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Preparation and Characterization of Isradipine as Surfactant Free Emulsion

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Abstract

Isradipine is the drug of choice for oral therapy of severe hypertension and urgent hypertension crises in pediatrics. It belongs to BCS class II. Its oral bioavailability will be approximately 15 to 24%. This study aims to prepare a stable, low-toxic, eco-friendly, surfactant-free oral oil-in-water emulsion of Isradipine for pediatric patients and enhance dosing accuracy. Isradipine surfactants–free emulsions (SFE) were prepared to protect this ester drug from hydrolysis, oxidation, and photosensitivity, increasing its dispersibility and absorption, thereby improving its bioavailability. The study used various oils, Sesame oil, Olive oil, Sunflower oil, Almond oil, Soybean oil, Canola oil, Grape seed oil, Cotton seed oil, Avocado oil, Corn oil, corn and grape oil for solubilizing Isradipine, and from these oils was chosen to use corn oil and grape seed oil for the preparation of Isradipine SFE. Different percentages of β-cyclodextrin stabilized SFE to encapsulate oil droplets. Twelve formulas were prepared and evaluated for organoleptic attributes, thermodynamic stability, dilution test, viscosity, pH, drug content, droplet size determination, and in-vitro dissolution. Among all the prepared SFE formulas, F3, containing 8g of β-CD and 15g of Corn oil, was chosen as the optimum SFE formula due to its small particle size range1451±0.01 nm, respectable pH, good organoleptic attributes, excellent thermodynamic stability, acceptable viscosity (1869.5±1.54), acceptable drug content percentage, and highest dissolution rate. F3 was further tested for drug excipient compatibility using Fourier Transform Infrared Spectroscopy (FTIR) and Scanning Electron Microscopy (SEM), Differential scanning calorimeter (DSC), showing complexation between the drug and oil droplets, and spherical droplets of Corn oil surrounded by β-CD.

Keywords: β-Cyclodextrin, Corn oil, Grape seed, Isradipine, Pediatric hypertension, Pickering emulsion, Surfactant free emulsion (SFE)

Introduction

Hypertension (HTN) is the third most common chronic pediatric disease, with a prevalence in Iraqi children increasing from 1.7% in 2006 to 19.6% in recent years. Factors contributing to this increase include family history, birth weight, high body mass index, insulin resistance, and sympathetic nervous system activation [(1)]. Hypertension is also common in Iraqi children with type 1 diabetes [(2)] and dyslipidemia among Iraqi teenagers [(3)]. Pediatric patients have unique pharmacokinetics, pharmacodynamics, administration routes, toxicity, and taste preferences compared to adults. This necessitates the development of convenient formulations for children
of all age groups due to their varying responses to active substances and excipients [(4, 5)].

The majority of drugs in the market are not suitable for children, leading to unsafe off-label or extemporaneous compounding practices. Thereby, crushing hard tablets containing the active pharmaceutical ingredient can alter the rate of drug dissolution and absorption, increasing risks of inaccurate dosing, hospitalization, elevated healthcare costs, contamination, and death would be increased. Therefore, this makes it necessary to have convenient formulations for children in all age groups [(6, 7)]. The optimal pediatric formulations should have low dosing frequency, appropriate dosage forms for different age groups, convenient administration, minimal impact on lifestyle, use of non-toxic, well-tolerated excipients, taste masking, easy production, elegant, stable, and cost-efficient manufacturing [(5)]. Liquid dosage forms are advantageous for pediatric patients and infants due to their greater dose flexibility and ease of swallowing [(7)]. Emulsions are dispersions of two immiscible liquids that are thermodynamically unstable and need to be stabilized by surfactants [(8)].

However, synthetic emulsifiers used in these systems have been linked to health problems and toxic symptoms with prolonged use. Clinical tests have shown that anionic emulsifiers may bind to the human body's proteins, enzymes, and phospholipid membranes, leading to adverse effects such as enzyme dysfunction, protein structure modification, and phospholipid changes in the cell membrane [9]. Pickering emulsion is a surfactant-free emulsion (SFE) stabilized by solid particles. These non-toxic, biocompatible, and biodegradable stabilizers are edible, natural substances, readily available, and inexpensive. This unique structure for SFE endows them with excellent stability compared to conventional emulsions due to irreversible adsorption on oil droplets, excellent biocompatibility, and environmental friendliness [10]. Isradipine is a calcium channel blocker drug. It is the drug of choice for oral therapy of hypertensive crisis, especially urgent hypertension. The usual dose of Isradipine for pediatrics is 0.05–0.1 mg/kg/dose/8hr up to 5 mg/dose [11]. Isradipine is a class II drug according to BSC, and its bioavailability is 15 to 24% [12]. β-Cyclodextrin (β-CD) is a natural starch derivative and its cyclic oligosaccharide. The outer surface of β-CD is hydrophilic, while the inner cavity is hydrophobic. This unique structure facilitates the encapsulation of hydrophobic substances and makes them more stable when exposed to light, heat, and oxygen. β-CD's amphiphilicity also makes it useful for stabilizing Pickering emulsions [13].

When oils are inserted in β-CD s, they form an insoluble complex that adsorbs at the oil-water interface, leading to stabilizing the Pickering emulsion. However, the success of this interaction depends on the structure of both the β-CD and oil [14]. This study aims to prepare a stable, low-toxic, eco-friendly, surfactant-free oral oil-in-water (O/W) emulsion of Isradipine for pediatric patients and enhance dosing accuracy. Thus, Isradipine, which is ester in structure, can be protected from hydrolysis, oxidation, and photosensitivity and increase its use dispersibility and absorption.

Materials and Methods

Materials

Isradipine was purchased from Hyper chem company, China, native β-CD, Sesame oil, Olive, Sunflower, Almond oil, Soybean oil, Canola oil, Grape seed, Cotton seed, Avocado oil, Corn oil, HCl, SDS, Methanol, deionized water.

Methods

Solubility study of isradipine

Isradipine's saturated solubility was tested in various oils: Sesame oil, Olive oil, Sunflower oil, Almond oil, Soybean oil, Canola oil, Grape seed oil, Cotton seed oil, Avocado oil, and Corn oil. To measure the solubility, in a plain tube, added 5mg of each oil, then added to it an extra amount from the powder of Isradipine. After being securely sealed, these tubes were kept in a water bath shaker for 48 h and at 25 ± 0.5 °C. After that, these tubes were put in a centrifuge and rounded for 20 min at a speed of 3000 rpm. Next, each sample's supernatant layer was filtered by a 0.45 µm filter syringe. Then, each filter was diluted by using methanol. Finally, the diluted filter was scanned at λ max of Isradipine in Ethanol 326 nm by a spectrophotometer [15, 16].

Construction of ternary phase diagrams

The pseudo-ternary phase diagrams consist of Corn oil, β-CD, and deionized water. The oil was chosen based on solubility studies and used to construct the diagram with Origin Lab software. To construct the ternary phase diagram, the Corn oil/β-CD/water ratios were determined for each point, and the necessary quantities of each component were calculated while maintaining a constant total volume of 100mg. The samples were prepared by dissolving β-CD in water and mixing the liquid phase with the oil using a homogenizer at 10,000 rpm for 5 minutes at 25°C. After emulsification, the phase diagrams were obtained through visual observations one hour after preparation, and the type of emulsion was determined through dilution testing. [17-19].

Formulations of surfactant-free emulsions of Isradipine

Isradipine SFE was prepared by using β-CD in different weights as stabilizers instead of surfactants with a selected oil based on a solubility study, as the oil phase, as seen in Table 1. The dose of drug incorporated in each one of these formulations was 2.5 mg of Isradipine/5 mg of SFE. The method of preparation is the mechanical method; where 50 mg of Isradipine was dissolved in the selected oil (oil phase), while in another beaker mixed the specialized amount of β-CD with deionized water (aqueous phase), then while continuously mixing the aqueous phase by using a homogenizer, dropped the oil phase slowly on it then the homogenizer still mixed for 5 minutes at 10,000 rpm at 25ºC to obtain surfactant free o/w emulsion. The percent of each component is based on a ternary phase diagram and references [20, 21]. As shown in the Table 1.

Evaluation of organoleptic attributes

The study assessed the sensory properties of emulsions, such as the color and the odor. The emulsion's texture was evaluated by distributing a small amount of SFE on the back of the hand. While consistency was assessed based on homogeneity. The ease of removal of emulsions was also assessed after washing the body part with tap water [22].

Thermodynamic stability studies

Emulsions, due to their different densities between oil and aqueous phases, rapidly separate into oil and water layers, making them thermodynamically unstable systems. The stability of emulsions means their ability to maintain their properties. Their stability depends on various phenomena like flocculation, sedimentation,

creaming, phase inversion, Ostwald ripening, and coalescence, which contribute to their destabilization [8].

Observation of phase separation

Ten mL of the prepared emulsions were stored in tubes fixed vertically under ambient conditions and evaluated for instability phenomena after 1, 2, 4, 6, and 24 h of preparation [23].

Heating-cooling cycle

Heating cooling means a plain tube containing the formula was stored at 4 °C for 48 h then, this tube was stored at 45 °C also for 48 h, and repeating this variation of temperature for six cycles, and the formulation stability was examined at each temperature [24].

Freeze-thaw cycle

By this test, the SFE of Isradipine formulas was firstly stored at -5 ºC (in a fridge) for 24 hrs. Then, at 27 ºC (at room temperature) for 24 hrs. Finally, in an oven at 40 ºC for 24 hr., this cycle was repeated six times. The results were recorded for further studies [25].

Centrifugation analysis

The emulsion resistance to external factors was evaluated using a centrifugation test, which involved centrifuging 10 gm of each emulsion's sample in a centrifuge tube at 3000 rpm for 30 minutes to assess its stability and accelerate the gravitational separation of dispersed phase particles [22].

$$\text{Emulsion stability}(\%) = \frac{\text{Hight of emulsion separation}}{\text{Total hight of emulsion}} \times 100 \ldots\ldots\ldots \text{Equation}(1)$$

Droplet test (Dilution test)

A droplet test was conducted to determine the type of emulsion formed O\W or W\O by adding one drop of each emulsion to water and oil, assessing its ease of dispersion through visual inspection. Rapid dispersion indicated that the continuous phase was the same [26].

Viscosity determination

The viscosity of a prepared SFE formula was measured for a non-diluted freshly prepared formula by using a digital viscometer with a spindle NO. 4, which was inserted into a glass beaker at a speed of 60 rpm [27].

Particle size determination

The SFE's mean of the particle size was measured using a laser particle size analyzer instrument (Malvern Instruments Ltd Great Britain) by taking the angle of detection at 90º and 25 ºC, after being diluted fivefold with double-deionized water before measurements [20].

pH measurement

The pH measurement was done using a pH meter. Glass electrode was dipped in SFE emulsion and the reading was noted [28]. The measurement was repeated three times for each sample, and the result was presented as mean ±SD.

Determination of drug content

Accurately, 5gm of each SFE formula, containing 2.5mg of Isradipine, was dissolved in 100 ml Methanol, then filtered using a 0.45 µm filter syringe and suitably diluted. The contents of Isradipine were determined using a UV/Vis spectrophotometer at the selected λ max 328 nm [12].

The in-vitro dissolution profile of Isradipine SFE

The in-vitro dissolution test of Isradipine SFE was conducted using USP dissolution apparatus type II. Each formula equivalent to 2.5 mg of Isradipine was placed in a dialysis bag. The paddle rotated at 50 rpm at 50 rpm at 37 ± 0.5°C in 250ml of dissolution medium, 0.1N HCl with SDS 1%w/v, to ensure sink condition. An aliquot of 5 ml samples was drawn at predetermined time intervals, and compensated by an equal volume of fresh dissolution medium then, samples were assayed spectrophotometrically using a UV-spectrophotometer at 328 nm. The same procedure was made for the pure drug [16, 29].

Selection optimum Isradipine surfactant free emulsion

The best formula of Isradipine SFE was selected according to the results obtained from the previous evaluation tests. Then, the selected formula will be further evaluated.

Evaluation of selected optimum Isradipine surfactant free emulsion

Fourier transform infrared spectroscopy (FTIR)

Isradipine powder and selected formula were analyzed using FTIR spectroscopy (Shimadzu, Japan) from 4000 - 400 cm^{-1} to determine potential Isradipine β-CD interaction [24].

Scanning electron microscopy (SEM)

By Scanning electron microscope, the morphological features, including (shape and surface characteristics) of SFE, were evaluated [21].

Differential scanning calorimeter (DSC)

The thermal properties of drug powder samples, β-CD, physical mixture of Isradipine and β-CD were examined using DSC /TA-60thermal analysis controller with the intercooler-2 cooling system (DSC-60, Shimadzu, Japan). Sample heating was run for each sample set for 50-250°C at the rate of 10°C/min, using nitrogen as blank gas [12].

Table 1. Components of Surfactant free emulsion for Isradipine.

F. NO.	β-CD (g)	corn oil(g)	Grape seed(g)	Water (g)	Isradipine (mg)
F1	4	15		81	50
F2	6	15		79	50
F3	8	15		77	50
F4	4	20		76	50
F5	6	20		74	50
F6	8	20		72	50
F7	4		15	81	50
F8	6		15	79	50
F9	8		15	77	50
F10	4		20	76	50
F11	6		20	74	50
F12	8		20	72	50

Results and Discussion

Solubility in oils

Isradipine solubility was indicated to be highest in Corn oil (4.9 mg/ml) and then in Grape seed oil (4.7 mg/ml) in comparison to other oils in Table 2, so it was selected as an oil phase for preparing SFE for Isradipine.

Table 2 .Saturation solubility of Isradipine in different oils

Oil	Solubility (mg/ml) mean ± SD*
Sesame oil	1.4±0.01
Olive oil	1.41±0.02
Sunflower oil	1.4±0.13
Almond oil	2.2±0.12
Soybean oil	2±0.06
Canola oil	2.4±0.06
Grape seed oil	4.7±0.03
Cotton seed oil	4.6±0.10
Avocado oil	4.4 ±0.04
Corn oil	4.9±0.017

Results of ternary phase diagrams

Ternary phase diagrams of oil/β-CD/water systems are used to analyze the emulsifying ability of β-CD for oils. Area (A) represents W/O due to high oil content, making it difficult to prepare SFE from this area due to SFE of Isradipine is for oral use. Oral emulsions are typically of the o/w type, as they are more palatable and acceptable [30]. Area (B) represents O/W emulsion, which can be used for the preparation of oral SFE but is grassy and less palatable due to high oil concentrations [30]. Area (C) is an O/W emulsion but cannot be used due to excess particles in the continuous phase, leading to multi-layer adsorption or a cementitious network structure [31]. Area (D) is not suitable for making O/W SFE of Isradipine due to its solubility in Corn oil. Area (E) is suitable for making O/W SFE of Isradipine based on its solubility. Area (F) is unstable due to low β-CD concentrations, and the β-CD complexes formed show surface activity but cannot form stable emulsions [32], as shown in Figure.1.

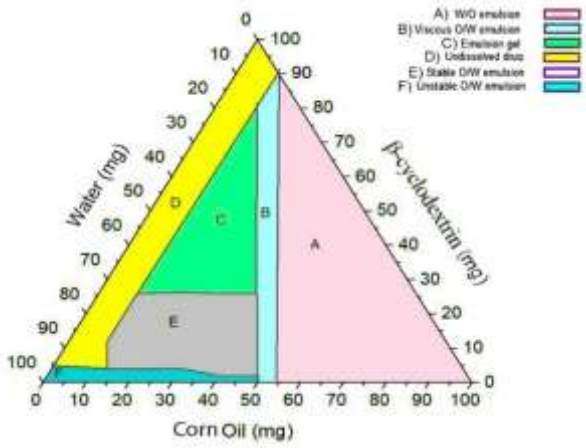

Figure 1. Ternary phase diagrams for Corn oil.

Evaluation of organoleptic attributes

All formulations freshly prepared have a yellowish white color for formulas containing Corn oil to greenish white for formulas containing Grape seed oil. Their appearance is homogenous, with a smooth texture, odorless, and no lumps were detected. They offer smoothness to the touch and were easily removed from the back of the hand by using water only.

Observation of phase separation

The study found that F1 and F4 exhibit phase separation after 24 hours, indicating they cannot be further investigated. However, other formulas remained thermodynamically stable during this time, maintaining emulsion stability without phase separation, flocculation, sedimentation, creaming, or phase inversion. The irreversible adsorption of β-CD on oil droplets causes β-CD in the continuous phase to cover the oil droplets' surface, preventing aggregation and improving emulsion stability. F1 and F4 have low particle concentrations leading to partial coverage of droplets by β-CD, causing phase separation [31].

Heating-cooling cycle

The purpose of this stability study is to identify the formulations that were stable against storage in extreme condition and ensures the system remain dispersed with no separation [33]. All formulas pass this test except F7, so only the formulations that remained stable at these temperatures were exposed to further studies, as shown in Table 3.

Freeze-thaw test

Freeze-thaw test is a commonly used parameter to evaluate the stability of emulsions. The formulation with either higher oil volume, higher particle concentration, or both exhibits superior freeze-thaw stability compared to the formulation with lower oil volume or particle concentration [34]. As shown in Table 3, F10 showed oiling-off after 2 cycles of freeze-thaw provided that evidence of coalescence was already evident so that all formulations passed this test except F10.

Centrifugation analysis

Formulas F3, F6, F9, and F12 with the highest amount of β-CD have lower creaming and higher stability compared to formulas F2, F5, F8, and F11 with the same amount of oil. Formulas F5, F6, F11, and F12 contain the highest amount of oil, have lower creaming and higher stability compared to formulas F2, F3, F8, and F9 containing less amount of oil with the same amount of β-CD formulas. The creaming index decreases rapidly with the increase in oil concentration and solid particle concentration in SFE [35].

Grape seed oil formulas (F8, F9, F10, F11, and F12) have a lower creaming percent compared to Corn oil formulas (F2, F3, F4, F5, and F6), so they have a higher stability because of the oil type can also influence the type or stability of emulsions obtained due to each oil's different polarity and viscosity [36], as shown in Table 3.

Table 3. Accelerated Stability Studies of Isradipine SFE

No. of formula	Heating-cooling cycle	Freeze-thaw cycle	Centrifugation test
F2	Pass	Pass	43
F3	Pass	Pass	31
F5	Pass	Pass	27
F6	Pass	Pass	21
F7	Not pass	Not pass	—
F8	Pass	Pass	24
F9	Pass	Pass	19
F10	Pass	Not pass	—
F11	Pass	Pass	21
F12	Pass	Pass	15

Droplet test

All prepared SFE formulas are dilutable with water. That indicates that all of them are O/W SFE [24].

Viscosity determination

The viscosity study found that formulas F3, F6, F9, and F12 had more viscous emulsions than formulas F2, F5, F8, and F11 due to higher amounts of β-CD. This is because excess particles form a network structure around each droplet, improving emulsion stability and increasing emulsion viscosity [36].

Formulas F5, F6, F11, and F12 had more viscous emulsions than the group of formulas F2, F3, F8, and F9 due to higher oil content [37]. This is because as oil content increased, the number of emulsified oil droplets increased and their size decreased, leading to increased interfacial area, allowing more interactions between one particle and another and increased emulsion viscosity [38].

Formulas F8, F9, F11, and F12, containing Grape seed oil, had higher viscosity compared to formulas F2, F3, F5, and F6, containing corn oil. The viscosity of SFE strongly depends on the type of oil, with the strongest van der Waals' forces formed between the alkyl chain of oil linked to a glycerol backbone of CD [14]. Other interactions, such as electrostatic, hydrophobic, and hydrogen bonding, also affect the viscosity of emulsions [39]. Each oil type can induce a change in the viscosity of the emulsions obtained due to its different polarity and viscosity [36], as shown in Table 4.

Particle size determination

The particle size range of the investigated formulas is 1451-5706 nm, with variations attributed to the amount of β-CD and amount of oil. The formulas F2, F5, F8, and F11 had larger particle sizes than formulas F3, F6, F9, and F12 respectively with the same amount of oil due to having a lower amount of β-CD. The increase in particle size by decreasing surfactant concentration can be explained by the partly coverage of oil droplets by solid particles, leading to coalescence and large droplets [40].

Formulas F5, F6, F11, and F12 had larger particle sizes than F2, F3, F8, and F9 respectively with the same amount of β-CD due to higher oil content and increased oil volume, leading to droplet coalescence and droplet size increase [41]. The smallest particle sizes were observed in Corn oil SFE formulas F2, F3, F5, and F6, while their sizes increased in corresponding Grape seed oil formulas

F8, F9, F11, and F12 due to the chemical character of the individual oils. The polar character of the oil influences particle adsorption, modifying droplet curvature and subsequently droplet size [42], as shown in Table 4.

Table 4. Viscosity (mP) and Mean droplet size of Isradipine SFE (mean ± SD, n= 3)

No. of formula	Viscosity (mP)	Mean droplet size(nm)
F2	1665.9±1.62	1825±0.1
F3	1869.5±1.54	1451±0.01
F5	2621±1.38	4121±0.3
F6	3115 ± 1.64	3109±0.02
F8	2938± 1.42	2123±0.004
F9	3398± 1.37	2045±0.05
F11	3574± 1.48	5706±0.02
F12	4826± 1.27	5164±0.009

Determination of pH

The pH range of all formulations (6.2-6.7). The acceptable pH range for oral solutions is (2-9), therefore all formulations have accepted pH values [30].

Drug content

The drug content related to all prepared Isradipine SFE formulas was within an acceptable range (95.0%-105.0%) and there has been no considerable difference between different formulations ($p > 0.05$), which meets British pharmacopeia requirements and indicates that there has been no precipitation of the drug in any of the prepared formulations [43].

In vitro drug release

The study reveals a flexible duration time for Isradipine release from each formula, with F3 completely releasing Isradipine after 90 minutes, while F2, F5, F6, F8, F9, F11, and F12 took more than 120 minutes to complete the release. Pure Isradipine showed 15.4% drug release at the end of 120 minutes due to its practically insoluble [12].

The percentage of drugs released from SFE increased with a decrease in particle size (F3>F2), (F6>F5), (F9>F8, and (F12>F11), because F3, F6, F9, and F12 have a higher of the percentage of β-CD so have the smaller particle size than F2, F5, F8, and F11 respectively, Smaller droplet size increases the total surface area for transfer, release, and absorption of the drug and improve the bioavailability [44].

The percentage of drugs released from SFE increased with a decrease in the viscosity (F2>F5), (F3 > F6), (F8>F11), and (F9>F12); the results revealed that the release of Isradipine was higher from formulas with less oil content, due to its lower viscosity [37].

The release of Isradipine SFE from Formulas that contain Corn oil F2, F3, F5, and F6 is rapid and faster than corresponding formulas that contain Grape seed oil F8, F9, F11, and F12 with the same amount of β-CD, this is due to Corn oil giving higher drug solubility, smaller particle sizes, and lower viscosity as mentioned above, as shown in Figure.2.

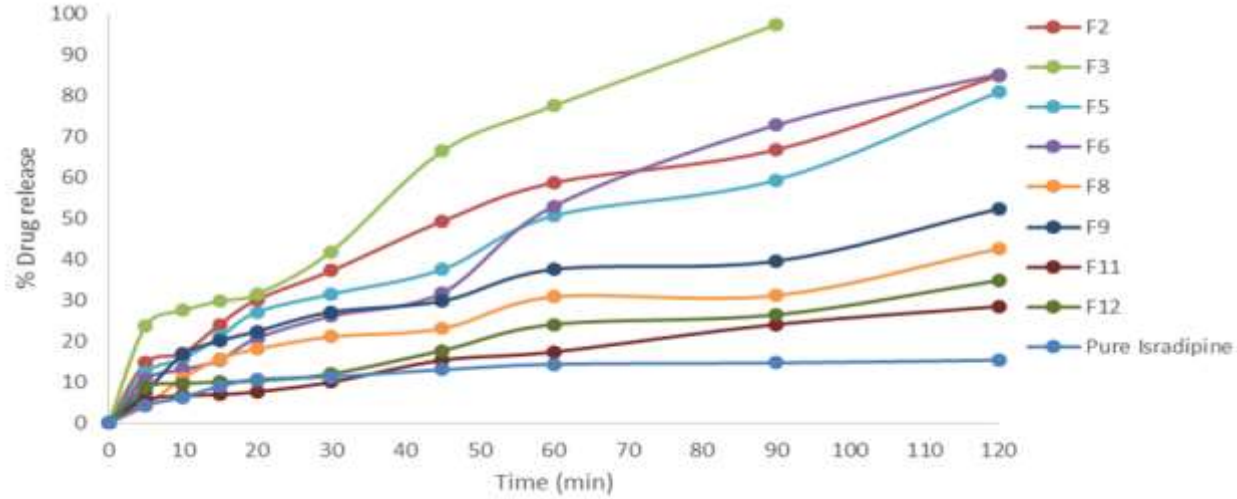

Figure 2. A comparative dissolution profile of Isradipine SFE (F2, F3, F4, F6, F8, F9, F10, F11, F12, and pure Isradipine) in 250ml of 0.1 N HCl (containing 1% SDS) dissolution medium at 37°C.

Selection of the Optimum Formula

Based on the previous results, F3 was chosen as the best Isradipine SFE formula since it had a globule size range of 1451±0.01 nm, respectable pH, good organoleptic attributes, excellent thermodynamic stability, acceptable viscosity 1869.5±1.54 mP, great % drug content and In vitro release 100% in 90 minutes. The selected formula was subjected to further studies.

Evaluation of selected optimum Isradipine surfactant free emulsion

Drug – Excipients Compatibility Study

The result of FTIR of pure Isradipine powder exhibited characteristic peaks at 3,346 cm–1 (N-H stretching), 1490 2 cm–1 (N-H bending),866 cm–1(N-H out of plane),1702 cm–1(=C-H stretching), 1647 cm–1 (C=C stretching), two bend 1110 cm–1,1158 cm–1(C-O stretching),1225 cm–1(C-N stretching),1543 cm–1 (N-O asymmetric stretching), and 1308 (N-O symmetric stretching) [45, 46], as shown in Figure.3.

The FTIR spectrum of the selected formula (F3) showed the disappearance of the bands of Isradipine as mentioned previously indicating the occurrence of complexation between the drug inside oil droplets and β-CD [47], as shown in Figure.4.

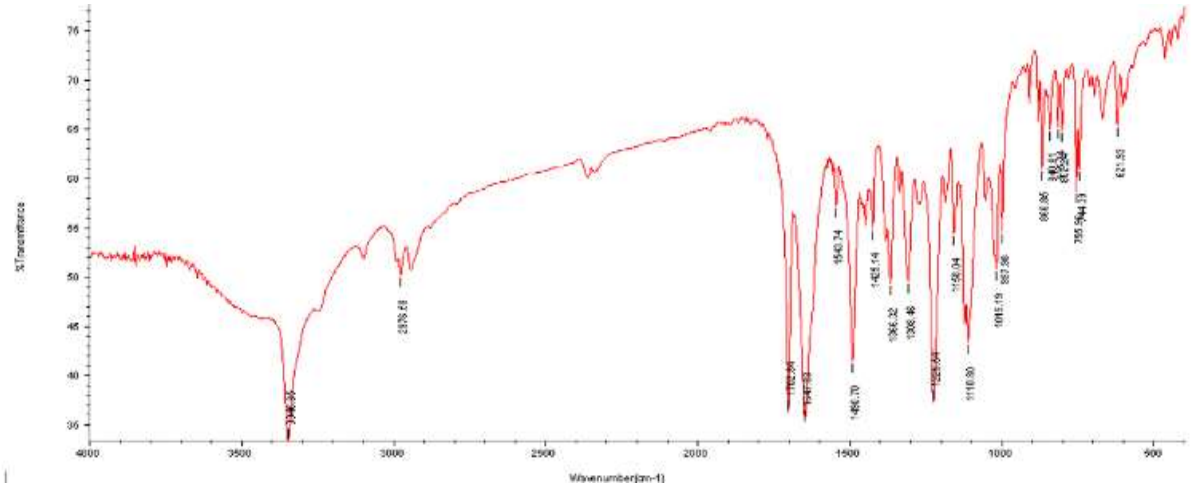

Figure 3. FTIR spectrum of Isradipine powder.

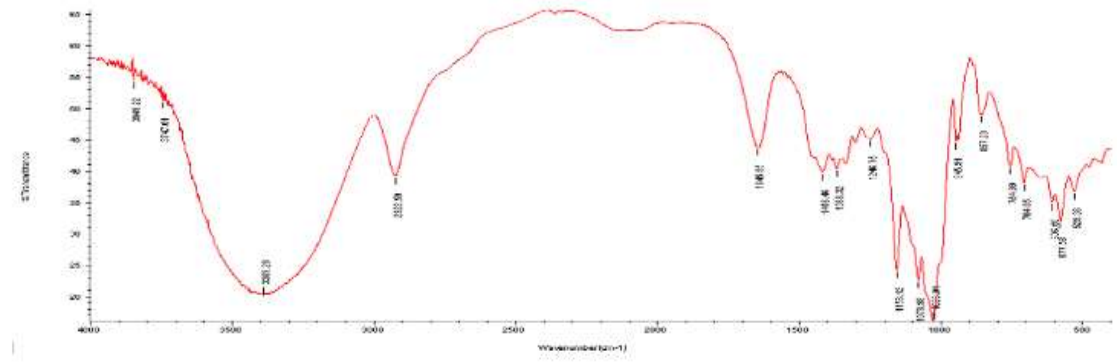

Figure 4. The FTIR spectrum of the selected formula (F3)

Scanning electron microscopy (SEM)

The SEM shows the spherical shape of spherical droplets of Corn oil that are surrounded by β-CD as shown in Figure 10.

The structure of the particles that were examined shows a good distribution of β-CD around Corn oil droplets [20], as shown in Figure.5.

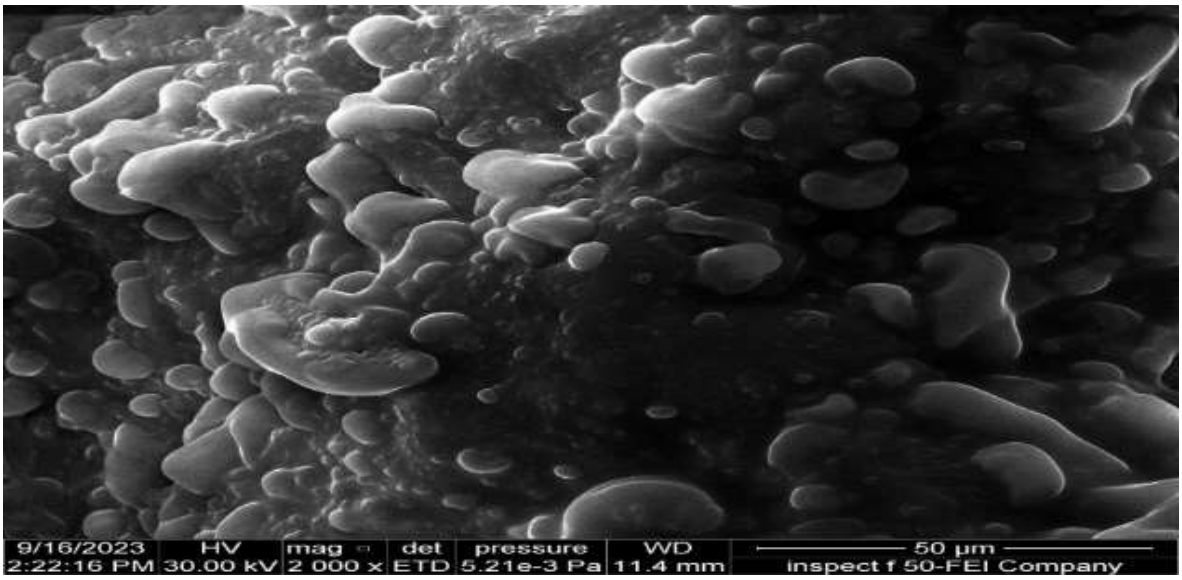

Figure 5. SEM of the selected formula (F3)

Differential scanning calorimeter (DSC)

The measured melting point via DSC is used to confirm the purity of the drug used in the study. The sharp peak that appeared in Figure.6 referred to the melting point of the drug is 170 °C and indicated the crystalline drug in nature [16].

The thermogram of β-CD showed a relaxation peak at 13.14°C exhibited in the thermogram of β-CD indicated the release of water (dehydration), as shown in the Figure.7. While Figure.8 for a physical mixture of Isradipine and β-CD showed two peaks appear in the physical mixture one peak for Isradipine and the other for β-CD. The peak of Isradipine is similar to the pure drug but with a little reduction in peak intensity and very little shift of the peak. This may be related to the smaller mass ratio of the Isradipine compared to β-CD or very little interaction occurs [47].

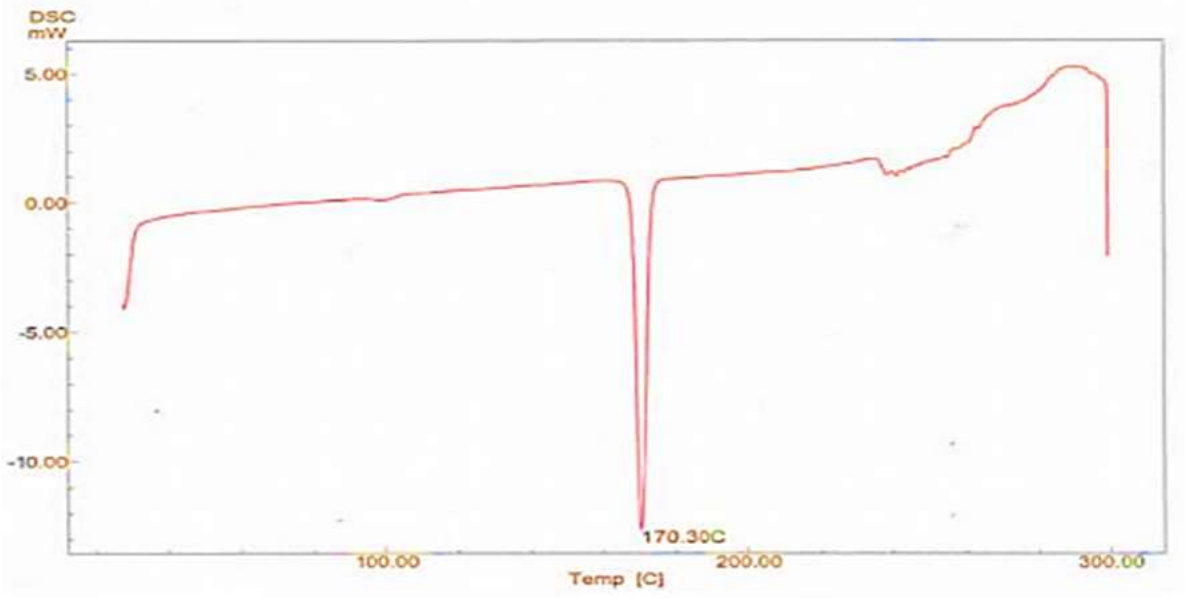

Figure 6. Differential scanning calorimetry of pure Isradipine.

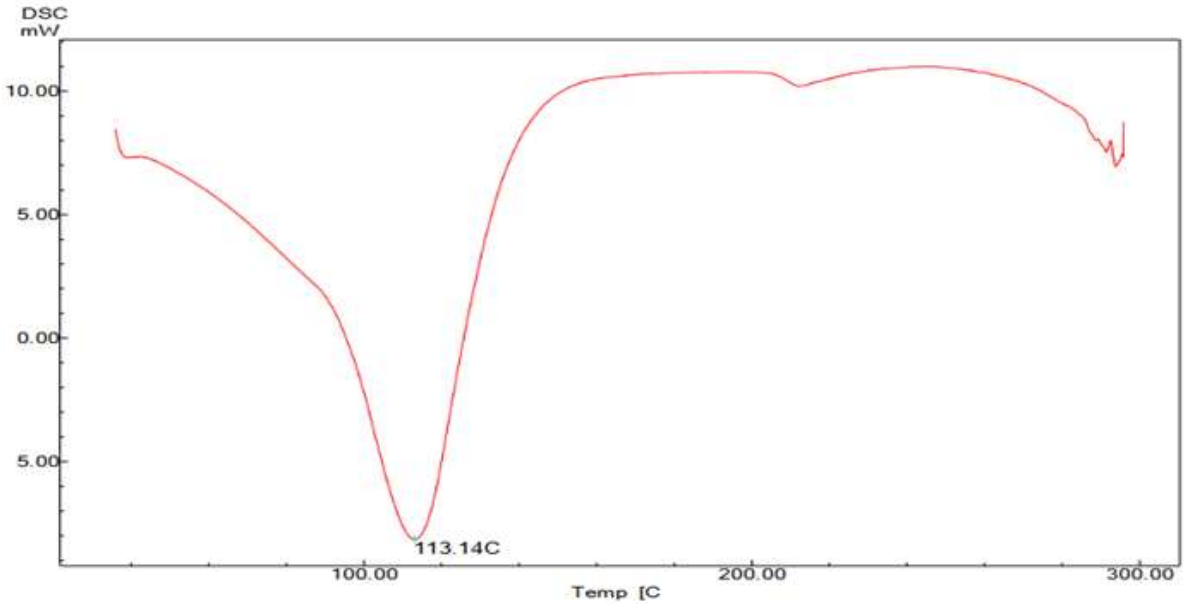

Figure 7. Differential scanning calorimetry of β-CD.

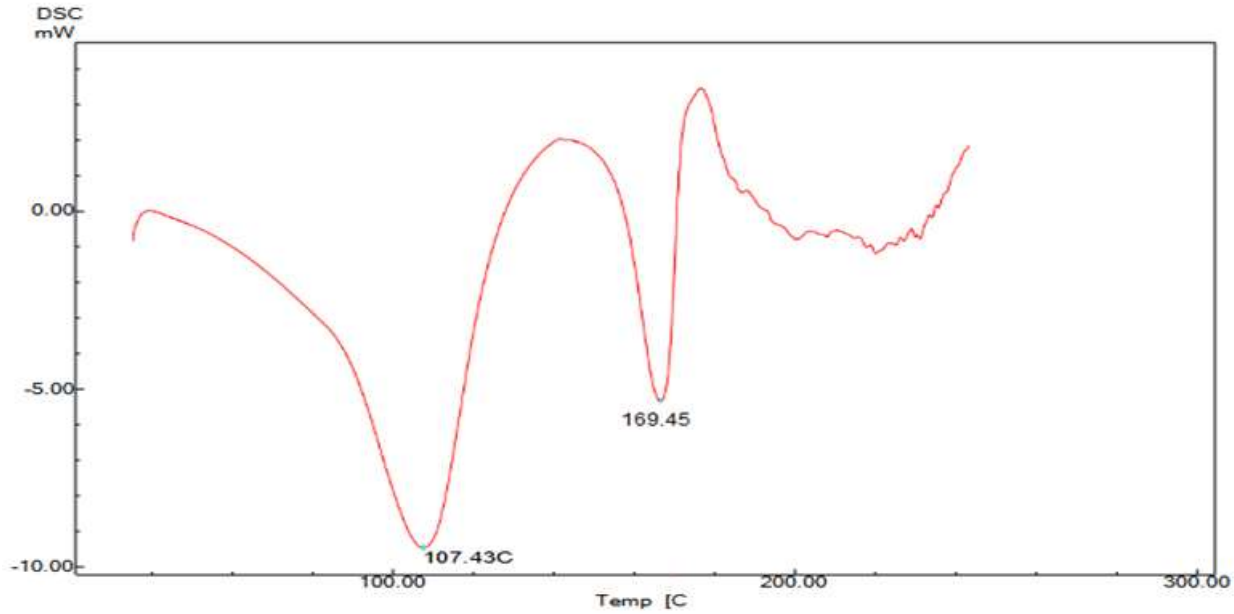

Figure 8. Differential scanning calorimetry of physical mixture of Isradipine and β-CD.

Conclusion

The study found that SFE provided an important pediatric dosage form for the oral water-insoluble drug. SFE that was prepared from Corn oil, β-CD was an encouraging method for improving the dissolution rate and solubility of Isradipine. It could be a prototype for developing other hydrophobic drug formulations using surfactant-free emulsion drug delivery systems.

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Conflicts of Interest

The authors declare that they have no conflicts of interest related to this work.

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Ethics Statements

This research did not use in vivo study.

Author Contribution

Study conception and design: Zahraa M.; data collection: Zahraa M.; analysis and interpretation of results: Zahraa M.and Fatima J.; draft manuscript preparation: Zahraa M.and Fatima J. All authors reviewed the results and approved the final version of the manuscript.

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تحضير وتوصيف الأسرادبين كمستحلب خال من المادة المستحلبة

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الخلاصة

الإسراديبين هو الدواء الفموي المفضل لعلاج ارتفاع ضغط الدم الشديد وأزمات ارتفاع ضغط الدم الطارئة عند الأطفال .ينتمي الدواء للأدويه المصنفه من الدرجة الثانية حسب نظام تصنيف الصيدلانيات البيولوجي. التوافر البيولوجي له منخفض بحوالي١٥-٢٤٪. هدفت الدراسة لتحضير أزرادبين مستحلب زيت في ماء خال من الموادالمستحلبة، منخفض السمية، صديق للبيئة ، للإسراديبين للمرضى الأطفال، وتحسين دقة الجرعة حيث تحدث الجرعة غير الدقيقة عن طريق سحق الأقراص. في هذة الدراسة حضر المستحلب الخال من المادة المستحلبه للأسرادبين لحماية الدواء الاستيري

من التحلل المائي والأكسدة والحساسية للضوء، وزيادة قابلية ذوبانه وامتصاصه، وبالتالي تحسين توافره البيولوجي. أستخدمت الدراسة مجموعة متنوعة من الزيوت لتذويب إالاسرادبين، بما في ذلك زيت السمسم وزيت الزيتون وزيت عباد الشمس وزيت اللوز وزيت الصويا وزيت الكانولا وزيت بذور العنب وزيت بذرة القطن وزيت الأفوكادو وزيت الذرة ومن بين هذه الزيوت، تم اختيار زيت الذرة وزيت بذور العنب لاستخدامها في تحضير المستحلب لخالي من المواد للأسرادبين. المستحلب الخال من المادة المستحلبة يستحلب بعدة نسب من البيتاسايكلودكسترين لتغليف جزيئة الزيت. تم تحضير اثني عشر تركيبة وتم تقييمها للصفات الحسية، ودراسة الاستقرار الديناميكي الحراري، واختبار التخفيف، وتحديد اللزوجة، وقياس الأس الهيدروجيني، ومحتوى الدواء، وتحديد حجم الجزيئات، ودراسة تحرر الدواء في المختبر. من بين جميع تركيبات المستحلب الخالي من المواد المستحلبة المحضرة، تم اعتبار التركيبة F3، التي تحتوي على ٨ جرام من البيتا سايكلودكسترين كجسيمات صلبة و ١٥ جرام من زيت الذرة ،هي التركيبة المثلى وكان لها حجم الجزيئات الصغر بمدى ١٤٥١ ± ٠,٠١ نانومتر، ودرجة حموضة معتبرة، وخصائص حسية جيدة، ودراسات استقرار ديناميكي حراري ممتازة، ولزوجة مقبولة (١٨٦٩,٥ ± ١,٥٤)، ونسبة محتوى دواء كبير والمعدل الأعلى لتحرر الدواء في المختبرمقارنة مع بقية التركيبات . تم بعد ذلك إخضاع F3 لدراسة توافق الدواء والسواغات بواسطة التحليل الطيفي بالأشعة تحت الحمراء بتحويل فوريه ,المجهر الإلكتروني الماسح و مسعر المسح التفاضلي. أشار التحليل الطيفي إلى حدوث معقد بين الدواء داخل قطرات الزيت و البيتا سايكلودكسترين بينما يظهر المجهر الإلكتروني الماسح الشكل الكروي للقطرات الكروية من زيت الذرة التي تحيط بها البيتا سايكلودكسترين .

الكلمات المفتاحية: بيتاسايكلودكسترين، زيت الذرة، زيت بذور العنب، ضغط الدم عند الأطفال، مستحلب بيكرنك، المستحلب الجاف الخال من المادة المستحلبة.