Journal of Advanced Zoology

ISSN: 0253-7214

Volume ***44*** *Special Issue-****2 Year 2023*** *Page* ***5118:5131***

Formulation and Evaluation of Instant Dissolving Film of a Poorly Soluble Drug Cilnidipine

Neelam Pawar[1], Neha[2], S Valarmathi[3*], Dolley Rout[4], Jyothirmayee Devineni[5], Ankur Patel[6], Nikhil Samson Shrisunder[7], Narender Boggula[8]

[1]Department Pharmaceutics, Hargobind Khurana Building, Chaudhary Bansilal University, New Campus, Prem Nagar, Bhiwani, Haryana-127031.
[2]Department Pharmaceutics, RKSD College of Pharmacy, Kaithal (Haryana) 136027.
[3*]Department Pharmaceutics, Annaiveilankannis College of Pharmacy Chennai 15.
[4]Department of Pharmaceutics, The Pharmaceutical College, Samaleswari Vihar, Tingipali, Barpali Odisha-768029.
[5]Department of Pharmaceutics and Biotechnology, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada-520010.
[6]Department of Pharmaceutics, Sardar Patel College of Pharmacy, Vidyanagar Vadtal road, Bakrol Gujarat -388315.
[7]Department of Pharmaceutics, Gandhi Natha Rangji College of Diploma Pharmacy, Solapur 13, Jain Boarding Complex, Budhwar Peth, Balives, Solapur – 413002.
[8]Department of Pharmaceutical Chemistry, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, India – 501 401.

[*]**Corresponding Author: S Valarmathi[3*]**
[3*]Department Pharmaceutics, Annaiveilankannis College of Pharmacy Chennai 15.
Email Id: [3*]sahanashree2012@gmail.com

Article History

Received: 06 September 2023
Revised: 05 November 2023
Accepted:08 December 2023

Abstract

The chemical formula in question is classified as a calcium antagonist, which includes cilnidipine (also known as dihydropyridine) as one of its component parts. This is accomplished through a process known as L-type calcium channel blockage, which prevents calcium from entering the capillaries and so accomplishes the desired effect. The consequence of this is a decrease in blood pressure. Intravenous administration of the medicine results in a higher level of bioavailability compared to oral administration of the drug in tablet form. This is due to the diminished solubility of the substance in water. Propylene glycol and PEG 400 were combined to create a polymer that lacked stickiness and hardness. The drug's solubility and release are greatly enhanced when inclusion complexes are made using cyclodextrin. Research on PEG 400 and propylene glycol drug release in vitro examined a number of independent factors, including pH, thickness, weight uniformity, percent drug content, folding endurance, disintegration time, and percent drug.

Keywords: *Clinidipine, Invitro study, Calibration curve, Calcium channel, Hypertension*

1. Introduction

Hypertension is the number one risk factor for CVD and death globally, yet it is also the most avoidable risk factor. In 2022, 31.1% of the adult population throughout the world was affected by hypertension, which is defined as systolic blood pressure equal to or greater than 140 mmHg and/or diastolic blood pressure equal to or greater than 90 mmHg.3) The world's population is getting older, which means more people are exposed to lifestyle risk factors like high-salt, low-potassium diets and insufficient physical exercise, which is leading to an increase in the prevalence of hypertension. Thirdly, there is a lack of global consistency in the changes seen in the prevalence of hypertension. Hypertension rates have risen sharply in low- and middle-income countries (LMICs) over the last two decades, whereas they have fallen somewhat in high-income countries (HICs).3) Due to these disparities in hypertension prevalence trends, it suggests that health care systems in LMICs may be facing a rapidly increasing burden of cardiovascular diseases linked to hypertension and blood pressure, and in some cases, a significant burden of infectious diseases all at once. A study that analyzed data from 844 studies performed in 154 countries with 8.69 million participants estimated that in 2021, the global mean age-standardized systolic BP was 127.0 mmHg in men and 122.3 mmHg in women, whereas the mean age-standardized diastolic BP was 78.7 mmHg in men and 76.7 mmHg in women. Higher mean systolic and diastolic BPs in both men and women were found in South Asia, Sub-Saharan Africa, and Central and Eastern Europe, while lower mean BPs were found in high-income Western and high-income Asia-Pacific regions. Social and environmental factors, including healthcare access, availability of antihypertensive medications, and regional variations in hypertension risk factors, such as obesity, alcohol consumption, unhealthy diet and lack of physical activity, likely contribute to these regional differences This study also reported that over the past 40 years, estimated mean BP has remained constant or decreased slightly worldwide. Estimated global mean age-standardized systolic BP remained fairly constant in men between 1975 (126.6 mmHg) and 2015 (127.0 mmHg) but decreased slightly in women during this period (from 123.9 mmHg to 122.3 mmHg). Trends for men and women were similar for estimated global mean age-standardized diastolic BP, with very little change in men and a slight decrease in women.

Cilidipine, a more recent addition to the family of dihydropyridine calcium antagonists, has shown promise as an antihypertensive with a longer half-life [3]. With its initial clearance in Japan in 1995, cilnidipine quickly gained permission from other nations, becoming one of the most extensively used anti-hypertensive drugs globally today. In vivo, cilnidipine reduces blood pressure by blocking sympathetic nerves at peripheral sympathetic nerve endings, as is the case with other L/N-type calcium channel blockers [4]. It has been shown to reduce systolic and diastolic blood pressure (SBP and DBP, respectively) [5], although it has no effect on plasma catecholamines or pulse rates (PR). Not only that, but it can also decrease the pressor response to acute cold stress in SHR rats, which is a condition where hypertension develops on its own [6]. Patients with hypertension and morning hypertension, in whom sympathetic nerve overactivity may play a role, have responded well to cilnidipine treatment. More so, research has shown that cilnidipine can significantly lower blood pressure in hypertensive patients with abnormal nocturnal blood pressure, especially while sleeping when sympathetic nerve activity is at its peak [7]. Because it lessens the efficacy of arterial endothelial dysfunction, cilnidipine is also useful for the long-term control of cardiovascular issues [8]. Cilnidipine does a great job at lowering blood pressure, and it has a lengthy half-life and rapid oral absorption rate to boot. Between 1.8 and 2.2 hours after oral administration, the drug reaches its peak concentration; its half-life is 7.5 hours. Although cilnidipine's half-life is shorter than that of other anti-hypertensive drugs, it continues to reduce blood pressure for a longer duration.

2. Material & Methods

Laboratory analyses were performed to determine the drug's purity after it was obtained from L.B. Chemical and Pharmaceutical Pvt Ltd.

Organoleptic properties:
Hand inspection of the reference drug and the sample drug was used to compare their physical qualities, The table contains the final results.

Table No .1: Organoleptic properties

Sr.no	Properties	Standard	Sample
1.	State	solid	Solid
2.	Color	yellow	Yellow
3.	Odor	Odorless	Odorless
4.	Solubility	Soluble in ethanol, methanol and insoluble in water	Soluble in ethanol, methanol and insoluble in water

Melting Point: Through the utilization of the capillary method, it was ascertained that the melting point of cilnidipine is 111^0c degrees Celsius. Temperatures ranging from 108^0c to 113^0c degrees Celsius are mentioned.

Spectroscopic Estimation of cilnidipine: Using a UV spectrometer, the maximum wavelength, λ-max, was found. Below you will find a discussion of the results related to wavelength.

Table No .2: wavelength of drug in different solvents

Solvents	λ-max (Reported)	λ-max (observed)
Methanol	240	240
Phosphate buffer pH 6.8	246	246
1% Sodium Lauryl Sulphate (SLS)	242	242

Calibration of Methanol: To measure the concentrations of the dissolving agents, the Cilnidipine in methanol calibration curve is shown in Figure 1(a), and the corresponding absorbance measurements are listed in Table 3. The spectra of cilnidipine in methanol can be shown in Figure 1(b). Regression analysis revealed a slope of 0.0795 and an intercept of 0.0396 for the calibration curve, leading to a correlation coefficient of 0.9908.

Table .3: Data for Calibration curve of cilnidipine in methanol at 240 nm					
Sr.no.	**Concentration (µg/mL)**	**Absorbance A=1**	**Absorbance A=2**	**Absorbance A=3**	**Absorbance, n=3**
1	2	0.221	0.228	0.223	0.224±0.003
2	4	0.379	0.389	0.381	0.383±0.005
3	6	0.526	0.548	0.543	0.539±0.011
4	8	0.673	0.696	0.677	0.682±0.012
5	10	0.221	0.208	0.219	0.802±0.009

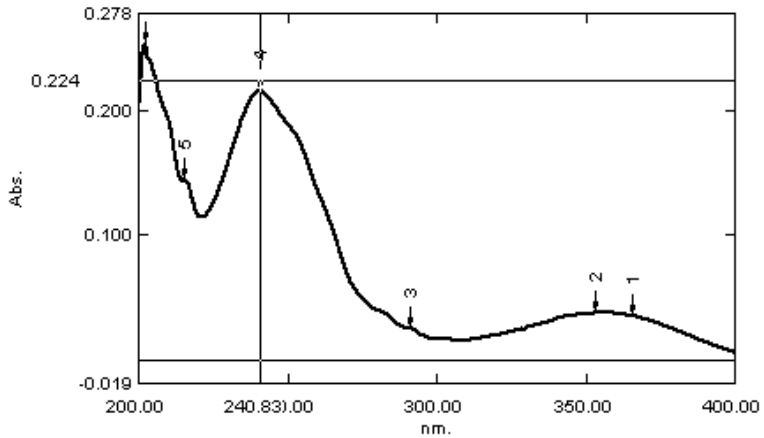


Fig. 1 (a) 2ppm spectra of Cilnidipine in Methanol at 240 nm

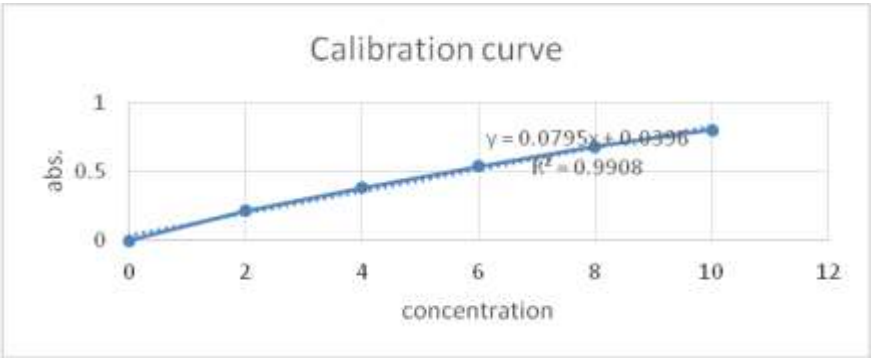


Fig. 1 (b) Calibration curve of Cilnidipine in Methanol at 240 nm

Calibration of phosphate buffer pH 6.8: Figure 2(a) and Table 4 show the results of a calibration curve that was used to test the dissolution rate of Cilnidipine in phosphate buffer with a pH of 6.8. In Fig. 2. (b), cilnidipine spectra in a 6.8-pH phosphate buffer are shown. An intercept of 0.0276 and a slope of 0.0426 were used in the regression analysis to get a correlation coefficient of 0.9926 for the calibration curve.

Table 4: Data for Calibration curve of cilnidipine in phosphate buffer pH 6.8 at 246 nm					
Sr. no.	**Concentration (µg/mL)**	**Absorbance A= 1**	**Absorbance A= 2**	**Absorbance A= 3**	**Absorbance, n=3**
1	0	0	0	0	0
2	2	0.129	0.133	0.128	0.13±0.002
3	4	0.219	0.214	0.215	0.216±0.002
4	6	0.283	0.29	0.285	0.286±0.003
5	8	0.373	0.376	0.367	0.372±0.004
6	10	0.449	0.439	0.447	0.445±0.005
7	12	0.519	0.546	0.534	0.533±0.01

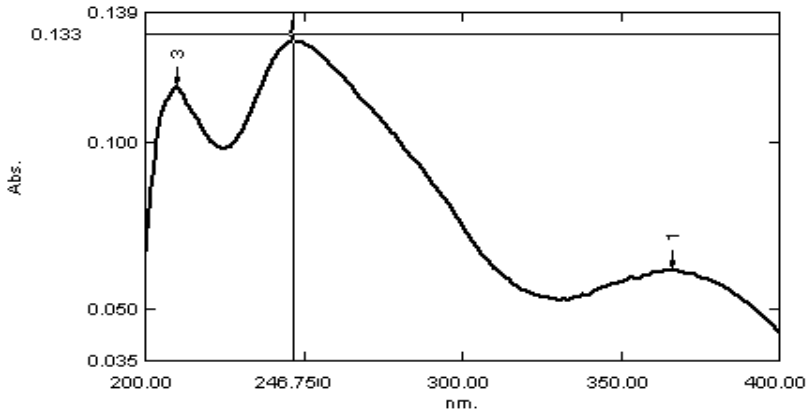


Fig. .2. (a) 2ppm spectra of Cilnidipine in phosphate buffer pH 6.8 at 246 nm

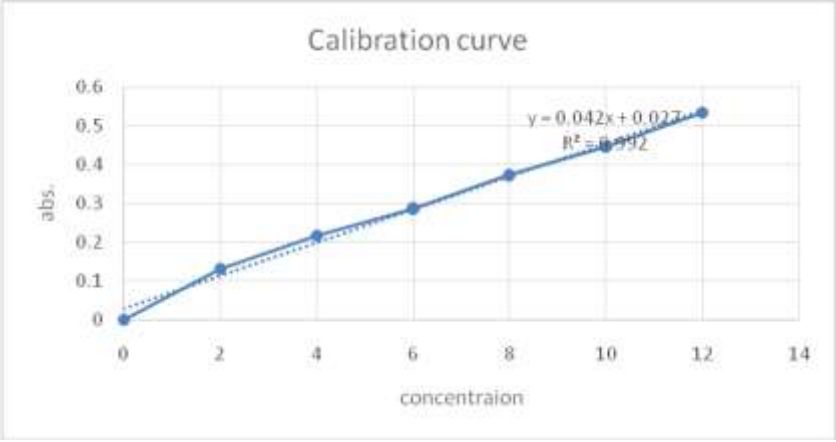


Fig. .2. (b) Calibration curve of Cilnidipine in phosphate buffer pH 6.8 at 246 nm

Calibration of 1% Sodium Lauryl Sulphate (SLS): A calibration curve for cilnidipine in 1% SLS was used to calibrate the solution, as shown in figure 3(a), and absorbance data can be found in table 5. Figure 3(b) shows the spectra of cilnidipine in 1% SLS.

Table.5: Data for Calibration curve of cilnidipine in 1% SLS at 242nm					
Sr. no.	**Concentration (µg/mL)**	**Absorbance A=1**	**Absorbance A=2**	**Absorbance A=3**	**Absorbance, n=3**
1	2	0.274	0.263	0.285	0.274±0.010
2	4	0.366	0.385	0.392	0.381±0.013
3	6	0.489	0.512	0.496	0.499±0.011
4	8	0.624	0.668	0.673	0.655±0.026
5	10	0.815	0.836	0.812	0.821±0.013
6	12	0.979	0.987	0.986	0.984±0.004

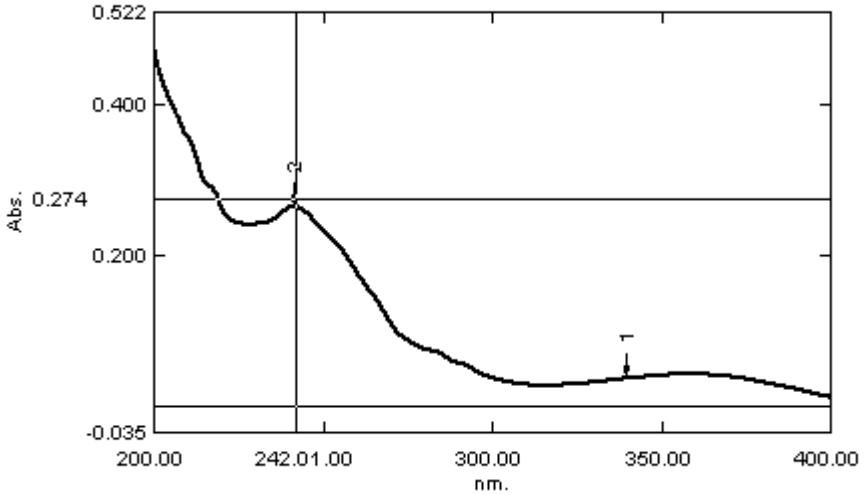


Fig. 3. (a) 2ppm spectra of Cilnidipine in1% SLS at 242 nm

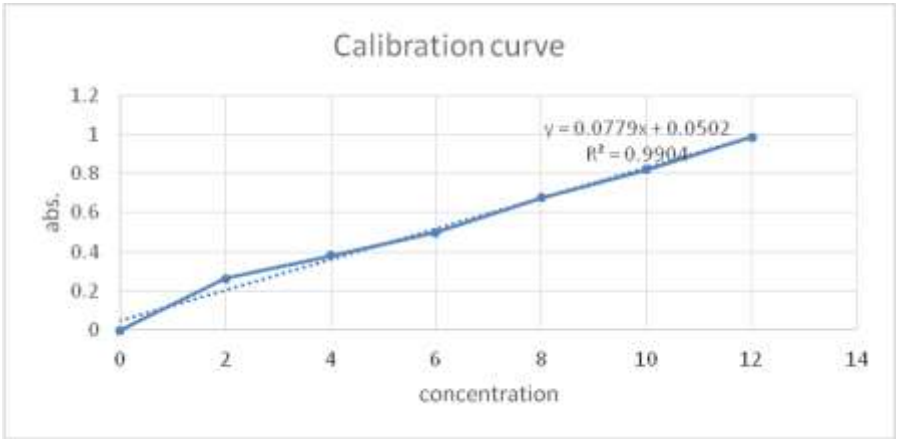


Fig. 3. (b) Calibration curve of Cilnidipine in 1% SLSat 242 nm

Identification of cilnidipine by FTIR

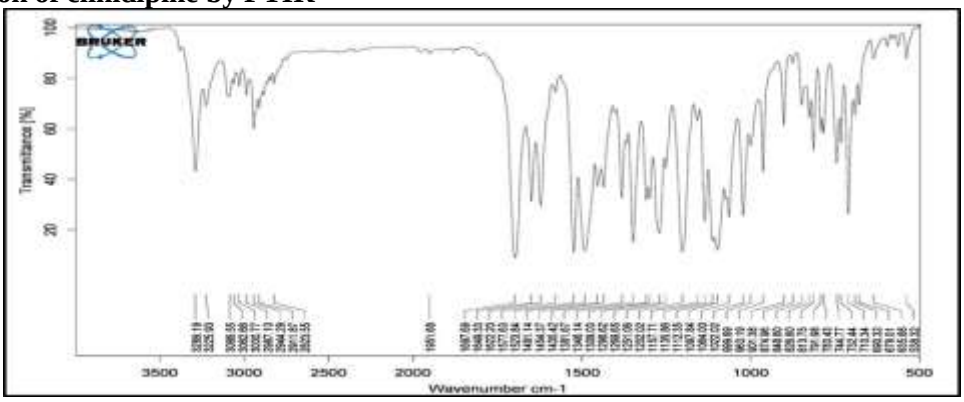


Fig. 4. Reference FTIR spectrum of cilnidipine

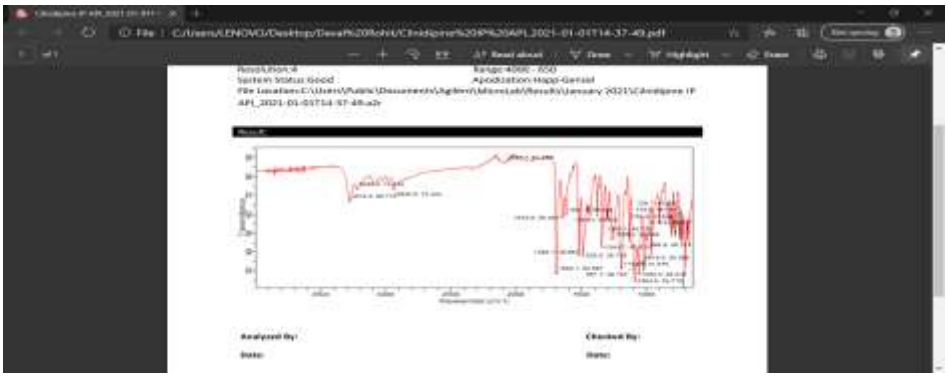


Fig. .5. Sample FTIR spectrum of cilnidipine

Table 6. IR scan of cilnidipine:

Functional group	Reference value (cm-1) of cilnidipine	Observed values (cm-1) of cilnidipine
-NO_2 stretching	1523.84	1520.8
-N-H stretch	3289.19	3278.2
-C-H stretch	2944.29	2940.9
>C=O stretching of ester	1697.69	1694.1
C-O stretching of ester	1097.84	1094.0

The fact that these findings align with reference standards indicates that the sample used in this study is, in fact, cilnidipine. It is reasonable to believe that the cilnidipine in the sample is of the greatest calibre due to the efforts made by this investigation to positively identify the medication.

Infrared spectroscopy studies of drug-excipient compatibility (FTIR):

The following FTIR spectrum displays chlorocilnidipine and a mixture of chlorocilnidipine, pullulan, PEG 4000, and -cyclodextrin. Here is a rundown of several possible spectrum interpretations.

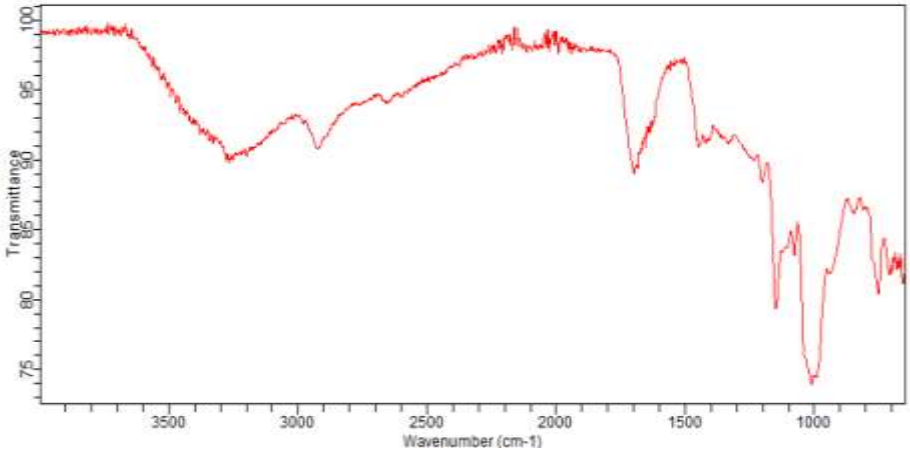


Fig. 6. FTIR spectra of pullulan

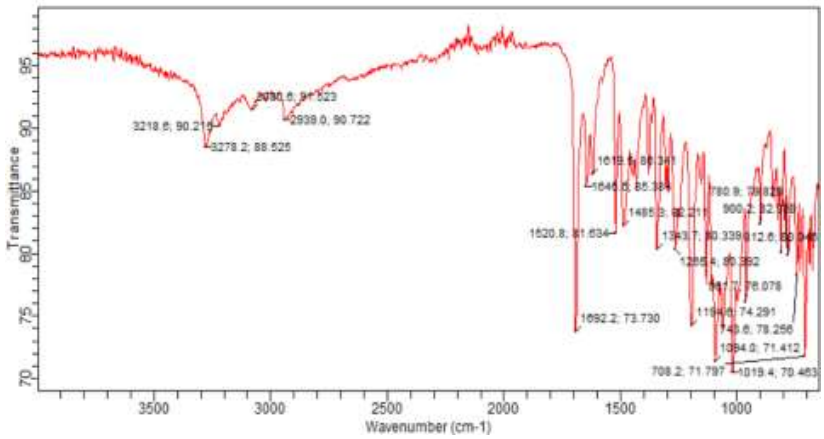


Fig. 7. FTIR spectra of cilnidipine + pullulan

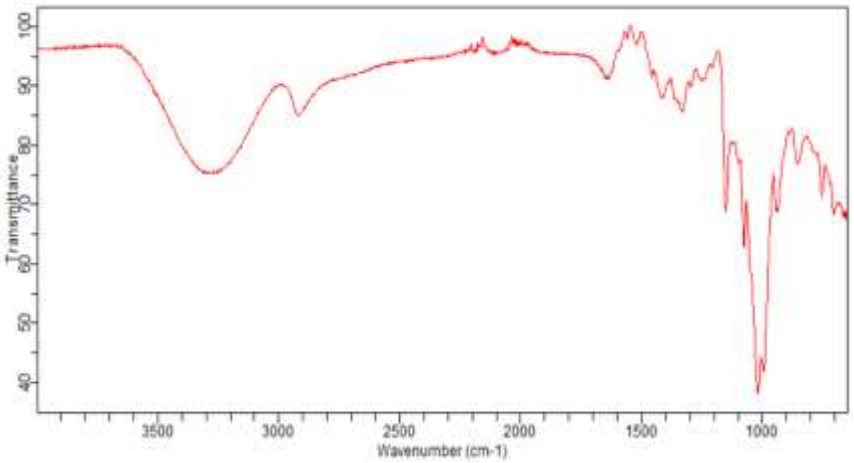


Fig..8. FTIR spectra of β-CD

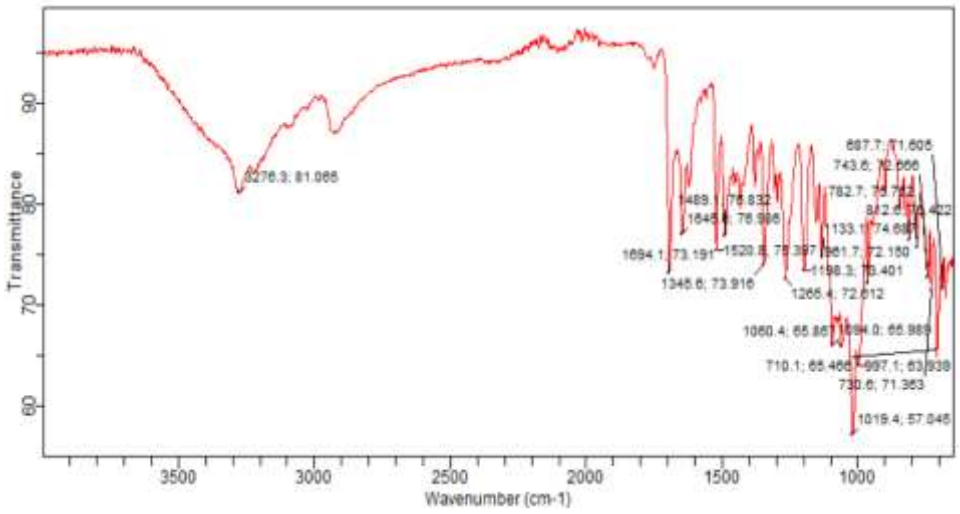


Fig..9. FTIR spectra of β-CD + cilnidipine

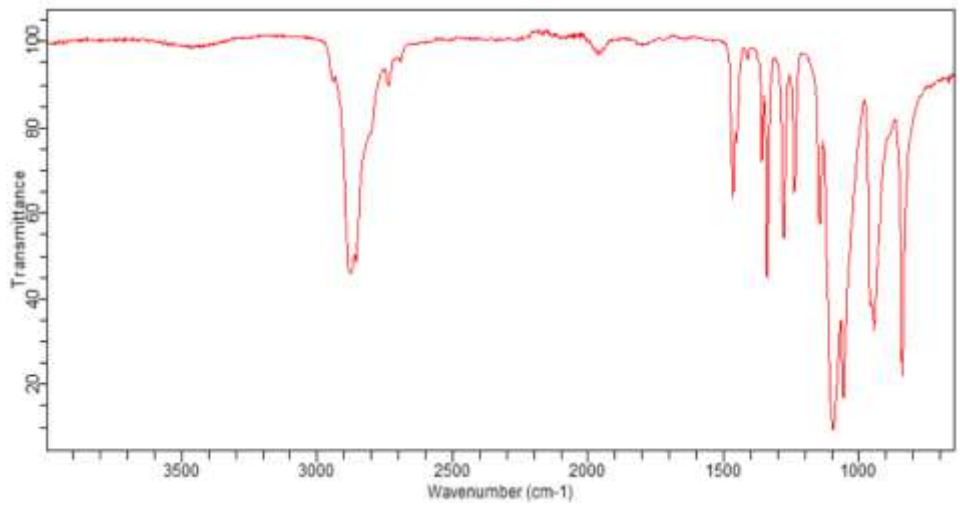


Fig. .10. FTIR spectra of PEG 4000

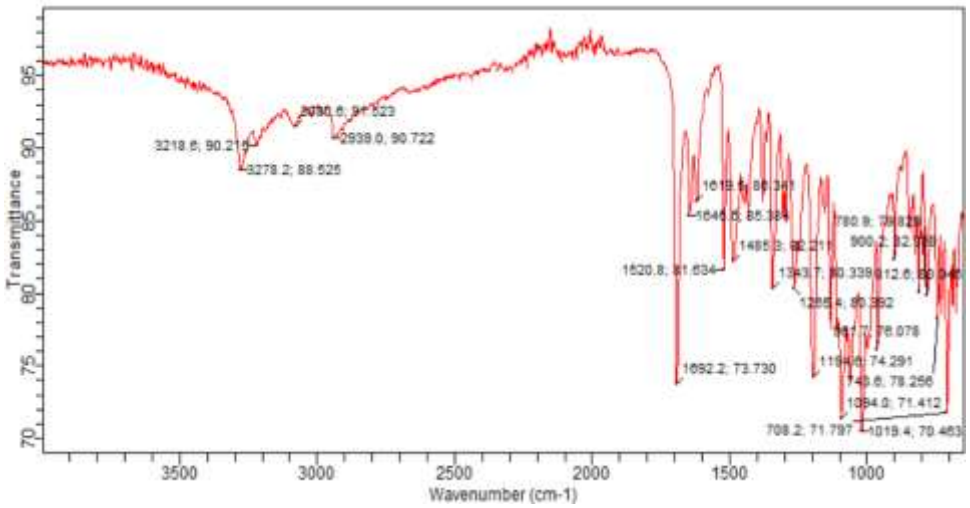
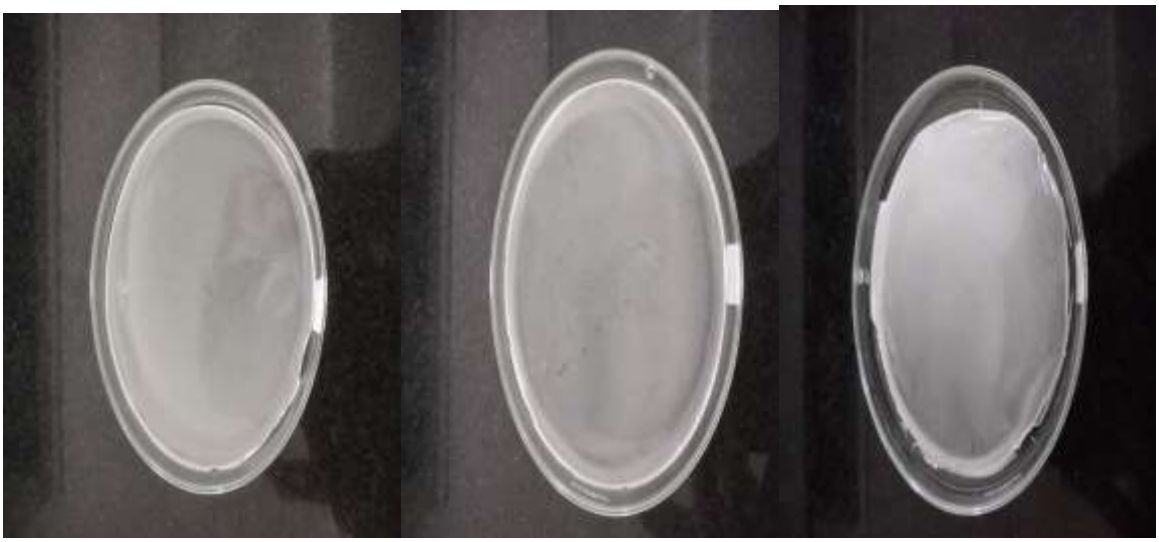


Fig. 11. FTIR spectra of cilnidipine + PEG 4000

Evaluation parameter of instant dissolving film of Factorial batches:

Physical appearance:



F-1 F-2 F-3

F-4 F-5 F-6

F-7 F-8 F-9

Table No. 7 Physical appearance of prepared film

Formulation	Smoothness	Transparency	Stickiness	Intact/Broken
F-1	Smooth	Semi Transparent	Non-sticky	Intact
F-2	Smooth	Semi Transparent	Non-sticky	Intact
F-3	Smooth	Semi Transparent	Non-sticky	Intact
F-4	Smooth	Semi Transparent	Non-sticky	Intact
F-5	Smooth	Semi Transparent	Non-sticky	Intact
F-6	Not smooth	Semi Transparent	Non-sticky	Intact
F-7	Smooth	Semi Transparent	Non-sticky	Intact
F-8	Not smooth	Semi Transparent	Non-sticky	Broken
F-9	Not smooth	Semi Transparent	Non-sticky	Broken

Table No.8 Mechanical properties of prepared film			
Formulation	Force at break (gm)	Tensile strength (MPa)	Surface pH
F-1	2674	8.745	7.0
F-2	1925	6.294	6.9
F-3	1727	4.983	6.9
F-4	2588	7.934	6.7
F-5	1870	5.732	6.8
F-6	1710	4.659	6.9
F-7	2575	7.894	7.1
F-8	1787	5.478	6.9
F-9	1628	4.435	6.8

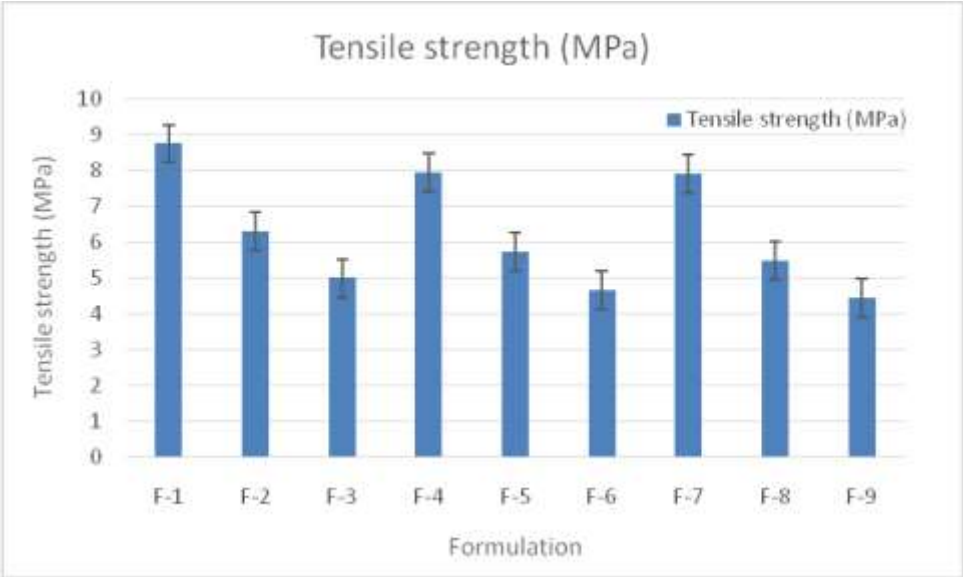


Figure No. 12 Comparison of Tensile Strength of film (F-1 to F-9)

3. Conclusion

Prior to preparing the fast-solving cilnidipine film that was used in this study, the drug's solubility was enhanced. ideal for the production of a cilnidipine film that dissolves quickly in water for the management of hypertension due to the drug's characteristics as a BCS class II medicine with low solubility and high permeability. The 5 mg dose of cilnidipine was administered in accordance with the drug combination's instructions, which state that it improves drug release or solubility by forming an

inclusion complex with -cyclodextrin. A factorial design was employed to examine the effects of PEG 400 and propylene glycol on the formulation. The optimisation method for instant film dissolving was completed using 32 different full factorial designs. Reducing the content of propylene glycol increased the percentage of drug release and increasing the tensile strength of the formulations, respectively. The stability tests showed that the revised formulation was just as stable as the original.

4. References

1. Catterall, W. A. (2000). Structure and regulation of voltage-gated Ca2+ channels. *Annual review of cell and developmental biology*, *16*(1), 521-555.
2. Perez-Reyes, E. (2003). Molecular physiology of low-voltage-activated t-type calcium channels. *Physiological reviews*, *83*(1), 117-161.
3. Moretti, A., Bellin, M., Welling, A., Jung, C. B., Lam, J. T., Bott-Flügel, L., ... & Laugwitz, K. L. (2010). Patient-specific induced pluripotent stem-cell models for long-QT syndrome. *New England Journal of Medicine*, *363*(15), 1397-1409.
4. Brini, M., Calì, T., Ottolini, D., & Carafoli, E. (2014). Neuronal calcium signaling: function and dysfunction. *Cellular and molecular life sciences*, *71*, 2787-2814.
5. 2018 Chinese Guidelines for prevention and treatment of hypertension: A report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. *J Geriatr Cardiol.* 2019;16:182–241.
6. A two-for-one bargain: using cilnidipine to treat hypertension and its comorbidities. Iyer RP, Lindsey ML, Chilton RJ. *J Clin Hypertens (Greenwich)* 2013;15:455–457.
7. Hypertensive and cardiovascular profiles of a newly synthesized dihydropyridine derivative 2-methoxyethyl (E)-3-phenyl-2-propen-1-yl(6)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl) pyridine-3,5-dicarboxylate (FRC-8653) Ikeda K, Hosino M, Iida H, Ohnishi H. *Pharmacometrics.* 1992;44:433–442.
8. Cilnidipine inhibits the sympathetic nerve activity and improves baroreflex sensitivity in patients with hypertension. Kishi T, Hirooka Y, Konno S, Sunagawa K. *Clin Exp Hypertens.* 2009;31:241–249.
9. Inhibitory effect of cilnidipine on pressor response to acute cold stress in spontaneously hypertensive rats. Hosono M, Hiruma T, Watanabe K, Hayashi Y, Ohnishi H, Takata Y, Kato H. *Jpn J Pharmacol.* 1995;69:119–125.
10. Changes in heart rate and plasma catecholamine levels accompanied with hypotesive action of calcium channel blockers in conscious SHR. Hiruma T, Hosono M, Watanabe K, Hayashi Y, Ohnishi H. *Jpn J Pharmacol.* 1995;67:267.
11. The effects of the L/N-type calcium channel blocker (cilnidipine) on sympathetic hyperactive morning hypertension: results from ACHIEVE-ONE. Kario K, Ando S, Kido H, et al. *J Clin Hypertens (Greenwich)* 2013;15:133–142.
12. Dual actions of cilnidipine in human internal thoracic artery: inhibition of calcium channels and enhancement of endothelial nitric oxide synthase. Fan L, Yang Q, Xiao XQ, et al. *J Thorac Cardiovasc Surg.* 2011;141:1063–1069.
13. Prolonged inhibition of vascular contraction and calcium influx by the novel 1,4-dihydropyridine calcium antagonist cinaldipine (FRC-8653) Yoshimoto R, Dohmoto H, Yamada K, Goto A. *Jpn J Pharmacol.* 1991;56:225–229.
14. In vitro and ex vivo Ca-antagonistic effect of 2-methoxyethyl(E)-3-phenyl-2-propen-1-yl(+/-)-1,4-dihydro-2,6-dimethyl- 4-(3- nitrophenyl)pyridine-3,5-dicarboxylate (FRC-8653), a new dihydropyridine derivative. Hosono M, Iida H, Ikeda K, et al. *J Pharmacobiodyn.* 1992;15:547–553.
15. Comparison of amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal edema in mild to moderate hypertensive individuals: A prospective study. Adake P, Somashekar

HS, Mohammed Rafeeq PK, Umar D, Basheer B, Baroudi K. *J Adv Pharm Technol Res.* 2015;6:81–85.
16. Renoprotective and antioxidant effects of cilnidipine in hypertensive patients. Soeki T, Kitani M, Kusunose K, et al. *Hypertens Res.* 2012;35:1058–1062.
17. Evaluation of renoprotective effect of cilnidipine in patients with mild to moderate hypertension and type 2 diabetes mellitus - a prospective study. Ramya R, Shahan OM, Anakha K. https://doi.org/10.22159/ajpcr.2021.v14i1.39962 *Asian J Pharm Clin Res.* 2021;14:144–146.
18. Blood pressure control with cilnidipine treatment in Japanese post-stroke hypertensive patients: the CA-ATTEND study. Aoki S, Hosomi N, Nezu T, et al. *Clin Exp Hypertens.* 2017;39:225–234.
19. The efficacy and safety of cilnidipine on mild to moderate essential hypertension: a systematic review and meta-analysis of randomized controlled trials in Chinese patients. Xu G, Wu H, Du B, Qin L. *Cardiovasc Hematol Disord Drug Targets.* 2012;12:56–62.
20. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. *Lancet.* 1999;354:1896–1900.
21. Comparison between cilnidipine and nisoldipine with respect to effects on blood pressure and heart rate in hypertensive patients. Minami J, Ishimitsu T, Higashi T, Numabe A, Matsuoka H. *Hypertens Res.* 1998;21:215–219.