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Solubility enhancement of Aceclofenac by Mixed Hydrotropy approach

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ABSTRACT: Background: Conventional Aceclofenac tablets are practically insoluble in water, and have a slow onset of action (45 to 60 min) hence belong to BCS Class 2 category and it has poor oral bioavailability (15 %), therefore cannot be given in emergency situations. **Aim:** The present work is to improve the solubility and dissolution properties of Aceclofenac so as to provide a fast-dissolving oral dosage form. **Method:** Solubility study of Aceclofenac was initially determined in 0.1 N HCl, phosphate buffer of pH 6.8, and distilled water. The solubility of Aceclofenac was enhanced by the mixed hydrotrophy method by using 4 hydrotropic agents that are sodium acetate, sodium benzoate, sodium citrate, and urea at concentrations of 5, 10, 15, and 20 % w/v solutions, also in a combination of 2, 3 and 4 hydrotropic agents but its total concentration was always 20 % w/v using distilled water as solvent. The optimized combination was utilized in preparing solid dispersions by the common solvent technique and was evaluated for the flow properties, FTIR, XRD, DSC, and SEM. The granules containing the solid dispersion form of the Aceclofenac were compressed to form tablets. **Results:** The drug shows the highest solubility in pH 6.8, in the case of an individual hydrotropic agent in 20 % sodium citrate. In different combinations of 2, 3, and 4 hydrotropic agents, the highest solubility was obtained in a solution of sodium acetate+sodium benzoate+sodium citrate+urea at an optimum ratio of 2.5: 5: 10: 2.5 w/v. At the end of 30 min, the dissolution study of conventional tablet and solid dispersions shows 74.6 and 99.51 % drug release respectively. **Conclusion:** It was concluded that the mixed hydrotropic solid dispersion is a novel, safe and cost-effective technique for enhancing the bioavailability of poorly water-soluble drugs.

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INTRODUCTION:

Among all newly discovered chemical entities, about 40 % of drugs are lipophilic and fail to reach the market due to their poor aqueous solubility [1]. For orally administered drugs solubility is one of the rate-limiting parameters to achieve their desired concentration in the systemic circulation in pharmacological response [2]. Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may

be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion [3,4]. The solubility of drug molecules plays a key role in their bioavailability. The aqueous solubility of poorly aqueous soluble drug molecules in the gastrointestinal fluid often causes unsatisfactory bioavailability. Poorly aqueous soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration of any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption [5]. However, various leading pharmaceutical companies have been able to triumph over technical hitches with very slightly aqueous soluble drugs, those with aqueous solubility of less than 0.1 mg/ml present some unique challenges. These drugs are particularly good candidates for advanced solubilization technologies developed by companies specializing in drug delivery. Solubilization of poorly aqueous soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development [6]. The drug absorption from the GIT is low/limited due to various significant factors like poor aqueous solubility was classified under BCS classification [7-9]. Class 1 - High solubility, high permeability, Class 2 - Low solubility, high permeability, Class 3 - High solubility, low permeability, and Class 4 - Low solubility, low permeability.

The success of any formulation depends on how efficiently solubility makes the dug available at the site of action. So, the solubility of the drug is an important parameter to increase drug availability [10].

The various methods to increase the solubility of BCS Class 2 drugs include both traditional and novel techniques like Hydrotropy, use of co-solvents and surfactants, micronization, inclusion complexation, solvent deposition and precipitation, nanoparticle technology, nanocrystal technology, super-critical technology, nanosuspensions, and microemulsion technology [11].

The hydrotropy is a solubilization process in which another solvent is used to raise the soluble of the mixtures. Due to the incidence of a large number of additives, it can make better solubility in the water [12]. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea, and poorly soluble drugs. Hydrotropic agents are ionic organic salts. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute [13]. In the following method, hydrotropy is classified in three ways as aromatic catatonics examples like Para amino benzoic acid hydrochloride, procaine hydrochloride, and caffeine. Aromatic anionic examples like sodium benzoate, sodium salicylate, sodium benzene sulphonate, sodium benzene disulphonate, and sodium cinnamate. Linear anionic examples like sodium alkanoate [14]. The advantages of this process are it suggests a superior solubilizing method and the solvent is independent through the pH also a wide range of compounds have been reported exhibit hydrotropic conditions [15,16]. A hydrotropic approach is a promising approach with great potential for poorly soluble drugs since it does not require chemical modification of the drug, the use of organic solvents, or the preparation of emulsion systems. The primary objective of this study was to enhance the solubility of aceclofenac using hydrotropes and their combinations so that oral bioavailability can be increased.

MATERIALS AND METHODS:

Aceclofenac was obtained as a gift sample from Karnataka Antibiotics Pvt. Ltd., Bangalore, India. Sodium Acetate was purchased from Thermo Fisher Scientific India Pvt. Ltd, Mumbai, India. Sodium benzoate was purchased from Thermo Electron LLS India Pvt. Ltd, Mumbai, India. Sodium citrate and urea were purchased from SD Fine Chem Ltd, Mumbai, India. All the chemicals and reagents used were of analytical grade.

Standard calibration curve of aceclofenac:

***Determination of λ_{max} of the drug*:**

A diluted solution of aceclofenac in phosphate buffer solution (pH 6.8) was scanned for absorption maxima against blank between 200 to 400 nm using a UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan). The maximum absorbance was found to be 275 nm.

***Preparation of phosphate buffer solution (pH - 6.8)*:**

About 28.80 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen orthophosphate were dissolved in sufficient water to produce 1000 ml in a volumetric flask.

***Calibration curve of Aceclofenac in phosphate buffer solution (pH 6.8)*:**

Accurately weighed aceclofenac (100 mg) was transferred into a 100 ml volumetric flask, dissolved,

and adjusted the volume up to 100 ml with phosphate buffer solution (pH 6.8) to get stock solution A. From stock solution A, 10 ml was pipette out into a 100 ml volumetric flask, and volume was made up to mark with phosphate buffer solution (pH 6.8) to get stock solution B. From stock solution B, known volumes were pipette out and made up to 10 ml with phosphate buffer solution (pH 6.8). Aliquots of solutions such as 0.2, 0.4, 0.8, 1.0,1.2, 1.4, 1.6, 1.8, and 2.0 ml are pipette out and made up to mark in a 10 ml volumetric flask to get 2 to 20 µg/ml concentration solutions and absorbance was recorded at 275 nm by UV-Visible spectrophotometer.

Solubility studies of the pure drug:

Solubility analysis was done which include the selection of a suitable solvent system to dissolve the drug. Dissolve accurately 10 mg of drug in 10 ml of water, 10 ml of 0.1N HCl, and 10 ml of Phosphate buffer pH 6.8 in a 100 ml conical flask separately. The samples were kept on a rotary shaker at 100 rpm for 24 h. After that, the volumes were made up to a 100 ml mark with respective solvents, then filter the solutions. The filtrate was analyzed at 275 nm by using a UV-Visible spectrophotometer.

Solubility studies of the pure drug in hydrotropic agents:

Initially, the solubility of Aceclofenac was determined individually in solutions of 4 hydrotropic agents namely sodium acetate (SA), sodium benzoate (SB), sodium citrate (SC), urea (UA), at a concentration of 5,10,15, and 20 % solutions using water as solvent (Table 3). For determining solubility, accurately measured 5 ml of a particular blend of a hydrotropic agent was taken in a 10 ml volumetric flask and an excess amount of drug (10 mg) was added and mechanically shaken until saturation solution was formed. The volumetric flask was shaken on a rotary shaker for 6 h at 100 rpm so that equilibrium solubility can be achieved and the solution was to equilibrate for 24 h. The aliquot was suitably diluted with purified water and centrifuged at 2500 rpm for 8 min in a centrifuge (Remi, India) machine and then the solution was filtered through a Whatman grade 41 filter. The filtrate was analyzed at 275 nm using a UV-Visible spectrophotometer [17]. It was shown that the solubility of aceclofenac was increased with the increasing concentration of hydrotropic agents. It was shown that solubility in 20 % urea solution was found to be much higher compared to that solubility in 5, 10, and 20 % urea solutions. Then different combinations of above mentioned 4 hydrotropic agents in different ratios were tried to determine enhancement in solubility so that the total concentration of hydrotropic agents was always 20 % w/v. The blend in the formulation F18 of SA+SB+SC+UA in the ratio 2.5: 5: 10: 2.5 gives the highest solubility enhancement and therefore this optimized combination of hydrotropes was selected for the preparation of solid dispersions.

Preparation of solid dispersion:

For the preparation of hydrotropic solid dispersion accurately weighed quantity of sodium acetate, sodium benzoate, sodium citrate, and urea were taken in a beaker and were mixed properly with the minimum quantity of warm purified water. Dissolution of the hydrotropic mixture was facilitated by placing it on a high-speed magnetic stirrer. After the complete dissolution of hydrotropic agents, Aceclofenac 100 mg was dissolved in the above solution, and the temperature was maintained in the range of 55 to 60 ºC so as to facilitate the evaporation of water. As evaporation proceeds, the speed of the magnetic bead automatically decreased and it stopped stirring when most of the water was evaporated, thus indicating the formation of solid dispersion (wet). The wet solid dispersion thus obtained was spread on several watch glasses and kept in a hot air oven maintained at 50±2 ºC so that the remaining moisture could also be evaporated easily and constant weight with no further weight loss could be obtained. After complete drying, solid dispersions were crushed using a glass mortar and pestle and passed through sieve # 44, and were finally stored in an airtight glass bottle.

Dissolution rate studies:

Solid dispersion equivalent to 50 mg of aceclofenac was tested in dissolution rate studies using USP type II Paddle dissolution apparatus at 50 rpm. The dissolution medium consists of 900 ml distilled water maintained at a temperature of 37±5 ºC. At a specific time, interval (5 to 60 min) 10 ml of sample were withdrawn and replaced with a fresh dissolution medium. The amount of dissolved drug in each aliquot was measured on a UV-Visible spectrophotometer at 275nm using a suitable blank. All the trials were conducted in triplicate and the average (±S.D.) reading was noted.

Micrometric properties:

Micrometric properties of the solid dispersions' studies were bulk density, tapped density, compressibility index, Hausner ratio, and angle of repose were determined.

Fourier Transform Infrared Spectroscopy (FTIR) analysis:

The FTIR spectrum of the pure drug Aceclofenac, aceclofenac hydrotropic solid dispersion was determined by using Bruker FTIR (ATR) spectrophotometer, applying the KBr disk technique. The FTIR analyses were carried out in the scanning range of 4000 to 400 cm^{-1} at room temperature. The obtained spectrum was compared with the standard FTIR spectrum of pure drug aceclofenac and FTIR spectra of hydrotropic agents, to determine the drug interaction between drug aceclofenac and excipients.

Differential Scanning Calorimetric (DSC) analysis:

In order to obtain the DSC thermograms of the drug, solid dispersion, and physical mixture, a DSC-60 Calorimeter (Shimadzu, Japan) instrument was employed and calibrated according to the manufacturer's recommendation. To carry out these studies, 3 mg of drug or formulation of the drug was weighed accurately and placed in an aluminium pan, sealed with an aluminium cap, and kept under nitrogen purging (atmosphere) with a flow rate of 50 ml/min. The samples were scanned in the range from 50 to 300 ºC with a heating rate of 10 ºC rise/min using the DSC.

Scanning Electron Microscopy (SEM):

SEM was used to investigate THE solid-state physical structure of the prepared solid dispersion. SEM photographs of Aceclofenac, its physical mixture with hydrotropic agents, and its solid dispersions were sputter-coated using an electrically conducting metal such as gold onto a drug and solid dispersion. Then the shape and surface topography of drug and solid dispersion was observed using an SEM model JEOL JSM -IT500.

X-ray diffraction (XRD) studies:

The X-ray diffraction patterns were recorded using an X-ray diffractometer. The powder X-ray diffraction spectra of aceclofenac, prepared hydrotropic solid dispersion and the physical mixtures were obtained using the Mini Flex 600 X-ray generator instrument, Rigaku (Rigaku International Corporation, Tokyo, Japan). The Cu as anode material and crystal graphite monochromator operated at a voltage of 50 mA, 40 kV. The samples were analyzed in the 2Θ angle range of 7 to 40 at scanning of speed 10º/ min and step size with reproducibility of 0.001 ºC for pure drug and solid dispersion. The position and intensities of diffraction peaks were considered for the identification and comparison of the physical state of the drug and solid dispersion. The X-ray diffractograms of aceclofenac, solid dispersion, and physical mixture were obtained.

RESULTS AND DISCUSSION:

The calibration study of aceclofenac was developed and good linearity with a regression coefficient of 0.999 (r^2 value) was observed so the tested concentration range obeyed Beer-Lambert's law as evident from Table 1 and Fig 1.

Table 1. Calibration curve of aceclofenac in phosphate buffer solution (pH 6.8).

Sl. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.141
3	4	0.245
4	6	0.358
5	8	0.490
6	10	0.610
7	12	0.733
8	14	0.836
9	16	0.963
10	18	1.070
11	20	1.187

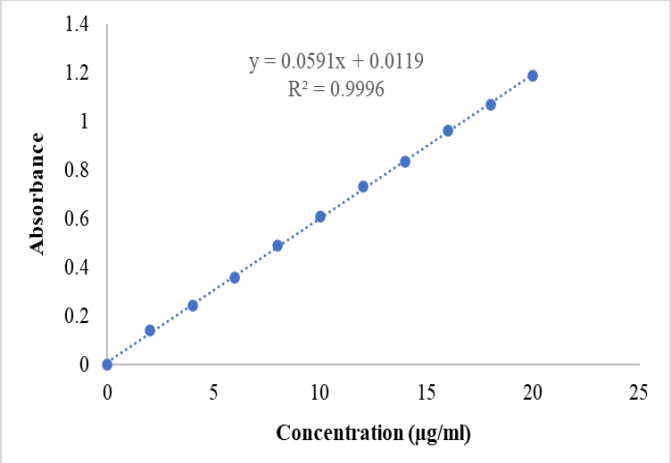

Fig 1. Calibration curve of aceclofenac in Phosphate buffer solution (pH 6.8).

In the determination of the solubility of aceclofenac maximum absorbance was shown by the drug which was dissolved in phosphate buffer (pH 6.8) at 275 nm (Table 2 and Fig 2). The solubility data of aceclofenac in different hydrotrophic agents are given in Table 3 and 4. The drug shows the highest solubility in 20 % sodium citrate. In different combinations of 2, 3, and 4 hydrotropic agents, the highest solubility was obtained

in a solution of sodium acetate + sodium benzoate + sodium citrate + urea at an optimum ratio of 2.5: 5: 10: 2.5 w/v.

Table 2. Solubility study of aceclofenac in different media.

Sl. No.	Solvent	Solubility (mg/ml)
1	Distilled water	0.0173
2	0.1 N HCl	0.0958
3	Phosphate buffer (pH 6.8)	0.1651

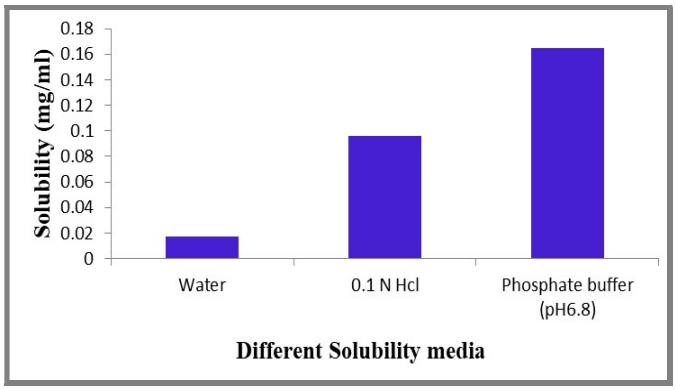

Fig 2. Comparison of solubility of aceclofenac in distilled water, 0.1 N HCl, and Phosphate buffer solution (pH 6.8).

Table 3. The solubility of aceclofenac in different hydrotropic agents.

Hydro-tropic agent	Concentration (% w/v)				Solubility enhancement ratio			
	5	10	15	20	5	10	15	20
Sodium acetate	0.39	0.52	0.59	0.62	22.43	30.2	34.1	36.0
Sodium benzoate	1.99	2.13	2.60	2.90	114.8	123.1	150.2	167.7
Sodium citrate	2.81	3.96	4.13	5.17	162.3	228.9	238.7	298.9
Urea	0.20	0.44	0.73	0.93	11.4	25.4	42.2	53.6

Table 4. The solubility of aceclofenac in a mixture of different hydrotropic agents.

Formulation Code	Combination	Total conc. (% w/v)	Individual conc. (% w/v)	Solubility (% w/v)	Solubility enhancement ratio
F1	SA+UA	20	10	1.966	113.646
F2	SB+UA	20	10	3.191	184.450
F3	SC+UA	20	10	3.582	207.052
F4	SA+SB	20	10	3.017	174.393
F5	SA+SC	20	10	3.792	219.190
F6	SB+SC	20	10	9.389	542.771
F7	SA+SB+UA	20	6.66	2.979	172.196
F8	SA+SC+UA	20	6.66	2.584	149.364
F9	SA+SB+SC	20	6.66	7.484	432.601
F10	SB+SC+UA	20	6.66	8.609	497.630

SA: Sodium Acetate, SB: Sodium benzoate, SC: Sodium citrate, UA: Urea.

Table 5: Solubility of aceclofenac in a mixture of different hydrotropic agents.

Formulation Code	Combination	Total conc. (% w/v)	Individual conc. (% w/v)	Solubility (% w/v)	Solubility enhancement ratio
F11	SB+SC+UA	20	5:10:5	9.735	562.716
F12	SB+SC+UA	20	7.5:10:2.5	9.869	570.462
F13	SB+SC+UA	20	10:2.5:7.5	5.932	342.890
F14	SB+SC+UA	20	10:7.5:2.5	6.932	400.693
F15	SA+SB+SC+UA	20	10:5:2.5:2.5	3.900	225.433
F16	SA+SB+SC+UA	20	2.5:10:2.5:5	4.931	285.028
F17	SA+SB+SC+UA	20	2.5:2.5:2.5:2.5	3.808	220.115
F18	SA+SB+SC+UA	20	2.5:5:10:2.5	9.953	575.317
F19	SA+SB+SC+UA	20	2.5:7.5:2.5:7.5	4.887	282.485
F20	SA+SB+SC+UA	20	2.5:5:2.5:10	5.838	337.456

SA: Sodium acetate, SB: Sodium benzoate, SC: Sodium citrate, UA: Urea.

It is showed that the dissolution rate studies that solid dispersions were dissolved completely within 2 min, and when observed visually, they were found to be dissolved only within 10 to 20 s (Table 5 and 6, Fig 3 and 4).

Table 6. Dissolution of solid dispersion and conventional tablet.

Time (min)	% Drug dissolved	
	Solid dispersion	Conventional tablet
1	97.14	37.8
5	96.42	45.9
10	97.63	56.7
20	98.95	64.8
30	99.51	74.6

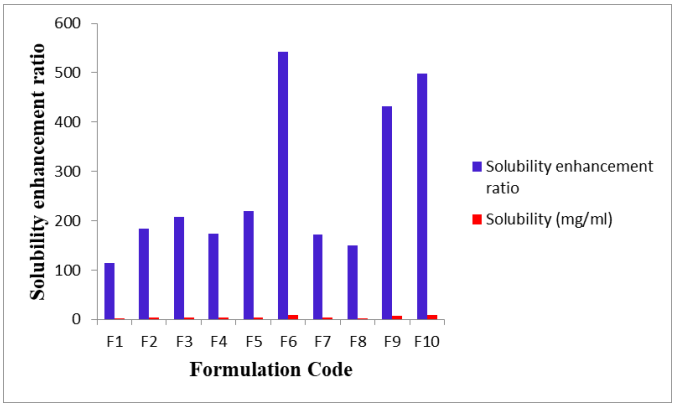

Fig 3. Comparison of Solubility of aceclofenac in hydrotropic agents.

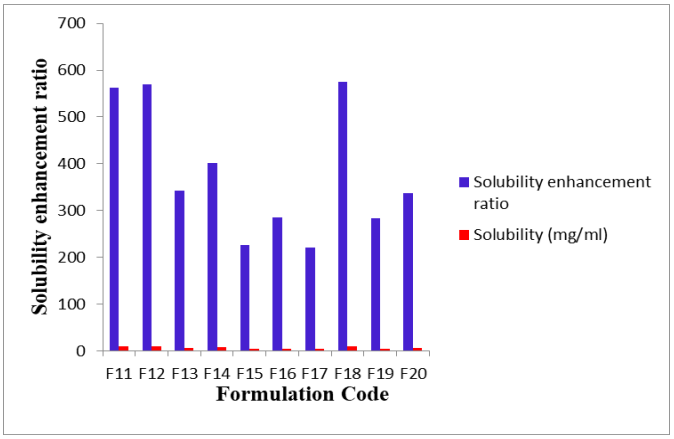

Fig 4. Comparison of Solubility of aceclofenac in different ratios of hydrotropic agents.

While, on the other hand, the conventional tablet does not get dissolved completely even after 30 min. The *in vitro* dissolution studies show that the percentage release of drug in the conventional tablet was 74.6 % and in solid dispersion is 99.51 % at 30 min (Table 6 and Fig 5) and from this, we can conclude that the dissolution rate of drug release is increased in the case of hydrotropic solid dispersions.

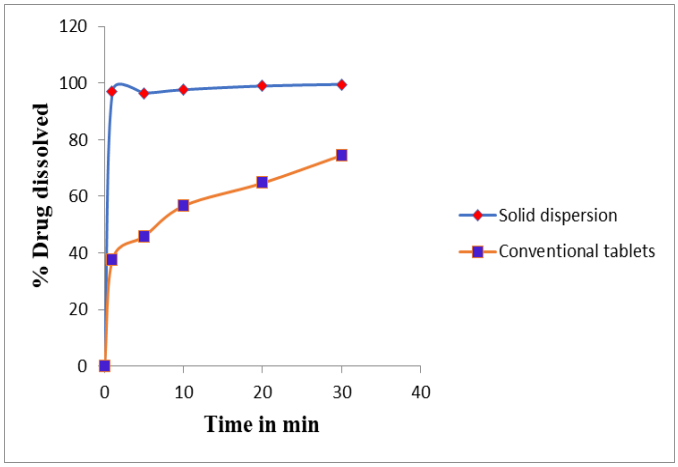

Fig 5. The comparison study of *in-vitro* dissolution profile of Solid dispersions and Conventional tablets.

The closeness of values of bulk density and tapped density indicates the free-flowing property of solid dispersions. The values of compressibility index, Hausner's ratio, and angle of repose indicate that the flow character of solid dispersion is fair and no aid is needed to increase the flow properties (Table 7).

Table 7. The micromeretic properties of solid dispersions.

Parameter	Result
Bulk density ($g/cm^{3)}$	0.6470
Tapped density($g/cm^{3)}$	0.7333
Compressibility index (%)	11.7687
Hausner ratio	1.1338
Angle of repose	27º

In the compatibility studies between drug and excipients, IR spectrum of pure drug and formulations and excipients was recorded. Similar peaks are obtained in drugs and formulations which indicates that the pure drug functional group present in all formulations, as evident from Fig 6 and 7.

DSC thermogram of Aceclofenac showed sharp endothermic peak at 162.53º. While the DSC curve of the physical mixture and solid dispersion both showed endothermic peaks near 164º and 160.73º which indicates the absence of any complex formation in the case of solid dispersion or physical mixture. The DSC report is presented in Fig 8.

SEM photographs of pure aceclofenac shows characteristic needle-shaped structures, indicating the crystallinity of aceclofenac (Fig 9). These needle-shaped structures can also be seen along with other structures of hydrotropic agents in photographs of the physical mixture. But in photographs of the solid dispersions, there are no distinguishable needle-shaped structures of

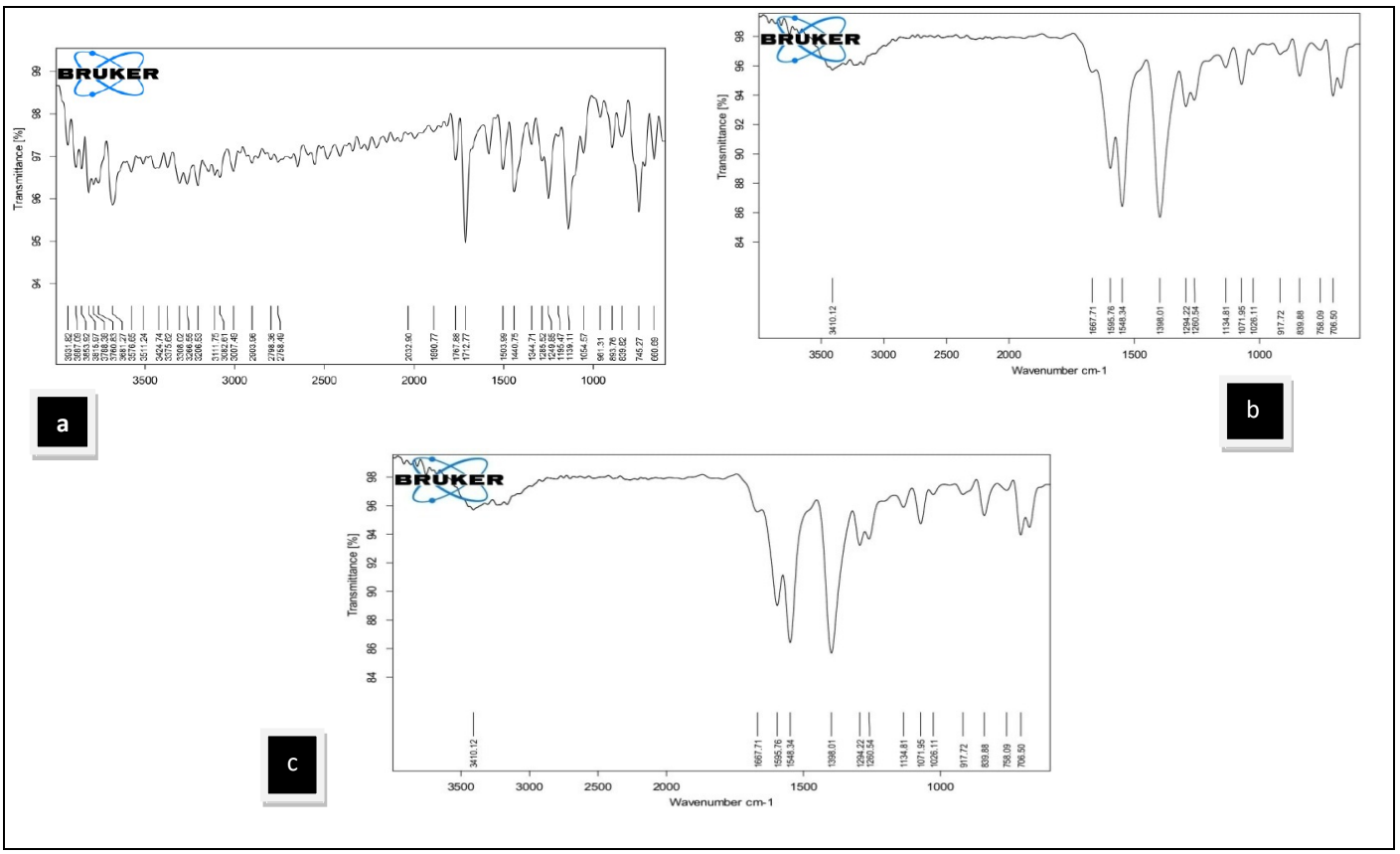

Fig 6. FTIR of (a) aceclofenac, (b) Physical mixture, (c) Solid dispersion.

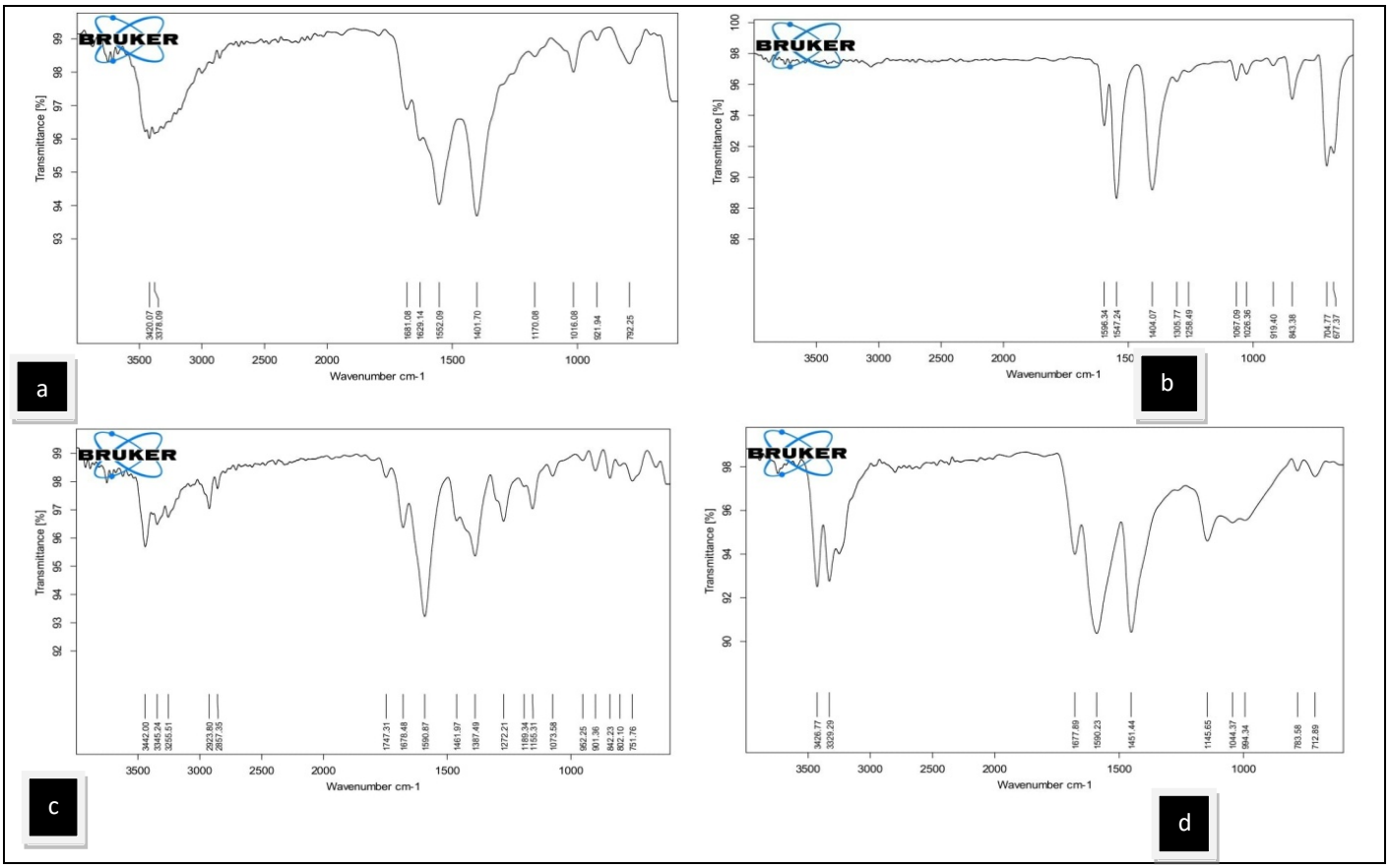

Fig 7. FTIR of (a) sodium acetate, (b) sodium benzoate, (c) sodium citrate, (d) urea.

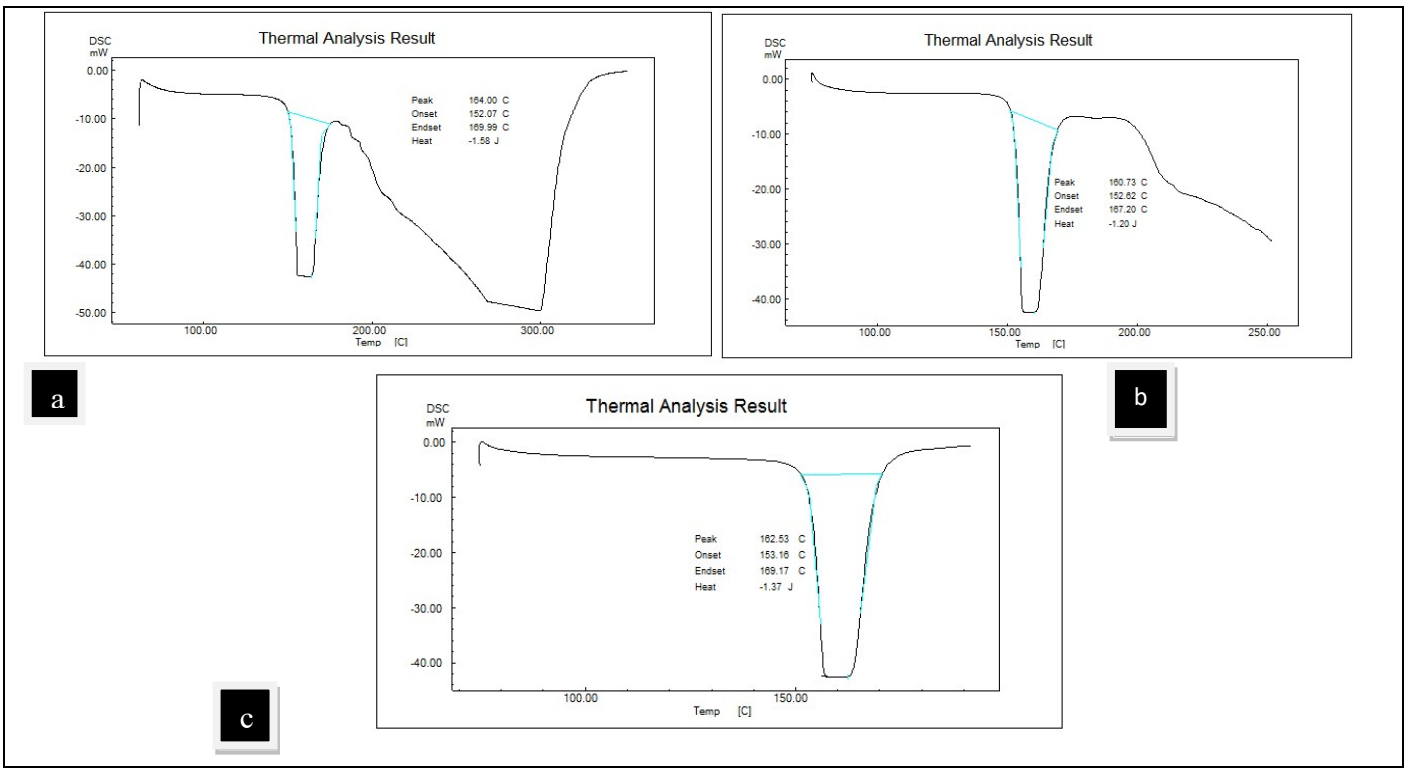

Fig 8. Differential scanning calorimetry thermograms of (a) aceclofenac, (b) Physical mixture, (c) Solid dispersion.

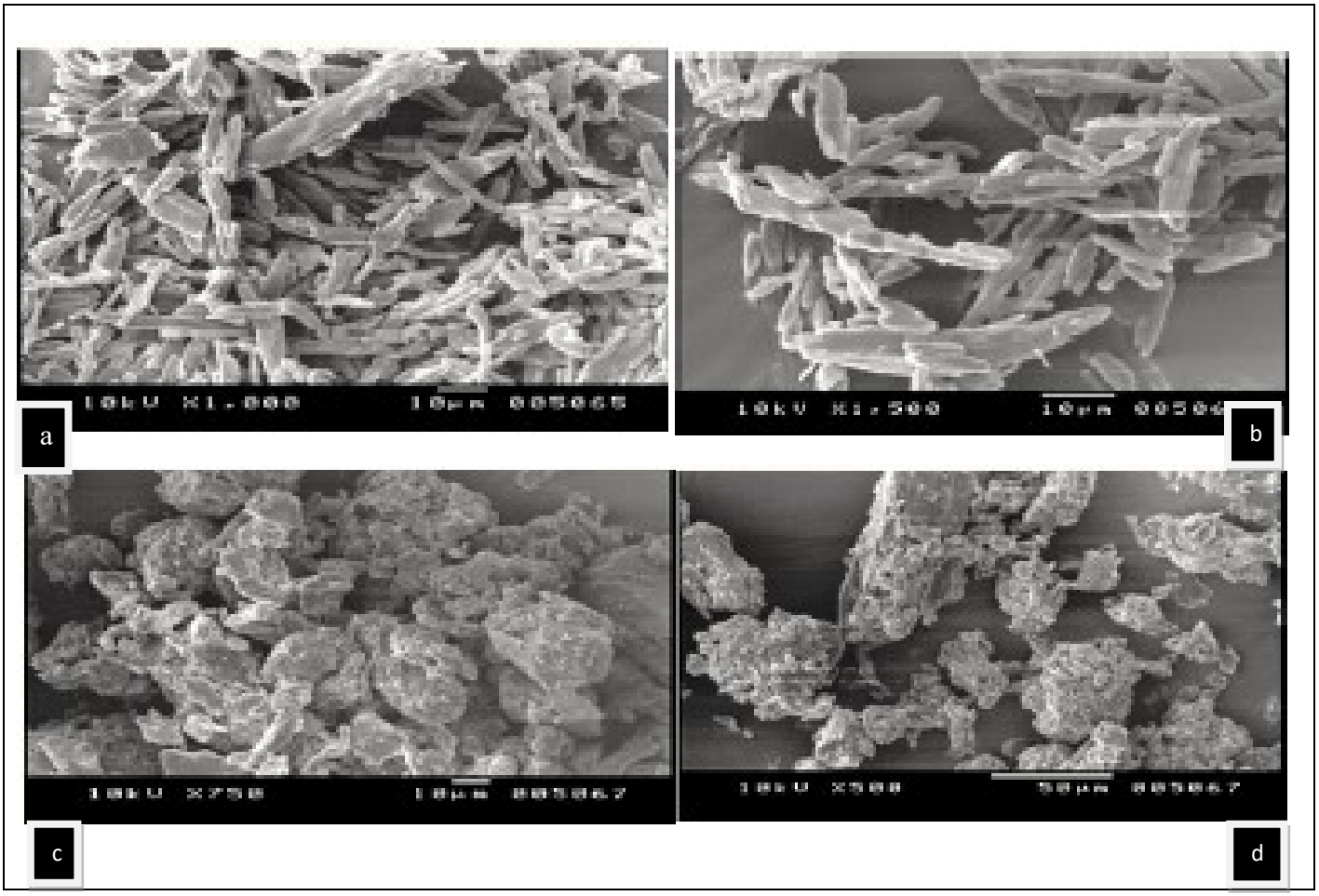

Fig 9. Scanning electronic microscopy of (a) Aceclofenac, (b) Physical mixture, (c) Solid dispersion, (d) Solid dispersion.

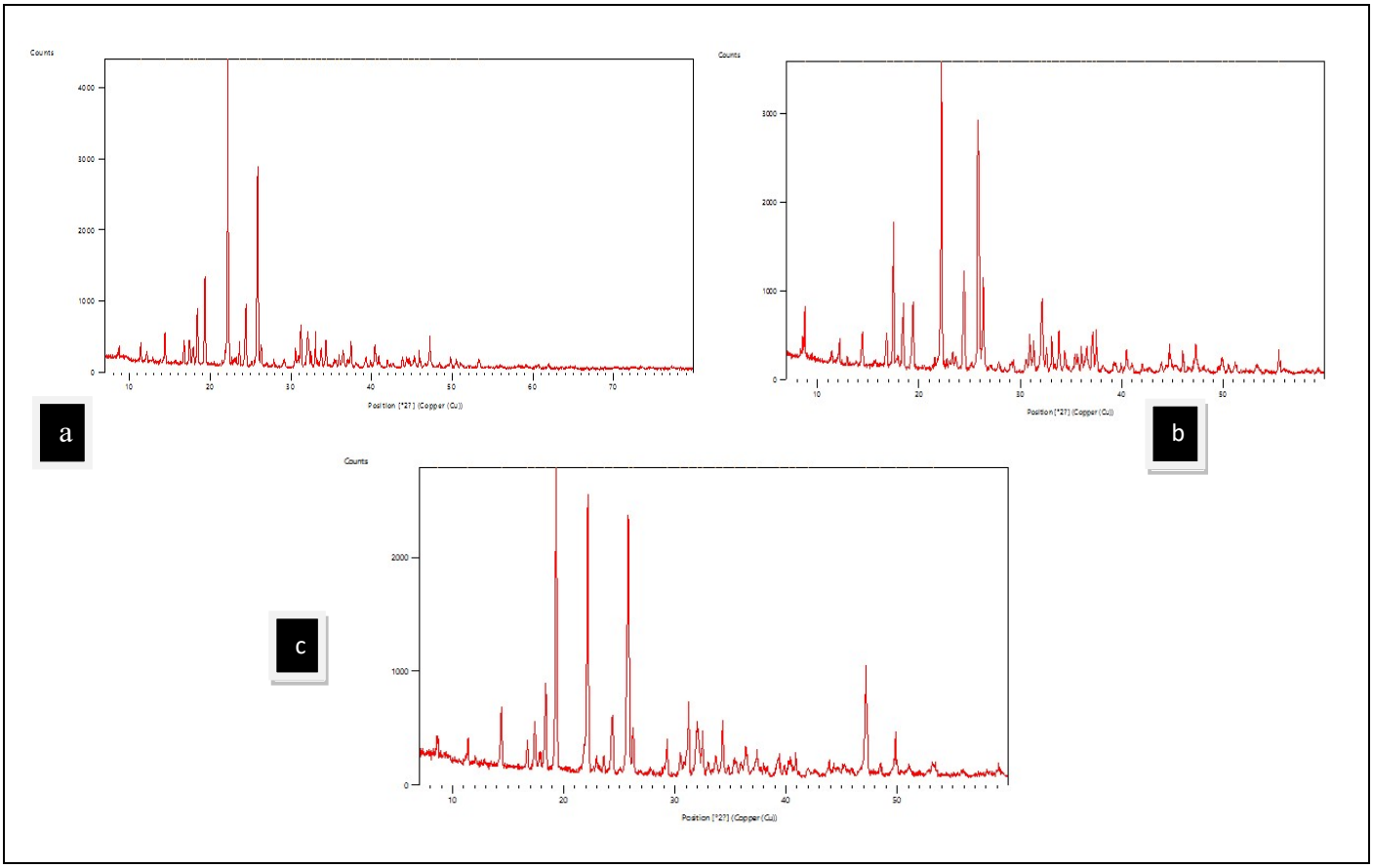

Fig 10. X-ray diffraction of (a) aceclofenac, (b) Physical mixture, (c) Solid dispersion.

Aceclofenac, suggesting the total miscibility of aceclofenac within the carrier.

Since the X-ray diffraction pattern of solid dispersion and physical mixture showed the same peaks at 2Θ range 7 to 55° (Fig 10) which are characteristic of pure aceclofenac, therefore it can be presumed that the formation of hydrotropic solid dispersion or physical mixture does not cause any physical and chemical interaction between aceclofenac and hydrotropes at the molecular level.

CONCLUSION

In conclusion, presently pharmaceutical industry has reached the point where the discovery of new drugs has become very difficult and expensive. Exploiting the maximal value that can be generated from existing compounds now constitutes importance. So, the hydrotropy technique is a solution for pharmaceutical companies to enhance existing products in which poor solubility is a major concern. Many useful drugs may be banned due to poor pharmacokinetic properties such as poor water solubility and hence poor bioavailability. Through hydrotropy, the water solubility of a drug may be improved thus enabling the maintenance of drugs in the existing product form. It can be concluded that the concept of mixed hydrotropic solid dispersion is a new, simple, cost-effective, safe, accurate, and precise method that involves the blends of hydrotropes which gives a synergistic effect on the solubility of poorly water-soluble drugs by dissolving the drug in nonionized form. The enhancement in solubility of Aceclofenac is a clear indication of its potential to be used in the future for other poorly water-soluble drugs in which low bioavailability is a major issue.

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