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# Formulation and Evaluation of a Novel Multiparticulate Drug Delivery System for Poorely Water Soluble Drug-Ziprasidone Hydrochloride Monohydrate.

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**Abstract:** Ziprasidone hydrochloride Monohydrate ZHM, chemically 5-[2-[4-(1, 2-benzothiazol-3yl) piperazin-1-yl] ethyl]-6-chloro-1, 3-dihydroindol-2-one hydrochloride; is an atypical antipsychotic with very poor water solubility and less oral bioavailability. The presented research work is about of preparation and evaluation of novel multiparticulate formulation based on nanostructured lipid carrier (NLC) drug delivery system of ZHM. NLC dispersion was prepared by pre emulsification using overhead stirrer, followed by high pressure homogenisation (HPH) method. The cryprotectant was added to NLC dispersion and freeze dried to obtain multiparticulate powder. NLC dispersion and freeze dried powder were characterised for particle size, drug release.

**Key words:** Novel Drug Delivery System (NDDS), poorly water soluble, Ziprasidone Hydrochloride Monohydrate (ZHM), Nanostructured Lipid Carrier (NLC), High Pressure Homogenisation (HPH).

## Introduction

Research in pharmaceutical Formulation development revolves around increasing therapeutic efficacy, patient safety, patient compliance and reducing dosing frequency, side effects, toxicity etc. Formulating a novel delivery system, an existing drug molecule can get a new life. Formulation scientists develop new drug delivery systems; new dosage forms by studying physicochemical properties, therapeutic properties, pharmacokinetic parameters, pharmacodynamics properties of drug, limitations and side effects of existing drug delivery systems and dosage forms of the drug under consideration. Drugs with poor water solubility are real challenge for formulation scientists to enhance their solubility which ultimately helps in improvement of all solubility dependent pharmacokinetic parameters of drug, hence it's in vivo performance and therapeutic efficacy.

Reduction in particle size of drug results in improvement in aqueous solubility of a drug. Many methods are explored by formulators for alteration of physicochemical properties of drugs, improvement of solubility profile, drug release pattern and bioavailability of drugs. Recent trends indicate that multiparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet. Evolution of an existing drug molecule from a conventional form to a novel delivery system can significantly improve its performance in terms of patient compliance, safety and efficacy. An appropriately designed Novel Drug Delivery System can be a major advance for solving the problems related to the release of the drug at specific site with specific rate.

Lack of safe polymers and solvents with regulatory approval and their high cost have limited the applications of polymeric nanoparticles. To avoid the disadvantages of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals. These lipid nanoparticles are known as Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) which are attracting wide attention of formulators worldwide. NLCs offer many advantages, refer figure 1.Nanostructured lipid carriers (NLCs) are drug-delivery systems composed of both solid and liquid

lipids as a core matrix. To obtain the blends for the particle matrix, solid lipids are mixed with liquid lipids, preferably in a ratio of 70/30 up to a ratio of 99.9/0.1**.**

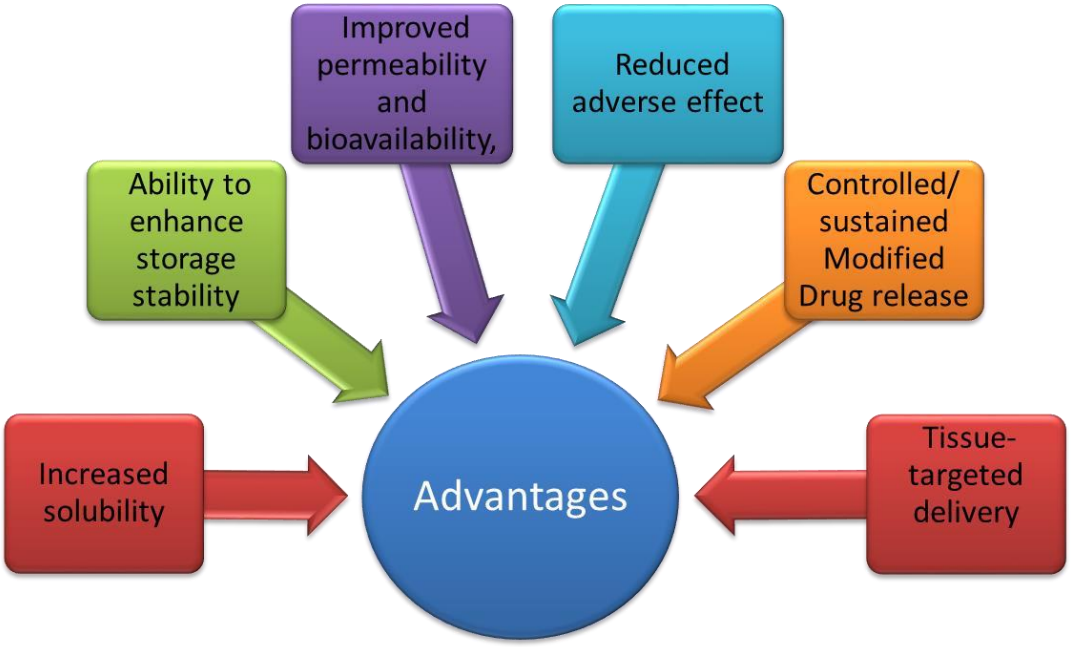


**Figure 1.**Advantages of Nanostructured lipid carriers (NLCs)

A drug used for the proposed formulation development work is **Ziprasidone hydrochloride Monohydrate. [15-23]**

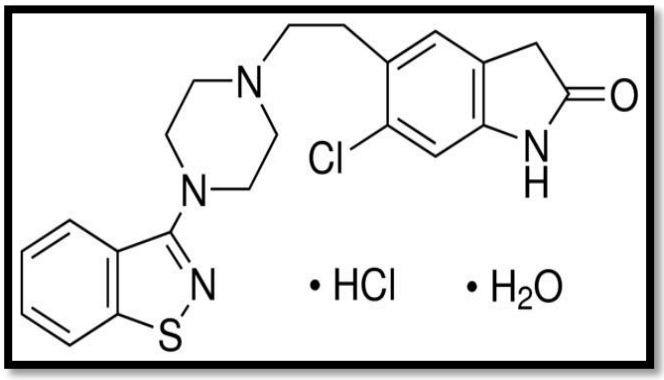


**Figure 2.** Chemical structure of Ziprasidone hydrochloride Monohydrate

Chemical name:

5-[2-[4-(1, 2-benzothiazol-3-yl) piperazin-1-yl] ethyl]-6-chloro-1, 3-dihydroindol-2-one hydrochloride

ZHM is an atypical antipsychotic with very poor water solubility. ZHM's antipsychotic activity is likely due to a combination of its antagonistic function at $D_2$ receptors in the mesolimbic pathways and at $5HT_2A$ receptors in the frontal cortex.

ZHM is a BCS Class II drug which is poorly water-soluble and also undergoes extensive first pass metabolism, so a novel formulation is required to overcome it. It has short biological half-life of 4-7 hours. The bioavailability of ZHM is 60%. It is extensively metabolised. Its absorption increases 2 folds when administered orally with food. Since, most of the patients with schizophrenia often eat a poorer diet and do not necessarily take their medicines as instructed.

In order to achieve sustained or controlled release of ZHM with enhanced bioavailability and no food effect, conventional matrix or coating-based delivery systems may be proposed, but poor water solubility of drug limits

their use, hence the current formulation development work is undertaken to develop Nanostructured Lipid Carrier (NLC) of ZHM with an aim to enhance its solubility, dissolution profile which will ultimately improve oral bioavailability and overcome the food effect of ZHM.

**Experimental:**

In preformulation studies, authentication of drug was done by UV spectrum, FTIR, DSC studies. Drug Excipient compatibility was checked and confirmed with the help of Differential scanning calorimetric (DSC) studies. The pH solubility profile was studied for ZHM.

**Preparation, optimisation and characterisation of ZHM loaded NLCs: [24-27]**

High pressure homogenization technique was used to prepare NLCs dispersion. An accurately weighed solid lipid (Precirol ATO 5), liquid lipid (Labrafil 1944) and stabilizer (Gelucire 50/13) were first mixed together in a glass vial along with the drug and then heated at 70-80˚C (5-10˚C above the melting point of lipid mixture) on a water bath. The melted lipid mixture and drug were mixed properly to fully dissolve the drug in melted lipid mixture so as to obtain a clear melting solution. In separate beaker double distilled water was heated at 70-80˚C. Then this hot aqueous phase maintained at same temperature was poured in the melted lipid mixture containing drug (oil phase). Stirring was carried out (at 500 rpm and temperature90°C) for 5 minutes by using overhead stirrer while maintaining the temperature at 70-80˚C. The coarse o/w emulsion is formed which was further high pressure homoginized for 30 minutes at High pressure homoginizer (GEA Niro- Soavi PANDA 2000) at 1000 Bar pressure .The resulting o/w nanoemulsions was immediately placed in ice bath maintained at 2-4˚C to cool it down rapidly under magnetic stirring for 10-15 minutes. The liquid nanodroplets of melted lipid transformed into solid nanoparticles at low temperature and leads to formation of NLCs dispersion.

After cooling, it was stored in refrigerator in cool condition as the shelf life of NLCs dispersion is more at cool condition as compared to room temperature. The schematic representation of preparation of NLC dispersion is shown in figure 2.

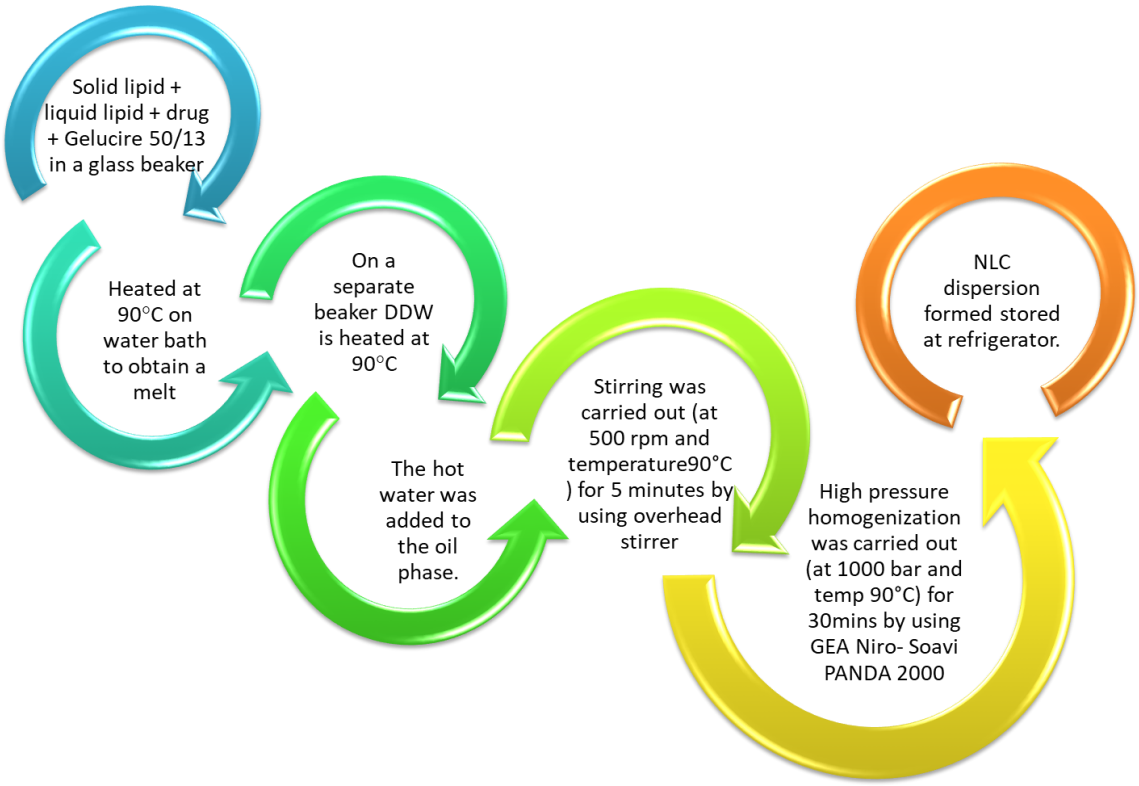


**Figure 3:** Preparation of NLC dispersion

**Optimization of NLC Dispersion:**

A $3^2$ randomized full factorial design was employed for carrying out the optimization of NLCs. Based on the results obtained in preliminary studies, amount of total lipid [X1] (i.e. Solid lipid and liquid lipid) and concentration of stabilizer [X2] were found to be the major variables in determining the entrapment efficiency (% EE) and mean particle size (MPS). So, these variables were selected as independent variables to obtain an optimised formula for maximum % EE and minimum MPS using $3^2$ factorial design. The effect of these independent variables was investigated on two dependent variables, namely % EE [Y1] and MPS [Y2] to evaluate the responses. The optimization was done by using the Design-Expert® software (Version 10; Stat-Ease; Inc.; MN; USA). Significance of the model was determine by comparisons of statistical parameters like standard deviation (SD), the multiple correlation coefficient ($R^2$), adjusted multiple correlation coefficient (adjusted $R^2$), predicted multiple correlation coefficient (predicted $R^2$) and predicted residual error sum of squares (PRESS). The best model was decided on the basis of higher values of adjusted $R^2$ and predicted

The operating conditions i.e. pressure and time of homogenisation during preparation of NLC dispersion were adjusted based on the results obtained in preliminary study and were later kept constant during the runs of optimization batches. The pre emulsification by overhead stirrer, followed by High pressure homogenisation at 1000 Barr using (GEA Niro- Soavi PANDA 2000) for 30 minutes.

**Characterization of NLCs dispersion:**

**% Entrapment efficiency (% EE):**

Entrapment efficiency corresponds to the percentage of drug encapsulated within and adsorbed onto the nanoparticles. The entrapment efficiency (% EE) was determined by measuring the concentration of unentrapped drug in the lipidic dispersions. The amount of free drug in the was estimated by using UV/VIS spectrophotometer at wavelength of 317 nm. The amount of incorporated drug was determined as the difference between the initial drug content and free drug in the supernatant.

**Particle size Analysis:**

Particle size (z-average diameter) and poly dispersity index (PDI) of the NLCs were measured using NAOPHOX particle size analyzer (SYMPATEC GmbH, Germany). Before measurement, the nanoparticle dispersion was diluted appropriately to yield a suitable intensity (particle count rate between 100 and 1000 kbps) with ultra-pure water. These diluted NLCs dispersion was poured into the cuvette which was then placed in the cuvette holder of the instruments and analysed using Nanophox software. All measurements were done in triplicate.

***In-vitro* drug release study:**

Drug release of ZHM from optimized NLCs dispersion was studied using dialysis membrane bag in pH 6.8 phosphate buffer (900 ml) using USP XXIII dissolution testing apparatus type II (LABINDIA DS 8000 auto sampler dissolution test apparatus) with rotating paddle at 50 rpm and bath temperature was maintained at 37 ± 0.5°C. 5ml samples were withdrawn at different time intervals of 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 h from dissolution medium and replaced with 5 ml of fresh buffer maintained at same temperature in order to maintain sink condition. The aliquots withdrawn were filtered through syringe filters and assayed for ZHM content using validated HPLC method. The % drug release versus time graph was plotted for optimized NLCs dispersion.

**Evaluation of capsules filled with ZHM loaded freeze dried NLC multiparticulate system:**

**Weight variation/Uniformity of weight of capsules**

Weight variation/ uniformity of weight of NLCs capsules were carried out as per Pharmacopoeia.

**Content uniformity assay of capsules**

Contents of 20 capsules were mixed. Powder containing 40 mg of ZHM was weighed and extracted in 100 ml of methanol from which 2.5 ml was diluted to 10 ml. Further dilutions were carried out and samples were filtered through syringe filter and assayed for ZHM content at detection wavelength of 317 nm using validated HPLC method.

**Results and Discussion:**

UV spectroscopy, DSC and FTIR studies were performed to authenticate drug sample. The drug excipient compatibility was also confirmed by DSC and

FTIR studies. The representative spectra and DSC thermogram are shown in figures 4 to 6. Serial dilution of ZHM were analysed by UV-visible spectrophotometer and calibration curve was constructed as shown in figure 7.

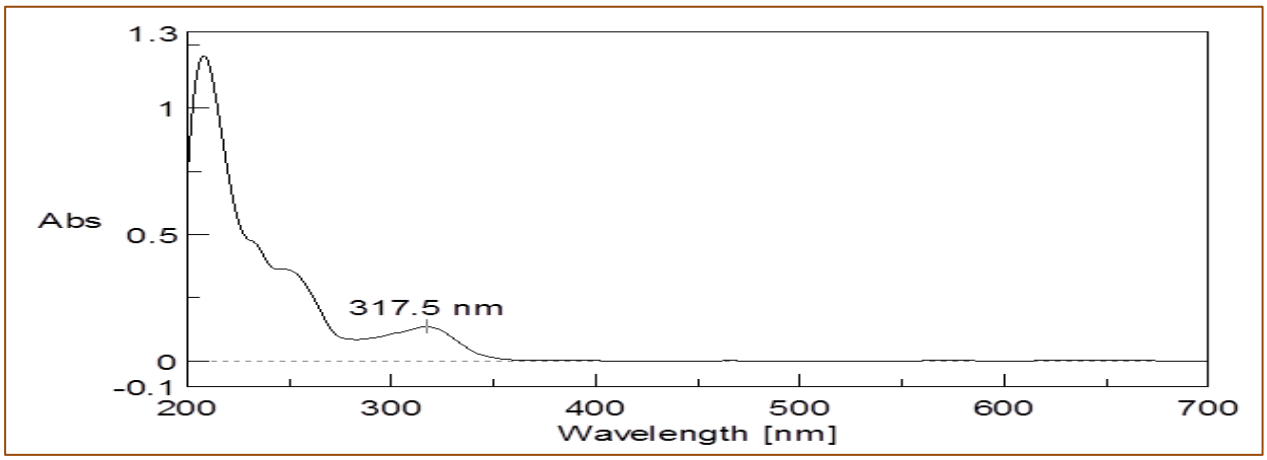


**Figure 4.**UV –Visible spectrum of ZHM in methanol.

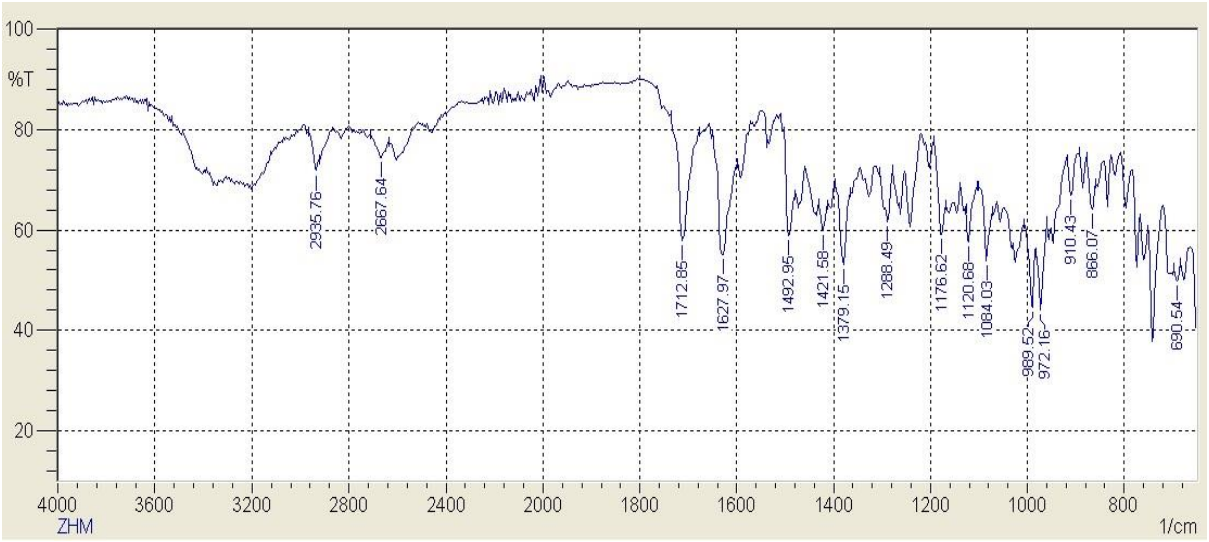


**Figure 5.** FTIR spectrum of ZHM.

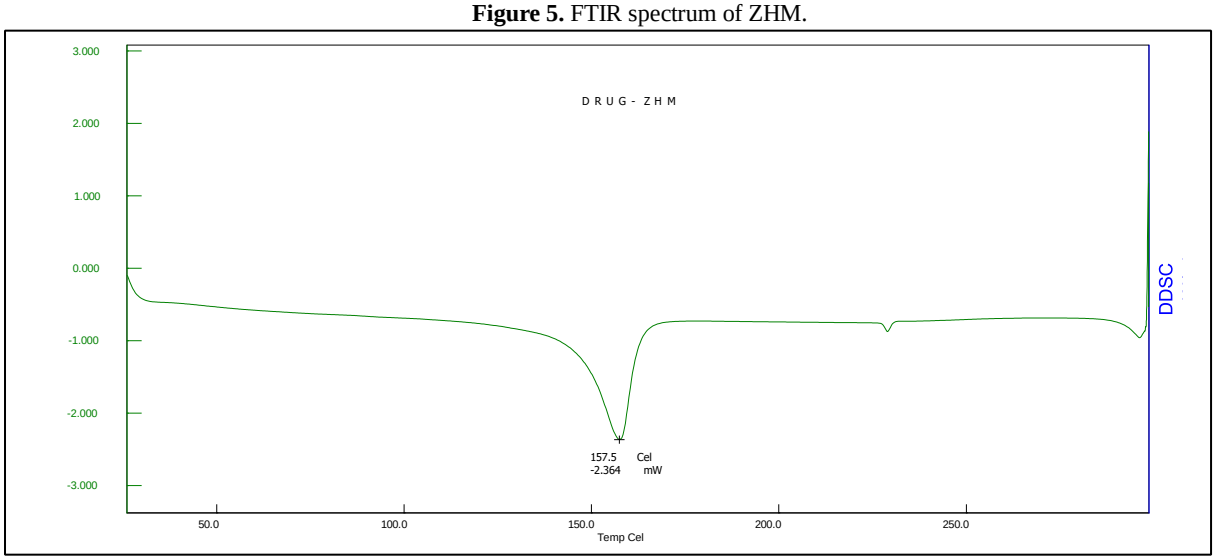


**Figure 6.** DSC thermogram of ZHM.

**Table 1:** instrumental parameters for DSC studies.

| INSTRUMENT | SIEKO SII, JAPAN |
|---|---|
| Heating rate | $10^0$ C/min |
| Range | $30^0$ - $300^0$ C |
| Inert gas | Nitrogen purged a rate of 50 ml/min |

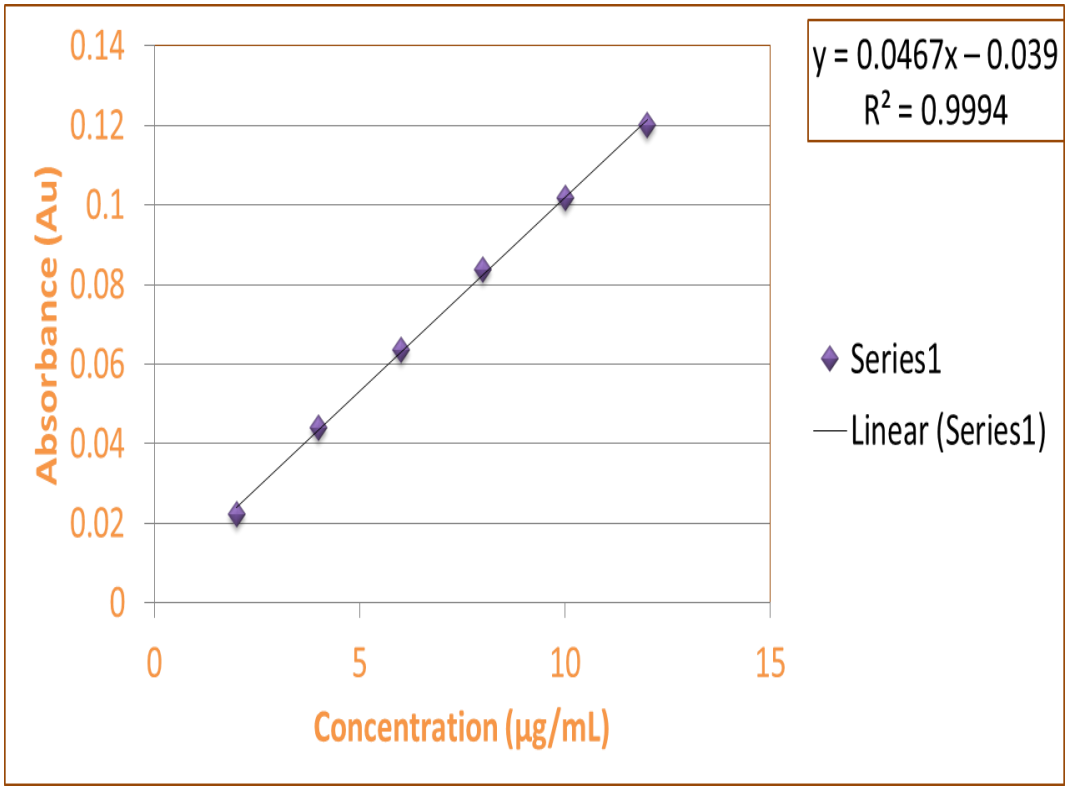


**Figure 7.** UV-Calibration Curve of ZHM in methanol.

The optimization was done by using the Design-Expert® software (Version 10; Stat-Ease; Inc.;
MN; USA). Design space was obtained to perform experiment. The effect of concentration of lipid and surfactant on drug entrapment and particle size was demonstrated by various plots, namely contour and overlay plots as shown in figures 8-10. The effect of concentration of lipid and surfactant on %EE: From the Contour plots it was clearly understood that the independent parameters such as lipid concentration and surfactant concentration affect the dependent variables such as % EE. The % EE for various factor level combinations was found in the range of 75.91% to 92.06%. The % EE increased when the concentration of total lipid was increased from 3 to 7% due to the increase in solubility of ZHM in Precirol ATO 5 and Labrafil M1944. The % EE of ZHM significantly decreased on increasing the concentration of total stabilizer from 200 to 300 mg.

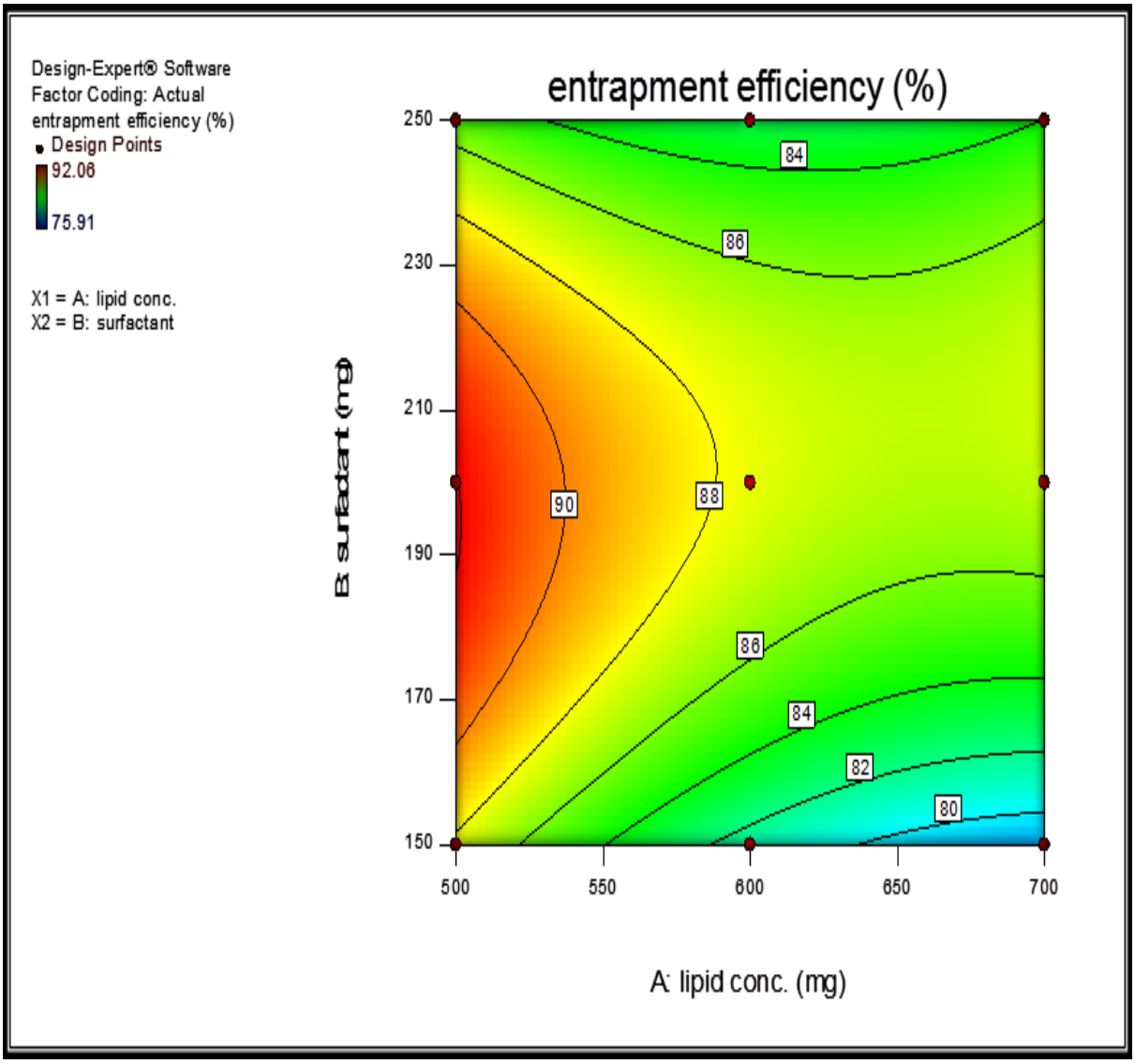


**Figure 8:** Contour plots showing the effect of concentration of lipid and surfactant on %EE

It was concluded that % EE increases with Conc. of Lipids and decreases with increase in concentration of Gelucire 50/13.

The EE of optimized formulation was found to be 84.11%.

**The effect of concentration of lipid and surfactant on Particle Size:**

The Poly Dispersity Index (PDI) gives information about the homogeneity of particle size distribution in the system. A small value of PDI is indication of narrow size distribution in the system whereas large value indicates wide size distribution in the system. The PDI of optimized NLCs batch was found to be 45.79% which indicates that there is narrow particle size distribution and hence stable for longer duration of time.

In optimization studies it was evident that the average particle size increases with Conc. of Lipids and decreases with increase in concentration of Gelucire 50/13. Contour plots showing the effect of concentration of lipid and surfactant on Particle Size is shown in figure 10. The average particle size of optimized formulation was found to be 175.69 nm. The distribution diagram of optimized batch of NLC dispersion is shown in figure 11. The zeta potential of particles was studied the results are given in figure 12.

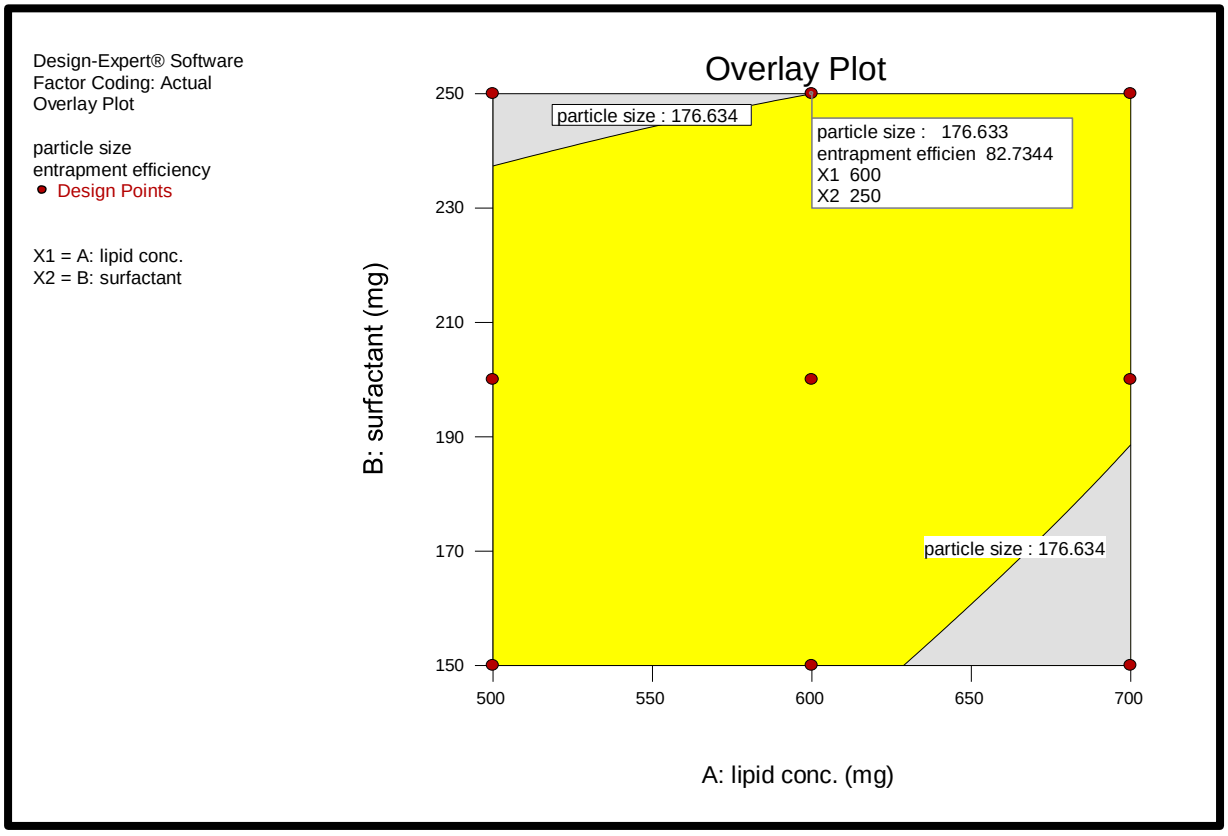


**Figure 9:** Overlay Plot for optimisation of lipid and surfactant concentration

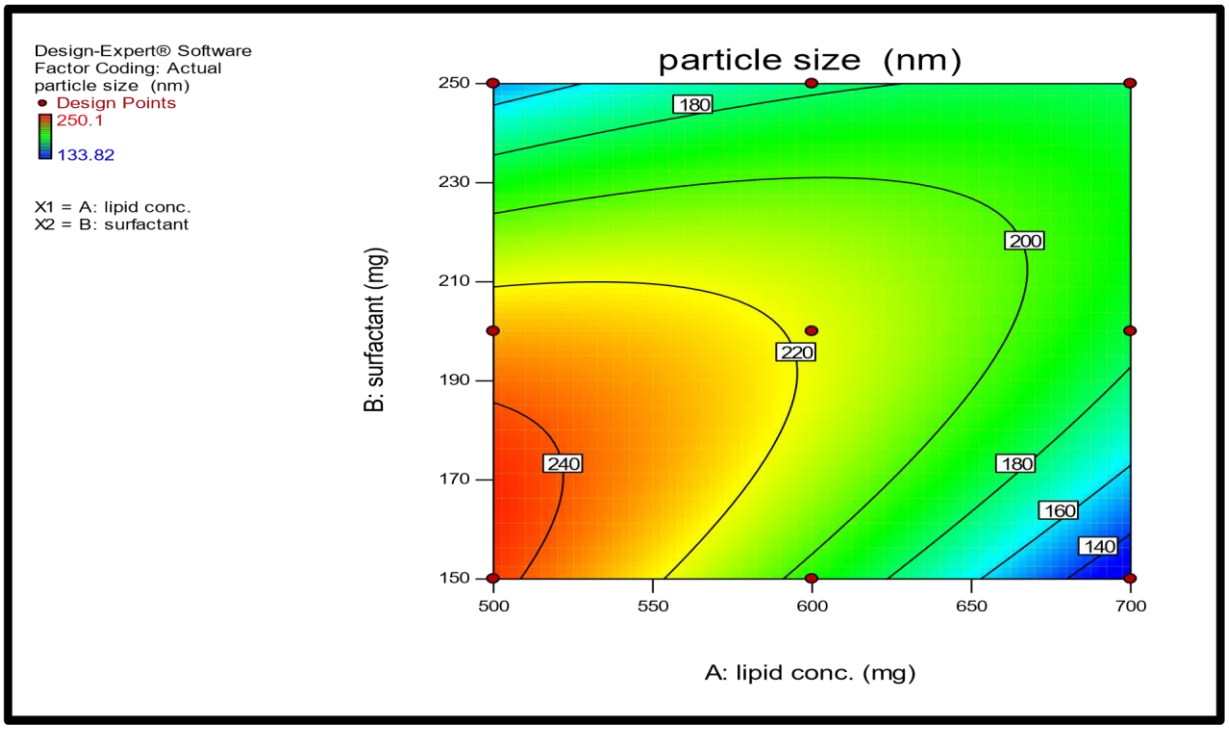


**Figure 10:** Contour plots showing the effect of concentration of lipid and surfactant on Particle Size

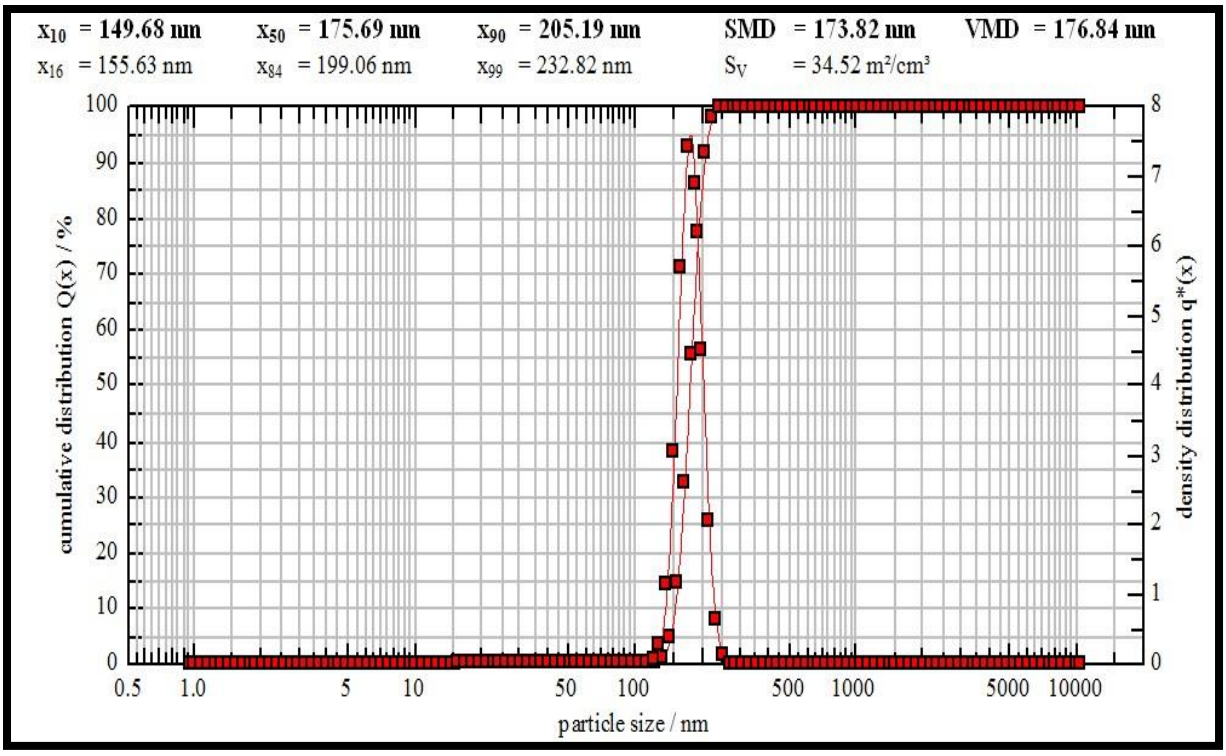


**Figure 11.** Distribution diagram of optimized NLC formulation

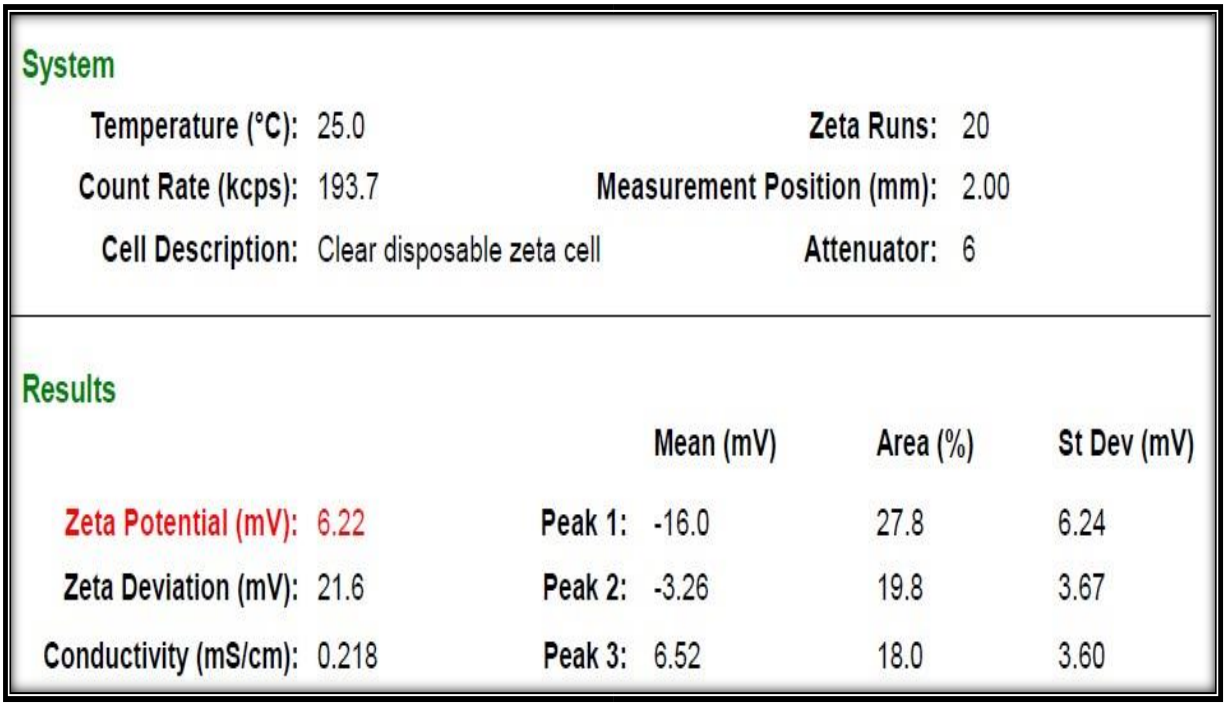


**Figure 12.** Results of Zeta potential studies of NLC dispersion.

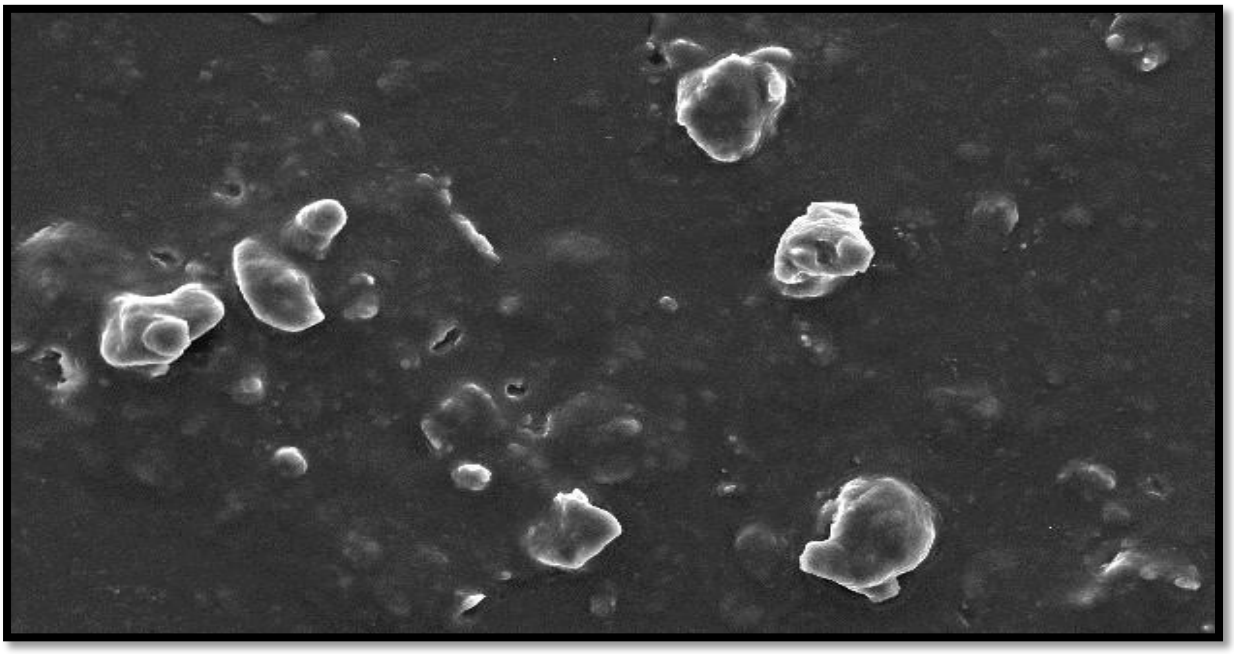

**Figure13.** SEM of drug loaded freeze dried NLC

***In-vitro* drug release :**

The occurrence of initial drug release clearly indicates the location of certain amount of ZHM onto the surface of NLCs, whereas the sustain release profile suggests the release of ZHM from the core of lipid matrix to the release medium.

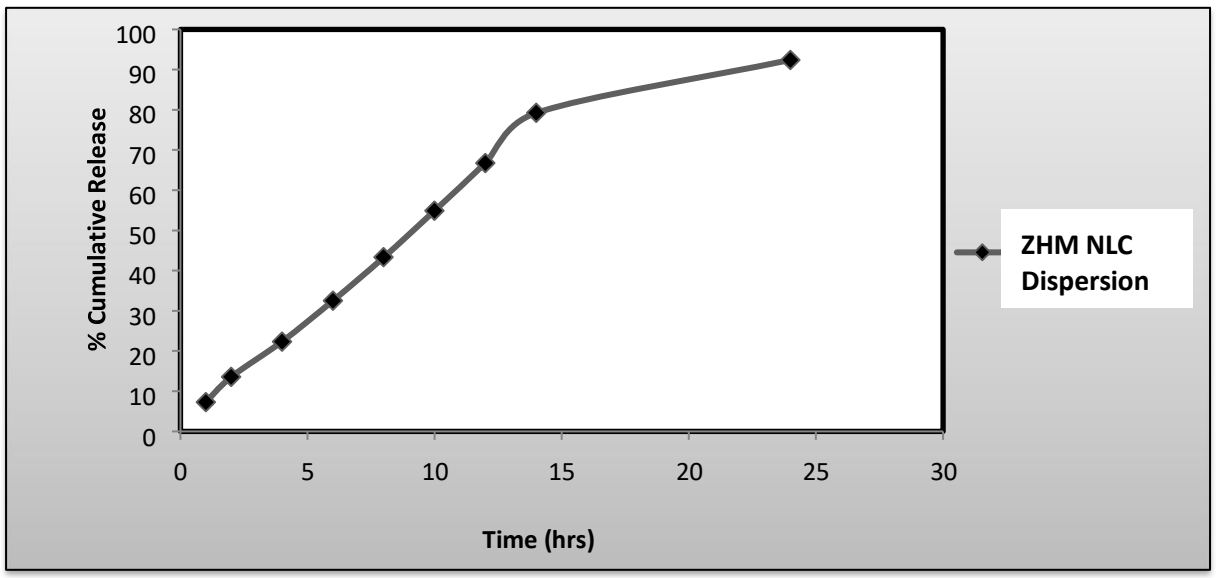


**Figure 14.** *In-vitro* drug release profile of optimized formulation

**Evaluation of capsules filled with ZHM loaded freeze dried NLC multiparticulate system:**

The percent compressibility and angle of repose of the NLC powder was found to be 12.55 % and 33.68$^{O}$ respectively. These results were indicating good flowability of the NLC powder. It was found that none of the capsule content deviates outside the range. Therefore, NLC capsules complies weight variation test as per IP procedure. The contents of all capsules were within the range of 85 to 115 %.

**Conclusion:**

The optimised NLC formulation was composed of drug- Ziprasidone Hydrochoride Monohydrate, Preciro ATO 5, Labrafi M1944, Geucire 50/13 and Distilled Water. NLCs were characterised for drug entrapment, particle size, zeta potential, and SEM studies. As Freeze drying converts the lipid dispersion to a solid state which increases the stability and avoid particle aggregation during storage. The NLCs dispersion of ZHM was freeze dried by employing a cryprotectant. The freeze dried powder equivalent to 40 mg of ZHM was filled in each capsules. The capsules were evaluated for weight variation, drug content, drug release and all results were within the acceptable limits.

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