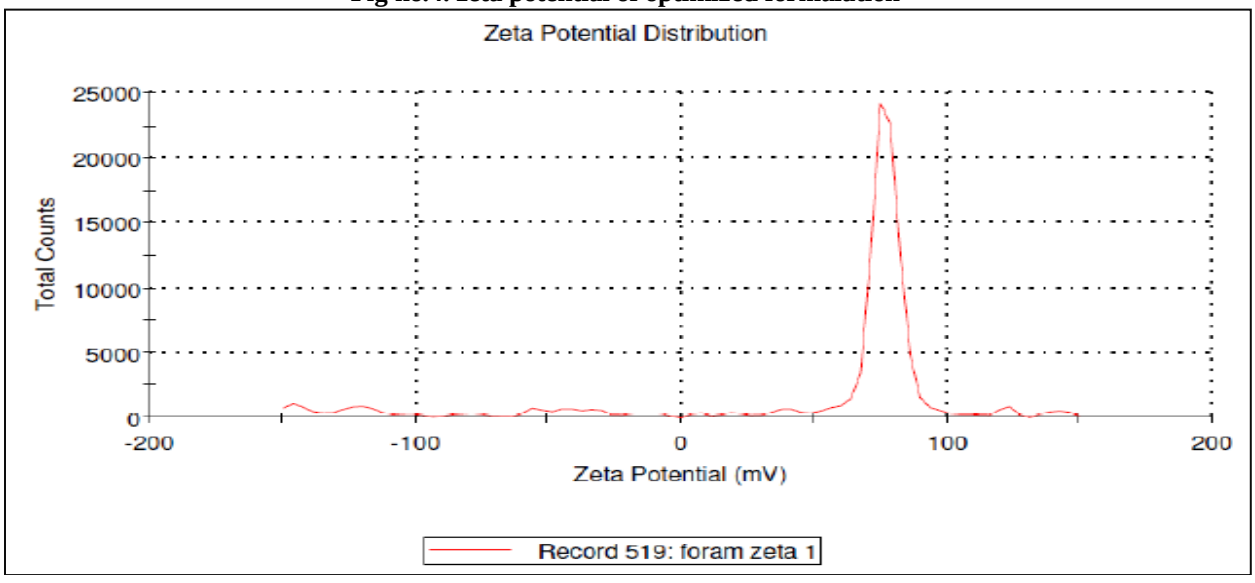


Fig no.4. zeta potential of optimized formulation



***In-vitro* diffusion study:**

In-vitro diffusion studies of developed lurasidone micro emulsions(1:2 and 1:3)were compared with that of pure drug .After 1hr virtually 99.11% of lurasidone was diffused from optimized formulation of lurasidone micro emulsion (LA1) and other formulations were compartively less than optimized formulation. Diffusion studies were carried out for a period of 2hrs and 30min. Pure drug formulation was found to be 89.08%.

Fig.no.5.*In-vitro* diffusion study of different formulation

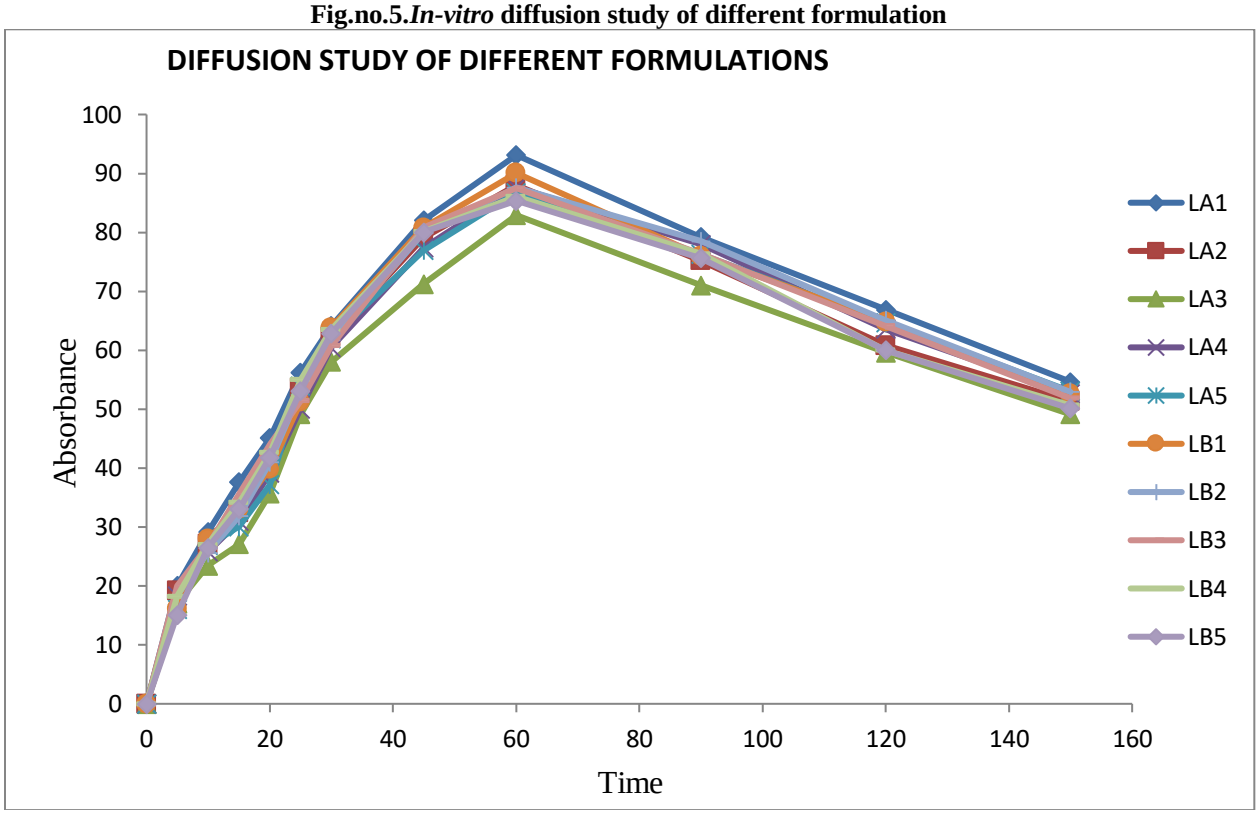
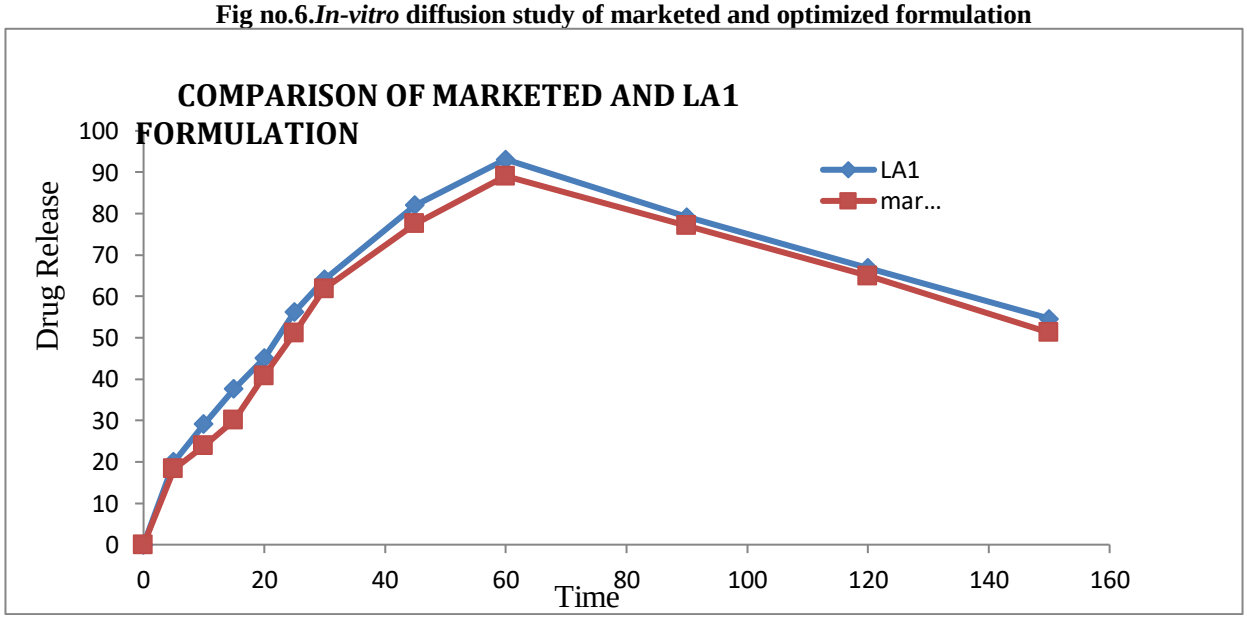


Fig no.6.*In-vitro* diffusion study of marketed and optimized formulation

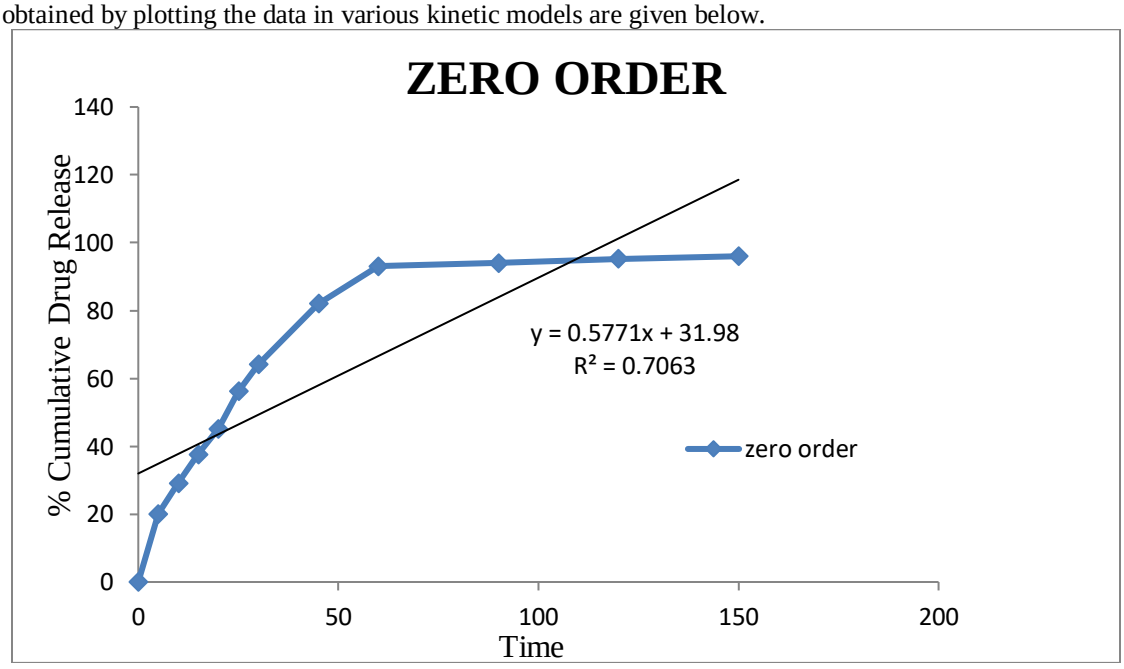


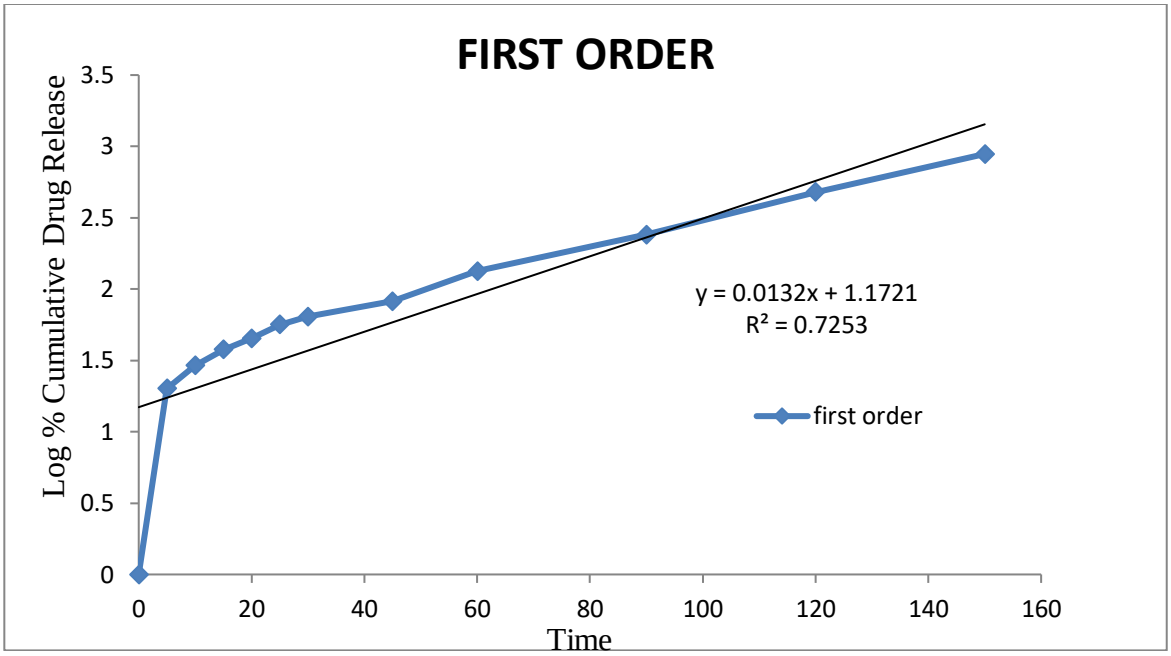
Drug content:
Drug content of selected formulation was given in table.

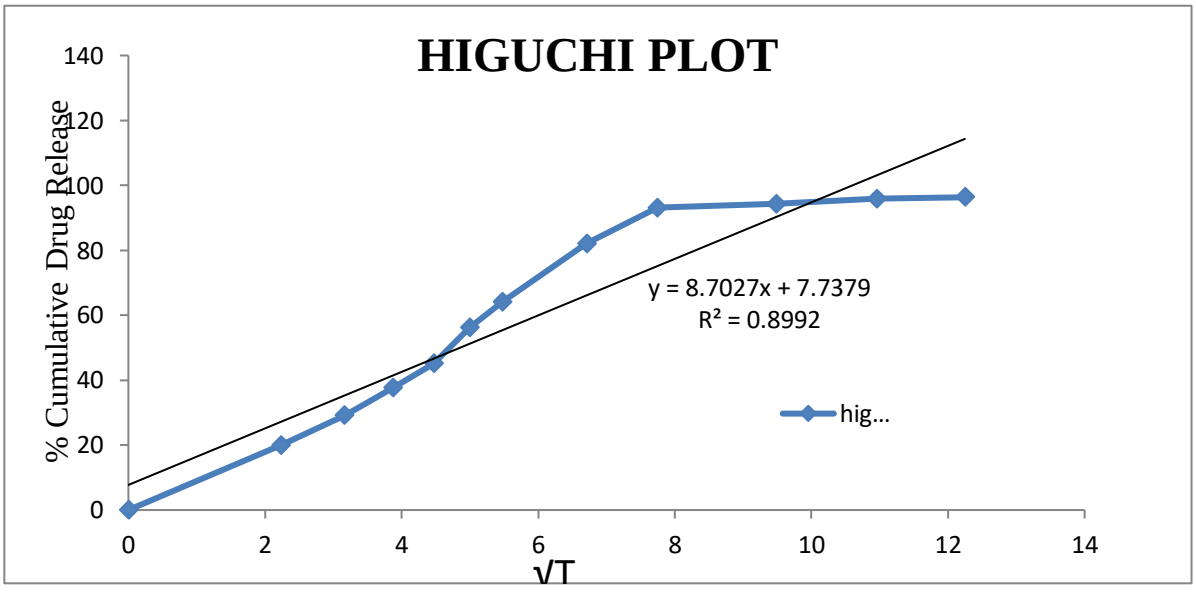
Table.4. Drug content analysis

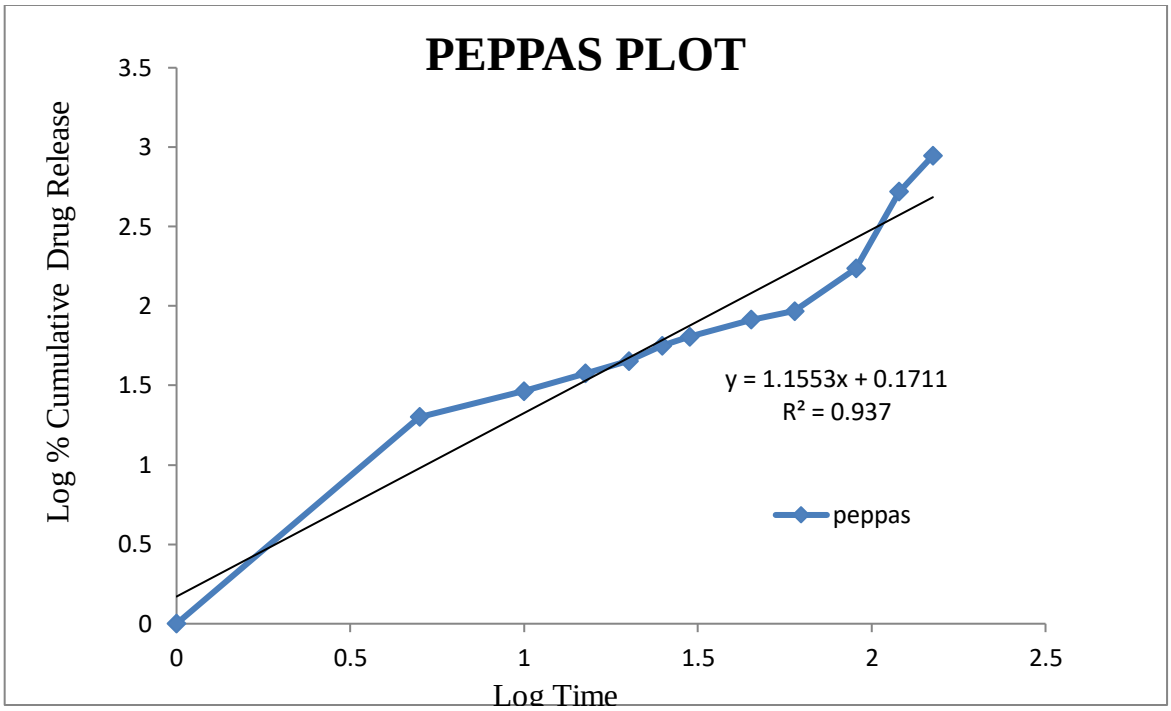
Formulation Code	Drug Content (%)
LA1	99.87
LA2	98.70
LA3	95.34
LA4	97.80
LA5	96.23
LB1	97.76
LB2	93.67
LB3	95.94
LB4	98.13
LB5	92.78

***In-vitro* release kinetics:**
Plots obtained by plotting the data in various kinetic models are given below.




FIRST ORDER
Log % Cumulative Drug Release
3.5
3
2.5
2
1.5
1
0.5
0
0
20
40
60
80
100
120
140
160
Time
y = 0.0132x + 1.1721
R² = 0.7253
first order


HIGUCHI PLOT
% Cumulative Drug Release
140
120
100
80
60
40
20
0
0
2
4
6
8
10
12
14
√T
y = 8.7027x + 7.7379
R² = 0.8992
hig...



Inference:

Based on the correlation values for the various kinetic models the first order kinetics has an R^2 value of 0.725. Hence the release of lurasidone is dependent on its concentration. The Higuchi model also shows R^2 value of 0.899, hence the mechanism of drug release is predominantly diffusion.

Stability studies:

Stability studies for the optimized formulations was performed for 3months. The formulation was examined periodically after 1month, 2month and 3month for phase separation, creaming or flocculation, and drug release was 98.39% by third month indicating the prepared formulation was stable.

Table no.5.Stability data for optimized formulation

Test performed	1Month	2Month	3Month
Clarity	Clear	Clear	Clear
Lurasidone precipitation	Absent	Absent	Absent
Lurasidone content	97.88	96.98	96.02
% lurasidone release	99.09%	98.620%	98.39%

CONCLUSION:

The objective of this study was to develop lurasidone micro emulsion for intranasal delivery. Micro emulsion region from the selected excipients was known from the pseudo-ternary phase diagram. Micro emulsion was prepared from sesame oil, tween-20 and plurololeique in the ratio 1:2 and 1:3. Micro emulsion was subjected to thermodynamic stability testing heating-cooling, centrifugation and freeze-thaw cycle. FTIR and DSC studies indicated there was no interaction between lurasidone and excipients. *In-vitro* diffusion studies were carried out in pH 6.4 buffer for 3 hours using keshary chien diffusion cell. The formulation LA1 showed higher percentage release of 99.03% and showed peppas release kinetics. Stability studies showed that LA1 was stable for a period of 3 months with no significant change in drug release.

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