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Chitosan-based dry oral emulsion for isradipine delivery: Eco-friendly and surfactant free approach

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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 the Biopharmaceutics classification system (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 it from hydrolysis, oxidation, photosensitivity, increasing its solubility and absorption, thereby improving its bioavailability. The study used corn and grape oil to prepare SFE for solubilizing Isradipine. The SFE was stabilized by different concentrations of Chitosan. Eight formulas were prepared using a homogenizer and mixed for 5 minutes at 10,000 rpm and 25ºC. The SFE formulas were evaluated and among all the prepared SFE formulas, F4 containing Chitosan 1% and 15g of Corn oil was chosen as the optimum SFE formula due to its small particle size range of 1451±0.01 nm, respectable pH, good organoleptic attributes, excellent thermodynamic stability, acceptable viscosity 1869.5±1.54 mg/ml, acceptable drug content percentage, and highest dissolution rate. F4 was further tested for Scanning Electron Microscopy (SEM). The study found that SFE provided an important pediatric dosage form for the oral water-insoluble drug.

KEYWORDS: Pickering emulsion; surfactant free emulsion (SFE); chitosan; corn.

1. 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]. HTN is also widespread in Iraqi children who have diabetes type 1[2] and dyslipidemia among Iraqi teenagers [3].

Pediatric patients have unique pharmacokinetics, pharmacodynamics, administration routes, toxicity, and taste preferences compared to adults, necessitating 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. Therefore, it is 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 categories, ease of administration, The excipients used in the formulation are safe, covering the undesirable taste, easy production, elegant, stable, and cost-efficient manufacturing [5].

Liquid oral dosage forms have many advantages in pediatric as well as infant patients due to their greater dose flexibility and ease of swallowing [7]. Emulsions are dispersions of two thermo-dynamically unstable-immiscible liquids that need to be stabilized by surfactants [8]. However, synthetic emulsifiers in these systems can cause problems in the patient's health in addition to toxic excipient symptoms with prolonged use. Clinical tests show that anionic emulsifiers may attach to proteins, or enzymes, or even

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membranes' phospholipids, leading to adverse effects such as dysfunction in this enzyme, modification of protein, and phospholipid changes in the membrane of the human cell [9].

Pickering emulsion is a 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 good stability, excellent biocompatibility, and environmental friendliness [10].These non-toxic, biocompatible, and biodegradable stabilizers are edible, natural substances, readily available and inexpensive. This unique structure for SFE endows them with good stability, excellent biocompatibility, and environmental friendliness [10].

Liquid emulsion offers several advantages over other dosage forms, including improved oral bioavailability, but it exhibits a lack of physicochemical stability. Dry emulsion formulations are a promising solution to these challenges [11].

Dry emulsions are prepared by using lyophilization, this process prolongs shelf-life by shielding the drug from oxygen, light, and water. Dry emulsions are also easier to handle and storage than liquid emulsions [12].

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 per kg/dose for each 8hr up to a maximum dosage of 5mg [13]. According to the biopharmaceutical classification system BCS, it's a class II [14].

The study aims to create a stable, eco-friendly, and oral O/W surfactant-free dry emulsion (SFDE) of Isradipine for pediatric patients, protecting it from hydrolysis, oxidation, and photosensitivity, and increasing its solubility and absorption.

2. RESULTS

2.1. Solubility study

The choice of the oil phase for SFE of Isradipine should be based on the highest Isradipine solubility in oil to obtain stable formulas with high drug miscibility and superior drug loading [15]. Table 1 showed that the Corn oil had a maximum solubility for Isradipine powder 4.9 mg/ml compared with the other oils used in the solubility test. For this reason, Corn oil was chosen for preparing SFE of Isradipine as an oil phase.

Table 1. Saturation solubility of Isradipine powder in various oils (mean ± SD, n= 3).

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

2.2. Evaluation of the prepared SFE

2.2.1. Evaluation of organoleptic attribute

All formulations freshly prepared have a brownish-white color. 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 by using only water.

2.3. Thermodynamic stability studies

2.3.1. Intrinsic Stability

The study found that F1 exhibits 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. This is due to the irreversible adsorption of Chitosan on the oil droplets, leading to completely covering them and preventing the oil droplets from aggregating and enhancing the stability of the emulsion. F1 had a low

concentration of Chitosan, the oil droplets will be uncovered entirely, leading to aggregate them and form the unstable emulsion [16].

2.4. Accelerated stability studies

2.4.1. Heating-cooling cycle

This study aims to evaluate the stability of the formulation under various storage temperatures and ensure the system remains dispersed with no separation [17]. All formulas pass this test except F5; thus, only the formulations that are still stable will be subject to further studies.

2.4.2. Freeze-thaw test

Freeze-thaw 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 [18]. F5 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 F5.

2.5. Viscosity determination

The viscosity range of the investigated formulas is 1157-526 mP, as shown in Table 2. The viscosity study found that when the concentration of Chitosan increases from 0.5-1w/w in formula, the viscosity of formula will increase due to extra particles building a network structure surrounding each droplet, enhancing emulsion viscosity and stability [19].

Formulas F6, F7 and F8 had more viscous emulsions than the formulas F2, F3 and F4, respectively, due to have a higher oil content and as the volume of oil increased, the emulsified oil droplets also increased, which caused a decrease in the aggregation of oil droplets and resulted in smaller droplet sizes; this increased the interfacial area permeating for further article interaction and increased emulsion viscosity [20].

2.6. Particle size determination

The investigated formulas have a particle size ranging from 1010-2509 nm, as shown in the Table 2. This variation is attributed to the concentration of Chitosan and amount of oil. The formulas contain a lower Chitosan concentration had larger particle sizes than formulas contain a higher Chitosan concentration, with the same amount of oil. This increase in particle size by decreasing surfactant concentration can be explained by the partial coverage of oil droplets by solid particles, leading to coalescence and large droplets [16].

Formulas F6, F7, and F8 had larger particle sizes than F2, F3, and F4, respectively, with the same concentration of Chitosan due to higher oil content. Increasing oil volume, leading to insufficient chitosan particles to cover oil droplets leading to droplet coalescence and droplet size increase [16].

Table 2. Viscosity (mP) and Mean droplet size of Isradipine SFE (mean ± SD, n= 3)

F. NO.	Viscosity (mP)	Mean droplet size(nm)
F2	526±1.62	1825±0.1
F3	654±1.54	1451±0.01
F4	847±1.38	1010±0.3
F6	908 ± 1.64	2509±0.02
F7	969± 1.42	2154±0.1
F8	1157± 1.36	1918±0.05

2.7. pH measurement

The formulas under investigation have a pH range 6.2-6.7. The acceptable range of pH for oral solutions is 2-9, therefore, all formulations have accepted pH values [21].

2.8. Determination of drug content

The tested formulas of SFE of Isradipine had a drug content exceeding 95%, and there were no significant differences in drug content among formulations ($p > 0.05$). So, all the prepared formulas of SFE of

Isradipine showed an acceptable drug content within the range specified by British pharmacopeia (95.0%-105.0%), indicating a good drug distribution in a formula without precipitation [22].

2.9. In vitro drug release

The study reveals a flexible duration time for Isradipine release from each formula, with F4 completely releasing Isradipine after 90 minutes, while F2, F3, F6, and F8 took more than 120 minutes without completing the release. Pure Isradipine at the end of 120 minutes showed only 15.4% of Isradipine was released, as illustrated in Figure 1.

The percentage of drugs released from SFE of Isradipine formulation increased with the increase in the Chitosan concentration, which led to decreased particle size, resulting in an increased surface area for drug transfer, which enhances drug release absorption and overall promotes drug bioavailability [23].

As the percentage of oils increased in the SFE of Isradipine formulation, there was a decrease in the percentage of drugs released in F6, F7, and F8 compared to F2, F3 and F4. These findings suggest that Isradipine released more from formulas with lower oil content because these formulations have a lower viscosity [15].

Pure Isradipine showed the lowest release at the end of 120 minutes due to its practically insoluble [14].

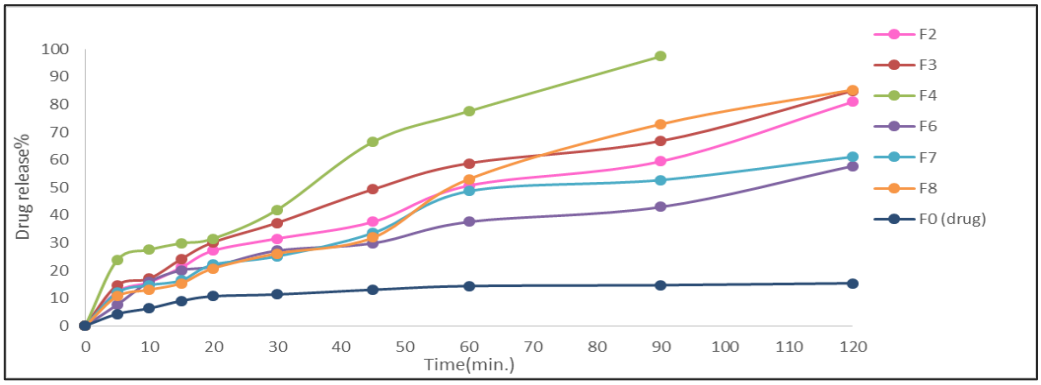

Figure 1. A comparative dissolution profile of Isradipine SFE (F2, F3, F4, F6, F7, F8, and F0) in pH 0.1N HCl with SDS 1%w/v and 250ml volume of dissolution medium at temperature 37 ± 0.5°C.

2.10. Selection optimum Isradipine surfactant free emulsion

Based on previous results, F4 was chosen as the optimum formula for Isradipine SFE because it had a particle size range of 1010±0.03 nm, respectable pH, good organoleptic attributes, excellent thermodynamic stability, acceptable viscosity of 847±1.38 mP, great % of drug content and 100% of Isradipine release in 90 minutes. F4 underwent additional studies.

2.11. Evaluation of selected optimum Isradipine lyophilized surfactant free emulsion

2.11.1. Flow Properties

The flow properties of the selected SFDE formula illustrates in the Table 3, and indicate that the SFDE of Isradipine has passable flowability and poor compressibility [24]. These flow properties are typical for powder with lipophilic core material and have previously been observed in dried oil-based powders [25].

Table 3. The Flow Properties of surfactant free dry emulsion of Isradipine (mean ± SD, n= 3).

Parameter	Result
Angle of repose	34.01 ± 0.015
Bulk density(g/cm3)	0.39 ± 0.024
Tapped density(g/cm3)	0.54 ± 0.014
Carr's index %	27.074 ± 0.163
Hausner's ratio	1.37 ±0.005

2.11.2. Scanning electron microscopy (SEM)

The SEM shows the spherical shape of spherical droplets of Corn oil that are surrounded by Chitosan as illustrated in Figure 2. SEM analysis revealed the absence of drug crystals, indicating complete Isradipine solubilization in the SFE [26].

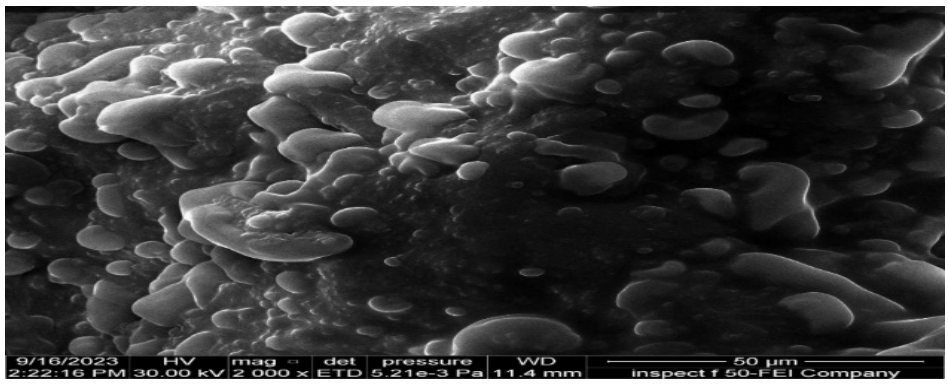

Figure 2. SEM for SFDE formula (F4).

3. CONCLUSION

The study found that surfactant free dry emulsion (SFDE) offered a promising pediatric dosage form for oral administration of water-insoluble drugs. SFDE prepared with Corn oil and Chitosan proved to be an effective method for enhancing the dissolution rate and solubility of Isradipine and could serve as a model for developing other hydrophobic drug formulations using SFDE.

4. MATERIALS AND METHODS

4.1. Materials

Isradipine was procured from China's Hyper-Chem Company. Chitosan obtained from Alpha Chemika, Mumbai, India. Olive oil is provided by Oilex, SA. Spain's Pomace of Olive oil. Almond oil, in addition to Avocado oil, got from Now (USA). Corn oil, Grape seed, Sesame oil, Sunflower, Soybean oil, Canola oil, and Cotton seed have been bought from China's "Shaanxi Guanjie Technology CO, LT". HCl purchase from Avantor Performance Materials. Sodium Dodecyl Sulfate (SDS) was purchased from Panreac Barcelona, Spain. Methanol was obtained from Sigma-Aldrich, Germany. Deionized water obtained from Alshumue, Baghdad, Iraq.

4.2. Methods

4.2.1. Isradipine solubility study

Isradipine's saturated solubility was tested in various oils: Sesame oil, Olive, Sunflower, Almond oil, Soybean oil, Canola oil, Grape seed, Cotton seed, Avocado oil, and Corn oil. To measure the solubility, in a small 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 (Karlkob gfl- Germany) for 48 h and at 25 ± 0.5 °C. After that, these tubes were put in a centrifuge (Hettich-Germany) 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 326nm by a spectrophotometer (Shimadzu 1800 UV/VIS spectrometer) [27, 28].

4.2.2. Preparation of Chitosan Solutions:

A Stock solution of chitosan with a 1.5w/v % was prepared. Firstly, an acetic acid solution of 1.5% v/v was prepared. Secondly, 1.5 g of Chitosan was slowly dissolved in an acetic acid solution and then continuously stirred at 500 rpm overnight. Then, the mixture was filtered to remove impurities using filter paper. Finally, the pH of the chitosan solution was adjusted to about 6-6.5 by using NaOH. Different Chitosan solutions with concentrations of 0.25, 0.5, 0.75, and 1% w/v were prepared by diluting from the stock solution of 1.5% w/v [26].

4.2.3. Formulations of surfactant-free emulsions of Isradipine

Isradipine SFE was prepared by using Chitosan in different concentrations as stabilizers instead of surfactants with a selected oil based on a solubility study (oil phase), as shown in Table 4. Isradipine's dose 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 2.5 mg of Isradipine was dissolved in the selected oil phase, while in another beaker mixed the specialized amount of Chitosan with deionized water (as the aqueous phase), then while continuously mixing the aqueous phase by using a homogenizer (Witeg HG-15D), dropped the oil phase containing drug slowly on it then the homogenizer still mixed for 5 minutes at 10,000 rpm at 25ºC to obtain surfactant free o/w emulsion [19, 26]. As shown in the Table 4.

The selected formula was lyophilized with 15g of Mannitol by using a drying system (Labconco, USA) to obtain SFDE [29].

Table 4. Components of Surfactant free emulsion for Isradipine.

F. NO.	Chitosan(g)	Corn oil(g)o	Water (g)
F1	16.67 (0.25%)	15	68.33
F2	33.34 (0.5%)	15	51.67
F3	50 (0.75%)	15	35
F4	66.67 (1%)	15	18.33
F5	16.67 (0.25%)	20	63.33
F6	33.34 (0.5%)	20	46.66
F7	50 (0.75%)	20	30
F8	66.67 (1%)	20	13.33

4.2.4. Evaluation of the prepared SFE

Assessment of organoleptic properties

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 [30].

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].

Intrinsic Stability

Ten mL of the emulsions prepared were stored in tubes fixed vertically under ambient conditions and evaluated for the presence of instability phenomena after 1, 2, 4, 6, and 24 h of preparation [31].

4.2.5. Accelerated Stability Studies:

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 stability of formulation was examined at each temperature [32].

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 [33].

4.2.6. Viscosity measurement

The viscosity of a prepared SFE formula was measured for a non-diluted freshly prepared formula by using a digital viscometer (NDJ-5S, China) with a spindle NO. 4, which was inserted into a glass beaker at speed 60 rpm [34].

4.2.7. Particle size determination

The SFE's mean. the particle size of SFE was determined by zetasizer (Malvern zetasizer ultra, Britain) by taking the angle of detection at 90^{o} and 25 ^{o}C, after being diluted fivefold with double-deionized water before measurements [29].

4.2.8. pH measurement

The measurement of pH was done by using a pH meter. Glass electrode was dipped in SFE emulsion and the reading was noted [35]. The measurement was repeated three times for each sample and the result was presented as mean ±SD.

4.2.9. Determination of drug content

The drug content determination was done by weighted 5 g of SFE formula, which was equivalent to 2.5 mg of Isradipine after that added to 100 ml of Ethanol and ensured dissolved, then filtered by filter syringe 0.45 µm and scanned at λ max of Isradipine in Ethanol 326nm by a spectrophotometer [14].

4.2.10. In-vitro dissolution study of Isradipine SFE

By using USP dissolution apparatus type II (Coley dissolution 8000-UK) with 250 ml of dissolution medium had a pH 0.1N HCl with SDS 1%w/v and paddle rounded at speed 50 rpm and temperature 37 ± 0.5°C, the dissolution was done for 5mg of Isradipine SFE equivalent to 2.5 mg of Isradipine deposited it in a dialysis bag and tighten. At specific time periods (5, 10, 15, 20, 45, 60, 90, and 120 min.) 5ml was drawn from dissolution media in the apparatus and recompensed by 5ml of 0.1N HCl with SDS 1%w/v. each drown was scanned at λ max of Isradipine in 0.1N HCl with SDS 1%w/v 332 nm by a spectrophotometer; the same thing was done for pure Isradipine powder [28, 36].

4.2.11. Selection optimum Isradipine surfactant free emulsion

The best formula of Isradipine SFE was selected according to the results that are obtained from the evaluation tests that included intrinsic stability, drug content, pH, particle size, viscosity, accelerated stability, and in vitro release study. Then, this formula will be dried by lyophilization to form surfactant free dry emulsion (SFDE)

4.2.12. Evaluation of selected optimum Isradipine lyophilized surfactant free dry emulsion

Flow Properties

These properties were determined in terms of angle of repose, Bulk density, Tapped density, Carr's index, and Hausner's ratio for the SFDE formula.

Determination angle of repose

This method known as the fixed funnel method, was used to evaluate the ability of the drug powder to flow. using a funnel fitted on a holder and far from the surface about 2 cm allowed the Isradipine powder to pour through the funnel until the cone formed touched the end of the funnel then the radius of the cone base was measured. After that, the following rule was applied to find the angle of repose. The angle of repose (Tan Ø) is equal to the height from the surface to the vertex of the cone subdivided by the radius of the base cone [37].

Bulk density and Tapped density

To measure the bulk density, firstly a specific weight of drug powder was weighed and transferred to a 50 ml graduated cylinder and recorded the volume of the powder in it. Finally, must be applied the rule of subdividing the weight of the Isradipine powder over the volume recorded to calculate the bulk density in g/ml [38].

To calculate the tapped density in g/ml, the graduated cylinder containing a specific weight of powder was tapped about 50 times, and recording the volume of powder reached then applied the rule of subdividing the weight of the Isradipine powder over the tapped volume [38].

Carr's index (compressibility index) and Hausner's ratio

Carr's index is a percentage difference between the tapped density and bulk density divided by the tapped density.

Hausner's ratio is the ratio of tapped density divided by the bulk density [25].

Scanning electron microscopy (SEM)

By Scanning electron microscope, the morphological features including (shape and surface characteristics) of SFE were evaluated [28].

4.2.13. Statistical analysis

The experimental results were expressed as a mean triplicate sample ± standard deviation (SD) and were analyzed according to one-way analysis of variance (ANOVA) using SPSS software at which the results would be significant when $p < 0.05$, and the results would be non-significant if $p > 0.05$.

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