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## Formulation development of nanostructured lipid carrier loaded emulgel of duloxetine hydrochloride

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### Abstract

The aim of this study was to prepare and evaluate emulgel incorporating nanostructured lipid carriers (NLC) of duloxetine hydrochloride for nasal application. NLC designed for nasal administration of duloxetine hydrochloride, were prepared by the hot homogenization technique. This duloxetine hydrochloride nanostructured lipid carrier was characterized for particle size, zeta potential and SEM. The lipid nanoparticles were incorporated in emulgel for convenient nasal application and evaluated for pH, Rheological analysis, drug content *In-vitro* drug release and stability studies. The preparation of aqueous NLC dispersion with a mean particle size lower than 200 nm has been obtained with uniform size distribution. Amongst all formulations, NLC loaded emulgel prepared with low percentage of stearic acid, Homogenized at 25000 (rpm) was found with the drug diffusion (97.67%). Accelerated stability study showed no significant change in the formulation upto 3 months. Finally it can be concluded that the NLC loaded emulgel of duloxetine hydrochloride may be one of the promising tool in controlling the drug release via. Intranasal drug delivery for effective and longer treatment required for antidepressant activity.

**Keywords:** duloxetine hydrochloride, nanostructured lipid carriers, intranasal drug delivery, emulgel, antidepressant activity

### Introduction

Duloxetine hydrochloride is a antidepressant drug. It is thought to block the reuptake of serotonin and norepinephrine in onuf's nucleus in the sacral spinal cord, there by activating pudendal motor neurons that increase the urethral striated muscle tone and the force of sphincter contraction. This increased sphincter activation prevents involuntary urine loss<sup>[1]</sup>.

The drug is BCS class II (low solubility, high permeability) therefore there is need for enhance the solubility of drug is incorporated in lipid matrix. Nanoparticle, such as solid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are stable colloidal system with notable advantages as drug delivery systems. SLN and NLC are colloidal carrier systems providing controlled release profiles for many substances.

NLC are prepared by mixing solid lipids (oil), prepared with varying stearic acid content and speed of homogenizer obtained NLC. The aim of this study was develop nasal emulgel containing NLC dispersions loaded with duloxetine hydrochloride. The NLC were prepared by high pressure homogenization method. Nanoparticle were characterized in terms of particle size, zeta potential and scanning electron microscopy. The influence of the NLC on *in vitro* drug release

Thus, NLC loaded emulgel of duloxetine hydrochloride can prolong drug release with better penetration across the nasal epithelial membrane<sup>[2]</sup>.

### Materials and Methods

#### Materials

Duloxetine hydrochloride was gifted by Lupin Pharmaceutical. Stearic acid was purchased from Research-Lab Fine Chem. Industry, Mumbai. Oleic acid obtained from Loba Chemie Pvt. Ltd, Mumbai. Sodium lauryl sulphate and Carbopol 934 were purchased from Molychem, Mumbai. All the other chemicals were of the analytical grade. Water was used I double-distilled quality.

#### Methods

##### Preparation of NLC dispersions

The NLC dispersions were prepared using hot high pressure homogenization method (HPH). In order to prepare NLC, table. 1 reports the composition of the prepared NLC dispersions<sup>[3, 4]</sup>.

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**Table 1:** Composition of formulation batches as per 3<sup>2</sup> Full Factorial Design.

| Formulation code              | F1    | F2    | F3    | F4    | F5    | F6    | F7    | F8    | F9    |
|-------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Ingredient                    | %     |       |       |       |       |       |       |       |       |
| Duloxetine Hydrochloride(w/v) | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1     |
| Stearic Acid(w/v)             | 35    | 35    | 35    | 20    | 20    | 20    | 5     | 5     | 5     |
| Oleic Acid(w/v)               | 1.5   | 1.5   | 1.5   | 1.5   | 1.5   | 1.5   | 1.5   | 1.5   | 1.5   |
| SLS(w/v)                      | 1.1   | 1.1   | 1.1   | 1     | 1     | 1     | 0.9   | 0.9   | 0.9   |
| Purified water(v/v)           | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   |
| Speed(RPM)                    | 15000 | 20000 | 25000 | 15000 | 20000 | 25000 | 15000 | 20000 | 25000 |

### Characterization of NLC

#### Determination of particle size, zeta potential, and polydispersity index

Particle size analysis of optimized batch was determined by the (nano zs, Malvern, Worcestershire, UK) instrument at 25°C, which is based on the Brownian motion. Sample were diluted in the particle free purified water to scattering intensity approximately 150300kps. The mean z-average diameter and polydispersity indices were obtained by cumulative analysis using Malvern software. Zeta potential is key indicator of the stability of formulation. The magnitude of zeta potential indicates the degree of electronic repulsion between adjacent, similarly charged particles in dispersion. Zeta potential of the optimized batch was measured by folded capillary cells using the zetasizer. 1ml sample was taken from formulated nano suspension and dispersed with 10ml double distilled water. The samples were ultrasonicated for 5min prior size determination measure the primary particle size. Then the sample was taken in disposable cuvette and placed in the instrument for size and zeta potential measurement [5, 6].

#### Scanning electron microscopy

The morphology i.e shape and surface characteristics of optimized batch of NLC was studied by scanning electron microscopy (SEM) (model JSM 840A, JEOL, Japan). The sputtering was done for nearly 5 minutes to obtain uniform coating on the sample to enable good quality SEM images. The SEM was operated at low accelerating voltage of about 25KV with load current of about 80MA.

### Evaluation of emulgel

#### Determination of pH

The pH of each formulation was determined using digital pH meter previously calibrated by pH 5 and pH 7. The pH value were recorded immediately after preparation. The pH of the formulation batches were determined in triplicate and the average mean was taken to obtain the pH ranges [7].

#### Viscosity

The viscosity of different emulgel formulation was determined at room temperature using a Brookfield viscometer type DV-II + PRO at 10, 20, 30, 40, 50 rpm using spindle (LPV) no. 64. The viscosity of the formulation batches was determined in triplicate and the average mean was then taken to obtain the viscosity of formulations. The viscosity results were also plotted against speed to obtain rheological behavior of formulations [7].

#### Drug content

The emulgel was taken containing 100mg drug in a volumetric flask and sufficient quantity of methanol was added to dissolve the formulation completely and volume was made up to 100ml with methanol to get a concentration of 1000µg/ml. The absorbance of prepared solution was

measured at 290 λ<sub>max</sub> by using UV visible spectrophotometer and % drug content was calculated in the range of 95-105% [7].

#### In-vitro drug release study (Diffusion study)

In-vitro release study of the formulated emulgel was carried out by using diffusion cell through Goat Nasal membrane. Diffusion cell with inner diameter 1.4cm was used for the study. The formulation 1 ml were placed in donor compartment and Freshly prepared 100 ml Phosphate buffer pH 6.8 in receptor compartment. Goat nasal membrane were mounted in between donor and receptor compartment. The position of the donor compartment was adjusted so that nasal membrane just touches the diffusion medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. 2ml of sample is withdrawn from receiver compartment after 30 min, 1, 2, 3, 4, 5, 6, 7 & 8 hrs and same volume of fresh medium is replaced. The withdrawn samples was diluted to 10ml in a volumetric flask with Methanol and analyzed by UV spectrophotometer at 290 nm [6, 8].

#### Drug release kinetic study

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing Zero order (cumulative % drug release v/s. time), Higuchi model (cumulative % drug retained v/s. Square root of time) [9].

#### Accelerated stability studies

To investigate the long-term stability as a function of storage condition, the selected drug loaded nanostructured lipid carrier formulations was stored at different temperatures accelerated and room temperature (40°C±2°C, 75± 5% RH) for 3 months and physical characteristics at the predetermined intervals of 30 days like appearance/clarity, pH, viscosity and drug content were evaluated [10].

### Result and Discussion

#### Particle size

The particle size of the optimized batch (F9) is given in table no.2.

**Table 2:** Size distribution and PDI

| Formulation code    | Particle size Z average (nm) | Particle size(nm) | PDI   |
|---------------------|------------------------------|-------------------|-------|
| Optimized batch(F9) | 131.7                        | Peak 1:144.5      | 0.495 |

The particle size of the Nanostructured Lipid Carrier formulation of optimized batch was found to be 131.7 nm. Shown in fig 1.

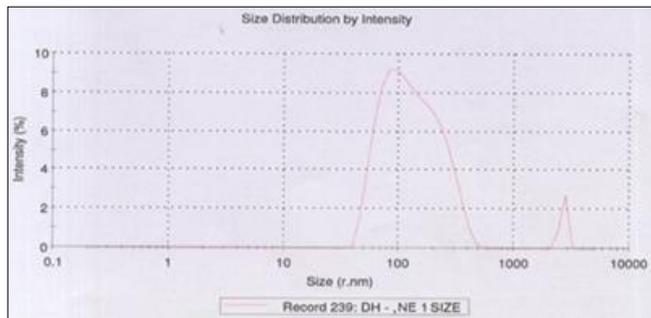


Fig 1: Graph of Particle size

**Zeta potential**

Zeta potential of optimized batch (F9) is given in table no.3

Table 3: Zeta potential

| Formulation         | Zeta potential | Zeta deviation |
|---------------------|----------------|----------------|
| Optimized batch(F9) | -18.0          | 4.87           |

Zeta potential shows the stability of the (colloidal dispersion) nanostructured lipid carrier under the stress testing condition according to ICH guidelines of stability studies of various pharmaceutical formulations. Zeta potential is affected by particle size, lowest particle size in nanosize i.e. 131.7, shows -18.0 mV zeta potential which indicates the thermodynamic instability of the dispersion. Shown in fig 2.

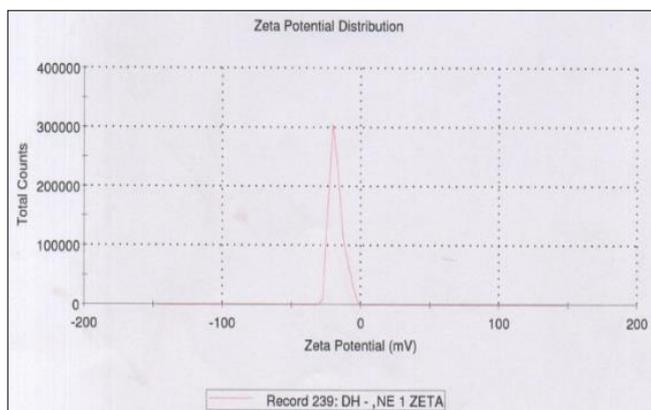


Fig 2: Graph of Zeta potential

**Scanning Electron Microscopy**

Scanning Electron Microscopy of NLC is shown in figure. The shape of the NLC was spherical and the size of the NLC was below micrometre range. Moreover, the micrograph also revealed the some agglomeration of nanoparticle which might be due to the evaporation of water present in formulation during sample preparation prior to SEM analysis. Shown in fig 3.

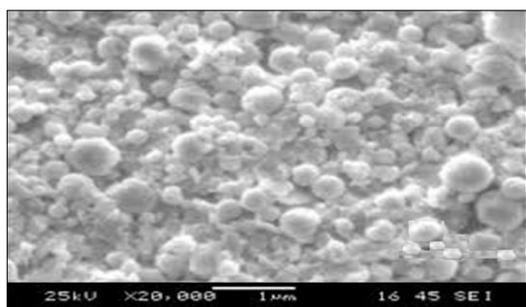


Fig 3: Scanning electron microscopy

**Evaluation of Emulgel**

**pH**

The pH of various emulgel was found to be in range of 6.26 to 6.35. pH value indicate the suitability of emulgel for nasal application.

**Viscosity**

The viscosity is resistance to flow which is important physical property for nasal preparation because it influence drug release as well as jellification the rheological behaviour of the emulgel indicates that the systems were shear thinning in nature showing decrease in viscosity at increasing shear rate. This viscosity result reflects that the decrease in proportion stearic acid and increase in speed of homogeniser results in decrease in viscosity. Shown in fig 4.

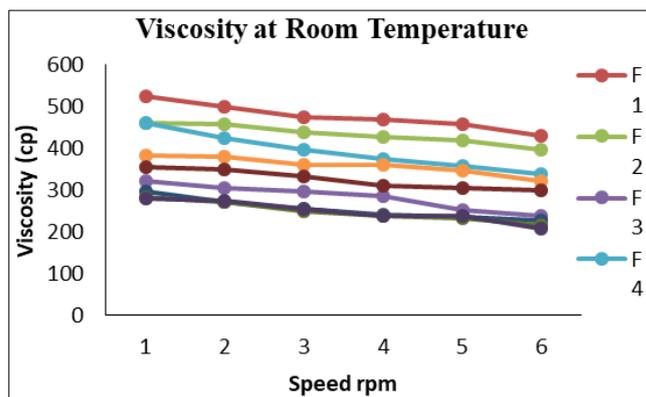


Fig 4: Viscosity of formulations

**Drug content**

The drug content was carried out to ascertain the concentration of drug in each formulation was uniform. The percentage drug content of all prepared emulgel formulations was found to be in the range 95-99%. Therefore uniformity of content was maintained in all formulations.

**In vitro drug release study**

The optimized formulation (F9) was subject to various test to study the effect of variables on its drug profile. In order to study the effect of concentration of stearic acid on drug release, it was found that decrease in concentration level of stearic acid in the formulation drug release rate was increased and increase in speed of homogenizer results in increase in the drug release.

Out of nine formulations maximum release after 8 hrs was found for F9 formulation. This indicates release of 97.67 % drug availability. Shown in fig 5.

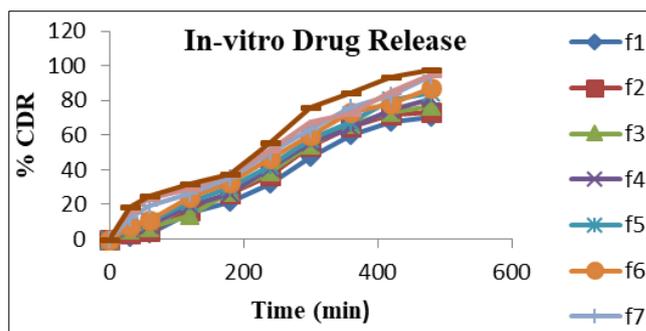
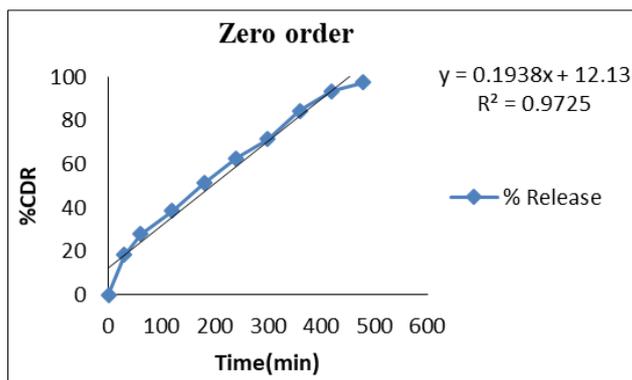


Fig 5: In vitro Drug release profile of optimized formulation (F1-F9)

**Dug release kinetics**

Out of the zero order and higuchi kinetics drug release study, it was observed that the optimized formulation shows the zero

order mechanism which is based on the process of diffusion of the drug and NLC from gel matrix. Shown in fig 6.



**Fig 6:** Model graph for Zero order release kinetics

**Accelerated Stability study**

Stability study of optimized F9 formulation was done at room temperature. The results of stability studies show that the formulation was stable at accelerated temperature condition (40 ± 2° C, 75 ± 5% RH). Results have been given in table no

4. A slight increase in pH and viscosity and a slight decreased in drug content were observed however, these were not significant so as to affect the quality and safety of the formulation after storage.

**Table 4:** Stability Study data for F9 formulation

| S. No | Observations | Before Stability Testing | During study          |
|-------|--------------|--------------------------|-----------------------|
|       |              |                          | 3 <sup>rd</sup> month |
| 1     | Clarity      | Creamy, white            | White cream like      |
| 2     | pH           | 6.30±0.005               | 6.32±0.008            |
| 3     | Drug content | 97.67 %                  | 96.60 %               |
| 4     | Viscosity    | 05                       | 522.8cp               |
|       |              | 10                       | 498.7cp               |
|       |              | 15                       | 475.2cp               |
|       |              | 20                       | 468.8cp               |
|       |              |                          | 540 cp                |
|       |              |                          | 503cp                 |
|       |              |                          | 488cp                 |
|       |              |                          | 472cp                 |

**Conclusion**

Stearic acid based nanostructured lipid carrier dispersion containing duloxetine hydrochloride having low particle size and long term physical stability are prepared successfully using high pressure homogenization technique lipid content and surfactant play important in particle size. Amongst all formulations, NLC loaded emulgel prepared with low percentage of Stearic acid, Homogenized at 25000 (rpm) was found to be better with the drug diffusion(97.67%). Finally it can be concluded that the NLC loaded emulgel of duloxetine hydrochloride may be one of the promising tool in controlling the drug release via. Intranasal drug delivery for effective and longer treatment required for antidepressant activity.

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