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Cilnidipine Nanoparticles Oral Film: Preparation and Evaluation

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ABSTRACT: Cilnidipine is a dihydropyridine class of calcium channel blockers, it is classified as a BCS class II drug, characterized by a low oral bioavailability of 13%. Consequently, the utilization of nanoparticle preparation is anticipated to enhance its bioavailability. The objective of the research is integrating cilnidipine nanoparticles into oral films as a means of enhancing patient adherence. The optimal polymers for the production of Cilnidipine films were PVA cold and or HPMC E5 at different concentration using casting technique with glycerol as plasticizer. The Nano suspension-based preparation of Cilnidipine's oral film containing the combination of polymers exhibited a significant enhancement in vitro dissolution, with a percentage exceeding 92.8% after 5 minutes, in contrast to the oral film that solely contained the drug. The findings of this investigation suggest that the incorporation of Cilnidipine nanoparticles into oral film result in improvement of drug dissolution.

KEYWORDS: Cilnidipine; HPMC E5; Nanoparticles; PVA cold.

1. INTRODUCTION

Cilnidipine is 1,4-dihydrocilnidipine (CLD) 2,6-dimethyl-4-(3-nitrophenyl) 3,5-Pyrrolidinocarboxylic Acid 2-Methoxyethyl (2-E) The novel dihydropyridine calcium channel blocker, 3-phenyl-propenyl ester [1]. The N-type voltage-dependent calcium channel controls sympathetic neurotransmission and norepinephrine release. In essential hypertension, once-daily cilnidipine reduced BP safely and more effectively than nifedipine without causing reflex tachycardia [2]. It is a yellow, odorless, crystalline powder with poor dissolving properties and low oral bioavailability at an effective dose of 10 mg p.o. It is freely soluble in acetonitrile, sparingly soluble in methanol and in ethanol (99.5), and practically insoluble in water [3].
Combined oxidation state (pKa = 11.39, logP = 5.54), BCS class II [(74)], melting point of approximately 110 degrees Celsius, oral bioavailability of approximately 6-30% Mass per mole = 492.52 grams [4].
The challenge of formulating drugs with poor water solubility has been a persistent issue in the pharmaceutical industry, posing a fundamental problem in the optimization of dosage forms Solubility characteristics determine dissolving rate, absorption, and bioavailability [5].

2. RESULTS and DISCUSSION

2.1. Evaluation of CLD Oral Film

2.1.1. Physical appearance of the film

All formulations for polymers containing HPMC E5 ($F_{NP}5$, $F_{NP}6$, $F_{NP}7$, $F_{NP}8$) had granules on the surface that were not transparent, brittle, or sticky in appearance. However, the formulas containing PVA cold and a combination of HPMC E5+PVAc ($F_{NP}1$, $F_{NP}2$, $F_{N4}3$, $F_{NP}4$, and $F_{NP}9$) were clear, homogeneous, and translucent in color. As illustrated in Figure 1.

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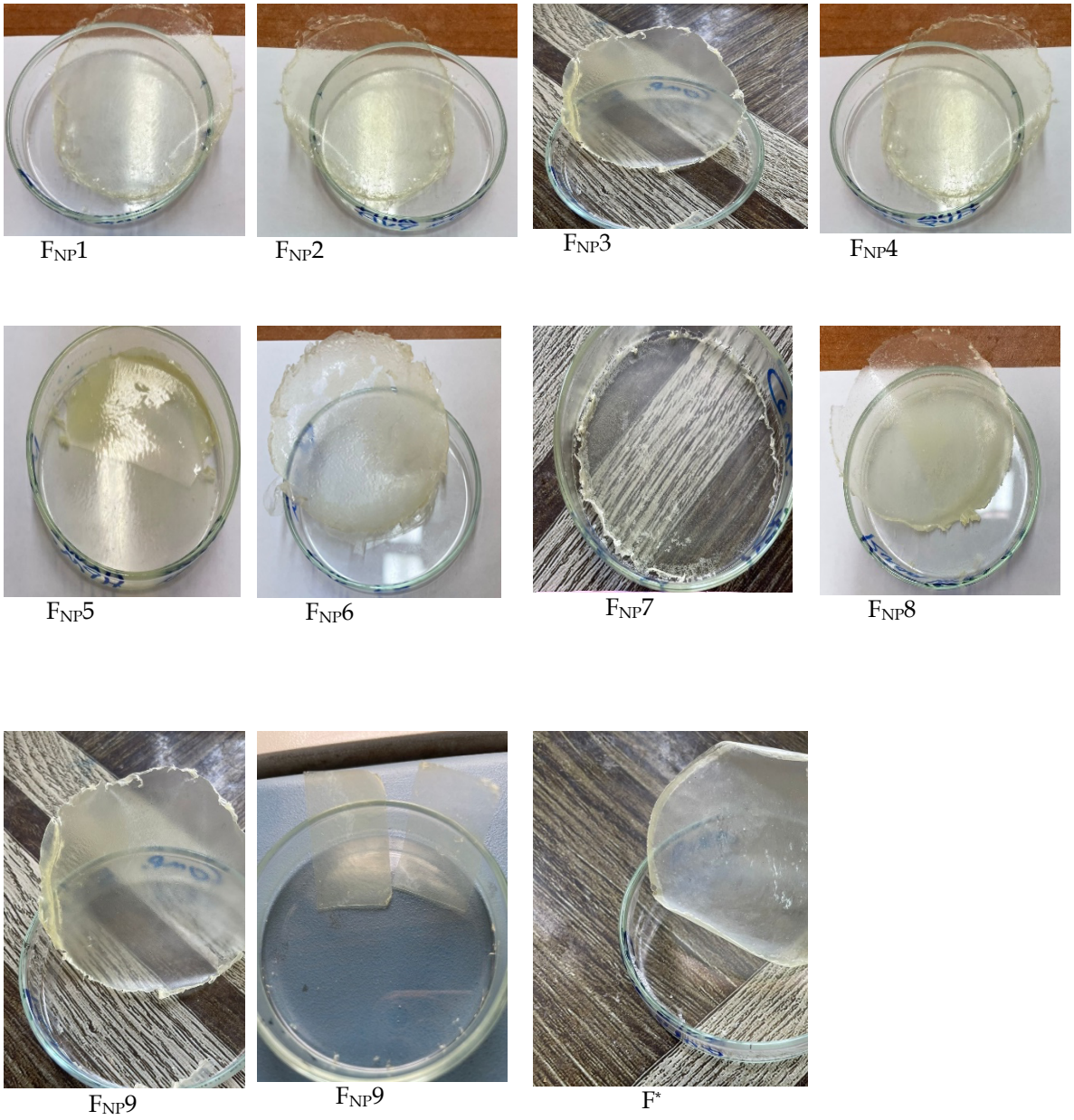

Figure 1. Physical appearance of CLD film

2.1.2. Weight uniformity Thickness of the film

As indicated in Table 1, the film weight and thickness were uniform, indicating proper and reproducible preparation method. The small standard deviation suggested homogeneous excipient dispersion in each formula [6].

2.1.3. Drug content of the film

As seen in Table 1, the drug content was in the acceptable within the range as mentioned in the indicating good processing [7].

2.1.4. Surface pH measurement of the CLD film

The pH of the film as presented in Table 1, it is noteworthy that all these pH ranges are consistent with that of oral mucosa. Furthermore, the films do not cause any irritation in the mouth, thereby rendering them suitable for use [8].

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2.1.5. Folding endurance of the film

All films have a higher folding number than 300 [9]. Indicating the suitability and strength of the polymers used as can be seen in Table 1.

2.1.6. Disintegration time of the film

Disintegration time in a second for all film due to the presence of cross povidone This disintegration enhancement is caused by the ability of cross povidone to wick saliva quickly into the film that leads to generating the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth, the major mechanism of disintegration for cross povidone is wicking mechanism in addition to the swelling mechanism [10] as seen in Table 1.

Table 1. Some physicochemical properties of the prepared oral films of CLD

F code	Weight of film (mg)	Thickness (mm)	pH	Folding endurance	Drug content %	In vitro Disintegration On time (Sec)
$F_{NP}1$	53 ± 2.543	0.023333±0.005774	6.6± 0.05	>300	95.33 ± 2.5	29 ± 1.0
$F_{NP}2$	51.355 ± 2.187	0.033333±0.011547	6.6 ± 0.2	>300	94 ± 3.51	17±1.0
$F_{NP}3$	51.6±0.76	0.046667±0.015275	6.6 ±0.11	>300	92 ±1.600292	15 ± 1.0
$F_{NP}4$	53.1± 0.55	0.303333±0.430387	6.6 ±0.11	>300	94±0.425245	21.6 ± 2.0
$F_{NP}9$	57.288 ± 1.589	0.053333±0.005774	6.7 ±0.1	>300	99.3 ± 0.06	12 ± 1.0

2.1.6.1. In vitro dissolution study of oral film

Figure 2 illustrates that the films containing PVA polymer ($F_{NP}1$, $F_{NP}2$, $F_{NP}3$, $F_{NP}4$) were found to release (72, 61, 67, 68) %, respectively, after 2 minutes, while a film containing both polymers ($F_{NP}9$) released 84% and reached 92.8% after 5 minutes; thus, $F_{NP}9$ was chosen as the best formula.

Due to its low solubility in phosphate buffer (pH 6.8), pure CLD oral film F* has a release percentage of 30.9% as seen in Figure 3.

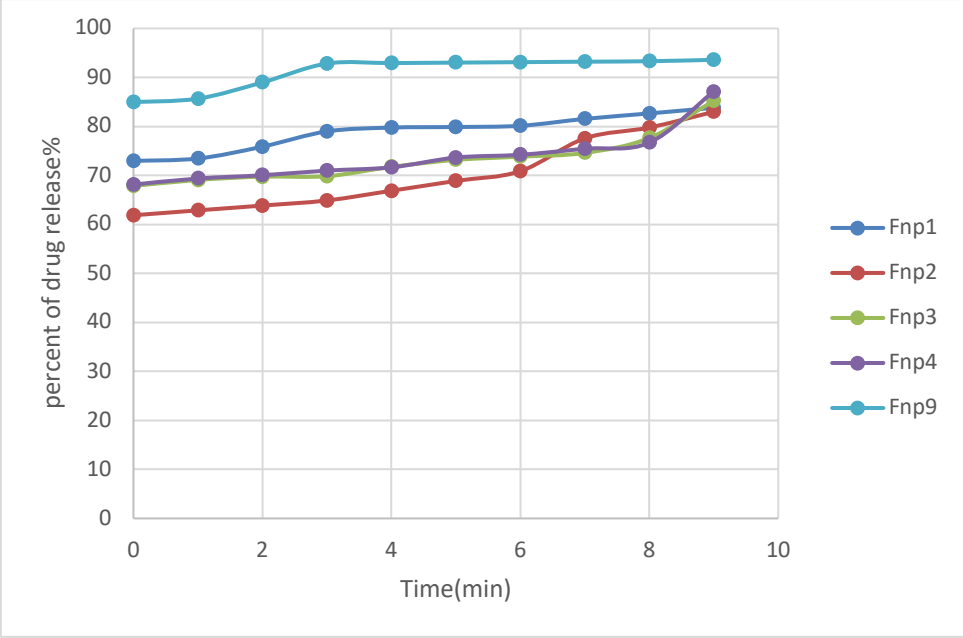

Figure 2. In vitro dissolution of ($F_{NP}1$, $F_{NP}2$, $F_{NP}3$, $F_{NP}4$, and $F_{NP}9$) film in phosphate buffer pH 6.8with 0.5% SLS

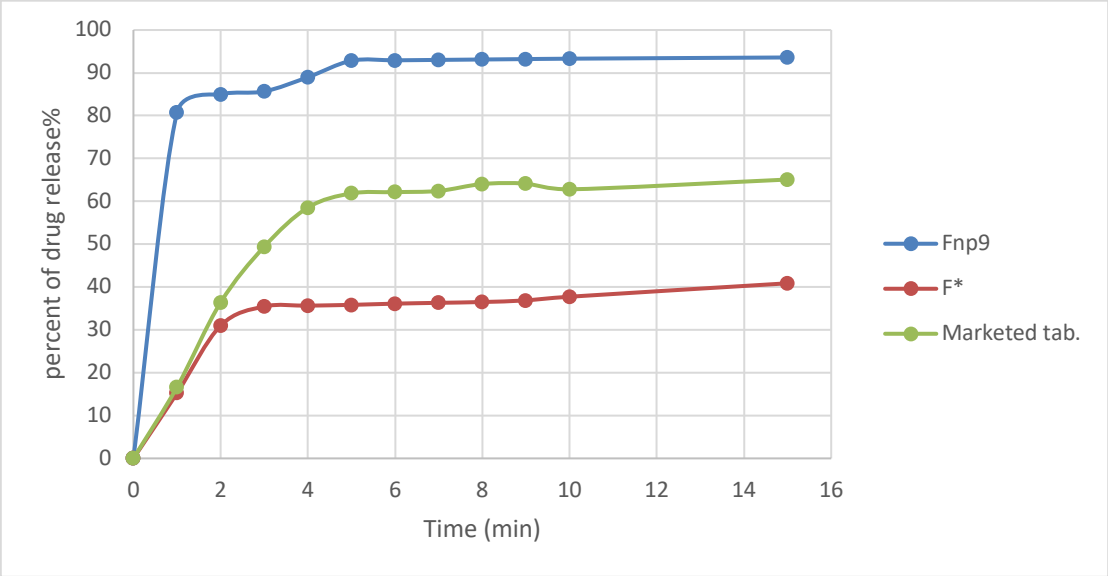

Figure 3. In vitro dissolution of CLD oral film(F*), Markted tab and $F_{NP}9$ oral film in phosphate buffer pH 6.8with 0.5% SLS.

3. CONCLUSION

PVA and HPMC E5 produced the best CLD nanoparticle films due to their excellent in vitro release and disintegration.

4. MATERIALS AND METHODS

4.1. Materials

Cilnidipine (CLD) was supplied by Hyperchem. China. Sodium lauryl sulfate (SLS), Glycerol (GL) were purchased from BDH Chemical Ltd, UK. Soloplus ® (SL)Basf SE, Germany. Methanol and Ethanol were purchased from Sigma-Aldrich, Germany.

4.2. Methods

4.2.1. Preparation of cilnidipine nanoparticles loaded fast dissolving film

Cilnidipine nanoparticles were prepared previously employing a bottom-up technique solvent (20mg CLD ethanol) anti-solvent (20 mg Soluplus + 4.76 l (30%) glycerol in DW) method [12].

Solvent-casting was used in preparing oral films of CLD NPs and pure cilnidipine as seen in table 2. The hydrophilic film forming polymer (PVA or HPMC E5 or their combination 50% or 45%) were dispersed in 5 mL DW at 70-80 °C on a magnetic stirrer, CLD NP dispersion was added to the polymer dispersion and stirred continuously for one hour for complete dispersion of the polymer, 30% or 25% wt. glycerol (plasticizer) was added together with mannitol (a cooling agent), vanilla extract (flavouring agent), and cross-polyvidone (a super disintegrant), this dispersion was covered and left overnight in a cool place to expel any air bubbles. The final homogeneous dispersion was cast on a 6 cm^2 Petri dish plate and dried in a 40°C oven for 24 hours. After drying, the films were cut to 2 * 3 cm^2, covered in aluminium foil, and stored in a cool area. Table 2 shows that CLD films F* were made by dissolving CLD in 3 mL of ethanol and dispersed in PVAc and HPMC polymer combination.

Table 2. Composition of oral film of Cilnidipine nanoparticles

Formula Code	CLD	PVA Cold (mg)	HPMC E5 (mg)	Cross Povidone (mg)	Glycerol mL	Mannitol (mg)	Vanilla (mg)
$F_{NP}1$	5	27(45%)		6	8.1 (30%)	3.6	3.6
$F_{NP4}2$	5	27(45%)		6	6.75 (25%)	3.6	3.6

$F_{NP4}3$	5	30(50%)		6	9(30%)	3.6	3.6
$F_{NP}4$	5	30(50%)		6	7.5(25%)	3.6	3.6
$F_{NP}5$	5		27(45%)	6	8.1(30%)	3.6	3.6
$F_{NP}6$	5		27(45%)	6	6.75(25%)	3.6	3.6
$F_{NP}7$	5		30(50%)	6	9(30%)	3.6	3.6
$F_{NP}8$	5		30(50%)	6	7.5(25%)	3.6	3.6
$F_{NP}9$	5	15(25%)	15(25%)	6	9(30%)	3.6	3.6
F*	5	15(25%)	15(25%)	6	9(30%)	3.6	3.6

F*: the oral film contains pure CLD

4.2.2. Evaluation of oral film of Cilnidipine

4.2.2.1. Visual appearance

CLD Films were assessed visually [11]. The films that were homogeneous and acceptable were further evaluated.

4.2.2.2. Weight and Thickness of film

Dosage uniformity requires weight homogeneity. On an electronic scale, the mass of 10 films chosen randomly from each patch were weighed. The weight of the film should be close to the mean [12]. The electronic vernier caliper (Shanghai, China) measured film thickness at different places (center and mid-center and near the edges). The average ± SD of three replicate was calculated [13].

4.2.2.3. Drug content

Each film was dissolved in 10 mL of methanol and then filtered through a 0.45mm membrane filter to establish chemical consistency. The average CLD concentration at 240 nm [14] was measured using UV spectroscopy (Shimadzu Japan) after the filtrate was diluted.

4.2.2.4. Surface pH measurement

The pH was measured using the pH meter (Hanna instrument, Romania) by touching the probe for 1 min., to a film dissolved in 2mL DW for 30 seconds. Average of 3 readings were determined [15].

4.2.2.5. Folding Endurance measurement

Film folding endurance indicates flexibility and durability. Folding manually the film till it breaks. The film's folding endurance number is folds before breaking [16].

4.2.2.6. In-vitro Disintegration time (DT)

The film was placed in a small petri dish with 10 mL of phosphate buffer 6.8 and shaken gently until it completely decomposed. Time recorded (from start to film destruction). The mean of three tests was taken. Despite no formal reference, fast oral film disintegrates in 5-30 seconds [17].

4.2.2.7. In vitro dissolution study

CLD film and CLD NP film release were studied using type II dissolution apparatus. The selected films were dissolved in 900 mL phosphate buffer containing 0.5 % SLS (to maintain sink condition) at 37° C and 50 rpm. Five milliliters were taken at (1,2,3,4,5,6,7,8,10, and 15 min) and filtered by 0.45 mm filter syringe and replaced with the same media. The absorbance was measured at the 241 nm using UV spectrophotometer (Shimadzu Japan). Reading was tripled. Cilnidipine's cumulative % drug release was plotted versus time [18].

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