Research Article

# Formulation and Evaluation of Nanosuspension of Nisoldipine

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**ABSTRACT**

The aim of this study was to formulate and evaluate nanosuspension of poorly water soluble drug (Nisoldipine) by Nanoprecipitation method with the help of urea and Tween 80 as stabilizer and surfactant respectively. Nanosuspension was subjected to various evaluation tests like drug content, saturation solubility studies, *In vitro* drug release studies, scanning electron microscopy, zeta potential studies. The spectral analysis revealed that there was no interaction between the drug & excipients. From these studies the $F_{17}$ formulation was considered to be the best among all other formulations and it was selected as optimized formulation.

**Keywords:** Nanosuspension, Nano precipitation – Ultrasonication, Nisoldipine.

## INTRODUCTION

More than 40% of the new molecules being generated through drug discovery programmes are poorly water-soluble or lipophilic compounds.[1] Formulating a poorly water soluble drug has always been a challenging task to the pharmaceutical scientists. Nisoldipine is an antihypertensive drug with poor water solubility, high permeability and it belongs to Class II of Bio pharmaceutical classification system (BCS). The formulation of nano-sized particles can be implemented to all drug compounds belonging to biopharmaceutical classification system (BCS) class II and IV to increase their solubility.[2]

There are many conventional methods to increase the solubility of poorly soluble drugs, which includes micronization, solubilisation using co-solvents, salt form, surfactant dispersions, and oily solutions. But nanotechnology is one of the most prominent and advanced technology. It deals with the nanoparticles (having high surface area) which are useful for increasing the solubility of poorly water soluble drugs.[3] The major goals in designing nanoparticle drug delivery system is to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen.[4]

### Nanosuspensions

Nanosuspensions are colloidal dispersed solid of nanosized drug particles stabilized by surfactants.[5] They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1 µm in size.[6] Size reduction of drug particles to nanometer range leads to an enhanced dissolution rate not only because of increased surface area but also because of saturation solubility.[7] The increase in the saturation solubility and solution velocity of nanoparticle is due to increase of vapour pressure of the particles.

For the manufacture of nanosuspensions, there are two conventional methods. Namely, 'Bottom-up' and 'Top-down' technologies.[8, 9] The Bottom-up technology is an assembling method from molecules to nano-sized particles, adopted in Microprecipitation / Nanoprecipitation, Micro emulsion, and Melt emulsification method. The Top-down technology is a disintegration approach from large particles, microparticles to nanoparticles, adopted in High-pressure homogenization and Media milling method.

## MATERIALS AND METHODS

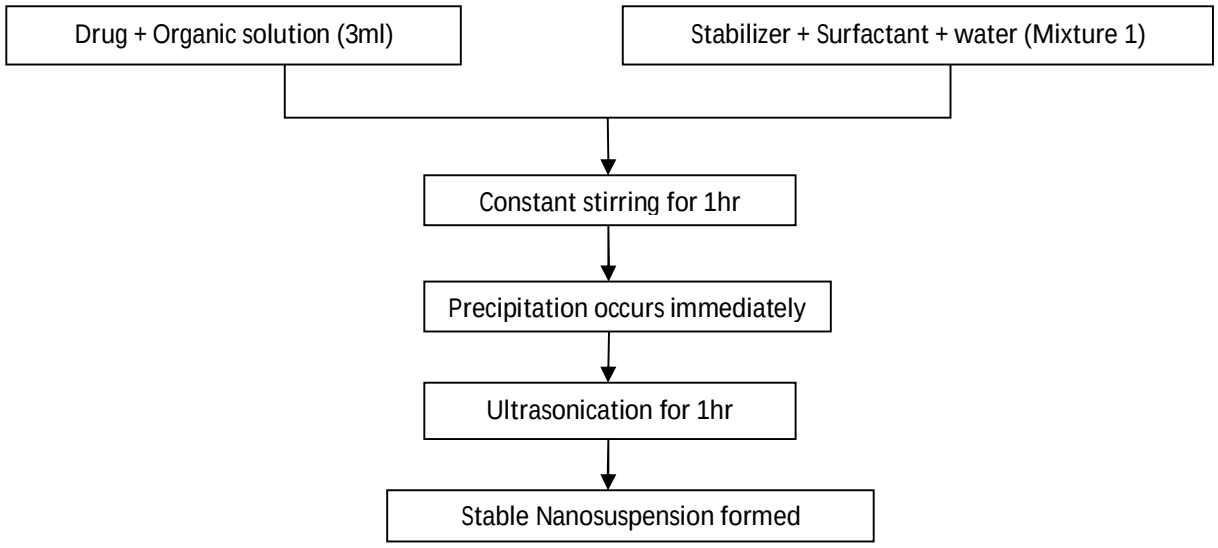
### Materials

Nisoldipine was a gift sample by Orchid Chemicals and Pharmaceutical Ltd., Chennai (India). PVP K30, Sodium Lauryl Sulphate, Methanol (S.D. Fine Chemicals, Mumbai), Urea (Moly Chem), Tween 80 (Himedia, Hyderabad), Poloxomer (Torrent Pharmaceutical Ltd) and all other materials and reagents used were of analytical grade of purity.

### Preparation of Nanosuspension

Nanosuspension of Nisoldipine was prepared by Nanoprecipitation method with various ratios of stabilizers. Stabilizer was dissolved in water and add surfactant to the stabilizer solution and labeled as mixture 1. This solution was kept on magnetic stirrer for uniform mixing. Drug was dissolved using defined volume of suitable solvent. This drug solution was slowly added drop wise to mixture 1 and continues the stirring on magnetic stirrer until complete evaporation of solvent. After 15 minutes, the solution was kept in sonicator for 1 hr. Thus, the nanosuspension was formed and preserved for further use.

**Formulation chart**




**Flow chart for preparation of Nanosuspension**

**Table 1:** Formulation Table for the Preparation of Nisoldipine Nanosuspension

| Formulation code | Nisoldipine | PVP K30 | Urea | SLS | Tween 80 | Poloxamer | Methanol | Water |
|---|---|---|---|---|---|---|---|---|
| $F_1$ | 40 mg | 20 mg | ---- | 0.01% | ---- | ---- | 3 ml | 30 ml |
| $F_2$ | 40 mg | 40 mg | ---- | 0.01% | ---- | ---- | 3 ml | 30 ml |
| $F_3$ | 40 mg | ---- | 20 mg | 0.01% | ---- | ---- | 3 ml | 30 ml |
| $F_4$ | 40 mg | ---- | 40 mg | 0.01% | ---- | ---- | 3 ml | 30 ml |
| $F_5$ | 40 mg | 40 mg | ---- | 0.02% | ---- | ---- | 3 ml | 30 ml |
| $F_6$ | 40 mg | ---- | 40 mg | 0.02% | ---- | ---- | 3 ml | 30 ml |
| $F_7$ | 40 mg | 40 mg | ---- | ---- | 0.1 ml | ---- | 3 ml | 30 ml |
| $F_8$ | 40 mg | ---- | 40 mg | ---- | 0.1 ml | ---- | 3 ml | 30 ml |
| $F_9$ | 40 mg | 40 mg | ---- | ---- | 0.2 ml | ---- | 3 ml | 30 ml |
| $F_{10}$ | 40 mg | ---- | 40 mg | ---- | 0.2 ml | ---- | 3 ml | 30 ml |
| $F_{11}$ | 40 mg | 40 mg | ---- | ---- | ---- | 5% | 3 ml | 30 ml |
| $F_{12}$ | 40 mg | ---- | 40 mg | ---- | ---- | 5% | 3 ml | 30 ml |
| $F_{13}$ | 40 mg | 40 mg | ---- | ---- | ---- | 10% | 3 ml | 30 ml |
| $F_{14}$ | 40 mg | ---- | 40 mg | ---- | ---- | 10% | 3 ml | 30 ml |
| $F_{15}$ | 40 mg | 40 mg | ---- | ---- | ---- | 15% | 3 ml | 30 ml |
| $F_{16}$ | 40 mg | ---- | 40 mg | ---- | ---- | 15% | 3 ml | 30 ml |
| $F_{17}$ | 40 mg | 40 mg | ---- | ---- | 0.3 ml | ---- | 3 ml | 30 ml |
| $F_{18}$ | 40 mg | ---- | 40 mg | ---- | 0.3 ml | ---- | 3 ml | 30 ml |

**Evaluation Tests for Nanosuspensions**

***Drug Content***

About 1 ml of nanosuspension preparation was taken and diluted appropriately with 0.1N HCl and the drug content of the samples were estimated by UV-Visible spectrophotometer at 238 nm.

***Redispersibility***

Redispersibility of nanosuspension stored in vials were determined by tilting the vial bottle up and down with hand till the sediment was uniformly dispersed in aqueous phase and the number of times tilted was noted and rated as fast, medium and slow.

The following grading was given:

a) 1-2 times -Very fast

b) 2-5 times -Fast

c) 5-10 times -Medium

d) More than 10 times -Slow

***Saturation Solubility Studies***

It was carried out by adding excess amount of the sample to distilled water (2 ml) and the samples were subjected to shaking in screw-capped vials for 24 hrs, the samples were further taken in test tubes and centrifuged at 1000 rpm for 10 mins after that samples were filtered through 0.22 µm membrane filter and the filtrate was diluted appropriately with distilled water and the drug content was estimated in UV-Visible spectrophotometer at 238 nm.

***Measurement of Particle Size and Zeta Potential of Nanosuspensions***

The mean size and zeta potential of Nisoldipine nanosuspensions were measured by photon correlation spectroscopy (PCS) using a Malvern Zetasizer (Nano ZS90). The prepared nanosuspensions of 100 µl were diluted to 5 ml with double distilled water and Zeta potential of the diluted dispersions was measured using Malvern Zetasizer (Nano ZS90). Sign of charge on the drug particles and their mean Zeta Potential values were obtained from the instrument.

***Fourier Transform Infrared Spectroscopic studies (FTIR)***

The FT-IR spectra of Nisoldipine pure drug, excipients, physical mixture of drug and excipients (Optimized formula) were recorded. The IR spectra were obtained using KBr disk method using an FTIR Spectrophotometer.

***Scanning Electron Microscopy***

For morphology and surface characteristics, prepared nanosuspension are coated with gold-palladium under an argon atmosphere at room temperature and then the surface morphology of nanosuspension was studied by Scanning Electron Microscopy.

***In vitro drug release (Dissolution) studies***

The *In vitro* drug release study was performed for all the formulations and pure drug powder using USP type II dissolution apparatus under the following conditions.

Dissolution test parameters

- ✓ Dissolution medium : 900 mL of 0.1N HCl
- ✓ Rotation speed : 50 rpm
- ✓ Temperature : 37 ± 0.5°C
- ✓ Sampling time : 5, 10, 15, 20, 30, 45, 60, 70 min

At predetermined time intervals aliquot samples (5mL) were collected and replenished with same volume of fresh medium. The aliquot samples (5mL) were filtered through 0.45 µm membrane filter and the filtrate was diluted appropriately and was estimated using UV-Visible spectrophotometer at $\lambda_{max}$ 238 nm.

**Table 2:** Evaluation parameters of nanosuspension of Nisoldipine

| Formulation | Drug content % | Redispersibility | Saturation solubility in water (mg/ml) |
|---|---|---|---|
| $F_1$ | 94.6333 | Medium | 0.537 |
| $F_2$ | 95.7433 | Fast | 0.621 |
| $F_3$ | 93.2343 | Medium | 0.528 |
| $F_4$ | 91.4333 | Fast | 0.501 |
| $F_5$ | 97.4533 | Fast | 0.775 |
| $F_6$ | 96.6774 | Fast | 0.734 |
| $F_7$ | 95.6777 | Fast | 0.725 |
| $F_8$ | 94.8756 | Fast | 0.733 |
| $F_9$ | 97.5664 | Fast | 0.942 |
| $F_{10}$ | 96.7845 | Fast | 0.921 |
| $F_{11}$ | 95.4533 | Fast | 0.825 |
| $F_{12}$ | 94.8777 | Fast | 0.836 |
| $F_{13}$ | 95.3788 | Fast | 0.932 |
| $F_{14}$ | 95.4784 | Fast | 0.887 |
| $F_{15}$ | 97.6744 | Very Fast | 0.989 |
| $F_{16}$ | 95.4866 | Fast | 0.856 |
| $F_{17}$ | 98.4666 | Very Fast | 1.018 |
| $F_{18}$ | 97.7655 | Fast | 0.967 |

**Table 3:** Cumulative % drug release from Nisoldipine nanosuspensions in 0.1N HCl

| Formulation code | % Cumulative Drug Release | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 5 min | 10 min | 15 min | 20 min | 30 min | 45 min | 60 min | 70 min |
| $F_1$ | 15.858 | 25.702 | 43.886 | 61.895 | 68.189 | 76.407 | 89.346 | 98.962 |
| $F_2$ | 26.751 | 45.459 | 60.146 | 68.364 | 76.582 | 89.171 | 95.815 | 100.18 |
| $F_3$ | 10.665 | 20.456 | 45.634 | 58.398 | 63.468 | 70.637 | 85.674 | 99.487 |
| $F_4$ | 30.597 | 40.389 | 58.398 | 61.370 | 70.462 | 78.855 | 89.346 | 94.591 |
| $F_5$ | 48.781 | 68.714 | 81.477 | 89.695 | 100.36 | ---- | ---- | ---- |
| $F_6$ | 40.738 | 61.370 | 79.379 | 87.597 | 94.591 | 100.01 | ---- | ---- |
| $F_7$ | 38.640 | 61.545 | 75.533 | 84.275 | 91.793 | 99.661 | ---- | ---- |
| $F_8$ | 30.597 | 58.398 | 70.462 | 81.477 | 87.597 | 98.787 | ---- | ---- |
| $F_9$ | 85.849 | 99.312 | ---- | ---- | ---- | ---- | ---- | ---- |
| $F_{10}$ | 80.079 | 91.269 | 100.18 | ---- | ---- | ---- | ---- | ---- |
| $F_{11}$ | 70.637 | 79.729 | 89.695 | 99.661 | ---- | ---- | ---- | ---- |
| $F_{12}$ | 68.889 | 76.757 | 93.367 | 100.18 | ---- | ---- | ---- | ---- |
| $F_{13}$ | 80.953 | 90.220 | 99.661 | ---- | ---- | ---- | ---- | ---- |
| $F_{14}$ | 75.008 | 86.373 | 100.18 | ---- | ---- | ---- | ---- | ---- |
| $F_{15}$ | 97.563 | 100.18 | ---- | ---- | ---- | ---- | ---- | ---- |
| $F_{16}$ | 87.947 | 93.717 | 99.836 | ---- | ---- | ---- | ---- | ---- |
| $F_{17}$ | 99.836 | ---- | ---- | ---- | ---- | ---- | ---- | ---- |
| $F_{18}$ | 90.744 | 100.18 | ---- | ---- | ---- | ---- | ---- | ---- |

### Measurement of particle size and zeta potential

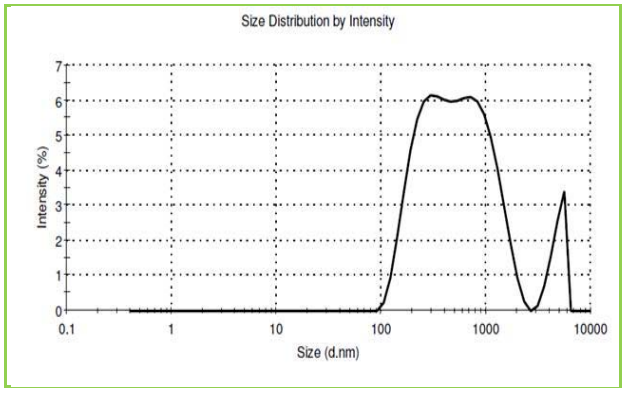



**Figure 1:** Graph Showing Size Distribution of Optimized Nanosuspension

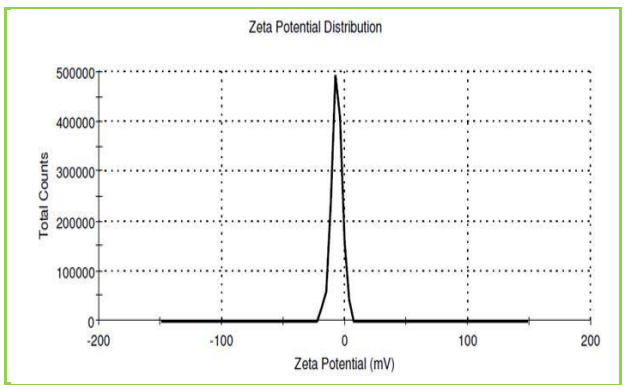



**Figure 2:** Graph Showing Zeta Potential of Optimized Nanosuspension

### Scanning Electron Microscopy

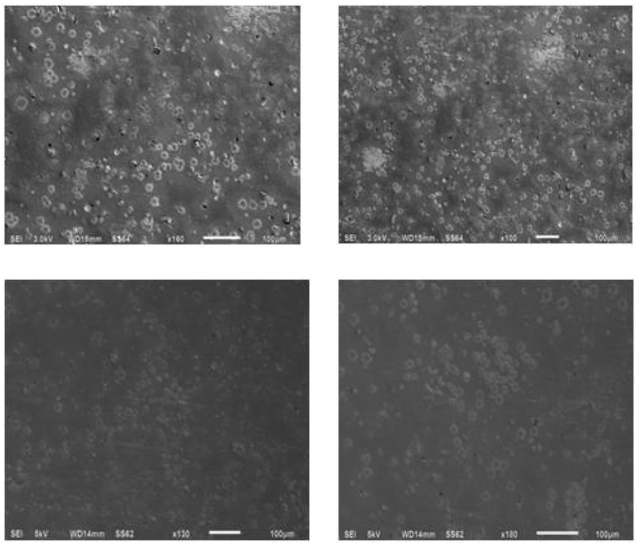


**Figure 3:** SEM Images of Nisoldipine Optimized Nanosuspension

## RESULTS AND DISCUSSION

### Fourier Transform Infrared Spectroscopic Studies (FTIR)

The drug content of the diluted samples of prepared nanosuspension formulations showed about 91.43 to 98.46 % of drug content. $F_{17}$ nanosuspension showed 98.46 % of drug (Table 2). Redispersibility was medium for formulations $F_1$ & $F_3$, Fast for formulations $F_2$, $F_4$ to $F_{14}$, $F_{16}$, and $F_{18}$ and Very fast for Formulations $F_{15}$ and $F_{17}$ (Table 2). The saturation solubility of all formulations

ranged from 0.501 to 1.018. The formulation $F_{17}$ showed higher value (1.018 mg/ml), followed by $F_{15}$ nanosuspension which showed (0.989 mg/ml) saturation solubility (Table 2).

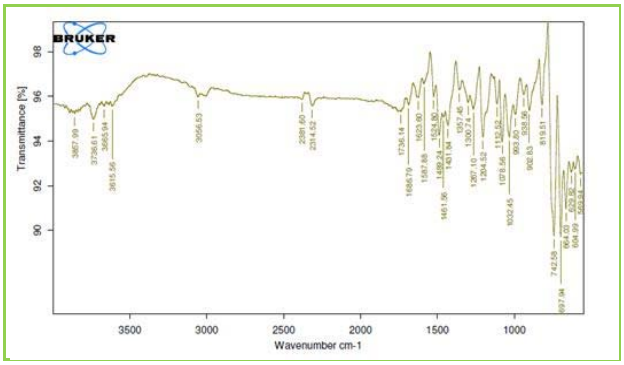



**Figure 4:** FTIR Spectra of pure Nisoldipine

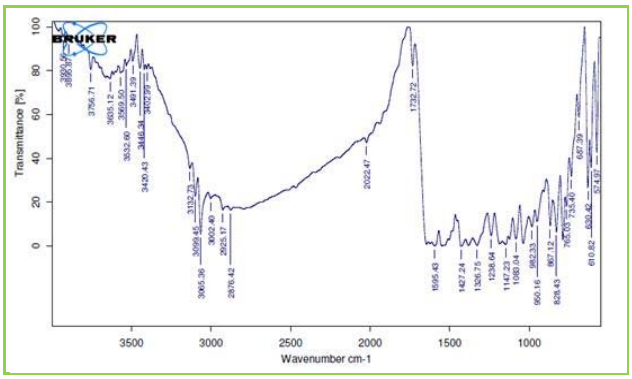



**Figure 5:** FTIR Spectra of Optimized Formulation

The cumulative % drug release observed was in the range of 10.6% to 99.8% within 5 minutes. However, $F_{17}$ formulation showed relatively more cumulative drug release i.e., 99.8% (Table 3).

Zeta potential gives certain information about the surface charge properties and further the long-term physical stability of the nanosuspensions. The mean size and Polydispersibility Index (PDI) of the drug in nanosuspension formulation ($F_{17}$) prepared by Nano precipitation-Ultra sonication method was found to be around 400 nm and the PDI was found to be 0.450 (Figure 2). The zeta potential of the formulation was found to be -6.70 mV (Figure 3).

Morphology of drug particles precipitated with Tween 80 as stabilizer showed nearly oval shaped particles in whole and the size ranges from nanosize to 100 µm (Fig.4). Moreover the nano-sized particles were very small & revealed by Scanning Electron Microscopy. Stabilizer was adsorbed on the surface of drug particle which inhibits particle growth. The FTIR spectra of pure drug, excipient and optimized formulation were recorded & shown in Figure 5, 6 & 7. The characteristic peaks of the optimized formulation followed the same trajectory as that of the drug and excipients alone with minor differences which indicates there are no drug-excipient interactions.

## CONCLUSION

Nanoparticle drug delivery is a promising approach for the formulation of Nisoldipine nanosuspensions. Nanosuspensions will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drug. A Nanoprecipitation method was developed to prepare nanosuspension of Nisoldipine using PVP K30 as stabilizer and tween 80 as surfactant.

The best nanosuspension of Nisoldipine can be obtained by 40 mg of PVP K30 and 0.3 ml of tween 80 using Nanoprecipitation method. Dissolution study in 0.1N HCl shows that nanosuspension formulation $F_{17}$ gives 99.8% drug release within 5 min. So, we concluded that nanosuspensions represent a promising alterative to current drug delivery systems aiming to improve the biopharmaceutical performance of drugs with low water solubility.

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