We experienced that during the applied production circumstances, the Avicel content of each composition had slightly changed the shaping parameter of the particles. So we did not use more than 40% Avicel PH101.
Summarizing our results, it can be established that the described process allows the production of drug containing pellets in one apparatus. The process is considerably influenced by the proper choice of the manufacturing parameters (intensity of mixing and feeding rate of the granulation liquid). Optimization of the process parameters offers the opportunity to prepare reproducible products of adequate physical parameters.

3. Experimental

3.1. Materials

Salicylic acid (Sigma-Aldrich Ltd., Budapest); Avicel® PH101 (Fluka, Germany), α-D-lactose monohydrate (Hungaropharma, Budapest); Amylum solani, Amylum tritici, Amylum maydis (Hungaropharma, Budapest).

3.2. Preparation of pellets

The pelletization was carried out in a Stephan UMC 5 electronic apparatus (Stephan Maschinen GmbH, Wien, Austria) equipped with different choppers. Five various compositions, containing Avicel PH101, lactose, amylum solani, amylum tritici, amylum maydis as well as salicyclic acid were prepared. The granulation liquid, distilled water, was atomized in a rate from 160 ml/min to 200 ml/min.

3.3. Particle size distribution of pellets

The prepared and dried pellets were fractionated using a Retsch AS 200 control type vibrating sieve (Retsch Verder GmbH, Haan, Germany). Sieving was done in 200 g parts, for 5 min with a 2.5 mm amplitude without intervals and sieving aids. The sieve fractions were the following: 1250–2000 μm; 800–1250 μm; 315–800 μm; 160–315 μm; 63–160 μm.

3.4. Friability

The weight loss of the particles by abrasion was controlled with a friabilator (Erweka GmbH, Germany) according to the official method.

3.5. Crushing strength

The crushing strength of 20 pellets from each composition were determined by measuring the collapsing force using a Dr. Schleuniger Pramatron Model 6D tablet tester (England).

3.6. Real density

The density of the solid particles was determined with a pyknometer as usual.

3.7. Flow properties

The outflow time of the particles from an ASTM funnel was determined. In the case of every sample the examined material quantity was 40 g.

3.8. Sphericity factor

The shape of the pellets was examined with a light microscope (Zeiss, Jena Germany) at 16× magnification. Major and minor axes of 12 particles of each composition were measured. The sphericity factor was determined as a mean value of 12 measurements.

3.9. Calculations

We used the equations described for the calculations of parameters qualifying the physical characteristics of the pellets as follows.
Real density (g/cm^3, eq. 1) has a great importance during the characterization of particles or powders.

$$\varrho = \frac{w}{\frac{w_1}{\varrho_1}} = \frac{b-a}{\frac{(d-a)-(c-b)}{\varrho_1}} \quad (1)$$

where w: weight of solid (g); w_1: weight of liquid (g); ϱ_1: density of liquid (g/cm^3); a, b, c, d: weights of various determinations (g).
Calculating the Carr's index (eq. 2) we can obtain information for the compressibility of particles.

$$\text{Carr's index} = 100(D_t - D_f)/D_t\ (\%)\,, \quad (2)$$

where D_t: tapped density (g/cm^3); D_f: fluff density (g/cm^3).
Hausner ratio (eq. 3) leads to an additional simplification from the point of compacting.

$$H = D_t/D_f\,. \quad (3)$$

Deformity factor (eq. 4) defines the shape of particles.

$$F = X_{min}/X_{max}\,, \quad (4)$$

where X_{min}: smallest measured diameter (μm); X_{max}: longest measured diameter (μm).

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Solid state stability of ketoprofen in the presence of different excipients

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Physical mixtures of ketoprofen (KT) were prepared using different excipients, namely, lactose, mannitol, sorbitol, β-cyclodextrin, polyvinylpyrolidone (PVP) K30, polyethyleneglycol (PEG) 20,000 and urea in a ratio of 2:1 (drug/excipient). The prepared samples as well as KT alone were stored at 40, 50 and 60 °C in sealed glass vials for 12 weeks. The fresh and stored samples were subjected to physical examination and instrumental analysis including m.p., IR and dissolution

rate. KT without additives was found to be physically stable or when mixed with either lactose, mannitol, sorbitol or β-cyclodextrin for 12 weeks at 60 °C. The m.p. of the drug alone or in presence of these excipients did not change. Also IR showed no change. On the other hand, KT mixtures with PVP K30, PEG 20,000 or urea were physically unstable on storage at 40, 50 and 60 °C. Their m.p. were found to decrease; the IR curves were also changed. All the tested excipients enhanced the dissolution of KT from its physical mixtures and could be arranged according to the extent of dissolution as follows: Lactose = Mannitol > β-cyclodextrin > PVP K30 = Urea > Sorbitol > PEG 20,000.

1. Introduction

Ketoprofen (KT) is a widely used anti-inflammatory drug. It is generally marketed in the form of capsules. Different types of polymers, fillers and lubricants are used in capsule formulations. Many drugs in the presence of certain excipients (in solid state) undergo significant physical changes, of the most significance are an increased rate of degradation [1, 2], reduction in the degree of crystallinity [3–7], formation of molecular complexes [8–10], reduction in the dissolution rate [11, 12].

Therefore, the aim of this work was to study the influence of different types of capsule excipients on the dissolution and stability of KT.

2. Investigations, results and discussion

The physical stability of KT and KT mixtures with different types of excipients were recorded in Table 1. Ketoprofen alone and KT mixtures with lactose, mannitol, sorbitol and β-cyclodextrin were physically stable and over the period of storage at 40, 50 and 60 °C. On the other hand, KT mixtures with PVP K30, PEG 20,000 and urea were physically unstable all over the period of storage (12 weeks).

The m.p. of the stored samples at 60 °C for KT mixtures with different excipients are shown in Table 2. It is clear that the m.p. of fresh and stored samples of KT alone and in mixtures with lactose, mannitol, sorbitol and β-cyclodextrin was nearly with the melting range of KT alone (93–96 °C). While the m.p. of fresh KT mixtures with PVP K30, PEG 20,000 and urea were 75, 61 and 73 °C, respectively, and was further lowered to 56, 56 and 51 °C after storage for 12 weeks. This indicates that these excipients form a pharmaceutical interaction with KT.

The DSC of KT and KT mixtures were illustrated in Fig. 1. The DSC curves of KT alone and KT with lactose, mannitol, sorbitol and β-cyclodextrin were nearly the same, where T onset ≈92 °C, endothermic melting peak ≈96 °C and T end 97.7 °C for both fresh and stored samples.

It was noticed that in the case of a KT/sorbitol mixture two peaks were observed, one at 95 °C for KT and the second at 97.2 °C for sorbitol (Fig. 1). The melting endothermic peaks for KT mixtures with PVP K30 and PEG 20,000 were at ≈94 °C while those of KT mixtures with urea were 74 °C for fresh samples. But after storage at 60 °C, no melting peaks were observed for the above mentioned three mixtures.

The IR analysis for fresh and stored KT and KT physical mixtures with of lactose, mannitol, sorbitol and β-cyclodextrin exhibited IR spectra which exclusively eliminated the possibility of interaction between KT and each of these excipients. Although the IR spectra of fresh physical mixtures of KT with PVP K30, PEG 20,000 and urea (Fig. 2) did not show any spectral change with respect to KT alone, however, after storage at 60 °C for 12 weeks, a significant change in the IR spectra was observed. In case of KT mixtures with PVP K30 and PEG 20,000, both illustrated >C=O of the carboxylic group at higher wave numbers ($1740 - 1695\ cm^{-1}$). This spectral finding may

Table 1: Physical examination of ketoprofen and its mixtures with different excipients stored at different temperatures

Ketoprofen excipients mixtures	Physical examination of KT and its mixture after											
	1 week			4 weeks			8 weeks			12 weeks		
	40 °C	50 °C	60 °C	40 °C	50 °C	60 °C	40 °C	50 °C	60 °C	40 °C	50 °C	60 °C
Ketoprofen (KT)	–	–	–	–	–	–	–	–	–	–	–	–
KT/Lactose	–	–	–	–	–	–	–	–	–	–	–	–
KT/Mannitol	–	–	–	–	–	–	–	–	–	–	–	–
KT/Sorbitol	–	–	–	–	–	–	–	–	–	–	–	–
KT/β, cyclodextrin	–	–	–	–	–	–	–	–	–	–	–	–
KT/PVP K30	L	D	D	D	D	D	D	D	D	D	D	D
KT/PEG 20,000	C	C	L	D	D	D	D	D	D	D	D	D
KT/Urea	C	C	C	C	C	C	C	C	D	C	C	D

C: caking, L: liquefaction, D: discoloration

Table 2: Melting point of ketoprofen and its physical mixtures with different excipients

Ketoprofen/excipients mixtures	Melting point record (°C)		
	Literature	Fresh mixture	Stored mixture*
Ketoprofen (KT)	93–96	95	94
Lactose	202	–	–
KT/Lactose	–	95	95
Mannitol	166	–	–
KT/Mannitol	–	92	93
β-Cyclodextrin	178	–	–
KT/β-cyclodextrin	–	93	90
Sorbitol	110–112	–	–
KT/Sorbitol	–	97	95
PVP K30	150	–	–
KT/PVP K30	–	75	56
PEG 20,000	60–63	–	–
KT/PEG 20,000	–	61	56
Urea	137	–	–
KT/Urea	–	73	51

* Stored at 60 °C for 12 weeks

Table 3: Kinetic data of the dissolution of ketoprofen and its fresh and stored physical mixtures with different excipients

Samples	Fresh samples					Stored samples*				
	Model	Correlation coefficient	Intercept	K**	$t_{1/2}$ (min)	Model	Correlation coefficient	Intercept	K**	$t_{1/2}$ (min)
Ketoprofen (KT)	Hixon Crowell	0.9984	0.3111	0.0544	11.8	Hixon Crowell	0.9961	0.2296	0.0613	11.8
KT/Lactose	Hixon Crowell	0.9961	0.0369	0.3004	3.0	Hixon Crowell	0.9769	0.4383	0.1003	5.1
KT/Mannitol	Hixon Crowell	0.9857	0.2828	0.2822	2.6	Hixon Crowell	0.9989	1.1975	0.1132	−2.1
KT/Sorbitol	Hixon Crowell	0.9998	0.8328	0.0960	1.3	Hixon Crowell	0.9995	0.5254	0.1080	3.9
KT/β, cyclodextrin	Hixon Crowell	0.9999	0.5984	0.1302	2.7	Diffusion Model	0.9946	32.9572	12.3518	1.9
KT/PVP K30	First Order	0.9920	1.6975	0.0918	7.55	First Order	0.9920	1.9725	0.0019	362
KT/PEG 20,000	First Order	0.9993	1.9135	0.0182	38.1	First Order	0.9953	2.0117	0.0074	93.2
KT/Urea	First Order	0.9982	1.8085	0.1261	5.5	Diffusion Model	0.9547	18.3606	7.7043	42.1

* Stored samples at 60 °C for 12 weeks
** Units of rate constant (K)
For first order: min.
For diffusion model: mg. ml. min.
For Hixon-Crowell: mg 1/3 min^{-1}

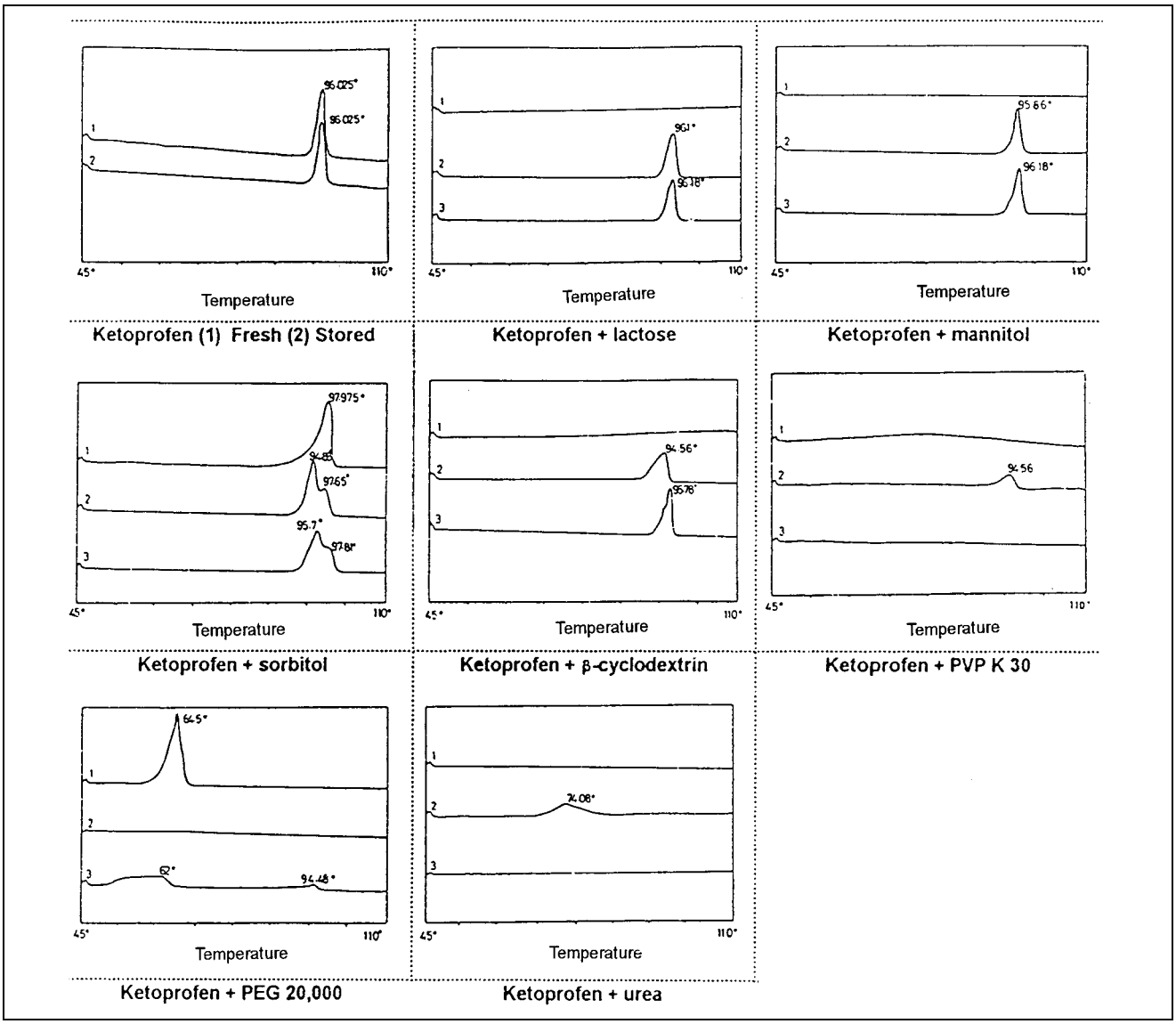

Fig. 1: Differential Scanning Calorimetry of ketoprofen and its mixtures with different excipients. 1: plain excipient; 2: fresh mixture; 3: stored mixture

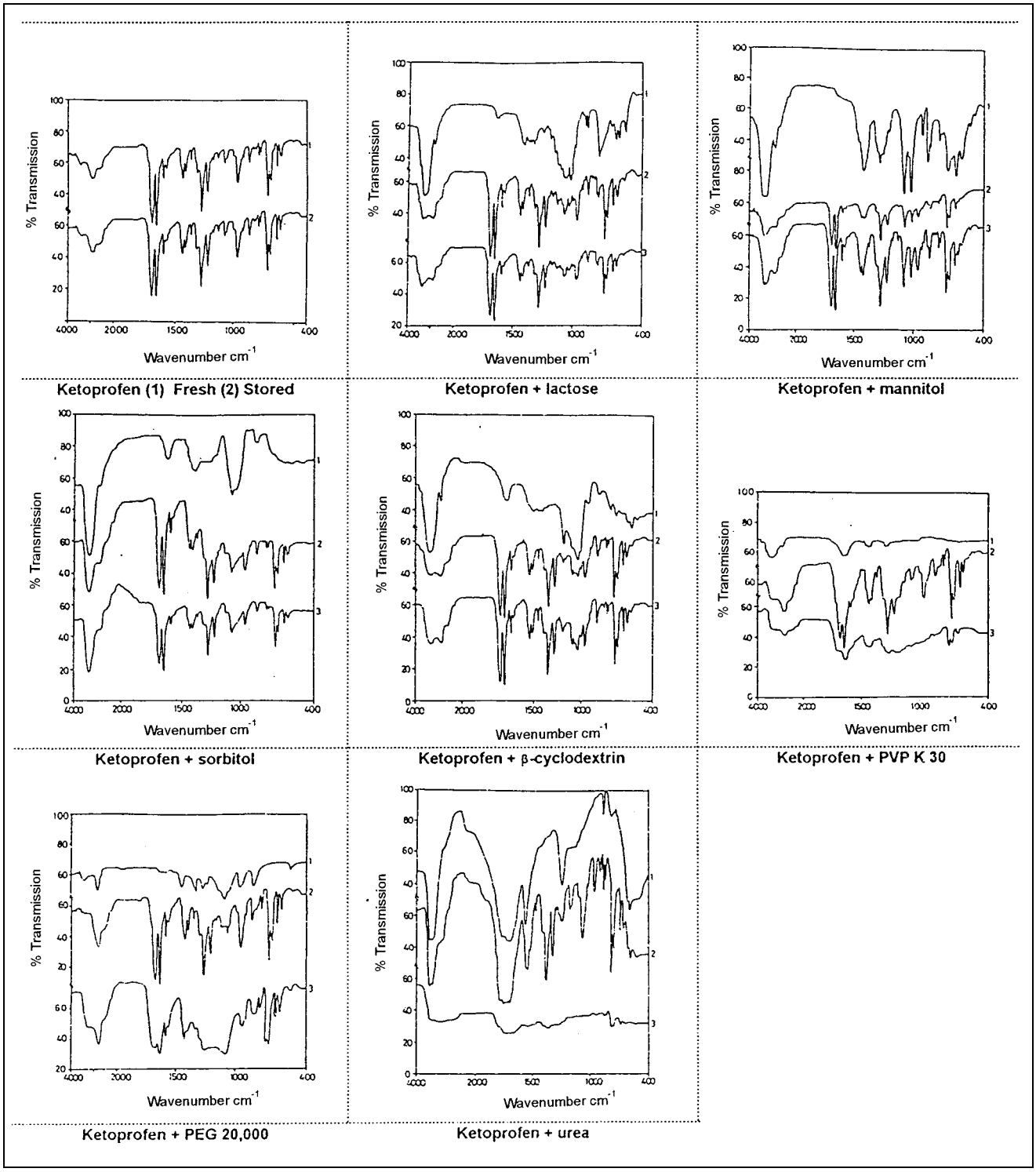

Fig. 2: IR-spectra of ketoprofen and its mixtures with different excipients. 1: plain excipient; 2: fresh mixture; 3: stored mixture

likely be attributed to partial estrification between the −COOH group in KT and the enolic OH group in PVP K30 or the terminal −OH group in PEG 20,000. But for KT mixtures with urea after storage, the IR spectrum was unsatisfactory which may be attributed to the deficiency in the manipulation since the mixture was noticed to liquefy upon storage.

Fig. 3 shows the dissolution profile of KT and KT mixtures with different excipients when fresh and when stored at 60 °C. The dissolution rate of KT alone was not greatly influenced by storage at 60 °C for 12 weeks, while, the dissolution rate of KT from physical mixtures with each of lactose, mannitol, sorbitol and β-cyclodextrin was slightly influenced by storage. The statistical and kinetic treatment of the dissolution data of fresh and stored samples of KT with poly-saccharides revealed that the drug is dissoluted according to the Hixon Crowell cube root law [13] (Table 3). This mechanism indicates that the dissolution at subsequent time intervals is a function of the decreased surface area of the drug [13]. But, with stored samples of KT β-cyclodextrin, KT dissoluted by the diffusion matrix mechanism [14]. This may be attributed to the inclusion of some of the drug within the cavity of β-cyclodextrin.

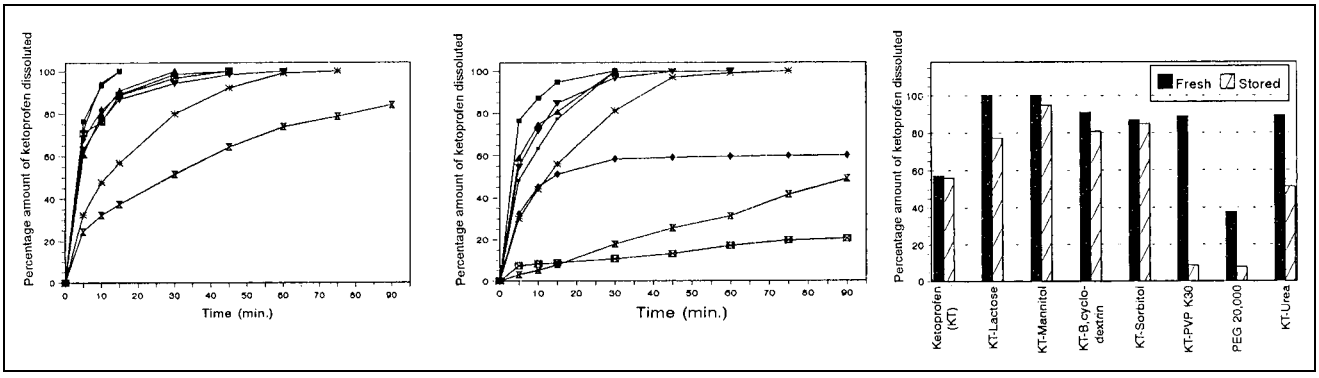

Fig. 3: Dissolution of ketoprofen from its mixtures with different excipients in Sorensens phosphate buffer of pH 7.4

- Plain drug
- KT-Lactose
- KT-Mannitol
- KT-B, cyclodextrine
- KT-Sorbitol
- KT-PVP K30
- KT-PEG 20,000
- KT-Urea

Table 3 shows that the intercept was higher in the case of sorbitol (0.8328) which may be explained by the higher solubility of sorbitol in water causing a flush concentration of the drug. Sorbitol was followed in this respect by mannitol and finally lactose (0.2828 and 0.0369, respectively). The dissolution rate of KT from its physical mixture with lactose was found to be the highest followed by that of mannitol and finally sorbitol. The $t_{1/2}$ value was found to be 1.3, 2.6, 2.7 and 3 min for sorbitol, mannitol, β-cyclodextrin and lactose, respectively.

(Table 3) also shows that the dissolution rate of KT from KT mixtures with PVP K30 and PEG 20,000 was greatly decreased on storage at 60 °C for 12 weeks. This could be attributed to an interaction between KT and each of the used polymers. This assumption is supported by changes in m.p. DSC, and IR which are previously mentioned. The kinetic treatment of dissolution rate of KT from these mixtures was found to follow first-order kinetics when fresh and after storage and the $t_{1/2}$ extended to account for 48 and 2.5 times that of fresh samples of PVP K30 and PEG 20,000, respectively. On the other hand, the dissolution rate of KT from the urea mixture followed the diffusion matrix which may be attributed to the formation of an adduct between the drug and urea, $t_{1/2}$ was 42.12 min.

3. Experimental

3.1. Materials

Ketoprofen (kindly supplied by Alex. Pharm. Co.), α-lactose anhydrous (El-Nasr Co.), sorbitol, mannitol, urea (kindly supplied by ADWIC Lab Chem.) β-cyclodextrin, polyethylene glycol (PEG) 20,000 (E-Merck-Germ.), polyvinylpyrrolidone (PVP) K30 (BASF, Germany). All other chemicals were of analytical grade.

3.2. Equipment

Automatic sieve shaker (Milan, Italy); Melting point apparatus (Straut Scientific SMP2, U.K.); pH meter HANNA HI 8417 (Italy); Diode Array Spectrophotometer 8450 HP USA; Infra-red Spectrophotometer (Shimatzu, IR-435-U-04, Japan); Differential Scanning Calorimetry (Perkin-Elmer DSC-4, USA); Dissolution Tester USP XXII (Pharmatest Type PTW 6452, Germany)

3.3. Methods

3.3.1. Preparation of ketoprofen mixtures

Mixtures of KT and each of the used excipients in a 2:1 ratio were prepared by gentle mixing in a glass mortar. The prepared samples were stored at 40°, 50° and 60 °C in tightly sealed colorless glass vials and evaluated for 12 weeks.

3.3.2. Physical evaluation of ketoprofen mixtures

Includes changes in appearance, caking, liquefaction and discoloration.

3.3.3. Instrumental analysis

Ketoprofen alone and KT physical mixtures with different types of excipients were subjected when fresh and after storage for 12 weeks at 60 °C for the following tests:

Melting point (m.p.): Determined by standard capillary-tube method using electro-thermal melting point apparatus.

Differential scanning calorimetry (DSC): Pulverized samples 5 mg of KT and KT mixtures were accurately weighed into aluminium lid and crimped into position. The pan was placed in the oven together with the blank, prepared exactly in the same way but without sample. Sample and blank were continuously purged with nitrogen gas with a flow rate of 25 ml/min. The thermograms were recorded over a temperature range of 45–110 °C at a constant heating rate of 10 °C/min.

Infra-red spectroscopy (IR): KT and KT mixtures (2–3 mg) were mixed with about 400 mg dry potassium bromide powder, and compressed into a transparent disc. The IR spectra were recorded.

Dissolution profile of ketoprofen: A quantity of KT or its physical mixtures with different excipients containing 50 mg of the drug was introduced into a rotating basket covered with a screen (stainless steel mesh size 50 μm). Aliquot samples were withdrawn and the absorbance of the samples was measured at 260 nm using phosphate buffer of pH 7.4 as a blank. The dissolution data were analyzed by linear regression according to the zero order, first order and simplified Higuchi model [14] and also according to the Hixon Crowell cube root law [13].

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