Acta Pharm. Sci. Vol 63:(1), 2025
Original article
DOI: 10.23893/1307-2080.APS6303

Formulation and characterization of lercanidipine HCl nanoparticles as fast-dissolving sublingual film

Zahraa A. ALSAFAR, Fatima J. JAWAD*

Baghdad University, College of Pharmacy, Department of Pharmaceutics, Baghdad, Iraq

ABSTRACT

Calcium channel blocker lercanidipine HCl treats hypertension and angina pectoris. It is a biopharmaceutical classification system (BCS) class II drug due to its poor water solubility. First-pass metabolism and low solubility reduce lercanidipine HCl oral bioavailability to 10%. This research aims to improve the dissolution rate of lercanidipine HCl by developing a nanosuspension and then transforming it into a sublingual fast-dissolving film with rapid disintegration, simple administration, and stability that will enhance patient adherence. The solvent-antisolvent precipitation technique produced lercanidipine HCl nanosuspension. Sublingual fast-dissolving films contain lercanidipine HCl nanoparticles produced by solvent casting. The dissolution rate increased significantly in nanosuspension. Film formulations using 50% polyvinyl alcohol and 30% glycerin produced excellent results. Formula F4 is optimal due to its 25-second disintegration and 99.8% in vitro drug release in 4 minutes. The study observed that lercanidipine HCl sublingual film offered an effective drug delivery system with improved disintegration and patient compliance.

Keywords: lercanidipine HCl, nanoparticles, PVA, solvent casting, sublingual film

*Corresponding author: Fatima J. JAWAD
E-mail: drfatimajalal@copharm.uobaghdad.edu.iq
ORCIDs:
Zahraa A. ALSAFAR: 0009-0004-7839-916X
Fatima J. JAWAD: 0000-0002-4906-6241
(Received 07 Mar 2024, Accepted 24 Apr 2024)

INTRODUCTION

Lercanidipine HCl (LER) is a dihydropyridine calcium channel blocker used to treat hypertension and alleviate angina pectoris. The antihypertensive effect of LER is due to its direct relaxation of vascular smooth muscle, leading to a decrease in total peripheral resistance and consequently lowering blood pressure[1]. Lercanidipine HCl is categorized as a biopharmaceutical classification system (BCS) class II drug because of its poor water solubility. The drug is very lipophilic with a Log P value of 6.4 at 20-25°C. The oral bioavailability of LER is about 10%, and its absorption from the gastrointestinal tract is erratic, mainly caused by extensive first-pass metabolism and poor solubility[2]. Nanotechnology currently provides many techniques for improving the dissolution of poorly water-soluble drugs. Nanoparticles are attracting significant interest from formulation researchers due to developments in formulation technology. Pharmaceutical nanoparticles are submicron-sized solid drug carriers that may or may not be biodegradable[3]. Nanoparticles are produced using a top-down technique without a need for a solvent. In contrast, the bottom-up technique requires an organic solvent mixed with immiscible water, causing the drug to precipitate because of its poor water solubility. The different types of nanoparticles comprise nanosuspensions, polymeric nanoparticles, lipid nanoparticles, and others[4]. Nanosuspensions are colloidal particle systems that are nanosized. Nanosuspensions enhance the solubility and dissolution of low-water-soluble drugs by their small particle sizes and large surface areas. Furthermore, they may modify the drug's pharmacokinetics to improve its effectiveness and safety. These advantages could increase the bioavailability of low-soluble drugs[5].

Ensuring solution stability via transformation to a solid state without aggregation is essential for successfully manufacturing and scaling up nanosuspensions. Formulating nanosuspensions into the polymer matrix of oral films stabilizes them by avoiding aggregation and allows for resuspension when dissolved[6]. Fast-dissolving films have been increasingly utilized in pharmaceutical manufacturing. Fast-dissolving dosage types have resolved difficulties with medication delivery to pediatric and older adults. This convenience offers marketing benefits and increases compliance among patients[7]. Films are usually made using either the solvent-casting technique or the hot melt extrusion technique. The solvent-casting process involves dissolving or dispersing the polymer and drug in an aqueous solvent and then casting a film by solvent evaporation. During extrusion, the drug and excipients are combined in a dry condition, heated, and then extruded in a molten state[8]. Sublingual films accel-

erate the onset of drug action by enhancing drug bioavailability through direct absorption into the circulatory system from the sublingual area, bypassing the gastrointestinal tract and hepatic first-pass metabolism. Sublingual films have advantages as they disintegrate fast when placed into contact with the tongue, without the need for liquid intake. They also provide correct dosing, painless administration, easy handling, and simple storage[9]. The project aims to develop lercanidipine HCl nanosuspension and convert it into sublingual film formulations to enhance stability and improve patient compliance.

METHODOLOGY

Materials

Lercanidipine HCl (LER) was obtained from Hyper Chem Company in China, Soluplus (SLU) was acquired from Kathy in China, methanol was purchased from Panreac Applichem in Spain, Polyvinyl alcohol cold (PVAc) from BASF in Germany, Hydroxypropyl methylcellulose E5 (HPMC E5) supplied by Baoji in china, Glycerin (GL) was obtained from BDH Chemical Ltd, Vanilla and Cross povidone from Chemical point in Germany, Mannitol supplied by Hopkin & Willims LTD in England and Sodium Lauryl Sulfate (SLS) was supplied by Alpha Chemika in India.

Methods

Preparation of lercanidipine HCl nanosuspension

Lercanidipine HCl nanosuspensions were produced using the solvent/anti-solvent precipitation process. 10 mg of LER powder was dissolved in 3 mL of methanol at room temperature and then added to 10 mL of deionized water containing soluplus as a stabilizer. The resultant solution was maintained at 37°C. A plastic syringe with a needle was put directly into an aqueous solution containing a stabilizer and drops of the drug's organic solution (organic phase) were at a 1 mL/min rate. The drug-to-stabilizer ratios used in generating the nanosuspension were 1:2. The mixture was agitated on a magnetic stirrer at 1500 rpm for 60 minutes to facilitate the evaporation of the volatile solvent[10,11].

Lercanidipine HCl nanosuspension fabrication as fast-dissolving sublingual films

Previously, lercanidipine HCl nanoparticles were synthesized via a solvent/anti-solvent method. Sublingual films of LER nanoparticles and pure LER were prepared via solvent-casting, as shown in Table 1. The hydrophilic film-forming polymer (PVAc, HPMC E5, or a combination of both) was dispersed in 10 mL of deionized water at 60°C using a magnetic stirrer for one hour estab-

lished at 1000 rpm until the polymer had completely dissolved. After cooling, a plasticizer (glycerin) was added to the mixture. Mannitol (a cooling and sweetening agent), vanilla (a flavoring agent), and cross povidone (an effective super disintegrant) were dissolved in 2 mL of deionized water. The solution obtained was then mixed with the polymeric solution while stirring continuously for 1 hour, creating a transparent solution. LER nanosuspension formulations were produced using a total volume of 10 mL. The formulations were added to the polymer solution and stirred for 2 hours to distribute the drug particles equally inside the polymer matrix, resulting in a more uniform and consistent formulation. The resulting dispersion was covered and left in a cool place for at least 24 hours in order to allow any air bubbles to escape. After being cast onto a Petri dish with a diameter of 6 cm, the final homogenous dispersion was dried for 24 hours at 40°C in an oven. Following drying, the films were divided into 2*3 cm^2 fragments, coated in aluminum foil, and kept in a cold place. A Petri dish with 28 cm^2 in surface area can accommodate four films. Each film has a surface area of 6 cm^2 and contains LER nanoparticles equal to 10 mg LER. Table 1 demonstrates how LER films F9 were created by adding LER to a polymer solution after it had already been dissolved in 3 mL of methanol[12].

Table 1. Sublingual film composition of lercanidipine HCl nanoparticles

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
LER (mg)	10	10	10	10	10	10	10	10	10
Soluplus (mg)	20	20	20	20	20	20	20	20	_
PVAc (mg)	60 (50%)	–	30 (25%)	60 (50%)	54 (45%)	–	27 (22.5%)	54 (45%)	60 (50%)
HPMC E5 (mg)	–	60 (50%)	30 (25%)	–	–	54 (45%)	27 (22.5%)	–	–
Glycerin (mg)	15 (25%)	15 (25%)	15 (25%)	18 (30%)	13.5 (25%)	13.5 (25%)	13.5 (25%)	16.2 (30%)	18 (30%)
Mannitol (mg)	6	6	6	6	6	6	6	6	6
Cross povidone (mg)	6	6	6	6	6	6	6	6	6
Vanilla (mg)	2	2	2	2	2	2	2	2	2

Evaluation of lercanidipine HCl nanosuspension

Measurements of the particle size and polydispersity index

The Malvern Zetasizer Nano Laser, manufactured by Ultra Rate Company in the USA, was used to analyze the size and distribution of lercanidipine HCl nanosuspension by dynamic light scattering (DLS) at room temperature. Both the polydispersity index (PDI) and particle size (PS) are determined[13].

Assessment of drug content

Methanol and a specific quantity of nanosuspension (1 mL) were mixed in a 10 mL volumetric flask. The sample was sonicated for one hour and filtered using a 0.45 µm filter syringe. The samples were analyzed using a UV-visible spectrophotometer with a wavelength of 236 nm, where the drug in methanol showed its peak absorption[14]. The drug content was calculated using the following equation:

Drug content = (Practical conc./Theoretical conc.) x 100% (Equation 1)

Measurement of entrapment efficiency

A 4mL sample of lercanidipine HCl nanosuspension was placed in an Amicon ultra-4 centrifugal filter with a molecular weight cut-off of 10 KD. The sample was centrifuged for 30 minutes at 4000 rpm to evaluate the entrapment efficiency (%EE) and quantify the amount of drug contained in the nanoparticles. The amount of unbound LER was determined using UV spectrophotometry at the maximum absorption wavelength of 236 nm[15]. The entrapment efficiency was determined using the following equation:

%EE = Actual amount of drug - Amount of free drug / Actual amount of drug x 100% (Equation 2)

Determination of *in-vitro* dissolution profile

The dissolution test for lercanidipine HCl nanosuspension formulation was conducted using USP apparatus type II (paddle type). A dialysis membrane with a molecular weight cutoff of 8000–14000 was loaded with a nanosuspension volume containing 10 mg of LER. The dialysis membrane was attached to the paddle and immersed in a 200 mL solution of pH 6.8 phosphate buffer containing 1% SLS. The paddle rotated at 50 revolutions per minute while the temperature was kept constant at 37 ± 0.5°C. At specific time points (5, 10, 15, 20, 25, 30, and 45 minutes), a 5 mL sample was taken out and substituted with a new dissolution media to maintain the sink condition. The amount of LER was determined using spectrophotometry at the specified wavelength of 239 nm for this medium[16].

Evaluation of lercanidipine HCl fast dissolving sublingual film

Visual appearance

Evaluate the formulated films for their visual characteristics. Films should be visually inspected for their appearance[17].

Disintegration time of the film

10 mL of phosphate buffer with a pH of 6.8 was added to a Petri dish. A film was placed on the surface of the buffer, and the time it took for the film to break down completely was measured. Estimations were conducted for three films, and the range was calculated[18]. The disintegration time varies according to the formulation, but it usually takes five to thirty seconds[19].

Film thickness

An electronic Vernier caliper is utilized to measure each film's thickness at five locations, including the center and four corners. The average standard deviation of five replicate measurements determines the outcomes[20].

Variations in film weight

Weight variation is examined by using ten randomly chosen films separately on an electronic scale and measuring the average weights. The weight of the acceptable film should not deviate substantially from the weighted average[21].

Measurement of folding endurance

Folding endurance demonstrates the film's flexibility. The measurement was taken manually by pressing the two sides of the film between the thumb and index finger. The film was frequently folded in the center until it broke. The number of times the film was folded before breaking was recorded as the folding endurance. The average of the triplicate observations is provided[22].

Drug content

The films were dissolved in 100 mL of phosphate buffer solution with a pH of 6.8, and 1% SLS was added. The mixture was stirred for 30 minutes using a magnetic stirrer. Samples are taken from the solution and filtered using a syringe filter with a pore size of 0.45 μm. The samples were analyzed for absorbance at a wavelength of 239 nm using a UV spectrophotometer. The amount was calculated using an equation developed from the calibration curve of LER in a buffer solution with a pH of 6.8, containing 1% SLS[23].

Surface pH study

The pH of a film is measured by placing it in a petri dish, dissolving the film with 2mL of distilled water, and then determining the pH by contacting the film surface with a pH meter electrode. It is essential to determine surface pH because acidic or basic pH might lead to oral mucous irritation[24].

In vitro dissolution study of the films

The drug was released from the films using USP dissolution apparatus type II. The dissolution media comprised 200 mL of phosphate buffer pH 6.8 solution with 1% SLS, maintained at a set temperature of 37 ± 0.5°C and stirred at a rate of 50 rpm. 5 mL samples were taken at particular times (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 15 minutes) and substituted with the same amount of new dissolution media. The obtained sample was filtered with a 0.45 µm syringe filter. The samples were analyzed using spectrophotometry at a wavelength of 239 nm[25].

Compatibility test by FTIR

Fourier Transform Infrared (FTIR) analysis was used to evaluate the compatibility between lercanidipine HCl nanoparticles and the excipients in the film formulation. A comparison examination was performed between the spectra of LER nanoparticles and the selected film formulation to confirm the absence of interactions and the existence of the drug's distinctive peaks. FTIR spectroscopy ranges from 4000 to 400 cm^{-1} [26].

Statistical analysis

Statistically significant findings were determined for probability values below 0.05, while statistically insignificant findings were classified for values equal to or over 0.05 all measurements and values repeated three times and reported the results as the mean ± standard deviation (SD)[27,28].

RESULTS and DISCUSSION

Evaluation of lercanidipine HCl nanosuspension

The Zeta Sizer was used to analyze a sample of lercanidipine HCl nanosuspension. The investigation obtained a particle size value of 92.94 nm and a polydispersity index (PDI) that was 0.2515. The drug content percentage of the LER nanosuspension formula was determined to be 99.2% ± 0.2516. The results met the criteria stated in the British Pharmacopoeia (BP) and were within the acceptable range of 95% to 110%[29]. The entrapment efficiency of LER was estimated to be 97.76% ± 1.0598. The drug's high encapsulation efficiency is due to its poor solubility in the exterior phase and high solubility in the organic

solvent. As a result, less drug gets transferred into the outer aqueous phase[30]. The lercanidipine HCl nanosuspension demonstrated 100% release after 20 minutes, but the pure lercanidipine HCl powder released just 33.6% after the same time interval, as seen in Figure 1. The similarity factor value estimated is 12.37, which is less than 50. The LER nanosuspension and the pure LER powder show significant variations in dissolution characteristics[31].

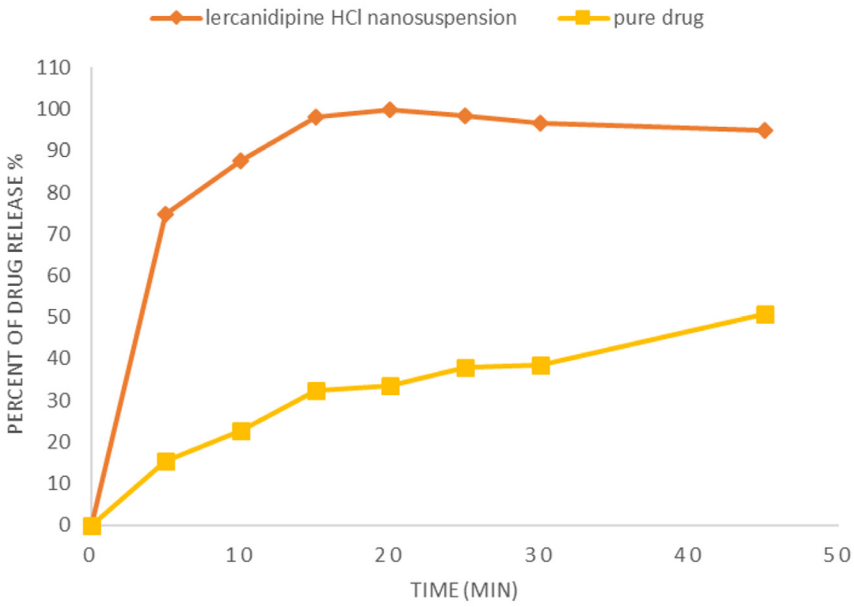

Figure 1. The dissolution patterns of the pure lercanidipine HCl and lercanidipine HCl nanosuspension in 6.8 buffer containing 1% SLS.

Evaluation of lercanidipine HCl fast dissolving sublingual film

Visual appearance

The polymer formulations, including HPMC E5 (F2, F6), exhibited high adhesion, making them difficult to remove from the Petri dish. Formulas F3 and F7, which included a combination of HPMC E5 and PVAc, displayed no transparency, brittleness, or stickiness in their appearance. The formulations containing PVAc (F1, F4, F5, F8, and F9) displayed a uniform, clear appearance with a smooth and homogeneous surface texture. That is seen in Figure 2. PVAc was selected as the best film-forming polymer because it produced a good film that could be separated from the Petri dish and the drug was distributed uniformly through the film. In contrast, HPMC is a film-forming polymer with good film-forming ability, but it did not generate satisfactory outcomes to give an excellent film because the drug is insoluble in water[32].

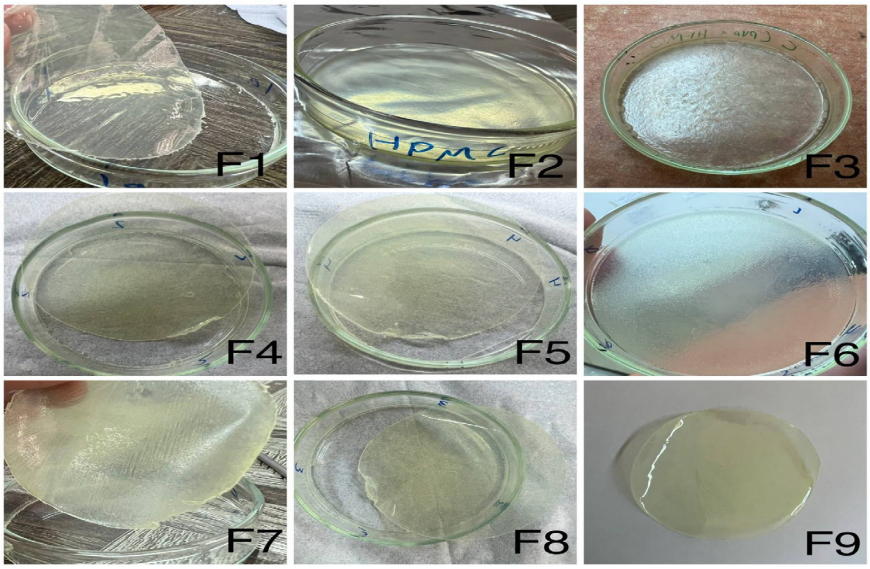

Figure 2. Displays the physical appearance of lercanidipine HCl films

Disintegration time of the film

The evaluation of *in vitro* disintegration demonstrated the following results for film disintegration times: 28 ± 1.0 seconds for F1, 25 ± 1.0 seconds for F4, 27 ± 1.5 seconds for F5, and 30 ± 1.0 seconds for F8. Cross-povidone causes film disintegration in a second for all films. Cross-povidone enhances disintegration by rapidly absorbing saliva into the film, resulting in volume expansion and hydrostatic pressures. This leads to rapid disintegration in the oral cavity, with wicking and swelling mechanisms as the main processes[33].

Film thickness

The average film thickness estimates for all formulations are displayed in Table 2. The thickness ranged from 0.108 ± 0.0083 to 0.124 ± 0.023 mm. A low standard deviation result suggests that the film formulation procedure is reproducible, producing films with uniform thickness and accurate dose in each film[34].

Variations in film weight

The measured weight of the films F1, F4, F5, and F8 were 117.8 ± 4.3, 121.6 ± 3.8, 110.8 ± 2.9, and 112.1 ± 6.4, respectively. The results demonstrate that the films average weight corresponds to the original formulations weight.

Measurement of folding endurance

All films in the study exhibited a folding endurance of more than 300, demonstrating the suitability and toughness of the polymers used, as shown in Table 2. Folding endurance of >300 reflects excellent flexibility[35]. The plasticizer enhanced the flexibility of the films, leading to an improvement in their folding endurance. After adding glycerin, the film became more flexible, and its folding endurance improved[36].

Drug content

The drug content in the film preparation was found to be 99% ± 0.3 for (F1), 100.7% ± 0.08 for (F4), 98.8% ± 0.19 for (F5), and 98.5% ± 0.05 for (F8). The outcomes illustrate that the drug nanoparticles are distributed equally within the film, confirming the effectiveness of the film manufacturing procedure as a uniform film and elevated drug content[37].

Surface pH study

The pH of the films ranged between 6.6 and 6.8. All these pH levels are compatible with the pH of the oral mucosa. The films are non-irritating to the oral cavity, making them acceptable for utilization[38].

Table 2. Displays the physicochemical properties of the prepared lercanidipine HCl sublingual films

F. Code	Drug content	Weight of film (mg)	Film thickness (mm)	Surface pH	Folding endurance	*In vitro* DT (sec)
F1	99% ± 0.3	117.8 ± 4.3	0.116 ± 0.011	6.6 ± 0.2	>300	28 ± 1.0
F4	100.7% ± 0.08	121.6 ± 3.8	0.108 ± 0.0083	6.7 ± 0.05	>300	25 ± 1.0
F5	98.8% ± 0.19	110.8 ± 2.9	0.124 ± 0.023	6.8 ± 0.11	>300	27 ± 1.5
F8	98.5% ± 0.05	112.1 ± 6.4	0.119 ± 0.011	6.6 ± 0.1	>300	30 ± 1.0

In vitro dissolution study of the films

The films that included PVAc polymer (F1, F4, F5, and F8) were found to release (78.6, 99.8, 77, and 92.5) %, respectively, after four minutes. Consequently, F4 demonstrated a greater release of its contents in an in vitro application. Figure 3 illustrates this result. Compared to this, the pure lercanidipine HCl film (F9) exhibited a release rate of just 41.8% for the same duration of time. The research project comprised a comparison of the release patterns of films that included F1, F4, F5, and F8, as well as a film that contained pure lercanidipine HCl (F9), which acted as a reference. The similarity factor f2 was used for comparison. Based on the information shown in Table 3, it was concluded that the value of the similarity factor obtained is less than 50. The LER nanoparticle films and the pure LER film show significant variations in dissolution characteristics.

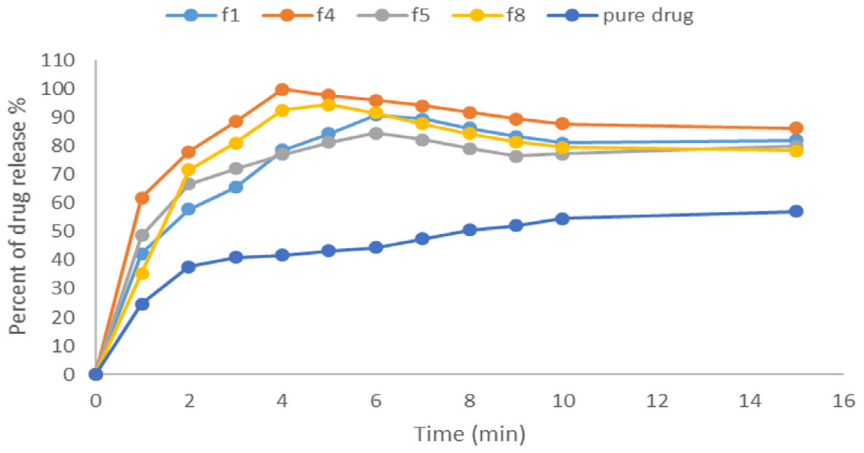

Figure 3. The *in vitro* dissolution of the pure lercanidipine HCl sublingual film and lercanidipine HCl nanoparticle films in phosphate buffer at a pH of 6.8 and 1% SLS.

Table 3. The similarity factor f2 results compare the release patterns of sublingual films containing lercanidipine HCl nanoparticles with those including pure lercanidipine HCl

F. Code	f2 factor
F1	25.13
F4	18.68
F5	26.61
F8	22.56

Characterization of the selected formula

The formulation identified as F4, including PVAc at 50% of the film weight and glycerin at 30% of the polymer weight, was selected as the preferred choice based on the disintegration time, weight uniformity, surface pH, drug content, Film thickness, and dissolution profile, as illustrated in Table 4.

Table 4. The features of the optimal lercanidipine HCl nanoparticle sublingual film

Parameter	F4
Drug content	100.7% ± 0.08
Disintegration time	25 ± 1.0
Weight	121.6 ± 3.8
Thickness	0.108 ± 0.0083
Surface pH	6.7 ± 0.05
Folding endurance	> 300
Drug release %	99.8 %

Compatibility test by FTIR

Figures 4 and 5 exhibit the Fourier Transform Infrared (FTIR) spectra of lercanidipine HCl nanoparticles and the best film preparation (F4), respectively. The optimized film formulation (F4) FTIR showed distinct peaks, which corresponded to those of the drug. This indicates no interaction between the drug and excipients in the film preparation[39].

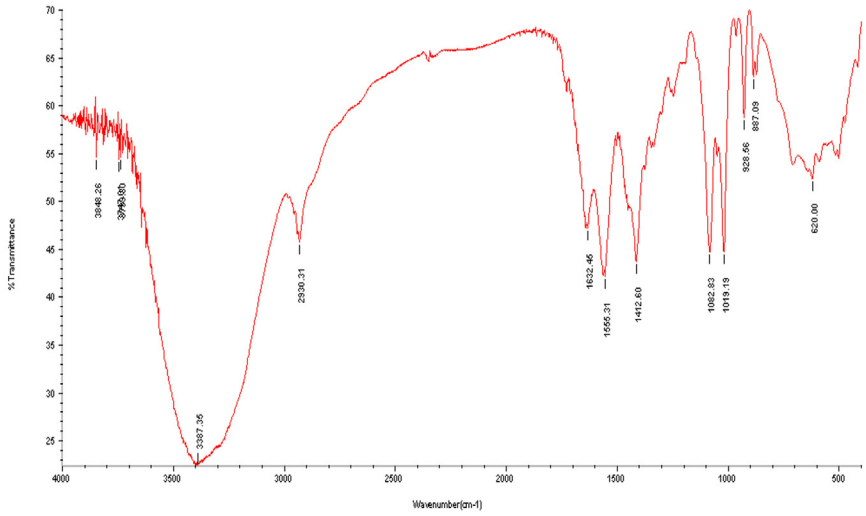

Figure 4. The FTIR spectra of lercanidipine HCl nanoparticles

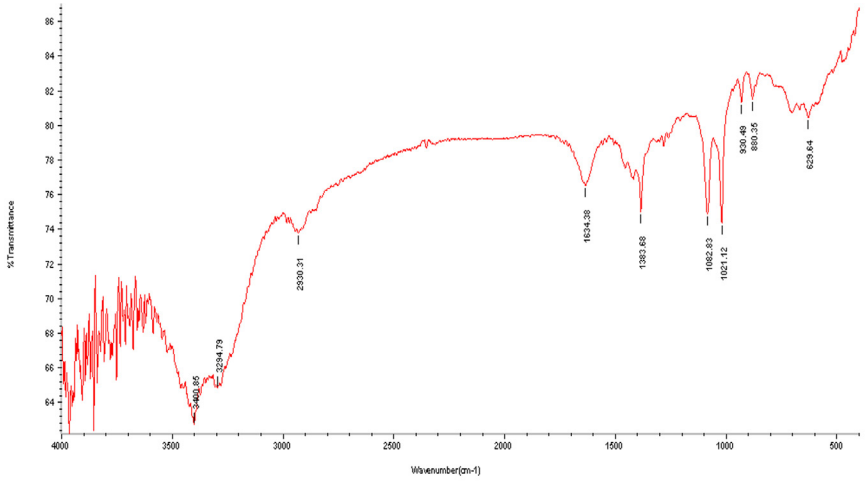

Figure 5. The FTIR spectra of the optimal film preparation (F4)

STATEMENT OF ETHICS

Ethics approval is not required in this study, as no human and experimental animal samples are not involved.

CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

AUTHORS CONTRIBUTIONS

Zahraa A. Alsafar collected data, analyzed and interpreted results, and prepared the initial manuscript. Zahraa A. Alsafar and Fatima J. Jawad participated in the final version of the text. Fatima J. Jawad supervised the project.

FUNDING SOURCES

Authors have no conflict of interests, and the work was not supported or funded by any drug company.

ACKNOWLEDGMENTS

The authors thank the Department of Pharmaceutics at the College of Pharmacy, University of Baghdad, for providing assistance in conducting the study.

REFERENCES

1. Hajdys J, Fularski P, Leszto K, Majchrowicz G, Stabrawa M, Młynarska E, et al. New insights into the nephroprotective potential of lercanidipine. Int J Mol Sci, 2023;24(18):14048. Doi: 10.3390/ijms241814048

2. Suthar V, Butani S, Gohel M. Solid self-emulsified nanostructures of lercanidipine hydrochloride: a potential approach to improve the fraction of the dose absorbed. J Drug Deliv Sci Technol, 2016;31:11-21. Doi: 10.1016/j.jddst.2015.11.001

3. Al-lami MS, Oudah MH, Rahi FA. Preparation and characterization of domperidone nanoparticles for dissolution improvement. Iraqi J Pharm Sci, 2018;27(1):39-52. Doi: 10.31351/vol27iss1pp39-52

4. Muhesen RA, Rajab NA. Formulation and characterization of olmesartan medoxomil as a nanoparticle. Res J Pharm Technol, 2023;16(7):3314-3320. Doi: 10.52711/0974-360X.2023.00547

5. Pınar SG, Oktay AN, Karaküçük AE, Çelebi N. Formulation strategies of nanosuspensions for various administration routes. Pharmaceutics, 2023;15(5):1520. Doi: 10.3390/pharmaceutics15051520

6. Sinha S. Nanoparticles loaded in consumable polymeric oral films: a smart dosage form design for oral administration. GSC Biol Pharm Sci, 2020;12(1):7-14. Doi: 10.30574/gscbps.2020.12.1.0153

7. Al-Nemrawi NK, Dave RH. Formulation and characterization of acetaminophen nanoparticles in orally disintegrating films. Drug Deliv, 2016;23(2):540-549. Doi: 10.3109/10717544.2014.936987

8. Bharti K, Mittal P, Mishra B. Formulation and characterization of fast dissolving oral films containing buspirone hydrochloride nanoparticles using design of experiment. J Drug Deliv Sci Technol, 2019;49:420-432. Doi: 10.1016/j.jddst.2018.12.013

9. Habib BA, Abd El-Samiae AS, El-Houssieny BM, Tag R. Formulation, characterization, optimization, and in-vivo performance of febuxostat self-nano-emulsifying system loaded sublingual films. Drug Deliv, 2021;28(1):1321-1333. Doi: 10.1080/10717544.2021.1927247

10. Shariare MH, Sharmin S, Jahan I, Reza H, Mohsin K. The impact of process parameters on carrier free paracetamol nanosuspension prepared using different stabilizers by antisolvent precipitation method. J Drug Deliv Sci Technol, 2018;43:122-128. Doi: 10.1016/j.jddst.2017.10.001

11. Abbas HK, Wais FM, Abood AN. Preparation and evaluation of ketoprofen nanosuspension using solvent evaporation technique. Iraqi J Pharm Sci, 2017:41-55. Doi: 10.31351/vol26iss2pp41-55

12. Shen C, Shen B, Xu H, Bai J, Dai L, Lv Q, et al. Formulation and optimization of a novel oral fast dissolving film containing drug nanoparticles by Box–Behnken design–response surface methodology. Drug Dev Ind Pharm, 2014;40(5):649-656. Doi: 10.3109/03639045.2014.884116

13. Jassim ZE, Hussein AA. Formulation and evaluation of clopidogrel tablet incorporating drug nanoparticles. Int J Pharm Sci, 2014:838-851.

14. Qureshia MJ, Phina FF, Patrob S. Enhanced solubility and dissolution rate of clopidogrel by nanosuspension: formulation via high pressure homogenization technique and optimization using Box Behnken design response surface methodology. J Appl Pharm Sci, 2017;7(2):106-113. Doi: 10.7324/JAPS.2017.70213

15. Toma NM, Abdulrasool AA. Formulation and evaluation of montelukast sodium nanoparticles for transdermal delivery. Int J Drug Deliv Technol, 2021;11(2):530-538.

16. Alwan RM, Rajab NA. Nanosuspensions of Selexipag: formulation, characterization, and *in vitro* evaluation. Iraqi J Pharm Sci, 2021;30(1):144-153. Doi: 10.31351/vol30iss1pp144-153

17. Kshirsagar T, Jaiswal N, Chavan G, Zambre K, Ramkrushna S, Dinesh D. Formulation & evaluation of fast dissolving oral film. World J Pharm Res, 2021;10(9):503-561.

18. Bala R, Sharma S. Formulation optimization and evaluation of fast dissolving film of aprepitant by using design of experiment. Bull Fac Pharm Cairo Univ, 2018;56(2):159-168. Doi: 10.1016/j.bfopcu.2018.04.002

19. Sheoran R. Fast dissolving oral films: a review with future prospects. Int J Pharm Pharm Res, 2018;12(2):15-32.

20. Abbas IK, Rajab NA, Hussein AA. Formulation and *in-vitro* evaluation of darifenacin hydrobromide as buccal films. Iraqi J Pharm Sci, 2019;28(2):83-94. Doi: 10.31351/vol28iss2pp83-94

21. Sumi S, Alam MN, Chowdury MI, Mazumdar MM, Chowdhury S, Alam SA. Effective development and evaluation of oral thin film of etoricoxib. World J Pharm Res, 2015;4:257-272.

22. Rashid A, Khalid SH, Irfan M, Asghar S, Rizg WY, Sabei FY, et al. *In vitro* and *in vivo* evaluation of composite oral fast disintegrating film: an innovative strategy for the codelivery of ranitidine HCl and flurbiprofen. Pharmaceutics, 2023;15(7):1987. Doi: 10.3390/pharmaceutics15071987

23. Al-Kubati SS, Ahmed MA, Emad NA. Palatable levocetirizine dihydrochloride solid dispersed fast-dissolving films: formulation and *in vitro* and *in vivo* characterization. Sci World J, 2022;2022. Doi: 10.1155/2022/1552602

24. Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F, Khan A. Orally disintegrating films: a modern expansion in drug delivery system. Saudi Pharm J, 2016;24(5):537-546. Doi: 10.1016/j.jsps.2015.02.024

25. Mady OY, Abulmeaty MMA, Donia AA, Al-Khureif AA, Al-Shoubki AA, Abudawood M, et al. Formulation and bioavailability of novel mucoadhesive buccal films for candesartan cilexetil in rats. Membranes, 2021;11(9):659. Doi: 10.3390/membranes11090659

26. Dharmasthala S, Shabaraya AR, Andrade GS, Shriram RG, Hebbar S, Dubey A. Fast dissolving oral film of piroxicam: solubility enhancement by forming an inclusion complex with β-cyclodextrin, formulation and evaluation. J Young Pharm, 2019;11(1):1-6. Doi: 10.5530/jyp.2019.11.1

27. Jabur MS, Manna MJ, Mohammed HR, Baqir LS, Abdulamir HA. Ocular hypotensive effect for the topical amlodipine 0.5% eye drop. Lat Am J Pharm, 2023;42:311-314.

28. Abdulhussein HA, Alwasiti EAR, Khiro NK, Nile AK. The potential impact of vascular endothelial growth factor rs699947 polymorphisms on breast tumors susceptibility in a sample of Iraqi females. Acta Pharm Sci, 2024;62:(2): 268-277. Doi: 10.23893/1307-2080.APS6217

29. Hussien RM, Ghareeb MM. Formulation and characterization of isradipine nanoparticle for dissolution enhancement. Iraqi J Pharm Sci, 2021;30(1):218-225. Doi: 10.31351/vol30iss1pp218-225

30. Asfour MH, Mohsen AM. Formulation and evaluation of pH-sensitive rutin nanospheres against colon carcinoma using HCT-116 cell line. J Adv Res, 2018;9:17-26. Doi: 10.1016/j.jare.2017.10.003

31. Santos Júnior AdF, Barbosa IS, Santos VL, Silva RL, Caetite Junior E. Test of dissolution and comparison of *in vitro* dissolution profiles of coated ranitidine tablets marketed in Bahia, Brazil. Braz J Pharm Sci, 2014;50:83-89. Doi: 10.1590/S1984-82502011000100008

32. Jassim ZE, Mohammed MF, Sadeq ZA. Formulation and evaluation of fast dissolving film of lornoxicam. Asian J Pharm Clin Res, 2018;11(9):217-223. Doi: 10.22159/ajpcr.2018.v11i9.27098

33. Sumaiyah S, Mentari J, Suryanto S. The effect of crospovidone on the dissolution profile of amlodipine besylate from fast orally dissolving film. Open Access Maced J Med Sci, 2019;7(22):3811. Doi: 10.3889/oamjms.2019.510

34. Kaewkroek K, Petchsomrit A, Septama AW, Wiwattanapatapee R. Development of starch/chitosan expandable films as a gastroretentive carrier for ginger extract-loaded solid dispersion. Saudi Pharm J, 2022;30(2):120-131. Doi: 10.1016/j.jsps.2021.12.017

35. Rani KC, Parfati N, Aryani NLD, Winantari AN, Fitriani EW, Pradana AT, et al. Development, evaluation, and molecular docking of oral dissolving film of atenolol. Pharmaceutics, 2021;13(10):1727. Doi: 10.3390/pharmaceutics13101727

36. Kittipongpatana OS, Trisopon K, Wattanaarsakit P, Kittipongpatana N. Fabrication and characterization of orodispersible composite film from hydroxypropylmethyl cellulose-crosslinked carboxymethyl rice starch. Membranes, 2022;12(6):594. Doi: 10.3390/membranes12060594

37. Krull SM. Formulation and dissolution of polymer strip films for the delivery of poorly water-soluble drug nanoparticles. [Doctoral thesis]. New Jersey: New Jersey Institute of Technology; 2017.

38. Gayathri D, Jayakumari LS. Evaluation of commercial arrowroot starch/CMC film for buccal drug delivery of glipizide. Polímeros, 2020;29:e2019047. Doi: 10.1590/0104-1428.06619

39. Shaikh F, Patel VB. Enhancement of dissolution of Lercanidipine hydrochloride using solid dispersion technique. Res J Recent Sci, 2015;2277:2502.