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# Formulation and characterization of floating biphasic tablet consisting of cefdinir nanosuspension

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***Abstract*---**Cefdinir (Cef) is a third-generation cephalosporin antibacterial agent with an extended spectrum and low solubility and permeability. In this study, cefdinir was prepared as nanosuspension and lyophilized to powder. The lyophilized cefdinir was further processed to develop a bilayer tablet. By utilizing the bilayer approach, the first therapeutic action is impacted by the immediate part's rapid disintegration and a prolonged release from the floating part is achieved. Floating system ensures a recognized extended-release in the gastric medium and avoids the numerous daily dosages. Different polymers were utilized with effervescent materials in different concentrations. The method employed in preparing tablets is direct compression. Every formulation undergoes through standard pre and post-compression floating tablet characteristics with unique results that allow for further comparison between various formulations and increase our understanding of the makeup of medications, polymers, additives, and preparation technique. The formula NFT8 was selected as the best formulation design. It contains (HPMC K4M 400 mg, Carbapol940 50 mg, sodium bicarbonate 100 mg, and citric acid 75 mg) and provided efficient floating characteristics for more than 24 hr as revealed by in vitro dissolution release.

***Keywords*---**floating system, cefdinir, soluplus®, bilayer tablet, sustained release.

## Introduction

Due to the variability of the gastrointestinal tract, pH of the commensal flora, stomach retention duration of the dosage form, surface area, and enzymatic action, limited bioavailability results and it is considered as the major obstacle observed in oral drug delivery. Traditional drug delivery systems may not be willing to surmount difficulties provided by the gastrointestinal tract (GIT), such as insufficient drug release, reduced dosage efficiency, and the need for repeated doses. As a result of the inability of traditional drug delivery systems to keep medications in the stomach, gastroretentive drug delivery systems (GRDDS) was designed (1). Many medications' oral bioavailability is hampered by their poor physicochemical properties or absorption in a specific region of the gastrointestinal tract (GIT), known to as the "absorption window." Extended stomach persistence improves bioavailability, decreases drug waste, and increases solubility for medicines that are less soluble in a high pH environment (2). As a result, formulation experts are constantly working to improve oral drug delivery systems by creating novel techniques. Gastroretentive systems, which use techniques to lengthen gastric residence duration, have recently gotten a lot of attention as an approach to enhance bioavailability of medications with a narrow absorption window, intestinal pH stability, local activity in the stomach, and low pH solubility. The length of time a drug stays in contact with the absorbing membrane affects the rate and degree of drug absorption which is known as gastric residence time (3). Medications that are largely absorbed in the stomach or upper GI tract, or drugs with solubility concerns in the intestinal fluid, benefit from extending the gastric residence period of dose forms. This improves medication breakdown and absorption in the stomach and/or small intestine by slowing the release of the drug in the stomach. This method also has the advantage of allowing for continuous or regulated drug delivery, which can lessen variations in systemic drug levels and improve patient compliance by reducing the number of doses necessary (4). Floating drug delivery system (FDDS) is a gastroretentive dosage form that can extend gastric residence time in order to achieve adequate drug bioavailability. Because the stomach fluid has a lower bulk density than the watery media, the system floats in it. Drugs like furosemide and theophylline, which have an absorption window in the stomach or upper small intestine, benefit from FDDS (5). As early as 1968, floating drug delivery methods were reported in the literature. These systems are made with a lower bulk density than gastric fluid, allowing them to float for longer periods of time without impacting the gastric emptying rate. Due to the acidity of the gastric fluid, effervescent floating drug delivery systems based on effervescent components will release carbon dioxide. Gas bubbles will be retained in the gel layer generated by hydrocolloids, which will cause the dosage form to float and maintain its buoyancy (6). FDDS is also effective for drugs that act locally in the proximal GI tract, such as antimicrobial therapy for Helicobacter pylori destruction in the management of peptic ulcer, for drugs that are unstable in the intestinal fluid, such as captopril, and for drugs with poor solubility in the intestinal tract, such as diazepam and verapamil HCl (5). Hydrocolloids that are extremely swellable and gel-forming are used in floating systems. To achieve appropriate swelling and drug release qualities, a range of polymers such as hydroxyl propyl methyl cellulose (HPMC), carboxymethyl cellulose, and carbopol are utilized (7).

Biphasic drug delivery systems deliver a precise amount of medicine quickly to improve a patient's condition immediately, followed by a sustained release to prevent repetitive dosage. Many illnesses, such as migraines, hypertension, and insomnia, require this form of administration(8). The bilayer tablet is designed to provide two different release rates or biphasic release of a drug from a single dosage form, with one layer formulated to achieve immediate release effect of the drug, with the goal of reaching a high plasma concentration in a short period of time, and the second layer designed as a sustained released layer, which provides effective plasma concentration by a maintenance dose of drug for an extended period of time (9).

When compared to traditional therapy, the bilayer tablet dosage form has a number of advantages over traditional dosage forms, including reduced drug administration frequency, enhanced patient compliance, reduced drug level volatility in blood, and a quantitative reduction in total drug usage (9). The bilayer tablet is an unique method for the effective and promising of controlled delivery design through many ways to deliver an effective drug transport system. The benefits of a bilayer tablet continue to outweigh the shortcomings of a single-layered tablet (10). The physical and chemical properties of the chemicals in the formulation, the interaction between the components in addition to the porosity, swelling, and tablet erosion are all significant factors that affect drug release in a bilayer tablet. These important factors determine the drug's ultimate release behavior. Also, the extent to which these factors impact drug's final release behavior will be different depending on the formulation (11). The conventional dose form causes a large variation of medication concentrations in the bloodstream, leading to the principle of sustained drug administration. The reason for creating sustained delivery systems is to decrease the frequency of dose, increase the medicine's efficiency, or provide constant drug distribution (12). Cefdinir (Cef) is a third-generation cephalosporin antibacterial agent with an extended spectrum and low solubility and permeability. It is classed as a BCS class IV medication with poor solubility and permeability. Cefdinir has a short half-life of (1.7 ± 0.6) hr and is believed to have partial absorption and limited bioavailability (16–21)% (13). Cefdinir has an estimated bioavailability of 21% and 16% following single 300 and 600 mg capsule administration, respectively, and an estimated absolute bioavailability of 25% after suspension administration. Cefdinir is not metabolized very well and is excreted through the kidneys. In randomized, controlled trials conducted in patients with a wide range of infections, oral cefdinir 300 mg twice daily or 600 mg once daily in adults and adolescents, or 14 mg/kg/day in one or two divided daily doses in pediatric patients, administered for 5 or 10 days, has shown excellent medical and bacteriological effectiveness at least similar to that of oral analog agents (14). The chemical structure of cefdinir is shown in figure (1).

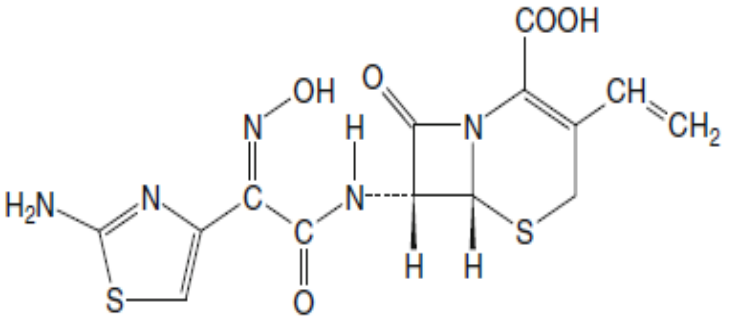



Figure (1): Chemical Structure Of Cefdinir (14)

Cefdinir's pharmacokinetics in humans are described as linear and dose independent for a range of single oral dosages ranging from 200 to 400 mg. Furthermore, due to its poor water solubility (453 g mL-1), cefdinir's oral bioavailability, which is around (16–21) %, is limited. Because of its low bioavailability, it has a decreased antibacterial activity, which could promote to antibiotic resistance (15). It belongs to BCS Class IV, which means it has limited solubility and permeability. Cefdinir comes in two different dose forms: capsules and suspensions. It has a crystalline structure and a compressibility difficulty, making it difficult to produce in tablet dosage form. Gastroretentive systems can stay in the gastric region for several hours, allowing medications to spend more time in the stomach. Prolonged stomach retention improves bioavailability, lowers drug waste, and increases solubility for medicines that are less soluble in a high pH environment (16). Cefdinir is given with an antacid because its activity is decreased when the gastric pH rises. This suggests that the medicine is absorbed mostly in the upper gastrointestinal tract. Cefdinir had higher absorption in the proximal GI tract and poor absorption, as well as antibiotic-associated colitis, when a large amount of drug entered the colon, suggesting it is a perfect choice for a gastroretentive drug delivery system that will lengthen the dosage form's gastric residence time, allowing for continuous drug release in the upper GI tract, where cefdinir absorption is well restricted (17). Nanosuspension technology got the main attraction in the pharmaceutical industry for the last two decades. It has an integral participation in constructing poorly water-soluble drugs by enhancing saturation solubility, dissolution rate, and, as a result, improved oral bioavailability. Particulate dispersions or solid particles with a size between 10 and 1000 nanometers are known as nanoparticles. For greater stability and simplicity of administration, medication nanoparticles are usually suspended in a liquid media (usually water). This is known as "Nanosuspension." The crystalline or amorphous state of the pure drug particles is possible. The nucleation and development of drug particles from a dissolved condition to the nanoscale range are involved in the precipitation approach (19). In this research, cefdinir was prepared as nanosuspension to increase in vitro dissolution and saturation solubility. Furthermore, the resultant nanosuspension was lyophilized and compressed as bilayer tablets to as floating gastroretentive drug delivery system.

## Materials and Method

### Materials

Cefdinir powder was purchased from (Sigma, USA), Soluplus® was obtained from (BASF, Germany). Carbopol 940 (Alpha Chemika, India), hydroxypropyl methyl cellulose E15 ( Alpha Chemika, India), hydroxypropyl methyl cellulose K4M ( Alpha Chemika, India), lactose (Thomas Baker (chemical)limited,India), poly vinyl pyrrolidine K30 (Direvo Industrial Biotechnology, Germany). Sodium bicarbonate(Himedia, India), citric acid (Panreac, Barcelona,Espana), magnesium stearate (Barbeher, GMBH, Germany) , Microcrystaline cellulose (MCC) PH 102 (FMC Bio Polymer-USA) , croscarmellose (Gbr-BDh-England) and crospovidone (Alpha Chemika, India).

### Methods

#### Preparation of cefdinir nanosuspension and freeze drying

The solvent evaporation approach, also known as the anti-solvent precipitation method, was used to make cefdinir nanosuspensions. At room temperature, cefdinir powder was dissolved in 2 mL of DMSO. This was placed into 20 ml of distilled water containing soluplus® kept at 25°C and agitated for 2 hr and 24 min at 1500 revolutions per minute (rpm) to allow the volatile solvent to evaporate. The drug's organic solution (organic phase) was introduced drop by drop into an aqueous solution of a stabilizer using a plastic syringe with the needle immediately in the solution (20).The ratios of drug to stabilizer used to prepare the nanosuspensions were 1:1. It can be turned to powder by freeze-drying the water out of the nanosuspension. The formulation was prepared in 400 mL total. A deep freezer was used to freeze four flasks for 24 hr at - 20°C. The instrument was run until dry powder was achieved, after which the frozen flasks were connected to the device's vacuum port, followed by four flasks each containing 100 ml of nanosuspension. It took (48 to 72) hr to sublimate a solvent from frozen materials (21).

#### Fourier transforms infrared spectroscopy (FTIR)

FTIR spectrophotometer (FTIR-8300 Shimadzu, Japan) using potassium bromide (KBr) pellet method was used to produce the fourier transforms infrared spectroscopy spectra of pure cefdinir, soluplus®, physical mixture of cefdinir nanosuspension and the liquid nanosuspension of the developed formulation. The goal of this study was to look for any signs of drug-stabilizer interaction. The measured spectrum ranged from 4000-400 cm-1 in wave number(22).

#### Preparation of the immediate release layer

This layer's preparation method is direct compression. All of the ingredients are combined and then ground for 5 min in a mortar and pestle. After that, gently combine a known weight of the mixture with the lubricant (magnesium stearate) to prepare for compression using a 10 mm punch and die (23). Table (1) includes the composition of the immediate release layer

Table (1): Composition Of Cefdinir Immediate Release Layer

| Formula | Lyophilized powder eq. to 100 mg cefdinir | (MCC) PH102 | Croscarmellose | Crospovidone | Magnesium stearate | Final weight |
|---|---|---|---|---|---|---|
| F1 | 100 mg | 86 mg | | 10 mg | 4 mg | 200 mg |
| F2 | 100 mg | 86 mg | 10 mg | | 4 mg | 200 mg |

**Precompression studies of the prepared nanoparticle powder**

In order to produce a homogeneous feed as well as reproducible filling of tablet dies, the flowability of a powder is crucial in the production of pharmaceutical dosage forms. Otherwise, large dose variances would arise. Angle of repose, Hausner's ratio, and Carr's index were used to assess the powder flowability of produced cefdinir tablets (24).

**Angle of Repose (θ)**

The maximum angle that can be formed between the surface of the powder pile and the horizontal plane is known as the angle of repose. It was done with a fixed funnel. A graph paper was laid on a level horizontal surface to which a funnel was fixed with the tip at a specific height, h. The conical pile's peak was carefully poured through a funnel until it touched the funnel's tip (16). The following equation was then used to compute the angle of repose:

Angle of repose is equal to tan-1(h/r).
where h is the pile's height and r is its radius (16).
Compressibility index (Carr's index)
An essential factor in determining the powder's flow behavior is the compressibility index. It is inextricably linked to cohesion, particle size, and flow rate property rate. Carr's index can be represented by Equation:

$$\text{Compressibility index}(\%) = \left[\frac{TD - BD}{TD}\right] \times 100$$

Where:
TD is the tapped density and BD is the bulk density. The ratio of powder mass to bulk volume is known as bulk density. Particle shape, cohesion, and size distribution all affect the bulk density. It is estimated by the following equation:
Bulk density=M/Vo
Where, M = mass of the powder, Vo = bulk volume of the powder (16)
A 100 ml measuring cylinder was filled with 10 g of dry, clean powder. Following that, the cylinder was struck 100 times from a fixed height, and the tapped volume was recorded.
Tapped density = M/Vt

which yields a value in gm/ml.
where M is the powder's mass and Vt is the powder's ultimate tapping volume (16)
Hausner's ratio
The Hausner's ratio is used to evaluate how well the powders will flow. Compressibility index and this approach are comparable. Equation represents the Hausner's ratio ( 16):

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

**Evaluation of the Immediate release layer**
**Disintegration Test**

The disintegration time was measured after placing the thin immediate layer in a disintegration equipment loaded with 0.1 N HCl at 37°C (23). In vitro dissolution study of the prepared immediate release layer. The USP dissolution test apparatus-II was used to conduct the in vitro dissolution research (paddle assembly). The dissolution test was carried out using the cefdinir immediate layer in 900 ml of 0.1 N HCL (pH 1.2) at 37°C 0.5 °C, 50 rpm, and samples (5 ml) were collected at regular intervals of (5, 10, 15, 30, 60, 90, and 120) min and substituted with freshly prepared media. Samples were filtered using filter paper and spectrophotometrically measured at 281 nm using a UV-Visible spectrophotometer (22).

**Preparation of effervescent gastroretentive floating layer**

The constituents of the formula are mixed and milled by mortar and pestle for 5 min the add a magnesium stearate as a lubricant before compression by tablet machine with 10 mm punch and die. Table (2) shows the composition of the floating layers.

Table (2): Composition Of The Floating Sustained Release Layer

| Ingredients (mg) | NFT 1 | NFT 2 | NFT 3 | NFT 4 | NFT 5 | NFT 6 | NFT 7 | NFT 8 | NFT 9 | NFT 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Selected nanosuspension formula | Eq. to 200 mg cef | Eq. to 200 mg cef | Eq. to 200 mg cef | Eq. to 200 mg cef | Eq. to 200 mg cef | Eq. to 200 mg cef | Eq. to 200 mg cef | Eq. to 200 mg cef | Eq. to 200 mg cef | Eq. to 200 mg cef |
| Carbopol 940 | 400 | | | 50 | 50 | 400 | 50 | 50 | 60 | 60 |
| HPMC E15 | | 400 | | 400 | | | 400 | | | |
| HPMC K4M | | | 400 | | 400 | | | 400 | 291 | 200 |
| Sodium Bicarbonate | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| MCC (PH102) | 30 | 30 | 30 | 30 | 30 | | | | | |
| Citric acid | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 |
| PVP K30 | | | | | | 30 | 30 | 30 | 30 | 30 |
| Lactose | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 75 | 75 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Magnesium Stearate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Total weight | 635 | 635 | 635 | 685 | 685 | 635 | 685 | 685 | 641 | 550 |

| Ingredients (mg) | NFT 11 | NFT 12 |
|---|---|---|
| Selected nanosuspension formula | Eq. to 200 mg cef | Eq. to 200 mg cef |
| Carbopol 940 | 50 | 50 |
| HPMC E15 | | |
| HPMC K4M | 400 | 400 |
| Sodium Bicarbonate | 50 | 150 |
| MCC | | |
| Citric acid | 75 | 75 |
| PVP K30 | 30 | 30 |
| Lactose | 40 | 5 |
| Magnesium Stearate | 10 | 10 |
| Total weight | 655 | 720 |

**Evaluation of gastro-retentive floating layer**
**Friability Test**

Using the automatic tablet friabilator (Roche friabilator) at 25 rpm for 4 min, the friability test was performed. Weight loss of each tablet and the batch was calculated following the friability test and dedusting in accordance with USP procedure. Calculations were made to determine the friability of each tablet and the entire batch, expressed as a percentage of the original weight. Calculating the standard deviation for the batch's percentage friability was made possible by determining the weight loss of individual tablets (25).

**Hardness Test**

It was measured using Monsanto hardness tester by measuring 6 tablets from each batch and take the average (10). The results were presented as mean ± SD.

**Tablet wight variation**

By utilizing an electrical balance (Radwag Wagi Elektroniczne, Poland) to weigh 10 tablets that are randomly selected, the weight fluctuation of the tablets was assessed. The results were presented as mean ± SD (26).

**Content uniformity Test**

Twenty tablets were broken milled into powder, which was then dissolved in 0.1N HCL to make the weight of one tablet. Additionally, appropriate dilutions were created, and a UV spectrophotometer was used to detect absorbance at a

wavelength of 281 nm (27). Experiments were made in triplicate and the results were expressed as mean ± SD.

**Determination of Floating Lag Time and Total Floating time**

The amount of time it takes for a tablet to "float" a medium surface to rise is the floating ag time and the total floating time (TFT) equals the time that a tablet floated on the surface. To The tablets were used to calculate the floating lag time. 0.1N HCL in a beaker with 100 mL, and the time needed for It was determined how high a tablet should rise. Next, the time frame was calculated for each formulation that remained on the surface as complete flotation (28). Experiments were made in triplicate and the results were expressed as mean ± SD.

**In vitro dissolution study of the prepared floating layer**

Utilizing the USP Dissolution Apparatus II, cefdinir release from the floating layer had been performed. The experiments were run for 24 hr in 900 mL of 0.1M hydrochloric acid (pH 1.2), at 37 0.5oC, and 50 rpm. To keep the sink condition, 5 mL aliquots of the release medium were removed and replaced with media of equal proportions. The samples were taken at predetermined time intervals of (15 ,30 ,120 ,240 ,360 ,480 600 ,720 ,840 ,960 ,1080,1200 ,1440) min. The samples were removed, filtered using 0.2 m Whatman filter paper, and then subjected to UV-visible spectrophotometer analysis at 281 nm following the proper dilution (29). Experiments were made in triplicate and the results were expressed as mean ± SD.

**Variables affecting release profile from cefdinir floating tablets**

**Effect of polymer type**

The prepared floating formulas NFT(1,2,3) which contain single polymer of ( carbopol 940 , HPMC E15 and HPMC K4M) respectively were used to study the effect of the type of polymer on the floating behavior and drug release from cefdinir lyophilized floating tablet. NFT (4,5,6,7,8) had a combination of two polymers of carbopol 940 with either HPMC E15 or HPMC K4M

**Effect of effervescent ratio**

Formulas NFT (11,8,12) which contain sodium bicarbonate 8%, 15% and 21% (w/w) of the total tablet weight respectively, were used to study the quantitative effect of the effervescent agent on the floating behavior of cefdinir lyophilized floating tablet.

**Effect of polymer concentration**

Formulas NFT (8,9,10) which contain HPMC K4M in three different concentrations 59%, 48% , 37% (w/w) respectively of the total weight of the tablet were used to study the polymer concentration on the floating behavior and drug release from cefdinir lyophilized floating tablet.

**Bilayer tablet preparation**

The prepared bilayer formula displays accepted results according to USP and references. The most effective floating component formula was chosen. Using a punch and die size of 10 mm, a known quantity of the chosen formula's powder was poured into the tablet machine. After being gently crushed to perform a rough side, the powder for immediate release was added, and the entire tablet was then compressed (23).

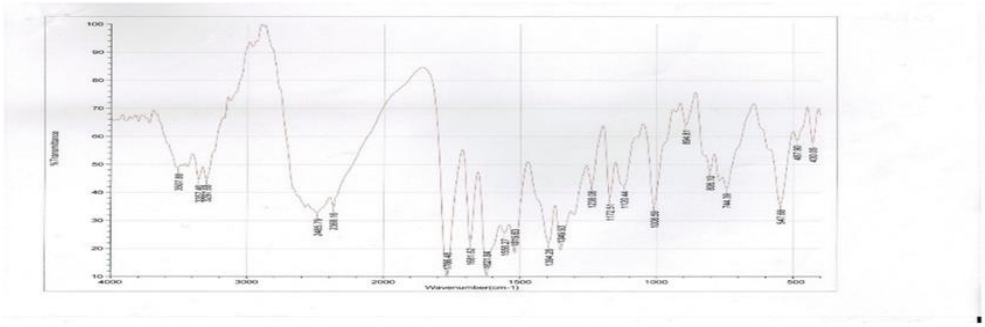
**Bilayer tablet evaluation**

In accordance with the methods previously covered in the floating sustained release layer evaluation, we investigate friability, hardness, floating lag time, total floating duration and drug content.

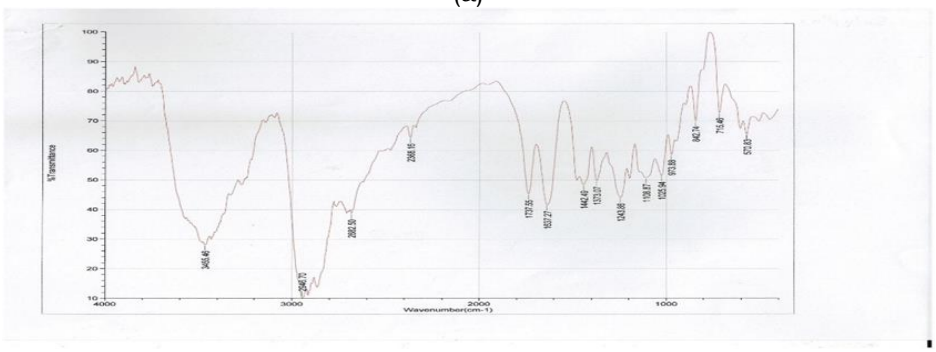
**Results and Discussion**

**Fourier transforms infrared spectroscopy (FTIR)**

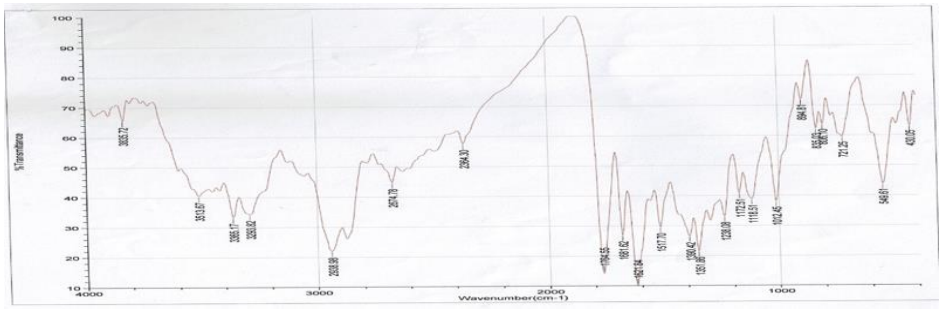
Fourier transforms infrared spectroscopy (FTIR) spectra of cefdinir pure drug, Soluplus® , physical mixture of cefdinir nanosuspension and lyophilized cefdinir nanosuspension are shown in figure (2). IR spectrum of Cefdinir (a) is characterized by principal absorption peaks at 3352.28 cm−1 (O − H stretch COOH), 3120.57 cm-1 (amino group), 2898 cm−1 (C−H stretch), 1621.84 cm-1 (oxime group), 1766.48 cm -1 (carbonyl group) , 1610 cm−1 (C=C aromatic), 1667 cm−1 (C = C alkene), 1544 cm−1 (N−H bending), 1428 cm−1 (C− N stretch) and 656 cm−1 (C−S). For soluplus®, the main peaks are 3465.46, 2946.7, 2682.50, 1737.55, 1637.27, 1442.49, 1373.07 and 973.88. These peaks are distinct from the peaks of cefdinir. Soluplus® showed inter- molecularly hydrogen bonded (–OH) stretching in the (3350–3550) cm−1 range, ester carbonyl stretching at 1729 cm−1, (C=O) stretching for tertiary amide at 1616 cm−1, (C–O) stretching for ester at 1233 and 1109 cm−1 and (CH3) bending at 1436 cm-1, as shown in figure (2) (b). The physical mixture of the nanosuspension blend is shown in figure (2) (c). The main spectra (cm-1) are 3835.72, 3513.67, 3365.17, 3293.82, 2938.98, 2674.78, 1764.55, 1681.62, 1390.42 and 721.25. FTIR spectra results shown the absence of interaction between cefdinir and soluplus® employed in the nanosuspension physical mixture. FTIR of the liquid nanosuspension formulation is shown in figure (2) (d). It should be noted that the main peaks previously reported with both cefdinir and soluplus® are disappeared. This can be attributed to the effect of nanosizing and the effect of soluplus® . This gives a prominent indication about decreasing degree of crystallinity of the drug. When compared to the FT-IR spectra of the pure drug, two peaks in the spectrum disappeared and other peaks were attenuated, which may indicate that the drug's crystallinity has decreased. Understanding the drug's potential polymorphic modifications after nanosizing depends on the assessment of its crystallized state (30).



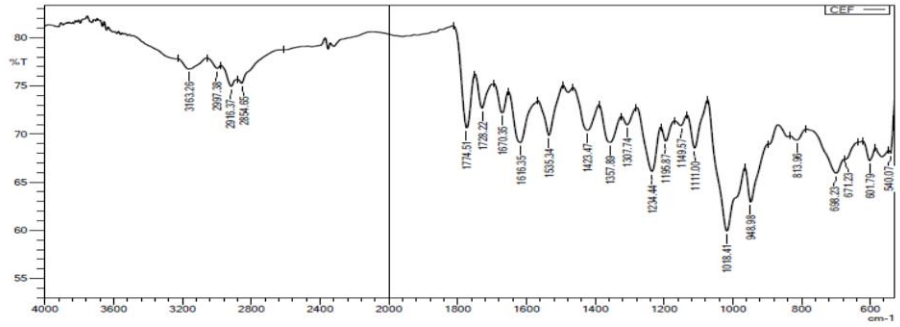
(a)



(b)



(c)



(d)

Figure (2): FTIR Of (a) Cefdinir Pure Drug , (b) Soluplus® ,(c) Physical Mixture Of Cefdinir Nanosuspension, (d) Liquid Cefdinir Nanosuspension

Evaluation of immediate release part
Precompression parameters
Two formulations were prepared for immediate release layer (F1 and F2). Precompression properties of (F1) and (F2) are shown in table (3).

Table (3): Precompression Properties Of Immediate Release Layer

| Formula | Angle of Repose | Carr's Index | Hausner Ratio | Type of Flow | |
|---|---|---|---|---|---|
| | | | | Angle of Repose | Carr's Index |
| F1 | 14 | 12 | 1.14 | Excellent | Good |
| F2 | 20 | 20 | 1.25 | Good | Fair |

**Disintegration Test**

The disintegration time was 1.5 min for F1 and 2.5 min for F2 as shown in table (4). F1 has lower disintegration time and will be selected as the best formulation for immediate release preparation. In addition, F1 has better precompression characteristics including angle of repose, Carr's Index and Hausner Ratio. So, F1 has better flowability than F2.

Table (4): Disintegration Time Of Immediate Release Layer

| Formula | Disintegration Time (min) |
|---|---|
| F1 | 1.5 |
| F2 | 2.5 |

In vitro dissolution study of the prepared immediate release layer. The best formulation ( F1 ) will be further studied for dissolution. The drug release from the immediate release layer can be shown in the figure (3).

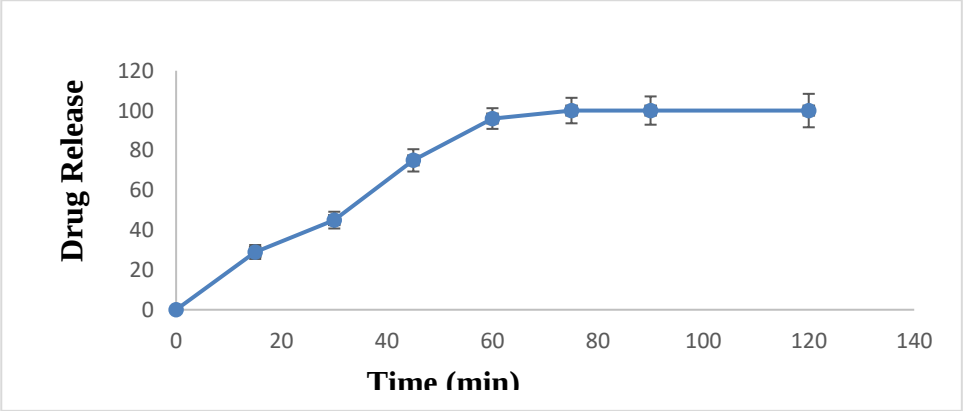



Figure (3): Release Of Cefdinir From Immediate Release Formula (F1) in 0.1 N HCL at 37°C (Mean ± SD) n= 3

Evaluation of floating sustained release layer
According to the USP guidelines, all results for the post-compression properties shown in Table (4). The produced bilayer tablets demonstrated the tablet generally recognized floating features and post-compression properties, as given in Table (5).

Table (4): Evaluation Of The Floating Formulations

| Formula Code | Hardness | Friability | Weight variation | Content Uniformity | FLT (sec) | TFT (hr) |
|---|---|---|---|---|---|---|
| NFT1 | 4.7 ± 0.3 | 0.32 ± 0.3 | 635 ± 9 | 95.3± 1 | 15 ± 3 | 9 ± 1 |
| NFT2 | 4.1 ± 0.7 | 0.54 ± 0.1 | 635± 8 | 94 ± 1.4 | 16 ± 5 | 5 ± 1 |
| NFT3 | 4.1± 0.3 | 0.49 ±0.3 | 635 ± 6 | 92 ±2 | 13 ± 7 | 6 ± 2 |
| NFT4 | 4.9 ± 0.5 | 0.24 ±0.2 | 685 ± 6 | 91 ±1 | 25 ± 8 | 18 ± 1.5 |
| NFT5 | 4.9 ± 0.3 | 0.22 ± 0.2 | 685± 9.5 | 94±2 | 22 ± 6 | > 24 |
| NFT6 | 4.8 ± 0.5 | 0.18 ± 0.4 | 635± 9.5 | 95 ±1.5 | 31 ± 2 | 24 ± 1 |
| NFT7 | 4.5± 0.2 | 0.21 ±0.2 | 685± 5.7 | 93.5 ±2 | 24 ± 5 | 7 ± 1.5 |
| NFT8 | 4.8 ± 0.4 | 0.14 ±0.6 | 685 ± 9.3 | 98 ± 1.9 | 20 ± 4 | > 24 |
| NFT9 | 4.3 ± 0.4 | 0.19 ± 0.3 | 641 ± 11 | 95 ± 1.2 | 24 ± 6 | 15 ± 1.5 |
| NFT10 | 4.6 ± 0.2 | 0.20 ± 0.8 | 550 ± 12 | 92.2 ±2 | 21± 3 | 10 ± 1 |
| NFT11 | 4.8± 0.4 | 0.23 ±0.6 | 655 ± 7 | 97.2 ±1 | 35 ± 2 | > 24 |
| NFT12 | 4.5± 0.6 | 0.29±0.4 | 720 ±10 | 96 ±1 | 11± 4 | > 24 |

(Mean ± SD) n= 3, FLT= Floating ag Time, TFL= Total Floating Time

Variables affecting drug release from floating sustained release layer
Effect of different polymer types on floating lag time (FLT) and total floating time( TFL) The prepared floating formulas NFT( 1-12 ) were developed using different release retarding gel forming polymers (Carbopol 940) and HPMC (K4M and E15) respectively as shown in the table (2). The floating tablets of the cefdinir lyophilized powder were prepared using sodium bicarbonate as gas generating agent, lactose as diluent. MCC(PH102) was used as a binder agent in NFT(1- 5) formulations only. On the other hand, PVP K30 was used a binder in NFT (6-12) formulations.

The cefdinir floating layer were prepared by direct compression technique. Citric acid and sodium bicarbonate were used in this study's gastric floating system as a gas producing agent. After reacting with sodium bicarbonate, citric acid, and

hydrochloride acid, carbon dioxide is produced, causing the tablets to float in the liquids for more than 12 hr in vitro. Due to the fact that cefdinir was primarily absorbed in the upper part of the GIT, the prolonged drug residence time in the stomach may result in enhanced absorption (17).

The tableting of a mixture of substances using direct compression (DC) eliminates the need for any prior granulation or agglomeration steps. Although there are only just few steps in the process, the many competing goals might make direct compression product development difficult. Since they increase the compactibility or tabletability of the compression mix, some diluents, such microcrystalline cellulose (MCC), can also be thought of as dry binders. True direct compression binders have better tabletability and can still function with light use (31). In our study, we used MCC as a binder in NFT (1- 5) formulations. Microcrystalline cellulose (MCC) is a crucial component in a variety of industries, including pharmaceutical (as binders, adsorbents, and flowability), food and beverage (as gelling agents, stabilizers, anti-caking agents, and suspending agents), and cosmetic (as thickeners, binders, and fat substitutes) (as binders) (32).

Hydrocolloids that form gel readily are used in floating systems. After coming into contact with an aqueous media, HPMC absorbs water to create a gel that regulates medication release. The concentration of the methoxy group affects how viscous the mass is (higher the concentration indicates the more viscosity). Cross-linked polyacrylic acid with a high molecular weight is called Carbopol (7).

According to the cross-linking groups, the polymers are divided into homopolymers and copolymers. The carboxylic groups of the Carbopol molecule have an attraction for water molecules and enlarge with hydration while remaining insoluble in water. The polymer is useful for the design of floating systems because of this characteristic(7). A previous study had revealed that the additional incorporation of Carbopol 940 into the formulation to enhance the gelling and adhesive characteristics of the locally applied nanogels and it was considered as a novel addition for the study (33). The floating lag time, or the amount of time the tablet took to rise to the medium surface, and the floating duration, or the amount of time it stayed buoyant, were also noted. After hydration, HPMC could create gel barriers around the tablet, which prevented further hydration of the tablet and kept the carbon dioxide in the gel for a longer period of time. The carbon dioxide may exit the tablet more quickly without the swelling gel when the gastric contents move, resulting in a somewhat shorter floating time (34).

In our study, NFT1 and NFT6 was prepared using Carbopol 940P as a gel forming polymer. The result showed that NFT1 had short floating lag time (FLT) and long total floating time (TFT). NFT1 sinks after 9 hr while NFT6 sinks after 24 hr. This can be attributed to Carbopol 940 characteristics previously discussed. NFT2 was prepared using HPMC E15 only. It had short FLT (16 ± 5) and short FLT (5 ± 1) hr. On the other hand, NFT3 was prepared using HPMC E4M only. It had FLT of (13 ± 7) sec and TFT of (6 ± 2) hr. The previous two formulations (NFT2) and (NFT3) were unable to float for long duration and they had bad integrity. Addition of Carbopol 940 had improved the tablet integrity and increased both FLT and TFT as reported with NFT4, NFT5 comparing with NFT2 and NFT3. According to

the FLT and TFT of the formulations prepared in this study, NFT8 was selected as the best formulation and was proceeded for drug release study. Cefdinir release from the optimum floating formulation (NFT8) in HCL (0.1 N) at 37°C is shown in figure (4). Drug release was 13% after 30 min and reached 24% after 2 hr. After 12 hr of floating duration, drug release was found to be 89.5%.After 16 hr, drug release from the floating formulation was 100%.

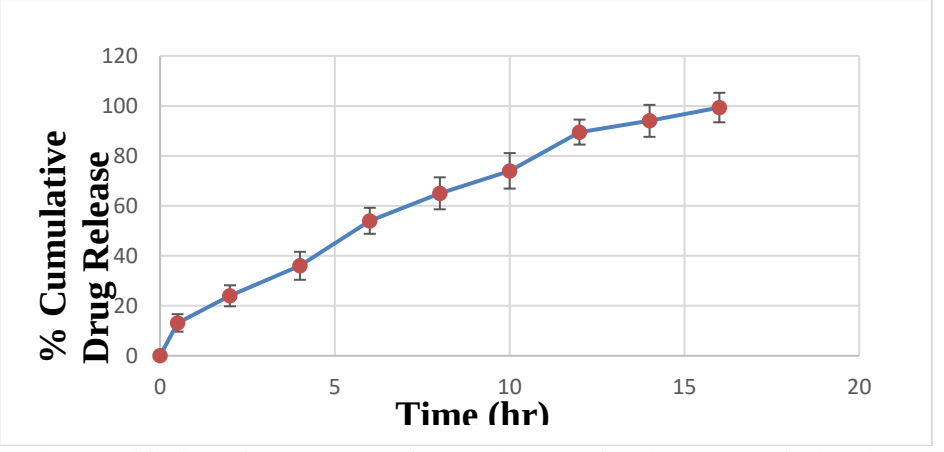



Figure (4 ): Cefdinir Release From The Optimum Floating Formulation (NFT8) in 0.1 N HCL at 37°C (Mean ± SD) n= 3

The type and concentration of the combined polymers had an impact on the drug release rate. When in contact with aqueous fluids, a higher concentration of HPMC K4M would encourage the production of extremely viscous gels. This would encourage slowing down the pace of medication release. According to a study by Siepmann and Peppas, the sequential regulation of drug release from HPMC matrices is as follows: at first, when the tablet first makes contact with the medium, water can enter the polymeric complex; as a result of water absorption, HPMC will swell and enlarge the complex. As a result of the polymers' concentration, the medicine will disintegrate and disperse out (28).

**Effect of effervescent ratio**

According to previous research, the floating lag time will be reduced as sodium bicarbonate concentration is increased (35). Formulas NFT (11,8,12) which contain sodium bicarbonate 8%, 15% and 21% (w/w) of the total tablet weight respectively. NFT11 was prepared with 8% sodium bicarbonate and had a long FLT (35 ± 2) sec and remained buoyant for more than 24 hr. NFT8 had 15% of sodium bicarbonate and had FLT (20 ± 4) sec and remained buoyant for more than 24 hr. On the other hand. NFT12 was prepared with 21% of sodium bicarbonate and had a very short FLT (11 ± 4) sec and had buoyancy duration of more than 24 hr.

**Effect of polymer concentration**

Formulas NFT (8,9,10) which contain HPMC K4M in three different concentrations 59%, 48% , 37% (w/w) respectively of the total weight of the

floating layer. NFT (8,9,10) had a close short floating lag time (less than 30) sec. On the other hand, TFL of these formulations was different. NFT8 had a TFL ( more than 24 hr). FOR NFT9, TFL was about (15 ± 5) hr and for NFT10, TFL was about (10 ± 1) hr.

**Preparation of the bilayer tablet**

The created bilayer formulation exhibits results that are acceptable by the USP and references. The results of bilayer post compression evaluation are shown in table (5).

Table (5): Properties Of Cefdinir Bilayer Tablet

| Floating Lag Time (FLT) (sec) | Total Floating Time (TFT) (hr) | Hardness (Kg) | Friability | Drug Content |
|---|---|---|---|---|
| 30 | > 24 | 5 | 0.46 | 99 |

**Conclusion**

The bilayer floating formulation of cefdinir tablets containing (HPMC K4M with Carbopol 940) extends the release window to more than 24 hr. The immediate release layer had a quick disintegration time and finished dissolving in 1 hr. For more than 24 hr, the floating layer is buoyant. This indicates that bilayer formulation is highly effective in treating bacterial infections, boosting drug bioavailability, and improving patient compliance.

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**Authors Contribution**

All of the authors had contributed equally

**Conflict of interest**

Declared none

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