European Journal of Applied Sciences – Vol. 13, No. 03
Publication Date: June 28, 2025
DOI:10.14738/aivp.1303.18997.
Muzib, Y. I., Roja, N., Ambedkar, Y. R. (2025). Formulation and Evaluation of Cilnidipine Loaded Nanocapsules Suspension for Hypertension Management. *European Journal of Applied Sciences*, Vol - 13(03). 483-491.

Formulation and Evaluation of Cilnidipine Loaded Nanocapsules Suspension for Hypertension Management

Y. Indira Muzib
Department of Pharmaceutics,
Institute of Pharmaceutical Technology,
Sri Padmavati Mahila Visvavidyalayam,
Tirupati-517502, Andhra Pradesh, India

N. Roja
Department of Pharmaceutics,
Institute of Pharmaceutical Technology,
Sri Padmavati Mahila Visvavidyalayam,
Tirupati-517502, Andhra Pradesh, India

Y. R. Ambedkar
Department of LPT, College of Veterinary Science,
Sri Venkateswara Veterinary University, Garividi,
Vizianagaram, Andhra Pradesh, India-535101

ABSTRACT

Hypertension is one of the major causes of cardiovascular diseases, necessitating effective and sustained drug delivery systems for optimal treatment. Cilnidipine, is a dual calcium channel blocker, has demonstrated significant efficacy in managing hypertension. Due to poor solubility and bioavailability its therapeutic potential is often limited. The main objective of this study was to develop, characterize, and evaluate cilnidipine-loaded nano capsule suspensions as an advanced drug delivery system for the treatment of hypertension. Cilnidipine nanocapsules (CN) were prepared using a solvent evaporation method, and their physicochemical properties, such as particle size, zeta potential, drug loading efficiency, and morphology, were systematically analysed. Developed 8 formulations (CN1-CN8) with various ratios 2 different polymers. The optimized cilnidipine nanocapsule suspension compatibility studies conducted by using Fourier transform infrared spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) that confirmed the absence of any interactions between drug and excipients showcasing uniformly distributed particles.CN8 formulation was showing better results among all remaining formulation. The stability studies confirmed the nanocapsules' suitability for long-term storage, making them an ideal candidate for clinical use. Cilnidipine-loaded nanocapsule suspensions offer a promising strategy for improving the management of hypertension by providing controlled release, reduced side effects, and enhanced therapeutic efficacy.

Keywords: Hypertension, Cilnidipine, Nanocapsule, Nanosuspension, Zeta potential.

INTRODUCTION

Hypertension or high blood pressure is a serious global health issue that affects millions of people and is a major risk factor for heart diseases like stroke, heart attack, and heart failure. Despite the availability of various medications, treating hypertension effectively is still challenging due to issues like poor drug absorption, limited effectiveness, and side effects from traditional medications [1,2]. Cilnidipine, a new type fourth generation calcium channel blocker, has shown promise for treating hypertension. It works by blocking both L-type and N-type calcium channels, which helps control blood pressure and prevent related complications. Cilnidipine is classified as BCS-II drug. However, its use is limited by poor water solubility, low absorption in the body, and quick removal from the system. To overcome these challenges, new drug delivery systems are being developed to improve cilnidipine's solubility, stability, and controlled release [3,4]. Nanocapsules are gaining attention because they can carry hydrophobic drugs, improve absorption, and release drugs in a controlled way. Nanocapsules are tiny, spherical carriers (10 to 1000 nanometers) that can deliver drugs directly to targeted areas in the body, reducing side effects and improving treatment. These can be given in different ways, such as orally, through injections, or topically [5]. This study focuses on creating and testing cilnidipine-loaded nanocapsule suspensions as a new approach to treating hypertension. The goal is to develop a system that overcomes the limitations of current cilnidipine formulations, offering a more effective, long-lasting, and convenient treatment. By studying the properties, release patterns, stability, and effectiveness of the nanocapsule suspension, this research aims to improve hypertension management. Coating nanocapsules with certain surfactants can change their surface properties, improving how they are distributed in the body. This leads to higher blood concentrations, longer circulation times, and less accumulation in organs like the liver and spleen. Nanocapsules can also cross the blood-brain barrier, which is a challenge for many drugs. Compared to other drug delivery systems, polymeric nanocapsules are more stable in the body and can release drugs in a controlled and sustained manner [6,7].

MATERIALS AND METHODOLGY

Cilnidipine was a gift sample from Yarrow chem products Mumbai, Eudragit S100 was a gift sample from Alpha Chemika, Mumbai, PLGA, Acetone and Potassium-di-hydrogen phosphate purchased from Hi media Laboratories, Soya lecithin, Ethanol and Benzyl benzoate were purchased from Merck Ltd, Mumbai.

Calibration Curve of Cilnidipine

An accurately weighed 10mg of cilnidipine was taken in to 100ml volumetric flask and dissolved in small quantity of methanol. The final volume was made up to 100ml with pH 6.8 phosphate buffer. The stock solution was then diluted with pH 6.8 phosphate buffer. The stock solution was then diluted with pH 6.8 phosphate buffer to obtain series of dilutions containing 10-90 µg/ml. These concentrations were further diluted to produce 1-9 µg/ml. the absorbance was measured at 240nm by using UV- Visible spectrophotometry against blank. The graph was plotted by taking concentration on X-axis and absorbance on Y-axis [8,9].

Preparation of Nanocapsule Suspension

Different ratios of the polymers were solubilized in 20 ml of solution prepared with equal proportions of acetone and ethanol and stirred for 30 minutes by 4000 rpm to form the organic

phase. 100 mg of soya lecithin was added to organic phase and continue the stirring about 1hour. A 100mg sample of the drug was solubilized in 2 ml of benzyl benzoate, and it was slowly added drop wise to the above organic phase with continuous stirring again one hour. The organic mixture was then gradually added drop by drop to the distilled water (30 ml) containing tween80 (0.75%) acts as the stabilizer, with continuous stirring. The organic solvent (acetone) was then evaporated by heating under reduced pressure. The resulting colloidal mixture was further concentrated to approximately 15 mL by centrifugation at 4000 rpm [10]. The formulation and composition were mentioned in Table no.1

Table 1: Formulation and Composition of Nanocapsule suspension

Formulation code	Drug: Polymer ratio		Phospholipid concentration (mg)	Amount of benzyl benzoate (ml)	Speed of rotation(rpm)
	Eudragit S100	Poly (d,1 lactide co-glycolide)			
CN1	1:0.5	-	100	2	4000
CN2	1:1	-	100	2	4000
CN3	1:2	-	100	2	4000
CN4	-	-	125	2	4000
CN5	-	1:0.5	100	2	4000
CN6	-	1:1	100	2	4000
CN7	-	1:2	100	2	4000
CN8	-	1:2	125	2	4000

Evaluation Parameters of Nanocapsule Suspension

Zeta Potential:

The zeta potential analysed with the help of laser doppler micro electrophoresis (Horiba scientific). 1-2 ml aliquot of sample was placed in an electrode cuvette and analysed by using zeta sizer [11].

Particle Size Distribution:

The Particle size of the Nanocapsule suspension was measured with Horiba scientific instruments (particle sizer analyser). Samples were obtained by appropriately diluting Nanocapsule suspension with adequate volume of water. The mean particle size was assessed with Laser diffractometer [12].

Determination of Encapsulation Efficiency:

Specified amount of formulation was taken and the solution was centrifuged at 2000rpm for 100min. 1ml of supernatant was taken and adjusted to 10ml with methanol. From this again 1 ml solution was withdrawn and adjusted to 10ml. This solution was analysed at the λ_{max} of 240nm. The encapsulation efficiency (EE %) could be achieved by the following equation [13].

$$\% \text{ Encapsulation Efficiency} = \frac{Amount\ of\ drug\ actually\ present\ in\ Nanocapsule}{Theoretical\ Drug\ Content} X\ 100$$

Drug-polymer Compatibility Studies:

FTIR spectra of cilnidipine, Eudragit S 100, PLGA (Poly lactide co glycolide) and optimized formulation were recorded using FTIR spectrophotometer (Bruker Alpha -T, Switzerland) to

investigate no interaction between cilnidipine and polymers in formulated nanocapsule suspension. The samples for FTIR spectroscopy were ground with KBr to make the pellets by means of hydraulic pellet press by applying pressure of 600kg/cm^2 . The prepared pellets were scanned over the wave number range from 4000-400cm^{-1} with resolution of cm^{-1}. The characteristic peaks of pure drug, polymers and drug loaded nanocapsule suspension were recorded [14].

Differential Scanning Calorimetry (DSC):
Samples were accurately weighed (5mg), sealed in aluminium pans and heated over a range of 100 – 200 °C under a nitrogen purge flow rate of 20ml/min with a rise in temperature of 10 °C/min [15].

Determination of Drug Content:
Drug content was analysed by taking a specified volume of Nanocapsule suspension formulation and ultra centrifuged at 2000 rpm and the volume of drug in the supernatant was assessed by using UV Visible spectrophotometer at the λ_{max} of 240nm. The formula used to calculate drug content was given below [16].

$$\textbf{Drug content (\%)} = \frac{Weight\ of\ drug\ Nanocapsules}{Weight\ of\ Naocapsules} \text{ X } 100$$

***In vitro* Drug Release:**
Cilnidipine release studies from nanocapsule suspension were carried out over 12 hrs through a dialysis membrane having a molecular weight cut off of 3500 Da. The dialysis bags were loaded with 5mL of drug loaded nanocapsule suspension (dialysis membrane was soaked for 12 hrs in dissolution medium before use). This was suspended in pH 6.8 phosphate buffer and was stirred magnetically at 100 rpm, temperature was maintained at 37 ± 0.5°C. 2 ml samples were withdrawn at regular time intervals 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hrs and were replaced by the same volume of pH 6.8 phosphate buffer to maintain sink conditions. The samples were filtered, diluted and their absorbance was measured at 240nm [16]. *In-vitro* drug release data obtained was fitted to different kinetic models like zero order, first order, Higuchi, Korsemeyer – Peppas models to know the mechanism of drug release from the formulations. The coefficient of correlation (R^2) values was considered to be main parameter for interpreting the release kinetics of drug from matrix system [17].

RESULTS AND DISCUSSION

Preformulation Studies of Cilnidipine
The Cilnidipine was in yellow coloured powder without any specific odour. The solubility was observed that the Cilnidipine was freely soluble in methanol, ethanol, pH 6.8 phosphate buffer, tween 80 and sparingly soluble in 0.1 N HCL and slightly soluble in water. Melting point test was conducted out for cilnidipine to examine the purity of drug by capillary method. Average melting point is 109.1 °C which is coinciding with the reported value (109-110 °C).

Calibration Curve of Cilnidipine
The results of concentration Vs absorbance values for construction of calibration curve are given in table no.2.

The curve is obtained with Beer-Lamberts equation of y = 0.031x and correlation coefficient value 'r'of 0.997 which is closer to unity.

Particle Size

The optimized formula CN8 was revealed 64.5 nm of particle size with 0.415 polydispersity index (PDI), respectively. The particle size (<100) indicates micrometer range. Polydispersity index (<0.5) indicates homogenous dispersion.

Drug Content

The % of drug content of all the eight formulations were found to be in the range of 79.2% to 95.7% maximum.

Encapsulation Efficiency

The Encapsulation efficiency of developed nanocapsule suspension was identified within the range of 74.42% to 89.6%. Maximum % encapsulation efficiency i.e. 89.6% was observed in the formulation CN8.

pH Determination

pH of nanocapsule suspension was determined by using ELICO U120 pH meter. The pH of the formulation was in the range of between 5.5-6.8. the CN8 formulation has the pH of 6.8 which is similar to the physiological pH.

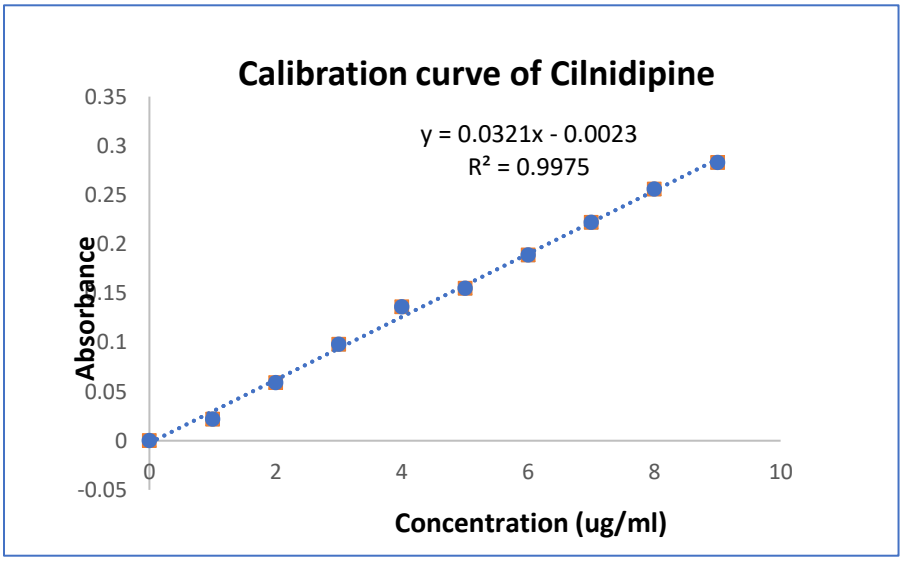

Fig. 1: Calibration curve of Cilnidipine

Drug- Polymer Compatibility Studies

The Infrared spectrum of pure drug, polymers and developed nanocapsule suspension were analysed making a KBr disc. Spectral recordings were performed using thermos Electron-based FTIR spectrometer over wavelengths 4000cm^{-1} to 400cm^{-1} shows that absence of incompatability between drug and polymers. FTIR spectrum of cilnidipine, polymers Eudragit S100 and PLGA, and optimized formulation are showed in Fig no 4. Aromatic 2°amine (N-H

stretch)-3380,C-N stretch-1270 ,-C-H-1379,Carbonyl (C=O stretch)-1698 cm^{-1} bending were observed in FTIR spectra of pure cilnidipine and in optimized formulation.

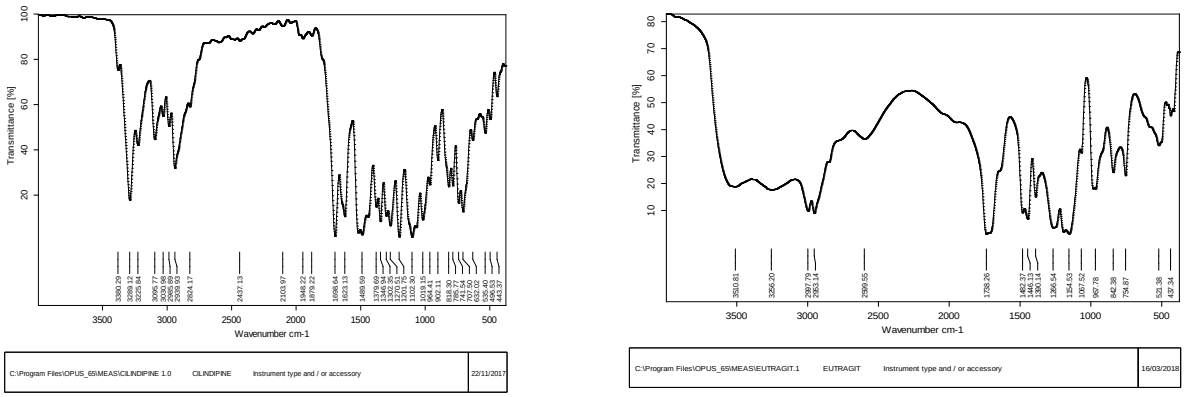

Fig no 2: FTIR spectrum of a) pure cilnidipine b) Eudragit S100

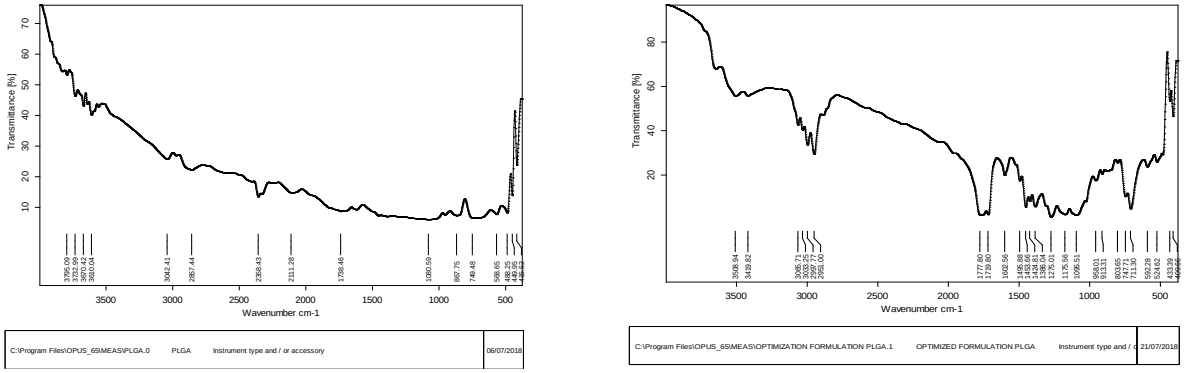

Fig no 3: FTIR spectrum of c) PLGA d) Optimized formulation of cilnidipine loaded nanocapsule

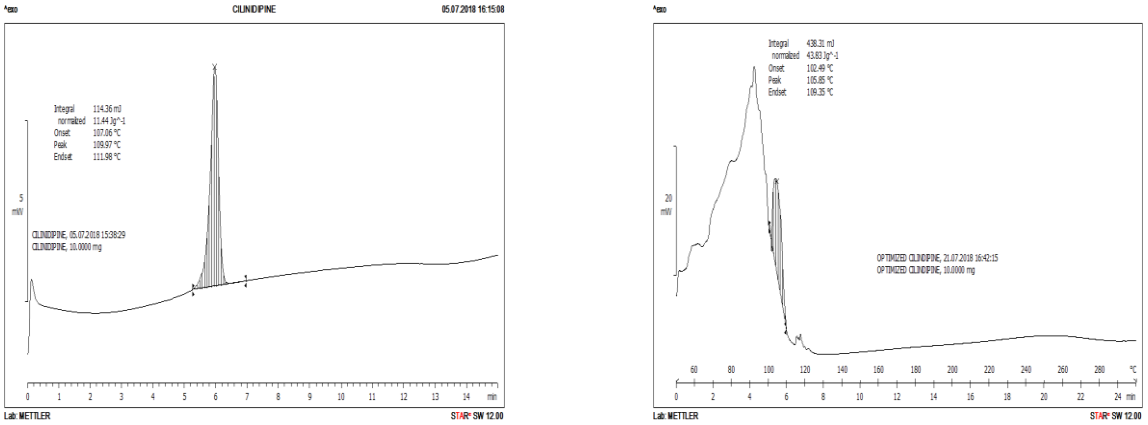

Fig no 4: DSC thermogram of a) Pure cilnidipine, b) Optimized formulation of cilnidipine loaded nanocapsule suspension

DSC thermogram of pure cilnidipine shows sharp peak at 109.9 ^{o}C corresponding to its melting point. The thermogram of cilnidipine loaded nanocapsule suspension containing PLGA showed a similar exothermic peak at 105.6 ^{o}C. This confirms there was no polymer drug interaction.

Phase Contrast Microscopy

The shape and surface morphology of the optimized formulation was examined by using phase contrast microscopy. The view of nanocapsule suspension showed a smooth, spherical shape. The phase contrast images of the nanocapsule suspension were shown in Fig.no5

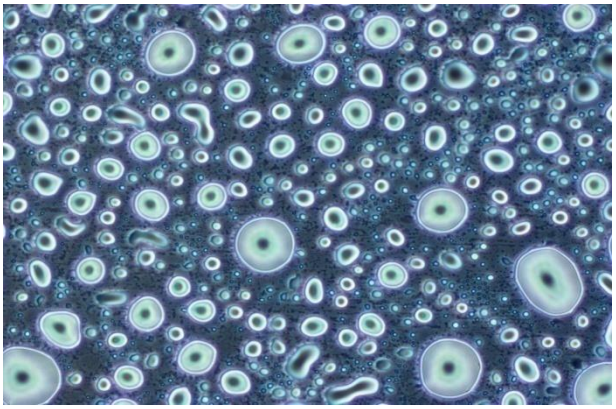

Fig 5: Particle shape of optimized formulation

Particle Size

Particle size of the nanocapsule suspension is a critical factor because it determines the rateand extent of drug release as well as absorption. The particle size (<100) indicates micrometer range. Polydispersity index (<0.5) indicates homogenous dispersion.Fig.no.6 represents the particle size of optimized formualation

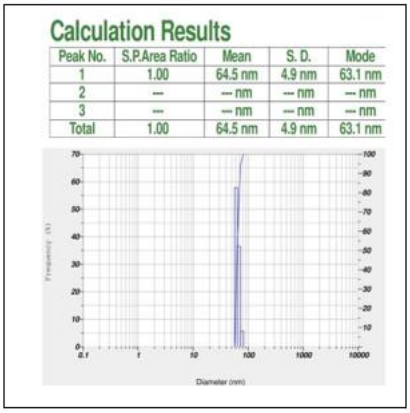

Fig no 6: particle size

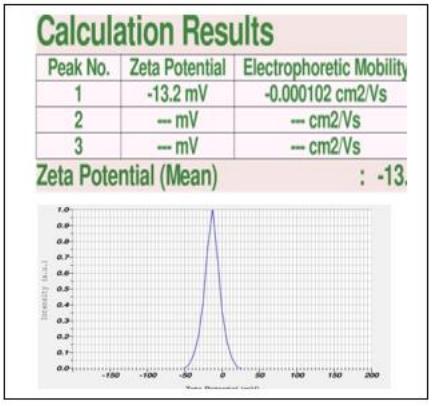

Fig no 7: Zeta potential of CN8 formulation

Zeta Potential

The high value of zeta potential indicates electrostatic repulsion between particle size, zeta potential under ±30 mV shows good physical stability. The measurements were carried out in the diluted nanocapsule suspension formulations and its values were determined from the electrophoretic mobility of the particles. Zeta potential of CN8 formulation represented in Fig.no.7. The high value of zeta potential indicates electrostatic repulsion between particle size, zeta potential under ±30 mV shows good physical stability. The measurements were carried out in the diluted nanocapsule suspension formulations and its values were determined from the electrophoretic mobility of the particles.

In vitro Drug Release Studies

In vitro drug release studies of cilnidipine loaded nanocapsule suspension were carried out using dialysis membrane. *In vitro* release profiles of cilnidipine loaded nanocapsule suspension was shown in the Fig.no.8. Percentage of drug release at the end of the 12th hr from formulations CN1 to CN8 were 80.16,83.6,85.42,90.6,79.6,82.5,88.47,93.8. From the studies CN8 was selected as a best formulation.*In-vitro* drug release data obtained was fitted to different kinetic models like zero order, first order, Higuchi models to know the mechanism of drug release from the formulations. The coefficient of correlation (R^2) values was considered to be main parameter for interpreting the release kinetics of drug from matrix system. The drug release mechanism follows zero order(R^2 0.968),first order($R^2$0.937) and Higuchi(R^2 0.941) suggested that the release mechanism was diffusion controlled.

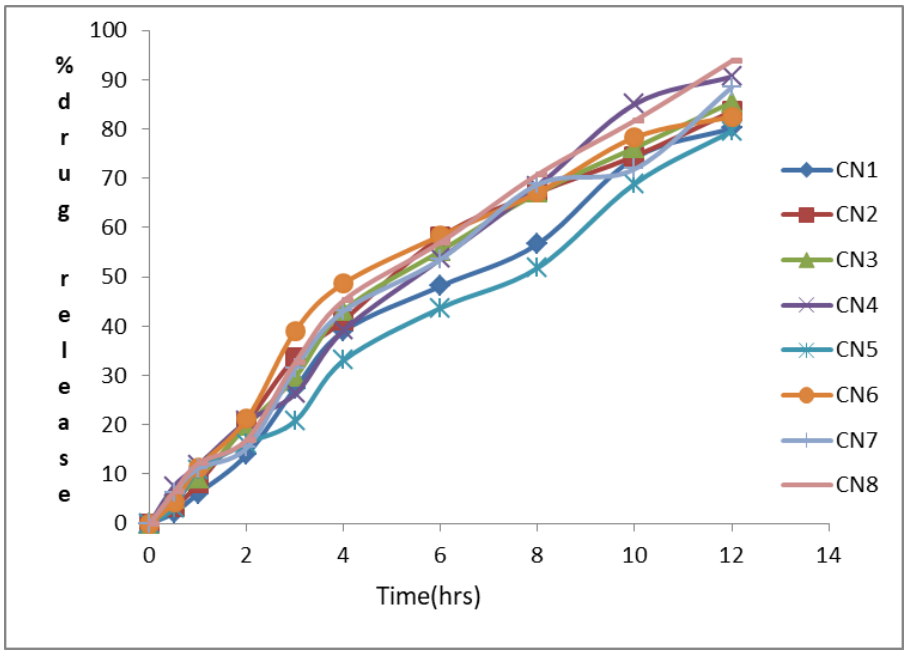

Fig no 8: *Invitro* drug release profile's of various formulations

CONCLUSION

Cilnidipine nanocasules formulated by solvent evaporation method. FT-IR and DSC results, concluded that the formulation has no incompatibility between drug and polymers both chemically and physically. Among all formulations CN8 has desirable particle size, entrapment efficiency, prolonged drug release. Based on the results, it can be concluded that the nanocapsule suspension of cilnidipine is the potential candidate for increase in aqueous solubility and bioavailability of drug.

ACKNOWLEDGEMENTS

Authors highly thankful to authorities of DST-CURIE, DST-FIST centres Sri Padmavati MahilaVisvavidyalayam, Tirupati for their kind support to complete this project work.

References

1. Paul G Hunter , Fiona A Chapman , Neeraj Dhaun. Hypertension: Current trends and future perspectives Br J Clin Pharmacol, 2021 ;87(10):3721-3736.
2. P.M. Kearney et al. Global burden of hypertension: analysis of worldwide data. Lancet (2005)
3. Shifa shaukat haju, sheela Yadav. Formulation and evaluation of cilnidipine mucoadhesive buccal film by solvent casting technique for the treatment of hypertension: International Journal of Pharmacy and Pharmaceutical Sciences, Vol 13, Issue 9, 2021.
4. K Sarat Chandra, G Ramesh. The fourth-generation Calcium channel blocker: Cilnidipine, Indian Heart J, 2013 Dec;65(6):691–695.
5. Salman Khan, Shazia Mansoor, Zeeshan Rafi, Bhawna Kumari, Ambreen Shoaib, Mohd Saeed, Sultan Alshehri, Mohammed. A review on nanotechnology: Properties, applications, and mechanistic insights of cellular uptake mechanisms. Journal of molecular liquids. Volume 348, 15 February 2022, 118008.
6. Pavankumar Kothamasu , Hemanth Kanumur, Niranjan Ravur, Chiranjeevi Maddu, Radhika Parasuramrajam, Sivakumar Thangavel. Nanocapsules: The Weapons for Novel Drug Delivery Systems. Bioimpacts. 2012 Apr 5;2(2):71–81.
7. Satyendra Kumar and Purshotam. Pharmaceutical nanotechnology: Applications in drug delivery, The Pharma Innovation Journal 2019; 8(4): 1315-1319.
8. Ana Luiza Lima, Tais Gratieri, Marcilio Cunha-Filho, Guilherme M. Gelfuso. Polymeric nanocapsules: A review on design and production methods for pharmaceutical purpose, Volume 199, ScienceDirect: 2022, 54-66.
9. Dr. Seema Firdouse1, Batool Mohiuddin, Muqtar Begum, Abdullah Ali Baig, Shaikh Mohd Aquib. UV spectrophotometric method development and validation of Cilnidipine API and marketed pharmaceutical dosage form: Int. J. of Pharmacy and Analytical Research Vol-9(2) jun-2020 [62-67]
10. Hetal Patel, Dulendra, Damahe, Sachin B. Narkhede SMT B.N.B. RP-HPLC Method Development and Validation for Simultaneous Estimation of Cilnidipine and Bisoprolol Fumarate in Tablet Dosage Form: International Journal of ChemTech Research. 2019,12(1): 269-276.
11. Shripathy D, Shreya H Alva, A R Shabaraya, Formulation and evaluation of polymeric nanoparticle by emulsion solvent evaporation method November 2023 IJSDR, Volume 8 Issue 11.
12. Lalita S. Nemade, Moreshwar P. Patil. Formulation development, optimization, and evaluation of lansoprazole loaded nanosuspension: International Journal of Applied Pharmaceutics. Vol 15, Issue 3, 2023, 208-219.
13. M. Ghoneim, Mohamed Rahamathulla, Umme Hani, Faiyaz Shakeel, Anusha Dudekula, Manjula Challa, Pradeep Kumar Mutcherl. Formulation and Evaluation of Itraconazole Nanocapsules: Himalayan Journal of Health Sciences 2022; 7(4): 33-41.
14. Remya PN, Damodharan N. Formulation, development, and characterisation of cilnidipine loaded solid Lipid nanoparticles. Asian journal of pharmaceutical and clinical research. Vol 11, Issue 9, 2018
15. Suray A. Al Hazzaa, Nawal A. Rajab. Cilnidipine Nanocrystals, Formulation and Evaluation for Optimization of Solubility and Dissolution Rate: Iraqi J Pharm Sci, Vol.32
16. (Suppl) 2023
17. S.D. Mankar and Arpita Tupe. Solubility enhancement and evaluation of Cilnidipine using solid Dispersion techniques. Int. J. Exp. Res. Rev., Vol. 32: 347-357 (2023).
18. Sri ram A, G Swapna, Audinarayana Nelavala. Formulation and Evaluation of Miconazole Nanocapsules: Future J. Pharm. Health. Sci. 2023; 3(4): 540-550.