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Physicochemical Characterization and Dissolution Studies of Ketoprofen Solid Dispersions with Cationic Polymers

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Abstract:
Background: Ketoprofen (KETO) is an example of drugs with limited solubility and high permeability that are classified as biopharmaceutics classification system (BCS) class II. Its poor water solubility can give rise to formulation problems and reduce its therapeutic efficiency and bioavailability.
Materials and Methods: A simple solution mixing method was used to formulate KETO into solid dispersion with cationic hydrophilic polymers; Eudragit® E (EE) and chitosan (CH). These solid dispersions were prepared at various drug:polymer ratios; 1:1, 1:2 and 1:3 by solvent evaporation methods. Physiochemical characteristics including %yield, %drug content, and in-vitro dissolution rate were evaluated for the produced formulations. Solid-state characterization was used to further rule out the optimized formulations by Fourier Transform Infrared Spectroscopy (FT-IR) as well as differential scanning calorimetry (DSC).
Results: The results revealed that, all SDs profoundly increased drug dissolution rate compared to the pure drug. The highest dissolution of KETO, amounting to 96.33 and 99.66%, was observed after 120 min. from KETO-EE and KETO-CH solid dispersion respectively at 1:3 drug:polymer ratio. FT-IR results suggested, the formation of H bonding between H atom from OH group of KETO and the carbonyl group in the EE, however, KETO chemical structure remained unchanged after being incorporated into CH solid dispersion. The amorphous property of KETO inside the EE or CH matrix in the solid dispersion was confirmed by DSC, thus, explained the enhanced dissolution rate.Our finding suggested that, KETO-EE solid dispersion at1:3 drug:polymer ratio is the best formulation in this study.
Key Words: Ketoprofen; Chitosan; Eudragit E; Solid dispersion; Solvent evaporation.

I. Introduction

Solid dosage forms such as tablets and capsules are the most available pharmaceutical dosage forms in the market that are more practical and acceptable for patients[1]. During developing solid dosage forms, the low solubility of the active pharmaceutical ingredients in the aqueous medium is one of the challenges faced by the pharmaceutical industry. The absorption process of a drug that is poorly water soluble in the gastrointestinal tract is limited by its dissolution process that is a rate-limiting step[2,3]. So, it is important to improve the dissolution rate of active pharmaceutical compounds in order to overcome this problem.

Ketoprofen (2-(3-benzoylphenyl) propionic acid) (KETO) is a classified as BCS class II drug owing to its low aqueous solubility[4]. It is a nonsteroidal anti-inflammatory drug used clinically to treat the acute and prolonged therapy of osteoarthritis, rheumatoid arthritis, dysmenorrhea, and to reduce the severity of moderate pain[5].

Several approaches have been previously reported to enhance the solubility and dissolution rate of KETO. These include; the formation of β-cyclodextrin inclusion complex[6,7], simple eutectic mixtures[8], nanoparticles[9,10]and multicomponent crystals[11]. The majority of these preparation techniques are challenging and require a lot of organic solvent, which is another issue. However, compared to nano and chemical modification approaches, solid dispersion (SD) is easier to manufacture and has a higher loading capacity and stability. This method become appealing in the pharmaceutical industry because of its scalable and economic characters[12-14]. It has been tested for KETO, in which, drug release in the upper section of the GIT is significantly influenced by the use of a hydrophilic carrier for SD[15-17].

Chitosan (CH) is a hydrophilic, cationic, polysaccharide polymer. It is derived by deacetylation of chitin in alkaline conditions or by enzymatic hydrolysis. It is of great interest due to its biocompatibility, biodegradability, bioactivity, nontoxic, and non-allergic properties[18,19]. Ketoprofen was previously found to dissolve more readily when it was made into an amorphous solid dispersion with chitosan using ethanol as the

organic solvent. This behavior was influenced by the drug/chitosan weight ratio as well as the molecular weight of the chitosan[20]. However, it is problematic where preparation used much organic solvent.

Eudragit® E (EE) is another example of cationic polymer that belongs to the class of methacrylate copolymers. Its component parts are 2:1:1 molar ratios of 2-dimethylaminoethyl methacrylate, methyl methacrylate, and n-butyl methacrylate. In gastric pH, it is soluble (up to 5). Its dimethylamino groups, are hydrated and fully protonated making it highly soluble at this pH[21]. These characteristics make it a strong candidate for enhancing hydrophobic drugs solubility through the formulation of SD with modified characteristics[22-25]. Because EE contains several basic tertiary ammonium groups and KETO as an acid (comprising COOH groups), the electrostatic interactions and salt production during manufacturing and/or drug dissolution may be of value.

In view of the aforementioned facts, the purpose of this work was to prepare KETO SD using relatively inexpensive and biocompatible cationic polymers (CH and EE) by a simple aqueous solution mixing method followed by solvent evaporation. The effect of these polymers on the dissolution rate of KETO was investigated. Moreover, physicochemical characterization was carried out using Fourier Transform Infrared Spectroscopy **(**FT-IR) as well as differential scanning calorimetry (DSC) to more thoroughly investigate any possible drug-polymer interactions that might be present in the generated solid dispersions.

II. Material And Methods

Materials

Ketoprofen, kindly supplied by Amriya Pharm. Ind. Co., Alexanderia, Egypt. Eudragit® E-100 (EE) (Röhm Pharma, Darmstadt, Germany). Chitosan (high molecular weight, Sigma-Aldrich Chemie, Germany). Potassium bromide for (FT-IR) (UVasol®, Merck, Darmstadt, Germany). All other solvents and chemicals used in this study were of analytical grade.

Preparation of solid dispersions

Ketoprofen solid dispersions with cationic polymers were prepared using the solvent evaporation approach. First, a solution of sodium acetate buffer (pH 4.5) was used to dissolve the required amount of either EE or CH (2% w/v). Next, a specific amount of KETO-ethanol solution in different drug:polymer ratios(**Table 1**)was added to the polymer solution while being magnetically stirred at 1500 rpm. Alcohol was removed using rotary evaporator (Stuart RE300 Rotary Evaporator, UK). Then, the viscous residues were dried at 40℃ for a period of 48 h. Using a pestle and mortar, the dry materials were grounded and passed through a sieve with a mesh size of 60. All of the developed formulations were stored in an airtight containers in a desiccator until further investigation.

Table 1: Composition of ketoprofen-solid dispersion formulations

Formulation code	Ratio of drug	Ratio of chitosan	Ratio of EE
KETO-CH-13	1	3	
KETO-CH-12	1	2	
KETO-CH-11	1	1	
KETO-EE-13	1		3
KETO-EE-12	1		2
KETO-EE-11	1		1

Ketoprofen(KETO), Eudragit E(EE), Chitosan(CH)

Determination of percentage yield and drug content:

After weighing all of the prepared SD formulations, the yield was determined in percent using the following equation:

$$\%yield = \frac{Weight\ of\ dried\ dispersion}{Weight\ of\ pure\ ketoprofen + polymer} X100$$

After precisely weighing and dissolving 50 mg of each formulation in 10 ml of ethanol, filtering the mixture with a 0.22 µm syringe filter, and the samples were measured spectrophotometrically at 260 nm after diluting with 0.1 N HCl. The drug content was calculated by the following equation[26]:

$$Drug\ content = \frac{Sample\ of\ 50\ Absorbance\ mg\ of\ formulation}{Absorbance\ of\ 50\ mg\ pure\ ketoprofen} X100$$

***In-vitro* dissolution studies**

In-vitro dissolution studies were carried out for pure drug and SDs in 900 ml of 0.1NHCl at 37 ± 0.5 °C using USP type II dissolution test apparatus (PTWS 120S, PHARMATEST, Germany) at speed of 50 rpm. Accurately weighed amounts of pure KETO and SDs equivalent to 50 mg drug were used for the dissolution studies. Aliquots of 5 ml were withdrawn with replacements of fresh medium at predetermined intervals of 15,

30, 45, 60, 90 and 120 min and filtered through 0.22 µmsyring filter. The withdrawn samples were analyzed for the drug content using UV-VIS spectrophotometer (6800 UV/VIS, Jenway, UK) at 260 nm against 0.1 N HCl. The %cumulative dissolved KETO was calculated and plotted against time. For each formulation, three measurements were carried out. DD120 (%drug dissolved from different formulae within 120 min) were calculated and used for comparison.

Statistical analysis

The results are shown as mean ± SD (n = 3). One-way analysis of variance (ANOVA), followed by the Tukey-Kramer multiple comparison test with a level of significance of $p < 0.05$, were used to determine the statistical significance of the differences in the percent of drug dissolved with InstatGraphpad prism software (version 9.4.1, San Diego, California).

Drug dissolution kinetics

In-vitro drug dissolution data were analyzed using first-order, zero-order, and diffusion-controlled release models. The Korsmayer-Peppas kinetic model, which represents the logarithmic relation of the fraction of drug released (m_t/m_∞) against the release time (t), was also used to confirm the release mechanism. Where, k is the kinetic constant, and n is the slope of log m_t/m_∞ vs log t, which represents the diffusional exponent for drug release. The release mechanism of KETO from SDs was proposed to be explained by model of the highest correlation coefficient (r^2).

Fourier Transform Infrared (FT–IR) Spectroscopy

In order to evaluate the interaction of polymers with the drug, the spectra of drug, polymers, optimum SDs, and the associated physical mixtures were determined using a FT-IR spectrophotometer (Thermo Fisher Scientific, Inc., Waltham, MA, USA). Two hundred mg of potassium bromide was added to about two milligrams of each sample, ground and compressed into discs with a hydraulic press. Eachdisc was scanned over the range of 500–4000 cm^{-1}. All samples were recorded for their characteristic bands.

Differential Scanning Calorimetry (DSC)

A differential scanning colorimeter (Shimadzu, Tokyo, Japan) was used to examine the thermal characteristics of drug, polymers, optimum SDs, and the related physical mixtures. Samples (4 mg) were heated between 50 and 450°C at heating rates of 10 °C/min while being heated in aluminum crimped pans under nitrogen gas flow. Indium (99.99% purity, m.p. 156.6 °C) was used as a standard during temperature calibration in DSC runs.

III. Resultsand Discussion

Percentage yield and drug content

To evaluate the effectiveness of the procedure used, the produced formulations were evaluated for %product yield and %drug content (**Table 2**). It is obvious that, all the prepared formulations produced high product yields ranging from 85.46 ± 0.72 to 92.96% ± 0.32. The drug content is in the range of 91.34± 1.76 to 97.99% ± 2.09 which lie within the accepted pharmacopeial limits. It has been hypothesized that, formulae with the highest drug content weredue to greater polymer concentrations in the SDs[26].

Table 2: Percentyield, % drug content and DD120 of KETO-SDs

Formulation code	% Yield	% Drug content	DD120
KETO-CH-13	92.96 ± 0.32	96.06 ± 0.19	99.66 ±4.50
KETO-CH-12	91.96 ± 0.65	92.34 ± 2.14	90.66 ± 4.04
KETO-CH-11	89.46 ± 0.72	91.34± 1.76	82.92 ±5.49
KETO-EE-13	90.96 ± 0.32	97.99 ± 2.09	96.33 ± 3.21
KETO-EE-12	88.96 ± 0.65	95.34 ± 1.29	98.13 ±1.15
KETO-EE-11	85.46 ± 0.72	92.34 ± 0.98	99.33 ± 5.13

Ketoprofen(KETO), Eudragit E(EE), Chitosan(CH), DD120(% drug dissolved during 120 min)

***In-vitro*dissolution rate**

Dissolution of KETO in addition to its SDs with EE or CH were performed in 0.1NHCl. DD120min (% drug dissolved during 120 min) were used for comparison and are illustrated in **Table 2**. Clearly, KETO dissolution was significantly ($P<0.05$) faster from all investigated SDs compared to the pure drug, where pure KETO dissolves with a very slow onset (DD120 min value 20.83%).

Dissolution curves of KETO-CH SDs at different drug:polymer ratios 1:1, 1:2&1:3 in reference to pure KETO over a period of 120 min are shown in **Fig. 1**. It can be clearly observed that, KETO-CH SDs significantly enhanced the dissolution rate of KETO ($P<0.05$) within 120 min as compared to pure KETO. Moreover, DD120min value significantly increased by increasing KETO:CH ratio from 1:1 to 1:3. Where,

DD120 min values were 82.92±5.49, 90.66±4.04 and 99.66±4.5 for KETO-CH-11, KETO-CH-12, KETO-CH-13 respectively. Similar outcomes were previously reported that, there was a noticeable improvement in theKETO dissolution relative to the amount of added polymer. By greatly expanding the contact area of KETO molecules with solutions, chitosan in dispersions may improve the drug solubility through improving wettability and reducing agglomeration of KETO molecules[20].

Fig. 2. shows the dissolution profiles of pure KETO, its SDs with EE at different drug:polymer ratios 1:1, 1:2, 1:3 over a period of 120 min. An obvious increase in the drug dissolution rate from KETO-EE SDs in 0.1 N HCl was clear compared to the pure drug. Gue et al., 2013[27] reported a significant increase in drug release rate and formation of super-saturated solutions from the KETO–EE extrudates in 0.1 M HCl. This can be attributed to the significant interactions between the COOH groups of the drug and the tertiary ammonium groups of the polymer resulting in molecular dispersion of the drug within the polymeric system, forming one single phase. Additionally, the hydrophilic carrier pH-dependent property, which promptly dissolves and exposes the drug to the dissolution medium in the form of fine particles, may also be responsible for this enhancement in dissolution[26,28]. It was also witnessed that, the ratio of polymers played a vital role in the drug dissolution rate. During the first pattern (from 0 to 60 min.) of dissolution curves in **Fig.2**, the drug dissolution rate from KETO-EE 13 was slightly slower compared to KETO-EE 12 and KETO-EE 11 which is a different behavior compared to KETO-CH SDs. This can be explained by the fact that, as the EE concentration rises, denser polymer networks form, providing greater resistance to the dispersion of water and drugs[27,29]. After that, no significant difference (P >0.05) was observed where, DD120 min values were 99.33±5.13, 98.13±1.15 and 96.63±3.21 from KETO-EE-11, KETO-EE-12, KETO-EE-13, respectively.

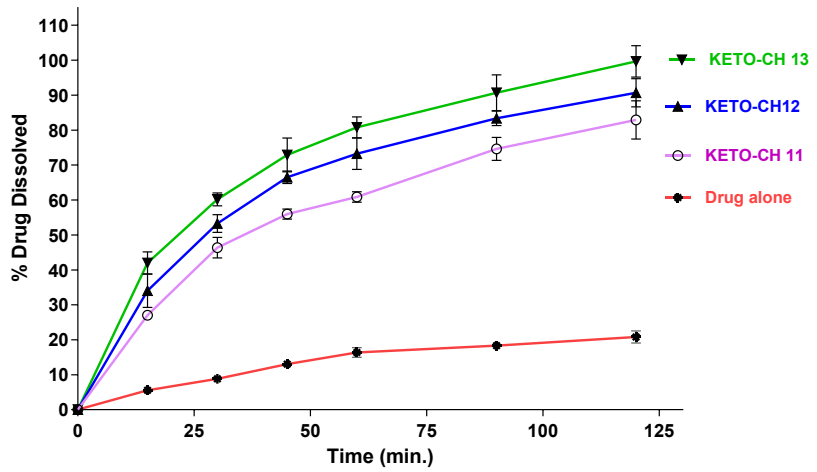

Fig.1 :*In-vitro* dissolution profiles of ketoprofen from chitosan solid dispersions in 0.1N HCl.

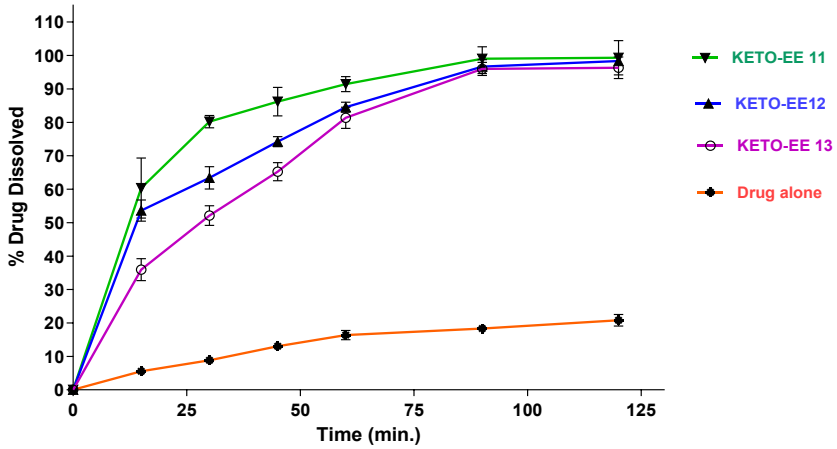

Fig.2 :*In-vitro* dissolution profiles of ketoprofen from Eudragit E solid dispersions in 0.1N HCl.

Table 3. depicts the kinetic analysis results of KETO dissolution from the prepared SDs. The findings showed that, the Higuchi model, which proposed release regulated by diffusion, provided the best explanation for the *in-vitro* dissolution of KETO from these SDs 0.1 N HCl. Accordingly, Koresmyer-peppas equation

determined that, a non-Fickian mechanism best explains how the drug dissolution, since n values were 0.958 and 0.994 (i.e. 0.5 < n < 1) suggesting that, the KETO dissolution process from these matrices is anomalous, which may confirm that these matrices combine both of erosion and diffusion[30].

Table 3. Kinetic modeling of drug dissolution data

Formula	Correlation coefficient (r^2)			Release order	Koresmyer-peppas		Main Transport mechanism
	Zero order	First order	Higuchi model		(r^2)	Diffusional exponent (n)	
KETO-EE-13	0.884	0.942	0.989	Higuchi	0.979	0.994	Non-Fickian
KETO-EE-12	0.914	0.973	0.974	Higuchi	0.962	0.973	Non-Fickian
KETO-EE-11	0.774	0.960	0.966	Higuchi	0.957	0.989	Non-Fickian
KETO-CH-13	0.909	0.868	0.988	Higuchi	0.971	0.958	Non-Fickian
KETO-CH-12	0.887	0.989	0.990	Higuchi	0.976	0.981	Non-Fickian
KETO-CH-11	0.925	0.993	0.995	Higuchi	0.982	0.992	Non-Fickian

The %yield, %drug content, dissolution profile and statistical analysis suggest domineeringly favorable effects on the dissolution rate of KETO from KETO-EE-13 and KETO-CH-13, and therefore, were designated for further physical characterization by FT-IR and DSC studies.

Fourier Transform Infrared (FT–IR) Spectroscopy

To evaluate the drug-polymer interaction in the prepared SDs, FT-IR was performed, this interaction frequently results in obvious changes in the solid dispersion spectrum. The FT-IR spectra of KETO, CH, their SD and the corresponding physical mixture in ratio of 1:3 are shown in **Fig. 3**. FT-IR spectrum of pure KETO showed two distinct sharp bands at 1695&1655 cm^{-1} corresponded to the stretching vibration of the carbonyl group in the carboxylic acid and in the ketonic group, respectively. These bands are due to the fact that, in the crystalline form, KETO molecules are bound together in dimmers[31] as shown in **Fig. 4**. Chitosan FT-IR spectrum exhibits a doublet band at 1649 cm^{-1} and 1587 cm^{-1}. The band at 1649 cm^{-1} is caused by the carbonyl stretching vibration of the secondary amide group, while the other at 1587 cm^{-1} is caused by the N-H bending vibration of the amino group[32]. The FT-IR spectra of KETO-CH physical mixture (1:3) and that of the pure KETO are exactly the same with no difference observed in bands position of KETO. On the other hand, the carbonyl and amino bands widened in the KETO-CH SD spectra due to a superposition of KETO and CH bands. These findings revealed that, the drug chemical structure remained unchanged after being incorporated into the polymer[20,33].

The FT-IR spectra of KETO, EE, their SD and the corresponding physical mixture in ratio of 1:3 are shown in **Fig. 5**. EE spectrum showed an absorption band at 1733 cm^{-1} indicative of the carbonyl group, also, the distinctive functional group peak of dimethylamino group is observed between 2770 & 2824 cm^{-1}[34]. The similarities were observed in pure KETO spectra with comparison to KETO-EE physical mixture (1:3) which demonstrates that, the components of the physical mixture do not interact chemically. However, at the same drug:polymer ratio, the FT-IR spectra of KETO-EE SD is somewhat different, where, the band arising from the ketone carbonyl at 1655 cm^{-1} shifted to 1659 cm^{-1}, whereas, that corresponding to the carboxylic group of KETO at 1698 cm^{-1} was not seen and shifted to higher wave number at 1729 cm^{-1}. This behavior may be a result of the drug interaction with EE, so, disruption of the carboxylic acid dimer of the crystalline KETO occurred causing the intermolecular hydrogen bonds in the drug crystals to break down, suggesting the creation of H bond between the KETO OH group and the carbonyl group in the EE polymer. And hence, the carboxylic group stretching vibration overlapped with the ester vibrations of EE and shifted to a higher wave number and was not detectable. Consequently, the H bonding between the polymer and KETO guaranteed both the high dissolution and sustained release, which is a crucial benefit in practical application[35].

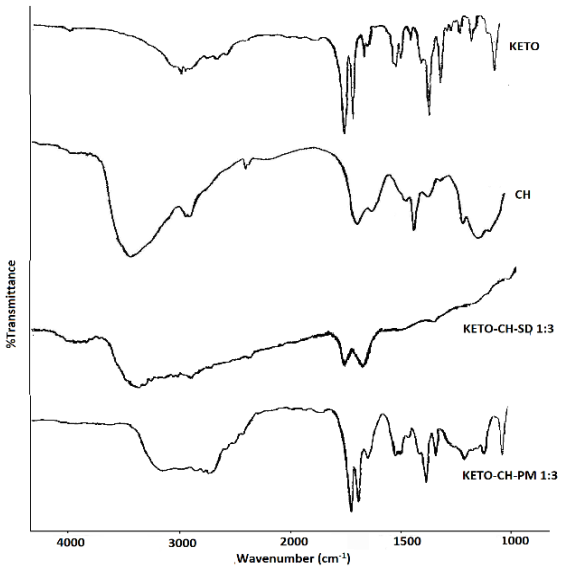

Fig. 3. FT-IR spectra of Ketoprofen (KETO), Chitosan(CH), Ketoprofen-Chitosan solid dispersion1:3 (KETO-CH SD 1:3)and Ketoprofen-Chitosan physical mixture 1:3 (KETO-CH PM 1:3).

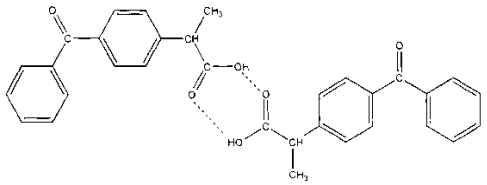

Fig. 4. Dimeric form of crystalline ketoprofen.

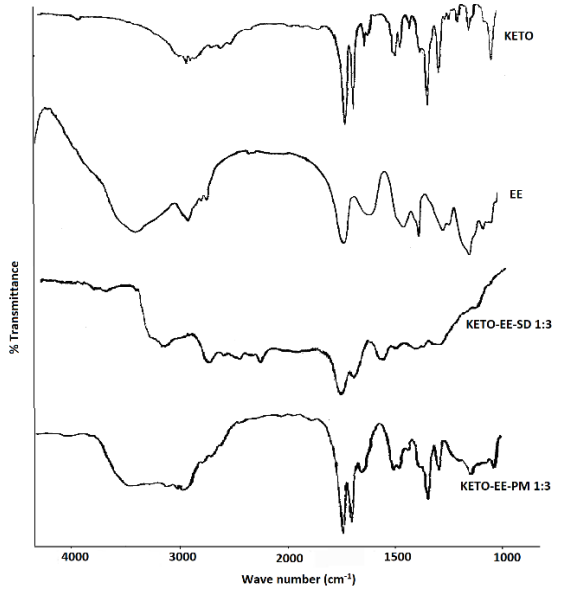

Fig. 5. FT-IR spectra of Ketoprofen (KETO),Eudragit E(EE), Ketoprofen-Eudragit E solid dispersion1:3 (KETO-EE SD 1:3) and Ketoprofen-Eudragit E physical mixture 1:3 (KETO-EE PM 1:3).

Differential Scanning Calorimetry (DSC)

The obtained DSC curves for pure KETO, CH, SD and their physical mixture at 1:3 are shown in **Fig. 6**. A melting endotherm for pure powdered KETO was visible at 96°C which corresponding to its melting point and indicated the crystalline state of the drug[20]. Scanning of CH showed an endothermic peak at 80.39°C that is broad, due to dehydration of the polymer, followed by a second exothermic one at 310°C[36]. Whereas, DSC thermograms of KETO-CH physical mixture showed the drug characteristic peak indicating the crystalline state of drug in the physical mixture, however, the height of this peak was lowered as a result of increasing carrier

concentration[7]. On the other hand, KETO-CH SD exhibited a broad endotherm with the disappearance of the sharp peak as a result of its overlapping with the broad chitosan melting peak. This finding confirmed the amorphous property of KETO inside the chitosan matrix in the solid dispersion[20,37].

Fig. 7 shows the obtained DSC curves for pure KETO, EE, the corresponding physical mixture and SD at 1:3 drug:polymer ratio. Scanning of EE showed a broad endothermic peak at 66.5°C, due to the polymer dehydration, followed by a second exothermic peak at 340°C, corresponding to the melting point of the polymer[38]. The DSC thermogram of KETO-EE SD showed a broad endothermal peak at 64.8 ºC corresponding to EE with complete disappearance of the KETO melting peak at 96°C. The complete disappearance of the KETO melting peak is an indication of reduced crystallinity and improved drug-EE complexation and hence, within the EE matrix, KETO is present as an amorphous or solid solution[26,33]. The thermographic profile of KETO-EE physical mixture showed a slight modification (**Fig. 7**), where, the endothermic peak occurred at a lower temperature (86.5 ºC) and become wider in comparison to pure KETO, which was related to the molten polymer solvent effect[35,39]. Consequently, the absence of the characteristic KETO sharp peak in KETO-CH SD 13 or KETO-EE SD 13 confirmed change in the crystal form and amorphization of KETO that could be the reason for the increased dissolution rate[26].

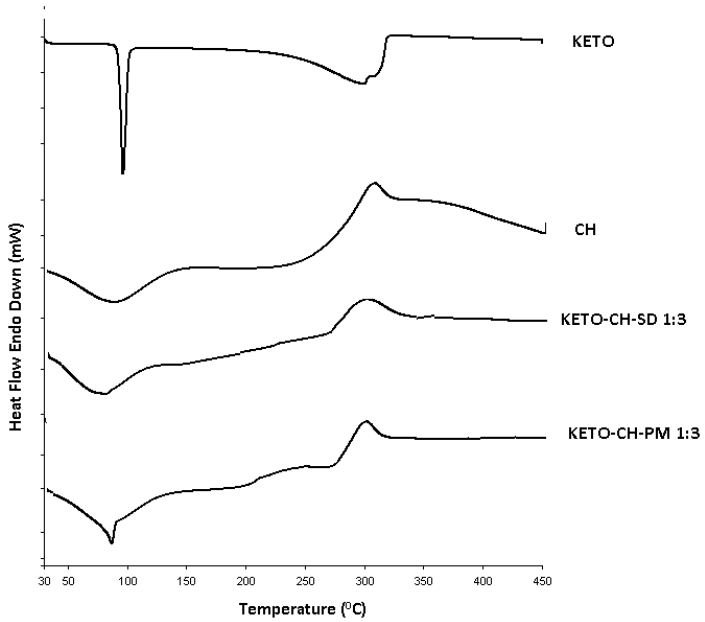

Fig. 6. DSC thermograms of Ketoprofen (KETO), Chitosan(CH), Ketoprofen-Chitosan solid dispersion1:3 (KETO-CH SD 1:3) and Ketoprofen-Chitosan physical mixture 1:3 (KETO-CH PM 1:3).

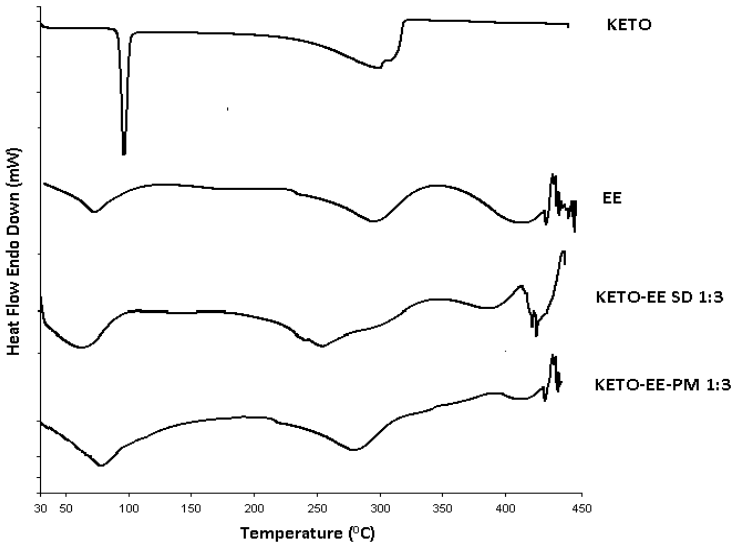

Fig. 7. DSC thermograms of Ketoprofen (KETO),Eudragit E(EE), Ketoprofen-Eudragit E solid dispersion1:3 (KETO-EE SD 1:3) and Ketoprofen-Eudragit E physical mixture 1:3 (KETO-EE PM 1:3).

IV. Conclusion

Solid dispersions of KETO with EE or CH were successfully prepared using a simple solution mixing method followed by solvent evaporation. Dissolution of KETO from these solid dispersions was significantly increased compared to pure drug and the percent increased depended on drug:polymer ratio. The release mechanism of KETO from these matrices is an anomalous which may verify that these matrices combine both erosion and diffusion. Hydrogen bonding formation between OH group in KETO and carbonyl group of EE was confirmed by FT-IR results. However, no chemical interaction was confirmed between KETO and CH in the SD. DSC measurement indicated that, KETO was dispersed in EE or CH matrices in amorphous state that might be responsible for enhanced dissolution rate. Collectively, KETO-EE SD at 1:3 drug:polymer proved to be prepared by a simple method, and at the same time guaranteed both the high dissolution and sustained release, which is a crucial benefit in practical application.

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