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Research Article

Employing Co-grinding Technique for Improving Cefpodoxime Proxetil Dissolution Characteristics

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Abstract

Cefpodoxime Proxetil (CP) is an oral prodrug. Its extremely poor solubility in the biological fluids, is what causes its poor bioavailability. And since dissolution is rate-limiting stage in attaining the required bioavailability, co-grinding technique was exploited, it comprises grinding the medicine with excipients (one or more excipients) to create nanoparticles. Formulations were prepared by dry co-grinding technique, for different durations 5, 10 and 20 minutes either alone or with the selected carrier using mortar and pestle. Different premixes of CP as binary or ternary mixtures using fixed concentration of the API (260mg of CP equivalent to 200mg Cefpodoxime base) along with various ratios of other additives. Carriers used were Aerosil 200, Glycine, polyvinylpyrrolidone (PVP) K25 and HPMC E6. The prepared formulations were characterized through dissolution testing, FTIR and DSC techniques. Dissolution parameters such as dissolution efficiency (DE%), amount released after 5 minutes (Q5) and 60 minutes (Q60) were calculated. Statistical evaluation covering student's T-test, f_1, dissimilarity factor and f_2, similarity factor was calculated. The findings from the binary mixtures of CP with Aerosil 200 has shown to be very promising, and hence, ternary mixtures of the CP/Aerosil 200 and one of the three carriers -namely, glycine, PVP K25 and HPMC E6- at the ratio of 1:1:1, were separately co-grounded to give mixtures where Q5 ranged from 60% – 68%, Q60 ranged from 80 to 100% and DE% ranged from 67-82%. These results are suggested augmenting effect of the large surface area of Aerosil 200 and the hydrophilic nature of the other carriers. Upon decreasing the weight ratios of Aerosil 200 and other carriers to 1:0.25:0.5, PVP K25 was the most effective tested polymer in terms of improving drug dissolution rate at the lowest weight ratio.

Keywords

Cefpodoxime Proxetil, Co-grinding, Aerosil 200, HPMC E6, PVP K25, Glycine

1. Introduction

The Numerous techniques can be used to create drug nanoparticles. One of these is the co-grinding technique, which involves grinding the medicine with excipients (one or more excipients) in order to create nanoparticles [1], Grinding is unlike comparable techniques, as it does not necessitate the use of hazardous organic solvents, making it preferable to other procedures from both an economic and environmental standpoint [2, 3].

A variety of techniques can be used to create drug nanoparticles. There is a difference between top-down and bottom-up technology. Bottom-up technologies begin with molecules, which are precipitated /crystallized in such a con-

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trolled manner to create the desired particle size. Bottom-up techniques are no longer the favored strategy for creating drug nanoparticles recently due to the use of organic solvents [4].

Co-grinding is a strategy of top-down disintegration in which the drug is ground with one or more excipients to produce nano-sized particles [5, 6]. One of the main advantages of co-grinding over competing methods is the fact that it is a simple procedure that does not employ organic solvents to produce nanosized particles, making it an economically and environmentally desirable technology [2]. Control of the grinding factors is essential, such as the rate of grinding, duration of grinding, grinding technique, volume of the grinding pot, the quantity of excipients used, and the ratio of the medicine to the excipients [4].

Two methods for producing co-crystals have been developed: neat grinding (also known as solid state grinding or dry grinding) and solvent drop grinding (also known as liquid assisted grinding or kneading) [7].

The process of neat/dry grinding can be accomplished either via the mechanical approach, by using a ball mill or the vibratory mill, or manually using a mortar and pestle. Co-crystals are sometimes formed because of this process. At least one of the reactants should have high solid-state vapor pressures for this strategy to be effective [8].

Dry milling techniques can also be used to create nanosuspensions. This technique is utilized to create stable nanosuspensions of poorly soluble medicines using soluble polymers and co-polymers. Through this method, you may generate a stable amorphous solid by reducing particles size to the submicron range. Several poorly water-soluble medications have been effectively formed into colloidal particles employing dry co-grinding with polyvinylpyrrolidone as a stabilizer.

Wet grinding techniques are used to create nanosuspensions employing high pressure homogenization and media milling using Pearl-ball mills. Lately, dry milling technology has permitted the production of nanosuspensions. Because of the improvement in surface polarity and a transfer of a crystalline drug to an amorphous drug, co-grinding improves the physicochemical characteristics and solubility of poorly water-soluble medicines. It has been reported that stable nanosuspensions may be made by dry co-grinding of insoluble medicines with soluble polymers and copolymers dispersed in a liquid medium [9]. The partial dissolution that might lead to uncontrolled recrystallization (particularly during drying) or chemical instability is a typical downside of the wet milling process [10]. Wet co-grinding was proven its efficiency in a wide group of APIs such as, nifedipine [3], hydrochlorothiazide [11].

Dry co-grinding may be done quickly, inexpensively, and without the need for organic solvents. An amorphous solid that is stable can be produced through the co-grinding approach to decrease particles to the nano range. Neat co-grinding has proven to improve the dissolution rate for numerous APIs such as phenytoin [12], furosemide [13], nifedipine [3], glibenclamide [14], Carbamazepine [2], meloxicam [4].

Regarding wet grinding, solvent should be added in a timely manner during the solvent drop grinding procedure. It is important to choose a solvent that can dissolve the molecule. A successful application to the solvent drop grinding approach is the caffeine glutaric acid co-crystal polymorph which was more successful in producing new co-crystals, more affordable, and ecologically acceptable than the evaporation method [15].

(Q5) was specifically chosen to highlight the rapid effect of the changes made in the formulations and to indicate the rapid absorption of the drug, while (Q60) was chosen because it is the endpoint of the pharmacopoeial limit.

The aim of this work is to accelerate the rate at which Cefpodoxime Proxetil dissolute to produce granules which be further compressed into tablets that dissolute quickly and cause the medicine to be absorbed better. And hence reach better availability at the site of absorption. This may be accomplished by development and verification of an appropriate quantitative method for determining Cefpodoxime Proxetil, determination of the dissolution rate of the unprocessed drug and characterization of co-grounded granules.

Cefpodoxime Proxetil (CP) is a poorly water-soluble drug. The chemical name of Cefpodoxime Proxetil is, (RS)-1-((Isopropoxycarbonyl) oxy) ethyl (+) - (6R, 7R) – 7 - (2-(2-amino-4-thiazolyl)-2-((Z)-methoxyimino) acetamido)-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo (4.2.0) oct-2-ene-2-carboxylate [17]. Cefpodoxime Proxetil (brand name Vantin or Orelox) [16, 17] is a semi-synthetic antibiotic of the cephalosporin class. which used commonly used in the management of respiratory tract and urinary tract infections [18]. It is mostly administered at dosages of 200mg tablet twice every day. Though its absolute bioavailability in humans is unknown, CP is known to be extensively and well-absorbed [16].

Excipients used in this research include: Poloxamer 188 (Pluronic F68); it often exists as cast solids or as white, waxy, free-flowing spherical grains having little flavor or odor. Used as tablet lubricant, wetting agent, emulsifying agent, dispersing agent, and solubilizing agent, commercially known as Pluronic F-68 [19]. Avicel PH 102 (Micro Crystalline Cellulose); it is refined, partly depolymerized, it is a crystalline powder that is white, odorless, and tasteless and is made up of porous units. It is functionally categorized as an adsorbent, tablet disintegrant, capsule diluent and a suspending agent. It is utilized in direct compression as well as wet granulation operations [19]. HPMC E6; hydroxypropyl methylcellulose E6 also known as Hypromellose which is a fibrous granular, white to creamy-white, flavorless, and odorless substance. Together with topical, nasal, and ocular pharmaceutical formulations, Hypromellose is widely utilized in oral formulations [19]. Glycine; Aminoacetic acid, Glycine is a sweet-tasting, white, crystalline powder that is odorless and crystalline. It is utilized in the pharmaceutical sector as a

nutritional supplement, tablet disintegrant, bulking agent, wetting agent, and buffering agent [19]. PVP K25: usually referred as Crospovidone. Crospovidone is an almost tasteless, odorless, white-colored to off-white-colored powder known to be hygroscopic, finely split, and free-flowing [19]. and Aerosil 200 which is also known as; colloidal silica, fumed silicon dioxide and other commercial names. It is an odorless, tasteless, bluish-white in color, light and loose amorphous powder. Aerosil dust inhalation could cause respiratory tract irritation, even though there is no correlation to silicosis (lung fibrosis), which could arise after exposure to crystalline silica [19].

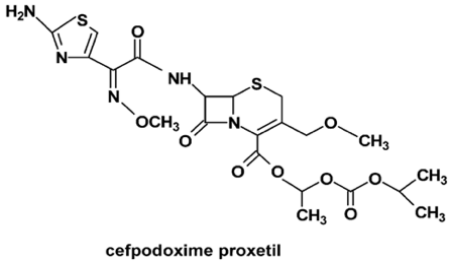
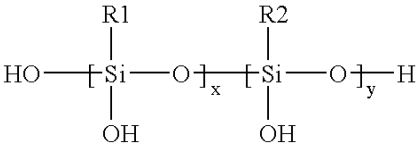
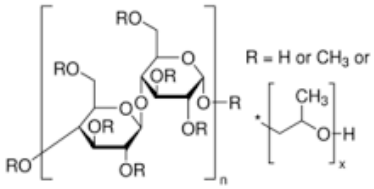
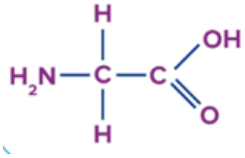
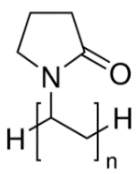
2. Materials and Methods

Cefpodoxime Proxetil (CP) is a poorly water-soluble drug. The chemical name of Cefpodoxime Proxetil is (RS)-1-((Isopropoxycarbonyl) oxy) ethyl (+) - (6R, 7R) – 7 - (2-(2-amino-4-thiazolyl)-2-((Z)-methoxyimino) acetamido)-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo (4.2.0) oct-2-ene-2-carboxylate [20].

2.1. Materials

CP was a gift from Pharco B International company, Pharco corporation, it was purchased from Aurobindo Pharma Ltd. -HITEC City, Hyderabad, India. Aerosil 200, PVP k25, HPMC E6 were purchased from Evonik, Germany and Glycine was purchased from Fisher Chemicals, USA. Reagents such as Methanol (Analar grade) and conc. HCl (Analar grade) were purchased from Merck, Germany. Table 1 shows the structures and melting points of CP and carriers used within this research.

Table 1. *Structures and melting points of CP and carriers used.*

Substance	Structure	Melting point (℃)
Cefpodoxime Proxetil [20]	 cefpodoxime proxetil	111 – 113 ℃
Aerosil 200 [21]		1600 ℃
HPMC E6 (Hypromellose) [22]		190-200 ℃
Glycine [23]		232–236 ℃
PVP K25 (Povidone) [24]		Softens at 150 ℃

2.2. Methods

2.2.1. Sample Spectrophotometric Assay of CP

A stock solution of CP was prepared by dissolving 10mg in 50 ml methanol (stock solution). Serial concentrations were prepared by transferring 2, 3, 4, 5, 6 and 7 ml each into 50ml volumetric flask and completing to volume using the dissolution medium (Glycine – sodium dihydrogen phosphate adjusted to pH 3). Agilent UV spectrophotometer was used in Absorbance mode at wavelength of maximum absorption 259 nm as stated by the USP monograph and as practically obtained by running the spectrum mode. The calibration curve was obtained by plotting the concentration versus absorption The obtained plot was linear with R^2 value of 0.9987.

2.2.2. Preparation of Cefpodoxime Proxetil (CP) Co-grinded Formulations

They were prepared by dry co-grinding technique. Cefpodoxime Proxetil (CP) was grounded for 10 minutes either alone or with the selected carrier using mortar and pestle. The dry powders were stored in air-tight containers. Different premixes of CP and one (Binary mixtures) or more carriers (Ternary mixtures) using fixed concentration of the API (260mg of CP equivalent to 200mg Cefpodoxime base) along with various ratios of other additives. The aim was to determine the optimum grinding time, optimum carrier, and their optimum concentrations to reach the fastest dissolution rate. Table 2 shows the composition of all successful CP trials and their weight ratios. The co-grinded mixtures are further proceeded for physical characterization and testing.

Table 2. *The ratio of different formulation components of Cefpodoxime Proxetil co-grinded mixtures.*

Formula	CP	Aerosil 200	Glycine	PVP K25	HPMC E6
Pure drug (CP)	1	---	---	---	---
F1	1	---	---	---	---
F2	1	1	---	---	---
F3	1	---	1	---	---
F4	1	---	---	1	---
F5	1	---	---	---	1
F6	1	1	1	---	---
F7	1	1	---	1	---
F8	1	1	---	---	1
F9	1	0.25	---	0.5	---
F10	1	0.25	---	---	0.5

2.2.3. FTIR

FTIR measurements were carried out to assess if the functional groups of CP were altered or not after the grinding and co-grinding process. The Fourier transform infrared (FTIR) spectra of Cefpodoxime Proxetil, the selected polymers were recorded using FTIR spectrophotometer (FTIR- Spectrometer, Perkin Elmer, Waltham, MA., USA) Samples were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press before scanning from 4000cm^{-1} to 400cm^{-1}.

Data collection was performed using a DLaTGS detector which was adjusted to potassium bromide diffuse reflectance mode. The position of each absorption band was determined using Opus IR, FTIR spectroscopy Software Version 10.6.0.

2.2.4. DSC

These studies involved recording the thermograms of the samples (Cefpodoxime Proxetil, the selected polymers) using a differential scanning calorimetry (DSC, DSC-60, Shimadzu, Kyoto, Japan). Samples equivalent to approximately 2mg of the drug were loaded into aluminum pans before crimping the lids using a Shimadzu crimper. The thermal behavior of each sample was investigated at a heating rate of 10 ℃ /min, covering temperature ranges of 25-400 ℃.

The instrument was calibrated with an indium standard. Data analysis was conducted under steady flow of nitrogen gas. The whole process was under computer control em-

ploying TA-60WS thermal analysis workstation and software for recording and analyzing the data.

2.2.5. In Vitro Drug Dissolution Studies

Dissolution studies were conducted according to the USP monograph of Cefpodoxime Proxetil oral tablets [25] as well as FDA recommendations for Cefpodoxime Proxetil. This utilized USP II dissolution method with the paddle speed being adjusted to 75 rpm. The dissolution equipment was Copley Scientific Dis 6000 (Nottingham, United Kingdom).

The dissolution medium consisted of 900 mL Glycine buffer pH 3.0 ±0.1. The release studies were performed at 37 + 0.5 ℃, at a stirring rate of 75 rpm. The formulations (200mg of the drug or its equivalent) were loaded into the dissolution vessels. Aliquots Samples (5mL) were withdrawn at predetermined time intervals (5, 10, 15, 30, 45 and 60 minutes) and replaced with equal volume of fresh dissolution medium kept at the same temperature so as to keep the volume constant throughout the experiment. The experiments were performed in triplicates The samples were immediately filtered and analyzed by UV spectrophotometer at λ_{max} 259 nm. The amount of drug released at each time interval was calculated and the cumulative amount of drug released was calculated and expressed as percentage of the initial amount of drug added as a function of time and thus constructing the drug release profile. Drug Dissolution Efficiency (DE) was calculated from the area under the dissolution curve at time, *t* (determined using the nonlinear trapezoidal rule) and expressed as a percentage of the area of the trapeziums described by 100% dissolution in the same time [26, 27] as shown in equation 1. Dissolution parameters to be tested are the efficiency od dissolution (DE%) and the percentage of CP released after 5 minutes (Q5) and after 60 minutes (Q60). Q5 was specifically chosen to highlight the rapid effect of the changes made to the formulations and to emphasize on the rapid absorption of the drug, while Q60 was chosen because it is the end point of the pharmacopoeial limit. The choice of pH3 was mainly because of the pharmacopeial monograph recommendation, and because it simulates the stomach's acidic environment as well as facilitating the ionization and solubility of acidic medicines such as CP (pKa of 2.2) during drug dissolution, hence improving their release from dosage forms. for acidic drugs. A pH of 3 is frequently employed in dissolving research [28].

$$\text{Dissolution Efficiency (D.E.)} = \frac{\int_{t1}^{t2} y.dt}{y100.(t_2 - t_1)} \text{ x } 100\% \text{ [27]} \quad (1)$$

Where, y is the dissolved product. DE is the area under the dissolution curve between time points t_1 and t_2 expressed as% curve maximum dissolution (y_{100}) over the same period.

To calculate the area under the curve (AUC), a model independent method is used, the trapezoidal method, where the AUC is the sum of all the trapeziums defined by Equation 2.

$$AUC = \sum_{i=1}^{i=n} \frac{(t_1 - t_{i-1})\,(y_{i-1} + y_i)}{2} \text{ [27]} \quad (2)$$

Where, t_i is the i^{th} time point, y_i is the percentage of the dissolved product at time t_i.

To prove the dissimilarity between CP and other formulations, difference factor, f_1, and similarity factor f_2 were applied [29]. The factor f_1 is proportional to the average difference between the two profiles, whereas factor f_2 is inversely proportional to the average squared difference between the two profiles, f_2 measures the closeness between the two profiles [30]. In order to compare between the dissolution profiles application of Equation 3 and Equation 4.

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \text{x } 100\% \text{ [29]} \quad (3)$$

$$f_2 = 50 \text{ x } \log\left\{ \left[1 + \frac{1}{n} \sum_{t-1}^{n} (R_t - T_t)^2 \right]^{-0.5} \right\} \text{x} 100 \text{ [29]} \quad (4)$$

Where n is the number of data points, R_t is the cumulative percentage of the reference dissolved at time t and T_t is the cumulative percentage of the test dissolved (%) at the same time.

Student t-test was applied to compare the dissolution results obtained by pure untreated CP and other formulations, the paired t-test was applied because the compared results have been subjected to the same dissolution conditions [31]. Based on Equation 5, Microsoft Excel t-test function calculates the results based on the data of the control formulation _pure CP_ compared to each formulation from F1 to 10. The test was run as a double tailed and under unknown variances.

$$t = \frac{\underline{X_1} - \underline{X_2}}{\sqrt{\frac{s_1^2 + s_2^2 - 2\rho s_1 s_2}{n}}} \text{ [31]} \quad (5)$$

Where, t is the student test value, $\underline{x}1$ and $\underline{x}2$ are the means of groups 1 and 2, respectively. n is the number of points taken for each sample and s_1 and s_2 are the standard deviations of formula 1 and formula 2, respectively.

3. Results and Discussion

3.1. FTIR Spectroscopy

The FTIR spectrum of pure unprocessed CP showed characteristic absorption bands which correspond to its main functional groups (Figure 1). The broad peak noted at 3350 cm^{-1} is due to the NH stretching of the secondary amine. A fork-shaped band recorded at 2950cm-1 can be accredited to NH_2 stretching with the peak at 1650 being attributed to N-H bending. The peaks that were observed at 1760, 1570 and 1112 cm^{-1} are assigned for C=O, C=N and C-N stretching vibration, respectively. This spectrum with its absorption bands correlates well with the published data for CP [32, 33].

In Figure 1 Aerosil 200 (Colloidal silicon dioxide) showed peaks at 3587cm-1 attributed to the hydroxyl groups, a large peak at 3289cm-1 due to Silicon (Si) atom, aldehyde group clearly showing at 2764, Also, Si-O-Si linkage is clear at 929cm-1, these results are similar to those obtained by other researchers [34].

Grounded CP (F1) showed the same peaks as CP which means that grinding process did not affect the functional groups and thus the activity of the drug is not expected to be altered. Co-grinded formula F2 (CP and Aerosil 200) recorded a broad peak at 3500cm-1 also shows the NH_2 fork shape, generally similar to the spectrum obtained by CP alone, only changes are noticed in the fingerprint area as it is binary combination of CP and Aerosil 200. This also indicates that the main functional groups have not been altered due to grinding nor to addition of Aerosil 200 suggesting physical interaction (Figure 1).

With respect to Figure 2, glycine is an amino acid having the chemical formula NH_2-CH_2-COOH, is expected to show the broad beard shape peak at about 3400cm-1 due to the carboxylic acid group and hydrogen bond and a fork shaped peak at about 2900cm-1 due to the primary amine. This was obtained as a broad peak was noticed at 3489cm-1 for the carboxylic acid OH group. Fork shaped peak was noted at 2920 and 1230cm-1 for primary amine group stretching and bending, respectively. Co-grinded formulation F3 composed of CP co-processed with glycine at different ratios, while F6 composed of CP, glycine in addition to Aerosil 200.

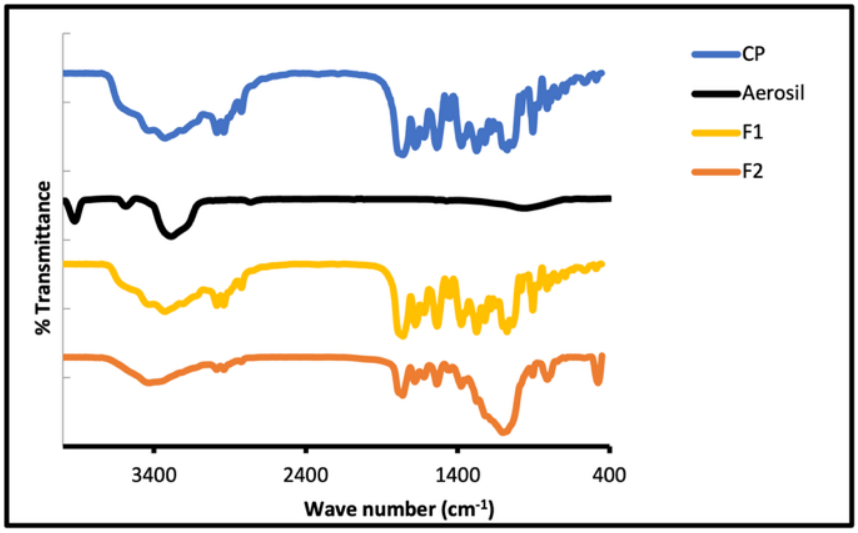


Figure 1. *FTIR spectra of CP, Aerosil 200 and co-grinded mixtures F1 and F2. Details of formulations are presented in Table 2.*

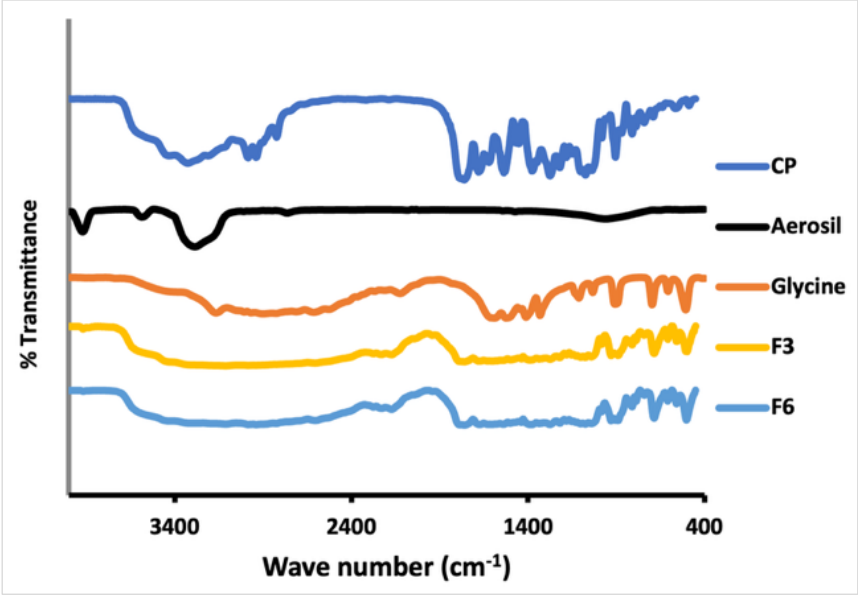


Figure 2. *FTIR spectra of CP, Aerosil 200, glycine and glycine containing formulations (F3 and F6).*

The FTIR spectra for the two composites were very similar to each other. The very broad peak at 3450cm-1 and the fork shaped peak of the NH_2 group have disappeared. This could be accredited to the probable interaction between COOH and NH_2 groups, or due to alteration of primary amine to secondary amine. The FTIR spectra for CP co-processed mixtures using PVP K25 as an inert additive are shown in Figure 3.

Those mixtures which are composed of CP and PVP K25 without (formula F4) or with Aerosil 200 at different weight ratios (formulations F7 and F9) (Table 2). Pure PVP K25 (which has main groups as tertiary amine, amide group C=O, C-N and CH2) showed the peak at 3400cm-1 attributed to C=O, another peak at 3150cm-1 reflecting amine group C-N and the characteristic peak at 1650cm-1 of the amide group. This goes in good conformance with published work Ambrus et al, Fayed et al. and SreeHarsha et al. [35-37]. Formula F4 (composed of CP and PVP) showed the broad peak between 3600 and 3065cm-1 attributed to hydrogen bonding resulting from OH and NH groups. Also showed a weak peak at 2900cm-1 of NH_2 of CP, as well as a peak at 1768cm-1 due to ketone or ester group of CP. Regarding F7, the fork shaped peaks of NH_2 of CP are still there and the broad peak at 3400cm-1 as well. Similarly, F9 gave the same FTIR spectra, which indicates that varying the ratios of the same formula at varying concentration did not affect the functional groups of CP and consequently its therapeutic behavior. It was noticed that the concentration of Aerosil 200 affected the intensity of the broad peak at 3400cm-1 of the formulations. Where F4 with 0% Aerosil 200 had the least peak intensity, formula F9 with 14% Aerosil 200 had the larger peak valley, while F7 with 33% Aerosil 200 had the largest peak valley at 3400cm-1.

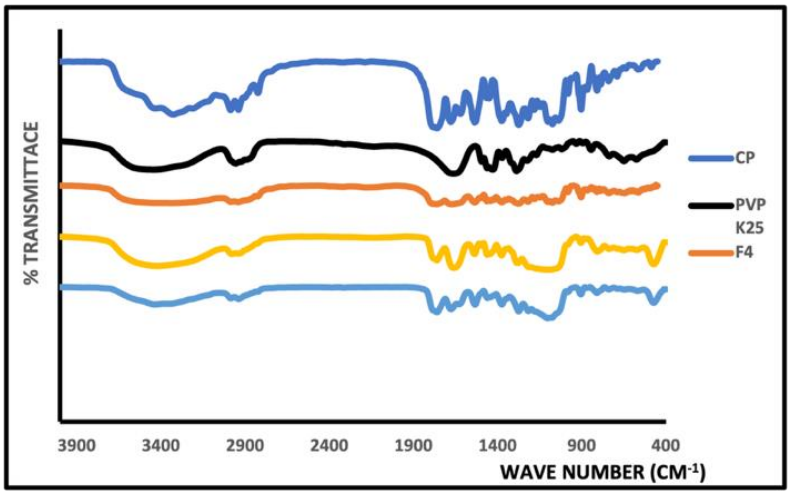


Figure 3. *FTIR spectra of CP, Aerosil 200, PVP K25, F4, F7 and F9.*

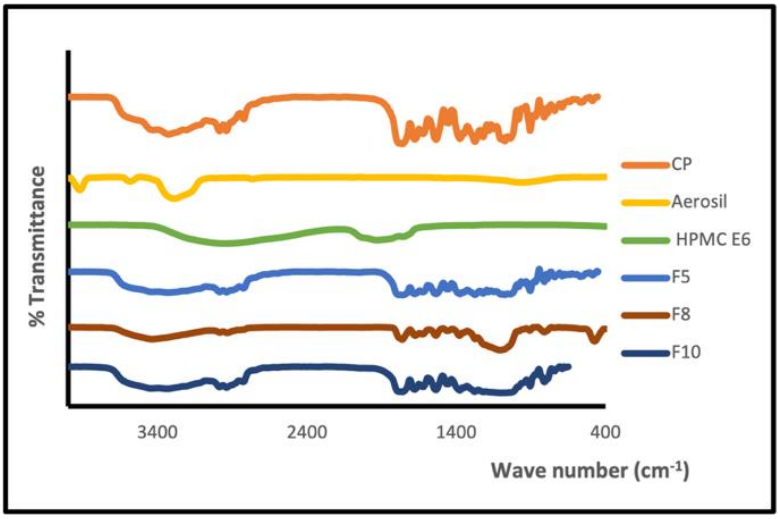


Figure 4. *FTIR spectra of CP, Aerosil 200, HPMC E6, F5, F8 and F10.*

In Figure 4, HPMC E6 (Hydroxypropyl Methylcellulose/Hypromellose), showed a broad characteristic peak at 3428cm^{-1} due to the OH hydroxyl group stretching, other peaks at 2901cm^{-1} due to aliphatic C-H stretching and 1643 cm^{-1} which indicate the aldehyde group, similar spectra found by Fayed et al. and Reddy and Karpagam, [38, 39]. Formula F5 (1:1 weight ratio of CP:HPMC) showed a broad peak at 3644 and 2900cm^{-1}. Formulations F8 (1:1:1 CP:HPMC:Aerosil 200, respectively) and F10 (1:0.5:0.25 CP:HPMC:Aerosil) showed the same pattern as F5. F5 and F10 peaks are quite similar to CP alone, this could be because of the percent of CP in the formulations is 50% and 57%, respectively. Regarding F8, it only has 33% CP giving same pattern but with less magnitude.

3.2. Differential Scanning Calorimetry (DSC)

Thermal analysis was employed to further investigate the interaction between CP and other carriers in order to elucidate potential physical and/or chemical reactions. Representative thermograms are shown in the following section. Figure 5 shows the recorded thermograms for pure CP, F1 (grounded CP), Aerosil 200, and glycine as well as their prepared formulations at different weight ratios.

The thermogram of pure CP showed an endothermic peak with an onset of 77.2 ℃, end 112 ℃ and transition mid-point (T_m) of 97.7 ℃. This endothermic peak can be attributed to the melting of the drug. A broad exothermic peak was noted at T_m of 226 ℃ with an onset of 204 ℃ and end of 250 ℃ which can be attributed to drug degradation. This thermogram is comparable to that reported by other investigators [32, 40]. While the thermogram of F1 (grounded CP) gave the same peaks as CP showing that the grinding process did not even affect the physical characteristics such as melting point but shall appear to enhance the dissolution properties as shall be evident by the dissolution profile.

Glycine thermogram showed one sharp endothermic peak at 254 ℃, with melting point onset at 244 ℃ and end at 264 ℃, this sharp peak denotes its purity and crystallinity, such peak is mentioned by [41]. Aerosil 200 (Colloidal silicon dioxide) as an amorphous powder with a melting point of 1600 ℃ [19] showed nearly a flat peak like previously reported thermograms. Formula F2 (CP:Aerosil 200 at 1:1 ratio) showed somehow flattened CP peak This would indicate reduced crystallinity of CP as a result of co-grinding with Aerosil., For formulations prepared using glycine, formula F3 (CP:Glycine at 1:1 ratio) reflected the disappearance of characteristic endothermic and exothermic peaks of CP indicating its transformation to the amorphous form. Meantime, the sharp endothermic peak of glycine was noted at slightly lower T_m of about 250 ℃ with reduced intensity. Addition of Aerosil 200 to CP/glycine mixtures produced formula F6 (CP:Glycine:Aerosil 200 at 1:1:1 weight ratio). The thermogram of F6 showed DSC thermograms similar to F3 (Figure 5).

The second group of formulations was the CP co-grinded with HPMC E6 in presence or absence of Aerosil 200 (F5, F8 and F10 as described in Figure 6 shows the thermogram of unprocessed CP and pure additives. The thermogram of pure HPMC E6 showed a broad endotherm which started at 60 ℃ and ended at 121 ℃. This broad peak could be due to the evaporation of bound moisture. Another broad peak was recorded at T_m value of 360 ℃ and can be assigned to its degradation.

The same thermal pattern of HPMC was stated in previous research work [42-44]. In binary combination with CP and in ternary combinations (F5, F8 and F10) this peak has disappeared denoting change in characteristics of HPMC E6, while CP peaks at about 280 ℃ were still there showing that the chemical characteristics of CP were not altered. It was noticed that in F8 where the ratio of Aerosil 200 was high (about 33%), the peaks tend to decrease in their magnitude, suggesting that the CP is adsorbed or coated inside the pores of Aerosil 200 this was noticed in glycine and PVP k25 trials as well, also mentioned by Chaudhari SP *et al.* and Bhagwat DA et al. [45, 46].

The DSC thermograms of PVP k25 containing formulations, namely, F4, F7 and F9 in different ratios -as shown in Figure 7- PVP k25 has a clear endothermic peak at about 80 ℃ that can be ascribed to the evaporation of water and it is characteristic for the amorphous PVP, similar thermograms of PVP were published by Gurunath et al., Marin et al. and Liu *et al.* [36, 47, 48] In F4 where no Aerosil 200 was added the peaks of both CP and PVP k25 were clear at approximately 80 ℃ and 250 ℃, where at the highest percent of Aerosil 200 (F7), an approximately flat thermogram of Aerosil 200 dominated indicating the adsorption or coating of both CP and PVP k25 denoting more amorphousization of the drug. This becomes clearer upon decreasing the percent Aerosil 200 in F9 where the peaks start to reappear. It was also noticed that a decrease of drug endothermic melting peak, accompanied by broadening and shifting to lower temperatures for all PVP K25 formulations, which was attributed mainly to PVP K25 content in the formulations. Almost whereas it depended markedly on the PVP content in the mixture. Almost complete disappearance of the drug melting peak, indicative of its amorphization, was observed in the 1:3, such results were previously concluded by Mura et al. [49].

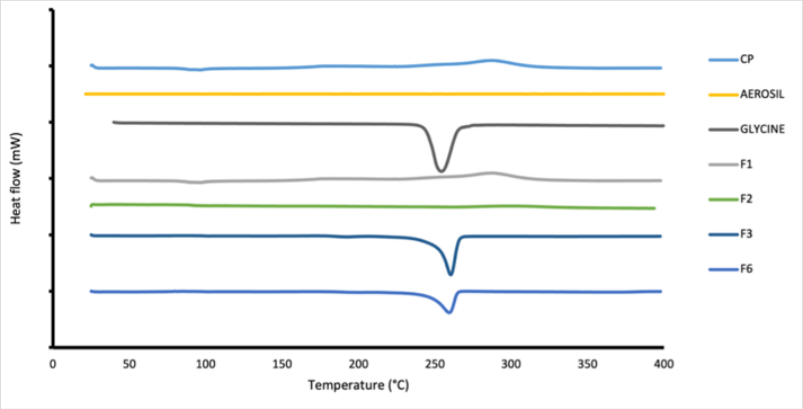


Figure 5. *DSC thermograms of pure CP, grounded CP, Aerosil, Glycine; individually and in combinations at different ratios.*

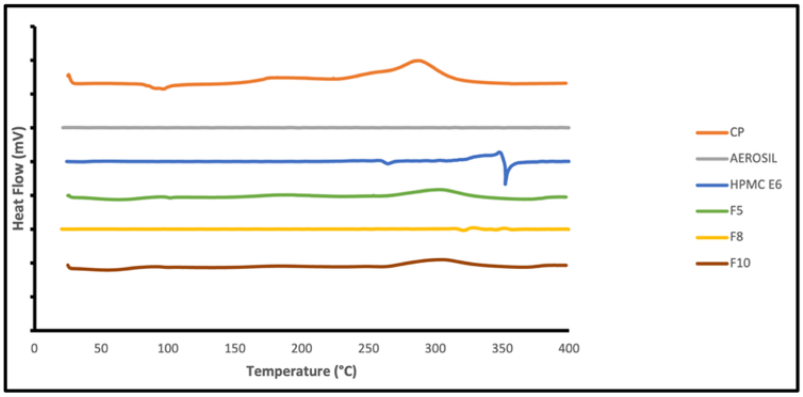


Figure 6. *DSC Thermograms of CP, Aerosil 200 and HPMC E6; individually and in combinations at different ratios.*

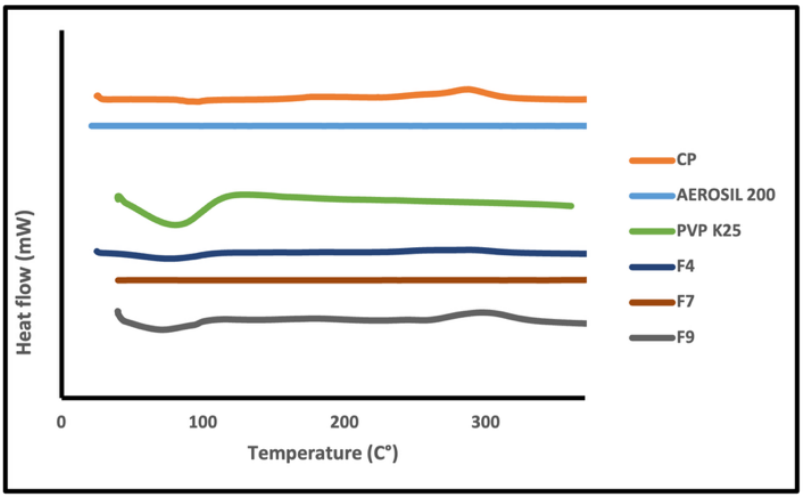


Figure 7. *DSC Thermograms of CP, Aerosil 200 and PVP K 25; individually and in combinations at different ratios.*

3.3. In Vitro Drug Dissolution Studies

3.3.1. Dissolution Results

The in-vitro drug release from the prepared formulations and unprocessed CP was conducted in triplicates, the standard deviation of each point was calculated and all ranged from 0.03 to 0.09. The used dissolution medium was glycine medium adjusted to pH 3 ±0.1. The obtained results are presented as percentage amount of CP released as function of time (Figure 8). The dissolution profiles were used to compute the dissolution parameters and are presented in Table 3 and graphically represented as histogram in Figure 9. These pa-

rameters were the percentage CP released after 5 min (Q5) and 60 min (Q60). The efficiency of dissolution (DE) after 60 minutes was calculated from the area under the dissolution profile at each time relative to the corresponding area assuming 100% dissolution at that time point [27].

Primarily, the pure CP dissolution was conducted, the quantity released either at Q5 or Q60 were unsatisfactorily very low, and this is attributed to the very hydrophobic nature of the drug as it is classified as class IV drug according to BCS [50]. The drug was processed by grinding for 10 minutes to increase the surface area of the drug exposed to the dissolution medium and hence increase its solubility, the results of F1 show evident enhancement of the dissolution as demonstrated in Figure 8A.

In the attempt of further enhancement of CP dissolution, grinding CP with an additive to form binary mixtures was introduced. Four additives were co-grounded each with CP separately in a weight ratio of 1:1, namely Aerosil 200, glycine, PVP K25 and HPMC E6.

Formulas F2, F3, F4 and F5, respectively- the effect of co-grinding with Aerosil 200 (F2) was the most obvious (DE up to 52%) due to its high surface area which incorporates drug particles and hence increases the wetting of the drug in the dissolution medium, also because of its chemical characteristics, it may establish hydrogen bonds with a variety of molecules thanks to its silanol group [51], similar findings was reported by Boghra et al. [52].

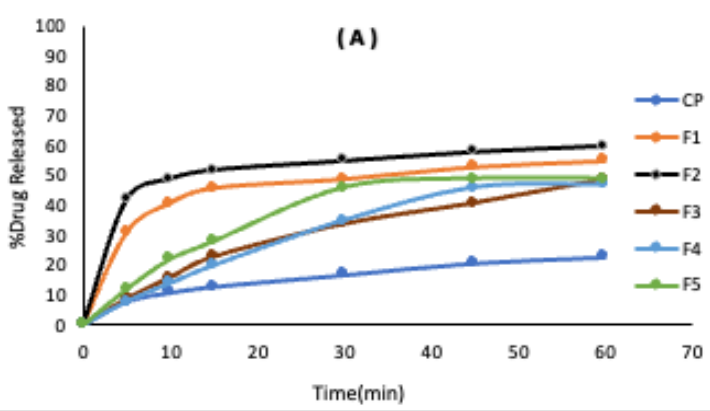
With respect to Glycine, amino acids are generally known to increase the dissolution of poorly soluble drugs [53]. The use of glycine as a wetting agent is mentioned in the handbook of pharmaceutical excipients [19], by the mechanism of attracting the dissolution medium and increasing its presence in the vicinity of the drug surface, moreover, it prevents the aggregation of the drug molecules with each other [53]. In our work, F3 gave the highest Q5 dissolution value (68%) as shown in Table 3.

Regarding formula F4 results mentioned in Figure 7, consisting of CP and PVP K25 in weight ratio of 1:1 (Table 2), PVP is polyvinylpyrrolidone or povidone and it is expressed as a K-value, in the range of 10 to 120. One of its main functions is acting as a dissolution enhancer when used in the ratio of 10-15% of the formula, in addition, mixing a variety of active medications of poor solubility with povidone (PVP) can improve their solubility, this crucial feature is attributed to its hydrophilicity -enhancing wetting effect-, and hydrogen bond–forming ability [19, 54].

The amorphous form, which has high energy and rapid molecular mobility decrease in drug crystallinity, may also contribute to such improved dissolution [55]. F4 DE% results were 31% compared to 16% of the pure drug of approximately 94% increase, boosted solubility was also mentioned in other studies of poorly soluble drugs.

Regarding HPMC E6, it is a hydrophilic polymer, safe, non-toxic which is widely used in the pharmaceutical industry, its concentration in the formula as well as its viscosity grade have tremendous effect on the release of the API. Two mechanisms are known for the release from HPMC which are erosion and diffusion, with drugs with low water solubility, drug release is mainly via erosion [56], HPMC is known to be a dispersing agent and a dissolution enhancer [19]. HPMC viscosity grades range from 3 to 15,000 mPa, which means that the grade used in this study (E6) is a low viscosity grade and thus will not hinder the release. F5 is the CP/ HPMC E6 1:1 formula, (as shown in table 2 and depicted in Figure 8A, recorded a DE of 37%, similar dissolution enhancement via HPMC was reported by Fayed *et al*. [38]. Generally, Amphipathic molecules such as HPMC can modify the surface.

Based on the previous findings from the binary mixtures, Aerosil 200 has shown to be very promising, and hence, ternary mixtures of the drug, Aerosil 200 and one of the three carriers -namely, glycine, PVP K25 and HPMC E6- at the ratio of 1:1:1, were separately co-grounded to give mixtures F6, F7 and F8, respectively. Results are shown in Table 3 and depicted in Figure 8B, where Q5 ranged from 60% – 68%, Q60 ranged from 80 to 100% and DE% ranged from 67-82%. All three carriers' dissolution profiles were nearly similar as shown in Figure 8B, as well as the similarity factor, f_2 results demonstrated later in this work. These prosperous results are suggested to be due to the augmenting effect of the large surface area of Aerosil 200 and the hydrophilic nature of the other carriers.



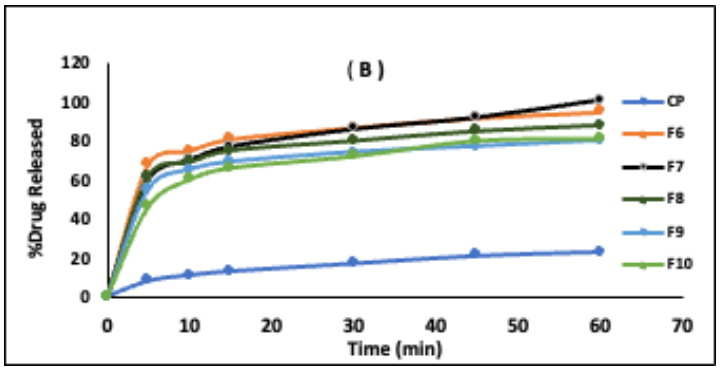


Figure 8. *(A&B) Dissolution profiles of binary (A) and ternary (B) co-grinded CP with different excipients using different concentrations of Aerosil 200.*

Upon trying to decrease the weight ratios of Aerosil 200 as well as the carriers – PVP K25 and HPMC E6 – to 1:0.25:0.5 in F9 and F10, respectively, they both gave nearly similar profiles with little superiority to PVP K25 (F9).

In an overall view, formulations from F2 to F5 aimed to compare the effect of binary combinations to the effect of ternary combinations, it was obvious that ternary combinations gave superior results. Upon referring to the dissolution results at Q5 (Table 3) and focusing on Glycine formulations (F3 & F6), it can be noticed that F6 gave highest dissolution value (68%), but the ratio of Aerosil 200 was tremendously high (50%) which could not be applied to industry due to incompressibility of the powder mixture as Aerosil 200 is very fluffy and nearly incompressible, therefore its ratio should be as minute as possible. Another reason to try to decrease the amount of Aerosil 200 is that it is a health hazardous material if inhaled it would cause irreversible damage to the lung cells and could range to death [21].

With respect to HPMC E6 formulations (F5, F8 & F10) again the unacceptable high ratio of Aerosil 200. F8 -although giving excellent results, 68% at Q5-, the Aerosil 200 percent has been decreased from 33% to 14% through F10, to give a compromise value of 46% at Q5.

With respect to PVP K25 formulations (F4, F7 & F9), F7 giving the highest Q5 value (60%) within this group of formulations, but again, upon decreasing the percent of Aerosil 200 in F9 from 33% to 14% giving decreasing dissolution results in a linear relationship between the percent of Aerosil 200 and dissolution values. F9 was the best compromise among this group of formulations.

Table 3. *Dissolution parameters of Cefpodoxime Proxetil (CP) from different formulations represented the amount released after 5 min (Q5), after 60 min (Q60) and percentage dissolution efficiency (DE%).*

Formula	% Released at Q5	% Released at Q60	DE 60 min%
Pure drug	8 ±0.51	23±0.25	16%
$F1_{pure}$	31±0.48	66±0.18	46%
$F2_{CP/Aero}$	9 ±0.39	49±0.26	52%
$F3_{CP/glycine}$	12±0.43	49±0.24	31%
$F4_{CP/PVP}$	42±0.24	60±0.13	31%
$F5_{CP/HPMC}$	8±0.46	47±0.40	37%
$F6_{CP/Aero/glycine}$	68 ±0.09	95 ±0.09	82%
$F7_{CP/Aer/PVP}$	60 ±0.13	100 ±0.10	81%
$F8_{CP/Aer/HPMC}$	62±0.24	88±0.26	76%
$F9_{CP/Aer/PVP\ low}$	55±0.30	80±0.29	69%
$F10_{CP/Aer0.25/HPMC}$	46±0.27	81±0.25	68%

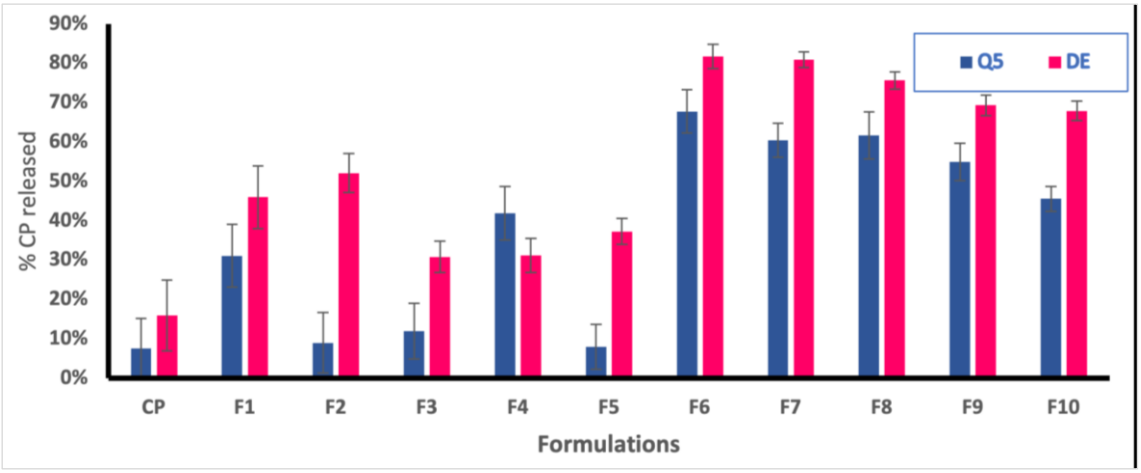


Figure 9. *Percentage amount of released of Cefpodoxime Proxetil after 5 minutes (Q5) and dissolution efficiency values (DE) of different formulations.*

In a nutshell, PVP K25 was the most effective tested polymer in terms of improving drug solubility. This finding was drawn from the observation that PVP K25 with lowest Aerosil 200 weight ratio with the drug (namely, F9), when compared to other polymers at the same weight ratio, produced the largest improvement in drug dissolution at the lowest weight ratio with the drug. Similar results were also obtained by Fayed et al. [40].

3.3.2. Statistical Analysis of Dissolution Testing

Difference and Similarity Factors

The dissolution profiles were assessed by applying the difference factor f_1, and the similarity factor f_2 in order to prove that the formulations gave different dissolution profiles from that of the pure CP. Generally, when the two profiles are identical, f_2=100. An average difference of 10% at all measured time points results in a f_2 value of 50 [29], FDA has set a public standard of f_2 value between 50-100 to indicate similarity between two dissolution profiles [30]. The results shown in table 4 prove that all formulations had dissimilar profiles from pure unprocessed CP as all f_1 results were more than 15 and all f_2 were below 50.

Table 4. *Comparison between CP dissolution profile and other formulations dissolution profiles.*

Formulation	Difference factor (%) *(f1)*	Similarity factor (%) *(f2)*
F1	45.7	25.1
F2	40.8	22.9
F3	114.2	41.6
F4	117.9	41.0
F5	80.3	35.4
F6	22.7	10.2
F7	23.2	10.5
F8	25.0	12.3
F9	27.9	14.7
F10	29.3	15.6

Table 5. *Results of student t- test values between pure untreated CP and different formulations.*

Formulation	T- test value (unequal variance)
F1	0.012
F2	0.005
F3	0.155
F4	0.185
F5	0.073
F6	0.003
F7	0.004
F8	0.003
F9	0.004
F10	0.005

Resulting *P*-value are all less than 0.05 except F3, F4 and F5, which proves that the differences are significant.

Our Null Hypothesis is that the sample mean and population mean are statistically different, as per the results listed in Table 5, all formulations accepted the null hypothesis of the

difference between them and pure CP, except highlighted formulations F3, F4 and F5, which in fact gave dissolution profiles similar to the that of pure CP.

Also, by applying student *t*-test to obtain the *P*-value in order to prove significance of data, students *t*-test was applied between pure untreated CP and all other formulations, the resulting data and enlisted in table 5.

4. Conclusion

Upon preparation of binary and ternary solid dispersion of CP, it was revealed that ternary combinations were more effective, PVP K25 as a carrier in ternary combinations (F9) was of higher quality than other carriers HPMC E6 and glycine. The exploitation of Aerosil 200 in the ternary combinations was of undeviating consequence on the enhancing the dissolution and this effect was directly proportional to its ratio.

Abbreviations

CP	Cefpodoxime Proxetil
PVP	Polyvinylpyrrolidone
HPMC	Hydroxypropyl Methylcellulose
FTIR	Fourier Transform Infrared Spectroscopy
DSC	Differential Scanning Calorimetry
DE%	Dissolution Efficiency Percent
℃	Degree Celsius
mW	Milliwatt

Author Contributions

Nouran Abdel Kader is the sole author. The author read and approved the final manuscript.

Data Availability Statement

The data is available from the corresponding author upon reasonable request.

Conflicts of Interest

The author declares no conflicts of interest.

References

[1] E. A. Essa and M. Dwaikat, "Enhancement of Simvastatin dissolution by surface solid dispersion: effect of carriers and wetting agents," *Journal of Applied Pharmaceutical Science*, vol. 5, no. 1, pp. 046–053, 2015, Accessed: Dec. 09, 2023. [Online]. Available: http://japsonline.com/abstract.php?article_id=1495

[2] M. Barzegar-Jalali *et al.*, "Enhancement of Dissolution Rate and Anti-inflammatory Effects of Piroxicam Using Solvent Deposition Technique," *Drug Development and Industrial Pharmacy*, vol. 28, no. 6, pp. 681–686, Jan. 2002, https://doi.org/10.1081/DDC-120003859

[3] H. Friedrich, A. Nada, and R. Bodmeier, "Solid State and Dissolution Rate Characterization of Co-Ground Mixtures of Nifedipine and Hydrophilic Carriers," *Drug Development and Industrial Pharmacy*, vol. 31, no. 8, pp. 719–728, Jan. 2005, https://doi.org/10.1080/03639040500216097

[4] L. Kürti, Á. Kukovecz, G. Kozma, R. Ambrus, M. A. Deli, and P. Szabó-Révész, "Study of the parameters influencing the co-grinding process for the production of meloxicam nanoparticles," *Powder technology*, vol. 212, no. 1, pp. 210–217, 2011, Accessed: Dec. 09, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0032591011002750

[5] K. Moribe, A. Pongpeerapat, Y. Tozuka, and K. Yamamoto, "Drug nanoparticle formation from drug/HPMC/SDS ternary ground mixtures," *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, vol. 61, no. 2, pp. 97–101, 2006, Accessed: Dec. 09, 2023. [Online]. Available: https://www.ingentaconnect.com/content/govi/pharmaz/2006/00000061/00000002/art00003

[6] C. Zapata, C. Frances, N. Le Bolay, and S. Molina-Boisseau, "Production of small composite particles by co-grinding in a media mill: Characterization of the granulometric and the mechanical properties," *Chemical Engineering Research and Design*, vol. 82, no. 5, pp. 631–636, 2004, Accessed: Dec. 09, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0263876204725368

[7] A. V. Mundhe, "Cocrystalization: an alternative approach for solid modification," *Journal of Drug Delivery and Therapeutics*, vol. 3, no. 4, pp. 166–172, 2013, Accessed: Dec. 09, 2023. [Online]. Available: http://jddtonline.info/index.php/jddt/article/view/555

[8] T. Friščić and W. Jones, "Recent Advances in Understanding the Mechanism of Cocrystal Formation via Grinding," *Crystal Growth & Design*, vol. 9, no. 3, pp. 1621–1637, Mar. 2009, https://doi.org/10.1021/cg800764n

[9] D. K. Mahapatra and S. K. Bharti, *Medicinal chemistry with pharmaceutical product development*. CRC Press, 2019. Accessed: Dec. 09, 2023. [Online]. Available: https://books.google.com/books?hl=en&lr=&id=FuiIDwAAQBAJ&oi=fnd&pg=PP1&dq=mahapatra+2019+medicinal+chemistry&ots=a-6CdK5X-G&sig=tZc5JbnUaLVoGyzsm-ROnvBK0mc

[10] B. Jagadish, R. Yelchuri, H. Tangi, S. Maroju, and V. U. Rao, "Enhanced dissolution and bioavailability of raloxifene hydrochloride by co-grinding with different superdisintegrants," *Chemical and Pharmaceutical Bulletin*, vol. 58, no. 3, pp. 293–300, 2010, Accessed: Dec. 09, 2023. [Online]. Available: https://www.jstage.jst.go.jp/article/cpb/58/3/58_3_293/_article/-char/ja/

[11] S. A. El-Gizawy, M. A. Osman, M. F. Arafa, and G. M. El Maghraby, "Aerosil as a novel co-crystal co-former for improving the dissolution rate of hydrochlorothiazide," *International journal of pharmaceutics*, vol. 478, no. 2, pp. 773–778, 2015, Accessed: Dec. 09, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S03785173 1400934X

[12] K. Yamamoto, M. Nakano, T. Arita, Y. Takayama, and Y. Nakai, "Dissolution behavior and bioavailability of phenytoin from a ground mixture with microcrystalline cellulose," *Journal of Pharmaceutical Sciences*, vol. 65, no. 10, pp. 1484–1488, 1976, Accessed: Dec. 09, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S00223549 15409797

[13] S.-C. Shin, I.-J. Oh, Y.-B. Lee, H.-K. Choi, and J.-S. Choi, "Enhanced dissolution of furosemide by coprecipitating or cogrinding with crospovidone," *International journal of pharmaceutics*, vol. 175, no. 1, pp. 17–24, 1998, Accessed: Dec. 09, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S03785173 98002609

[14] A. Mitrevej, N. Sinchaipanid, and V. Junyaprasert, "Effect of Grinding of β-Cyclodextrin and Glibenclamide on Tablet Properties. Part I. in vitro," *Drug Development and Industrial Pharmacy*, vol. 22, no. 12, pp. 1237–1241, Jan. 1996, https://doi.org/10.3109/03639049609063243

[15] M. Sevukarajan, T. Bachala, R. Sodanapalli, and R. Nair, "Co-Crystals: An Emerging Trend in Pharmaceutical Industry," *Research Journal of Pharmacy and Technology*, vol. 4, no. 6, pp. 891–902, 2011, Accessed: Dec. 09, 2023. [Online]. Available: https://www.indianjournals.com/ijor.aspx?target=ijor:rjpt&volume=4&issue=6&article=008

[16] Pharmacia and Upjohn, "Vantin," Pamphlet, 2013.

[17] Sanofi, Aventis, "Orelox," Pamphlet, 2017.

[18] V. K. Kakumanu, V. Arora, and A. K. Bansal, "Investigation of factors responsible for low oral bioavailability of cefpodoxime proxetil," *International journal of pharmaceutics*, vol. 317, no. 2, pp. 155–160, 2006, Accessed: Dec. 09, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S03785173 06002213

[19] R. Raymond, *Handbook of pharamceutical excipients*, 6th ed. USA: Pharmaceutical press, American Pharmaceutical Association.

[20] PubChem, "Cefpodoxime." Accessed: Dec. 11, 2023. [Online]. Available: https://pubchem.ncbi.nlm.nih.gov/compound/6335986

[21] Medisca, "Silicon dioxide," MSDS, 2020.

[22] PubChem, "HYPROMELLOSE 2910 (6 MPA. S)." Accessed: Jun. 14, 2025. [Online]. Available: https://pubchem.ncbi.nlm.nih.gov/substance/472406530

[23] PubChem, "Glycine." Accessed: Jun. 14, 2025. [Online]. Available: https://pubchem.ncbi.nlm.nih.gov/compound/750

[24] PubChem, "1-Ethenyl-2-pyrrolidinone homopolymer." Accessed: Jun. 14, 2025. [Online]. Available: https://pubchem.ncbi.nlm.nih.gov/substance/11528385

[25] "USP Monographs: Cefpodoxime Proxetil Tablets." Accessed: Jun. 14, 2025. [Online]. Available: http://www.pharmacopeia.cn/v29240/usp29nf24s0_m14113.html

[26] G. M. El Maghraby and A. H. Alomrani, "Effect of binary and ternary solid dispersions on the in vitro dissolution and in-situ rabbit intestinal absorption of gliclazide," *Pak J Pharm Sci*, vol. 24, no. 4, pp. 459–468, 2011, Accessed: Dec. 09, 2023. [Online]. Available: https://www.researchgate.net/profile/Gamal-El-Maghraby/publication/51682009_Effect_of_binary_and_ternary_solid_dispersions_on_the_in_vitro_dissolution_and_in-situ_rabbit_intestinal_absorption_of_gliclazide/links/540cb45c0cf2df04e75473af/Effect-of-binary-and-ternary-solid-dispersions-on-the-in-vitro-dissolution-and-in-situ-rabbit-intestinal-absorption-of-gliclazide.pdf

[27] K. A. Khan, "The concept of dissolution efficiency," *Journal of pharmacy and pharmacology*, vol. 27, no. 1, pp. 48–49, 1975, Accessed: Dec. 09, 2023. [Online]. Available: https://academic.oup.com/jpp/article-abstract/27/1/48/6196131

[28] O. Helen Chan and B. H. Stewart, "Physicochemical and drug-delivery considerations for oral drug bioavailability," *Drug Discovery Today*, vol. 1, no. 11, pp. 461–473, Nov. 1996, https://doi.org/10.1016/1359-6446(96)10039-8

[29] J. W. Moore and H. H. Flanner, "Mathematical comparison of dissolution profiles," *Pharmaceutical technology*, vol. 20, no. 6, pp. 64–74, 1996, Accessed: Dec. 09, 2023. [Online]. Available: https://pascal-francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=3112822

[30] V. P. Shah, Y. Tsong, P. Sathe, and R. L. Williams, "Dissolution Profile Comparison Using Similarity Factor, f2," *Dissolution Technol.*, vol. 6, no. 3, pp. 15–15, 1999, https://doi.org/10.14227/DT060399P15

[31] T. K. Kim, "T test as a parametric statistic," *Korean journal of anesthesiology*, vol. 68, no. 6, pp. 540–546, 2015, Accessed: Dec. 09, 2023. [Online]. Available: https://synapse.koreamed.org/articles/1156170

[32] F. Khan, R. Katara, and S. Ramteke, "Enhancement of Bioavailability of Cefpodoxime Proxetil Using Different Polymeric Microparticles," *AAPS PharmSciTech*, vol. 11, no. 3, pp. 1368–1375, Sep. 2010, https://doi.org/10.1208/s12249-010-9505-x

[33] C. S. R. Rao, K. Sharath, V. Kowmudi, and N. Suresh, "Development and in-vitro evaluation of cefpodoxime proxetil gastro-retentive floating tablets," *International Journal of Applied Pharmaceutical Sciences and Research*, vol. 1, no. 01, pp. 31–41, 2016, Accessed: Dec. 09, 2023. [Online]. Available: https://www.sierrajournals.com/index.php/IJAPSR/article/view/1025

[34] T. Jutarosaga, J. S. Jeoung, and S. Seraphin, "Infrared spectroscopy of Si–O bonding in low-dose low-energy separation by implanted oxygen materials," *Thin Solid Films*, vol. 476, no. 2, pp. 303–311, 2005, Accessed: Dec. 09, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0040609004014294

[35] R. Ambrus, Z. Aigner, L. Catenacci, G. Bettinetti, P. Szabó-Révész, and M. Sorrenti, "Physico-chemical characterization and dissolution properties of nifluminic acid-cyclodextrin-PVP ternary systems," *Journal of thermal analysis and calorimetry*, vol. 104, no. 1, pp. 291–297, 2011, Accessed: Dec. 11, 2023. [Online]. Available: https://akjournals.com/view/journals/10973/104/1/article-p291.xml

[36] S. Gurunath, B. K. Nanjwade, and P. A. Patila, "Enhanced solubility and intestinal absorption of candesartan cilexetil solid dispersions using everted rat intestinal sacs," *Saudi Pharmaceutical Journal*, vol. 22, no. 3, pp. 246–257, 2014, Accessed: Dec. 09, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1319016413000388

[37] N. SreeHarsha *et al.*, "Spray dried amorphous form of simvastatin: Preparation and evaluation of the buccal tablet," *Indian J. Pharm. Educ. Res*, vol. 54, pp. 46–54, 2019, Accessed: Dec. 09, 2023. [Online]. Available: https://www.ijper.org/sites/default/files/IndJPhaEdRes_54_1-46.pdf

[38] N. D. Fayed, M. A. Osman, and G. M. El Maghraby, "Enhancement of dissolution rate and intestinal stability of candesartan cilexitil," *Journal of Applied Pharmaceutical Science*, vol. 6, no. 5, pp. 102–111, 2016, Accessed: Dec. 09, 2023. [Online]. Available: https://japsonline.com/abstract.php?article_id=1867

[39] K. A. Reddy and S. Karpagam, "Cellulose Orodispersible Films of Donepezil: Film Characterization and Drug Release," *Pharm Chem J*, vol. 51, no. 8, pp. 707–715, Nov. 2017, https://doi.org/10.1007/s11094-017-1679-z

[40] S. H. Patil and G. S. Talele, "Natural gum as mucoadhesive controlled release carriers: evaluation of Cefpodoxime Proxetil by D-Optimal design technique," *Drug Delivery*, vol. 21, no. 2, pp. 118–129, Mar. 2014, https://doi.org/10.3109/10717544.2013.834416

[41] L. J. Bonales, V. Muñoz-Iglesias, O. Prieto-Ballesteros, and E. Mateo-Martí, "Preservation of glycine coordination compounds under a gamma radiation dose representative of natural mars radioactivity," *Sci Rep*, vol. 12, no. 1, p. 13677, Aug. 2022, https://doi.org/10.1038/s41598-022-17802-y

[42] N. S. Barakat, I. M. Elbagory, and A. S. Almurshedi, "Controlled-release carbamazepine matrix granules and tablets comprising lipophilic and hydrophilic components," *Drug Delivery*, vol. 16, no. 1, pp. 57–65, Jan. 2009, https://doi.org/10.1080/10717540802518157

[43] F. Barboza, D. D. Vecchia, M. P. Tagliari, M. A. S. Silva, and H. K. Stulzer, "Differential scanning calorimetry as a screening technique in compatibility studies of acyclovir extended release formulations," *Pharm Chem J*, vol. 43, no. 6, p. 363, Jun. 2009, https://doi.org/10.1007/s11094-009-0304-1

[44] A. Mesnukul, K. Yodkhum, and T. Phaechamud, "Solid dispersion matrix tablet comprising indomethacin-PEG-HPMC fabricated with fusion and mold technique," *Indian Journal of Pharmaceutical Sciences*, vol. 71, no. 4, p. 413, 2009, Accessed: Dec. 09, 2023. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2865813/

[45] S. P. Chaudhari, M. Bhadiyadra, and R. H. Dave, "Evaluating the effect of the porous and non-porous colloidal silicon dioxide as a stabilizer on amorphous solid dispersion," *Journal of Drug Delivery and Therapeutics*, vol. 10, no. 5, pp. 255–263, 2020, Accessed: Dec. 09, 2023. [Online]. Available: http://jddtonline.info/index.php/jddt/article/view/4323

[46] D. A. Bhagwat and J. I. D. Souza, "Formulation and evaluation of solid self micro emulsifying drug delivery system using aerosil 200 as solid carrier," *International current pharmaceutical journal*, vol. 1, no. 12, pp. 414–419, 2012, Accessed: Dec. 11, 2023. [Online]. Available: https://www.researchgate.net/profile/Dr-Durgacharan-Bhagwat/publication/259970490_Formulation_and_Evaluation_of_Solid_Self_Micro_Emulsifying_Drug_Delivery_System_using_Aerosil_200_as_Solid_Carrier/links/56a3c75a08ae1b6511308eab/Formulation-and-Evaluation-of-Solid-Self-Micro-Emulsifying-Drug-Delivery-System-using-Aerosil-200-as-Solid-Carrier.pdf

[47] D.-G. Yu, Z.-P. Liu, L. Cui, Z. Zhao, and L. Chen, "Electrosprayed core– shell solid dispersions of acyclovir fabricated using an epoxy- coated concentric spray head," *IJN*, p. 1967, Apr. 2014, https://doi.org/10.2147/IJN.S59516

[48] M. T. Marın, M. V. Margarit, and G. E. Salcedo, "Characterization and solubility study of solid dispersions of flunarizine and polyvinylpyrrolidone," *Il Farmaco*, vol. 57, no. 9, pp. 723–727, 2002, Accessed: Dec. 09, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0014827X02012624

[49] P. Mura, M. Cirri, M. T. Faucci, J. M. Ginès-Dorado, and G. P. Bettinetti, "Investigation of the effects of grinding and co-grinding on physicochemical properties of glisentide," *Journal of pharmaceutical and biomedical analysis*, vol. 30, no. 2, pp. 227–237, 2002, Accessed: Dec. 09, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0731708502002522

[50] S. C. Arora, "DEVELOPMENT, CHARACTERIZATION AND SOLUBILITY STUDY OF SOLID DISPERSION OF CEFPODOXIME PROXETIL BY SOLVENT EVAPORATION METHOD".

[51] A. Y. Bazeed, A. Nouh, E. A. Essa, and G. M. El Maghraby, "EXPLORING DRY CO-GRINDING APPROACH AS A TOOL TO IMPROVE THE DISSOLUTION RATE OF POORLY SOLUBLE DRUG," *European Journal of Biomedical*, vol. 7, no. 7, pp. 100–103, 2020, Accessed: Dec. 11, 2023. [Online]. Available: https://www.researchgate.net/profile/Alaa-Bazeed-2/publication/344397191_EXPLORING_DRY_CO-GRINDING_APPROACH_AS_A_TOOL_TO_IMPROVE_THE_DISSOLUTION_RATE_OF_POORLY_SOLUBLE_DRUG/links/5f7086d0a6fdcc00863f841b/EXPLORING-DRY-CO-GRINDING-APPROACH-AS-A-TOOL-TO-IMPROVE-THE-DISSOLUTION-RATE-OF-POORLY-SOLUBLE-DRUG.pdf

[52] R. J. Boghra, "Solubility, dissolution rate and bioavailability en-hancement of irbesartan by solid dispersion technique," *Chemical and Pharmaceutical Bulletin*, vol. 59, no. 4, pp. 438–441, 2011, https://doi.org/10.1248/cpb.59.438

[53] N. Elgindy, K. Elkhodairy, A. Molokhia, and A. Elzoghby, "Lyophilized flutamide dispersions with polyols and amino acids: preparation and in vitro evaluation," *Drug Development and Industrial Pharmacy*, vol. 37, no. 4, pp. 446–455, Apr. 2011, https://doi.org/10.3109/03639045.2010.522190

[54] Y. Luo, Y. Hong, L. Shen, F. Wu, and X. Lin, "Multifunctional Role of Polyvinylpyrrolidone in Pharmaceutical Formulations," *AAPS PharmSciTech*, vol. 22, no. 1, p. 34, Jan. 2021, https://doi.org/10.1208/s12249-020-01909-4

[55] F. S. Emami *et al.*, "Force Field and a Surface Model Database for Silica to Simulate Interfacial Properties in Atomic Resolution," *Chem. Mater.*, vol. 26, no. 8, pp. 2647–2658, Apr. 2014, https://doi.org/10.1021/cm500365c

[56] K. C. Sung *et al.*, "Effect of formulation variables on drug and polymer release from HPMC-based matrix tablets," *International journal of pharmaceutics*, vol. 142, no. 1, pp. 53–60, 1996, Accessed: Dec. 09, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/0378517396046443

Biography

Nouran Abdel Kader is a Lecturer at Alexandria University, Industrial Pharmacy Department. She is also a Lecturer at German International University, Pharmaceutical Engineering Department. She completed her PhD in Pharmaceutical technology from Tanta University in 2023, and her Master of industrial pharmacy in ophthalmic liposomes and ocular inserts from Alexandria University in 2015. Dr. Abdel Kader has been a production manager as well as a research and development (R&D) manager in multinational pharmaceutical factories. In addition, she holds a Master of Business Administration (MBA) in global management. She has participated in multiple research collaboration projects in recent years.

Research Field

Nouran Abdel Kader: Industrial pharmacy, pharmaceutical engineering, Pharmaceutical technology, Pharmaceutics, pharmaceutical manufacturing and Good Manufacturing Practices.