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pH- Modified Solid Dispersions of Cefdinir for Dissolution Rate Enhancement: Formulation and Characterization

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Abstract:

Objective: Cefdinir is a poorly- water-soluble drug, it belongs to Biopharmaceutical Classification System class IV, which shows that it may have limited therapeutic effects due to its low solubility and poor bioavailability. The aim of the present work was to design a pH-modified solid dispersion (pH_M-SD) that can improve the dissolution rate of cefdinir and subsequently its bioavailability.

Materials and Methods: pH_M-SDs of cefdinir were prepared at different drug-to-carrier ratios by the spray-drying technique. The solid dispersions were investigated by dissolution studies at different pH media, drug release kinetics were studied, and their solid-state characterizations were performed by FTIR spectrophotometer, Scanning electron microscopy (SEM), Differential scanning calorimetry (DSC), and Powder X-ray diffraction (PXRD).

Results: PVP- based and HPMC- based pH_M-SDs exhibited a marked improvement in the dissolution behavior when compared with crystalline cefdinir powder, whereas Eudragit L100-based pH_M-SDs showed lower dissolution at pH 1.2 and 4.5.

FTIR results may indicate a formation of a salt between cefdinir and the alkalizer. Solid-state characterization may indicate a change in crystallinity of cefdinir into an amorphous state. Mathematical modeling of *in vitro* dissolution data indicated the best fitting with Korsmeyer–Peppas model and the drug release kinetics primarily as Fickian diffusion.

Conclusion: According to these observations, pH_M-SD in the presence of an alkalizer for a poorly water-soluble acidic drug, cefdinir, appeared to be efficacious for enhancing its dissolution rate.

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1. INTRODUCTION

Cefdinir is a third-generation oral cephalosporin antibiotic [1]. It belongs to BCS class IV, with low solubility resulting in low bioavailability of about 21% for capsules and 25% for suspension [2]. Its solubility is highly dependent on the pH of the media [3, 4].

In formulation development, weakly acidic or basic drugs pose a major challenge as the solubility depends significantly on the pH of the dissolution media. This gives rise to pH-dependent drug release, as the formulation is exposed to different pH ranges in the gastrointestinal tract. This indicates a need to carry out formulation optimization for such drugs while developing them into a dosage form [5].

Several approaches have been investigated to improve the dissolution rate and bioavailability of Cefdinir, including nanosuspensions [6, 7], amorphization [8], cyclodextrin complexation [4, 9], self-emulsification [10], and solid dispersions (SDs) [11-16].

Among these approaches, the application of SDs is attracting increasing attention [11-16] but, notwithstanding the positive results in these researches, none of them was able to achieve a pH-independent dissolution behavior which is important for improving the bioavailability of weakly acidic or basic drugs due to their exposure to different pH degrees along the gut after oral administration.

Besides that, the solubilization capacity of SDs has generally been limited by the carrier type, recrystallization, or spring-like precipitation upon exposure to an aqueous solution [17, 18]. To improve the solubilization capacity of SDs, extra agents were introduced [19]. The additives included surfactants [12], and pH modifiers [20, 21]. Because cefdinir has a pH-dependent solubility [3, 4] modulating the pH in solid dosage forms, which is the 'microenvironmental pH' (pH_M), seems to be a promising way to modify the release rate of cefdinir.

In this article, a poorly water-soluble weakly acidic drug (cefdinir) loaded pH_M-SDs were prepared using PVP-K30 (Polyvinylpyrrolidone), HPMC 606 (hydroxypropyl methylcellulose), or Eudragit L100 (ethyl polymethacrylate) in different drug: polymer ratios (1:1, 1:2 w: w). The alkalizer (NaOH) was selected as a pH-modifier based on solubility results. The pH_M-SDs were prepared using the spray-drying technique. The Spray-drying technique was used because it is mainly aimed

at generating amorphous materials and is the technique of choice for particle size reduction. We also assessed their physicochemical characteristics through an FTIR spectrophotometer, Scanning electron microscopy (SEM), Differential scanning calorimetry (DSC), and X-ray diffraction (PXRD). We have also studied *in vitro* release in media with different pH.

2. MATERIALS AND METHODS

2.1. Materials

Cefdinir was obtained from (lupin Co. Ltd, India). PVP-K30 was obtained from (Ashland Inc, America). Hydroxypropyl methylcellulose was purchased from (Shine-Etsu chemical Co. Ltd, Japan). Eudragit L100 was procured from (Evonik Industries, Germany). NaOH was obtained from (Carl Roth Gmbh & Co®, Germany). All other used reagents and solvents were of analytical grade and were used as received.

2.2. Instruments

- Mini spray dryer (Buchi-191) (Germany).

- UV-VIS Spectrophotometer (T80) from (PG, United Kingdom).

- Infrared spectrophotometer (FTIR) (Vector 22) from (Bruker, Germany).

- Differential Scanning calorimetry (DSC 131) from (Setaram, France).

- Powder X-ray diffraction device (PXRD) from (Bruker D8, West Germany).

- Dissolution apparatus (PTDT7) from (Pharmatest, Germany).

- Scanning electron microscopy (SEM, VEGA II LSH, TESCAN, Czech Republic).

- Hermle Z 200 A Centrifuge, Germany

2.3. Solubility of Cefdinir and Screening for pH Modifiers

The solubility of Cefdinir in various solvents (pH 1.2 HCl buffer, pH 4.5 acetate buffers, pH 6.8 phosphate buffer, and distilled water), alkalizers (1% w/v solution of aqueous sodium hydroxide, potassium hydroxide, and sodium bicarbonate). Solubility measurements were performed in triplicate using the shake flask method [22]. Excess cefdinir (100) mg was added to 10

Table 1:   The Composition of the Prepared pH$_M$- SDs Systems of Cefdinir

Code	Cefdinir (mg)	Na OH (mg)	PVP K30 (mg)	HPMC 606 (mg)	Eudragit L100 (mg)
F1	300	30.35	300	____	____
F2	300	30.35	600	____	____
F3	300	30.35	____	300	____
F4	300	30.35	____	600	____
F5	300	30.35	____	____	300
F6	300	30.35	____	____	600

mL of each solution. The samples were subjected to a constant shaking for 72 hours, then centrifuged (5000 x g, 30 min, using Hermle Z 200 A Centrifuge, Germany), filtered (0.45 micron), diluted, and analyzed by UV-VIS spectrophotometer (PG Instruments T80 UV/VIS spectrophotometer, United Kingdom) at 287 nm [23, 24].

2.4. Manufacturing of pH$_M$-SDs

The pH$_M$-SDs containing Cefdinir were prepared by a spray drying technique. The detailed compositions of SDs are shown in Table **1**.

Briefly, cefdinir was dispersed in deionized water, then PVP-K30 (or HPMC 606, or Eudragit L100) solution was gradually added to cefdinir suspension with a continuous stirring to reach the desired weight ratio (1:1, or 1:2 w:w, drug: polymer). NaOH (0.1 N) was added dropwise until the pH reaches 7 (the solutions become clear after the addition of NaOH in PVP-K30 and HPMC- based formulation, which indicates the complete dissolution of cefdinir before spraying).

The resulting solutions were immediately dried using Buchi mini spray dryer B-191, Germany.

The following conditions were used: inlet temperature 160 °C, outlet temperature 83 ± 6 °C, airflow rate 600 l/h, and pump rate 5.3 ± 0.2 ml/min, Spray nozzle 0.7 mm, Aspirator 80%.

2.5. Process Yield and Drug Content Estimation

Amorphous solid dispersions obtained from the spray drying were weighed (Weighing Analytical Balance Sartorius M2P, Germany). Yield the percentage was calculated by Eq. (1) [25].

$$Yield(\%) = \frac{Weight\ of\ amorphous\ solid\ dispersion}{Initial\ weight\ of\ drug\ and\ polymer} \times 100 \quad (1)$$

The total drug content in the sample was estimated by dissolving a predetermined amount of solid dispersion in a 6.8 pH phosphate buffer and was sonicated for 15 min.

The solution was suitably diluted with freshly prepared PBS 6.8 pH and was assayed by a UV-VIS spectrophotometer (T80 PG Uv/Vis spectrophotometer, United gangdom) for drug content at 287 nm [23, 24] using Eq. (2) [26]. Each experiment has been repeated three times. Before adopting this analytical method, its selectivity for the drug was confirmed by conducting a spectroscopic scan of a solution of the used polymers in phosphate buffer with the same concentrations used in the formulations.

$$Percent\ drug\ content = \frac{Practical\ content}{Theoritical\ content} \times 100 \quad (2)$$

2.6. Characterization of the SDs

2.6.1. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of samples were recorded using a Bruker Vector 22 spectrophotometer. Samples were compressed into KBr disks in a hydraulic press to prepare sample-KBr-blends. KBr pellets were characterized from 400 to 4000 cm^{-1} and with a resolution of 2 cm^{-1} [24].

2.6.2. Scanning Electron Microscope (SEM)

The morphology and particle size of pure cefdinir and the prepared pH$_M$-SDs were observed through scanning electron microscopy (SEM, VEGA II LSH, TESCAN, Czech Republic). Before SEM imaging, samples were coated with gold by a sputter coater. Approximately 1 mg of each sample was placed onto a double-sided adhesive strip on a sample holder. SEM images were taken at 10,000× magnification.

2.6.3. Differential Scanning Calorimetry (DSC)

The thermal properties of samples were characterized by the DSC instrument, DSC 131 (SETARAM, France). Each sample was accurately weighed (equivalently to 5 mg) into an aluminium pan and heated in the range of 30 – 300 °C, at a scanning rate of 10 °C/min under nitrogen airflow of 50 mL/min [24].

2.6.4. Powder X-Ray Diffraction

Powder X-ray diffraction patterns of cefdinir and the pH_M-SDs were obtained using Bruker's D8 Advance diffractometer (Karlsruhe, West Germany). PXRD patterns were recorded using Germanium monochromatic and Cu radiation with a nitrogen filter at a voltage of 50 KeV and a current of 30 mA. The samples were analyzed over the 2θ range of (3 - 60)° [24].

2.7. Drug Release Studies

Dissolution studies were carried out using the USP paddle method at (37± 0.2)°C in a Pharma test PT-DT7 dissolution tester (Germany) at 50 rpm with 900 mL of HCl buffer (pH 1.2), acetate buffer (pH 4.5), and phosphate buffer (pH 6.8) fluids as dissolution media [15]. The pH_M-SDs (equivalent to 300 mg of cefdinir) and pure drug were dispersed in the dissolution media, and at predefined intervals, 5-ml samples were withdrawn at (2, 5, 10, 15, 20, 30, 45, and 60) minutes, filtered through 0.45 μm syringe filter, and assayed via UV-VIS spectrophotometer (T80 PG, United Kingdom) for released drug at λ_{max} (280, 286, and 287 nm) for HCl buffer pH=1.2, acetate buffer pH=4.5, and phosphate buffer pH=6.8, respectively. An equivalent amount of release medium was supplemented to keep the volume constant. Each experiment was repeated six times.

2.8. Statistical Analysis of the Drug Release Profile

All the results were expressed as mean values ± standard deviation. The difference between percentages (fractions) of released cefdinir at each time interval from the pure drug, and prepared pH_M-SDs were statistically evaluated by using a two-tailed Student's t-test. All data analysis was performed using the Microsoft Excel 2019 software. A confidence limit of $p<0.05$ was fixed for the interpretation of the results.

Percent dissolution efficiency (%DE) was also computed to compare the relative performance of various carriers in solid dispersion formulations [27].

The magnitude of %DE at 10 min (%DE10 min) and 30 min (%DE30 min) for each formulation were computed as the percent ratio of area under the dissolution curve up to the time, t, to that of the area of the rectangle described by 100% dissolution at the same time [28].

$$\%DE = \left(\frac{\int_0^t y\,dt}{y100\,t} \right)100 \tag{3}$$

2.9. Mathematical Modeling of Release Kinetics

The *in vitro* drug release data were fitted to various release kinetic models [29-31] viz. first-order, Higuchi, Hixson-Crowell cube root, Korsmeyer–Peppas, and zero-order model employing the following set of equations:

First-order model

$$F= F_{max} * [1-e^{(-k1.t)}] \tag{4}$$

Zero-order kinetic model

$$F= F_0 + k_0.t \tag{5}$$

Higuchi model

$$F= F_0 + k_{H}.\, t^{0.5} \tag{6}$$

Hixson-Crowell cube root model

$$F= 100* [1-(1-k_{HC}*t)^{\wedge}3] \tag{7}$$

Korsmeyer–Peppas model

$$F= k_{KP}*t^n \tag{8}$$

where F is the fraction (%) of drug released in time t, F_0 is the initial fraction of the drug in the solution resulting from a burst release. Various other terms viz. k_{KP}, k_o, k_1, $k_{HC,}$ and K_H refer to the release kinetic constants obtained from the linear curves of Korsemeyer–Peppas, zero-order, first-order, Hixson-Crowell cube root law, and Higuchi model, respectively. Model fitting using Eqs. (4)–(8) was accomplished by using DDSolver software (add-in program for Microsoft Excel) [32].

3. RESULTS AND DISCUSSION

3.1. Solubility Results

As expected for a weakly acid, cefdinir solubility highly depends on the pH of the media "Figure **2**".
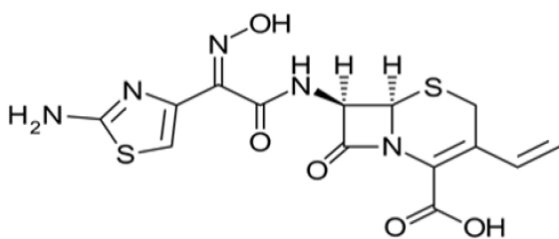
Figure 1: Chemical structure of cefdinir.

Cefdinir can be classified as practically insoluble in water (0.47) mg/ mL. The solubility of cefdinir "Figure **2**" was sharply increased over pH 4.5. This is because Cefdinir has three ionizable groups with the following pKa values: −COOH group of cephem moiety (pKa = 1.9), −NH2 group of the aminothiazole moiety (pKa = 3.3), and =N–OH group of the oxime moiety (pKa = 9.9) [33]. According to the Henderson-Hasselbalch equation, the -COOH group of the cephem moiety (pKa = 1.9) is almost completely ionized over about pH 4.5, likely causing the observed increased aqueous solubility of cefdinir over about pH 4.5. The pH-dependent solubility (as shown in "Figure **2**") indicated that a neutral to basic pH environment might facilitate

drug dissolving. Consequently, alkalizers were chosen as the pH modifiers; and to choose the best alkalizer, Cefdinir solubility in 1% w/v aqueous solution of different alkalizers (i.e. 1% w/v solution of aqueous sodium hydroxide, potassium hydroxide, and sodium bicarbonate) was studied. The solubility of Cefdinir in various solvents, alkalizer solutions were presented in Figure **2**. Based on the solubility, sodium hydroxide was selected for the development of the pH_M-SDs. The Spray-drying technique was used because it is mainly aimed at generating amorphous materials and is the technique of choice for particle size reduction [19]. In order to avoid using organic solvents during the preparation process, sodium hydroxide (NaOH) was used as an alkalizer to increase the solubility of cefdinir in the polymeric solutions.

3.2. Process Yield and Drug Content Estimation

Figure **3** shows the UV-VIS spectrophotometric scan of cefdinir solution and polymers solution. As we can see there was not any interference by polymers in UV analysis at 287 nm. The process parameters and drug-
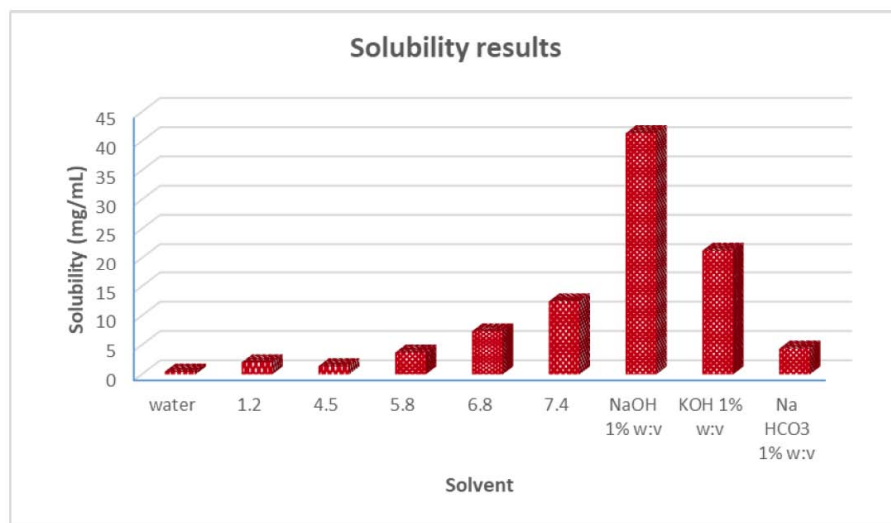

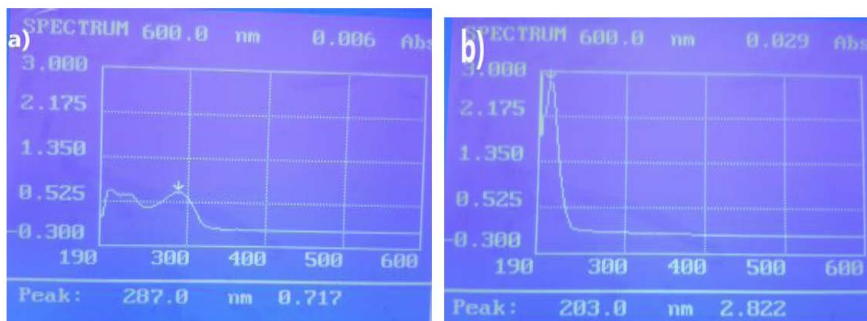**Figure 2:** the pH-dependent solubility of cefdinir.

Figure 3: UV-VIS scan of a solution of **a**) Cefdinir, **b**) used polymers at the same concentration used in formulations F1 to F6.

Table 2:   Particle Characterizations, Process Yield and Drug Content of Prepared pH$_M$-SDs

Formulation code	Particle size (µm)±SD	Process yield (%)	Drug content (%)
F1	1.706±0.128	80.55	96.083±1.325
F2	1.493±0.172	78.56	97.986±2.745
F3	1.988±0.164	50.93	99.628±2.867
F4	1.869±0.124	44.19	97.065±1.023
F5	1.862±0.182	75.67	100.312±4.031
F6	1.796±0.164	70.63	98.659±3.002

carrier content load will influence the yield (%) of the spray-dried product. The process yield and estimated drug content for each formula are shown in Table **2**.

F3 and F4 showed lower yields, which could be due to the stickiness of the product [34]. Drug content results (Table **2**) indicated that the formulation composition and preparing process had almost no effect on the drug content of the SDs [35, 36].

3.3. Fourier Transform Infrared Spectroscopy (FTIR)

"Figure **4a**" shows the FTIR spectra of cefdinir, PVP-K30, F1, and F2. The FTIR spectra of HPMC, F3, and F4 are shown in "Figure **4b**", whereas the FTIR spectra of Eudragit L100, F5, and F6 are present in "Figure **4c**".

FTIR spectrum of Cefdinir "Figure **4a**" is characterized by principal absorption peaks at 3300 cm^{-1} (O-H stretch COOH), 2978 cm^{-1} (C-H stretch cyclic), 2898 cm^{-1} (C-H stretch), 1781 cm^{-1} (C-O),1763 cm^{-1} (co of β-lactam), 1667 cm^{-1} (C-C alkene), 1610 cm^{-1} (C-C aromatic), 1544 cm^{-1} (N-H bending), 1428 cm^{-1} (C-N stretch) and 656 cm^{-1} (C-S) [4]. The FTIR spectrum of pure PVP K30 (Figure **4a**) produced a characteristic absorption band at 1658 cm^{-1}. This can be attributed to the carbonyl group [37]. The very broadband at 3440 cm^{-1}
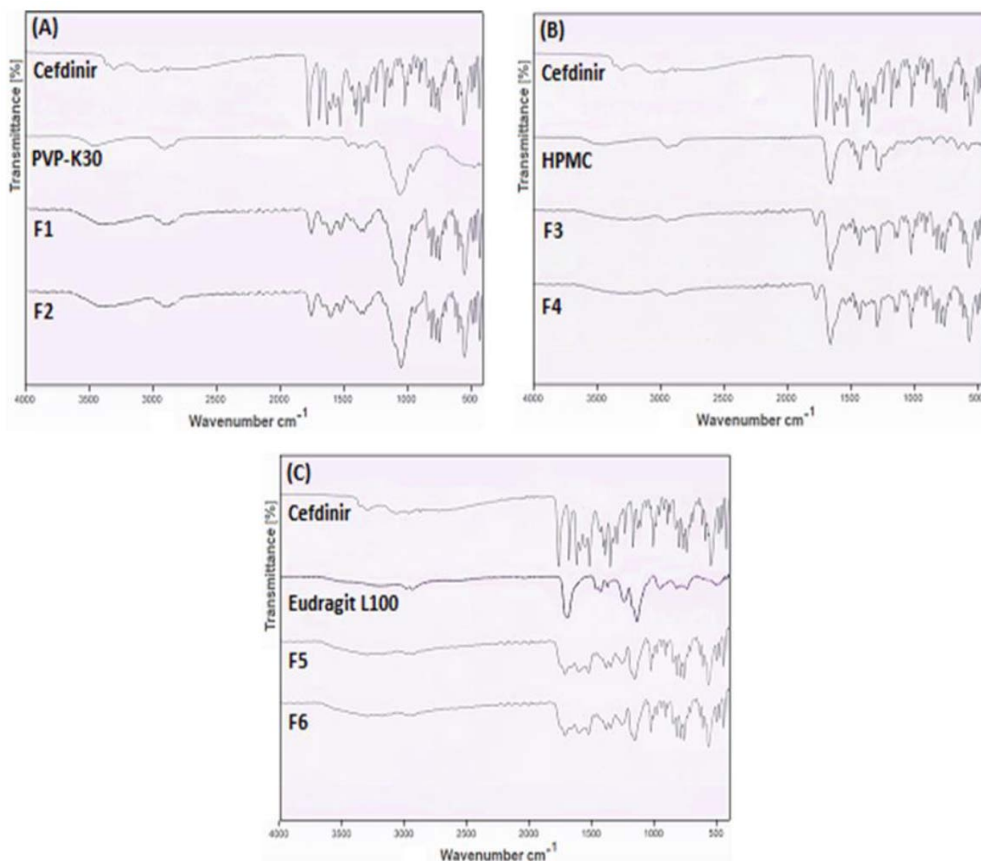
Figure 4: FTIR spectra of Cefdinir and different formulation.

indicates the presence of moisture, revealing the hygroscopic nature of PVP K30 [37]. In the FTIR spectrum of HPMC (Figure **4b**), the broad absorption band at 3456 cm^{-1} indicates the stretching frequency of the –OH groups. The bands at 2948 and 1065 cm^{-1} represent the stretching vibration of C–H and C–O bonds, respectively. The bending vibration of –OH groups on the HPMC appeared at 1419 cm^{-1} [38]. The spectrum of Eudragit L100 (Figure **4c**) has a characteristic band of OH (3170 cm^{-1}), CH Stretching Aromatic (3067 cm^{-1}), CH Stretching Aliphatic (2954 cm^{-1}), C=O(1598 cm^{-1}) [39].

On the other hand, all pH_M-SDs (F1, F2,…..F6) exhibit strong absorbance between 1650 and 1550 cm^{-1} (1614 cm^{-1} for pH_M-SDs prepared with PVP-K30), (1654 cm^{-1} for pH_M-SDs prepared with HPMC), (1561 cm^{-1} for pH_M-SDs prepared with eudragit L100). This strong absorbance may be attributed to the carboxylate group of cefdinir [40]. And the carbonyl peaks due to carboxylic acid interactions at 1710 and 1735 cm^{-1} are not seen in the spectra of the prepared formulations due to loss of proton [40]. FTIR data may indicate direct conversion from crystalline cefdinir to amorphous salt [40].

3.4. Scanning Electron Microscope (SEM*)*

SEM was used to compare the morphology and particle size of each formulation. SEM micrographs of pure cefdinir and its pH_M-SDs are shown in "Figure **5**". Pure drug consisted of acicular shaped particles with a mean particle size (2.413 ± 1.29) µm. On the contrary, the solid dispersions appeared in the form of spherical particles and the original morphology of cefdinir disappeared which was supported by DSC, and PXRD. Particle sizes for prepared pH_M-SDs are shown in Table **2**.
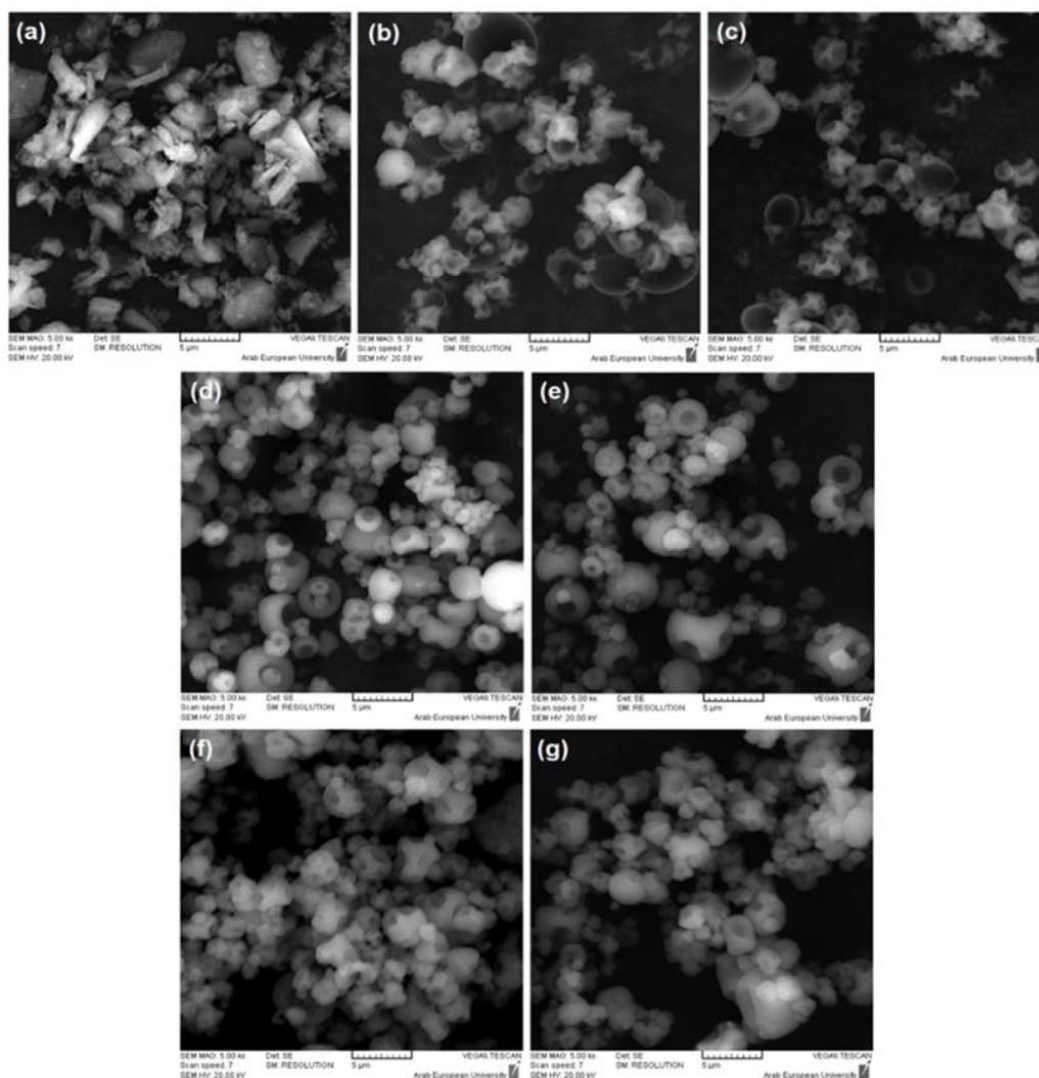

Figure 5: Scanning electron microscopy at magnification (X10,000) of **a**) pure cefdinir **b**) F1 **c**) F2 **d**) F3 **e**) F4 **f**) F5 **g**)F6.

3.5. Differential Scanning Calorimetry (DSC)

The solid state of the drug in the pH$_M$-SDs was characterized by using DSC, and PXRD. The endotherm in the thermogram of pure cefdinir "Figure **6**" at 60.35°C indicates the glass transition temperature of cefdinir [41] and the sharp exotherm at 227.33°C represents drug degradation [42]. These results were in good agreement with the reported DSC curve of cefdinir anhydrous [42]. DSC thermogram of PVP K30 reveals glass transition temperature at 175.43 °C, with the absence of any melting point peak "Figure. **7**" [43, 44]. This result suggests an amorphous characteristic

of PVP K30 [43]. Besides, a broad endotherm ranging from (48.08 to 99.51) °C is observed in the thermogram of pure PVPK30 which was attributed to the water loss from the hygroscopic polymer upon heating [43]. The DSC thermogram of HPMC "Figure **8**" shows no sharp endothermic peaks indicating no exact melting points [45]. A broad endothermic bend in the thermogram appears from (41.87 to 118.53) °C, which might be due to the volatilization of adsorbed water [46]. The thermogram of Eduragit L100 "Figure **9**" showed two endothermic peaks. The first is a broad peak between (46.78 and 115.44) °C, which can be explained by the evaporation of the absorbed moisture [47]. The other
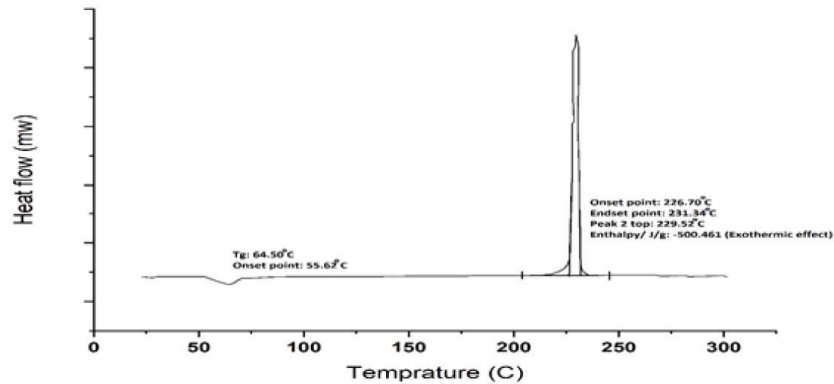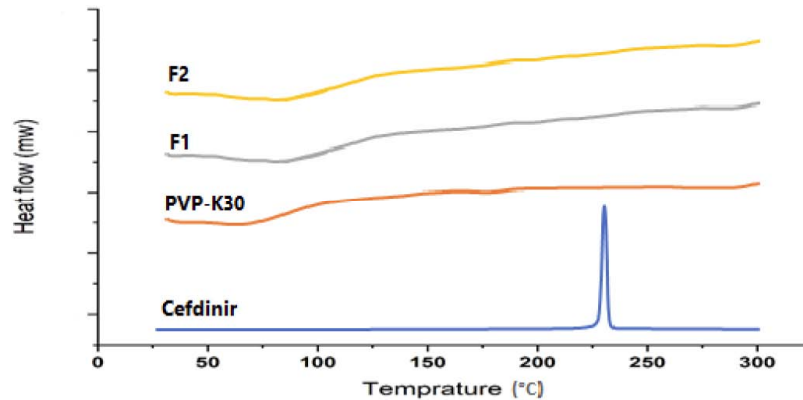

Figure 6: DSC thermograms of Cefdinir.

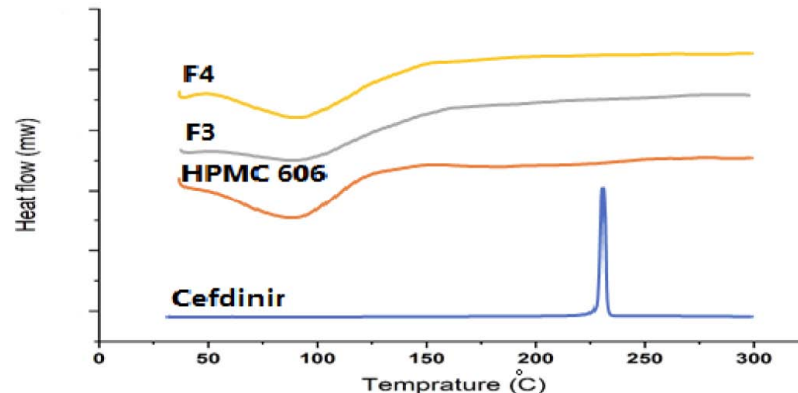**Figure 7:** DSC thermograms of Cefdinir, PVP, F1, and F2.

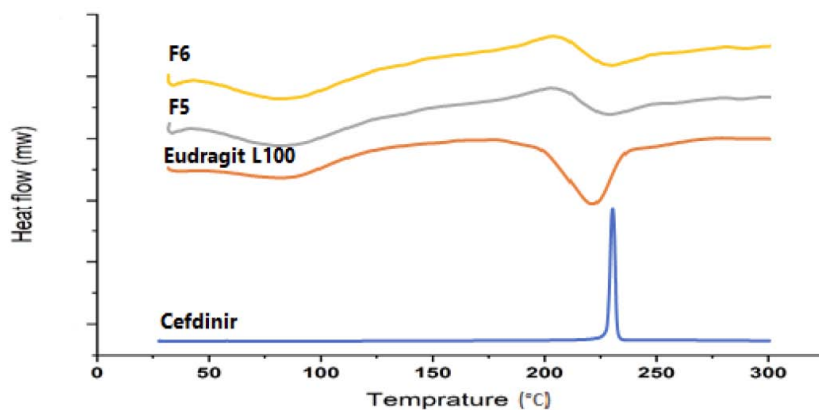**Figure 8:** DSC thermograms of Cefdinir, HPMC, F3, and F4.

Figure 9: DSC thermograms of Cefdinir, Eudragit L100, F5, and F6.

peak appeared at a higher temperature with an onset 195.61 °C, endset of 236.64 °C, which may be due to the glass transition of the polymer [48].

On the other hand, DSC thermograms of different pH_M-SDs are also shown in "Figures **7**, **8**, and **9**". However, there is no exothermic peak observed at the melting point of Cefdinir in the thermograms of prepared solid dispersions. The absence of a peak indicates complete conversion into an amorphous form [49], [50].

3.6. Powder X-Ray Diffraction

The PXRD pattern of pure cefdinir "Figure **10**" showed characteristic peaks at 5.85°, 11.7°, 16.1°, 21.15°, 22.25°, 24.4°, 26.2°, and 28.8° of 2θ [4].

On the other hand, all pH_M-SDs were characterized by a complete absence of any peaks corresponding to the crystalline form of cefdinir "Figure **10**".

According to FTIR, DSC, and PXRD results, they suggested the conversion of the crystalline cefdinir into amorphous salt, and they showed a good correlation with each other.

3.7. Drug Release Studies

The dissolution studies for different pH_M-SD formulations were performed in HCl buffer (pH 1.2), acetate buffer (pH 4.5), and phosphate buffer (pH 6.8) fluids. As shown in "Figure **11**" Cefdinir (pure drug) and its SDs (F1 to F6) showed relatively higher dissolution at pH 6.8 "Figure **11c**" compared to pH 1.2 and pH 4.5
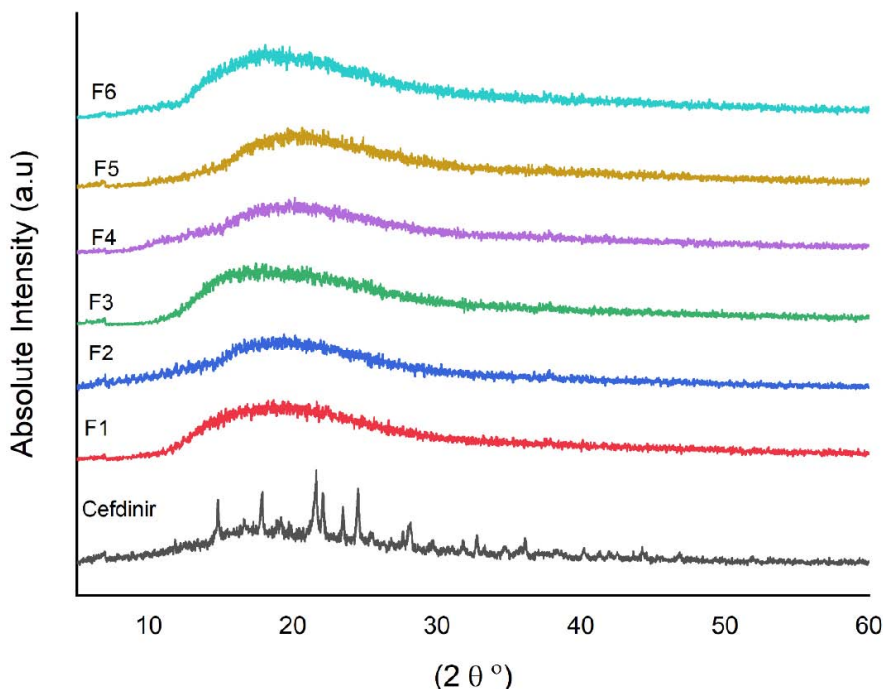

Figure 10: Comparison of PXRD diffractograms of pure cefdinir and its prepared pH_M-SDs.
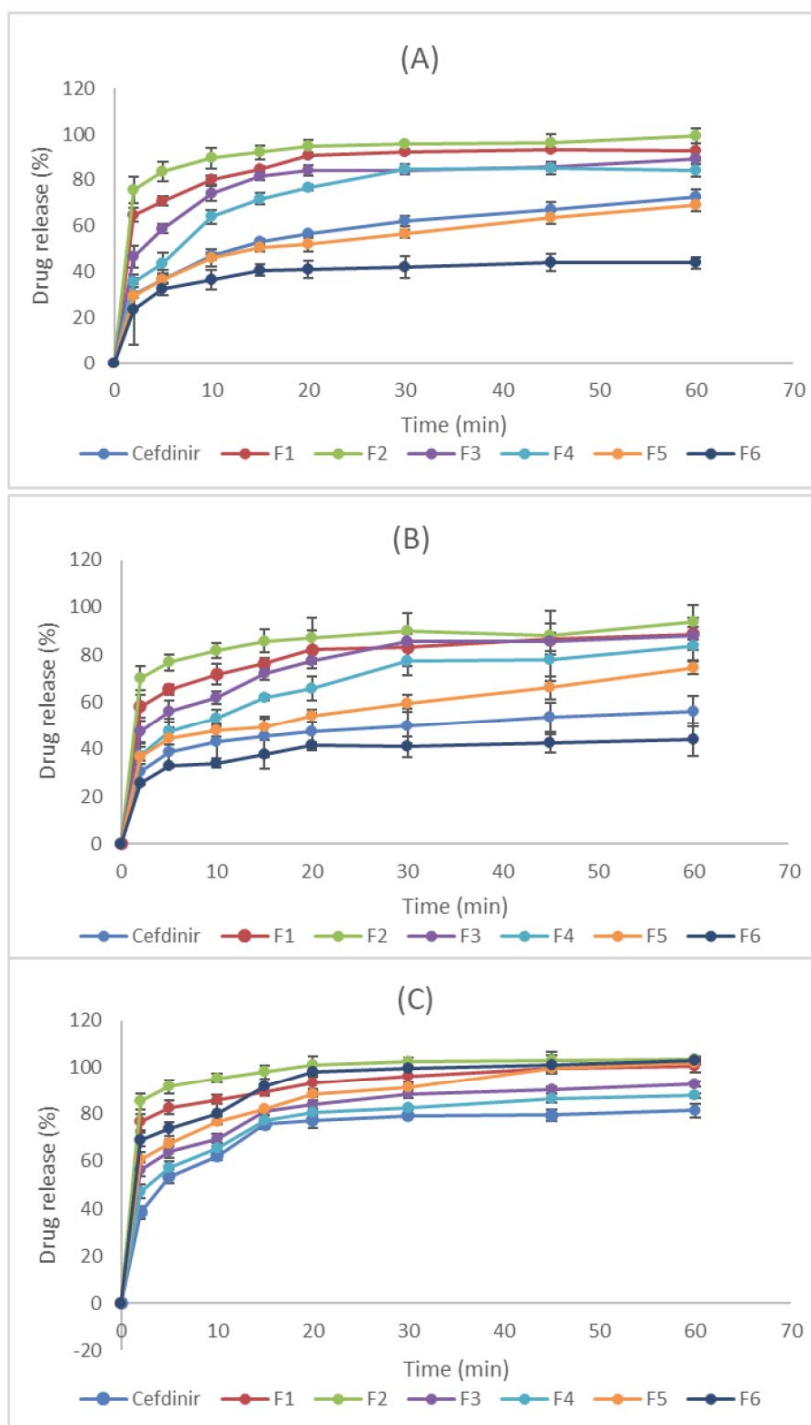
Figure 11: Drug release profile from pure cefdinir and different formulation (from F1 to F6) in: (**A**) HCl pH 1.2 (**B**) Acetate buffer pH 4.5 (**C**) Phosphate buffer pH 6.8.

"Figure **11a**, **11b**", due to the poor solubility of cefdinir at low pH.

3.7.1. Effect of Different Carriers on the Dissolution of Cefdinir from Solid Dispersions

Table **3** enlists the dissolution parameters of Cefdinir solid dispersions with various carriers (PVP-K30, HPMC, and Eudragit L100).

It could be also found that PVP-based pH_M-SDs showed an enhanced dissolution at all studied media compared to the pure drug at all time points according to two-tailed Student's t-test ($p<0.05$), especially in phosphate buffer, it was found that the PVP-K30 based SDs (F1 and F2) could reach the highest dissolution rate within 30 min, while the HPMC-based SDs (F3 and F4) exhibited lower drug release (Table **3**). This might

Table 3: Dissolution Parameters of Cefdinir and Various Solid Dispersion Formulations

Formulation	DP_{5min}[a]	DP_{15min}[a]	DP_{60min}[a]	$\%DE_{10min}$[b]	$\%DE_{30min}$[b]
HCl buffer pH=1.2					
Pure drug	36.64	52.94	72.73	33.91	48.54
F1	70.77	84.73	92.86	64.51	80.44
F2	83.73	92.07	99.33	74.79	87.4
F3	58.77	81.81	89.38	53.73	72.79
F4	43.59	71.81	84.29	42.32	64.71
F5	36.59	50.81	69.33	38.85	48.59
F6	32.59	40.73	43.94	28.03	35.66
Acetate buffer pH= 4.5					
Pure drug	38.42	45.24	56.23	33.63	42.41
F1	65.42	76.24	88.78	58.68	72.64
F2	76.88	85.76	93.74	68.75	80.8
F3	56.06	71.97	88.23	49.76	67.39
F4	47.33	61.83	83.74	41.56	57.91
F5	44.45	49.29	74.45	38.86	48.59
F6	32.76	37.68	43.96	28.03	35.56
Phosphate buffer pH= 6.8					
Pure drug	53.53	75.59	81.41	46.57	65.86
F1	82.76	89.63	100.80	73.78	86.07
F2	91.76	98.14	103.54	81.86	93.92
F3	63.98	81.19	92.79	57.11	74.13
F4	57.37	77.26	87.71	51.09	69.29
F5	67.34	82.01	102.21	61.31	77.85
F6	73.63	91.65	103.264	66.84	85.38

[a]DP: Percent drug released at particular time.
[b]%DE: Percent dissolution efficiency at particular time.

be due to the increased wettability of the drug caused by PVP-K30, and the changes in the drug crystallinity imparted by the alkalizer [40], the probable reduction in Cefdinir particle size [28], the modulation of microenvironmental pH surrounding particles [51, 52]. For HPMC-based SDs, although HPMC 606 has a rapid hydration property in the aqueous solution, it showed a relatively higher swelling property during the dissolution test and further retarded the drug release from the pH_M-SDs [53].

For eudragit L100 based pH_M-SDs, the highest release was observed at pH 6.8, because eudragit L100 is soluble in intestinal fluid from pH 6 [54]. At pH 1.2 and 4.5 eudragit L100 is insoluble, but drug release from the eudragit L100 based pH_M-SDs was significantly impacted by the microenvironmental pH induced by the solubilized drug. Solubilized cefdinir salt or solubilized

pH modifier (alkalizer: NaOH) increased the microenvironment pH which dissolved the polymer and released the drug slowly even at lower pH media (1.2 and 4.5) [55]. While at pH 6.8 pH_M-SDs based on eudragit L100 showed dissolution rates higher than pH_M-SDs based on HPMC. As we can see in Figure **11**, F5 and F6 showed a significant enhancement in drug release in phosphate buffer (pH 6.8) at all time points vis-a`-vis F3 and F4 according to Student's t-test ($p < 0.05$).

3.7.2. Effect of Concentration of the Carriers on the Dissolution of Cefdinir from solid Dispersions

Table **3** reveals that drug dissolution improved to varying degrees with the rise in the amount of each carrier. In contrast to all other explored carriers, HPMC, at higher carrier concentrations showed rather decreased drug release rates vis-a`-vis pure drug,

which could be because of the protective viscous layer which had been formed around the drug compact during dissolution [56].

For comparative analysis of all the formulations, %DE values at two times, representing the early and late phase of dissolution study, were computed. The %DE values in the initial time period of dissolution study (e.g., %DE10 min) provide comparative information for very fast releasing formulations, whereas, %DE30 min values furnish relative information about both fast and slow releasing formulations.

The value of %DE10 min for pure drug (33.91, 33.63, and 46.57 in HCl buffer, acetate buffer, and phosphate buffer, respectively) was enhanced from miniscule (42.32, 41.56, and 51.09 for HPMC system) to very

high (74.79, 68.75, and 81.86 for PVP-k30 system) at 1:2 w/w drug: carrier ratio.

However, the ratio of drug to carrier has been shown to have an effect on drug release. For pH_M-SDs based on PVP-K30, the more carrier present, the more a drug is converted into the amorphous form, which leads to greater drug release [21, 57]. And this was obvious in drug release studies "Figure **11**". F2 showed an enhanced dissolution rate in comparison with F1 at (2, 5, 10, and 15 mins) according to a two-tailed Student's t-test ($p<0.05$). This result was in agreement with a previous study which showed that the drug dissolution from pH_M-SDs increased when increasing the drug/carrier ratio and stopped increasing when the ratio reached above 1:2 [58].

Table 4: **Statistical Parameters of Various Formulations Obtained after Fitting the Drug Release Data to Various Release Kinetic Models**

Formulation	Mathematical models for drug release kinetics										
	Zero order		First order		Higuchi		Hixson-Crowell		Korsemeyer–Peppas		
	HCl buffer pH=1.2
	Slope	r^2	Slope	r^2	Slope	r^2	Slope	r^2	Slope	r^2	n
Cefdinir	0.669	0.861	0.07	0.794	11.1	0.436	0.01	-0.623	25.58	0.992	0.257
F1	0.434	0.647	0.24	0.619	16.5	-5.93	0.03	-4.923	61.33	0.950	0.113
F2	0.315	0.669	0.34	0.696	3.29	0.832	0.03	-16.64	74.11	0.952	0.075
F3	0.564	0.579	0.13	0.880	6.05	0.758	0.03	-0.856	47.60	0.886	0.166
F4	0.761	0.648	0.07	0.909	8.02	0.820	0.02	0.383	34.54	0.922	0.241
F5	0.601	0.964	0.11	0.475	5.84	0.961	0.01	-1.961	26.98	0.986	0.233
F6	0.262	0.694	0.23	0.729	2.78	0.844	0.01	-1.334	25.36	0.932	0.156
	Acetate buffer pH=4.5
Cefdinir	0.372	0.822	0.16	0.710	3.73	0.938	0.01	-5.570	28.51	0.988	0.169
F1	0.465	0.779	0.23	0.601	4.72	0.897	0.02	-4.159	54.10	0.979	0.125
F2	0.314	0.709	0.33	0.621	3.23	0.855	0.03	-14.47	67.91	0.966	0.078
F3	0.658	0.774	0.09	0.669	6.68	0.909	0.02	-0.566	42.10	0.967	0.191
F4	0.739	0.848	0.08	0.726	7.35	0.955	0.02	-0.200	32.00	0.981	0.240
F5	0.591	0.964	0.15	0.475	5.60	0.966	0.01	-1.961	29.88	0.977	0.212
F6	0.253	0.694	0.19	0.726	2.61	0.844	0.01	-8.884	25.12	0.948	0.142
	Phosphate buffer pH=6.8
Cefdinir	0.583	0.581	0.11	0.902	6.26	0.762	0.02	-0.510	40.28	0.870	0.190
F1	0.380	0.838	0.35	0.505	3.79	0.954	0.03	-13.58	72.05	0.993	0.084
F2	0.258	0.666	0.41	0.635	2.71	0.835	0.03	-33.83	83.45	0.957	0.057
F3	0.570	0.754	0.18	0.611	5.82	0.895	0.03	-1.808	51.41	0.958	0.152
F4	0.610	0.703	0.13	0.764	6.33	0.861	0.02	-0.777	44.47	0.948	0.178
F5	0.674	0.865	0.18	0.551	6.68	0.963	0.03	-1.512	53.29	0.992	0.162
F6	0.559	0.724	0.22	0.512	5.74	0.867	0.03	-3.282	62.45	0.938	0.131

Therefore, in the presence of an alkalizer, a smaller amount of pH modifier might still provide a high degree of saturation solubility in the pH_M-SD formulation [59]. This phenomenon might be related to the process of forming the solid dispersions; the crystalline structure of the drug and alkalizer were converted to the amorphous state, resulting in an increased dissolution rate of the drug. Obviously, adding NaOH to SDs enhanced the Cefdinir dissolution rate [58].

For weakly acidic drugs, such as Cefdinir, including an alkalizer as a pH modifier in the solid dispersion can enhance the drug release. The pH modifier achieves this by increasing the micro-environment pH, which is described as the pH of the saturated solution in the environment immediately surrounding the drug particles [20]. Whereas for HPMC-based pH_M-SD, F4 showed a lower dissolution rate in comparison with F3 at time points (2, 5, 10, 15, and 20 mins) according to two-tailed Student's t-test ($p<0.05$). This can be explained by the fact that HPMC is a water-soluble polymer, but it formed a protective viscous layer around the drug compact during dissolution [56]. It is likely that drug diffusion through the HPMC layer and erosion of the latter affect drug release; consequently, it will take some time for the drug to be released from solid dispersions containing large amounts of HPMC, but it will not influence the dissolution endpoint as also observed in the current study [56, 60].

Maximum values of various dissolution parameters observed for PVP-K30 formulation (F2) construe attainment of the very high rate of drug dissolution, comparable to that obtained for formulations.

3.8. Mathematical Modeling of Release Kinetics

Table **4** enlists the regression parameters obtained after fitting various release kinetic models to the *in vitro* dissolution data.

Based on the determination coefficient (r^2), the Korsmeyer–Peppas model is the function that best fits the dissolution data of Cefdinir and prepared pH_M-SDs at different pHs.

Overall, the values of diffusional exponent 'n', obtained from the slopes of the fitted Korsmeyer–Peppas model, ranged between 0.057 and 0.257. all the solid dispersions tended to exhibit Fickian diffusional characteristics, as the corresponding values of n were lower than the standard value for declaring Fickian release behavior, i.e., 0.4500 [30].

4. CONCLUSION

In this study, a pH_M-SD was used to increase the dissolution rate of a poorly water-soluble weakly acidic drug, such as Cefdinir, in a pH-dependent manner. Among the three types of polymers, PVP-K30 based pH_M-SDs significantly increased the drug dissolution in media with different pH (1.2, 4.5, and 6.8). The major contributing factors for enhancing the dissolution in SD containing alkalizer were the modulation of pH_M and the formation of an amorphous state through molecular interactions, which was verified using FTIR, SEM, DSC, and PXRD analyses. In fact, the system also might fit for the other poorly water-soluble weakly acidic drugs because of their similar physical characters.

AUTHORS´ CONTRIBUTION

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies with human and animal subjects performed by any of the authors.

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