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SOLUBILITY AND DISSOLUTION ENHANCEMENT OF KETOTIFEN BY SOLID DISPERSION TECHNIQUE

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Ketotifen (KT) solid dispersions and physical mixtures were prepared with the objective of solubility and dissolution improvement using Hydroxypropyl-Beta-Cyclodextrin (HP-β-CD), Pluronic 127 (PF-127), Pluronic 68 (PF-68), Polyethylene glycol 6000 (PEG 6000),and Polyethylene glycol 4000 (PEG 4000). The saturation solubility and in-vitro dissolution studies showed remarkable improvement in solubility and drug dissolution of these new solid dispersions and physical mixtures over pure ketotifen. The XRD, DSC, IR and SEM studies indicated the transformation of crystalline ketotifen (in pure drug) to amorphous ketotifen (in solid dispersions). This study concluded that the improved solubility as well as drug dissolution of these new ketotifen solid dispersions may be attributed to improved wettability and reduction in drug crystallinity, which can be modulated by appropriate level of hydrophilic carriers.

INTRODUCTION

Nearly 40% of the new chemical entities currently being discovered are poorly water-soluble drugs[1]. Most formulation strategies for such drugs are targeted at enhancing their dissolution rate and/or solubility by achieving their fine dispersion at absorption level[2]. Bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate-determining step for the onset of therapeutic activity[3&4]. Therefore, poorly aqueous soluble drugs are usually characterized by low bioavailability due to their lower absorption[5]. Enhancement of bioavailability can be attained by various approaches to improve drug solubility as well as drug dissolution.

Numerous techniques have been used to increase the solubility of poor water soluble drugs which include micronization in which the enhancement of drug absorption is done via reducing its particle size[6&7], formation of inclusion complexes of drugs with α-, β-, γ-cyclodextrins by copreciptating and spray-drying[8&9], formation of the amorphous form of the drug which is a highly energetic form of the drug and usually has a lower melting point and a higher dissolution rate than the stable crystal form[10], formation of drug solid dispersions[11-13] as supersaturated systems by using diverse types of carriers, ranging widely from water-soluble to amphiphilic to lipid-soluble ones[14-18]. Solid dispersion is a group of solid products consisting, generally, of a hydrophobic drug and hydrophilic matrix[19-21]. Fast and immediate drug dissolution from solid dispersions has been observed due to increased wettability and dispersibility of drug particles, existence of the drug in amorphous form with improved solubility, and absence of aggregation of drug particles using various hydrophilic carriers[22-25].

Ketotifen is a widely used antiallergy drug with a variety of biological effects, including the inhibition of the release of myotonic mediators, leukotrienes in particular; the inhibition of slow reacting substances- induced bronchoconstriction *in-vivo*, calcium antagonistic properties, and the prevention or reversal of decreased beta-adrenoceptor sensitivity[26]. Ketotifen belongs to the second-generation H1-antihistamine drugs[27].

Ketotifen has chemical structure shown in figure 1. The molecular weight of its free form is 309.43 and the Log P is 2.2[28].

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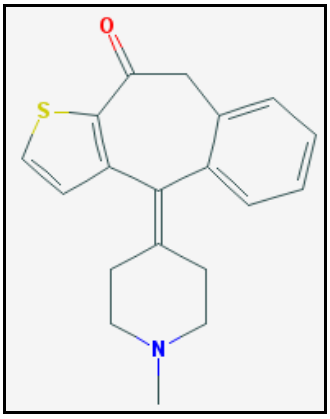


Fig. 1: The chemical structure of ketotifen.

Ketotifen is widely used as tablets, capsules, syrups, nasal drops and eye-drops (as fumarate salt). Oral ketotifen formulation is usually administered twice a day, and the dosing usually lasts for several years with daily dose of 2 mg, and the bioavailability is about 50% in humans[29]. Therefore, there is a significant need for the development of a more convenient dosage form for children, ketotifen suppository.

The objectives of this investigation are: (i) preparation of ketotifen solid dispersions and physical mixtures, (ii) characterization of newly prepared ketotifen solid dispersions and physical mixtures by X-ray diffraction (XRD), Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and Scanning electron microscopy (SEM), and (iii) estimation of drug solubility and evaluation of drug dissolution of prepared ketotifen solid dispersions and physical mixtures to compare these data with pure drug data.

EXPERIMENTAL

Materials

- Ketotifen was supplied from Pharco Co., Egypt.
- Hydroxypropyl-β-cyclodexetrin was supplied from Sigma Chemi CO; Germany.
- Pluronic F-127(PF-127) and pluronic F-68 (PF-68) were supplied from Sigma-Aldrich Chemie, Germany.
- Polyethylene glycol (PEG 6000, PEG 4000) were supplied from Sigma Chem. CO., USA.
- All chemicals were of pharmaceutical grade and were used as received.

Methods

Preparation of ketotifen solid dispersions by solvent evaporation technique

Solid dispersions of ketotifen (KT) with different polymers: Hydroxypropyl-β-cyclo-dexetrin, Pluronic F-127 (PF-127), pluronic F-68 (PF-68), Polyethylene glycols (PEG 6000, PEG 4000) at various weight ratios (1:1, 1:3, 1:5, 1:7) were prepared by the solvent evaporation method as follows. Weighed quantity of KT was dissolved in a minimum amount of absolute ethanol; the appropriate amount of each polymer was added. The resulting mixture was stirred until evaporation on magnetic stirrer and then the co-precipitates were then scrapped and stored in a desiccator over anhydrous $CaCl_2$, to constant weight. The evaporated product was ground in a mortar and passed through a sieve and stored in a desiccator until further evaluation. A specified sample of the prepared solid dispersion was assayed for the drug content.

Determination of percent drug content

Weight amount of solid dispersions, each sample equivalent to 5 mg of ketotifen were separately taken and added to 10 ml of ethanol in stoppered conical flasks. The sealed flasks were agitated on a rotary shaker for 1 hr. The solution was diluted with ethanol and was assayed by a UV-VIS spectrophotometer for drug content at 301 nm using the following expression: Percent drug content = (actual drug content in solid dispersions / theoretical drug content in solid dispersions) x 100.

Preparation of ketotifen physical mixtures

Ketotifen (KT) and solid carriers were sieved through 180 µm sieve, and then the physical mixtures in the ratios (1:1, 1:3, 1:5 and 1:7) were prepared by simple, gentle mixing using spatula and paper method. A specified sample of each prepared physical mixture was assayed for the drug content.

Determination of solubility

Saturated solubility of pure ketotifen (KT) was determined and then compared with these data of ketotifen solid dispersions and physical mixtures of respective ratios. The known excess samples (ketotifen solid dispersions, physical mixtures and pure ketotifen), 10 mg equivalent weight of ketotifen was added to 10

ml distilled water in a glass beaker covered with foil and these samples were rotated at 100 rpm in a water bath (37±0.5°C) for 24 hrs. The samples were then filtered through 0.45 µm membrane filter, suitably diluted, and analyzed by UV-VIS spectrophotometer at 301 nm wavelength. All experiments were carried out in triplicate.

Dissolution studies

Dissolution studies of pure ketotifen (KT), ketotifen solid dispersions and physical mixtures of different ratios were studied using U.S.P. XXIV (U.S.P., 2000) dissolution apparatus II (paddle type). Weighed amounts equivalent to 10 mg of KT were dispersed over 500 ml of phosphate buffer pH 7.4 at 37±0.5°C and stirred at 100 rpm for 2 hrs. At fixed time intervals, samples (2 ml) were withdrawn and equal amount of fresh dissolution medium was added. Withdrawn samples were filtered through 0.45 µm membrane filters, and spectrophotometrically assayed for drug content at 301 nm wavelengths using a UV-VIS spectrophotometer. All experiments were carried out in triplicate. The cumulative amount of the drug dissolved during the n^{th} sample (Q_n) was estimated by the following equation:

$$Q_n = C_n.V + V_s.\sum_{1=i}^{n-1} Ci$$

Where C_n is the measured concentration in the n^{th} sample, V is the volume of dissolution medium and V_s is the volume of sample[26&27].

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of drug alone, the selected physical mixtures and solid dispersions were done at the scanning range of 400-4000 cm^{-1}. Potassium bromide (KBr) disk method was used. The samples were ground, mixed thoroughly with KBr and compressed at a pressure of 6 ton/cm^2 using IR compression machine.

Differential scanning calorimetry (DSC) analysis

The samples were analyzed by DSC-50 differential scanning calorimeter (Shimadzu, Seisakusho Ltd, Kyoto, Japan). Samples (3-5) mg were accurately weighed into solid aluminum pans and heated at a scanning rate of 10°C /min from 0-300°C in the presence of nitrogen at a flow rate of 20 ml/min.

Transition temperature (°C) and heats of fusion of melting endotherms on the thermograms were calculated using the DSC-T50 program, which directly integrates the melting endothermic peaks giving the heat of fusion (ΔH, Joule/g).

Powder-X-ray diffraction (p-XRD) studies

Powder X-ray diffraction patterns were recorded on an X-diffractometer Phillips PW 1050 (Bragg-Brentano), the radiation used was generated by a copper Kα filter, with a wavelength of 1.5418 A° at 40 mA and 35 kV. Samples were scanned over a range of 2θ values from 4° to 60° at a scanning rate of 0.06°/min.

Scanning electron microscopy (SEM)

The SEM analysis was carried out using a JSM- 6400 (Jeol, Japan) by coating the samples with a thin layer of gold using ion sputtering at 15 kV. Digital images of the samples were obtained.

RESULTS AND DISCUSSION

Determination of solubility

The Amount solubilized of KT in water at 37°C from its solid dispersions (SD.) and physical mixtures (P.MIX.) using different carriers at different drug: carrier ratios (1:7, 1:5. 1:3, 1:1) are displayed in tables 1,2.

It is clear that HP-β-CD > PF-127 > PF-68 > PEG 6000 > PEG 4000 in solubilizing effect on KT. Also it was noted that as the amount of polymer increased, the amount of drug solubilized increased.

The maximum amount solubilized was in solid dispersion containing 7 parts of HP-β-CD. The high affinity to HP-β-CD might be due to the hydrophilicity of HP-β-CD, which gave good adjustment of KT to the cyclodextrin cavity. The higher solubilizing effect of PF-127 over PF-68 could be due to more lipophilicity of PF-127 than PF-68 resulting in more interaction with lipophilic part of KT[30]. In the case of PEG 6000 the hydrophilic effect increased with the increase in the polymer chain than PEG 4000, supporting the humectation of the drug leading to enhancement in aqueous solubility.

Table 1: Solubility of ketotifen (KT) from its solid dispersions (SDs.) with different carriers in water at 37°C.

Carrier	Amount solubilized of KT (mg/ml)			
	1:7	1:5	1:3	1:1
PF-127	0.225 ± 0.087	0.195 ± 0.044	0.183 ± 0.019	0.154 ± 0.023
PF-68	0.189 ± 0.013	0.165 ± 0.032	0.142 ± 0.076	0.124 ± 0.091
PEG 6000	0.180 ± 0.042	0.151 ± 0.079	0.118 ± 0.083	0.112 ± 0.0112
PEG 4000	0.157 ± 0.063	0.133 ± 0.071	0.103 ± 0.094	0.094 ± 0.056
HP-β-CD	**0.408 ± 0.083**	0.342 ± 0.076	0.301 ± 0.023	0.157 ± 0.099

Solubility of KT in water at 37°C was 0.**0411** mg/ml.

Table 2: Solubility of ketotifen (KT) from its physical mixtures (P.MIXs.) with different carriers in water at 37°C.

Carrier	Amount solubilized of KT (mg/ml)			
	1:7	1:5	1:3	1:1
PF-127	0.195 ± 0.083	0.159 ± 0.097	0.139 ± 0.015	0.124 ± 0.067
PF-68	0.145 ± 0.066	0.115 ± 0.045	0.103 ± 0.074	0.094 ± 0.09
PEG 6000	0.136 ± 0.0563	0.1 ± 0.029	0.088 ± 0.02	0.068 ± 0.076
PEG 4000	0.118 ± 0.0354	0.091 ± 0.078	0.077 ± 0.0299	0.047 ± 0.0432
HP-β-CD	**0.337 ± 0.059**	0.284 ± 0.084	0.248 ± 0.043	0.136 ± 0.085

Solubility of KT in water at 37°C was **0.0411** mg/ml.

Dissolution studies

The dissolution of KT in phosphate buffer (PH 7.4) at 37°C and from its solid dispersions (SD.) and physical mixtures (P.MIX.) using different carriers at drug: Carrier ratios (1:7), (1:5), (1:3) and (1:1) are displayed in tables 3-10 and figures 2-9.The results obtained show that:

The improvement of dissolution rates of KT by different carriers was ranked as: HP-β-CD > PF-127 > PF-68 > PEG 6000 > PEG 4000.

The percent of drug dissolved from solid dispersions (SD.) was higher than the percent of drug dissolved from physical mixtures (P.MIX.) which in turn was higher than that dissolved from the untreated drug.

Dissolution rate of KT increased by increasing the ratio of the carrier used. This is might be due to conversion of the drug from crystalline form into an amorphous one. Also might be due to the particle size reduction of the drug. Moreover, polymers encircling the drug leading to decrease the aggregation of drug particles allowing faster dissolution.

Fourier transform infrared spectroscopy (FT-IR)

In the IR spectrum illustrated in figure 10. KT shows its characteristic peaks at 3097.1 cm^{-1} assigned for thiophene group Stretching, 3000-2840 cm^{-1} assigned to aromatic stretching, 1650 cm^{-1} for carbonyl group[31].

The spectrum of HP-β-CD illustrated an intense broad band at 3500-3300 cm^{-1} corresponding to the free –OH stretching vibration[32].

The spectra of pluronic copolymers (Figs. 11-12) showed broad band of –OH stretching vibration from 3330 to 3710 cm^{-1} for PF-127 and 3355-3610 cm^{-1} for PF-68. C-H stretching of OCH groups from 2900 to 3095 cm^{-1} and C-H stretching from 1058 to 1144 cm^{-1} [33].

The IR spectra of PEG 4000 and PEG 6000 (Figs. 13-14) showed a characteristic band at 3000 cm^{-1} corresponding to $-OCH_3$ stretching[34].

The spectra of the physical mixtures (P.MIX.) at the ratio of 1:7 of KT with different polymers were superposition of pure components spectra, indicating the absence of interaction between KT and any polymer used[35].

Table 3: Shows *in-vitro* dissolution of pure KT and its solid dispersions with different carriers at ratio 1:7 (drug : carrier) in phosphate buffer at 37ºC.

Time (min.)	% Dissolved of Ketotifen (KT)					
	Drug alone	HP-β-CD	PF-127	PF-68	PEG 6000	PEG 4000
5	22.03 ± 0.465	**99.97 ±** 0.231	85.17 ± 0.924	81.799 ± 0.555	73.05 ± 0.144	70.98 ± 0.228
10	24.14 ± 2.061	**100** ± 0.456	94.94 ± 1.89	90.55 ± 1.077	76.71 ± 0.153	75.4 ± 0.678
15	27.61 ± 2.412	**100** ± 1.096	100 ± 0.633	99.89 ± 2.613	84.69 ± 0.333	80.85 ± 2.642
30	33.42 ± 2.069	**100** ± 0.672	100 ± 1.021	100 ± 0.285	91.49 ± 1.98	86.699 ± 1.782
60	38.33 ± 1.957	**100** ± 0.343	100 ± 0.103	100 ± 0.178	94.04 ± 1.53	90.32 ± 1.851
120	40.25 ± 3.888	**100** ± 0.906	100 ± 1.001	100 ± 1.808	99.86 ± 0.036	93.98 ± 0.912

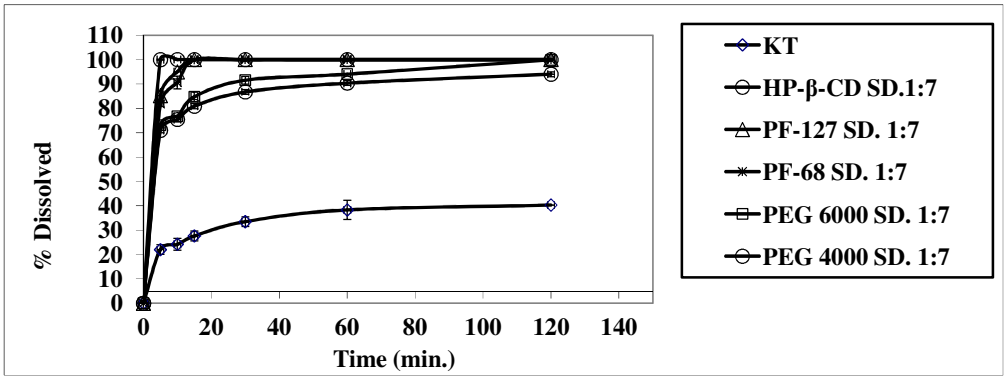


Fig. 2: Shows *in-vitro* dissolution profiles of pure KT and its solid dispersions with different carriers at ratio 1:7 (drug: carrier) in phosphate buffer at 37ºC.

Table 4: Shows *in-vitro* dissolution of pure KT and its solid dispersions with different carriers at ratio 1:5 (drug: carrier) in phosphate buffer at 37ºC.

Time (min.)	% Dissolved of Ketotifen (KT)					
	Drug alone	HP-β-CD	PF-127	PF-68	PEG 6000	PEG 4000
5	22.03 ± 0.465	**98.49 ± 1.122**	81.9 ± 0.993	78.14 ± 0.224	70.92 ± 1.239	64.03 ± 0.345
10	24.14 ± 2.061	**99.3 ± 0.786**	92.4 ± 1.541	80.68 ± 0.768	74.81 ± 2.604	69.17 ± 0.752
15	27.61 ± 2.412	**100 ± 0.539**	96.1 ± 1.023	83.75 ± 2.675	77.63 ± 1.783	73.31 ± 1.006
30	33.42 ± 2.069	**100 ± 0.34**	99.33 ± 2.043	89.73 ± 0.923	81.59 ± 0.945	79.12 ± 0.982
60	38.33 ± 1.957	**100 ± 0.681**	100 ± 0.971	92.33 ± 1.033	86.42 ± 1.845	83.11 ± 0.347
120	40.25 ± 3.888	**100 ± 0.0237**	100 ± 0.084	96.71 ± 1.785	88.89 ± 1.312	85.68 ± 0.189

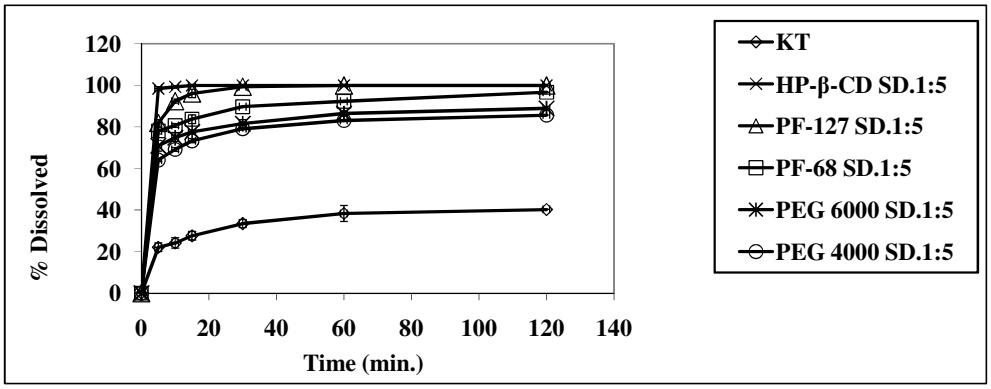


Fig. 3: Shows *in-vitro* dissolution profiles of pure KT and its solid dispersions with different carriers at ratio 1:5 (drug: carrier) in phosphate buffer at 37ºC.

Table 5: Shows *in-vitro* dissolution of pure KT and its solid dispersions with different carriers at ratio 1:3 (drug: carrier) in phosphate buffer at 37ºC.

Time (min.)	% Dissolved of Ketotifen (KT)					
	Drug alone	HP-β-CD	PF-127	PF-68	PEG 6000	PEG 4000
5	22.03 ± 0.465	**91.09 ± 1.137**	80.13 ± 0.184	73.44 ± 0.275	60.49 ± 0.986	57.14 ± 1.098
10	24.14 ± 2.061	**95.77 ±** 0.952	84.11 ± 0.241	75.02 ± 0.179	61.30 ± 1.2785	59.33 ± 2.003
15	27.61 ± 2.412	**98.54 ±** 0.291	86.47 ± 0.168	76.19 ± 0.154	65.17 ± 1.504	60.11 ± 1.613
30	33.42 ± 2.069	**100 ± 0.725**	89.07 ± 0.173	80.37 ± 0.184	69.33 ± 0.6733	64.12 ± 0.556
60	38.33 ± 1.957	**100 ± 0.82**	90.88 ± 0.278	84.74 ± 0.122	71.41 ± 0.954	68.05 ± 1.093
120	40.25 ± 3.888	**100 ± 0.63**	93.98 ± 0.497	85.98 ± 0.144	75.03 ± 0.2938	69.99 ± 0.394

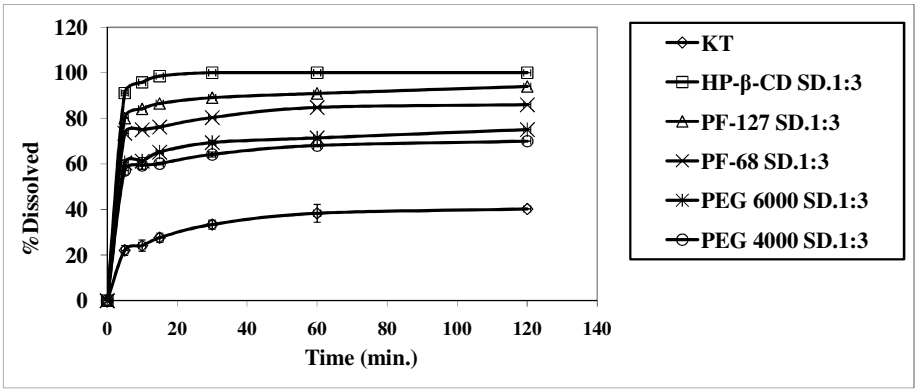


Fig. 4: Shows *in-vitro* dissolution profiles of pure KT and its solid dispersions with different carriers at ratio 1:3 (drug: carrier) in phosphate buffer at 37ºC.

Table 6: Shows *in-vitro* dissolution of pure KT and its solid dispersions with different carriers at ratio 1:1 (drug: carrier) in phosphate buffer at 37ºC.

Time (min.)	% Dissolved of Ketotifen (KT)					
	Drug alone	HP-β-CD	PF-127	PF-68	PEG 6000	PEG 4000
5	22.03 ± 0.465	**89.02 ± 0.3544**	67.42 ± 1.467	59.79 ± 0.761	58.90 ± 2.178	53.81 ± 0.782
10	24.14 ± 2.061	**93.06 ±** 0.2499	69.22 ± 2.964	62.04 ± 1.453	59.99 ± 1.239	54.41 ± 0.459
15	27.61 ± 2.412	**95.96 ±** 0.7237	72.63 ± 1.004	65.87 ± 1.249	60.28 ± 0.942	55.90 ± 1.379
30	33.42 ± 2.069	**97.88 ±** 0.3608	76.20 ± 0.9504	68.18 ± 0.974	63.78 ± 0.641	61.24 ± 1.746
60	38.33 ± 1.957	**100 ± 0.569**	77.97 ± 0.348	71.55 ± 1.735	66.90 ± 1.677	62.93 ± 0.894
120	40.25 ± 3.888	**100 ± 0.72**	81.10 ± 1.515	73.91 ± 1.345	69.07 ± 1.291	65.17 ± 0.537

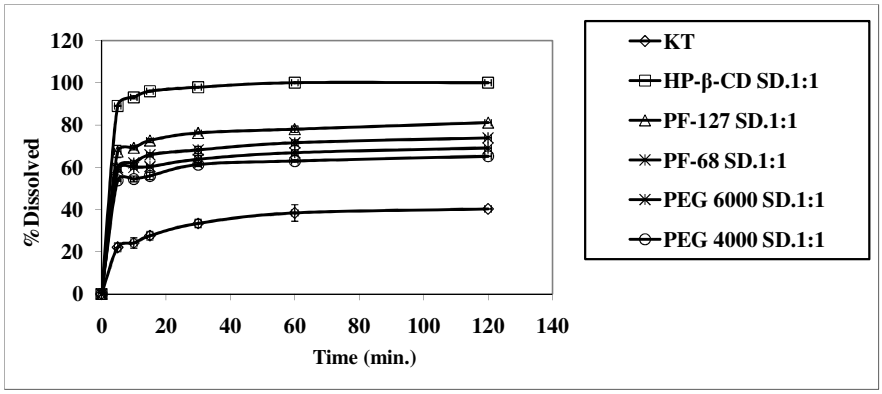


Fig. 5: Shows *in-vitro* dissolution profiles of pure KT and its solid dispersions with different carriers at ratio 1:1 (drug: carrier) in phosphate buffer at 37ºC.

Table 7: Shows *in-vitro* dissolution of pure KT and its physical mixtures with different carriers at ratio 1:7 (drug: carrier) in phosphate buffer at 37ºC.

Time (min.)	% Dissolved of Ketotifen (KT)					
	Drug alone	HP-β-CD	PF-127	PF-68	PEG 6000	PEG 4000
5	22.03 ± 0.465	**82.2 ±** 0.87	72.4 ± 0.576	67.3 ± 0.889	63.57 ± 0.355	58.55 ± 1.267
10	24.14 ± 2.061	**94.5 ±** 0.9111	84.88 ± 1.912	76.11 ± 0.495	70.97 ± 1.908	65.5 ± 0.435
15	27.61 ± 2.412	**99.19 ±** 2.652	94.32 ± 2.345	85.63 ± 0.777	75.82 ± 1.008	68.59 ± 0.966
30	33.42 ± 2.069	**100 ±** 0.712	100 ± 1.014	91.96 ± 0.233	82.55 ± 2.542	74.26 ± 1.89
60	38.33 ± 1.957	**100 ±** 0.903	100 ± 0.71	98.96 ± 0.288	87.4 ± 1.099	79.5 ± 0.964
120	40.25 ± 3.888	**100 ±** 1.89	100 ± 0.443	99.87 ± 0.972	93.96 ± 0.367	82.95 ± 0.563

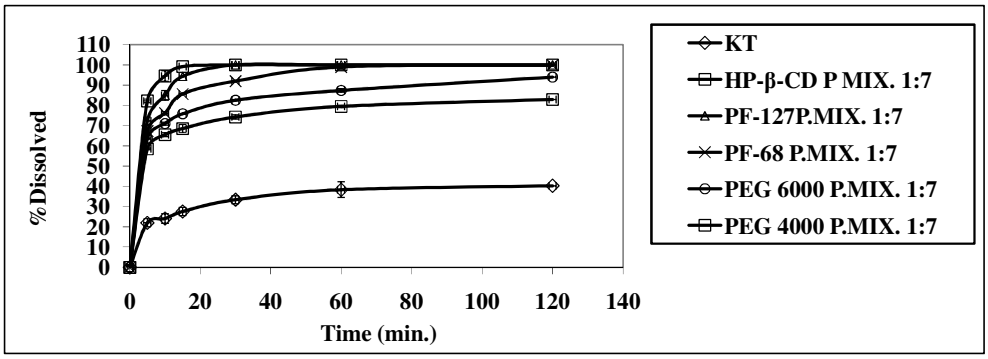


Fig. 6: Shows *in-vitro* dissolution profiles of pure KT and its physical mixtures with different carriers at ratio 1:7 (drug: carrier) in phosphate buffer at 37ºC.

Table 8: Shows *in-vitro* dissolution of pure KT and its physical mixtures with different carriers at ratio 1:5 (drug: carrier) in phosphate buffer at 37ºC.

Time (min.)	% Dissolved of Ketotifen (KT)					
	Drug alone	HP-β-CD	PF-127	PF-68	PEG 6000	PEG 4000
5	22.03 ± 0.465	**77.03 ± 1.2784**	69.98 ± 2.011	66.11 ± 0.783	60.08 ± 1.187	56.91 ± 1.844
10	24.14 ± 2.061	**80.22 ± 0.8153**	72.14 ± 0.918	70.03 ± 0.914	61.39 ± 1.834	58.08 ± 1.983
15	27.61 ± 2.412	**82.40 ± 0.9144**	79.21 ± 0.734	75.19 ± 1.340	65.02 ± 0.723	59.92 ± 2.431
30	33.42 ± 2.069	**96.01 ± 0.3987**	85.90 ± 1.145	81.06 ± 1.921	74.48 ± 0.980	63.18 ± 1.313
60	38.33 ± 1.957	**99.91 ± 0.2143**	89.90 ± 1.632	83.97 ± 0.873	83.57 ± 1.058	69.96 ± 1.007
120	40.25 ± 3.888	**100 ± 0.93**	95.01 ± 0.653	89.99 ± 0.659	85.32 ± 2.30	71.98 ± 0.786

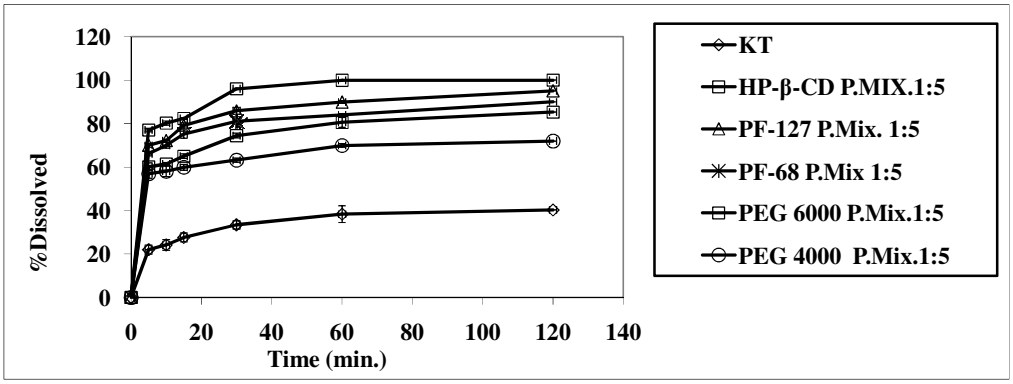


Fig. 7: Shows *in-vitro* dissolution profiles of pure KT and its physical mixtures with different carriers at ratio 1:5 (drug: carrier) in phosphate buffer at 37ºC.

Table 9: Shows *in-vitro* dissolution of pure KT and its physical mixtures with different carriers at ratio 1:3 (drug: carrier) in phosphate buffer at 37ºC.

Time (min.)	% Dissolved of Ketotifen (KT)					
	Drug alone	HP-β-CD	PF-127	PF-68	PEG 6000	PEG 4000
5	22.03 ± 0.465	**73.9 ± 1.041**	63.45 ± 0.448	64.23 ± 2.003	57.43 ± 1.824	40.4 ± 0.445
10	24.14 ± 2.061	**78.15 ± 1.1454**	71.02 ± 1.1276	65.90 ± 0.982	58.97 ± 1.671	41.97 ± 0.676
15	27.61 ± 2.412	**79.97 ± 0.843**	75.14 ± 0.8452	67.11 ± 0.634	60.15 ± 0.569	43.67 ± 0.926
30	33.42 ± 2.069	**90.03 ± 1.9201**	83.55 ± 0.9134	74.59 ± 1.409	64.22 ± 1.091	48.79 ± 0.328
60	38.33 ± 1.957	**95.13 ± 0.5233**	87.62 ± 0.567	77.42 ± 2.281	66.71 ± 0.875	50.78 ± 0.993
120	40.25 ± 3.888	**98.44 ± 0.794**	91.42 ± 0.9978	79.17 ± 0.869	70.19 ± 0.349	56.09 ± 1.165

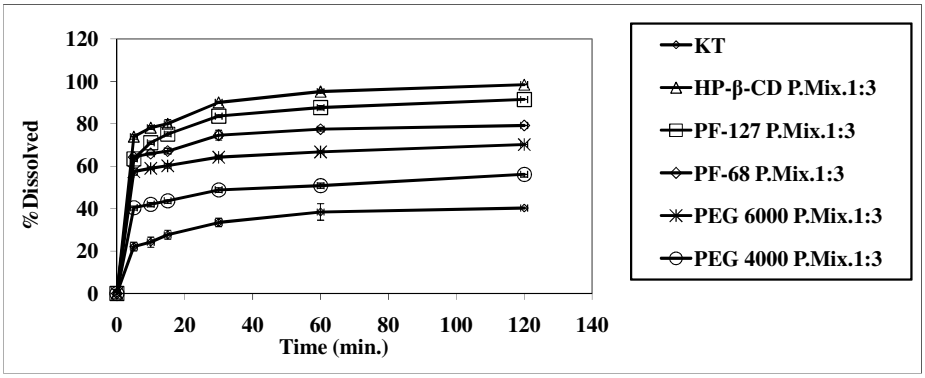


Fig. 8: Shows *in-vitro* dissolution profiles of pure KT and its physical mixtures with different carriers at ratio 1:3 (drug: carrier) in phosphate buffer at 37ºC.

Table 10: Shows *in-vitro* dissolution of pure KT and its physical mixtures with different carriers at ratio 1:1 (drug: carrier) in phosphate buffer at 37ºC.

Time (min.)	% Dissolved of Ketotifen (KT)					
	Drug alone	HP-β-CD	PF-127	PF-68	PEG 6000	PEG 4000
5	22.03 ± 0.465	**70.81 ± 1.0987**	61.69 ± 1.813	60.33 ± 2.005	51.24 ± 1.571	38.73 ± 0.820
10	24.14 ± 2.061	**76.30 ± 0.6721**	63.22 ± 0.843	63.09 ± 1.249	52.5 ± 0.449	40.02 ± 0.649
15	27.61 ± 2.412	**80.01 ± 0.7906**	66.82 ± 0.239	65.87 ± 0.398	55.94 ± 0.846	41.57 ± 1.762
30	33.42 ± 2.069	**83.45 ± 1.1802**	71.97 ± 0.911	70.17 ± 1.278	59.22 ± 1.222	47.39 ± 0.673
60	38.33 ± 1.957	**89.78 ± 2.117**	74.44 ± 1.188	73.26 ± 0.874	62.48 ± 0.983	49.98 ± 1.132
120	40.25 ± 3.888	**93.16 ± 0.985**	78.89 ± 1.937	77.56 ± 0.568	67.87 ± 0.773	53.18 ± 2.009

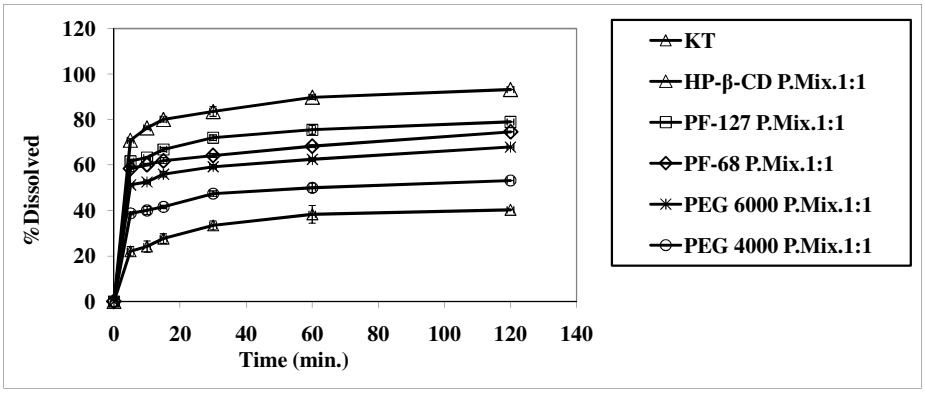


Fig. 9: Shows *in-vitro* dissolution profiles of pure KT and its physical mixtures with different carriers at ratio 1:1 (drug : carrier) in phosphate buffer at 37ºC.

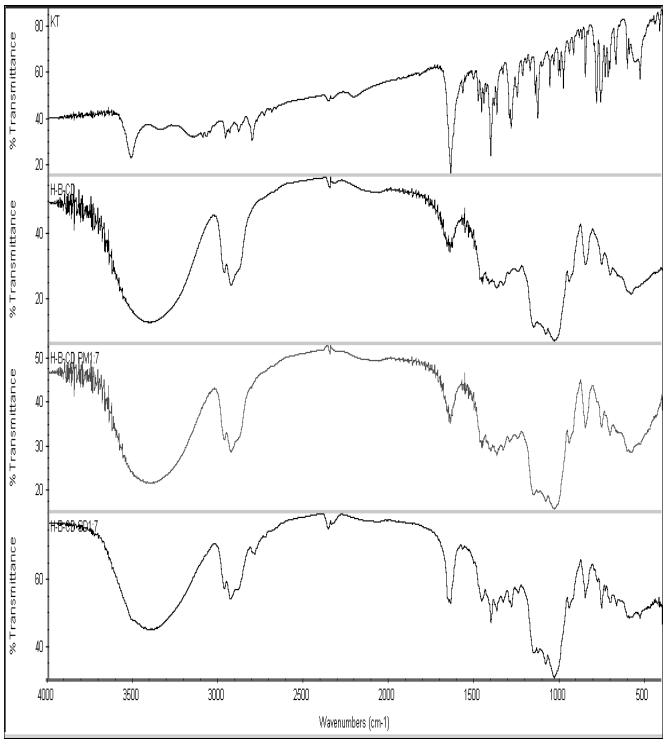


Fig. 10: Comparative study of the FTIR spectra of (a) pure drug KT; (b) HP-β-CD polymer; (c) P.MIX. 1:7; and (d) SD. 1:7.

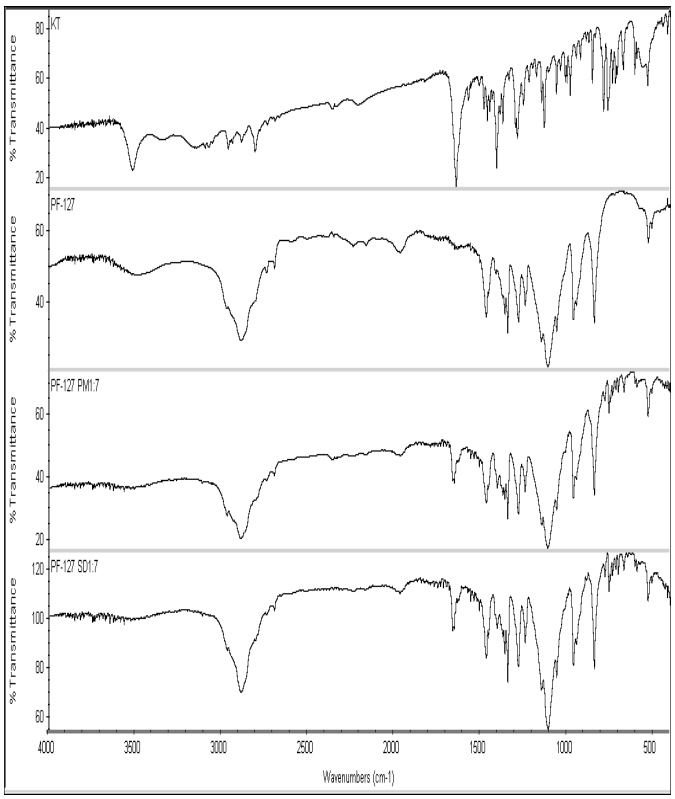


Fig. 11: Comparative study of the FTIR spectra of (a) pure drug KT; (b) PF-127 polymer; (c) P.MIX. 1:7; and (d) SD. 1:7.

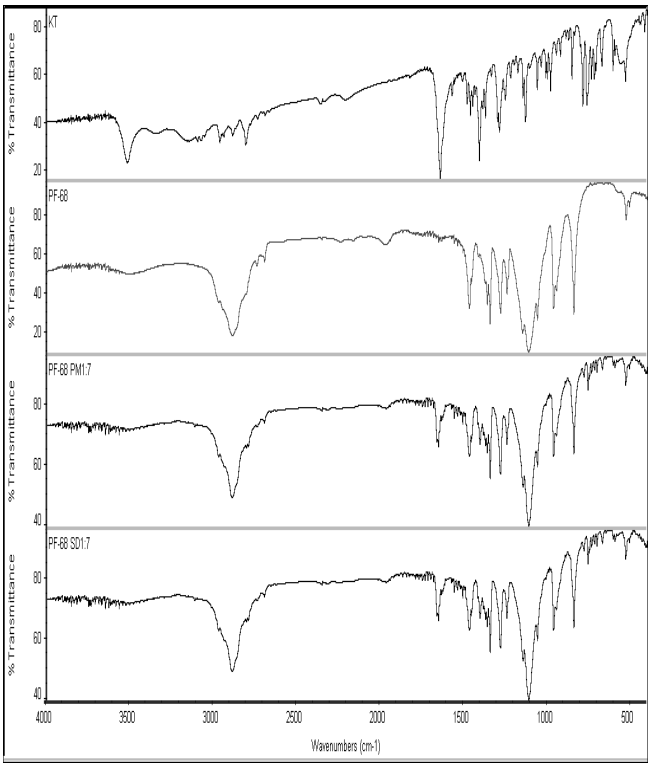


Fig. 12: Comparative study of the FTIR spectra of (a) Pure drug KT; (b) PF-68 polymer; (c) P.MIX. 1:7; and (d) SD. 1:7.

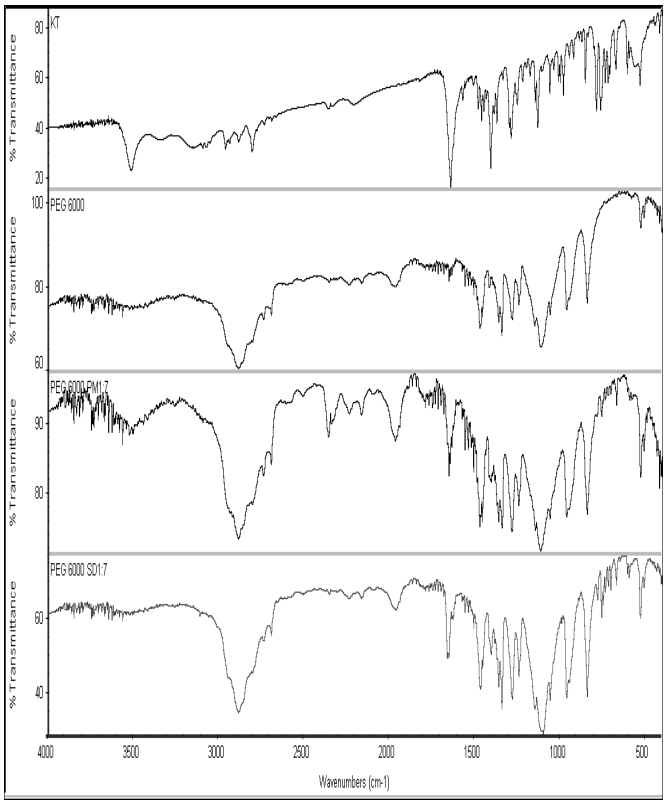


Fig. 13: Comparative study of the FTIR spectra of (a) pure drug KT; (b) PEG 6000 polymer; (c) P.MIX. 1:7; and (d) SD. 1:7.

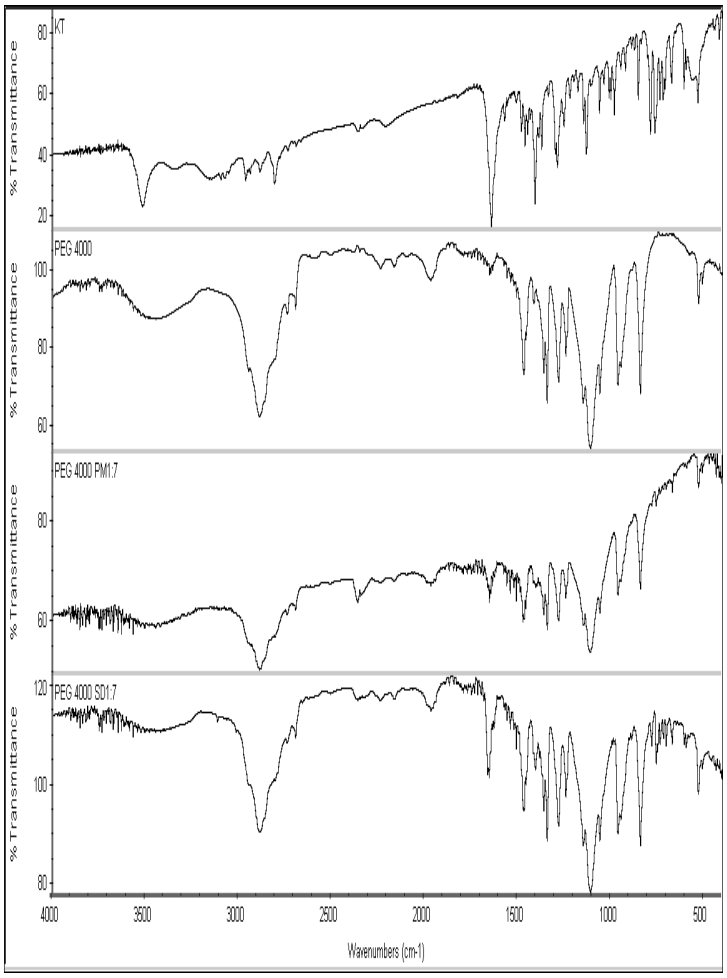


Fig. 14: Comparative study of the FTIR spectra of (a) pure drug KT; (b) PEG 4000 polymer; (c) P.MIX. 1:7; and (d) SD. 1:7.

The IR spectra of KT solid dispersions (SD.) at the ratio of 1:7 Showed the band of thiophene strongly stretched, this is might explained by the dissociation of the intermolecular hydrogen bonds associated with crystalline drug molecules and there was a decrease in intensity of drug's aromatic stretching this is might be due to the restriction of KT within the polymer cavity.

Differential scanning calorimetry (DSC) analysis

The DSC thermograms of drug (KT), different polymers (HP-β-CD, PF-127, PF-68, PEG 6000 and PEG 4000) as individual components, as well as drug: Carrier (1:7) solid dispersions and the corresponding physical mixtures are shown in figures 15-19. Table 11 shows the endothermic peaks and Δ H of KT, HP-β-CD, PF-127, PF-68, PEG 6000 and PEG 4000, their corresponding solid dispersions and physical mixtures at ratio (1:7).

KT thermogram showed endothermic peak at 157°C[31]. While the melting point of the pure polymers are 51.87, 53.6, 60.35 and 64.45°C for PF-68, PF-127, PEG 4000 and PEG 6000, respectively[33&34]. In the case of HP-β-CD owing to its amorphous nature, a broad endothermic peak was observed at about 100°C corresponding to water loss[36].

The DSC curves of the solid dispersions and physical mixtures showed one peak corresponding to the melting point of the polymers. The disappearance of the endothermic peak of KT melting in solid dispersions confirmed the presence of KT in an

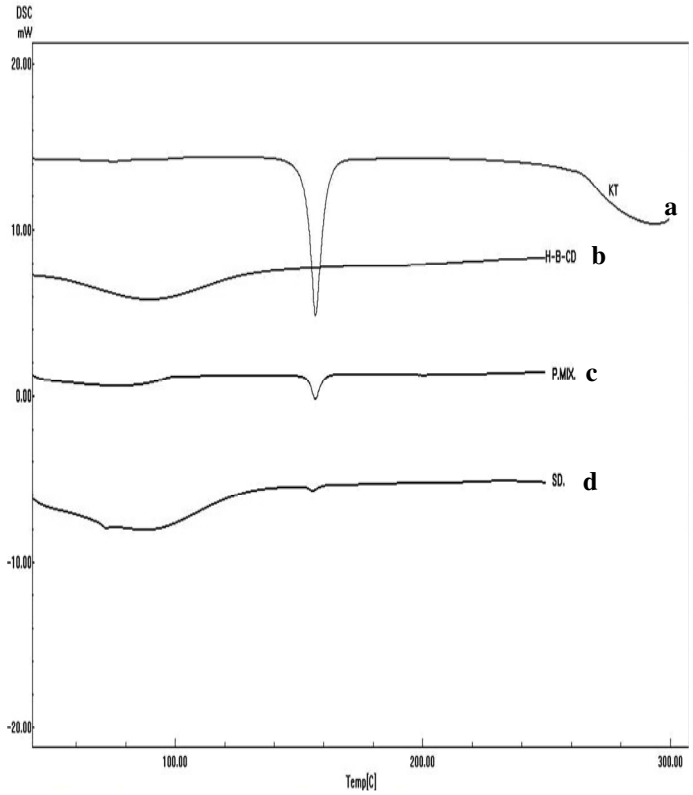


Fig. 15: Shows DSC thermograms of (a) pure drug KT, (b) HP-β-CD polymer, (c) physical mixture of KT with HP-β-CD 1:7, (d) solid dispersion of KT with HP-β-CD 1:7.

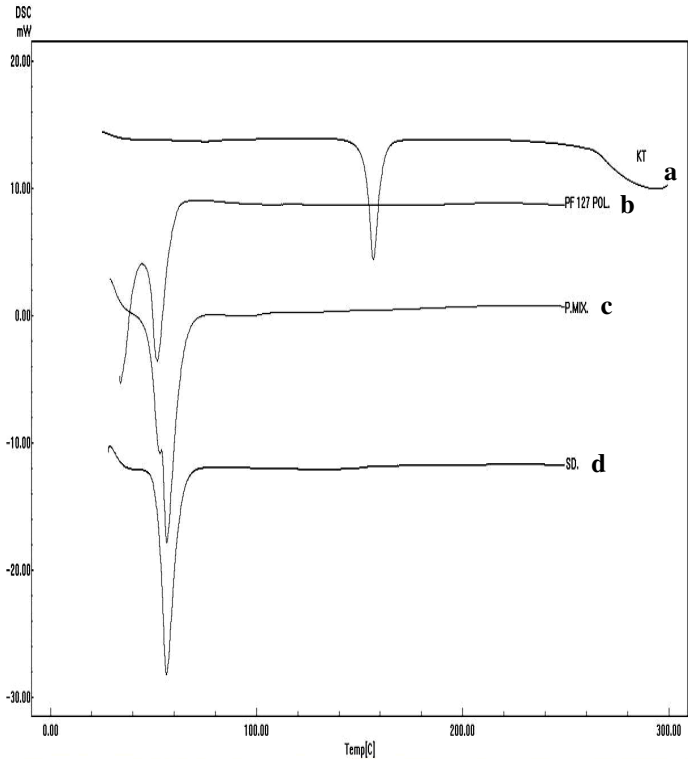


Fig. 16: Shows DSC thermograms of (a) pure drug KT, (b) PF-127 polymer, (c) physical mixture of KT with PF-127 1:7, (d) solid dispersion of KT with PF-127 1:7.

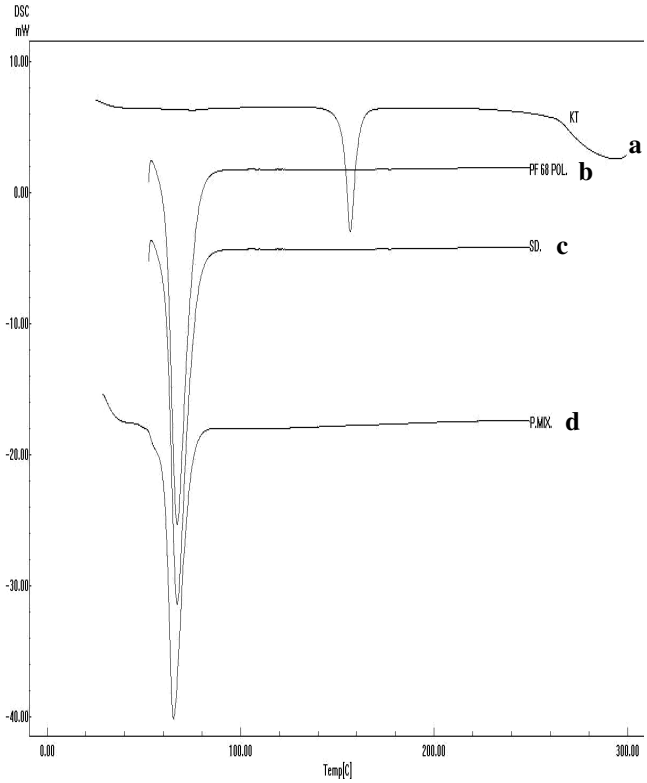


Fig. 17: Shows DSC thermograms of (a) pure drug KT, (b) PF-68 polymer, (c) solid dispersion of KT with PF-68 1:7, (d) physical mixture of KT with PF-68 1:7.

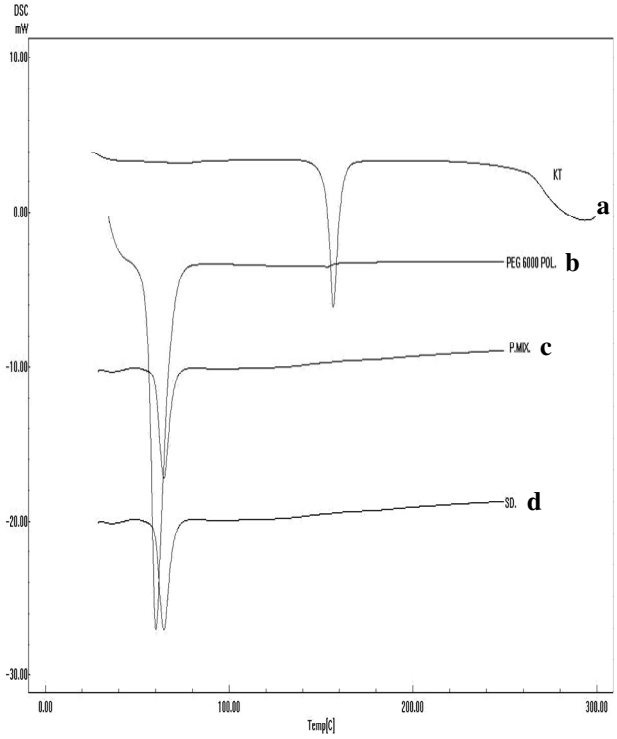


Fig. 18: Shows DSC thermograms of (a) pure drug KT, (b) PEG 6000 polymer, (c) physical mixture of KT with PEG 6000 1:7, (d) solid dispersion of KT with PEG 6000 1:7.

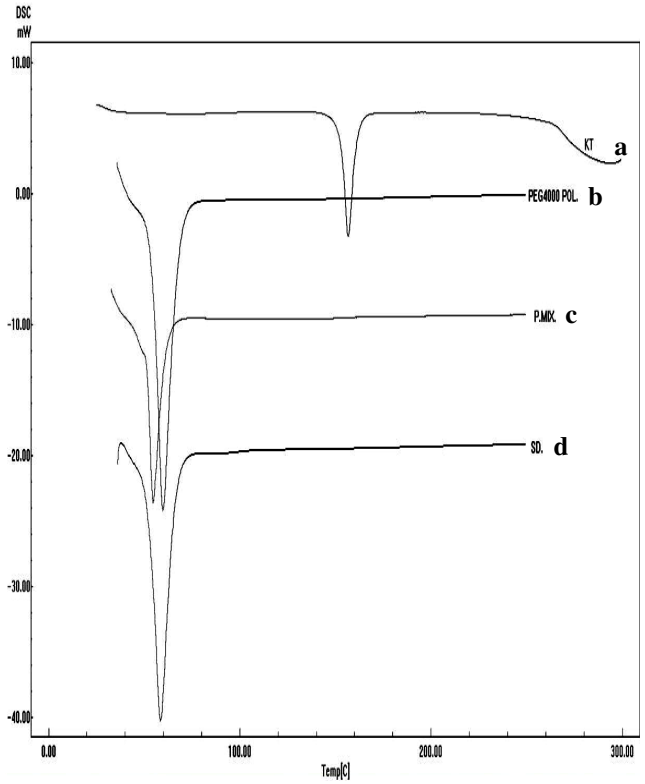


Fig. 19: Shows DSC thermograms of (a) pure drug KT, (b) PEG 4000 polymer, (c) physical mixture of KT with PEG 4000 1:7, (d) solid dispersion of KT with PEG 4000 1:7.

Table 11: the endothermic peaks and Δ H of KT, HP-β-CD, PF-127, PF-68, PEG 6000, and PEG 4000, their corresponding solid dispersions and physical mixtures at ratio 1:7.

System	Onset point (ºC)	Endothermic peak (ºC)	Δ H (J/ g)
KT	**149.97**	157	-83.45
HP-β-CD	80.38	89.86	-125.8
KT/ HP-β-CD (1:7) SD.	78.38	86.51	-90.56
KT/ HP-β-CD (1:7) P.Mix.	79.52	83.45	-101.49
PF-127	47.27	53.6	-126.0
KT/ PF-127 (1:7) SD.	46.09	52.49	-71.74
KT/ PF-127 (1:7) P.Mix.	46.51	52.99	-89.13
PF-68	45.91	51.87	-104.52
KT/ PF-68 (1:7) SD.	46.77	51.6	-80.73
KT/ PF-68 (1:7) P.Mix.	44,97	50.18	-69.37
PEG 6000	58.45	64.45	-184.9
KT/ PEG 6000 (1:7) SD.	57.68	63.93	-99.14
KT/ PEG 6000 (1:7) P.Mix.	57.98	64.05	-87.98
PEG 4000	52,75	60.35	-147.93
KT/ PEG 4000 (1:7) SD.	51.89	59.96	-132.11
KT/ PEG 4000 (1:7) P.Mix.	52.51	60.13	-100.19

amorphous form. However, the disappearance of the endothermic peak of KT melting in physical mixtures could be due to its solubility in the melted polymer. Moreover, the similarity between results obtained for solid dispersions and physical mixtures confirmed the absence of interaction between KT and all the polymers used.

Powder-X-ray diffraction (p-XRD) studies

X-ray diffractograms of KT, HP-β-CD, KT/HP-β-CD 1:7 SD and corresponding KT/ HP-β-CD 1:7 P.Mix. are shown in (Fig. 20). Diffractograms confirmed the crystalline nature of KT[31] while HP-β-CD was presented as an amorphous structure[32,35&36]. The diffractogram of physical mixture (P.Mix.1:7) could be considered as a superposition of the pure components with some variation in shape and intensities of the peaks. However, the observed lower intensity of the peaks may be due to particle size reduction during mixing and dilution of the pure crystalline components. On the other hand the diffractogram of solid dispersion (SD. 1:7) showed a disappearance of crystalline pattern of KT.

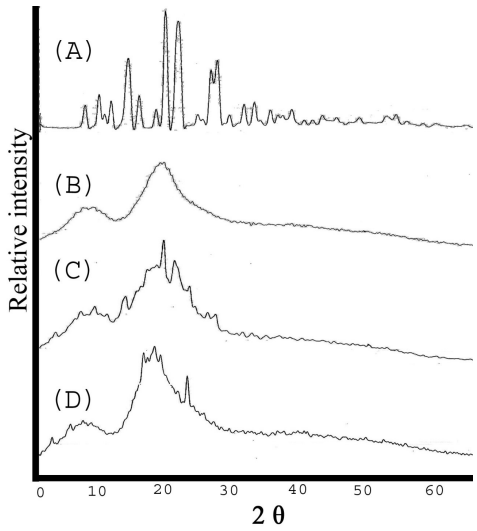
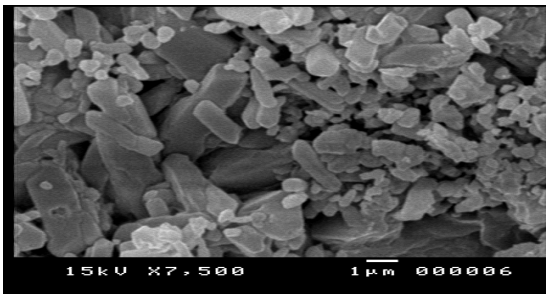


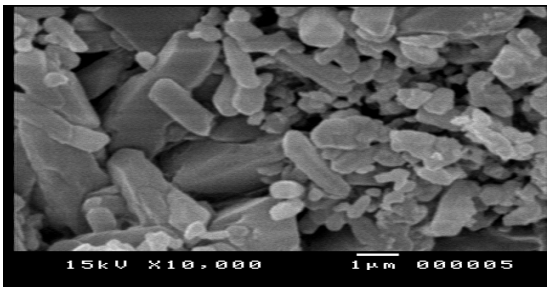
Fig. 20: Powder X-ray diffractograms of (A) pure drug KT, (B) HP-β-CD polymer, (C) physical mixture of KT with HP-β-CD 1:7, and (D) solid dispersion of KT with HP-β-CD 1:7.

Scanning electron microscopy (SEM)

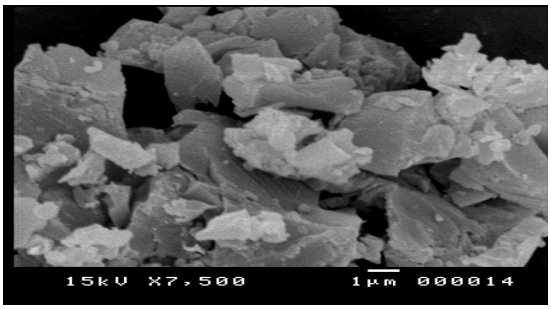
Photomicrographs of KT and KF/HP-β-CD solid dispersion 1:7 are shown in figure 21. The drug alone appeared as crystals of hexagonal shape. While KF/HP-β-CD solid dispersion revealed absence of crystalline structure of the drug. Thereby supporting the transformation of the drug into an amorphous state.



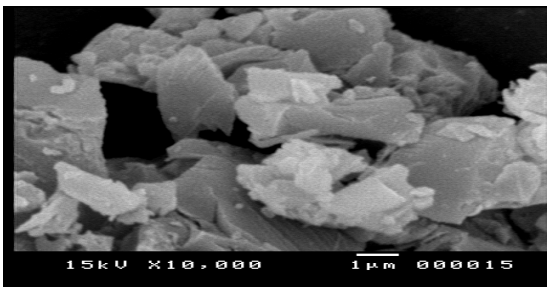
(A)



(B)



(C)



(D)

Fig. 21: SEM photomicrographs: (A) and (B) shows: pure drug KT; (C) and (D) shows: SD. of KT with HP-β-CD 1:7.

Conclusion

Ketotifen solid dispersions were prepared using Hydroxypropyl-Beta-Cyclodextrin (HP-β-CD), Pluronic 127 (PF-127), Pluronic 68 (PF-68), Polyethylene glycol 6000 (PEG 6000) and Polyethylene glycol 4000 (PEG 4000) at different ratios of drug: carrier (1:1, 1:3, 1:5 and 1:7) by solvent evaporation technique. The XRD and DSC studies indicated the transformation of crystalline KT (in pure drug) to amorphous KT by the solid dispersion technology. The saturation solubility and *in-vitro* dissolution studies showed a remarkable improvement in both the solubility as well as drug dissolution of these new KT solid dispersions than those of pure KT and KT physical mixtures. The best results obtained by the solid dispersion of KT with HP-β-CD in the ratio of drug: carrier 1:7. This study concluded that the improved solubility as well as drug dissolution of these newly prepared KT solid dispersions may be attributed to the decreased drug crystallinity, which can be modulated by appropriate level of hydrophilic carriers.

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نشرة العلوم الصيدلية
جامعة أسيوط

تحسين ذوبانية عقار الكيتوتيفن في الماء وزيادة معدل إتاحته في المحلول

فرجاني عبد الحميد محمد محمد – دينا فتح الله محمد – أمنية علي السيد

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تم إجراء دراسة مقارنة لتحضير ودراسة خصائص المشتتات الصلبة والحبيبات المذيبة وقياس معدل إتاحة العقار في المحلول من هذه النظم. في هذه الدراسة تم استخدام بوليمر الهيدروكسي بروبايل بيتا سيكلودكسترين وعديدات الايثيلين جليكول ذات الاوزان الجزيئية (٤٠٠٠، ٦٠٠٠) وكذلك البلورنك (ف ٦٨، ف١٢٧) بنسب وزنية مختلفة ولتحقيق ذلك الهدف اشتملت الدراسة على:

١- تحضير المشتتات الصلبة والحبيبات المذيبة من العقار مع الهيدروكسي بروبايل بيتا سيكلودكسترين وعديدات الايثيلين جليكول والبلورنك بنسب وزنية (١:١، ١:٣، ١:٥، ١:٧) (حامل:عقار).

٢- توصيف هذه النظم المحضرة ودراسة خواصها الفيزيوكيميائية وذلك لتوضيح طبيعة التفاعل بين العقار والبوليمرات التي تذوب في الماء. وقد تم ذلك باستخدام عدة طرق منها القياس بالاشعة تحت الحمراء ، التحليل الحراري ، حيود الاشعة السينية ، والتصوير باستخدام الميكروسكوب الالكتروني. وكانت النتائج كالتالي:

- دلت طريقة القياس بالأشعة تحت الحمراء على توافق العقار مع الجزيئات الكبيرة محل الدراسة.
- أوضحت طريقتا التحليل الحراري وحيود الأشعة السينية أن لهما نفس السلوك الحراري مثل مخلوطهما الفيزيائي الذي له نفس النسب الوزنية وقد أوضحت أيضاً هذه الدراسة ان العقار قد ذاب في البوليمرات المنصهرة.
- أوضحت طرق حيود الأشعة السينية والتحليل الحراري والميكروسكوب الالكتروني نقص درجة التبلور للعقار نتيجة لتكون المشتتات الصلبة والحبيبات المذيبة للعقار مع البوليمرات التي تذوب في الماء.

٣- خصائص معدل إتاحة العقار من النظم المحضرة مع البوليمرات التي تذوب في الماء: تم قياس معد ل إتاحة الكيتوتيفين من النظم موضوع الدراسة ومقارنته بمخلوطه الفيزيائي مع البوليمرات طبقا لطريقة الكمية المنتشرة في محلول الفوسفات المنظم ذي الأس الهيدروجيني (٧,٤) ، وقد أوضحت نتائج الدراسة التالي:

- معدل إتاحة العقار من النظم المحضرة مع بوليمر الهيدروكسي بروبايل بيتا سيكلودكسترين وعديدات الايثيلين جليكول والبلورنك كان أعلى بصورة ملحوظة من معدل إتاحة العقار بمفرده.
- وجد انه كلما زادت نسبة المادة الحاملة في النظم المحضرة زاد معدل إتاحة العقار.
- تم الوصول لأعلى معدل إتاحة للعقار من النظم المحضرة مع بوليمر الهيدروكسي بيتا سيكلودكسترين بنسبة وزنية (١:٧) (حامل:عقار).