Original Article

Exploration Into Crystalline Forms Of Prulifloxacin

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DOI: 10.47750/pnr.2022.13.S08.524

Abstract

Some new crystalline forms of prulifloxacin, a fluoroquinolone antibiotic, were successfully prepared through solvent evaporation and solvent change (combined antisolvent addition/cooling) methods of crystallization using selected solvents of different polarities. The physicochemical differences among procured crystalline form and prepared new crystalline forms were established by characterization through melting point determination, polarizing microscopy, Fourier transform infra-red spectroscopy (FT-IR), powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) and thermo gravimetric analysis (TGA) techniques. Among prepared crystalline forms at least five forms have been ascertained to be definitely newer polymorphs of prulifloxacin as proven by significant characteristic differences.

Keywords: crystalline form, differential scanning calorimetry (DSC), fourier transform infra-red spectroscopy (FT-IR), polarizing microscopy, polymorph, powder X-ray diffraction (PXRD), Prulifloxacin, solvates, thermo gravimetric analysis (TGA).

INTRODUCTION

Most drugs happen to exist in different crystalline forms. Many of excipients and also APIs have different crystal lattices with different internal packing three dimensional molecular arrays resulting in polymorphic forms [(1)]. Polymorphism and crystallinity are considered among the prime determinants through which the optimization of drug substances is mandatory in the development of a stable, effective, safe, and reproducible dosage form [(2)]. Existance of polymorphism is done in order to study the possibilities of physical stability and bioavailability of physical form of drug in a dosage form such as tablets, capsules and more specifically for suspensions, solutions, and other semisolid dosage forms [(3, 4, 5)]. Exhaustive research for all possible crystal forms of a substance used in preparation of medications should be performed so as to test the crystallinity and the solubility differences between the different crystalline forms. This helps in preventing variations among the batches of APIs as well as formulations prepared from possible crystalline forms of APIs. Conversion of one form into another during processing or storage may result into pharmacokinetically nonequivalent batches or dosage forms [(6)]. These significant differences in physical and chemical properties of various crystalline forms warrants researchers to pay the attention towards polymorphic aspect of substances used/considered for the purpose of formulation of pharmaceuticals [(7)]. The quinolones, especially 6-fluoroquinolones, are synthetic antibacterial agents which have proved to be potential alternative of other popular antibiotics such as penicillins, cephalosporins and macrolide antibiotics which are extensively used in clinical practices in the field of antibacterial therapy[(8)]. Fluoroquinolones have sufficient broad spectrum of antibacterial activity against Gram-positive, Gram-negative, anaerobes and mycobacterium pathogens. Many types of infections can be treated with great efficacy using these antibiotics since they possess good-to-moderate oral absorption and good enough tissue penetration and favorable pharmacokinetics in human beings [(9)]. Prulifloxacin: 6-Fluoro-1-methyl-7-[4-[(5-methyl-2–oxo-1,3-dioxol-4-yl) methyl]-1-piperazinyl]- 4-oxo-1H,4H-[1,3] thiazeto [3,2-a]quinoline-3-carboxylic acid, a generation fluoroquinolone antibiotic (Figure 1) is one such quinolone with proven safety [(10)] and clinical outcomes in antibacterial therapies [(11, 12, 13)]. Through review of literature only a limited number of crystalline/polymorphic forms of prulifloxacin [(14, 15, 16, 17, 18)] have been noticed, and therefore, this fluoroquinolone antibiotic has been experimented here for preparation of other possible crystalline forms. The evolved new crystalline forms were tested for differences in melting points. Selected crystal forms showing differences in melting points were characterized by polarizing microscopy, Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction (PXRD), and differential scanning calorimetry - thermo gravimetric analysis (DSC-TGA).

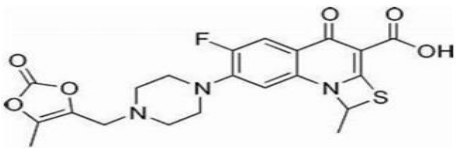

Figure I: Chemical structure of prulifloxacin

MATERIALS AND METHODS

MATERIALS

Prulifloxacin drug sample was supplied as gift sample for research purposes by Hetero Drugs Limited, Hyderabad, India. All other synthesis and analytical grade solvents and reagents were procured from store and laboratories of pharmacy department of the university- Mahatma Jyotiba Phule Rohilkhand University, Bareilly.

METHODS

New crystalline forms of prulifloxacin were prepared by solvent evaporation method [(1)] and combined antisolvent addition/cooling method [(19)] for recrystallization. Under *solvent evaporation method* a suitable amount of drug was dissolved in solvent of choice at 40^0C. The hot solution was filtered through whatman filter paper to remove any undissolved drug and was kept in 500 ml beaker at 40^0C to evaporate the solvent. Recrystallized drug was scrapped off, washed with petroleum ether, dried in rota-vapour and stored in a desiccator. The solvents used were acetonitrile, dichloromethane, and dimethylformamide. Under solvent change (*combined antisolvent addition/cooling)* method a suitable amount of drug was dissolved in 100 ml solvent at 60^0C to prepare supersaturated solution of the drug in the solvent. The hot solution was filtered through whatman filter paper at the same temperature to remove any undissolved drug and added at once with stirring to 100 ml filtered distilled water kept at 4^0C in an ice bath on the magnetic stirrer. The precipitated material was collected by filtration and dried in an oven at 40^0C and then washed with petroleum ether, dried in rota-vapour and stored in a dessicator. The solvents used were dichloromethane, dimethylformamide, and dimethylsulfoxide. Preparation of amorphous form was attempted first by reducing the size of crystalline form in the ball mill and then by reducing manually in mortar-pestle.

Melting point determination

Melting points of the parent drugs and prepared new crystalline forms were determined using melting point apparatus. The crystals of each sample were filled in the capillary tube and placed into melting point apparatus. The temperature was increased slowly and the temperature at which solid crystals turned into liquid state was recorded as melting point of the crystal form under test. Each determination was repeated thrice, and the averages were reported.

Characterization of crystal forms

Prepared crystal forms along with parent bulk (procured crystalline form of prulifloxacin) were characterized by following methods:

Polarizing microscopy

Polarizing microscopy on prepared new crystalline forms and procured crystalline form was carried out using WILD HEERBRUGG, ORTHOPLAN; (Switzerland) microscope.

Fourier transform infrared spectroscopy (FT-IR)

FTIR spectra of prepared new crystalline forms and procured crystalline form were recorded using KBr pellets by SHIMADZU, FTIR SPECTROMETER, (Japan) in the range of 400-4500 Cm^{-1} at SRMSCET (PHARMACY) Bareilly.

Powder X-ray diffraction (PXRD)

Prepared new crystalline forms and procured crystalline form of prulifloxacin were analyzed by PXRD technique. PXRD spectra were recorded using Bruker D8 X-Ray Diffractometer at Institute Instrumentation Centre, I.I.T. Roorkee under the following parameters.

Temp.	: 25^0C
Points	: 0.1
Steps	: 0.0190
Step time	: 19.2 sec.
Typical width	: 0.20
Minimum height	: 3000 Lin (counts)
Diffraction angle	: 2θ from 5.0000 to 49.9930

Differential scanning calorimetry and thermal gravimetric analysis (DSC-TGA)

Prepared crystalline forms and procured crystalline form of prulifloxacin were also analyzed by DSC-TGA technique. DSC endotherm and TGA spectra of prepared crystal forms have been recorded using Perkin Elmer DSC-TGA apparatus at Department of chemistry, Kumaun University, Nainital over a temperature range of 0 to 450^0C for DSC and 0 to 500^0C for TGA respectively.

RESULTS AND DISCUSSION

Six crystalline forms of prulifloxacin were prepared by solvent evaporation and combined antisolvent addition/cooling methods and one form by comminution. Solvents only from class-II (limited use) and class-III (safe) of ICH-Q3C categories (safer solvents to be used for biological system), were used in crystallization. Class-I (unsafe) and class-IV (without adequate data on safety in biological systems) were not used at all. Attempts for preparation of amorphous

form by comminution in mortar-pestle and using ball mill couldn't result into amorphous form as evident from polarizing microscopy. However, size of crystals and the crystallinity were markedly reduced as can be seen through microscopy and PXRD spectrum. Resulting crystalline forms of prulifloxacin have been assigned codes as shown in Table 1.

Table 1: Evolved crystalline forms with assigned codes

S. No.		Solvent & method used for preparation of crystal form	Code
1.	Form B	Acetonitrile / Solvent Evaporation method	ACN (SE)
2.	Form C	Dichloromethane / Solvent Change method	DCM (SC)
3.	Form D	Dichloromethane / Solvent Evaporation method	DCM (SE)
4.	Form E	Dimethylformamide / Solvent Change method	DMF (SC)
5.	Form F	Dimethylformamide / Solvent Evaporation method	DMF (SE)
6.	----------	Dimethyl sulfoxide/ Solvent change method	DMSO (SC)

Crystal morphology (crystal habits) of prepared and procured crystal forms of prulifloxacin as revealed through polarized microscopy has been described in Table 2.

Table 2: Crystal habits of various crystal forms of prulifloxacin

S. No.	Crystal form	Crystal habit and Appearance
1.	Procured form	Small platy crystals
2.	Comminuted form	Same as procured crystalline form but smaller in size
3.	ACN (SE)	Irregular shaped small plates
4.	DCM (SC)	Acicular
5.	DCM (SE)	Irregular shaped small and thin plates
6.	DMF (SC)	More or less like procured drug
7.	DMF (SE)	Irregular shaped large plates
8.	DMSO (SC)	Thin and platy crystals

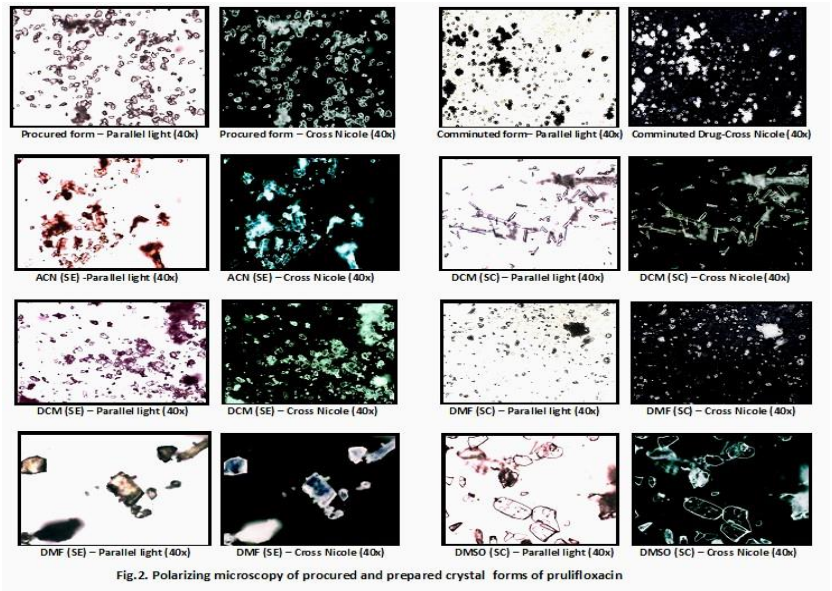

Figure II. Polarizing microscopic pictures of procured and prepared crystalline forms

All the crystal forms were found to be anisotropic as studied under polarizing microscope (Fig.2). Comminuted form has been found to be like crystals of procured drug but smaller in size. Crystal forms resulted from solvent evaporation method were found to be irregular shaped small plates for solvent acetonitrile; irregular shaped small and thin plates for dichloromethane; and irregular shaped but comparatively larger plates for dimethylformamide. Crystals resulted from solvent change (combined antisolvent addition/cooling) method were found to be acicular for solvent dichloromethane; more or less like procured drug for dimethylformamide; thin and platy for dimethyl sulfoxide.

Melting point determination

Crystalline forms of prulifloxacin coded as DMF (SC) and DMSO (SC) showed least average melting points: 190.33^{0}C & 194.66^{0}C. Crystalline forms of prulifloxacin coded as ACN (SE) & DCM (SC) showed average melting points equal to 205.66^{0}C & 207.66^{0}C. Crystalline forms coded as DCM (SC) & DMF (SE) showed average melting points equal to 212.33^{0}C & 211.33^{0}C. Procured crystalline form and comminuted form were found to show highest range of average

melting points equal to 218.66^{0}C and 219.33^{0}C. Average melting points of three batches of prepared crystalline forms have been shown in table 3.

Table 3: Average melting points of procured and prepared crystalline forms of prulifloxacin

Sr. no.	Crystal forms	M. P. of 1st batch (^{0}C)	M. P. of 2nd batch (^{0}C)	M. P. of 3rd batch (^{0}C)	Average M. P. (^{0}C)
1.	Procured form	218	220	218	218.66
2.	Comminuted form	217	221	220	219.33
3.	ACN (SE)	206	207	204	205.66
4.	DCM (SC)	208	207	208	207.66
5.	DCM (SE)	211	214	212	212.33
6.	DMF (SC)	190	190	191	190.33
7.	DMF (SE)	212	211	211	211.33
8.	DMSO (SC)	195	193	196	194.66

Fourier transform infrared spectroscopy (FT-IR)

Procured and prepared crystal forms of prulifloxacin were characterized by FTIR. The FTIR spectra are shown in Fig. 3 and the data of spectral bands along with % transmittance has been given in table 4. Procured crystalline form of prulifloxacin showed C=O stretching of carboxylic group at 1709.97 cm^{-1}, N-H stretching at 1370.48 cm^{-1}, C-F stretching at 1133.23 cm^{-1}. FTIR spectra of crystalline form ACN (SE) showed corresponding absorption bands at 1716.72, 1375.30, 1124.55 cm^{-1} respectively. Similarly FTIR spectra of DCM (SC) crystalline form showed absorption bands at 1709.97, 1386.68, 1133.23 cm ^{1}. FTIR spectra of crystalline form DCM (SE) showed absorption bands at 1713.83, 1378.2, 1122.62 cm ^{1}. DMF (SC) crystalline form of prulifloxacin showed characteristic absorption bands at 1709.97, 1383.02, 1123.58 cm ^{1}. FTIR spectra of crystalline form DMF (SE) showed absorption bands at 1713.83, 1386.88, 1123.58 cm ^{1}. Crystalline form DMSO (SC) showed absorption bands at 1709.97, 1370.48, 1133.23 cm ^{1}. FTIR spectra of prepared crystalline forms, when compared with procured crystalline form, were found to have all the characteristic bands of prulifloxacin. This suggests that the solvents used for recrystallization of prulifloxacin for preparing new crystalline forms didn't make any change in the chemical structure of the drug. However, shifting of bands along with changed % transmittance; origin of new absorption bands in FTIR spectra of prepared crystalline forms; and disappearance of certain non-characteristic absorptions bands indicate that prepared crystalline forms appear to be different from procured form of prulifloxacin, except crystalline form DMSO (SC) which has nearly all the IR bands similar to that of procured form.

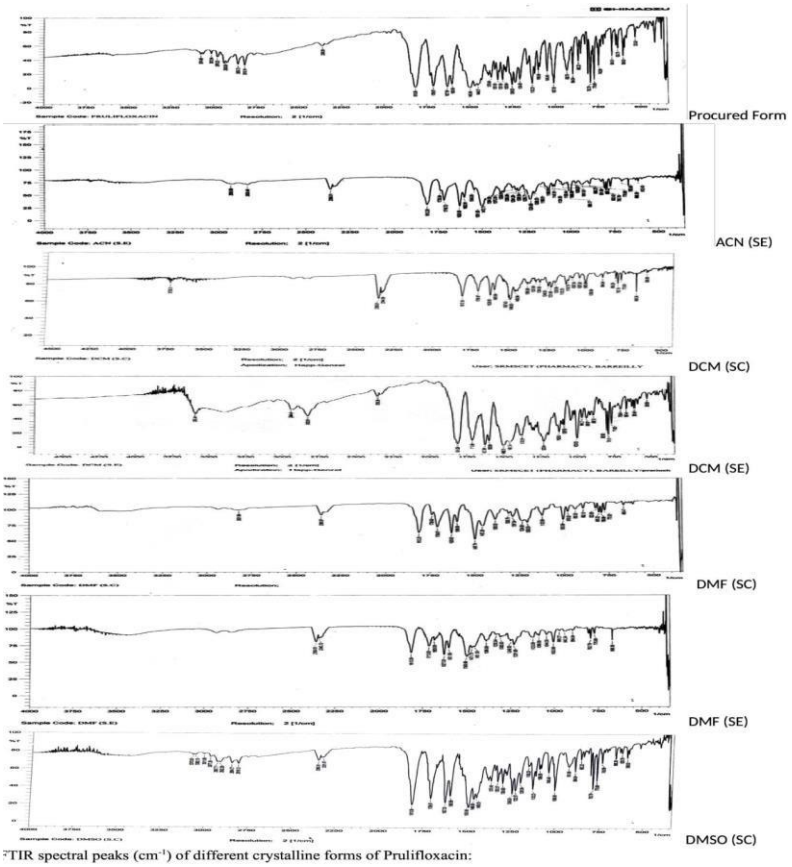

Figure III. FTIR spectra of crystalline forms of prulifloxacin

Table 4: Data of FTIR spectra of procured and prepared crystals of prulifloxacin

Procured drug	**ACN(SE)**	**DCM(SC)**	**DCM(SE)**	**DMF(SC)**	**DMF(SE)**	**DMSO(SC)**
No. of bands= 32	**38**	**28**	**25**	**24**	**25**	**37**
525.62 (%T= 72)	Disappeared	Disappeared	526.59 (%T= 68)	Disappeared	Disappeared	Disappeared
598.92 (%T= 45)	612.43 (%T= 76)	599.89 (%T= 94)	611.46 (%T= 55)	Disappeared	Disappeared	598.92 (%T= 74)
630.75 (%T= 57)	Disappeared	Disappeared	Disappeared	Disappeared	Disappeared	629.79 (%T= 78)
664.51 (%T= 45)	668.36 (%T= 66)	668.36 (%T= 72)	667.40 (%T= 53)	665.47 (%T= 107)	668.36 (%T= 84)	668.36 (%T= 73)
743.59 (%T= 32)	Disappeared	Disappeared	Disappeared	Disappeared	Disappeared	743.59 (%T= 68)
	705.98 (%T= 76) **New**		706.94 (%T= 53) **New**			
770.60 (%T= 10)	770.60 (%T= 66)	770.60 (%T= 86)	770.60 (%T= 33)	772.52 (%T= 98)	770.60 (%T= 92)	770.60 (%T= 47)
792.78 (%T= 07)	792.78 (%T= 64)	792.78 (%T= 83)	791.81 (%T= 17)	789.88 (%T= 95)	792.78 (%T= 85)	792.78 (%T= 39)
	802.42 (%T= 64) **New**	806.28 (%T= 88) **New**	802.42 (%T= 24) **New**	805.32 (%T= 96) **New**		
				822.68 (%T=102) **New**		
862.22 (%T= 38)	Disappeared	Disappeared	Disappeared	Disappeared	Disappeared	862.22 (%T= 71)
894.04 (%T= 20)	889.22 (%T= 71)	894.04 (%T= 89)	892.12 (%T= 44)	892.12 (%T=102)	894.04 (%T= 95)	894.04 (%T= 58)
928.76 (%T= 24)	931.66 (%T= 68)	Disappeared	939.37 (%T= 39)	935.52 (%T=100)	940.34 (%T= 94)	931.66 (%T= 63)
	969.27 (%T= 72) **New**		969.27 (%T= 40) **New**	978.92 (%T= 97) **New**	969.27 (%T= 95) **New**	
1007.85 (%T= 06)	999.17 (%T= 50)	1006.89 (%T= 84)	1003.03 (%T= 12)	1003.99 (%T= 85)	1003.99(%T= 80)	1006.89 (%T= 37)
1045.46 (%T= 22)	1041.61 (%T= 70)	1045.46 (%T= 88)	Disappeared	Disappeared	1044.50 (%T= 91)	1045.46 (%T= 57)
	1058.97 (%T= 75) **New**					
	1088.86 (%T= 66) **New**	1087.90 (%T= 88) **New**	1087.90 (%T= 31) **New**		1088.86 (%T= 90) **New**	
1096.58 (%T= 24)	1100.44 (%T= 66)	1097.54 (%T= 88)	Disappeared	Disappeared	Disappeared	1096.58 (%T= 61)
		1118.76 (%T= 85) **New**				
1133.23 (%T= 06)	1124.55 (%T= 56)	1133.23 (%T= 82)	1122.62 (%T= 21)	1123.58 (%T= 91)	1123.58 (%T= 86)	1133.23 (%T= 39)
	1141.91 (%T= 63) **New**					
	1168.91 (%T= 72) **New**					1160.23 (%T= 64) **New**
	1198.81 (%T= 56) **New**					
1204.60 (%T= 12)	1206.53 (%T= 50)	1205.56 (%T= 83)	Disappeared	1206.53 (%T= 80)	Disappeared	1205.56 (%T= 45)
	1224.85 (%T= 40)	1231.60 (%T= 78)	1230.64 (%T= 08)	1234.50 (%T= 82)	1231.60 (%T= 76)	1232.57 (%T= 37)
1249.93 (%T= 03)	1255.71 (%T=56)	1249.93 (%T= 79)	Disappeared	Disappeared	1249.93 (%T= 81)	1249.93 (%T= 34)
	1260.54 (%T= 57) **New**					
	1294.29 (%T=53) **New**			1287.54 (%T= 90) **New**		
1303.94 (%T= 10)	1305.86 (%T= 55)	1304.9 (%T= 84)	Disappeared	1308.76 (%T= 94)	1306.83 (%T=87)	1304.90 (%T=44)
1331.90 (%T=10)	1329.01 (%T= 60)	1331.9 (%T= 84)	Disappeared	Disappeared	1330.94 (%T= 91)	1332.87 (%T= 46)
1370.48 (%T= 15)	1375.30 (%T= 52)	Disappeared	1378.2 (%T= 16)	1383.02 (%T= 85)	Disappeared	1370.48 (%T=47)
	1394.59(%T= 52) **New**	1386.68 (%T= 82) **New**			1386.88 (%T= 82) **New**	
1449.57 (%T= 03)	Disappeared	Disappeared	Disappeared	1457.28 (%T= 75)	1451.50 (%T= 73)	1450.53 (%T= 29)
	1472.71 (%T= 30) **New**	1465.96 (%T= 73) **New**	1461.14 (%T= 06) **New**		1471.75 (%T= 71) **New**	1466.93 (%T= 27) **New**
1495.86 (%T= 00)	1501.65 (%T= 24)	1496.83 (%T= 64)	1498.75 (%T= 03)	1497.79 (%T= 52)	1500.68 (%T= 57)	1500.68 (%T= 18)
		1507.43 (%T= 66) **New**				

	1545.05 (%T= 58) **New**					
1600.99 (%T= 04)	1602.91 (%T= 43)	1600.99 (%T= 75)	1600.99 (%T= 09)	1599.06 (%T=80)	1601.95 (%T= 71)	1600.99 (%T= 31)
1627.99 (%T= 02)	1628.95 (%T= 27)	1628.95 (%T= 70)	1627.99 (%T= 03)	1629.92 (%T= 63)	1627.03 (%T= 60)	1627.03 (%T= 22)
					1683.93(%T= 83) **New**	
1709.97 (%T= 03)	1716.72 (%T= 38)	1709.97 (%T= 73)	1713.83 (%T= 09)	1709.97 (%T= 73)	1713.83 (%T= 74)	1709.97 (%T= 28)
	1735.04 (%T= 58) **New**			1738.90(%T= 92) **New**		
1815.09 (%T= 02)	1812.20 (%T= 30)	1813.16 (%T= 67)	1815.09 (%T= 05)	1812.20 (%T= 64)	1815.09 (%T= 63)	1815.09 (%T= 20)
		2344.58 (%T= 73)**New**			2340.72 (%T= 85)**New**	2331.07 (%T= 73) **New**
2358.08 (%T= 61)	2360.01 (%T= 62)	2360.01(%T= 64)	2358.08 (%T= 72)	2360.97 (%T= 91)	2360.01 (%T= 80)	2360.01 (%T= 70)
2816.19 (%T= 32)	2835.48 (%T= 70)	Disappeared	2832.59 (%T= 43)	2821.98 (%T= 99)	Disappeared	2818.12 (%T= 65)
2855.73 (%T= 34)	Disappeared	Disappeared	Disappeared	Disappeared	Disappeared	2854.77 (%T= 66)
						2922.28 (%T= 67) **New**
2930.00 (%T= 40)	2930.96 (%T= 71)	Disappeared	2944.46 (%T= 53)	Disappeared	Disappeared	2937.71 (%T= 67)
2978.22 (%T= 45)	Disappeared	Disappeared	Disappeared	Disappeared	Disappeared	2977.26 (%T= 74)
3012.94 (%T= 50)	Disappeared	Disappeared	Disappeared	Disappeared	Disappeared	3011.98 (%T= 76)
						3062.13 (%T= 75)
3074.66 (%T= 49)	Disappeared	Disappeared	Disappeared	Disappeared	Disappeared	3075.63 (%T= 75)
			3597.4 (%T= 47) **New**			
		3735.31(%T= 82) **New**				

Powder X-ray diffraction (PXRD)

Powder X Ray Diffraction patterns of the prepared crystalline forms of prulifloxacin ACN (SE), DCM (SC), DCM (SE) and DMF (SC) have shown significant differences in the positions as well as intensities of the peaks indicating the prepared crystalline forms to be entirely new crystalline forms of prulifloxacin. However, Powder X Ray Diffraction patterns of the prepared crystalline forms DMF (SE) and DMSO (SC) show no considerable differences with that of procured and comminuted form. PXRD patterns of all the forms of experiment have been depicted in figure 4.

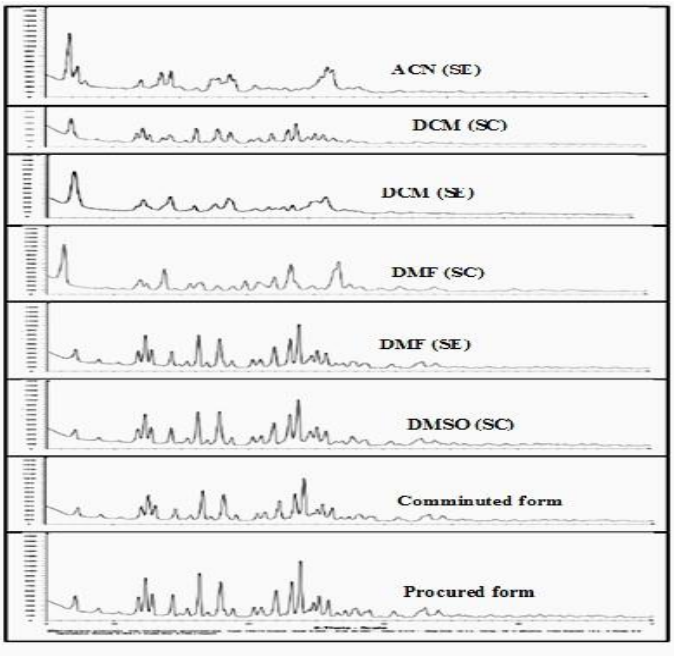

Figure IV: PXRD patterns of all the subjective crystalline forms of Prulifloxacin

Differential scanning calorimetry

DSC curves of procured and prepared crystalline forms ACN (SE), DCM (SC), DCM (SE) and DMF (SC) were constructed from obtained data and have been shown in figure 5. Differential Scanning Calorimetry for DMF (SE) and DMSO (SC) crystalline forms were not recorded due to indifferences in PXRD patterns with that of procured crystalline forms. Marked differences in endothermic peaks and exothermic peaks for procured crystalline form and prepared crystalline forms ACN (SE), DCM (SC), DCM (SE), and DMF (SC) are indicative of new polymorphic forms undergoing transitions with the progression of temperature.

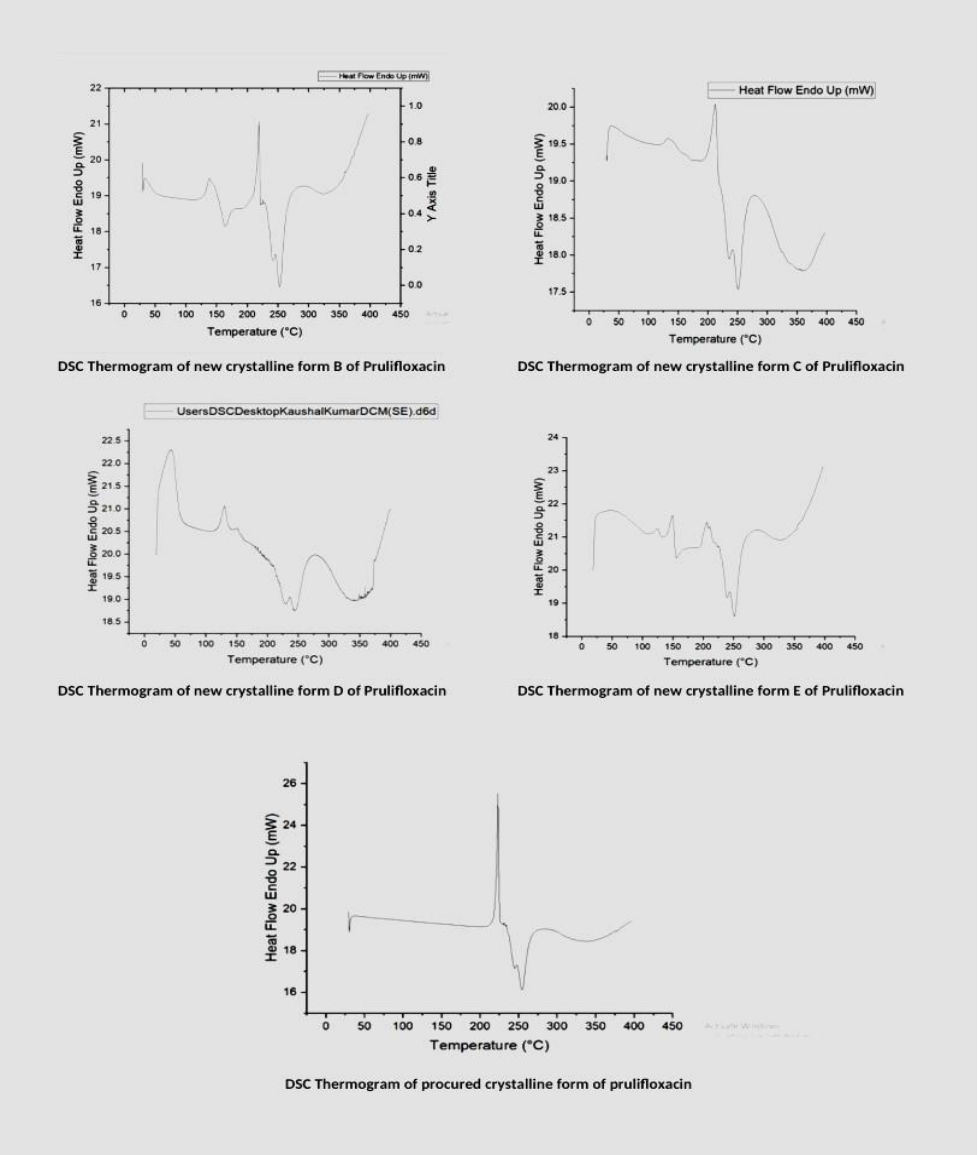

Figure V: DSC Thermogram of crystalline forms of Prulifloxacin

Thermal gravimetric analysis

TGA curves of procured crystalline forms and prepared crystalline forms ACN (SE), DCM (SC), DCM (SE) and DMF (SC) were constructed from obtained data and have been shown in figure 6. TGA curves for DMF (SE) and DMSO (SC) crystalline forms were not recorded due to indifferences in PXRD patterns with that of procured crystalline forms. Weight loss prior to melting in case of prepared crystalline forms ACN (SE), DCM (SC), DCM (SE) indicates the prepared forms to be solvate pseudo-polymorphic forms of prulifloxacin. Though, TGA curve of DMF (SC) crystalline form doesn't suggest for solvated form, different rates of weight loss during melting phase from procured form are sufficient for this crystal form to be different from procured form.

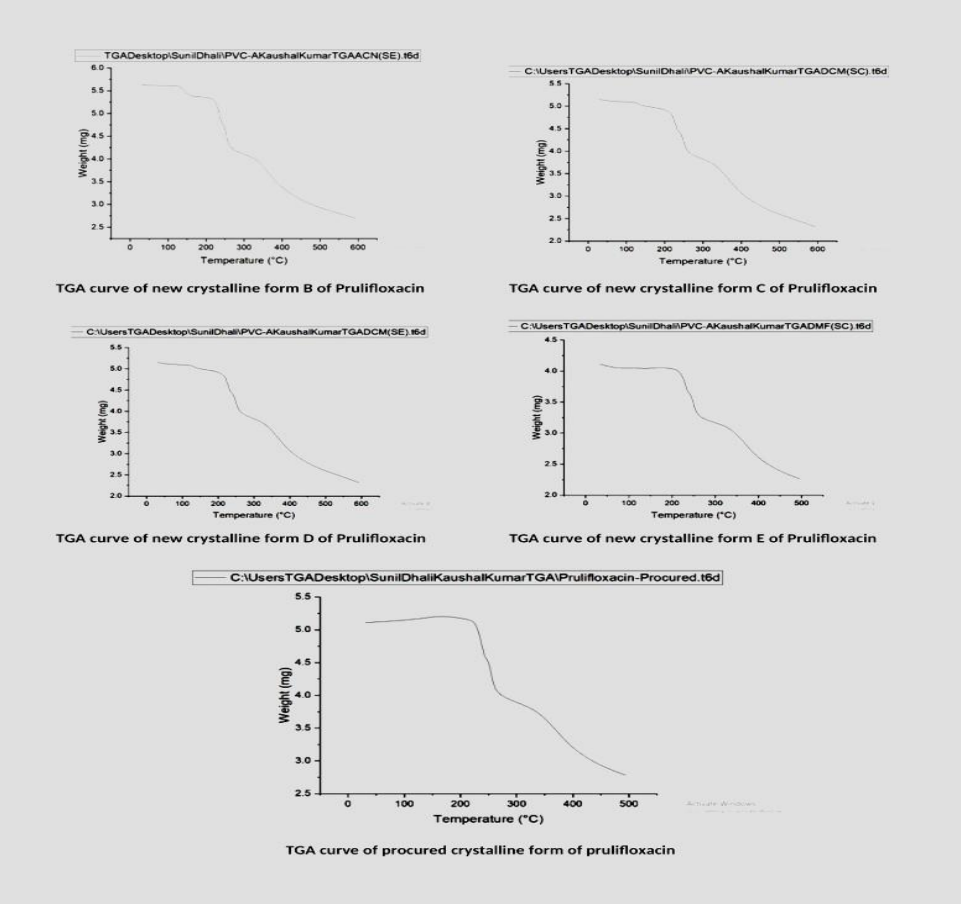

Figure 6: TGA curves of crystalline forms of Prulifloxacin

CONCLUSION

Results of characterization of prepared crystalline forms of prulifloxacin by polarizing microscopy, FTIR spectroscopy, PXRD, DSC and TGA are assuring the existence of at least five new crystalline forms of prulifloxacin prepared by us. Crystal forms prepared by some other researchers may have low or higher degree of resemblance with these crystal forms; however, the data of characterization techniques is thought to be different to a significant level of variation. Thus present work has come up with five crystal forms, termed as Form B, Form C, Form D, Form E and Form F of prulifloxacin crystals. Further in vitro and in-vivo studies on stability, pharmackokinetic and pharmacodynamic aspects of these crystalline forms of a valuable fluoroquinolone antibiotic (prulifloxacin) may result in considerable changes in the fields of anti-infective therapies and IPR related monopolies.

CONFLICT OF INTERESTS

None

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