Formulation of Cefdinir Ternary Solid Dispersion and Stability Study under Harsh Conditions

Naamaa A. Naama *, Ghaidaa S. Hameed*, Dalya Basil Hanna **, Zainab H. Mahdi***
Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.
****Department of Clinical Laboratory Sciences, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.***
*****Department of pharmaceutics, College of Pharmacy, Applied science private university, Amman, Jordan.***

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Corresponding Author email:
ghaidaahameed@uomustansiriyah.edu.iq
Orcid: https://orcid.org/0000-0003-1470-6808

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Abstract:

Cefdinir (CEF) is classified as a third-generation cephalosporin within class IV of the Biopharmaceutical Classification System (BCS). Cefdinir has low solubility and permeability, which may reduce oral bioavailability.

The aim of this research was the preparation of cefdinir ternary solid dispersion in order to enhance its solubility. Then, after evaluating this ternary SD, investigate its stability under harsh conditions. In addition, formulation and evaluation of CEF ternary SD as capsule dosage form. The ternary SD is prepared by the solvent evaporation method using CEF, curcumin, and polyvinylpyrrolidone k30 in a weight ratio of 1:1:1. The ternary SD is subject to evaluation using Differential Scanning Calorimetry (DSC), Powder X-ray Diffractometry (PXRD), and Fourier Transform Infrared Spectroscopy (FTIR), saturated solubility, release, antibacterial activity, and a two months stability study under conditions of 40 ºC and 75% relative humidity. Then, six different capsule formulas were prepared using different excipients; each formula contained 300 mg of CEF. The capsule formulas were subjected to pre-formulation and capsule evaluation tests, which included weight variation, drug content, disintegration time, and *In-vitro* dissolution tests. The selected optimum capsule formula was subjected to further antibacterial activity test. Evaluation of ternary SD showed that, the system is totally amorphous with enhanced dissolution, saturated solubility, and antibacterial activity compared to pure CEF. Stability studies showed that, ternary SD remains amorphous after two months. Compared to commercial capsules (Sefarin® 300 mg) and other formulas, the F6 formula released 90% of CEF in 30 min. Antibacterial activity test results showed that the F6 formula was active against Staphylococcus aureus and Proteus vulgaris bacterial isolate. This research concludes that CEF solubility, antibacterial activity enhancement, and stability insurance could be obtained by preparing CEF ternary SD. All the ternary SD prepared capsule formulas showed enhancements in release compared to commercial capsules.

Keywords: Cefdinir, Ternary solid dispersion, Polyvinylpyrrolidone k30, Stability, Capsule.

صياغة السفدينير المشتت الثلاثي الصلب ودراسة الثباتية تحت الظروف القاسية

نعماء عدنان نعمة*, غيداء سليمان حميد*, داليا باسل حنا , زينب حسن مهدي العبيدي*****
**فرع الصيدلانيات، كلية الصيدلة، الجامعة المستنصرية، بغداد، العراق.*
***فرع العلوم المختبرية السريرية، كلية الصيدلة، الجامعة المستنصرية، بغداد، العراق.*
****فرع الصيدلانيات، كلية الصيدلة ، جامعة العلوم التطبيقية الخاصة، عمان، الاردن.*

الخلاصة:
يتم تصنيف سيفديني رباعتباره أحد السيفالوسبورينات من الجيل الثالث ضمن الفئة الرابعة من نظام تصنيف الأدوية الحيوية. يتمتع سيفديني بقابلية ذوبان ونفاذية منخفضة، مما قد يقلل من التوافر البيولوجي عن طريق الفم. الهدف من هذا البحث هو تحضير سيفديني المشتت الصلب الثلاثي من أجل تعزيز قابليته للذوبان. ثم، بعد تقييم نظام المشتت الثلاثي الصلب هذا، التحقق من استقراره في ظل ظروف قاسية. بالإضافة إلى ذلك، تم صياغة وتقييم مادة سيفديني المشتت الثلاثي الصلب كجرعة كبسولة. يتم تحضير المشتت الثلاثي الصلب بطريقة التبخر بالمذيبات باستخدام سيفديني، كركمين، والبولي فينيل بيروليدون k30 بنسبة وزن 1:1:1. يخضع المشتت الثلاثي الصلب للتقييم باستخدام قياس سعرات المسح التفاضلي، وقياس حيود مسحوق الأشعة السينية، ومطياف فورييه لتحويل الأشعة تحت الحمراء، والذوبان المشبع، والتحرر، والنشاط المضاد للبكتيريا، ودراسة الاستقرارية لمدة شهرين في ظل ظروف 40 درجة مئوية و75% رطوبة نسبية. بعد ذلك، تم تحضير ستة صيغ كبسولة جلاتينيه صلبة مختلفة باستخدام سواغات مختلفة؛ تحتوي كل تركيبة على 300 ملغ من سيفديني. خضعت تركيبات الكبسولات لاختبارات ما قبل الصياغة وتقييم الكبسولة، والتي شملت اختلاف الوزن، ومحتوى الدواء، ووقت التحلل، واختبارات الذوبان في المختبر. تم إخضاع تركيبة الكبسولة المثالية المختارة لمزيد من اختبار النشاط المضاد للبكتيريا. أظهر تقييم المشتت الثلاثي الصلب أن النظام غير متبلور مع زيادة الذوبان والذوبان المشبع والنشاط المضاد للبكتيريا مقارنة بالسيفديني النقي. أظهرت دراسات الاستقرار أن المشتت الثلاثي الصلب يظل غير متبلور بعد شهرين. بالمقارنة مع الكبسولات التجارية (Sefarin® 300 mg) والتركيبات الأخرى، فإن تركيبة F6 تطلق 90% من سيفديني في 30 دقيقة. أظهرت نتائج اختبار النشاط المضاد للبكتيريا أن تركيبة F6 كانت فعالة ضد العزلة البكتيرية للمكورات العنقودية الذهبية والمتقلبة الشائعة. يخلص هذا البحث إلى أنه يمكن الحصول على قابلية ذوبان سيفديني وتعزيز النشاط المضاد للبكتيريا وتأمين الاستقرار من خلال تحضير سيفديني المشتت الصلب الثلاثي. أظهرت جميع صيغ الكبسولات المحضرة تحسينات في الإطلاق مقارنة بالكبسولات التجارية.

الكلمات المفتاحية: سيفديني، المشتت الصلب الثلاثي، بولي فينيل بيروليدون، الثباتية، كبسولة.

Introduction

Most active pharmaceutical components are insoluble (1), leading to bioavailability problems (2). A number of strategies have been developed to increase the solubility, dissolution, and bioavailability of active pharmaceutical compounds (3). These strategies include cyclodextrin complexes, solid dispersions, co-crystal, nanocrystals, and salt production (4, 5).

Amorphous solid dispersions (ASDs) are widely used to enhance the solubility an d bioav-ailability of water insoluble drugs (6, 7). Hydrophobic active pharmaceutical ingredients (APIs) are dispersed in a hydrophilic polymeric matrix to form ASD in a solid state (8, 9) Enhancing wettability, particle size, prevention of aggregation, and drug conversion from crystalline to amorphous phase are all key components of enhancing solubility (10, 11).

Through the use of a polymeric carrier such as PVP and soluplus (12) and the binary solid dispersion approach, APIs are transformed into an amorphous state (13), ternary solid dispersion (TSD), on the other hand, is the solid dispersion of an active agent in two components when they are both solid. To improve solubility and stability, the third component might be an additional polymer, surfactant, excipient, suitable medication, or carrier (14). Tian et al. found that the third component may significantly improve the physical stability of SDs by serving as a linker between the drug and polymer (15). Xiangjun Shi et al. study how polymers and drug-polymer(s) interactions increase telmisartan (TEL) ternary solid dispersions' stability and bioavailability. Solvent evaporation created TEL amorphous solid dispersions with PVP K30 and/or Soluplus at various concentrations. TEL-PVP K30–Soluplus

ternary solid dispersions had higher dissolution (over 90% release at 60 min), better amorphous stability (physically stable in 90 days), and better oral bioavailability than pure TEL and TEL-PVP K30/Soluplus binary solid dispersions (16). Curcumin is a hydrophobic polyphenol that has various properties, including anti-inflammatory, antioxidant, anticarcinogenic, and antimicrobial (17) with a low molecular weight of 368.39 g/mol (18).

Some studies have previously demonstrated that curcumin potentiates the effects of chemical antibiotics against bacteria strains (19).

The third generation oral cephalosporin a ntibiotic Cefdinir (CEF) is categorized as semisynthetic and exhibits broad antibac terial activity against both gram positive and gram-negative bacteria (20, 21). Its medicinal uses include treating urinary tract infections and upper and lower respiratory tract infections (22). Besides being very good at killing *Staphylococcus aureus* and *Streptococcus pneumoniae*, CEF also kills *Streptococcus pyogenes*, *Escherichia coli*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, and *Enterobacter aerogenes* (23). Cedinir belongs to BCS class IV (24) and has an elimination half-life of 1.7 h (25). This weakly acidic drug (26) has a pKa of 8.70 (27) with log P of −1.52 (28), and pH-dependent water solubility, has low oral bioavailability (16%–21%) (29). Cefdinir has a volume of distribution (Vd) of 1.6-2.1 L/kg and T max 3 h (30) while Cmax were 1.6 mg/L, CEF undergoes minimal hepatic metabolism and is excreted via the renal system, renal clearance was ≈2 mL/min/kg following single oral doses (31).Cefdinir soluble in different solvents include methanol, ethanol, n-hexane, dichloromethane, and Dimethyl Sulfoxide (32) Cefdinir has a chemical name of [6*R*-[6α,7β(*Z*)]]-7-[[(2-amino-4-thiazolyl)(hydroxyimino) acetyl] amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo [4.2.0]-oct-2-ene-2-carboxylic acid (33), the structure of CEF is seen in Figure (1) There are two marketed dosage forms of CEF: capsule (300mg), oral suspension (125mg/5mg and 250mg/5ml) (34).

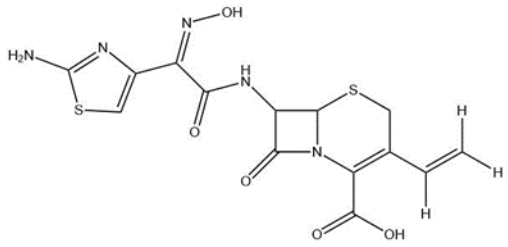


Figure (1): Cefdinir structure

A lot of work has gone into improving cefdinir solubility. They included micronization and amorphousization of CEF, which can be made by dissolving CEF in methanol and evaporating the solvent to get the powder. To compare the size effect, spray-drying (SD) and supercritical anti-solvent (SAS) were used to prepare amorphous cefdinir (35). Simple solid dispersion of CEF was achieved by solvent evaporation with a varied PVP K–30 and sodium lauryl sulfate (SLS) ratio then the optimized SD was then formulated as fast disintegrating

tablets (36). Cefdinir solid dispersions were also made by spray-drying method using polyvinylpyrrolidone K30 (PVP K30), carboxymethylcellulose-Na (CMC-Na), and hydroxypropylethylcellulose (HPMC) at a weight ratio of 1:1 (drug:polymer) (37). Cefdinir complexed with cyclodextrins (33), which raised drug solubility in tablets compared to CEF alone (23). Niosomal encapsulation and nanosuspension have enhanced the solubility and oral bioavailability of cefdinir (24, 34). Moreover, loading cefdinir onto nanographene oxide sheets boosted dissolution with hydrophilic polymers (38).

The use of ternary solid dispersion system consists of cefdinir, curcumin and PVP for enhancing the solubility, release and antibacterial activity of cefdinir can provide another promising strategy which has not been tested before. However, this study aimed to enhance cefdinir solubility by ternary SD system, ensure ternary SD stability and then filled the ternary SD in hard gelatin capsules with different excipient.

Materials and Methods

Materials

Cefdinir (Hubei widely Chemical Technology Co.,Ltd, China), Polyvinylpyrrolidone K30 (PVP) (HiMedia Laboratories, India), Turmeric curcumin (Xi'an Sonwu Biotech Co.,Ltd, China), Croscarmellose sodium (H.L. Blachford Ltd, Mississauga, ON, Canada), Microcrystalline cellulose (JRS Pharma, Rosenberg, Germany), Talc (Alladin Industrial Co., Shanghai, China), Lactose (Alpha Chemika, India), Hydrochloric acid (HCl) (Thomas Baker (Chemicals) Pvt. Ltd, India). Methanol (Sisco research Laboratories Pvt. Ltd, India).

Methods

Preparation of solid dispersion formulas

By using solvent evaporation method (39-41), Cefdinir, curcumin and PVP in a molar ratio of 1:1:1 (250 mg of each component) were dissolved in 250 ml of methanol and evaporated using a rotating vacuum evaporator for 30 min at 50 ºC under reduced pressure (150 mbar) to create the ternary solid dispersion formula.

Determination of saturated solubility

In 0.1N HCl (pH 1.2), CEF pure drug and ternary SD saturated solubility were done in triplicate. The drug was put in an excess amount (about 25 mg) in 10 ml of the buffer. 48 h of stirring at 200 rpm at 25 °C was followed by filtration through a 0.45 m syringe filter, dilution, and UV spectrophotometer analysis at 281 nm (42).

Stability study

A stability experiment was carried out by maintaining the CEF pure drug and ternary SD at extreme temperature and humidity conditions for two months. Studies on the stability of CEF pure drug and ternary SD were conducted in incubator and desiccator at 40 ºC and 75% relative humidity (43, 44). The 75% relative humidity was achieved using a desiccator that contained saturated sodium chloride (45). Characterization by DSC, PXRD, FTIR, antibacterial activity and release study were done for each sample at zero time, after 1 and after 2 months.

Capsule pre-formulation tests

1. Angle of Repose

A fixed-height funnel is used to pour powder of each formula onto a bottom plate in the fixed funnel method. Angle of

repose is computed for each formula in the following equation (46):

$$\mathbf{Tan\emptyset = h/r} \ldots\ldots \text{eq (1)}$$

The height of the con is h, the radius of the plate is r, and Tan Ø is the tan of the angle of repose. The relation-ship between angle of repose and powder flow is shown in Table (1).

Table (1) Relation-ship between Angle of Repose and Powder Flow (47)

Angle of repose	Powder flow
< 25	Excellent
25-30	Very good
31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
> 56	Very poor

2. Compressibility Index (Carr's index) and Hausner's ratio

An initial bulk volume (V_0) of each formula powder was added to a 10-milliliter graduated cylinder, which was then constantly tapped using a standard method until a constant volume (Vt) was reached. Next, using equations 2 and 3, the Hausner 's ratio and the compressibility index were calculated (48, 49).

$$\textbf{Hausner's ratio} = V_0/V_t \ldots\ldots \textbf{eq (2)}$$

$$\textbf{Compressibility Index} = (V_0 - V_t)/V_0 \times 100 \ldots\ldots \textbf{eq (3)}$$

The relationship between flow type and the values of Carr's index and the Hausner's ratio is shown in Table (2).

Table (2) The relationship between flow type and the values of Carr's index and the Hausner ratio (50)

Carr's index	Hausner 's ratio	Powder flow
5–10	1.05–1.11	Excellent
11–15	1.12–1.18	Good
16–20	1.19–1.25	Fair
21–25	1.27–1.33	Passable
26–31	1.35–1.45	Poor
32–37	1.47–1.59	Very poor
38–45	1.16–1.82	Exceedingly poor

Capsule formulation

The powder mixture was manually filled into the hard gelatin capsules using an analytical balance (51). Since the capacity by weight of 00 size capsule according to the powder density is 546 mg (52), the ternary SDs and excipient powder combination were placed into two hard gelatin capsules of 00 size. The talc use was as a glidant while lactose was used as a diluent, Croscarmellose sodium used as a superdisintegrant, and Microcrystalline cellulose was used as a filler. Each capsule's formulation components is shown in the following Table (3):

Table (3): Composition capsule Formulas of CEF

Components (mg)	F1	F2	F3	F4	F5	F6
Cefdinir, curcumin and PVP	900	900	900	900	900	900
Talc	70	70	70	70	70	70
Lactose		50	70	30		100
Croscarmellose sodium		50	30	70		
Microcrystalline cellulose pH 101					100	
Total weight of each formula	970	1070	1070	1070	1070	1070

Evaluation of the physical properties of capsule

1. Weight Variation

The weight of each capsule was measured separately for twenty capsules, and then the average weight of the capsule was determined. The individual weights of each capsule have to be between 90% and 110% of the average weight, with the lower limit being 90% and the upper limit being 110% (53).

2. Drug content

Following the blending of ten capsules, an amount equivalent to 300 mg of drug was measured, moved to a 100 milliliter volumetric flask, dissolved in 0.1N HCl, filtered, diluted, and measured using spectrophotometry at 281 nm, concentration then amount of CEF was determined by applying equation of calibration curve which was previously constructed in 0.1N HCl (53)

3. Disintegration test

A disintegration tester (ERWEKA, USA) measured the disintegration durations of six capsules in 900 milliliters of 0.1 N HCl, pH 1.2, in a cylindrical container at 37 °C ± 0.5 °C. Jar fluid should be halfway full. Randomly insert six capsules into the basket-rack assembly's tubes. Put a plastic disk on each capsule and start the machine. Disks should lightly rub capsules. When the monitor revealed no capsule fragments or soft residue, disintegration occurred. Disintegration time was recoded as the average of three tests of each formula (n=3)(54, 55).

4. *In-vitro* dissolution study for all formulas of CEF capsules

The USP Apparatus type I (Basket) was used for all dissolution studies at 37 ± 0.5 °C. Sefarin® (marketed product of CEF) and all capsule formulas were agitated at 50 rpm in 900 ml 0.1N HCl (pH 1.2). The trail tripled. Using a 0.45 mm filter

syringe. Samples of 5 ml were withdrawn after 15, 30, 45, 60, and 120 min and replaced with warmed (37 °C) medium to maintain volume. At 281 nm samples were analyzed using a UV-Vis spectrophotometer (56).

5. Antibacterial activity of selected optimum capsule formula

In-vitro antibacterial activity of the optimal formula was evaluated against *Staphylococcus aureus* and *Proteus vulgaris* isolates using agar well diffusion. Isolated bacteria grew in nutrient broth at 37 °C for 24 h. Muller-Hinton agar was made per manufacturer directions to evaluate items for antibacterial activity. Using a sterile cotton swab, 100 µL of 1.5 x 10^9 cells/ml from each bacterial solution was placed in each petri dish. A sterile pasture pipette punctured six-mm agar medium wells (57).

Optimal formula corresponding to 300 mg of drug was dissolved in 0.1 N HCl, vortexed, then centrifuged at 13000 rpm for 5 min. Muller-Hinton agar wells received sample supernatants. The inhibition zone surrounding each well was measured after 24 h at 37°C.

Statistical analysis

The FDA-recommended model-independent drug release % approach was used to assess the dissolution profile variation between the produced formulations and the pure drug. Every research finding has been shown as means ± standard deviations (SD). The "one-way analysis of variance" (ANOVA) test, the Duncan test, and the t-test were used to do the analysis at 95% significance ($p < 0.05$). The "Statistical Package for the Social Sciences" (SPSS) version 27 for Windows was used to conduct the statistical analysis.

Results and Discussion

Determination of saturated solubility

Table (4) shows pure drug (CEF as received) and ternary SD formulation saturated solubility in 0.1N HCl. Compared to CEF, SD formulas have much higher solubility. The drug's full transition from crystalline to amorphous, as shown by DSC and XRPD (at zero time in Figure 2.b and Figure 3.b), and molecular dispersion in the hydrophilic carrier increase its solubility. Previous research supported this finding (37).

Table (4): Saturated solubility study of pure drug and ternary SD

Formulation	Saturation solubility (mg/ml)
CEF pure	1.76523 ± 0.21
Ternary SD	4.701337 ± 0.30

(Results were expressed as mean± SD, n=3)

Stability results

The DSC thermographs (Figure 2) of pure drug and ternary mixture at zero time, one and two months showed that the melting peak of pure drug (Figure 2a) still visible at the same point while in the case of ternary mixture (Figure 2b) the absence of melting peak in both conditions indicated the stability of ternary mixture in both harsh conditions.

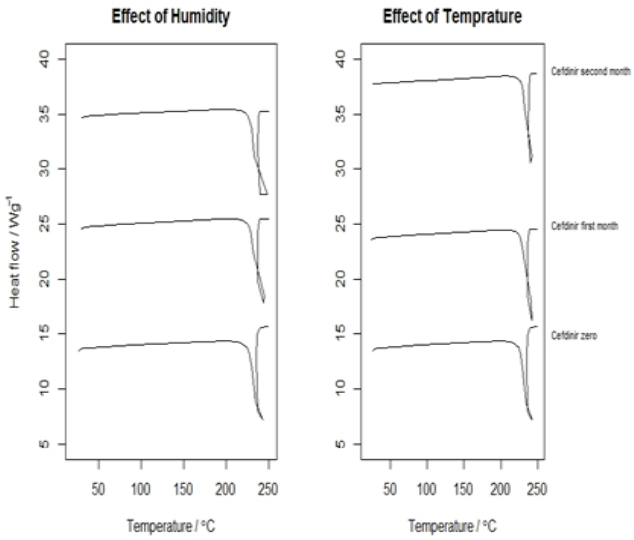


Figure (2) a. The DSC thermograph of pure Cefdinir under harsh condition (40 ºC and 75% relative humidity) at zero time then after one and two months

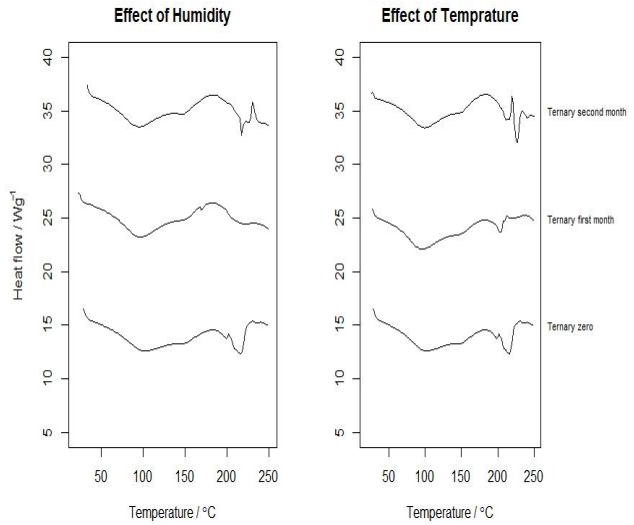


Figure (2) b. The DSC thermograph of Cefdinir ternary SD under harsh condition (40 ºC and 75% relative humidity) at zero time then after one and two months one and two months

While, Figure (3) showed the PXRD results of both pure CEF and the ternary mixture at zero time. Then after one month and two months. The pure drug (Figure 3a) showed no change in a sharp Braggs peaks along the storage period of time while the ternary mixture PXRD (Figures3b) showed amorphous hallo without any appearance of Bragg peaks indicting the stability of the ternary SD even in harsh conditions, confirming this idea. This was correlated to the previous study by Ahmad B. Albadarin et al. who examined a novel combination of hydroxypropyl methylcellulose phthalate (HPMCP-HP-50) and Soluplus® polymers to improve the physicochemical stability and solubility of Itraconazole

(ITZ) amorphous solid dispersions (ASDs). The crystalline active pharmaceutical ingredient (API) was converted to an amorphous form in ternary systems using hot melt extrusion (HME). The DSC, PXRD, and FTIR measurements indicated that the ASDs were physically and chemically stable at 20 °C and 50% RH for 12 months, indicating that the mixture was miscible therefore it was stable (58).

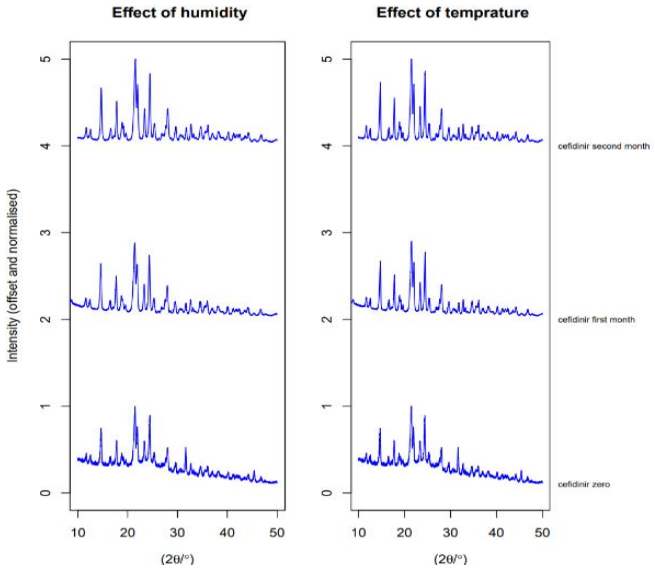


Figure (3) a. The PXRD of pure Cefdinir under harsh condition (40 ºC and 75% relative humidity) at zero time then after one and two months

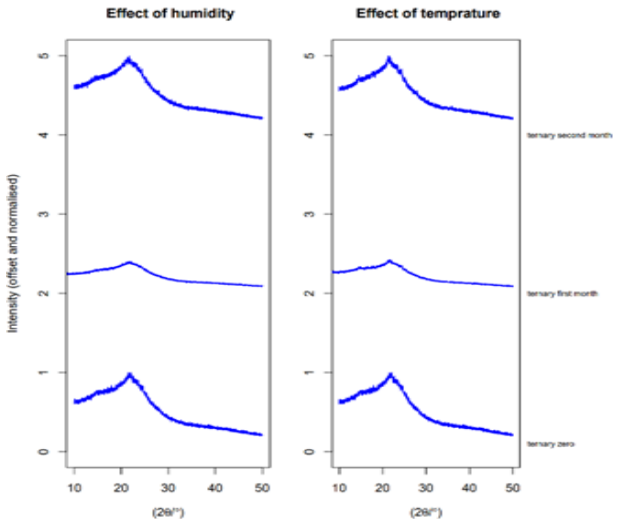


Figure (3) b. The PXRD of Cefdinir ternary SD under harsh condition (40 ºC and 75% relative humidity) at zero time then after one and two months

The FTIR as seen in Figure 4 showed the FTIR of CEF alone (Figure 4a) and in ternary mix (Figure 4b) in which there was no changing in the peaks or formation of new peaks confirming the stability of this mixture in both conditions.

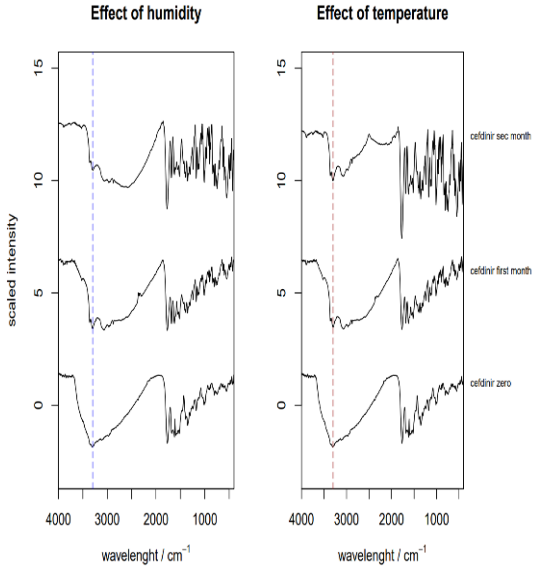


Figure (4) a. The FTIR spectrum of pure Cefdinir under harsh condition (40 ºC and 75% relative humidity) at zero time then after one and two months

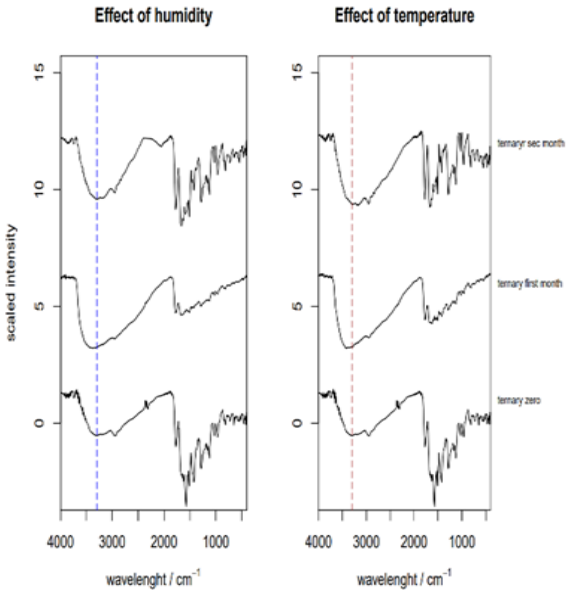


Figure (4) b. The FTIR spectrum of Cefdinir ternary SD under harsh condition (40 ºC and 75% relative humidity) at zero time then after one and two months

Figure 5 represent dissolution profile of pure drug and ternary mixture under harsh temperature and humidity condition at zero time, then after one and two

months, the dissolution profile (Figure 5a) of pure CEF and release behavior (Figure 5b) of ternary mix in both temperature and humidity investigations show non-significant ($p > 0.05$) change following two months of storage.

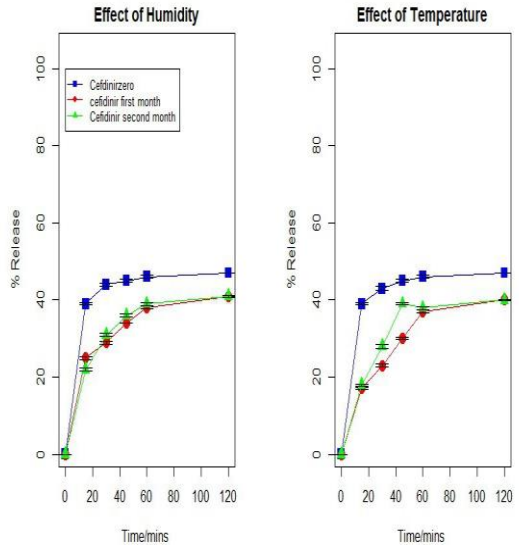


Figure (5) a. Dissolution profile of pure cefdinir

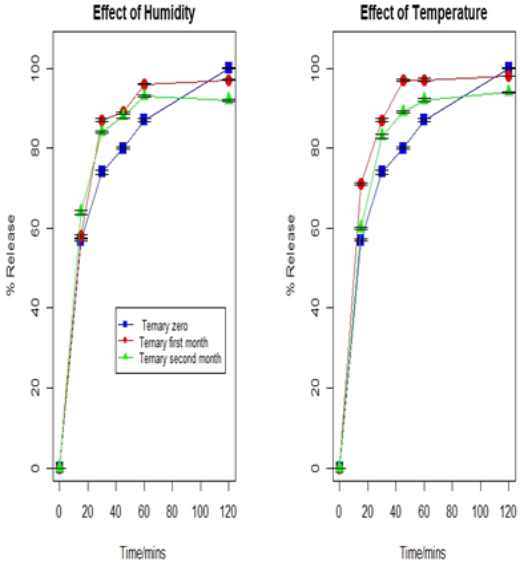
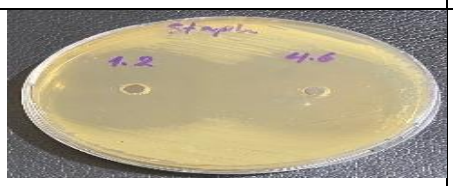
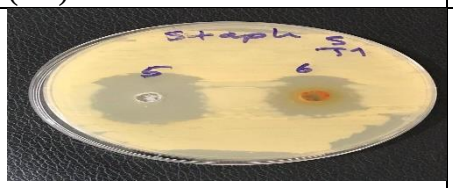
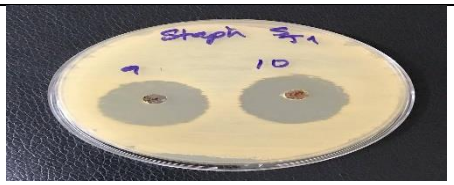
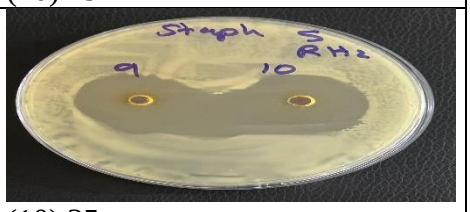


Figure (5) b. Dissolution profile of cefdinir ternary SD

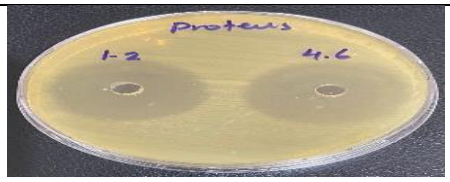
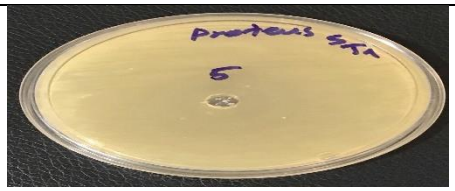
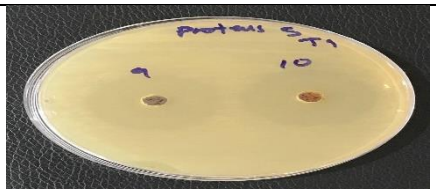
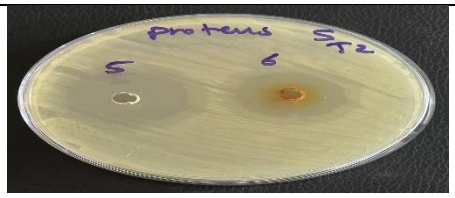
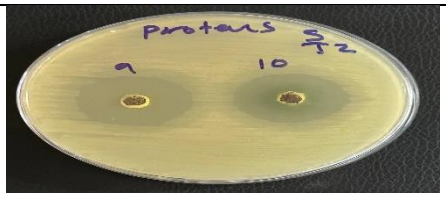
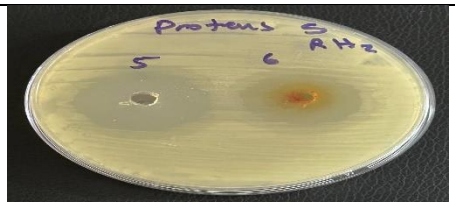
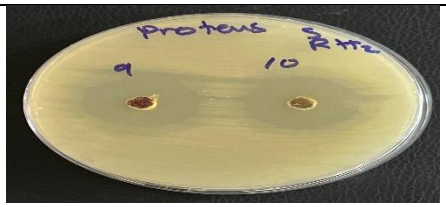
The Tables 5 and 6 represent antibacterial activity of pure drug and ternary mixture under harsh temperature and humidity condition at zero time, then after one and two months, the results show some decline in antibacterial activity of pure drug and ternary system as compared to pure drug and ternary SD at zero time respectively.

Table (5) Antibacterial activity of pure cefdinir and CEF ternary SD against *Staphylococcus aureus* at zero then after one and two months

	Cefdinir	Ternary SD
At zero time	 (1.2) 35 mm	 40 mm
After one month under 40 °C temperature	 (5) 30 mm	 (10) 29 mm
After one month under 75% relative humidity	 (5) 34 mm	 (10) 35 mm
After two months under 40 °C temperature	 (5) 32 mm	 (10) 29 mm
After two months under 75% relative humidity	 (5) 30 mm	 (10) 35 mm

The number between brackets represents the number of zone present on the plate. For example, the plate of cefdinir at zero time contains two zones of inhibition, and the zone with no. (1.2) represents the zone for cefdinir at zero time, which represents the zone we want to show. If there are no brackets, there is only one zone of inhibition in the plate.

Table (6) Antibacterial activity of stability study of cefdinir and ternary SD against *Proteus vulgaris*

	Cefdinir	Ternary SD
At zero time	 (1.2) 30 mm	 (40) 40 mm
After one month under 40 °C temperature	 15 mm	 (10) 30 mm
After one months under 75% relative humidity	 (5) 30 mm	 (10) 33 mm
After two months under 40 °C temperature	 (5) 30 mm	 (10) 25 mm
After two months under 75% relative humidity	 (5) 30 mm	 (10) 30 mm

The stability study results indicate that using PVP K30 as a polymer produces a miscible mix, stabilizing the ternary amorphous solid dispersions of CEF for two months in both temperature and humidity conditions.

These stability study findings are in line with earlier research on a ternary combination of Na_2CO_3, PVPK30, and telmisartan. PVP K30 was used as the polymeric carrier in this SD formulation, which stabilizes the amorphous solid dispersions of telmisartan. As a result, the formulation remained stable in vitro and maintained its amorphous structure for two months in both ambient and accelerated conditions (59).

Previously, febuxostat (FEB) solid dispersions were created using solvent evaporation employing PVP K30 and poloxamer188 as carriers. FEB, PVP K30, and poloxamer in a 1:3:3 optimized solid dispersion. Besides increasing saturation solubility, dissolution studies, and bioavailability, the FEB solid dispersion exhibited exceptional stability after 90 days. This work validates using PVP K30 and poloxamer188 as co-carriers for FEB solid dispersion (60).

Results of capsule pre-formulation

1. Angle of Repose

Table (7) displays the angle of repose values for each capsule formula. The results lie between very good and good flow characteristics for the formulation combination. These results indicate that all powders in the capsule formulas have acceptable flowability. According to Pharmacopeia (61).

Table (7) angle of repose values of capsule formulas

Formula	Angle of repose	Flow description
F1	29.7	Very good
F2	31.2	Good
F3	32	Good
F4	32	Good
F5	32.8	Good
F6	33.69	Good

2. Compressibility Index (Carr's index) and Hausner 's ratio

Table (8) displays the Hausner 's ratio and Carr's index findings. All capsule formulations were found to fall within the acceptable flow characteristic range. According to pharmacopeia (61).

Table (8) Hausner 's ratio and Carr's index results of capsule formulas

Formula	Carr's index	Hausner 's ratio	Flow description
F1	12 %	1.136	Good
F2	12.9 %	1.142	Good
F3	12.5 %	1.148	Good
F4	13.7 %	1.159	Good
F5	13.63	1.157	Good
F6	13 %	1.15	Good

Characterization of capsules dosage form

1. Weight variation test

There was no change in the weight of the capsules since the weight variation findings were within acceptable limits (53). The weight variation test used to confirm uniformity of the dosage unit (to ensure that every tablet and capsule contains the same amount of drug substance with a defined allowed variation within a batch) (62).

Table 9 represent the average weight of each capsule formula.

Table (9) The average weight of the capsule formulas

F1	F2	F3	F4	F5	F6
1185.08 mg ± 7.42	1285.35 mg ± 8.2	1257.9 mg ± 5.48	1231.38 mg ± 6.51	1230.99 mg ± 6.37	1286.35 mg ± 7.31

(Results were expressed as mean± SD, n=3)

2. Drug content

Table 10 illustrates the range of drug content for all capsule formulations, which was determined to be between 98.19 and 100.42. This range of drug content variation from the label claim of 100 % to be acceptable (63).

Table (10) Drug content of capsules in different formulas

Formula	**Cefdinir content %**
F1	99.67 ± 3.51
F2	98.19 ± 5.74
F3	98.56 ± 2.63
F4	99.05 ± 3.25
F5	99.18 ± 4.24
F6	100.42 ± 1.24

(Results were expressed as mean± SD, n=3)

3. Disintegration test

All capsules formula disintegrates within 5 min as shown in Table 11. This disintegration time is within which is within the time frame specified by USP for hard gelatin capsules (64). The disintegration test is important to show how quickly the capsule shell dissolved, allowing for the drug to be released (65).

Table (11): Disintegration time of capsule formulas

Parameter	**marketed product**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
disintegration time (min)	5 ± 0.31	5 ± 0.28	3.82 ± 0.48	4.05 ± 0.51	3.51 ± 0.43	4.29 ± 0.25	4.69 ± 0.39

(Results were expressed as mean± SD, n=3)

4. *In-vitro* dissolution of CEF capsules

Comparing capsule formulas (F1-F6) to cefdinir commercial capsule (Sefarin®), all had greater release levels (significant $p < 0.05$) within 2 h as seen in Figure (6) Capsule formula F4 (containing 70 mg Croscarmellose sodium and 30 mg lactose) demonstrated higher initial (non-significant $p > 0.05$) release (up to 71 % within the first 15 min) as compared to formula F2 (containing 50 mg Croscarmellose sodium and 50 lactose) and both were highe (non-significant $p > 0.05$) than F3 (containing 30 mg Croscarmellose sodium and 70 lactose) as shown in Figure (6). This may be associated with the fact that F4 and F2 have higher concentrations of

croscarmellose sodium, which function as disintegrants by swelling (66, 67). Prior research used direct compression to introduce simvastatin SD into a matrix of rapid disintegrating tablets (RDTs). The main variable controlling RDT disintegrations and simvastatin dissolving properties was the amount of croscarmellose sodium superdisintegrant present. The greatest and lowest percentages of croscarmellose sodium were used to generate those RDT formulations. RDT disintegration was accelerated and water wicking was maximized due to the increased superdisintegrant added percentage and reduced compression force (68).

Formula 5 (containing 100 mg microcrystalline cellulose) showed slow release in comparing with the other formulas, this results may be may be due to the way that microcrystalline cellulose functions as a binder and diluent (69).

In the case of formula F6 (containing 100mg lactose), the release reaches approximately (97.82 % within 2 h). Although the difference in release between the prepared capsule formulas is non-significant, formula 6 (F6) was selected as an optimum formula for further antibacterial activity investigation since it has the highest release profile after 2 h compared to other formulas.

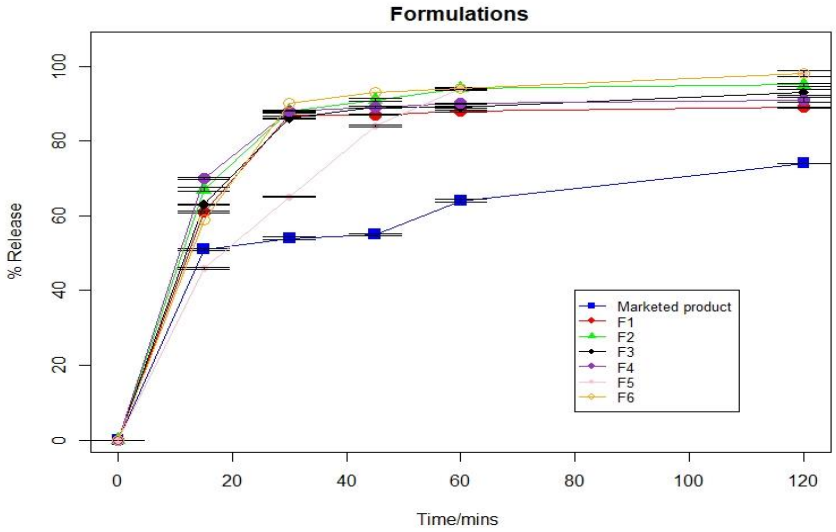


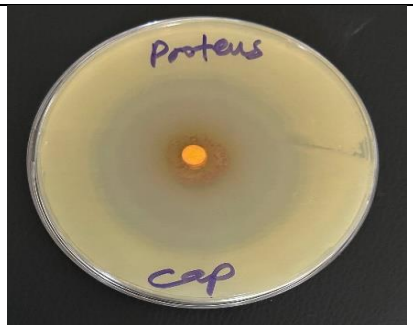
Figure (6) Dissolution profile of cefdinir capsule formulas in 0.1N HCl (pH1.2) at 37ºC

5. Antibacterial activity of selected optimum capsule formula

The results of an agar well diffusion test showed that the optimal capsule formula (F6) was effective against bacterial strains of *Proteus vulgaris* and *Staphylococcus aureus*.

Table (12) illustrates the CEF optimal capsule formula's inhibitory zone against *Proteus vulgaris* and *Staphylococcus aureus*. The enhanced apparent solubility of the drug in prepared formula might be the reason for the increase in antibacterial activity (70).

Table (12) Inhibitory zone of cefdinir optimum capsule formula against *Staphylococcus aureus* and *Proteus vulgaris*

Bacteria	Zone of inhibition of cefdinir as received	Zone of inhibition of cefdinir in cap formula (F6)
Staphylococcus aureus	 (1.2) 35 mm	 50 mm
Proteus vulgaris	 (1.2) 30 mm	 55 mm

Conclusions

The solubility of cefdinir was successfully enhanced by preparing ternary SD of cefdinir with curcumin and pvp with enhancement in release behavior to 100 % within 120 min and in antibacterial activity against *Staphylococcus aureus* and *Proteus vulgaris* isolates. The ternary SD stability investigation indicates that the system remains amorphous after two months under the harsh conditions of 40 °C and 75% relative humidity. The ternary SD was formulated as a capsule dosage form in which F6 was chosen as the selected formula (with a composition of 900mf ternary mix, 70mg talc, and 100mg lactose). As a future work, this formulation required further *in-vivo* study.

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