ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 10, Issue 4, 2017

Online - 2455-3891
Print - 0974-2441

Research Article

EFFICACY OF COMBINATION SOLID DISPERSION TECHNOLOGY ON DISSOLUTION PERFORMANCE OF NALIDIXIC ACID AND CEFDINIR

NIDHAL K MARAIE*, ANAS T ALHAMDANY, AMEERA A RADHI

Department of Pharmaceutics, College of Pharmacy, Al-Mustansiriya University, Baghdad, Iraq.
Email: pharm.dr.nidhal.khazaal@unomustansiriyah.edu.iq

Received: 03 January 2017, Revised and Accepted: 13 January 2017

ABSTRACT

Objective: The aim of this study was to formulate a new developed solid dispersion (SD) containing fixed dose combination of nalidixic acid and cefdinir (500:300 mg) to improve dissolution rate of poorly soluble drugs via a new mechanism as well as the conventional mechanism of SD represented by the presence of hydrophilic carrier.

Methods: Through this objective eight newly developed SD formulas of fixed dose combination of nalidixic acid and cefdinir (500:300 mg) and (polyethylene glycol 6000 and poloxamer 188) in different ratio were prepared, in addition to SD of each drug alone and simple mixture of individual SD (SMSD) prepared by means of fusion technique. Moreover, SDs beside pure drugs, simple mixture, and physical mixture (PM) were characterized by dissolution tests, solubility studies, powder X-ray diffractometer (PXRD), differential scanning calorimetry (DSC), Fourier transform-infrared (FT-IR) spectroscopy and scanning electron microscopy (SEM).

Results: From *in vitro* dissolution tests, PXRD, DSC, FT-IR, and SEM; it is indicated the presence of a physical complex between cefdinir and nalidixic acid in their SD containing combination of fixed dose of both drugs. This will affect the crystallinity of the second drug and their dissolution behavior in addition to the conventional mechanism owing to the presence of hydrophilic carrier (poloxamer 188).

Conclusion: It was concluded that the newly prepared formula of SD containing fixed dose combination of nalidixic acid and cefdinir will be promising for higher dissolution profile than that from SD of each drug alone or SMSD of each drug.

Keywords: Nalidixic acid, Cefdinir, Poloxamer 188, Polyethylene glycol 6000, Combinational solid dispersion, Fusion method.

 DOI: http://dx.doi.org/10.22159/ajpcr.2017.v10i4.16913

INTRODUCTION

Diverse methods applied to improve solubility of poorly water-soluble drugs including salt formation, complexation, micronization, micellar solubilization, use of surfactant, cosolvency, use of prodrug, drug derivatization, pH alteration, chemical modification, solid dispersion (SD), hydrotrophy, and others [1]. SD is one of the most viable and economic promising approaches that represent an ultimate challenge to the formulation scientists in the pharmaceutical industry, clinical application, and marketability employed to improve the oral bioavailability of poor water soluble drugs whose absorption is dissolution rate limited [2]. SD is accomplished through reducing drug particle size to the absolute minimum, increasing porosity, converting the crystalline forms of drug into amorphous form and hence improving drug wettability. SD refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method [3,4].

Combination of more than one active ingredient is referred to as combination SD, where the possibility of the presence of one drug may affect the solubility of another one [5]. To investigate such possibility; nalidixic acid and cefdinir are used where such combination therapy is commonly applied for treatment of many infectious diseases such as urinary tract infection [6,7]. Nalidixic acid (class II) is a quinolone group drug that has a high bacteriostatic and bactericidal activity against infections caused by Gram-negative organisms. It is a drug with poor aqueous solubility often low absorption and poor bioavailability. Thus improvement in aqueous solubility and dissolution rate are necessary [8]. Cefdinir (class IV) is an oral extended spectrum antibiotic which belongs to third generation cephalosporins with low solubility and low permeability resulting in a low oral bioavailability characteristic [9].

This study was undertaken to investigate the feasibility and efficacy of formulating SD containing fixed dose combination of nalidixic acid and cefdinir on their solubility/dissolution profile in comparison to SD containing each drug separately and simple mixture of their individual SDs in addition to physical mixture (PM) of the two pure drugs. The proposed combination SD technology may improve the absorption rate of the poorly soluble drugs and suggesting an additional mechanism to enhance drug dissolution via SD technology.

MATERIALS AND METHODS

Materials

Nalidixic acid (Sigma Chemical Co. [Aldrich], USA), cefdinir (Buchang Pharma, China), poloxamer 188 (M/S Provizer Pharma, India), polyethylene glycol 6000 (PEG 6000) (Sigma Chemical Co. (Aldrich), USA).

Methodology

Preparation of combination SDs containing fixed dose of nalidixic acid and cefdinir

The recommended dose for nalidixic acid is 500 mg and for cefdinir is 300 mg. accordingly, SDs containing combination of nalidixic acid and cefdinir (500:300 mg) were prepared using fusion method. Nalidixic acid and cefdinir (SD1-SD8) as showed in (Table 1) were added to the molten carrier (poloxamer 188 or PEG 6000) in a water bath at 60°C, with continuous stirring for 15 minutes until a homogenous dispersion was formed. The dispersion was then left to solidify at room temperature, and then samples were passed through an 80-mesh sieve and kept in well-closed glass containers in a desiccator for further studies [10].

Preparation of SD of nalidixic acid and cefdinir each separately

SD containing nalidixic acid 500 mg containing (SD9) or cefdinir 300 mg (SD10) with poloxamer 188 in ratio (1:6) was prepared by fusion method as mentioned earlier [10] and showed in (Table 1).

Preparation of simple mixture of individual SDs (SMSDs)

A mixture was prepared by simple mixing of the previously prepared nalidixic acid SD9 and cefdinir SD10 in a mortar for 5 minutes until a homogenous mixture was obtained. The resulting mixture SMSD was then sieved [11].

Preparation of physical mixture (PM) of nalidixic acid and cefdinir

PX of pure nalidixic acid and pure cefdinir powder (500:300 mg) (PM) was prepared by mixing them with poloxamer 188 in ratio (1:6) for 5 minutes in a mortar until a homogenous mixture was obtained. The resulting mixture was then sieved. The powder was kept in well-closed glass container in desiccators for further analysis [12].

Evaluation of SDs

***In vitro* dissolution testing**

Dissolution test was performed for pure powders of nalidixic acid and cefdinir for combination SD of nalidixic acid and cefdinir (SD1-SD8), SD containing each drug separately (SD9 and SD10), SMSD, and PM of pure drugs in the presence of Poloxamer 188; using the dissolution apparatus (Copley - UK) Type II paddle method with rotation speed 50 rpm for 90 minutes. The dissolution medium was 900 ml phosphate buffer pH 6.8 thermo-stated at 37±0.5°C. Five milliliters samples were withdrawn after specific time intervals filtered before analysis and equal volumes of fresh phosphate buffer, maintained at 37°C, were added to the dissolution medium to maintain sink condition. The release of nalidixic acid and cefdinir was assayed by ultraviolet spectrophotometer (Shimadzu 1650 pc-Japan) at 257 nm and 287 nm, respectively, and quantified using a calibration curve in the same media [13,14].

All samples were analyzed in triplicate, and release curves were plotted using calculated mean values of % cumulative drug release.

Saturated solubility studies

Saturated solubility in phosphate buffer pH 6.8 was applied for nalidixic acid and cefdinir from the prepared combination SD7, SD containing nalidixic acid and cefdinir (SD9 and SD10), SMSD; in comparison to solubility from the pure powders of each drug as well as from PM of the two pure drugs with Poloxamer 188. The study was conducted in thermostatic shaker bath for 48 hrs at 37±5°C. Finally, the solutions were filtered and the filtrate was diluted for determining drug concentration spectrophotometrically, the absorbance was measured at 257 nm for nalidixic acid and 287 nm for cefdinir [15].

Powder X-ray diffraction (PXRD)

PXRD patterns for each of pure powders of nalidixic acid and cefdinir, combination SD7, SD containing each drug separately (SD9 and SD10), SMSD, and PM of pure drugs in the presence of Poloxamer 188 were recorded for structural and crystal size characterization using PXRD (Shimadzu 6000, Japan) under the following conditions. Nickel-filtered CU-Kα radiation (λ=1.54060 Å). The voltage and current was 40 KV 30 mA, respectively, and smoothed 90. Measurement was carried out in the range 5° and 60° using a step size of 0.05° and 0.6 seconds per step [16].

Thermal analysis

Differential scanning calorimetry (DSC) curve for each of pure powders of nalidixic acid and cefdinir, combination SD7, SD containing each drug separately (SD9 and SD10), SMSD, and PM of pure drugs in the presence of Poloxamer 188 were measured with a DSC instrument (DSC-60, Shimadzu - Japan). The samples were accurately weighed and heated in sealed aluminum pan at a rate of 10°C/minutes between 30°C and 250°C under a nitrogen gas flow of 40 mL/minutes during the study. Empty iridium pan was used as a reference [17].

Fourier transform-infrared (FT-IR) spectroscopy

FT-IR spectra for each of pure powders of nalidixic acid and cefdinir, poloxamer 188 also for combination SD7, SD containing each drug separately (SD9 and SD10), SMSD, and PM of pure drugs in the presence of Poloxamer 188 recorded by FT-IR spectrophotometer (8400S, Shimadzu - Japan) using potassium bromide pellets. The samples were scanned from 4000 to 400/cm. The compatibility of drug in the formulation was confirmed by IR spectra of pure drugs and formulations were determined [18].

Scanning electron microscopy (SEM)

The SEM analysis was carried out for each of pure powders of nalidixic acid and cefdinir, poloxamer 188, also for combination SD7 and SMSD using SEM (Inspect S50, FEI - Netherland). Before examination, samples were mounted on an aluminum stub using a double sided adhesive tape and then making it electrically conductive by coating with a thin layer of gold (approximately 24 nm) in vacuum. The SEM was operated at an acceleration voltage of 10 KV [19].

RESULTS AND DISCUSSION

***In vitro* dissolution studies**

It was evident that the pure nalidixic acid exhibited a slow dissolution in phosphate buffer pH 6.8 as showed in (Figs. 1 and 2), where the percentage of drug dissolved after 90 minutes was 60.09%. This is due to its hydrophobicity and poor wettability; leading to agglomeration of nalidixic acid particles and floating of drug powder on the surface and consequently hindering its dissolution [20].

All combinational SD formulas (SD1-SD8) showed a significant enhancement in nalidixic acid release ($p<0.05$) compared to the pure

Table 1: Formulations of SD prepared and their compositions

Formula number	Drug: Nalidixic acid (mg)	Drug: Cefdinir (mg)	Carrier: PEG 6000 (mg)	Carrier: Poloxamer 188 (mg)	Drug: Carrier ratio
SD1	500	300	1600		1:2
SD2	500	300	3200		1:4
SD3	500	300	4800		1:6
SD4	500	300	6400		1:8
SD5	500	300		1600	1:2
SD6	500	300		3200	1:4
SD7	500	300		4800	1:6
SD8	500	300		6400	1:8
SD9	500			3000	1:6
SD10		300		1800	1:6
SMSD	500	300		4800	1:6
PM	500	300		4800	1:6

SD: Solid dispersion, SMSD: Simple mixture of individual solid dispersion, PM: Physical mixture of nalidixic acid: cefdinir: poloxamer

drug. Formulations containing PEG 6000 as a hydrophilic carrier (SD1-SD4) showed a significant increase ($p<0.05$) in the dissolution rate with increasing its concentration. A best release obtained for (SD3) after 90 minutes was 90.95% where the drug to polymer ratio was 1:6. As a suggested mechanism; the presence of PEG 6000 as a hydrophilic carrier improves drug wettability and causes rapid penetration of the dissolution medium into the particles. On increasing PEG 6000 concentration (SD4), the release of nalidixic acid slightly decreased than that of (SD3) due to the formation of viscous boundary layer around the drug particles that slows down its diffusion into the dissolution medium [21].

Formulations prepared with poloxamer 188 as a hydrophilic carrier (SD5-SD8) showed a higher dissolution rate than those prepared with PEG 6000 and formula (SD7) showed maximum drug release; where it is 95.02% in 90 minutes. This may be attributed to the surfactant property of poloxamer (micellar solubilization) and its great hydrophilicity resulting in a greater wettability of the drug. However, higher concentration of poloxamer 188 (SD8) led to slight decrease in dissolution rate in comparison to (SD7). This is related to the gelling property of the polymer at higher concentration which increases the viscosity of the diffusion boundary layer adjacent to the dissolving surface [22].

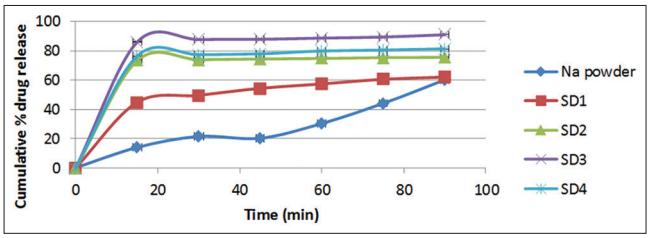

Fig. 1: Dissolution profiles of nalidixic acid from the combination solid dispersions (SD) using polyethylene glycol 6000 as carrier (SD1-SD4) and pure nalidixic acid (n=3) (mean±standard deviation)

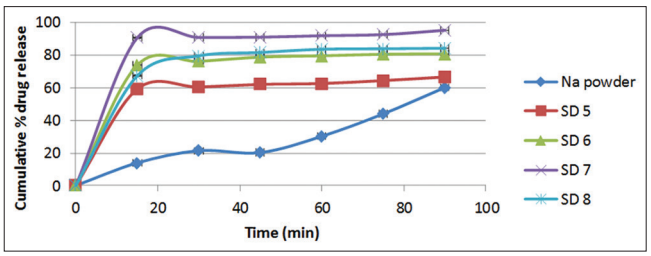

Fig. 2: Dissolution profiles of nalidixic acid from the combination solid dispersions (SDs) using poloxamer 188 as a carrier (SD5-SD8) and pure nalidixic acid (n=3) (mean±standard deviation)

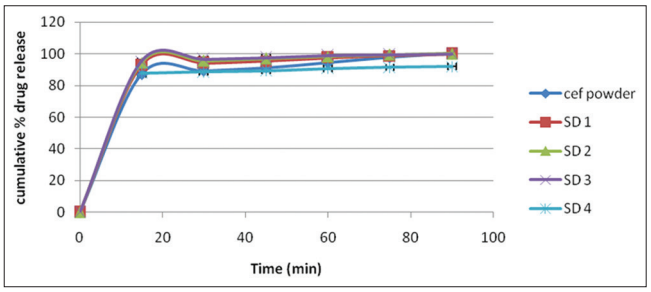

Fig. 3: Dissolution profiles of cefdinir from the combination solid dispersions (SDs) using polyethylene glycol 6000 (SD1-SD4) and pure cefdinir (n=3) (mean±standard deviation)

Figs. 3 and 4 showed that there was no significant difference in the dissolution of cefdinir from the prepared formulas (SD1-SD8) in comparison to dissolution of pure drug since cefdinir is highly soluble in phosphate buffer pH 6.8 where it is highly soluble.

Accordingly, the dissolution of drug from (SD7) for combinational SD containing nalidixic acid and cefdinir in the presence of 1:6 ratio of poloxamer was compared to their dissolution from their individual SD (SD9 and SD10), SMSD and PM of pure drugs in the presence of Poloxamer 188. Based on the drug dissolution profiles; formula (SD7) selected to be the optimum formula.

The release of nalidixic acid (Fig. 5) from the optimum formula (SD7) and (SMSD) was significantly ($p<0.05$) greater than that from (SD9) and (PM). While there was no significant change in the dissolution profile of cefdinir (Fig. 6) from all formulas; in which cefdinir shows high release from all these formulas [14]. The release of nalidixic acid from (SD7) which contains combinational SD of nalidixic acid and cefdinir was slightly higher than that from (SMSD). These results suggest an additional mechanism of increasing solubility and dissolution of nalidixic acid in SD. It may be attributed to the solvent effect of cefdinir on nalidixic acid. Nalidixic acid was dispersed in cefdinir matrix in

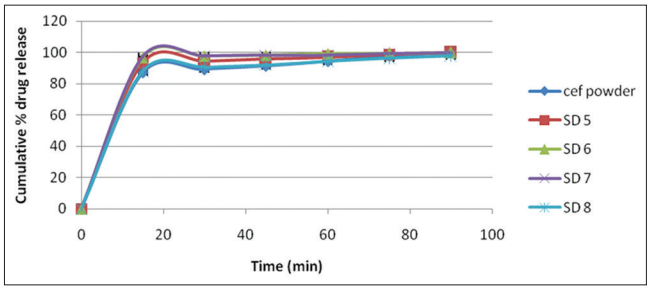

Fig. 4: Dissolution profiles of cefdinir from the combination solid dispersions (SDs) using poloxamer 188 (SD5-SD8) and pure cefdinir (n=3) (mean±standard deviation)

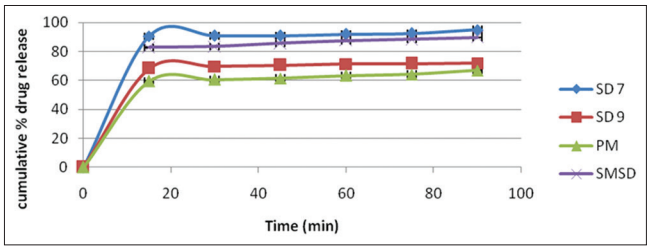

Fig. 5: Dissolution profiles of nalidixic acid from the combination solid dispersion (SD) SD7, SD containing drug separately (SD9), physical mixture (PM), and simple mixture of individual SD (SMSD) (n=3) (mean±standard deviation)

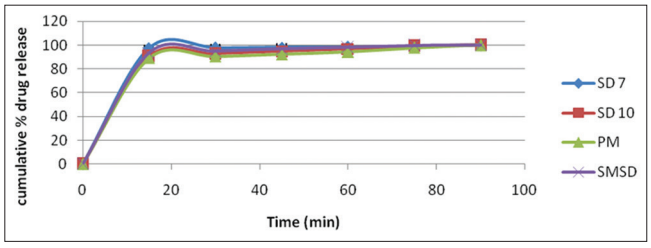

Fig. 6: Dissolution profiles of cefdinir from the combination solid dispersion (SD) SD7, SD containing drug separately (SD10), physical mixture and simple mixture of individual SD (SMSD) (n=3) (mean±standard deviation)

amorphous or solid solution in SD, and on exposure to dissolution medium, the matrix dissolves and releases the dispersed drug in a pure state of subdivision which facilitates dissolution of nalidixic acid [23]. This is added to the conventional mechanism observed in SD prepared using hydrophilic carrier of poloxamer [24].

Saturated solubility studies

The results of saturated solubility of nalidixic acid and cefdinir from formulations (SD7, SD9, SD10, SMSD, and PM) and pure drugs in phosphate buffer pH 6.8 are presented in Table 2.

It was observed that the saturated solubility of nalidixic acid from optimum combinational SD7 was about two-fold higher than that from simple mixture of individual solid dispersion of both drugs (SMSD) suggesting the presence of a physical complex between nalidixic and cefdinir, such complex observed during the method of preparation of the (SD7) formulas where the temperature used in fusion method enhanced such complex in the solid state as well as in the liquid state. In addition to the solvent effect of cefdinir that was observed in the dissolution study. Solid state complex is reported for SD of hydrochlorothiazide - losartan potassium [23].

No significant increase in solubility of cefdinir in phosphate buffer pH 6.8 from all the prepared formulas due to its high ionization in this pH (Table 3) [25].

PXRD

The PXRD patterns for each of pure powders of nalidixic acid and cefdinir, SD7, SD9, SD10, SMSD, and PM are showed in (Fig. 7).

The spectrum of pure nalidixic acid and pure cefdinir showed a higher number of reflections of higher intensity. Thus, PXRD pattern of pure nalidixic acid showed a numerous sharp distinctive, narrow and strongly intense diffraction peaks that represent a highly stable crystalline nature of the drugs [26,27].

On the other hand, the PXRD of (SD7 and PM) showed decrease in the intensity of peaks and disappearance of some sharp distinctive peaks for (SD7) in comparison to (PM) and pure drugs and the formation of broadened peaks as an evident of decrease in degree of crystallinity and predict for the amorphous form appearance compared to the pure powders of both drugs. This can be attributed to the change in the orientation during the crystal growth phase leading to formation of imperfect crystals or amorphonization that will dissolve at fastest rate due to higher internal energy and greater molecular motion which develop thermodynamic properties relative to crystalline materials [28,29].

Table 2: Saturated solubility of nalidixic acid in comparison to solid dispersion formulas, SMSD and PM

Formulation	Nalidixic acid solubility (mg/ml)
Pure nalidixic acid	0.195±0.04
SD7	0.586±0.03
SD9	0.265±0.06
SMSD	0.3±0.05
PM	0.227±0.02

Saturated solubility data represent (mean±SD) (n=3). SD: Solid dispersion, SMSD: Simple mixture of individual solid dispersion, PM: Physical mixture

Table 3: Saturated solubility of pure cefdinir in comparison to SD formulas, SMSD and PM

Formulation	Cefdinir solubility (mg/ml)
Pure cefdinir	0.73±0.03
SD7	1.1±0.02
SD10	0.84±0.04
SMSD	0.95±0.05
PM	0.79±0.03

Saturated solubility data represent (mean±SD) (n=3). SD: Solid dispersion, SMSD: Simple mixture of individual solid dispersion, PM: Physical mixture

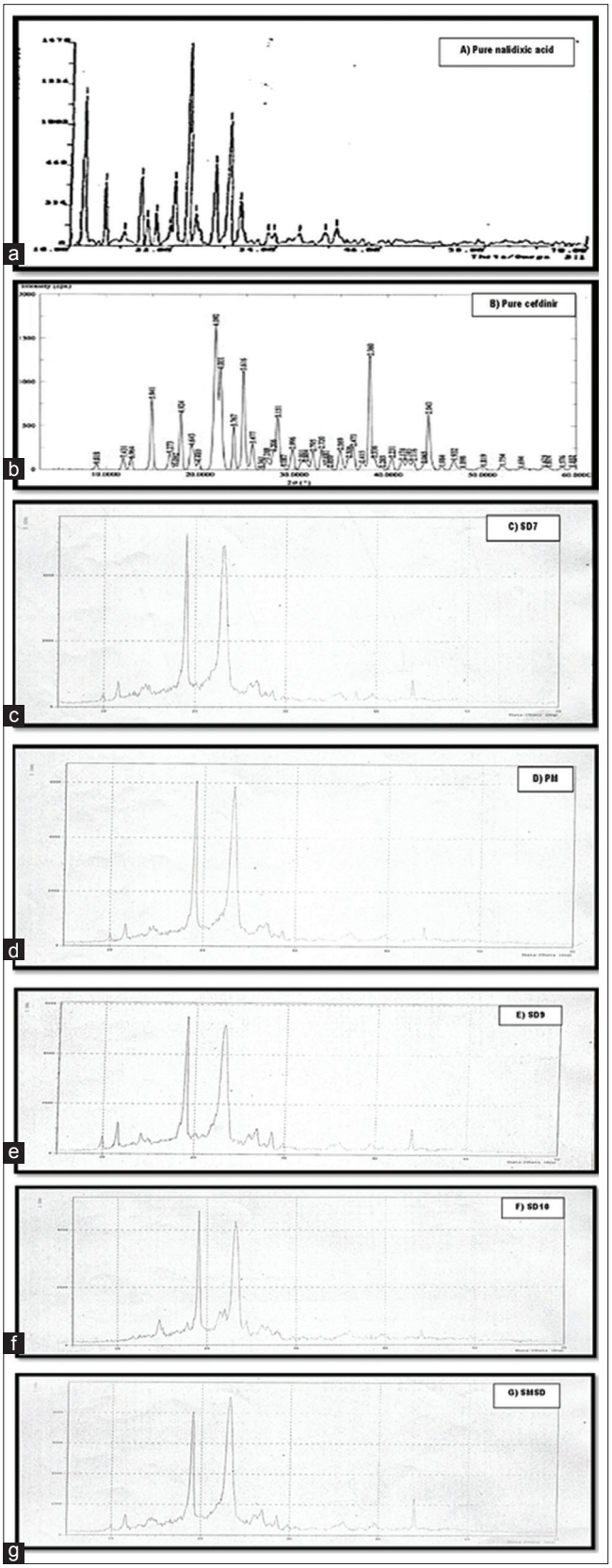

Fig. 7: Powder X-ray diffraction patterns of (a) pure nalidixic acid, (b) pure cefdinir, (c) SD7, (d) physical mixture (PM), (e) SD9, (f) SD10 and (g) SMSD

Formulas (SD9, SD10, and SMSD) showed shift in the number and intensities of peaks in PXRD than the pure drugs, the base of the peaks in (SD9, SD10, and SMSD) were also found to be boarder in nature but less extent than that observed with (SD7) resulting a change in crystallinity [30,31]. Therefore, the results obtained from PXRD agreed with that of dissolution study where (SD7) showed high drug release.

Thermal analysis

As showed in (Fig. 8), DSC thermogram of nalidixic acid and cefdinir presents a sharp endothermic peak at 228°C and 155°C, respectively, corresponding to their melting points. Similarly, the DSC curve of poloxamer 188 shows one endothermic effect, associated with its melting at 56.7°C.

The DSC thermograms of SDs (SD9, SD10, and SMSD) gave boarder peak for polymer with shifted position than that of pure polymer indicating miscibility of drug with the polymer. Furthermore, it showed board peak for cefdinir and nalidixic acid indicating the amorphous structure in these formed SD (SD9, SD10, and SMSD). The absence of endotherm in PM suggested the dissolution of the crystalline drug particles within the molten polymer due to the heating phase during analysis [32]. While (SD7) showed wide endothermic peak at 46.74°C with disappearance

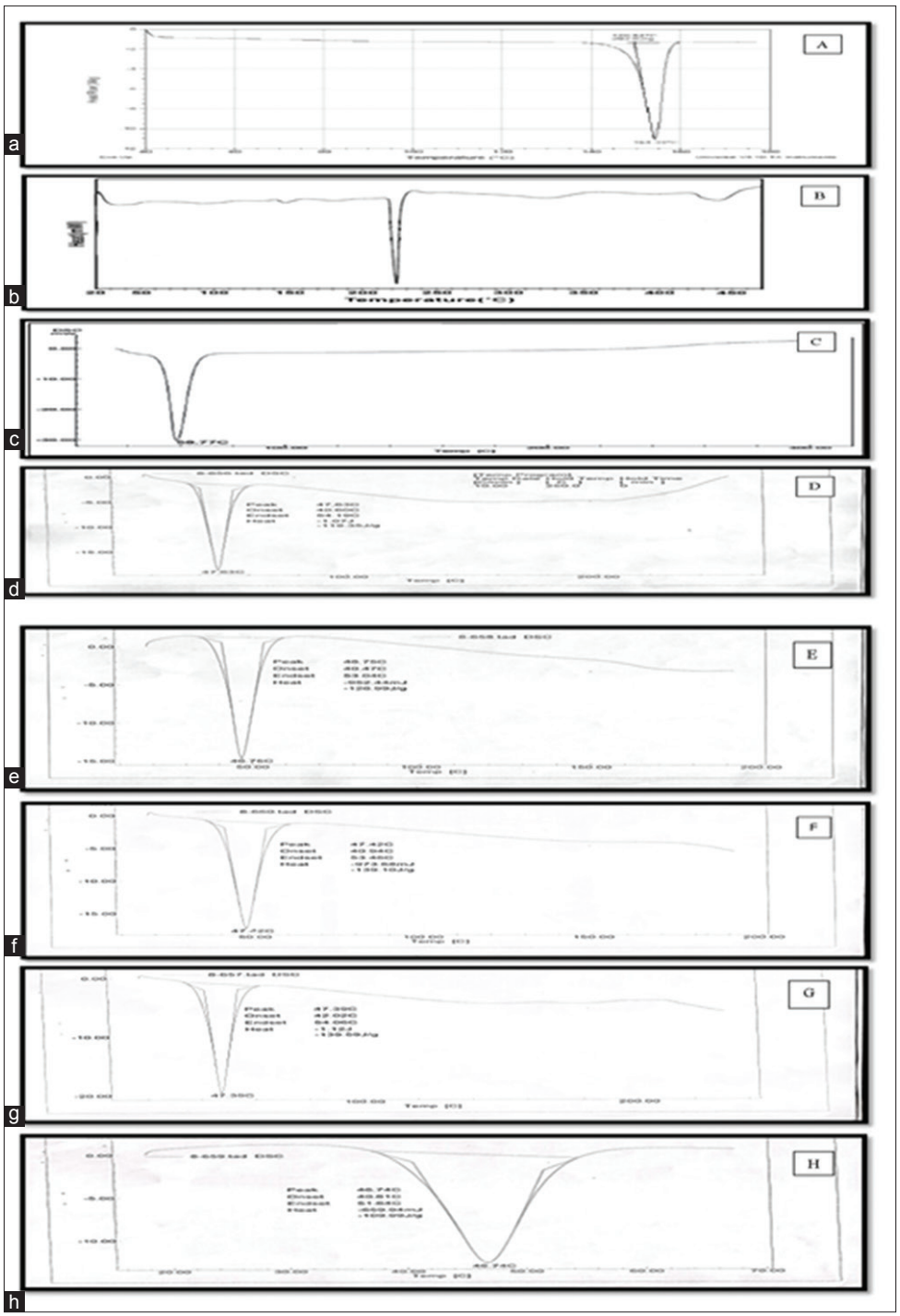

Fig. 8: Differential scanning calorimetry thermograms of (a) pure cefdinir; (b) pure nalidixic acid; (c) poloxamer 188; (d) SD9; (e) SD10; (f) simple mixture of individual SD (SMSD); (g) physical mixture (PM) (h) SD7

of end peaks for cefdinir and nalidixic acid, suggesting a complex formation between cefdinir and nalidixic acid within SD formula that may give new peak for such complex melting point and this supporting the interpretation obtained from dissolution study [33,34].

FT-IR spectroscopy

The IR spectrum of pure nalidixic acid powder as showed in (Fig. 9a) is characterized by principle absorption bands at 3043.77/cm, 2983.98/cm (C-H stretching vibrations), 1785/cm (C=N stretching vibrations),1712.85/cm(C=Oasymmetricstretchingvibrations),1616.4/cm (c-c asymmetric stretching vibrations) and 1518.03/cm(c-c symmetric bending), 1473.66, 1440.87 (C-N stretching), 1352.14 and 1327.07/cm (N-C-H deformation), 1253.77/cm (CH_3 bending), 1228.7/cm (C-O-H symmetric bending), 1130.32, 1101.39, 1051.24, 1004.95 and 972.16/cm (C-C-H asymmetric and symmetric bending vibrations), 804.34/cm (O=C-C asymmetric bending), 656 and 635/cm (C-C-C bending), 455/cm, 485/cm, 400/cm (CN=C, N-C-N, and C-N-C bending vibrations) [35].

The IR spectrum of pure cefdinir powder as showed in (Fig. 9b) is characterized by absorption peaks at 3360/cm (N-H stretching vibration of amide group) while NH_2 group appears symmetrical and asymmetrical stretching at 3298.8/cm, the band 3070.78/cm due to aromatic (C-H), 2968.55/cm and 2877.89/cm (aliphatic C-H), 1766.85/cm and 1683.91/cm (carbonyl group), 1624.12/cm (C-O stretch, asymmetric and symmetric in COOH), 1595.18/cm and 1558.54/cm (C=N), 1519.96 (N-H bending amide II band) and 1352.14 (NH_2 bending vibration) [36].

The IR spectrum of poloxamer 188 as showed in (Fig. 9c) is characterized by principal absorption peaks at 2883/cm (C-H stretch aliphatic), 1341/cm(in-plane O-H bend) and 1099/cm (C-O stretch), which were consistent in all binary systems with the drug. The IR spectrum of (SD7) as shown in (Fig. 9d) illustrates the presence of all nalidixic acid and cefdinir peaks with decreased intensity and smoothened thus indicating a strong physical complex between both drugs due to intermolecular hydrogen bonding in SDs [37].

FT-IR spectrum of (SMSD) as showed in (Fig. 9e) demonstrates the lack of any new peaks in the SD and also no differences in the position of absorption bands, indicating the absence of significant interactions between both drugs and carrier [38].

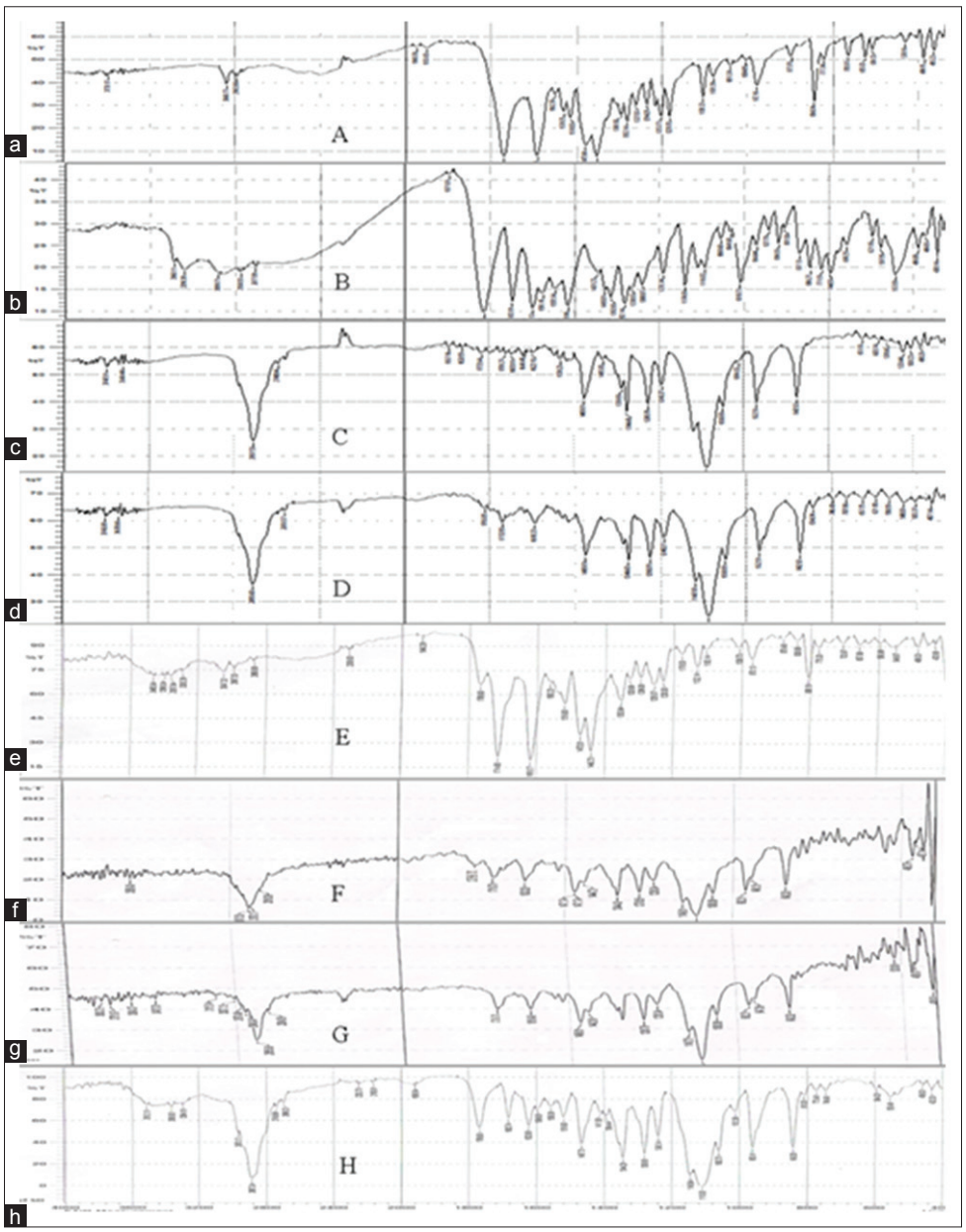

Fig. 9: The FT-IR spectra for (a) pure nalidixic acid powder; (b) pure cefdinir powder; (c) poloxamer 188; (d) SD7; (e) simple mixture of individual SD (SMSD); (f) physical mixture (PM); (g) SD9 and (h) SD10

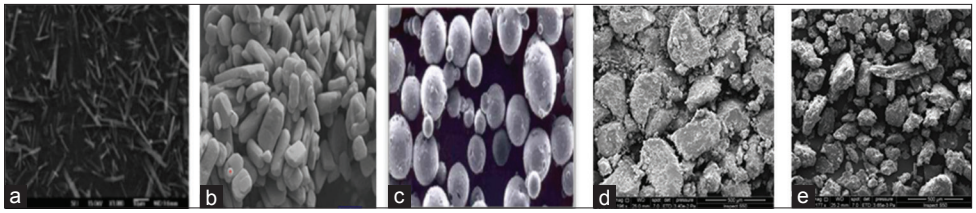

Fig. 10: Scanning electron microscopy for (a) pure cefdinir powder; (b) pure nalidixic powder; (c) poloxamer 188; (d) SD7 and (e) simple mixture of individual SD (SMSD)

FT-IR spectrum of the (PM) as showed in (Fig. 9f) displayed the superimposition pattern of both drugs and polymer peaks with decreased peak intensity and little shifting of the peaks during cogrinding revealing the inert nature of the carrier used for formulation [39].

The IR spectrum of SD9 and SD10 as showed in (Fig. 9g and 9h), respectively; presented all characteristic bands are well defined and appeared clear in the spectrum with no change in frequency and shape of bonds, which suggested that no significant redistribution of electronic density in the structure of the organic molecule appeared. This indicated that there is no strong interaction between each drug and polymers in each formula [40]. This study agreed with our conclusion obtained in PXRD, DSC, and dissolution study.

SEM

SEM of pure nalidixic acid powder and pure cefdinir powder showed crystal form and poloxamer 188 showed globular forms as showed in (Fig. 10). In SD of fixed dose combination (SD7) and SMSD; the structure of both drugs crystal is completely different from the pure drug. These findings demonstrated that the drug was changed in amorphous form which was confirmed by our PXRD and DSC studies [41].

From the results of PXRD, FT-IR, SEM, and DSC; it is indicated the presence of a physical complex between cefdinir and nalidixic acid in their SD containing combination of fixed dose of both drugs that affect the crystallinity of the second drug and their dissolution behavior in addition to the conventional mechanism due to the presence of hydrophilic carrier (poloxamer 188).

CONCLUSION

From the previous studies, it was noticed that the optimal formula (SD 7) has led to the possibility of preparation of SD containing fixed dose combination of nalidixic acid and cefdinir. A higher dissolution profile is approved than that from SD of each drug alone or SMSD of each drug. This suggesting a new mechanism for drug dissolution that involves a physical complex between nalidixic acid and cefdinir that have higher dissolution rate than each drug alone and even higher than SD containing each drug alone. Such complex present in the solid state and in the solution state in addition to action of cefdinir that may act as a solvent (a new carrier) for nalidixic acid; thus improving its dissolution, as well as the conventional mechanism for SD that is represented by the existence of poloxamer 188 as a (hydrophilic carrier).

AKNOWLEDGMENT

The author would like to thank Al-Mustansiriya University (www.uomustansiriyh.edu.iq) Baghdad-Iraq for its support in the present work. Also, the author is appreciative and great thanks for assistant professor Dr. Ayad M.R. Raaufin the department of pharmaceutical chemistry, college of pharmacy, Al-Mustansiriya University, Baghdad-Iraq, for his help and generosity.

REFERENCES

1. Siahi-Shadbad MR, Ghanbarzadeh S, Barzegar-Jalali M, Valizadeh H, Taherpoor A, Mohammadi G, *et al.* Development and characterization of solid dispersion for dissolution improvement of furosemide by cogrinding method. Adv Pharm Bull 2014;4(4):391-9.
2. Anshu S, Jain CP. Preparation and characterization of solid dispersions of valsartan with poloxamer 188. Der Pharm Lett 2010;2(2):54-63.
3. Anju K, Sunil KP, Pragya N. Solubility enhancement studies of solid dispersion. WJPP 2015;4(10):2126-42.
4. Linda F. Remington, Essentials of Pharmaceutics. 1st ed. USA: Pharmaceutical Press; 2006. p. 238.
5. Niraj, Jyoti, Srivastava VK, Hemesh S, Narendra S. Solubility and dissolution enhancement of antihypertensive Agent(S) using solid dispersion techniques. Int J Clin Chem Lab Med 2015;1(1):23-8.
6. Leigh AP, Nemeth MA, Keyserling CH, Hotary LH, Tack KJ. Cefdinir versus cefaclor in the treatment of uncomplicated urinary tract infection. Clin Ther 2000;22(7):818-25.
7. Taori A, Nema R, Kohli DV, Uppadhyay RK. Nalidixic acid prodrugs: Amides from amino acid ester and nalidixic acid. Arch Pharm Res 1991;14(1):48-51.
8. Nazik AE, Shalaby AA, Abd Bl-Khalek MM. Dissolution of nalidixic acid solid dispersions: Systems of NAL-inclusion and linear polymeric compounds. Drug Dev Ind Pharm 2008;9(6):1031-45.
9. Suman T, Muzammil AS, Ramesh B, Kishan V. Development and *in vivo* evaluation of cefdinir nanosuspension for improved oral bioavailability. Int J Pharm Sci Nanotechnol 2014;7(3):2553-60.
10. Thirupathi A, Reddy A, Narayana AD, Meshram S, Sampathi S. Solid state characterization of the polymorphic changes in candesartan cilexetil solid dispersion with poly ethylene glycol 8000. IJPSR 2014;6(1):27-32.
11. Rao BR, Chandrasekhar B. Preparation and characterization of pioglitazone HCl solid inclusion complex a solubility enhancement technique. Int J Biopharm 2014;5(3):180-3.
12. Kour P, Kumar M, Kataria MK, Bilandi A. Dissolution rate enhancement of pioglitazone by solid dispersion technique. IAJPR 2015;5(7):2664-81.
13. Mallick S, Sahu A, Pal K. Dissolution behaviour of nalidixic acid solid dispersions using water soluble dispersion carriers. Acta Pol Pharm 2004;61(1):21-30.
14. Japanese Pharmacopoeia. 17th ed. Japan: Pharmaceuticals and Medical Devices Agency under the Authority of the Ministry of Health, Labour and Welfare; 2016.
15. Mohan A, Madhavi M, Swetha G, Jyosthna P. Preparation, *in vitro* and *in vivo* characterization of solid dispersions of lamotrigine using solvent evaporation technique. IOSR J Pharm 2015;5(1):54-9.
16. Yadav B, Tanwar YS. Development, characterization and *in vitro* evaluation of flurbiprofen solid dispersions using polyethylene glycols as carrier. J Appl Pharm Sci 2016;6(4):60-6.
17. Gavali RD, Patil SS. Enhancement of dissolution profile by preparing solid dispersion using spray drying method. Der Pharm Lett 2016;8(5):362-72.
18. Balata G, Mahdi M, Bakera RA. Improvement of solubility and dissolution properties of ketoconazole by solid dispersions and inclusion complexes. Asian J Pharm Sci 2010;5(1):1-12.
19. Howlader SI, Chakrabarty JK, Faisal KS, Kumar U, Sarkar R, Khan MF. Enhancing dissolution profile of diazepam using hydrophilic polymers by solid dispersion technique. Int Curr Pharm J 2012;1(12):423-30.
20. Essa EA, Dwaikat M. Enhancement of simvastatin dissolution by surface solid dispersion: Effect of carriers and wetting agents. J Appl Pharm Sci 2015;5(1):46-53.
21. Deshmukh KR, Jain SK. Development of aceclofenac mouth dissolving tablets using solid dispersion technique: *In-vitro* evaluation. IJPER 2012;46(2):97-104.
22. AbdAlaziz DM, Sammour OA, Elshamy AA, Neseem DI. Formulation and evaluation of binary and ternary solid dispersions of domperidone by solvent evaporation method. Afr J Pharm Pharmacol 2014;8(3):66-80.
23. Panneerselvam M, Natrajan R, Selvaraj S, Rajendran NN. A novel drug-drug solid dispersion of hydrochlorothiazide - losartan potassium. IJPBS 2010;1(4):68-80.
24. Manvi P, Narendra P, Bhaskar VH. Preparation, characterization and *in*

vitro evaluation of repaglinide binary solid dispersion with hydrophilic polymers. Int J Drug Dev Res 2011;3(1):107-17.
25. Jain S, Mishra A, Garg G, Modi RK. Formulation and characterization of fast disintegrating tablets containing cefdinir solid dispersion. Int J Pharm Life Sci 2012;3(12):2190-9.
26. Mustafa RA, Nidhal KM, Ashour HD. Loading of clarithromycin and paclitaxel on synthesized CDS/NIO nanoparticles as promising nano carriers. Int J Pharm Pharm Sci 2016;8(5):322-33.
27. Shahad M, Nidhal M, Ashour HD. Preparation and comparative evaluation of Fe+2/Fe+3 and Mg+2/Fe+3 LDHs as promising nano carriers for class II and class IV drugs. J Nat Sci Res 2015;5(14):126-37.
28. Monica R, Yogesh M, Kaushik T, Sucheta B. Dissolution improvement of simvastatin by surface solid dispersion technology. Dissolution Technol 2010;17(2):27-34.
29. Marco VC, Andréa CL, Marta MV, Maria OP, Fábio CP, Liliane NP, *et al*. Development and evaluation of praziquantel solid dispersions in sodium starch glycolate. Trop J Pharm Res 2013;12(2):163-8.
30. Kumar P, Kumar S, Kumar A, Chander M. Physicochemical characterization of solid dispersions of cefdinir with PVP K-30 and PEG 4000. Int J Pharm Sci Nano 2010;3(2):948-56.
31. Anmar AI, Daniela M, Victor C, Valintina A. Preparation and evaluation of meloxicam solid dispersion by melting method. Farmacia 2013;61(6):1216-32.
32. Shah S, Joshi S, Lin S, Madan PL. Preparation and characterization of spironolactone solid dispersions using hydrophilic carriers. AJPS 2012;7(1):40-9.
33. Roni MA, Dipu MH, Kibria G, Rahman H, Rony MD, Jalil RU. Dissolution enhancement of poorly soluble carbamazepine by using polymeric solid dispersions. IJPSR 2011;2(1):49-57.
34. Gorniak A, Karolewicz B, Czapor-Irzabek H, Gladysz O. A physicochemical and dissolution study of ketoconazole - pluronic F127 solid dispersions. Farmacia 2016;64(2):244-51.
35. Muthu S, Elamurugu PE, Yusuf E. Density functional theory and abinitio studies of vibrational spectra of nalidixic acid. IAPS 2011;15(2):205-22.
36. Bansal S, Aggarwal G, Chandel P, Harikumar SL. Design and development of cefdinir niosomes for oral delivery. J Pharm Bioallied Sci 2013;5(4):318-25.
37. Sharma A, Chandra PJ, Yuveraj ST. Preparation and characterization of solid dispersions of carvidolol with poloxamer 188. J Chil Chem Soc 2013;58(1):1553-7.
38. Margrit A, Azza H, Hanas EN, Fakhr-Eldin G. Enhancing oral bioavailability of carvidolol using solid dispersion technique. Int J Pharm Pharm Sci 2016;8(7):193-9.
39. Krishnamoorthy V, Nagalingam A, Priya Ranjan Prasad V, Parameshwaran S, George N, Kaliyan P. Characterization of olanzapine-solid dispersions. Iran J Pharm Res 2011;10(1):13-24.
40. Vivek S, Swati M. Formulation of alternative dosage from for cephalosporin (CEFDINIR). Asian J Biomed Pharm Sci 2014;4(33):29-42.
41. Pina MF, Zhao M, Pinto JF, Sousa JJ, Craig DQ. The influence of drug physical state on the dissolution enhancement of solid dispersions prepared via hot-melt extrusion: A case study using olanzapine. J Pharm Sci 2014;103(4):1214-23.