

## **Preparation and Evaluation of Film Coated Ketoprofen Tablets**

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### **ABSTRACT**

*This study deals with formulation and enhanced dissolution characteristics of ketoprofen through preparation of its nanoparticles solid dispersion systems(NSDS) with different synthetic polymers aiming to increase its dissolution rate of this poorly water soluble drug. The carriers used to prepare solid dispersion of nanoparticles include B-cyclodextrins , PEG3350 , PEG6000 , PVP K30 and PVPK90 . Results of studies revealed that ketoprofen depicted its least solubility at lower pH values and had good solubility in basic medium. The official dissolution medium of ketoprofen is pH 7.5 pH .Lyophilization of ketoprofen with different polymers improved its flowability to great extent which in-turn improved its solubility and dissolution in comparison with plain drug. Ketoprofen nanoparticles prepared with a blend of B-cyclodextrins , PEG 6000 and PVP K30 exhibited the highest dissolution rate(102.2%) when compared with other nanoparticles prepared with other polymers . It was found that the dissolution and solubility data were in accordance with XRPD , DSC and FTIR. The kinetic analysis revealed that dissolution data of the most formulae were according to Higuchi model, zero and first order kinetics.*

**Keywords:** ketoprofen , Film coating , Hydroxypropyl methylcellulose , Release pattern

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### **INTRODUCTION**

Ketoprofen [2-(3-benzoylphenyl)propionic acid] has pharmacologic actions similar to those of other prototypical NSAIDs, widely used in order to reduce pain, inflammation and stiffness caused by several conditions such as osteoarthritis,rheumatoid arthritis, ankylosing spondylitis or abdominal cramps associated with menstruation. The gastrointestinal irritation and ulcerogenic effect with short half - life (1.5 to 2 hours) has led to the design of film coated ketoprofen tablets . The mechanism of action of ketoprofen is mainly associated to the inhibition of the body's ability to synthesise prostaglandins. Ketoprofen is usually formulated and administered as a racemic mixture of R and S enantiomers, which are equivalent on a per weight basis. It exhibits enantiomeric selectivity, only enantiomer displaying pharmacodynamic activity[1,2] Conventional dosage forms of this drug, administered orally, are rapidly and almost completely absorbed from the gastro-intestinal tract, the peak plasma concentrations occurring within 1–3 h [3-5] . Ketoprofen is an appropriate model drug for formulation of controlled release dosage forms due to its short plasma elimination half-life and poor solubility in un ionised water, which affects its bioavailability[6,7] . Therefore, in order to maintain therapeutic plasma levels, modified release dosage forms may be beneficial, allowing only one daily administration of the drug with consequent improvement of patient compliance[8].

Thus, the present work includes the investigation of the effects of diluents and binding agents on micromeritic properties , moisture content of drug powder and the prepared granules of different formulations as well as to study the effect of film coating on tablets evaluation including their characteristics and bioavailability.

**MATERIALS AND METHODS****Materials**

Kp was kindly , supplied from Kahira Co.( Cairo , Egypt) ;Maize starch , Hydroxypropyl methycellulose(HPMC) , Propylene glycol , Talc , Stearic acid , Potassium dihydrogen phosphate and disodium hydrogen phosphate-2-hydrate were donated by Pfizer Co.(Egypt) ; other reagents and chemicals are of analytical grades.

**Formulation of different prepared ketoprofen tablets**

These formulations are illustrated in table(I)

**Table(1): Different Formulations of kp Tablets**

\*Lubricant:stearic acid and talc(1:1)

\*\*Film coat:HPMC , Propylene glycol and talc(5:

Formulation Number*	ketoprofen (mg)	Starch(mg) as a diluent	Starch (mg) as a biner	Starch (mg) As a disintegrant	HPMC (mg) as a binder	Croscarmellose (mg) as super disintegrant	Lubricant* (mg)	Film** Coat (mg)
I	100	17	6	17	-	-	6	4
II	100	34	6		-	-	6	4
III	100		6	34	-	-	6	4
IV	100	28	-	-	4.5	7.5	6	4
V	100	26.5	-	-	6	7.5	6	4
VI	100	25	-	-	7.5	7.5	6	4

**Preparation of starch paste**

Disperse the calculated weight of maize starch in about its weight cold water , after about 15 minutes transfer into ten times the weight of boiled water , stir until the formation of a translucent mass free from lumps.

**Preparation of HPMC binder**

The calculated weight of HPMC was dispersed in a hot water at about 80°C , then stir until a clear mucilage is formed.

**Preparation of coating material**

The calculated weight of HPMC was dissolved in distilled water as previously mentioned to obtain 10% solution. The amount of propylene glycol was added and mixed well with HPMC solution then the calculated weight of talc was dispersed in the final solution by shaking and homogenizing.

**Preparation of granules using starch paste**

The calculated weight of kp and maize starch(calculated on the dried bases)diluent was dry mixed for 5 min using planetary mixer(Progressive Instruments , Bombay ,India) , then the mixed powder was mixed well with the prepared starch paste until an acceptable coherent mass is formed(FI and FII). The calculated weight of kp alone is directly mixed with starch paste to obtain the coherent mass(FIII).

The coherent masses were granulated by passing them manually through a no.12 mesh sieve(1400um) , dried in a hot air oven for 18 hr at 50°C and then re -sieved through a no. 16 mesh sieve(1000um). The calculated amount of starch(disintegrant) and lubricant are mixed well with dried granules of different formulations (FI,FII and FIII). The time of drying was taken as 18 hrs because it gives a moisture content of the range of 1-2%.

**Preparation of granules using HPMC mucilage**

The calculated amount of kp and maize starch were mixed for 5 min in a planetary mixer and then moistened with the binder solutions(HPMC mucilage) to produce granules containing different concentrations of the binder(3,4 and 5%). Massing was continued for 5 min , and the wet masses were granulated by passing them manually through a no.12 mesh sieve , dried in a hot air oven for 18 hr at 50°C , and then re-sieved through a no. 16 sieve . The calculated amounts of croscarmellose (superdisintegrant) and lubricant were mixed well with different formulations(FIV , FV and FVI).

**Validation the prepared granules**

The degree of mixing(M) of granules was determined , three different samples of each formulation was determined by spectrophotometric assay using spectrophotometer( Model SPD-10A , Shimadzu, Japan) at 260nm. The sample size was 100mg of granules . The value of M was calculated using the equation

$M=1-D/D_0$  where D is the standard deviation estimated from the analyzed samples , and  $D_0$  is the standard deviation of the completely unmixed system . That is:

$D_0=\{Y(1-Y)\}^{1/2}$  where Y is the proportion of kp in granule formulation . In each case , M was found to be >0.97

**Preparation of tablets**

Quantities(146 mg) of the mixed formulations were compressed for 1 min , predetermined loads(40-60 N) using tablet machine(Royal Artist , Bombay,India) . A compression set of 10 mm biconcave round shape were used before each compression . The weights and dimensions were determined to be within  $\pm 1$ mg and 0.01 mm respectively.

**Film coating of tablets**

Tablets were coated in a pan coater(Progressive Instrument , Bomay , India) using the previously prepared coating dispersion . Pan rotation speed 15 rpm , spraying rate was adjusted and continue until an increase in the weight of the tablets of about  $8\pm 1$  mg was obtained[7]. The coated tablets were dried for a period of 30 min using IR lamp (Progressive Instuments, Bombay, India) then hot air oven (Progressive Instrument , Bomay , India)at 50°C for 18 hrs.

**Evaluation of kp powder and granules of different formulations****Determination of micromeritic properties**

Exactly 10 gm of kp powder or granules were weighed on chemical balance and transferred into a 100 ml measuring cylinder. The cylinder was dropped on a wooden platform from a height of 2.5 cm three times at 2 seconds interval. The volume occupied by the drug or granules was recorded as BV. The cylinder was then tapped on the wooden platform until the volume occupied by the drug or granules remained constant. This was repeated three times for drug powder and granules of different formulations. The data generated was used in calculating BD , TD , CI and Hausner's ratio (HR) [10] .

$$BD=10/BV \quad , \quad TD=10/TV \quad CI = 100(TD-BD)/ TD \quad HR = TD/BD$$

Angle of Repose:10 gm of kp powder or granules was placed in a plugged glass funnel which had a distance of 10 cm from the flat surface. The drug powder or granules were then allowed to flow through the 8 mm funnel orifice by removing the cotton plug from the funnel orifice. The height of the heap (h) formed as well as the radius of the heap (r) was noted. The angle of repose ( $\theta$ ) was calculated as [10]  $\theta = \tan^{-1} h/r$

**Determination MC of kp powder and granules of different formulations**

10gm of kp powder or granules was put into a crucible and dried to constant weight in a hot air oven at 105°C. the moisture content(MC) was deduced as difference between the initial( $W_0$ ) and final weight ( $W_f$ ) of the granules expressed as a percentage and calculated as [9] :  $MC = 100 ( W_0 - W_f ) / W_0$

**Tablet evaluation[11]**

Tablet weight uniformity: Twenty tablets were weighed individually using a digital balance with the precision of 0.05 mg and readability of 0.1 mg, from which the mean was calculated and standard deviations determined.

Tablet Hardness: The hardness of tablets were determined individually with the Monsanto hardness tester, following 10 tablets were used and the mean hardness was calculated[12] . Friability: The friability of 10 tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de-dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula;  $F = (W_0 - W) / W_0 \times 100$

**Disintegration Test**

The disintegration time of tablets was determined according to the method described in the British Pharmacopoeia 1998. Six tablets were placed in each compartment of the disintegration apparatus, with water thermo-stated at  $37 \pm 10$  °C as the medium. The tablets were considered to have passed the test after the 6 tablets passed through the mesh of the apparatus in 15 minutes.

**Drug Content Estimation**

Five randomly chosen tablets of each of the formulations tested. The kp tablets each containing approximately 100mg kp were grinded in mortar and dissolved in methanol. The solutions filtered and analyzed spectrophotometrically (UV 1601, Shimadzu, Japan) at 260nm after suitable dilution. All the experiments were performed in triplicate.

**Dissolution study**

The release rate of the tablets were determined at  $37 \pm 0.5^\circ\text{C}$  in a dissolution medium of 1000 ml pH 7.2 phosphate buffer using USP 25 paddle method [13] (Pharmatest, Germany) at 100 rpm. The amount of kp that had dissolved after different periods of time until 1 hr was determined spectrophotometrically at 260nm, replacing the sample with an equal volume of pH 7.2 phosphate buffer at the same temperature to keep the volume of dissolution medium constant during dissolution test. All determinations were made in triplicate. The dissolution rate of different tested formulations was compared to the commercial tablet formulation (FC).

**Study design**

The studies were carried out to compare the oral absorption of kp from tablet formulation FIV (treatment A) to the commercial tablet formulation FC (treatment B) following administration of single doses of 100 mg each using crossover design. Five healthy male volunteers participated in the study. The subjects ranged in age from 29 to 41 (mean 32), in height from 169-179 cm (mean 172 cm) and in weight from 67 to 83 kg (mean 70 kg). All subjects were prohibited from taking medicines and smoking for one week before the beginning of the studies to the end of the test. All subjects are fasted for at least 12 hrs before the study day. The tablets were ingested with 200 ml of water. No food was allowed for two hours after dosing. Venous blood samples (5 ml) were collected into heparinized tubes at the following time points: 0 (pre-dose), 15, 30, 60, 120, 240, 360, 480, 600 min after administration. Plasma was obtained by centrifugation at 2000 rpm for 10 min. The plasma was pipette into glass tubes and then frozen until the time of analysis.

**HPLC condition [14]**

Specific, accurate, precise and reproducible high-performance liquid chromatography (HPLC) method with diode-array detector (DAD) was developed and validated for the determination of kp in human plasma using flubiprofen as an internal standard. The chromatographic separation was achieved on an onyx monolithic C18 (100 x 4.6 mm) analytical column with an isocratic mobile phase consisting of acetonitrile/potassium dihydrogen phosphate ( $\text{KH}_2\text{PO}_4$ ) 0.01 M, (40:60, v/v) adjusted to pH 3.5. The flow was set at 5 ml x min<sup>-1</sup> and the wavelength at 254 nm. The total analysis time was less than 5 min. The ratio of peak area of analyte to internal standard was used for quantification.

**Calibration curve**

Standard samples were prepared by transferring aliquots of standard solutions of kp at concentrations of (1-100 ng/ml) into centrifuge tubes provided with tight sealing polyethylene caps, containing 1 ml plasma. To each tube add 1ml of flubiprofen (internal standard) in menthol. One ml acetonitrile was added to each sample vortexed for 20 seconds and centrifuged for 10 minutes at 3000 rpm. The upper layer was transferred to another tube filtered through 0.45 um Millipore filter, evaporated by nitrogen at ambient temperature, then reconstituted with 100 U mobile phase, 20 uL were injected (Rheodyne injector, Model 7161, Cotate California, USA equipped with 20 uL injector loop) on to the column for analysis.

**Plasma analysis**

The plasma obtained from the five subjects after receiving treatment A and treatment B was assayed as described above without the addition of drug.

**Pharmacokinetic analysis**

Pharmacokinetic characteristics from plasma data following administration of the two treatments (treatment A and treatment B) were used to calculate  $t_{1/2}$ ,  $k_{el}$  calculated as ( $k_{el} = 0.693/t_{1/2}$ ),  $AUC_{0-t}$  calculated ( $AUC_{0-t} = C_{p_0} + C_{p_1}/2 \cdot t_1 + C_{p_1} + C_{p_2}/2 \cdot (t_2 - t_1) + \dots$ ),  $AUC_{(0-\infty)}$  calculated ( $AUC_{(0-\infty)} = C_{p_0} + C_{p_1}/2 \cdot t_1 + C_{p_1} + C_{p_2}/2 \cdot (t_2 - t_1) + \dots + C_{p_{last}}/k_{el}$ ).

**Statistical analysis**

The release data of different kp tablet formulations were treated statistically applying t-test and probability.

**Kinetic analysis**

The release data of different kp tablet formulations were treated kinetically according to zero . first order kinetics , Higuchi Square Root , Korsmeyer Peppas and Hixon Crowell Cube Root models.

**RESULTS****Table(II): Micromeritic Properties and Moisture Content of kp powder and granules of different formulations**

Formula	Tested Property					
	DC(%)	WU( gm)	H (N)	F (%)	HFR*	D (min)
FI	99.85	149.8±1.05	68.4(±0.5)	0.80(±0.05)	85.50	62(±0.02)
FII	99.99	149±1.16	41.3(±1.0)	0.85(±0.03)	48.59	55(±0.08)
FIII	100.12	150.1±1.26	16.2(±0.8)	92.6(±0.02)	0.17	2(±0.06)
FIV	100.00	150.2±1.36	25.4(±1.4)	0.90(±0.03)	28.22	5.0(±0.02)
FV	98.00	149.6±1.46	42(±0.9)	0.89(±0.02)	47.19	15(±0.03)
FVI	100.40	150.3±1.56	65(±1.1)	0.36(±0.02)	180.56	30(±0.04)

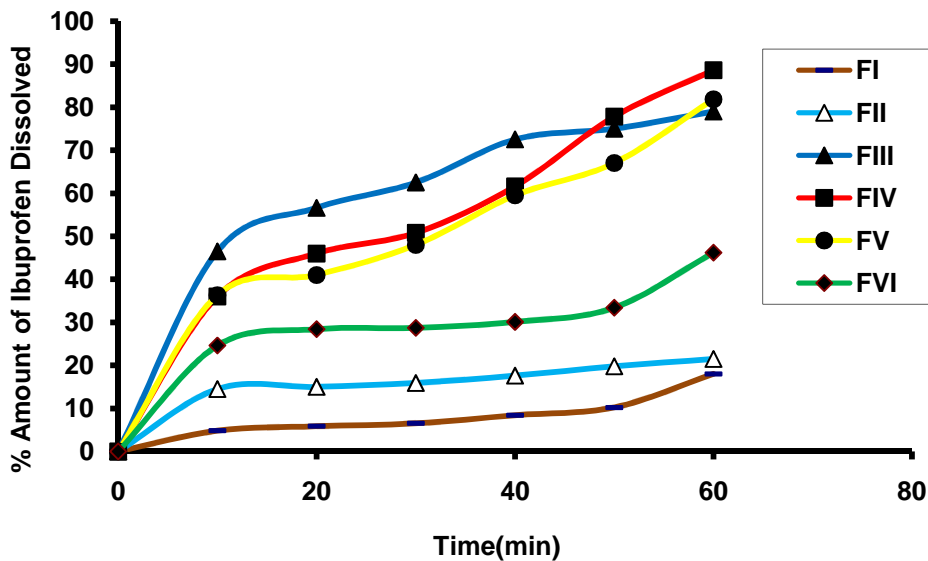
**Table (III): Properties of Uncoated kp Tablets Using Different Formulations**

Formulation/Drug	Property					
	BD (gm/ml)	TD (gm/ml)	HR	CI	θ (degrees)	MC (%)
KP poder	0.256±0.003	0.395±0.006	1.540±0.021	35.004±0.010	66.420±0.053	11.200±0.050
FI	0.332±0.005	0.372±0.008	1.120±0.040	10.753±0.004	18.833±0.002	11.100±0.023
FII	0.322±0.006	0.380±0.008	1.180±0.002	15.263±0.070	19.633±0.026	10.820±0.024
FIII	0.321±0.001	0.385±0.008	1.199±0.005	16.623±0.007	24.250±0.062	11.100±0.021
FIV	0.392±0.002	0.423±0.003	1.079±0.012	7.329±0.006	28.540±0.062	8.680±0.024
FV	0.353±0.003	0.385±0.010	1.091±0.021	8.312±0.043	33.241±0.025	9.720±0.006
FVI	0.345±0.023	0.379±0.004	1.099±0.006	8.971±0.051	35.420±0.024	10.010±0.007

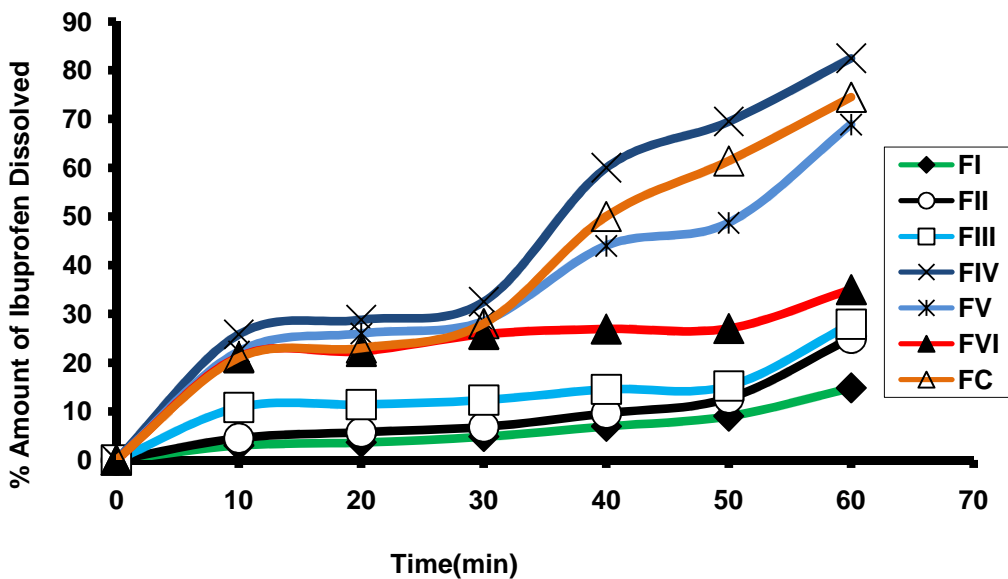
**Table (IV): Properties of Coated Kp Tablets Using Different Formulations**

Formulation	Tested Property			
	Hardness(N)	Friability(%)	HFR**	Disintegration(min)
FI	74(±0.4)	0.22(±0.01)	336.36	110(±0.02)
FII	50.1(±0.30)	0.48(±0.03)	104.4	96(±0.06)
FII	18.6(±0.25)	74.1(±0.01)	0.25	2(±0.05)
FIV	29.7(±0.41)	0.50(±0.02)	59.4	8(±0.01)
FV	49.3(±0.4)	0.20(±0.01)	535.9	56(±0.08)
FVI	70(±0.16)	0.09(±0.01)	760.87	101(±0.03)
FC*	93(±0.20)	5.25(±0.21)	17.71	10(±0.02)

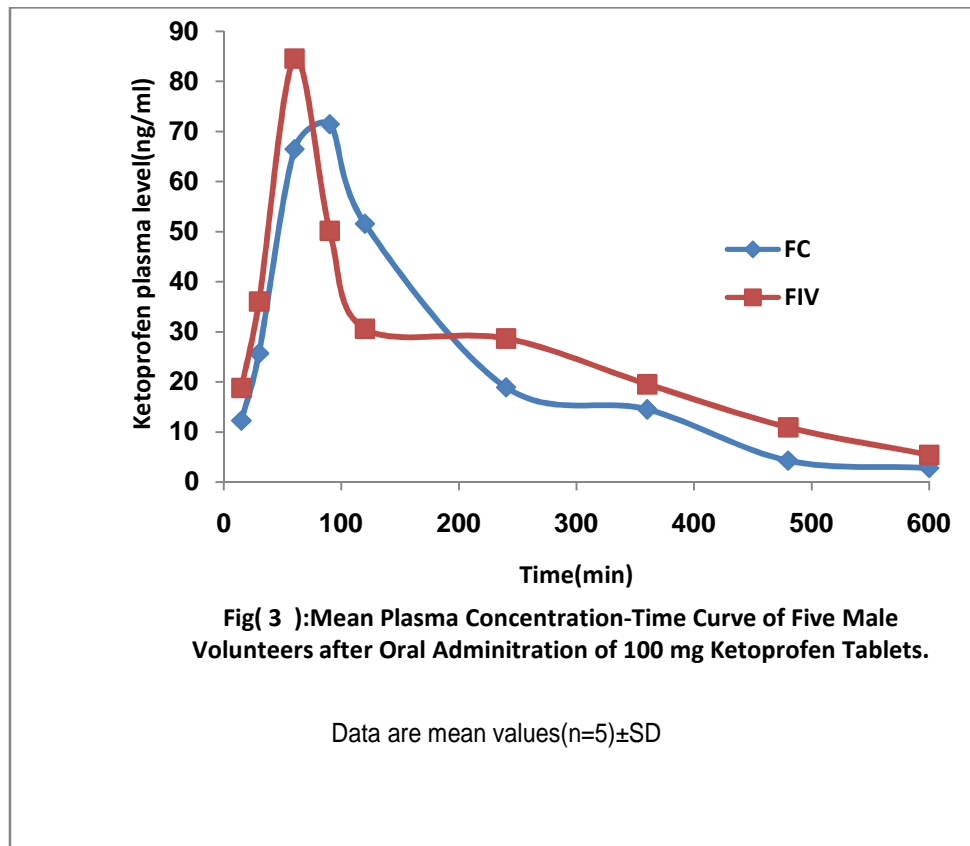
\*commertial formula



Fig(1):Dissolution Profile of Different Uncoated KP Tablet Formulations in pH 7.2 Phosphate Buffer at 37°C.



Fig(2):Dissolution Profile of Different Coated kp Tablet Formulations in pH 7.2 Phosphate Buffer at 37°C.



Table( V )Statistical Analysis of Pharmacokinetic Parameters of Kp for FIV and FC

Pharmacokinetic parameter	Standard error	DF	t	Probability(P)
Cp	4.581	8	0.400	0.696
C <sub>max</sub>	1.019	4	12.640	0.0002
AUC <sub>0-t</sub>	2.800	4	1.05	0.3528
AUC <sub>(0-∞)</sub>	20.635	4	78	0.0001
t <sub>1/2</sub>	0.489	4	62.87	0.0003

P<0.05 : Significant      t<sub>tab</sub>< t : significant      t<sub>tab</sub> at DF 4 = 2.78      t<sub>tab</sub> at DF 8 = 2.31

Table(VI):Mean pharmacokinetic parameters of kp after administraron of 100mg FIV tablets or FC tablets to five fasted volunteers

Parameter	FIV	FC
C <sub>pmax</sub> (ng/ml)	84.59	71.50
AUC <sub>0-t</sub> (ng min/ml)	15608.30	14212.80
AUC <sub>(0-∞)</sub> (ng min/ml)	16313.49	14699.01
t <sub>1/2</sub> (min)	90	120
K <sub>el</sub> (min <sup>-1</sup> )	0.0077	0.0058
C <sub>p1ast</sub> / K <sub>el</sub> (ng .min ml <sup>-1</sup> )	705.19	486.21

**DISCUSSION**

Table(2) shows the various properties of kp powder in comparison to the prepared granules of different formulations. The kp powder exhibited a comparatively lower TD , BD and higher MC when compared to other granular formulations .The low TD and BD and high MC indicate that kp was not highly porous and of poor flowing properties. The low BD results when the void spaces created by larger powder particles were not filled by smaller particles in distribution leading to consolidation of powder particles. The confirmation of the non free flowing

nature of kp powder was gotten from the fact that , its HR was greater than 1.2 which indicate low inter particulate friction powder[15] . The better flow properties of granular formulations than kp were confirmed by their higher CI compared to that of kp powder. This index as a one – point measurement does not always show the ease of consolidation of powder granules[16] . The angle of repose is known to be a measure of flowability and the angle of repose of kp powder was 66.42°, it indicates poor flowing properties of powder. Whereas those of granular formulations were as follow: for FI , FII , FIII ,FIV , FV and FVI respectively. This , indicates good flowability of these formulation which was confirmed by their lower H.R which were less than 1.2 and lower CI.

Hardening strength(H) and friability(F) are important factors for pharmaceutical tablets that often from a part of manufacturer's own specifications. Friability is important because the tablet is likely to be subjected to different abrasive motions during production , film coating and subsequent use. These are now requirements for these tests in the British Pharmacopoeia There is no clear limits for acceptance or rejection of tablet batches . In case of H , this probably because the desired strength depends largely on the intended use of the tablets[17]. For , the reason is probably because the principles of the test are not understood . In general , convectional compressed tablets lose less than 1% of their weight the F test are usually considered acceptable[18].

Table(3) illustrates the drug content of different tablet formulations , different values of WU , H , F , HFR and D of different uncoated kp tablet formulations. The values of DC were found to be not less than 98% ,. H increased , and those of F decreased with increasing binder concentration(FIV , FV and FVI). It is well known that increasing the concentration of plastoelastic binding agent leads to an increase in plastic deformation of the formulation of more solid bonds in the resulting tablets to provide more resistance to tablet fracture and abrasion [19,20] . H and F of formulations I, II and III were greatly affected by diluents-binder ratio rather than binder concentration . H increases with the increase of diluents-binder ratio. The ranking order was FII>FI>FIII. kp tablet formulations I , II ,IV , V and VI had F values<1% whereas , FII had a very high F value (92.6%). This suggests that , at certain concentrations of HPMC polymer should be able to provide adequate protection for the tablets against abrasive motions during handling . The values of H and F provide measures of tablet strength and weakness , respectively. Thus . the HFR can be used as a measure of the mechanical strength of kp tablets. The higher the HFR , the stronger the tablet . The value of D increased as the binder concentration increased. The ranking of values of D for tablets containing different binder concentrations was FVI>FV>FIV whereas , the ranking of values of D for the first three formulations was FI>FII>FIII. When the rank orders for the six formulations are compared , it is notable that tablets of FIII exhibited the lowest strength.

Table(4) reveals the effect of film coating on H, and D of different formulations of kp tablets . It is clear that the film coating increased the values of both parameters i.e improved the mechanical strength of tablets . All the tested formulations gave acceptable friability values except FIII and FC.

Fig(1) depicted that the amount of kp dissolved from different kp tablet formulations was a function of disintegration D , because disintegration of tablets plays a vital role of the dissolution process , since it determines , to a large extent , the area of contact between solid and liquid as well as the ratio of additives and their characters. The ranking of amounts of kp dissolved after 1 hr from different formulations was 88.6 , 81.8 , 79 , 46.2 , 21.5 and 17.9 % for FIV, FV , FIII , FVI ,FII and FI respectively. The amount of kp dissolved from FIV and FV after 1hr were in accordance with USP

Fig(2) shows the effect of film coating on the release profile of kp from different tablet formulations . The presence of film coat reduced the rate of drug release from all formulations. This is because , the presence of film coat increases the adhesive strength of the tablets . The amounts of drug dissolved after 1 hr were 82.5 , 74.5 , 68.9 , 35 , 27.9 , 18.0 and 4.8% for FIV , FC , FV , FVI , FIII , FII and FI respectively.

Bioavailability is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action . the absorption of drug from GIT depends on both pharmaceutical factors (particle size , bulk and tapped density etc.) and barrier functions (age , gastric emptying time , etc) [21,22] . The rate and extent of absorption of kp were found to be statistically different after administration of FIV and FC tablets (table 5) . The pharmacokinetic data of kp following administration of FIV and FC tablets are illustrated in table (6) . No remarkable differences in the shape of concentration-time courses between the two treatments were found(fig3 ). The results revealed that,  $C_{max}$  ,  $AUC_{(0-\infty)}$  and  $t_{1/2}$  were significantly different whereas  $C_p$  and  $AUC_{0-t}$  were not significantly different.

Based on these results , it can be concluded that FIV tablets with improved properties is a potential formulation for kp.



**CONCLUSION**

The results suggest that 3% HPMC could be useful as a suitable binding agent to produce tablets with good mechanical properties and acceptable drug release profile and hence considerable influence on the bioavailability of sparingly soluble drugs such as kp.

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