Original Article

Influence of solvents on the crystal habit and properties of rofecoxib and celecoxib: No evidence of polymorphism

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Abstract

Background: In many cases, drugs can exist in more than one crystalline form; the phenomenon is known as "polymorphism." Though the polymorphs are chemically identical, they exhibit different physicochemical properties, viz., melting point, solubility, X-ray diffraction pattern, etc., which further affect the biological properties of drugs. The purpose of this work was to study the effect of solvents on crystallization, solubility and dissolution of rofecoxib and celecoxib. **Materials and Methods:** The crystals were prepared by using different solvents. The melting point, solubility, dissolution, Fourier-transformed infrared (FT-IR), X-ray diffraction (XRD), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) studies were carried out to confirm the polymorphism in drugs. **Result:** The results indicate that the crystals obtained from different solvents exhibited different physicochemical properties. Though FT-IR and XRD gave an indication of different crystal morphs, DSC proved absence of any polymorphic behavior in the crystals of rofecoxib and celecoxib. **Conclusion:** Crystals having the desired physicochemical properties may be obtained by selecting solvents of specific polarities.

Key words: Celecoxib, crystallization, polymorphism, rofecoxib

INTRODUCTION

Most pharmaceutical powders have crystals in the range of 0.5-300 μm in diameter. In the design of dosage forms, crystalline materials are often employed. Many drugs can exist in more than one crystalline form, i.e., the molecules exhibit different space-lattice arrangements in the crystal. There are a variety of reasons for such differences in the crystal. It largely depends on how the crystallization of drug is conducted, the nature of solvent(s) used, the conditions such as temperature, pressure, cooling rate, agitation, use of the co-solvents, presence of other solutes and ions.[1-3] Such information regarding the industrial processing of bulk drugs is a closely guarded secret by the manufacturers. Though the polymorphs are chemically identical, they exhibit different physicochemical properties, viz., melting point, solubility, X-ray diffraction pattern, etc.[4,5]

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These physicochemical properties further affect the biological properties of drug molecules. Chloramphenicol palmitate exists in polymorphic state that is shown to influence significantly the bioavailability of drugs. Metastable polymorphs and amorphous chloramphenicol palmitate have better bioavailability compared to its stable polymorphs.[6]

Chemicals that are capable of forming hydrogen bonding can exhibit polymorphism.[7] Nearly all the organic compounds having long chains also exhibit polymorphism. Aqueous solubility of drugs is important for bioabsorption

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and the drug action. In case of slightly soluble drugs, polymorphism will significantly alter the biological properties. Since dissolution is an important prerequisite for drug absorption in most of the acidic drugs, polymorphism influences drug absorption to a great extent.[8,9]

As different polymorphs arise through different arrangements of the molecules or ions in the lattice, these will have different interaction energies in the solid state. Under a given set of conditions, the polymorph with the lowest free energy will be the most stable one, and other polymorphs will tend to transform into it.[5]

The present work involves the study of effect of solvents on crystallization (or polymorphism) of drugs, to optimize the experimental conditions for obtaining polymorphs, to characterize the crystal habit and to study the solubility and dissolution behavior of these crystals. The drugs selected for the study are rofecoxib and celecoxib. Both the drugs are nonsteroidal anti-inflammatory drugs (NSAIDs). Rofecoxib is chemically 4-[4-(Methyl sulfonyl) phenyl (-3- phenyl-2(5H)-furanone][10] It is active at low dose and has less gastric toxicity.[11] Rofecoxib primarily inhibits Cyclooxygenase [COX] enzymes that are involved in the synthesis of prostaglandins, which are involved in mediating inflammation, swelling, pain and fever.

Celecoxib is chemically 4-[5-(4-methyl phenyl)-3-(trifluoromethyl]-1H-pyrazole -1- yl] benzene sulfonamide.[12] It is also related to the same category of the drugs. It is a diaryl-substituted pyrazole derivative containing a sulfonamide substituent. Celecoxib offers unique therapeutic prospects of alleviating pain and inflammation with the untoward gastrointestinal, renal and platelet effects commonly seen with NSAIDs.[13] The drug was studied for its solid state characterization.[14]

MATERIALS AND METHODS

Materials

Rofecoxib and celecoxib pure drugs were received as gift samples from Ipca Laboratories Ltd., Mumbai; and Aarti Drugs, Mumbai, respectively. Ethanol, methanol, acetone, isopropanol and ethyl acetate were procured from S. D. Fine Chemicals Limited, Mumbai.

Methods

Preparation of crystals

Among the solvents used for crystallization, only five solvents gave encouraging results for rofecoxib; and three solvents, for celecoxib. The other solvents, such as hexane, water and chloroform, did not give crystals, may be due to poor solubility. Though several methods were used for their preparation, only shock cooling at low temperature (4°C to 6°C) gave encouraging results. During cooling, the containers were always closed with stoppers. Occasional agitation was used to verify the crystals. This enhanced the formation of crystals. The nuclei were separated and acted as seeds for further crystal growth. The crystals from the solution were separated and dried at room temperature. The surface moisture was removed by storing the sample over calcium chloride desiccators for 1 to 2 weeks. The influence of the solvents on the crystal habit could be highlighted.

About three times the crystals were prepared in order to get reproducibility. Large-scale crystallization (1 to 2 g) was also attempted so as to get sufficient quantity for characterization.

Characterization of crystals

Melting point

The determination of melting points of the crystals was carried out in open capillaries by using electrical melting point apparatus [4] of Serwell Instruments Inc., Bangalore.

Fourier-transformed Infrared (FT-IR) spectroscopy

To perform the FT-IR analysis, the sample powder was dispersed in KBr powder to prepare pellets and analyzed.[4] FT-IR spectra were obtained by powder-diffused reflectance on a FT-infrared spectrophotometer type FT-IR 1600, Perkin-Elmer.

X-ray diffraction

Diffraction patterns were obtained using a Scenting, USA, diffractometer system.[15] CuKα radiation (α= 1.540606 A) and a scan speed of 2° (2θ) min^{-1} were used, and the diffraction pattern was analyzed.

Differential scanning calorimetry

All dynamic differential scanning calorimetry (DSC) studies were carried out on Dupont 9900 thermal analyzer with 910 DSC module. Calorimetric measurements were made with empty cell (high-purity alpha alumina discs of Dupont Company) as the reference. The instrument was calibrated using high-purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 5°C min^{-1}.

Scanning electron microscopy

Scanning electron microscopy (SEM) photographs were taken with a scanning electron microscope model s 240, Cambridge Instrument. The photographs were observed for morphological characteristics of the crystals.

Physicochemical properties

Solubility Studies of Rofecoxib and Celecoxib crystals: The solubility of rofecoxib and celecoxib crystals was studied in

distilled water.[16] About 10 mg of sieved crystals (44/60) were added to 10 mL of distilled water in glass ampoules, and the ampoules were sealed. This amount was sufficient to obtain saturated solution. These ampoules were shaken for 8 hours at 25°C by keeping in a constant-temperature shaker bath. The ampoules were then broken, and solutions were filtered with the help of Whatman filter paper. The absorbance of the filtrate was measured at λ_{max} values of 262 and 247 nm, respectively, by using UV-visible spectrophotometer (UV-1601 PC, Shimadzu, Japan).[17,18] This method was performed in triplicate.

Dissolution studies of rofecoxib and celecoxib crystals: USP XXI dissolution apparatus type-I was employed in the present studies. The sample (10 mg) was encapsulated in a gelatin capsule and transferred to the dissolution medium [500 mL hydrochloric acid (pH, 1.2) solution]. The dissolution medium was stirred at a rate of 100 rpm by maintaining the temperature at 37±0.5°C. Five milliliters of the aliquots was withdrawn periodically at an interval of 20 minutes for 2 hours with the help of guarded pipette. The absorbance was measured at λ_{max} values of 267 and 248 nm, respectively.[17,18]

RESULTS AND DISCUSSION

Different techniques of identifying habit and characterization of amorphous or crystalline solids are available. A single method may not give absolute proof for these modifications. Therefore, all the methods are to be analyzed before deciding whether morphological changes did occur.

General morphology of rofecoxib and celecoxib crystals

The crystals of rofecoxib obtained from different solvents were observed through a magnifying lens using a microscopic method [Figure 1]. The general findings are given in Table 1. It was not possible to identify crystallinity of crystals of celecoxib obtained from different solvents by the naked eye, magnifying lens or microscopy.

Melting points of rofecoxib and celecoxib crystals

Melting points of the rofecoxib and celecoxib crystals were determined using open capillary method. The melting point of commercial sample of rofecoxib was 203°C. The difference in the melting points of rofecoxib crystals obtained from ethyl acetate (183°C), methanol (180°C), acetone (185°C), ethanol (184°C) and isopropanol (178°C) gave a primary indication of polymorphs.

The melting point of commercial sample of celecoxib was 169°C. The melting points of celecoxib crystals obtained from ethanol (134°C), methanol (130°C) and acetone (128°C) also showed deviation from the melting point of commercial sample.

A perusal of the above results with regard to melting points indicates that the melting points of crystals of rofecoxib and celecoxib were less than those of their respective commercial samples. Rofecoxib crystals obtained from isopropanol gave the lowest melting point in comparison with the other rofecoxib crystals. Celecoxib crystals obtained from acetone gave the lowest melting point in comparison with the other celecoxib crystals. Reproducible results were obtained, though melting points were monitored over a period of 45 days on storage. In other words, the polymorphic transformations were not observed.

FT-IR spectroscopic analysis

Solid samples of drugs must be used, since polymorphs of a compound may have identical spectra in solution.

Rofecoxib crystal analysis

The FT-IR spectra were obtained for the crystals of rofecoxib from different solvents and are presented in Figure 2 for commercial sample and crystals obtained from methanol, isopropanol, acetone and ethyl acetate, respectively. The commercial sample was used for comparison. The spectral analysis was done in two parts: the first was for the identification of drug using characteristic bands, and the second was for identification of polymorphs (or crystal habit). From the structure of rofecoxib, the characteristic bands were identified and are given in Table 2. From Table 2, it can be inferred that the compound under study was rofecoxib only. The crystals prepared in this work also showed the characteristic bands.

A perusal of Table 3 indicates that crystals obtained from methanol, isopropanol and ethyl acetate might be different

Table 1: General observations regarding rofecoxib crystals obtained from different solvents

Solvent of crystallization	Description of crystals
Ethyl acetate	Small size, irregularly shaped, plate shaped.
Methanol	Long needles with finger-like crystal growth in a few cases.
Acetone	Small size, irregular shaped platy type.
Ethanol	Needle shaped; length was shorter compared to that of crystals obtained from methanol and longer than that of the crystals obtained from isopropanol.
Isopropanol	Needle shaped, shorter in length and sticky.

Table 2: Comparison of literature values with the observed values for various characteristic bands of the commercial samples of rofecoxib and celecoxib

Characteristic bands	Rofecoxib commercial sample		Celecoxib commercial sample	
	Literature values, cm^{-1}	Observed values, cm^{-1}	Literature values, cm^{-1}	Observed values, cm^{-1}
C-H stretching aromatic	3030(s)	3018	~3030	3237
C-H stretching alkane	2962-2853(s)	2929	--	--
C-C multiple bond stretching aromatic	~1660(s)	1646	~1660(s)	1631
Cyclic α, β-unsaturated lactone	1760-1740(s)	1747	--	--
S=O stretching vibrations- sulfonamides	1160-1140(s)	1149	1180-1140(s) 1350-1300(s)	1164(s) 1348(s)
Intermolecular hydrogen bonding	3550-3450(s)	3461	--	--
N-H stretching, primary	--	--	~3500 ~3400(m)	3432(m)
N=N stretching	--	--	1630-1575(v)	--
C-F stretching	--	--	1400-1000	1135(s)

Key: 's' = strong, 'v' = variable, 'm'= medium.

Table 3: Infrared spectra for characteristic polymorphic (crystal habit) changes of rofecoxib crystals

Solvent Used	Bands, cm^{-1}	Intensity of Bands	Inference
Commercial sample	3461	Broad	
	3018, 2929, 495	Sharp	
	1595	Sharp	
Methanol	3018	Not sharp	Polymorph
	2929	Not sharp	
	495	No band	
	1089, 1035, 960	Low intensity	
	1594	Disappeared	
Isopropanol	3018	Disappeared	Polymorph
	2929	Not sharp	
	3436	High	
	495	No band	
	1089, 1035, 960	Low	
	661, 617, 592	Disappeared	
	1486, 1446	Disappeared	
	1421, 1402	Disappeared	
	1594	Disappeared	
Acetone	1089, 1035, 960	Low intensity	Same as commercial sample
Ethyl acetate	3018, 2929	Not sharp	Polymorph
	1089, 1035, 960	Low	
	1594	Disappeared	

Table 4: Infrared spectra for characteristic polymorphic (crystal habit) changes of celecoxib crystals

Solvent used	Bands, cm^{-1}	Intensity of bands	Inference
Commercial sample	3432	Doublet	
	3237	Shoulder	
	1631	Broad	
	1498 and 1473	Absent	
	561	Absent	
Methanol	3338	Doublet	May be
	3230	Shoulder	polymorph
	1614	Broad	
	1498 and 1473	New bands	
	561	(sharp)	
		Present	
Ethanol	3426	Doublet	May be
	3230	Shoulder	polymorph
	1617	Broad	
	1498 and 1473	Absent	
	561	Present	
Acetone	3338	Singlet	May be
	3230	Single peak	polymorph
	1631	Absent	
	1498 and 1473	New bands	
	561	(sharp)	
		Present	

crystal morphs due to difference in IR spectra compared to the IR spectrum of commercial sample. The IR spectra failed to show any characteristic band in the fingerprint region.

Celecoxib crystal analysis

The FT-IR spectra were obtained for the crystals of celecoxib from different solvents and are presented in Figure 3 for commercial sample and crystals obtained from methanol, acetone and ethanol, respectively. From Table 2, it can be inferred that the compound under study was celecoxib only. The crystals prepared in this work also showed the characteristic bands.

A perusal of Table 4 indicates that crystals obtained from methanol, isopropanol and ethyl acetate might be different crystal morphs due to difference in IR spectra compared to the IR spectrum of commercial sample. The IR spectra failed to show any characteristic band in the fingerprint region.

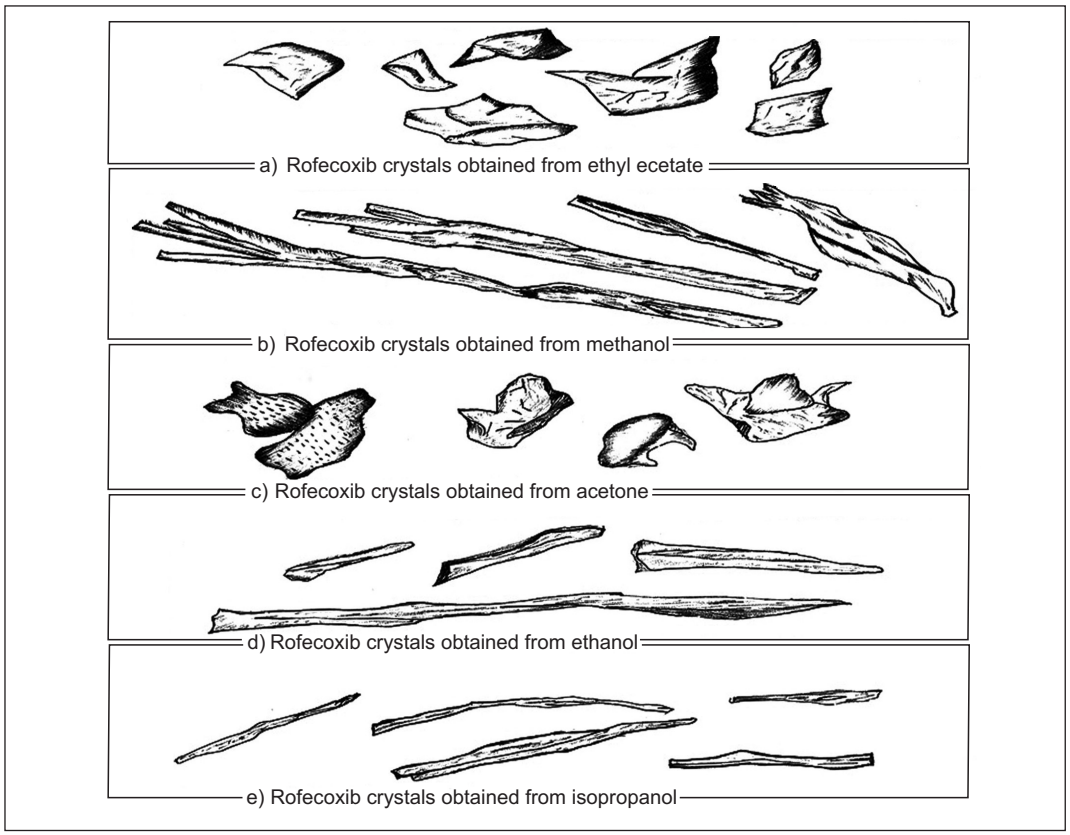

Figure 1: Binocular observation of rofecoxib crystals

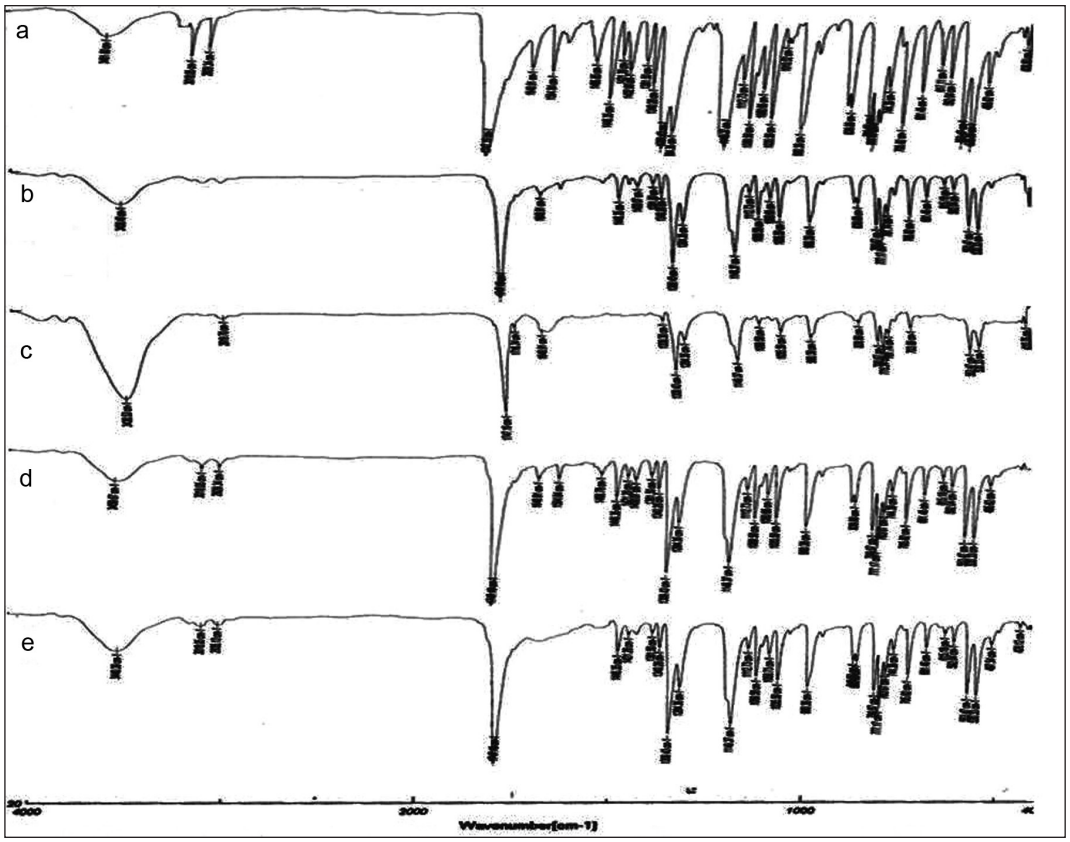

Figure 2: FT-IR spectra of rofecoxib crystals obtained from (a) commercial sample, (b) methanol, (c) isopropanol, (d) acetone and (e) ethyl acetate

Table 5: X-ray diffraction for characteristic polymorphic (crystal habit) changes of rofecoxib crystals

Solvent of crystallization	Peak 2θ calue	Intensity	Other	Inference
Methanol	23.2568	100	Region from 17 to 22 θ is different	Polymorph was observed
	15.9478	91		
	22.2758	44		
Isopropanol	15.9945	100	-Do-	Polymorph was observed
	22.2280	80		
	10.96	53		
Acetone	22.1921	100	A peak at 36 θ	Polymorph was observed
	23.2794	70	Region from 17 to 22 is different	
	15.9950	44		
Ethyl acetate	22.2300	100	10.96d is missing	Polymorph was observed
	16.0150	32		
	23.3425	32		

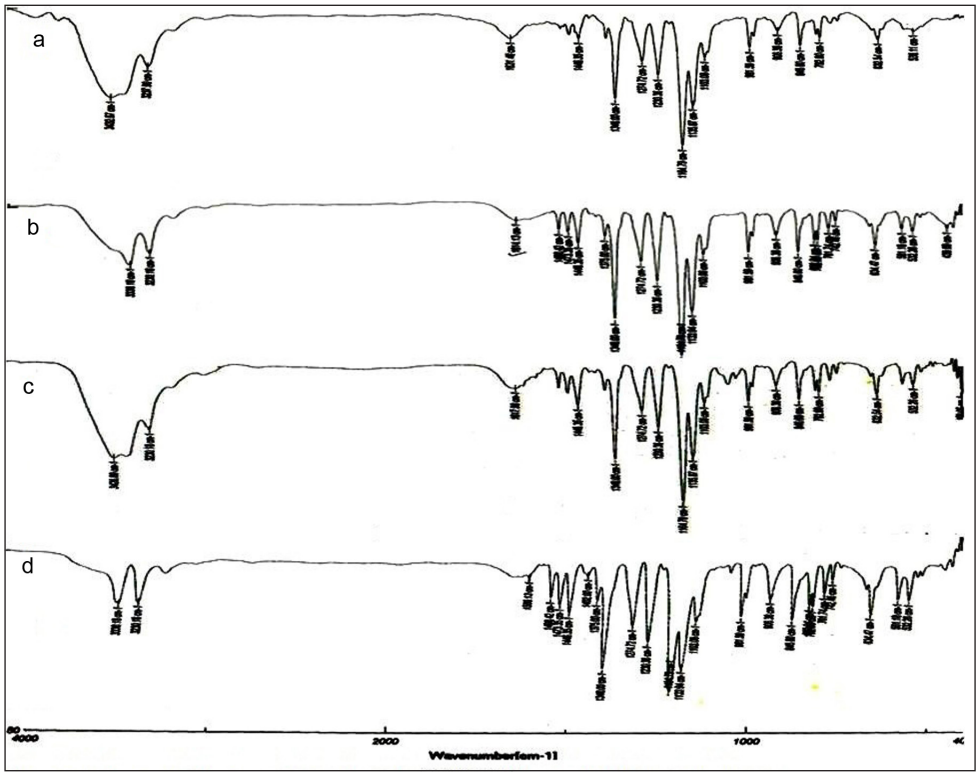

Figure 3: FT-IR spectra of celecoxib crystals obtained from (a) commercial sample, (b) methanol, (c) ethanol and (d) acetone

X-ray differaction pattern

Rofecoxib crystal analysis

The X-ray diffraction (XRD) spectra of crystals of rofecoxib are given in Figure 4. The characteristic changes are given in Table 5.

A perusal of Table 5 indicates that the crystals obtained from methanol, isopropanol and ethyl acetate showed different XRD patterns. It can be inferred that these three types of crystals of rofecoxib were of different crystal habits or different polymorphs. Further, XRD support was obtained to indicate that rofecoxib crystals from acetone were also of a different crystal habit or crystal morph, though IR spectra did not yield positive indication; however, conformation was required from DSC analysis.

Celecoxib crystal analysis

The XRD spectra of celecoxib crystals are given in Figure 5. The data are tabulated for ready reference in Table 6.

A perusal of Table 6 indicates that the crystals obtained from methanol, ethanol and acetone showed different XRD patterns. It can be inferred that these three types of crystals of celecoxib were of different crystal habit or different

Table 6: X-ray diffraction for characteristic polymorphic (crystal habit) changes of celecoxib crystals

Solvent of crystallization	Peak 2θ value	Intensity	Other	Inference
Methanol	16.0946	100	The variation of peak at	Polymorph was observed
	19.6250	95	21.40 (79)	
	21.4833	79	22.29 (56)	
			23.47 (33)	
Acetone	16.0080	100	The variation of peak at	Polymorph was observed
	21.3830	70	21.383 (70)	
	14.7350	62	22.206 (57)	
	19.5000	55	23.320 (37)	
Ethanol	19.5758	100	The variation of peak at	Polymorph was observed
	16.0550	92	21.40 (83)	
	22.2500	89	22.25 (89)	
			23.375 (58)	

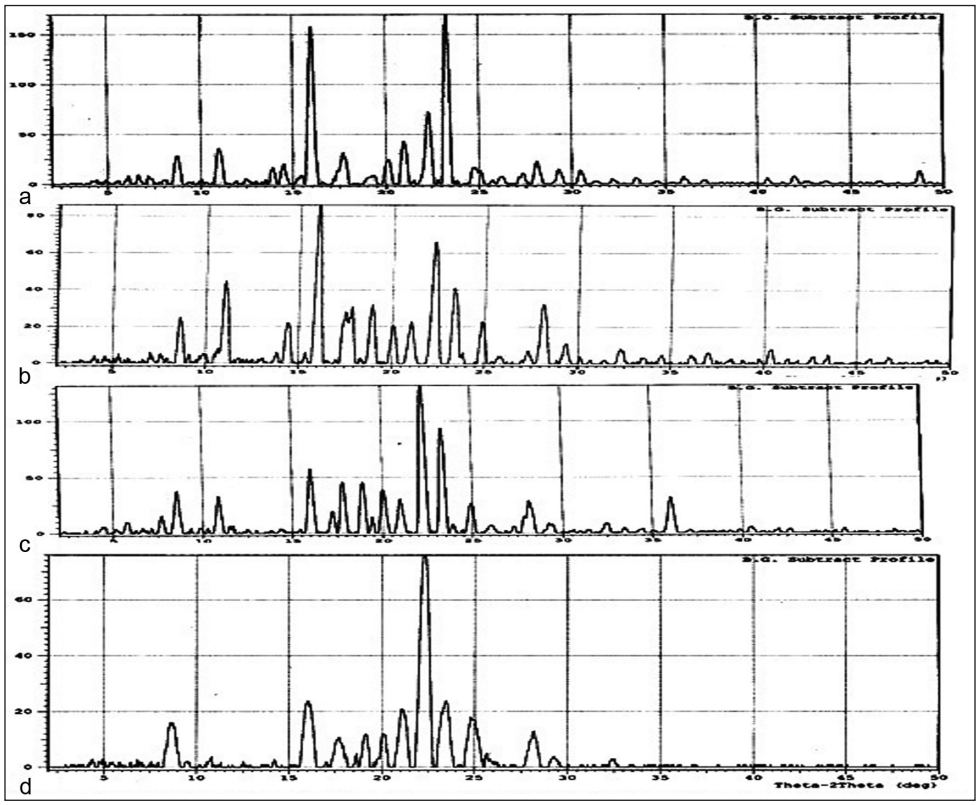

Figure 4: X-ray diffraction spectra of rofecoxib crystals obtained from (a) methanol, (b) isopropanol, (c) acetone and (d) ethyl acetate

crystal morphs. Though crystals obtained from ethanol and methanol did not give any clue of polymorphism through IR spectra, XRD pattern highlighted the differences; further evaluation was needed to confirm the polymorphism.

Differential scanning calorimetry analysis

Crystalline materials in powdered state showed characteristic DSC patters made up of peaks of varying intensities in certain positions. Each powder pattern of the crystal lattice is characteristic for a given polymorph.

Rofecoxib crystal analysis

The DSC of commercial sample and the DSC of crystals obtained from various solvents for rofecoxib are recorded in Figure 6. The characteristic changes are given in Table 7.

A perusal of the values of molar heat of fusion (H_f) in Table 7 indicates that values of ΔH_f were lower for the crystals obtained from the solvents, i.e., isopropanol and ethyl acetate, than the corresponding value for pure rofecoxib, whereas the ΔH_f values for the rofecoxib crystals obtained from ethanol, methanol and acetone were found to be higher than the corresponding value for pure rofecoxib. The peak onset values were found to remained almost same, i.e., unchanged for all the rofecoxib crystals and pure rofecoxib. Thus, a

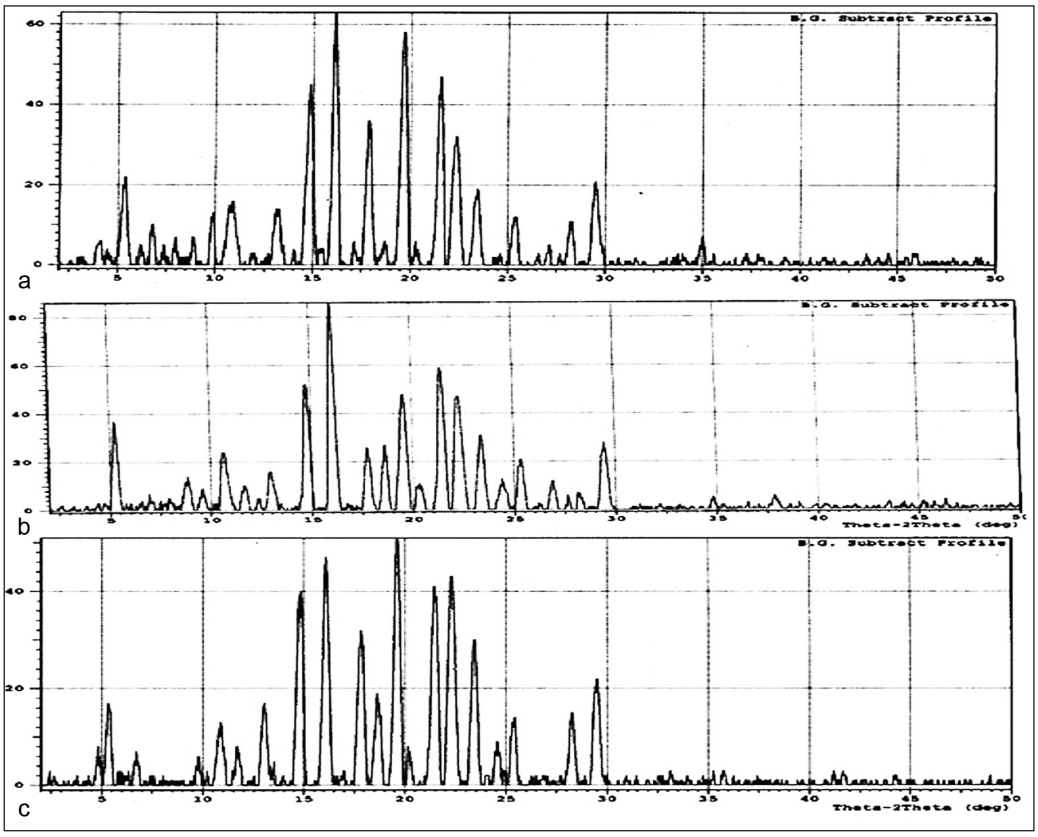

Figure 5: X-ray diffraction spectra of celecoxib crystals obtained from (a) methanol, (b) acetone and (c) ethanol

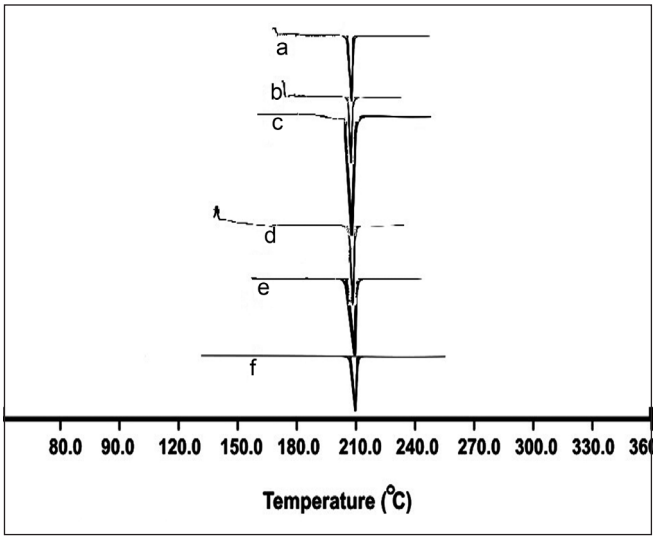

Figure 6: Differential scanning calorimetry spectra of rofecoxib crystals obtained from (a) methanol, (b) isopropanol, (c) acetone, (d) ethyl acetate, (e) ethanol and (f) commercial sample

Table 7: Differential scanning calorimetry for characteristic polymorphic (crystal habit) changes of rofecoxib crystals

Solvent of crystallization	Peak onset, °C	ΔH_f, J/g	Inference
Pure drug	208.49	89.09	--
Isopropanol	209.47	59.21	No polymorph
Ethyl acetate	209.77	63.44	No polymorph
Ethanol	209.44	93.36	No polymorph
Methanol	209.01	132.91	No polymorph
Acetone	209.21	175.88	No polymorph

Table 8: Differential scanning calorimetry for characteristic polymorphic (crystal habit) changes of celecoxib crystals

Solvent of crystallization	Peak Onset, °C	ΔHf, J/g	Inference
Commercial drug	161.65	83.54	
Ethanol	161.40	137.63	No polymorph
Methanol	161.63	136.57	No polymorph
Acetone	161.66	131.52	No polymorph

polymorphic phenomenon was not proven as far as the DSC data was concerned.

Celecoxib crystal analysis

The DSC of commercial sample and the DSC of the crystals obtained from various solvents for celecoxib are recorded in Figure 7. The characteristic changes are given in Table 8.

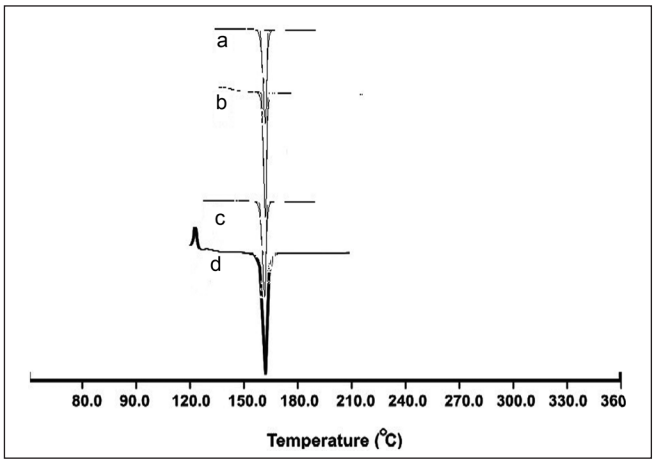

Figure 7: DSC spectra of celecoxib crystals obtained from (a) methanol, (b) acetone, (c) ethanol and (d) commercial sample

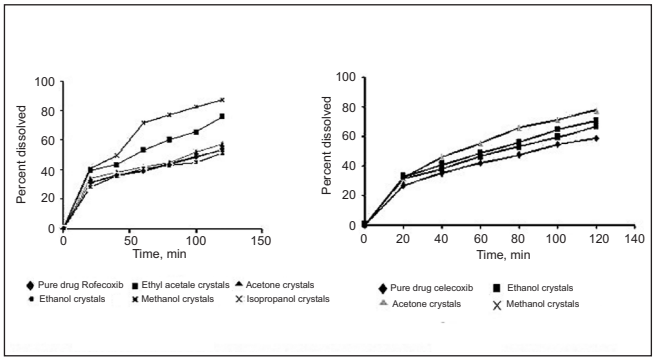

Figure 9: Dissolution profile of the drugs (a) rofecoxib and (b) celecoxib and their crystals obtained from different solvents

Table 9: Solubility data of crystals of rofecoxib and celecoxib obtained from different solvents

Solvent of crystallization	Solubility (mg/mL) of Rofecoxib crystals Mean ± S.D.#	Solubility (mg/mL) of celecoxib crystals Mean ± S.D.#
Acetone	0.0033 ± 0.0005	0.001833 ± 0.0001
Isopropanol	0.003299 ± 0.0003	--
Ethyl acetate	0.002543 ± 0.0001	--
Methanol	0.002468 ± 0.0005	0.001820 ± 0.0003
Ethanol	0.002938 ± 0.0003	0.003037 ± 0.00009
Commercial sample	0.003575 ± 0.0004	0.002406 ± 0.0001

#Each reading is an average of three determinations.

A perusal of the values of molar heat of fusion (H_f) in Table 8 indicates that values of ΔH_f were higher for the crystals obtained from the solvents, i.e., ethanol, methanol and acetone, than the corresponding value for pure celecoxib. The peak onset values were found to remain almost same, i.e., unchanged for all the celecoxib crystals and pure celecoxib. Thus, as per the DSC results, celecoxib crystals failed to show any polymorphic changes.

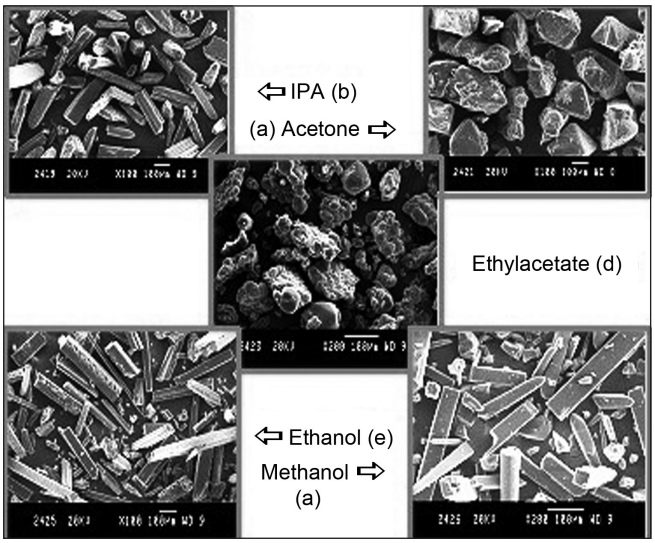

Figure 8: SEM spectra of rofecoxib crystals obtained from (a) methanol, (b) isopropanol, (c) acetone, (d) ethyl acetate and (e) ethanol

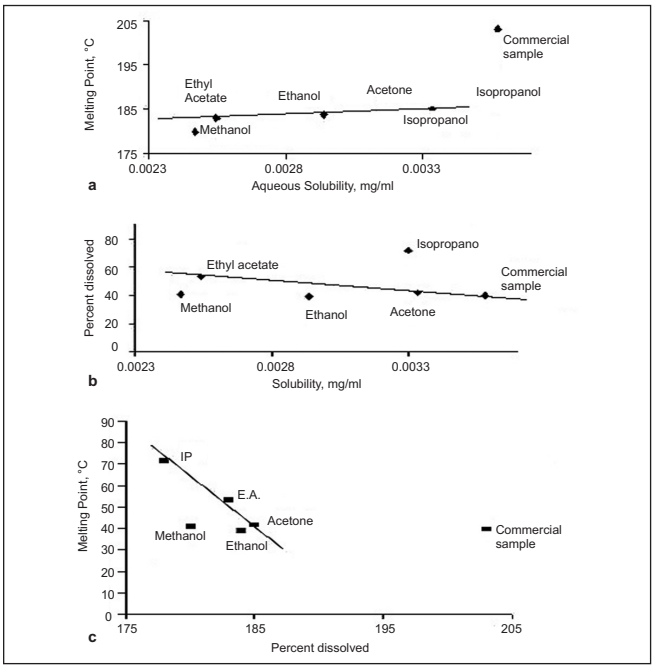

Figure 10: Co-relations — (a) melting point vs. aqueous solubility, (b) percent dissolution vs. aqueous solubility and (c) melting point vs. percent dissolution of rofecoxib crystals

Scanning electron microscopy analysis

Rofecoxib crystal analysis

SEM analysis of rofecoxib crystals [Figure 8] showed that all the crystals of rofecoxib prepared from different solvents were platy (rectangular) in shape, except the crystals obtained from acetone. This might be due to an influence of different polarity of solvents from which they were recrystallized.

Solubility behavior of rofecoxib and celecoxib crystals

Data for solubility in water have been obtained for different

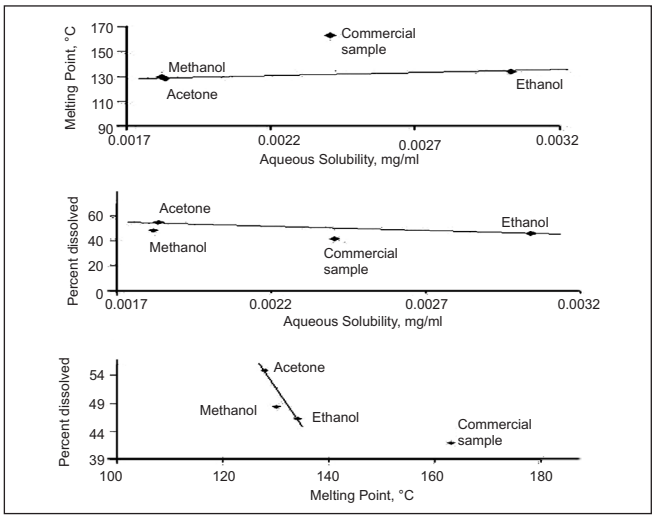

Figure 11: Co-relation — (a) melting point vs. aqueous solubility, (b) percent dissolution vs. aqueous solubility and (c) melting point vs. percent dissolution of celecoxib crystals

crystals of rofecoxib and celecoxib after shaking for 8 hours at 25°C [Table 9].

Crystals of rofecoxib obtained in acetone and isopropanol were shown to have aqueous solubility to the same extent. On the other hand, crystals obtained in ethyl acetate and methanol were shown to have aqueous solubility to the same extent, but reduced when compared to that of acetone and isopropanol. Commercial sample showed the highest aqueous solubility when compared with all the crystals. In general, crystals have low aqueous solubility compared to amorphous forms.

Crystals of celecoxib obtained in methanol and acetone were shown to have aqueous solubility to the same extent. Crystals obtained from ethanol and the commercial samples were shown to have aqueous solubility higher than those obtained from methanol and acetone crystals. Ethanol crystals were shown to have the highest aqueous solubility among all the four.

Dissolution behavior of rofecoxib and celecoxib crystals

For the dissolution studies, water was selected as a dissolution medium. There was no dissolution of drug due to low aqueous solubility. Therefore, several alternative media were studied, and finally hydrochloric acid (pH, 1.2) solution was selected. Dissolution studies were carried out by dissolution apparatus type I.

In this study, crystals were filled in hard gelatin capsule and added to the dissolution medium. The dissolution rate–time profile for rofecoxib and celecoxib crystals is shown in Figure 9. The trend of dissolution rate was different from the solubility data because hydrochloric acid (pH, 1.2) solution was used instead of distilled water (medium for solubility determination). The order of dissolution of rofecoxib crystals after 60 minutes was isopropanol > ethyl acetate > acetone > methanol > commercial sample > ethanol; whereas for celecoxib crystals, the order of dissolution after 60 minutes was acetone > methanol > ethanol > commercial sample.

The trend of dissolution data was different from the solubility results. This might be because of the media (hydrochloric acid; pH, 1.2) used for dissolution study, as dissolution was not possible with distilled water as a medium. Moreover, intrinsic solubility refers to the amount of solute that goes into the solution to make it saturated at constant temperature, whereas dissolution refers to the rate at which the solute goes into the solution.

INTERRELATIONSHIPS OF PHYSICOCHEMICAL PROPERTIES OF CRYSTALS

Rofecoxib

Melting point vs. aqueous solubility

Though commercial sample showed high melting point, its aqueous solubility was also high. Among crystals also, a similar behavior was observed. The data are plotted in Figure 10.

Aqueous solubility vs. percent dissolution

The aqueous solubility data of rofecoxib crystals and percent dissolution at the end of 60 minutes were extracted. The data are plotted in Figure 10.

A perusal of Figure 10 indicates that the percent dissolution of commercial sample of rofecoxib in HCl (pH, 1.2) solution was low, though its aqueous solubility was high. For crystals obtained from ethyl acetate, methanol, ethanol and acetone, the aqueous solubility was decreased; percent dissolution of rofecoxib was increased. The HCl (pH, 1.2) medium had antagonistic effect on the aqueous medium. One possible reason for this behavior could be the dissociation constant. This could be ruled out, because rofecoxib did not have any functional groups that exhibit dissociation constant. Hence co-relation might not be relevant.

Melting point vs. percent dissolution

The data with regard to melting point of rofecoxib crystals and percent dissolution at 60 minutes were extracted. These data are also plotted in Figure 10.

A perusal of Figure 10 indicates that lower the melting point is, the higher is the dissolution of crystals in HCl (pH, 1.2) solution. This behavior was observed in case of commercial sample also.

Celecoxib

Melting point vs. aqueous solubility

The data with regard to melting point and aqueous solubility were extracted. The data are plotted in Figure 11. A perusal of Figure 11 indicates that higher the melting point of celecoxib crystals is, the higher is the aqueous solubility.

Aqueous solubility vs. percent dissolution

The data with regard to aqueous solubility of celecoxib crystals and percent dissolution at the end of 60 minutes were extracted. The data are plotted in Figure 11.

A perusal of Figure 11 indicates that for crystals obtained from ethanol, methanol and acetone, the aqueous solubility was decreased, whereas percent dissolution of celecoxib was increased. The HCl (pH, 1.2) medium had antagonistic effect on the aqueous medium with regard to its dissolution. One possible reason for this behavior could be the dissociation constant. Dissociation constant of celecoxib is weekly acidic with a pK_a of 11.1. Same types of interactions might be possible for enhanced dissolution.

Melting point vs. percent dissolution

The data with regard to the melting point of celecoxib crystals and percent dissolution at 60 minutes were extracted. These data are also plotted in Figure 11.

A perusal of Figure 11 indicates that the lower the melting point is, the higher is the dissolution of crystals in HCl (pH, 1.2) solution. This behavior was observed in case of commercial sample also. This behavior is in tune with the general principles.

The analysis of results gave significant observations, which were discussed in the light of current concepts and interrelationships among the other experimental results.

CONCLUSION

The melting points of rofecoxib and celecoxib crystals obtained from different solvents were different, providing the *prima facie* evidence for differences in crystal habit or polymorphism. FT-IR and XRD data provided further evidence for polymorphism in the crystals obtained from rofecoxib and celecoxib. The crystals obtained from the solvents of different polarities showed different crystal habits and dissolution patterns. Hence we could conclude that isopropanol and acetone are the best solvents for recrystallization of rofecoxib and celecoxib, respectively. Moreover, from the DSC data, it could be concluded that there was no occurrence of polymorphism in the obtained crystals. However, further studies might be needed in order to conclude precisely about the presence or absence of difference in crystal morphs.

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