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Formulation and Evaluation of Nanosuspension Containing Poorly Water Soluble Ciclopirox Olamine as topical antifungal agent

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Abstract:

Nanosuspension is a Novel concept, that administered topically can increases the residence time of drugs in stratum corneum and epidermis, while decreasing the drug's absorption related side effect throughout the body. It can act as a drug reservoir and by altering the vesicular composition or surface characteristics can change the rate of drug release and the affinity for the target site. The Cilopirox Olamine loaded nanosuspension was developed using Hydroxypropyl methyl cellulose and Poly Vinyl Alcohol to enhance its water solubility and improved topical delivery. The ciclopirox olamine loaded nanosuspension were developed by solvent evaporation method using Tween 80 and ethanol in 1:2 molar ratio, the feasibility of nanosuspension successfully demonstrated in the investigation. The prepared nanosuspension were found to be smooth with good drug content as of 85.50%, better entrapment efficiency as of 92±2.15% having optimum drug release of 85.79±0.743 percent. The partical size Malvern Zeta Sizer found out to be 219.1nm and zeta potential as of-31.1mV.The results revealed that Ciclopirox Olamine loaded nanosuspension can be successfully developed as a topical drug delivery system using polymers HPMC and PVA in the ratio of 1:10 enhancing the particular surface area and bioavailability of nanosuspension. The formulation B7 also show better drug release as compared with marketed formulation. From the present study, it was clear that the nanosuspension enhance the particular surface area, solubility, bioavailability, increase drug loading, reduced dose frequency and give fast onset of action.

1. INTRODUCTION

A major challenge for the pharmaceutical research has always been the formulation of a poorly water soluble drugs (Marisko, et al., 2003) (Muller, et al., 1998). There are several conventional approaches that have been reported for increasing the solubility of drugs which are not highly soluble. These techniques include micronization (Vandana, et al., 2014), cosolvents-based solubilisation (Nayak, et al., 2012), solid dispersions (Sinha, et al., 2010), and precipitation (Savjani,et al., 2012). This precipitation method has the drawback that the drug must be soluble in at least one solvent and that solvent must be miscible with an antisolvent. Additionally, drugs that are both poorly soluble in aqueous and nonaqueous conditions are unable to administered applying the precipitation approach (Jacobs, et al., 2000) (Kocbek, et al., 2006). The diameter of the suspended particles in nanosuspensions, which are colloidal dispersions and biphasic systems made up of drug particles dispersed in an aqueous media, is less than 1 μm . A suitable size-reduction technique and a suitable stabiliser can be used to produce nanosuspension (Bohm, et al., 1999) (Patravale, et al., 2004).

The nanoprecipitation method in bottom-up technology has many benefits, including being a simple process that is quick and simple to execute. The drug is dissolved in a solvent before being combined with a nonsolvent to precipitate the small drug particles (Lakshmi, et al., 2010). To increase their dissolution rate and oral bioavailability, a nano-suspension of danazol, naproxen, and zaltoprofen has been created using the precipitation process (Liversidge, et al., 1995) (Papdiwal, et al., 2014).

2. Method and Materials

Ciclopirox Olamine drug was gifted by Glenmark Pharmaceuticals Ltd, Goa India. The other chemicals

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like; HPMC, PVA, mineral oil, ethanol, tween 80, dichloromethane and methanol w e r e provided by Loba Chemie Pvt Ltd, India.

2.1 Formulation of Ciclopirox Olamine loaded Nanosuspension using Solvent Evaporation Method

The formulation of nanosuspension were performed by using solvent evaporation method and 9 runs were generated. The concentration of polyvinyl alcohol and HPMC was selected as independent variables. Particle size, and entrapment efficiency were selected as dependent variables given in Table 1. The formulations were coded as B1 to B9. Three different concentrations of the polymer were selected for the optimization studies. It signifies how the responses change when the two factors are changed concurrently. All the possible combination of polymers concentration were optimized at three different levels low (-1), medium (0), and high (+1) concentrations respectively (Rodrigues et al., 2022).

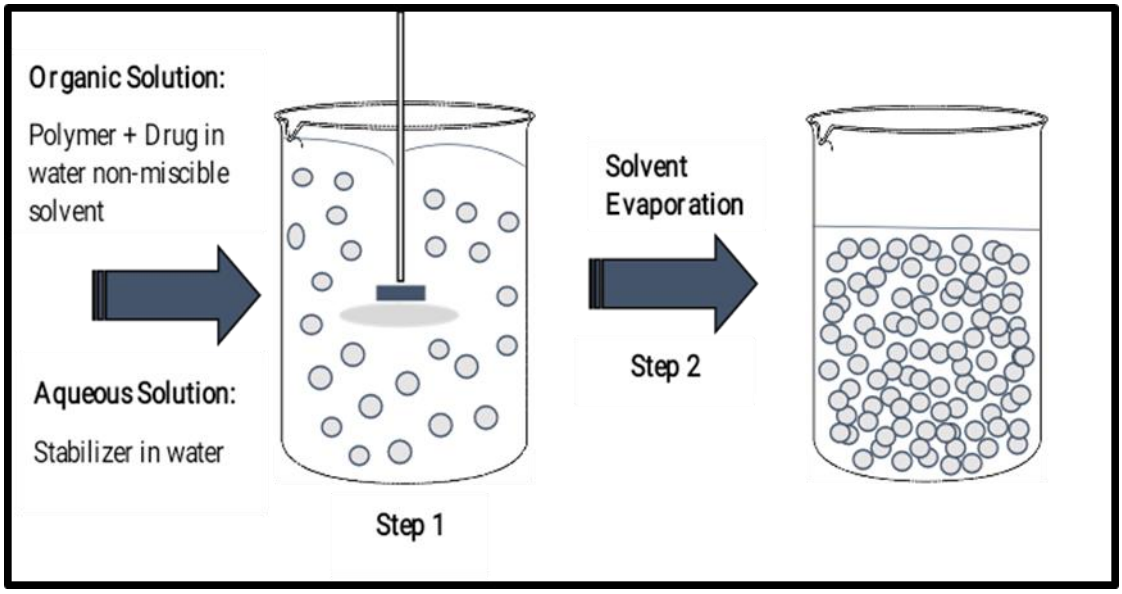

Fig. 1 Solvent Evaporation Method

Table 1. Formulation of Drug loaded Nanosuspension

Batch no.	Amount ofdrug (mg)	Amount of polymer HPMC (mg)	Amount of polymer Polyvinyl alcohol (mg)	Volume of solvent Dichloromethane(ml)	Volume of solvent Ethanol (ml)	Volume of surfactant Tween 80	Mineral oil(ml)	Distilled water(ml) up to
B1	1	3	0.4	0.25	3.6	1.2	0.5	10
B2	1	3	0.3	0.1	2.5	1.25	0.1	10
B3	1	2	0.3	0.58	2.0	1.0	0.15	10
B4	1	2.5	0.2	0.2	3.0	1.0	0.25	10
B5	1	1	0.4	0.3	4.0	1.0	0.3	10
B6	1	2	0.2	0.5	3.0	1.5	0.2	10
B7*	1	2	0.2	0.5	2.4	1.2	0.2	10
B8	1	3	0.3	0.4	2.8	1.4	0.35	10
B9	1	1	0.4	1.2	1.0	3.0	0.4	10

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3. Characterization of Nanosuspension

3.1 Physical Appearance:

The prepared samples of nanosuspension were observed for two weeks at room temperature for agglomeration and colour change to evaluate the physical appearance (Jassem NA, et al., 2017).

3.2 Particle size

The particle size is one of the most basic and important measurement for nanoparticles characterization. It determines the size and distribution of the particles. The Average particle size and shape of the formulated nanosuspension was determined by using Malvern Zeta sizer ZS using water as dispersions medium. The sample was scanned 3 times for determination of particle size (Architha Aithal et al., 2019). Diluted with distilled water (1: 200) and filled in disposable polystyrene cuvette. Measurement of particle size was done based on the dynamic light scattering (DLS) theory.

3.3 Zeta potential

Zeta potential (ZP) is widely used for quantification of the magnitude of the electrical surface charge at the double layer. The surface charge or the charge of a Nanosuspension determines its interactions with the target. The significance of ZP is that its value can be related to the stability of formulation. More than 30 mV ZP value in water indicates good stability of NS. It can be measured by using additional electrode in the particle size equipment. Approximately 1 ml of NS was dispersed in 1 ml of distilled water by sonication, and it was subjected to ZP analyzer (Hanumanaik et al., 2020).

3.4 pH- Measurement

pH of the formulation was determined by using digital pH meter. In pH meter, electrode was washed by distilled water and then dipped into the formulation to measure pH (R. Jadhav et al., 2022).

3.5 Viscosity

The viscosity of the formulated batches was determined using a Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 63. Viscosity is a measure of a liquid sresistance to flow which describes the internal friction of a moving fluid. The viscosity of CPO loaded Nanosuspension was measured at 25°C using a Brookfield viscometer with spindle number 63 was lowered perpendicularly into the nanosuspension placed in a beaker taking care that the spindle did not touch the bottom of the beaker. The spindle was rotated at a speed 50rpm to 100rpm and the readings were recorded after 30 s when the suspension level stabilized (Mahajan et al., 2021).

3.6 Drug Content

Taken 10mg of the drug in 100ml volumetric flask and volume was made up to 100ml with Ethanol. The content of nanosuspension was determined by UV-spectroscopy at 306nm.

3.7 Entrapment Efficiency

The entrapment efficiency (%EE) is the amount of drug entrapped in the formulation. The EE is determined by separating the unentrapped drug from the vesicles, using various techniques such as mini column centrifugation. In this process, direct or indirect methods can be used to determine the %EE. Determining the drug amount embedded in Nanosuspension is of major significance, because it determines the release characteristics and consequently the therapeutic potency. Nanosuspensions (10 ml) were centrifuged at 10,000 rpm and 6°Cusing a cooling centrifuge for 30 min. The supernatant was separated out and the absorbance was measured for the free drug content by UV spectrophotometer (Shimadzu UV Spectrophotometer 1800) at 306 nm. Entrapment efficiency was determined by subtractingthe amount of free drug from the initial amount of drug (Sherje et al., 2017).

Actual drug content Loading Efficiency =100Theoretical drug content

3.8 Shape and Surface Morphology (SEM)

For morphological study (particle size, shape) of CPO loaded Nanosuspension, Scanning Electron Microscopy (SEM) was used. The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes even if there was a clear difference in crystallization state of raw material and the product obtained by co- precipitation. SEM images of the formulated nanosuspension were taken by scanning electron microscope. A concentrated aqueous suspension of samples was spread over a slide and dried under vacuum. Surface topography was captured by the machine operated at 15 kV acceleration voltages. The sample was shadowed in a cathode evaporator with a gold layer of 20 nm thick. Microphotograph was

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captured and processed by an image processing program and individual Nanosuspension diameters was measured and surface characteristic feature of the nanosuspension was examined (Hammad et al., 2022).

3.9 *In- vitro* Drug Release

In vitro release of drug from nanosuspension formulations confers the release behavior of the drug from nanosuspension. Suitable diffusion cell apparatus method can be employed based on drug and type of formulation as per the aim of the study. Nanosuspension was modified diffusion cell apparatus. The drug release from nanosuspension was determined using a dialysis tube (donor compartment) containing the known quantity (1ml) of the nanosuspension in a water-jacketed beaker containing 300ml of phosphate buffer pH 7.4 at 37± 1ºc for 2 hrs. The content of the beaker were agitated on a magnetic stirrer. Sample withdrawn 5ml for 0,15,30,45,60,75,90,105,120 minutes periodically and replaced with 5ml volume of fresh phosphate buffer 7.4, sample were diluted suitably and filtered through a filter paper. CPO content was determined by UV-method at 306nm.

4. Result and Discussion

Main objective of this study was to formulate ciclopirox olamine (CPO) drug loaded Nanosuspension using polymer to enhance water solubility of CPO and improved topical delivery. This formulation reduced the side effects, minimized the dosing frequency and dose.

The present work aimed at formulating CPO Nanosuspension with polymer name PVA using emulsion solvent evaporation method. This method was simple and cost effective.

Ratio of HPMC and PVA produced greater yield. Particle size and Zeta potential was determined by Malvern Zeta sizer. The Particle size analysis was confirmed that the prepared sample were in the nanometer range. Average Particle size obtained for the formulations B7 is 219.1nm shown in Fig.2. Zeta potential values indicated that the formulated Nanosuspension are stable with -31.1mV shown in Fig.3. The particle size and Zeta potential result formulation B7 was selected for SEM analysis to identify the surface morphology of prepared Nanosuspension. The SEM image revealed the porous, smooth feature of Nanosuspension and it could be due to the in-ward diffusion of Dichloromethane in the HPMC polymeric surface of Nanosuspension during the fabrication.

Then the developed CPO loaded Nanosuspension was further subjected to in-vitro drug release to optimize the drug release of prepared formulation. Diffusion cell apparatus was used to assess the in vitro drug release by using dialysis tube.

The *in-vitro* drug release data was found that formulations B3, B6 & B7 showed the release 82.61±0.147, 83.05±0.725 and 85.24±0.725 respectively shown in Fig. 5, at the end of 2 hours. Marketed formulation was also compared with formulations and Increase of drug release was observed as a function of drug: polymer ratio. It was observed that the drug release decreased with an increase in the amount of polymer for each formulation. This is because the newly developed nanosuspension was believed to exhibit a core shell structure with a hydrophobic core formed by HPMC and a hydrophilic shell formed by PVA macromolecules.B7 formulations was well fitted in First order drug release kinetics as the plots showed the highest linearity.

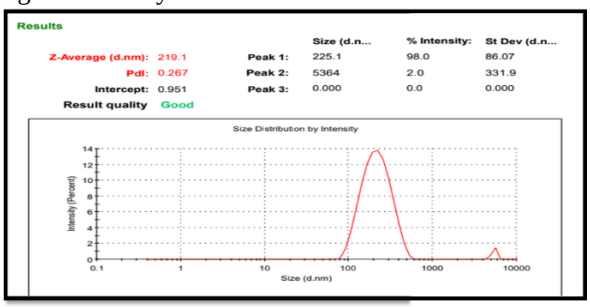

Fig 2. Particle Size of Ciclopirox Olamine loaded Nanosuspension

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Fig 3. Zeta Potential of CPO loaded Nanosuspension

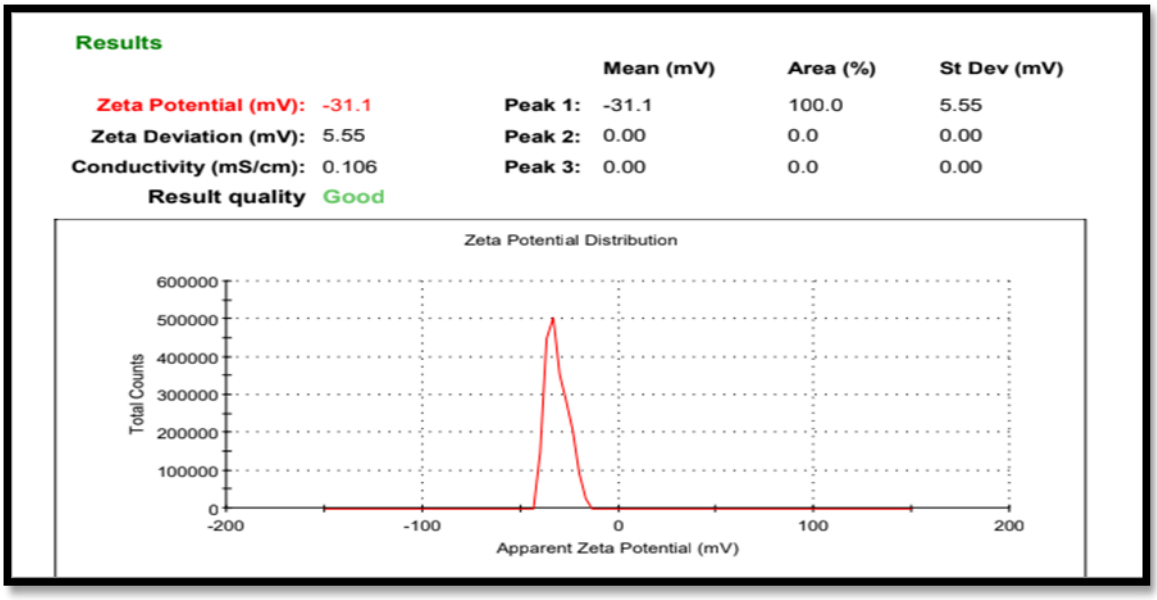

Table 2. pH of Nanosuspension ±S.D. Mean (n=3)

Batch No.	pH
B1	3.91±0.047
B2	3.95±0.094
B3	5.05±0.081
B4	4.00±0.014
B5	3.86±0.094
B6	4.98±0.016
B7*	4.45±0.081
B8	6.46±0.124
B9	5.30±0.047

Drug Content

The total drug content of the drug loaded Nanosuspension was in between 80.08 to 92.54 % respectively, which indicates loss of drug was lower during preparation process. The total drug content of the optimized formulation B7 was found to be 85.50%. The result were shown in Table 3.

Table 3. Drug content of formulated Nanosuspension

Formulation Code	Entrapment Efficiency
B1	69.41±0.163
B2	73.30±0.127
B3	78.00±0.192
B4	72.29±0.164
B5	75.34±0.158
B6	79.38±0.162
B7*	85.50±0.157

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B8	65.58±0.163
B9	70.18±0.183

Table 4. Entrapment Efficiency of Formulated Nanosuspension

Formulation Code	Entrapment Efficiency
B1	69.41±0.163
B2	76.30±0.127
B3	77.24±0.157
B4	73.29±0.164
B5	71.34±0.158
B6	78.38±0.162
B7*	92.00±0.192
B8	75.58±0.163
B9	69.18±0.183

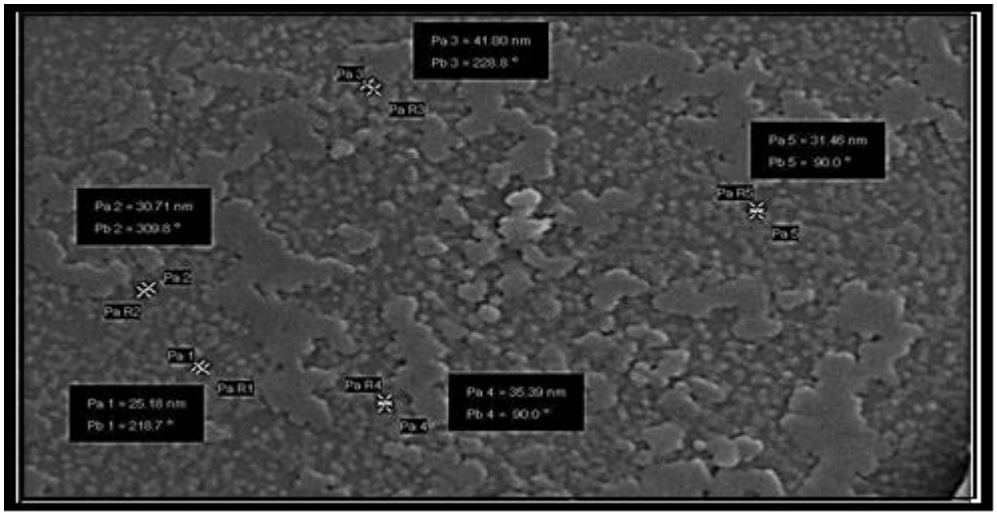

Fig 4. SEM image of CPO loaded Nanosuspension

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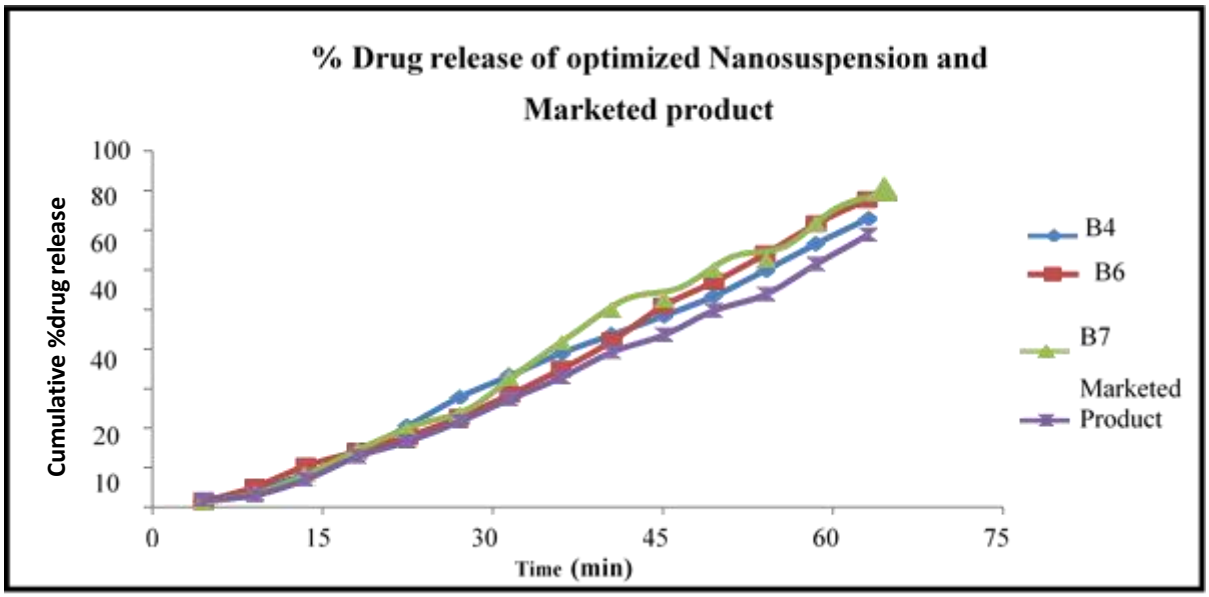

Fig 5. *In-vitro* Drug Release Studies of Optimized Three (B3, B6 and B7) formulation and marketed product

Data Analysis via Drug Release Kinetic Studies

The formulation of the nanosuspension was subjected to in-vitro release studies, using Franz diffusion cell apparatus using 7.4 phosphate buffer and egg membrane. The fitting of drug dissolution profile against kinetics models were analyzed using Microsoft Excel program. It was shown that almost all the developed formulations followed higuchi's release kinetics as the plots showed the highest linearity.

Formulation (B7*)

The zero order reaction graph between cumulative % drug release vs. time of formulation (B7) was given in the Fig. 6 in which the R^2 value was found to be 0.9954.

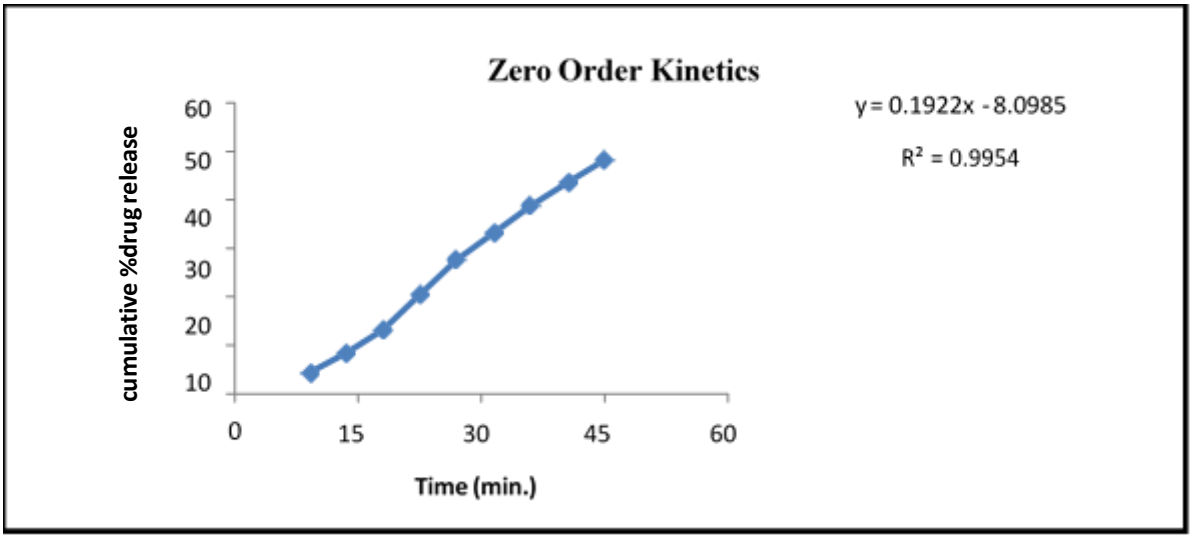

Fig. 6. Zero Order Release Kinetic of Formulation (B7)

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The higuchi's graph between log cumulative% drug release vs. square root of time of formulation (B7) was given in Fig. 8 in which R^2 value was found to be 0.995.

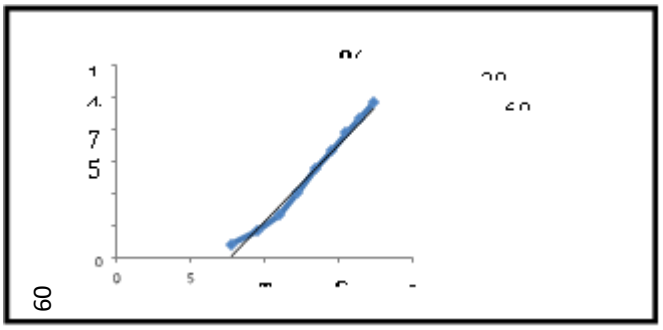

Fig. 7. Higuchi Release Kinetic of Formulation (B7)

Table 5. Kinetic Data of Optimization of Nanosuspension

Formulation	Zero order (R^2)	First order(R^2)	Higuchi (R^2)	Kors-peppas(R^2)
B3	0.987	0.862	0.962	0.981
B6	0.961	0.830	0.951	0.985
B7*	0.995	0.893	0.995	0.991

It was shown that B7* developed formulation was followed Zero order & Higuchi release kinetics as the plots showed the highest linearity.

CONCLUSION

The purpose of this research was to prepare Ciclopirox olamine loaded Nanosuspension for Sustained release of drug, the carrier used in this study has great solubility and improved drug loading which provide high bioavailability, reduce the dosing frequency and side effects and gave fast onset of action.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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