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Formulation and Evaluation of Ketoprofen Fast Dissolving Tablets

Abdalwali A. Saif[1], Mahmood M. Alburyhi[2], Maged Alwan Noman[3]

[1, 2]Associate Professor in Pharmaceutics & Industrial Pharmacy, Faculty of Pharmacy, Sana'a University, Sana'a Yemen.
[3]Professor in Pharmaceutics & Industrial Pharmacy, Faculty of Pharmacy, Sana'a University, Sana'a Yemen.

Abstract: Pharmaceutical manufacturing has largely grown in recent years. This and many other factors have led to the ability of manipulating pharmaceutical dosage forms and routes of administration. One example of such unique dosage forms is Fast Dissolving Tablets (FDTs), which are solid dosage forms intended to be dissolved in mouth in a relatively short time, ranging from a few seconds to up to 3 minutes. In this research, ketoprofen was chosen to be the active pharmaceutical ingredient (API) in a fast dissolving tablets formulation, being a model of non-steroidal anti- inflammatory drugs (NSAIDs). Ketoprofen is widely used as an analgesic, and being so, the faster the effect, the better the dosage form. Therefore solid preparation of Ketoprofen with superdisintegrants like Croscarmellose sodium, and/or Crospovidone in different ratios were prepared with a view to increase its effect by decreasing the time required for the drug to be released. The ingredients of the formulation were tested for incompatibles by using IR method; all ingredients were compatible. Ketoprofen and the excipients were mixed together and submitted to pre-formulation tests. The powders were then compressed into tablets by direct compression method. The prepared batches of tablets were evaluated for hardness, friability, disintegration time, wetting time and *in-vitro* drug release which tested in comparing with Profenid®. Ketoprofen FDTs prepared showed better results than Profenid® depending on dissolution test. Formula no.5 and no.10 showed the best disintegration times of 30 seconds, and maximum drug release from Formula No 3, 4, 5, 10 about 98% in 2 minutes.

Keywords: Fast Dissolving Tablets, Ketoprofen, Superdisintegrants, Direct Compression

Introduction:

Over the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing[1]. Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of already used drug molecule by formulating a convenient dosage forms for administration and to achieve better patient compliance. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects. For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of drug administration, owing to its several advantages and high patient compliance compared to many other routes. Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available[1].

One important drawback of these dosage forms however is the difficulty to swallow. It estimated that 35% of the population was affected by this problem, which results in a high incidence of non-compliance and ineffective therapy[2]. Pediatric and geriatric patients experience difficulty in particular, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water and also in following conditions like: Parkinsonism, Motion sickness, Unconsciousness and Mentally disabled persons. To fulfill these medical needs, the pharmaceutical technologists have developed a novel type of dosage form for oral administration, the Fast Dissolving Tablets (FDT), tablets that disintegrate and dissolve rapidly in saliva without water[3].

Researchers have formulated FDT for various categories of drugs, which used for therapy in which rapid peak plasma concentration is required to achieve desired pharmacological response. These include neuroleptics, cardiovascular agents, antihistamines and analgesics. Fast dissolving tablets

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Maged Alwan Noman (Correspondence)
magedalwan65 @ gmail.com
+9677775994168

are synonyms with orally disintegrating tablets, mouth dispersible tablet, melt in mouth tablet, rapid melt, porous tablet or rapidly disintegrating tablet. Fast dissolving tablets are tailor made for these patients as they immediately release the active drug, when placed on the tongue, by rapid disintegration, followed by dissolution of the drug. European pharmacopoeia defines FDT, as "Orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed[4]

Fast dissolving tablets disintegrate within 3 minutes[5]. FDTs combine the advantage of both liquid and conventional tablet formulations allowing the ease of swallowing the drug in the form of liquid dosage form. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. The main purpose of this work is to improve patient compliance without compromising the therapeutic efficacy. The performance of FDT depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick intake of water into the tablet matrix, which creates porous structures and result in rapid disintegration. Hence the basic approaches to develop FDT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble excipients in the formulation[6].

Most fast dissolving delivery system tablets should include substances to mask the taste of the active ingredient. This masked active ingredient is then swallow by the patient's saliva along with the soluble and insoluble excipients[7].

The first FDT form of a drug to get approval from the U.S., food and drug administration (FDA) was a Zydis FDT formation of Claritin (loratadine) in December 1996[8]. It was followed by a Zydis FDT formulation of Maxalt (rizatriptan) in June 1998[9].

Objective: In the present study, an attempt was made to develop fast-disintegrate tablets of Ketoprofen, and to investigate the effect of superdisintegrants ratio on the release profile of the drug in the prepared tablets.

Materials:
Ketoprofen an active ingredient chosen, a gift sample by modern Medical Company, Sanaa Yemen. While Croscarmellose sodium, Crospovidone, Magnesium stearate, Microcrystalline cellulose, Colloidal silicon dioxide, Mannitol, Sorbitol, Aspartame and Calcium carbonate were a gift sample by Shephaco Pharmaceutuical Industry, Sana'a, Yemen. Polyvinylpyrrolidone PVP K30, Potassium dihydrogen orthophosphate, Disodium hydrogen orthophosphate, Phosphoric acid and Methanol were a gift by Yedco Pharmaceutical Industry, Sana'a Yemen. Profenid tablets ((Sanofi- Aventis, France), Pronid Tablets (Modern Pharma, Sana'a, Yemen) and Keto tablets (Sheba Pharma. Pharmacutical Industry, Sana'a, Yemen) were purchase from the local market. All other reagents were of analytical grade.

Equipments:
Fourier transform infrared spectrometer (FT/IR-4200) (JASCO, Japan)., Balance (Sartorius, Italy)., Oven (Incubator (Stuart scientific, UK)., UV/VIS – Spectrophotometer (V-530) (JASCO, Japan)., Melting point tester (SMP40 (stuart)., Tablet machine (CIP machineries PVT.LTD. India)., Dissolution tester (JASCO DT-810, Japan)., Friability tester, Disintegration tester and Hardness tester (Rimek, India)., Digital Over Head Stirrer, (Ace Glass, USA)., PH meter (HANNA, Italy).

Drug Identification Tests:
Melting Point. Melting point of the ketoprofen was determined by capillary method; one side closed capillary filled with drug and put into the Melting Point Apparatus. Temperature were noted at which solid drug changed into liquid.

Infrared Spectral Assignment. IR study were aimed to study the compatibility of excipients with ketoprofen. Each excipient was mixed with ketoprofen in equal amounts, then from each sample a small amount was taken (approx. 2-3 mg) and mixed with about 100 mg of potassium bromide. The KBr- sample mixtures were grinded separately for each sample using Agate mortar and pestle. The grinded powders were compressed into discs under pressure of about 10000 pounds per square inch. The tablets were mounted in IR compartment and analyzed. The infrared spectra of the drug-excipient mixtures were recorded over a wave number of 4000 cm^{-1} to 500 cm^{-1}. On analysis of the IR spectra of the reference spectra given in British Pharmacopoeia (2013) and pure drug, no major differences were observed in the characteristic absorption peak pattern[10].

.***Calibration Curve***[11]. 50 mg of Ketoprofen was weighed accurately and dissolved in 5 ml of methanol in a 100 ml of volumetric flask and volume was made up to 100 ml with the Sorenson's buffer (pH 6.8). 10 ml of this solution was diluted with 100 ml Sorenson's buffer (pH 6.8) to obtain a stock solution of 50 mg From this stock solution, aliquots of 1 ml, 2 ml, 3 ml, 4 ml and 5 ml were taken and transferred to 10 ml volumetric flask and volume was made up to 10 ml with Sorenson's buffer (pH 6.8). The absorbance of these solutions was measured at 260 nm[3] against a blank Sorenson's buffer (pH 6.8).

The calibration curve was plotted between concentration and absorbance.

Method Formulation of Fast Dissolving Tablets : Fast dissolving tablets containing selected solid dispersion were prepared by direct compression method using single punch tablet machine to produce convex faced tablets part of them weighing 250mg and others 400mg. 100 tablets were prepared for each batch. The tablet formulations were developed by using Super-disintegrants (Croscarmallose sodium and Crospovidone) in varying concentration (2-10%). All the ingredients shown in Table (1) were passed through sieve no. 70 and were co-grounded in a glass pestle motor. These blends were evaluated for mass-volume relationship (Bulk Density and Tapped Density[12], Hauser's Ratio[13], and Compressibility Index[14] and flow properties Angle of Repose[12]. The mixed blended drug-excipients were compress using a single punch tablet machine to produce convex faced tablets.

Taste Masking. ketoprofen which has unacceptable bitter taste have been ratified by using different effervescing agents like Stearic acid ,*calcium carbonate* and isopropyl alcohol in different ratios. ***Calcium carbonate*** was used, which was added to ketoprofen in 1:1.5 ratio by using PVPK 30 as a binding agent and purified water as a solvent. This complex was put in oven at 45°C till forming paste then this paste was triturated in mortar then passed through 70# sieve[15]. All excipient except silicon dioxide and orange flavor, were blended with specified quantity of ketoprofen for 15 minutes, whereas the other excipients were blended for 5 minutes and added to the former excipients. Then all formulae passed through sieve #70 for particle size uniformity. Then compressed directly by using single batch tablet machine (Rimek) after testing powder properties as shown in pre-formulation tests.

Table (1) : Formulae used in the preparation of Ketoprofen tablets containing different Concentrations of Superdisintegrants

No	Materials	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
1	Ketoprofen	100	100	100	100	100	100	100	100	100	100	100	10	100	100
2	Crospovidone	5	10	15	20	25	-	-	24	32	40	-	-	-	16
3	Croscarmillose-	-	-	-	-	-	5	10	-	-	-	24	32	40	16
4	Mannitol SD	100	95	90	85	80	100	95	42	34	26	42	34	26	34
5	Sorbitol	20	20	20	20	20	20	20	20	20	20	20	20	20	20
6	Calcium	-	-	-	-	-	-	-	150	150	150	150	15	150	150
7	PVP K30	-	-	-	-	-	-	-	10	10	10	10	10	10	10
8	Aspartame	-	-	-	-	-	-	-	22	22	22	22	22	22	22
9	Orange flavor	6	6	6	6	6	6	6	12	12	12	12	12	12	12
1	*Mg- stearate*	2	2	2	2	2	2	2	4	4	4	4	4	4	4
1	Colloidal S	2	2	2	2	2	2	2	2	2	2	2	2	2	2
1	MCC	11	11	11	11	11	11	11	14	14	14	14	14	14	14
	SUM	**246**	**246**	**246**	**246**	**246**	**246**	**246**	**400**	**400**	**400**	**400**	**40**	**400**	**400**

***Formulae number 1, 2, 3, 4, 5, 6, & 7 weigh 246 mg, while formulae 8, 9, 10, 11, 12, 13 &14 weigh 400 mg.**

CHARACTERIZATION OF FAST DISINTEGRATING TABLETS

Pre-formulation Tests of powder and Characterization of Blends for FDT were carried out as shown in table (2). The prepared tablets of **ketoprofen** Fast Dissolve Tablets were evaluated for different Pre Compressional properties like, (Angle of Repose, Bulk Density, Tapped Density, % Compressibility and Hausner's Ratio) [16], as shown in table (3).

Post Compressional properties like, general appearance, diameter, size, shape, Weight Variation[17], Friability, Hardness[18,19], Thickness, Disintegration Time[19], Wetting Time[20,21], Drug Content, Water Absorption Ratio[22], and In vitro Dispersion Time[22] were illustrated in table (4). In vitro Dissolution Profile[17, 23, 18] for all formulae were shown in table (5). Also Identification Tests like Melting point[3], IR Spectrum and calibration curve of Ketoprofen were conducted.

Table (6): Sample numbers in IR compatibility studies.

Sample No	Component(s)
Sample 1	Ketoprofen
Sample 2	Croscarmellose+ Ketoprofen
Sample 3	Crospovidone + Ketoprofen
Sample 4	Mannitol + Ketoprofen
Sample 5	MCC + Ketoprofen
Sample 6	Magnesium stearate + Ketoprofen
Sample 7	Colloidal silicone dioxide +Ketoprofen
Sample 8	Talc + Ketoprofen
Sample 9	Orange flavor + Ketoprofen
Sample 10	Sorbitol (liquid) + Ketoprofen
Sample 11	Mixture + ketoprofen
Sample 12	Mixture without talc + Ketoprofen

Functional group of Ketoprofen according to spectrum:
As illustrated in table (6), Ketoprofen and Ketoprofen combination with excipients were tested. The principal IR absorption peaks of ketoprofen at 1698 cm-1 (carboxylic acid carbonyl) and 1655 cm-1 (ketonic carbonyl) appeared in the spectra of ketoprofen as well as the microcapsules. These observations indicated no chemical interaction between the drug and other excipients used as shown in figures (7.1 – 7.24).

Calibration curve: The calibration curve of Ketoprofen was prepared in Sorenson's buffer (pH 6.8). The plot of different concentrations of Ketoprofen versus absorbance as illustrated in figure (1).

Table (2): Pre-formulation Tests of powder and Characterization of Blends for FDT.

F	App. Wt	App Vol	Tapp. Wt	Tapp. Vol	App. D	Tapp. D	Voids	Porosity	Bulkness
F 1	11.12	26.04	10.98	18.00	0.42	0.61	0.31	30.76%	2.36
F 2	10.60	25.20	10.65	17.45	0.41	0.59	0.29	30.75%	2.44
F 3	15.31	40.81	15.14	33.66	0.38	0.45	0.21	21.40%	2.67
F 4	15.40	38.72	14.5	33.20	0.39	0.43	0.14	14.21%	2.56
F 5	15.24	38.30	14.21	33.53	0.40	0.42	0.13	13.00%	2.50
F 6	14.52	36.86	14.55	29.10	0.38	0.48	0.21	21.05%	2.62
F 7	14.22	36.12	14.25	28.51	0.39	0.49	0.21	21.06%	2.54
F 8	14.80	36.01	15.12	29.02	0.41	0.52	0.19	19.40%	2.43
F 9	15.04	40.00	14.85	33.00	0.38	0.45	0.18	17.50%	2.67
F 10	14.97	38.11	15.013	30.04	0.39	0.5	0.22	21.05%	2.54
F 11	14.97	38.02	14.99	29.03	0.39	0.52	0.24	23.68%	2.54
F 12	14.76	36.00	41.9	29.00	0.41	0.52	0.19	19.40%	2.43
F 13	14.97	38.00	15.00	30.01	0.39	0.50	0.22	21.05%	2.54
F 14	15.01	40.02	14.85	33.11	0.38	0.45	0.18	17.50%	2.67

Table (3): Pre – Compressional Parameters (Angle of Repose, % Compressibility, Bulk Density, flowability and taste) of different Tablet formulations

Formula	Angle of Repose	Carr's Index	Hausner's Index	Flowability	Powder Taste
F 1	22.90	30.60%	1.44	passable	Bitter
F 2	24.05	30.50%	1.26	Passable	Bitter
F 3	21.31	16.70%	1.20	Good	Slightly bitter
F 4	18.02	9.30%	1.11	Excellent	Slightly bitter
F 5	13.04	4.70%	1.05	Excellent	Slightly bitter
F 6	25.14	20.40%	1.26	Good	Bitter
F 7	24.23	19.80%	1.24	Good	Bitter
F 8	24.02	19.50%	1.24	Good	No Bitterness
F 9	23.03	17.50%	1.21	Good	No Bitterness
F 10	26.06	21.05%	1.27	Passable	No Bitterness
F 11	27.63	23.75%	1.31	Passable	No Bitterness
F 12	24.72	19.50%	1.24	Good	No Bitterness
F 13	26.63	21.03%	1.27	Passable	No Bitterness
F 14	22.19	17.40%	1.21	Good	No Bitterness

Table(4): Evaluation of Ketoprofen FDTs.

No.	Average Weight (mg)± S.D	Thickness (mm) ± S.D	Friability (mg)± S.D	Hardness (mg)± S.D	Wetting Time (min) ± S.D	Water Absorption Rate %	Dispersion Time (min) ± S.D	Disintegration Time (sec) ± S.D
F 1	247.21±3.705	3.528±0.001	2.457±0.007	5.950±0.164	4.711±0.016	24.45%	6.420±0.030	260.33±5.202
F2	247.79±4.036	3.507±0.001	2.503±0.008	5.500±0.447	4.436±0.146	30.55%	4.061±0.053	241.67±2.422
F 3	249.31±3.074	3.524±0.001	2.460±0.011	5.467±0.103	3.110±0.1020	43.70%	1.061±0.011	38.467±0.797
F 4	249.78±2.347	3.527±0.009	2.049±0.010	4.350±0.207	3.482±0.025	47.90%	1.511±0.010	34.350±0.367
F 5	249.68±2.029	3.542±0.001	2.494±0.007	4.750±0.164	2.222±0.019	45.91%	1.330±0.011	30.383±0.421
F 6	251.52±4.694	3.528±0.005	2.056±0.080	6.000±0.141	4.36±0.185	38.75%	7.547±0.025	70.411±0.424
F 7	251.57±4.018	3.527±0.001	2.519±0.004	6.117±0.007	4.486±0.086	40.00%	5.801±0.010	63.667±0.467
F 8	399.53±2.169	5.512±0.001	3.979±0.009	3.117±0.147	6.186±0.169	25.00%	3.042±0.015	40.083±0.248
F 9	397.36±5.908	5.518±0.001	4.004±0.016	2.267±0.163	4.001±0.011	29.30%	2.567±0.0153	30.467±0.531
F 10	403.57±5.470	5.519±0.008	4.162±0.011	3.033±0.137	3.240±0.114	28.92%	2.247±0.015	30.067±0.294
F 11	397.00±3.559	5.018±0.002	3.953±0.0149	2.850±0.055	8.012±0.022	15.53%	8.317±0.021	56.483±0.519
F 12	399.36±4.003	5.008±0.001	3.099±0.008	4.933±0.151	6.016±0.022	11.11%	7.147±0.006	52.051±0.152
F 13	400.157±4.598	5.032±0.002	3.987±0.012	4.967±0.051	5.380±0.053	25.22%	6.110±0.0165	38.067±0.543
F 14	399.47±5.957	5.012±0.001	3.978±0.009	4.051±0.083	8.452±0.0432	20.20%	5.501±0.012	123.616±0.962

Table(5): Dissolution profile of Ketoprofen fast dissolving tablets using Sorenson's buffer.

Formula	% after 2 min	% after 5 min	% after 10 min	% after 15 min
F1	16.86%	26.42%	55.86%	69.47%
F2	35.93%	97.42%	99.89%	101.25%
F3	98.43%	100.63%	101.13%	101.58%
F4	98.26%	99.56%	103.20%	103.20%
F5	99.00%	101.31%	104.63%	104.63%
F6	16.86%	23.65%	49.44%	67.56%
F7	19.46%	42.40%	68.52%	83.22%

F8	42.11%	46.40%	52.00%	61.37%
F9	40.79%	53.03%	76.25%	84.29%
F10	98.54%	99.37%	99.63%	99.63%
F11	28.48%	46.43%	75.45%	92.57%
F12	19.75%	37.16%	63.06%	89.54%
F13	26.97%	44.16%	89.17%	97.36%
F14	9.78%	14.17%	23.17%	42.67%
Profenid*	9.47%	19.63%	25.02%	39.97%

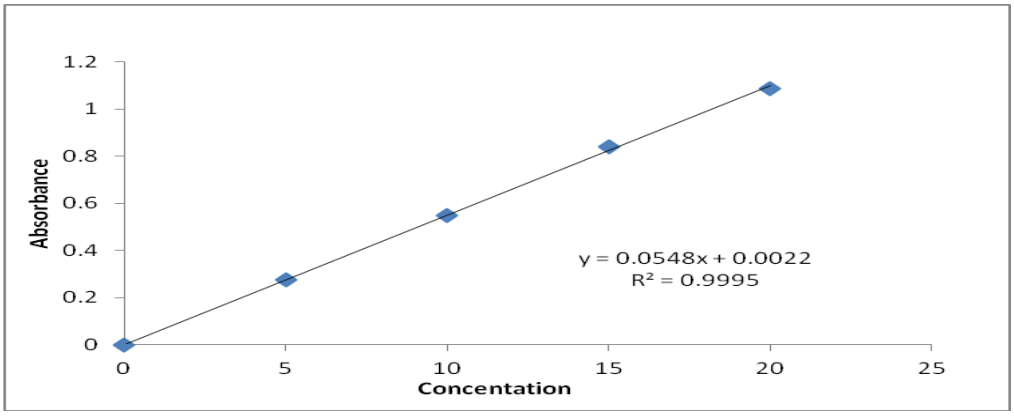


Figure (1): Calibration Curve of Ketoprofen

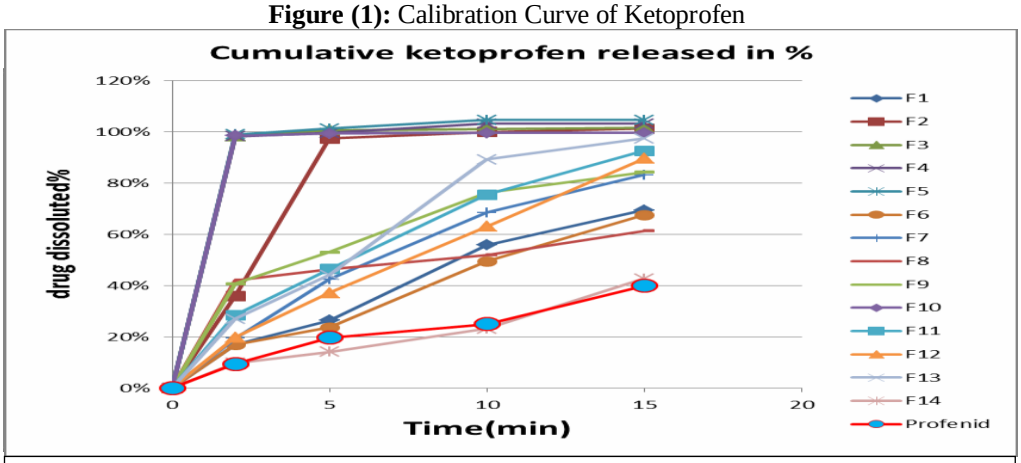


Figure (2): Cumulative dissolution release of ketoprofen

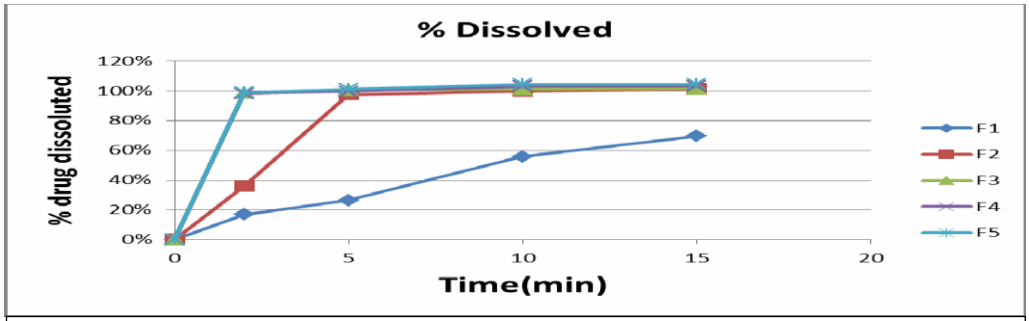


Figure (3): Dissolution release of ketoprofen form F1-F5

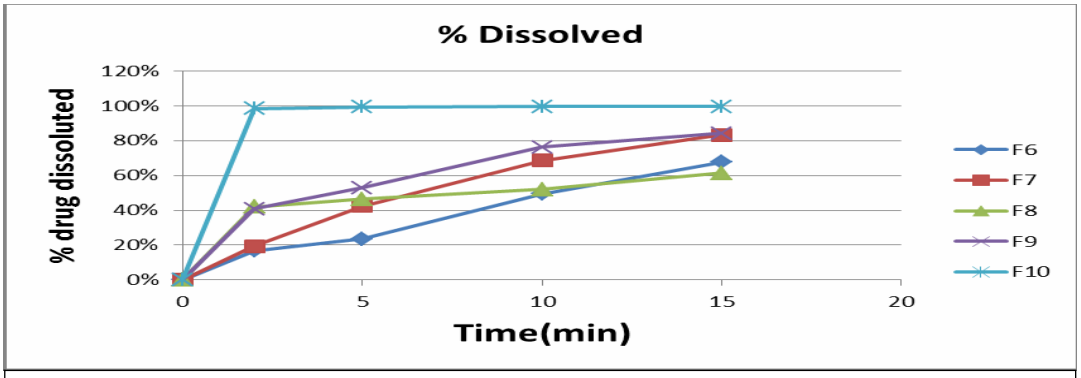


Figure (4): Dissolution release of ketoprofen form F6-F10

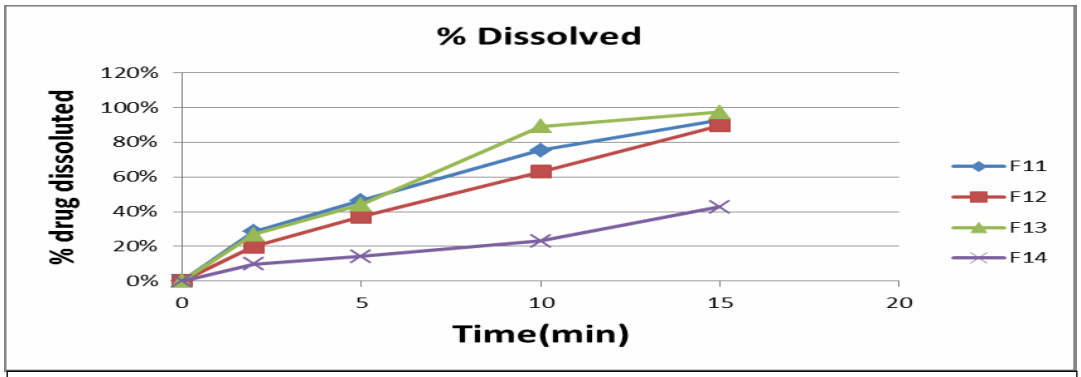
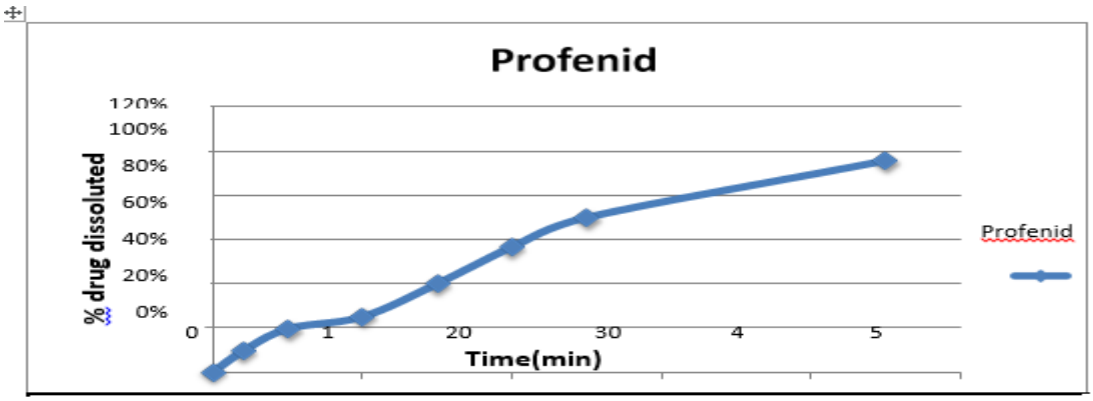


Figure (5): Dissolution release of ketoprofen form F11-F14



Figure(6): Dissolution profile of Profenid

Results and Discussion

Regarding Infrared spectroscopy (drug-excipient interaction), the characteristic peaks of ketoprofen (principal peaks of ketoprofen are at wave numbers 1700, 1655, 1445, 1285, 1230, 965, 715 cm-1) seemed to be identical with that of standard ketoprofen curve from British Pharmacopeia as shown in Figures (7.1 – 7.24). This clearly indicates that there is no drug excipient interaction.

Melting point[3] of ketoprofen purity was determined using capillary method, The sample started to melt at 94C°, and turned into liquid at 95.4 C°, thus indicating that the sample used was pure according to British Pharmacopeia.

As shown in Table (7), figure (1), **Calibration curve** of Ketoprofen was prepared using Sorenson's buffer (pH 6.8). The plot of different concentrations of Ketoprofen versus absorbance was found linear at 260 nm. Slope, intercept and correlation coefficient values were found 0.054824, 0.00218 and 0.9995

respectively.

As illustrate in **table (3),** Compressibility index (Carr's index), show that all formulae passed the test and some with excellent rate.

For Hausner's ratio is another non-official measure for powder flow, show that most formulae had good ratio which indicating good powder flow. Angle of repose is another parameter which have been tested and the results were good, and all of the formulae passed the test as shown in table (3).

Good flow prosperities may be attributed to the addition of colloidal silicon dioxide as lubricant and magnesium stearate as glidant in the 1% W/W and 0.5% W/W respectively.
After compression of powder, the tablets were evaluated for their organoleptic characters (Color, Odor, Taste), physical appearance (Shape, Surface Texture), quality control parameter (Thickness, Diameter, Weight Variation, Hardness, Friability, Disintegration Time and Dissolution Test) and non-official Tests (Wetting Time, Water Absorption Rate and Dispersion Time).

For organoleptic characters (Color, Odor, Taste) as shown in table (3), indicate that all tablets of each formula were white in color, have orange odor due to addition of orange flavor in each formula by 3% W/W, rounded in shape with biconvex and scored surface. Taste of tablets differed mainly in the formulae, where Formulae F1 to F7 were irritant to GIT, especially the throat, and bitter in taste, which is attributed to ketoprofen, while F8 to F14 were not, because modification was done to these formulae in an attempt to reduce the irritation and bitterness. Calcium carbonate and polyvinylpyrrolidone (PVP-K30) complex were used as the main *masking agent*, based on a study by *SIVAKRANTH. M* et.al. [(15)]. The modified formulation showed good results, and Formulae F8 to F14 had almost no bitterness.

As shown in table (4**), Weight Variation** parameter for formulae F1 to F7 and F8 to F14 as found to be in between 228.43 - 264.02 mg and 375.72 - 423.41 mg respectively, which are within the acceptable limit for uncoated tablets as illustrated in British Pharmacopeia (B.P) and United State Pharmacopeia (USP). In addition, as thickness, parameter is concern of formulae F1 to F7 and F8 to F14 was found to be in between 3.00 - 3.70 mm and 4.67 – 5.7 mm. respectively., which are within the acceptable range.

As shown in table (4), the mechanical strength of tablets was found to be in the range of 4.35 to 6.11 Kg/cm2 for formulae F1 to F7 and it was 2.26 to 4.97 Kg /cm2 for F8 to F14 respectively, which are satisfactory strength to withstand the applied mechanical shocks.
Friability of all formulae was found to be less than 1%, which indicates tablets' ability to withstand abrasion in handling, packaging and shipment[4]. The result were shown in table (4).

In Vitro Wetting time was also studied to know the time required for complete wetting of tablets when placed on tongue. The in vitro wetting time of all formulae when placed on tongue were varied between 2.20 to 8.46 min. Water absorption ratio found to be within 11.11% to 47.9% where the lowest formulae in the percent is F12 while F 4 is the best one. Significant variation in the values of both tests was observed between formulae, which might be explained due to different concentrations of superdisintegrants that have been employed in each formulae; due to addition of calcium carbonate to F8 to F14 which were characterized by low water absorption ratio and somehow high wetting time as comparing to F1 to F7. This can be attributed to calcium carbonate being practically insoluble in water (0.0013 g/100 mL) (25°C) [24]. The results are shown in Table (4). It is also due to higher weight of F8 to F14 tablets than F1 to F7, which weighed 400 mg that need more time for wetting by water, while F1 to F7 weighed 246 mg. Another reason that can explain the higher values of both tests is due to the unavailability of Flash Mannitol in Yemen at a time, so it was replace by standard mannitol.

As shown in table (4), Dispersion time were found to be between 1.06 to 8.30 min in which it is characterized by relatively higher values in Formulae F8 to F14 than F1 to F7. This could be attributed to calcium carbonate solubility issue, and the two sizes of tablets prepared (250mg and 400mg), where the later required more time for complete dispersion. Another reason of higher dispersion time in formulae containing croscarmellose (which being highest in F13), is that it's less hygroscopic than crospovidone (being highest in F10). So normally crospovidone will take up water faster than croscarmellose[(25)], and therefore lower dispersion time was found in formula F10.

As shown in table (4), d**isintegration time** of FDTs was tested in comparison with conventional tablets (Profenid® & Pronid® tablets). FDTs were characterized by lower disintegration time than conventional tablets. The results of disintegration time of FDTs were found to be between 30 to 260 sec., the shortest formula in time was F5 while the longest was F1. Results of conventional tablets were between 5-6 minutes. Formulae number 5 & 10 were characterized by shortest time because both consist of

10% W/W of crospovidone as superdisintegrant while formulae number 1,2 &14 have the longest time because F1 and F2 consist of only 2-4% W/W of crospovidone as superdisintegrant and F14 consist of (2% : 2%) of crospovidone with croscarmallose-Na.

In vitro drug release studies are one of the most important experiments to prove if the FDTs are convenient to be used for rapid action. The study was applied to all formulae prepared using eight digital dissolution tester at 37.5 C^o and the test were carried at different time intervals of time 2 , 5 , 10 & 15 minutes.

Results illustrated in table (5), shown that formulae number 4, 5 & 10 reached to 98% drug release only after 2 minutes. In addition, formulae number 2 and 3 reached to 98% drug release through 5 minutes, while formulae number 1, 6, 7, 8, 9, 11, 12 & 13 drug release were gradually increased with increasing the time of dissolution. So, the best formulae according to drug release study were number 4, 5 &10 which consist of 8-10 % W/W of crospovidone as superdisintegrants while formula number 14 was the least in percent of drug release which reached drug release of only 42.67% after 15 minutes, this formula consist of (2% : 2%) of crospovidone : croscarmallose-Na. Same study were used in comparison with conventional tablets (Profenid®) to show how much FDTs formulae have been improved in drug release.

As shown in table (5), figure (6), conventional tablets (Profenid®) have been studied under similar conditions that were employe in studying FDTs and the results obtained showed that maximum drug release of 95% Profenid® through 45 minutes.

Conclusion:

ketoprofen, an NSAID, was selected as a model for preparation of fast dissolving tablets by direct compression technique. Fast dissolving tablets were prepare by adding different concentrations of superdisintegrants and several formulae of ketoprofen FDTs have been prepared, utilizing different excipients. Masking taste of bitterness characters of Ketoprofen has been done to decrease compliance for formulated tablets. All prepared FDTs were evaluated for weight variation, thickness uniformity, friability, hardness, wetting time, water absorption time, dispersion time, disintegration time, and dissolution time.

IR spectroscopy has been used for identification of Ketoprofen as pure drug and for all excipients as an indication of interaction (compatibility) between ketoprofen and the used excipients. Most of the IR chromatograms seemed to be identical with the chromatogram of pure ketoprofen. Melting point measurement and calibration curve were used to identify and standardize ketoprofen sample.

As for preformulation tests, bulk density of powder mixtures varied between 0.375 to 0.423, tapped density was found in the range of 0.42 to 0.611. Most of powder blends of all formulation had Hausner's ratio less than 1.3 indicating good flowability, compressibility index was found mostly less than 30%, and the angle of repose was found to be less than 30^o.

In the evaluation of tablets, the mean thickness of all formulae was found to be 3.5 mm for formulae F1 to F7, and in the range of 5 mm to 5.5 mm for formulae F8 to F14, the average weight of formulae F1 to F7 was 250 mg, and for formulae F8 to F14 was 400 mg. The friability of all formulae was less than 1%, indicating good resistance to packing and handling. The mean hardness for formulae F1 to F7 was between 4.5 to 6 kg, and for formulae F8 to F14 was between 2.5 to 5 kg. The wetting time of all formulae was in the range of 2.20 to 8.46 in minutes, and dispersion time of all formulae was found to be between 1.06 to 8.30 minutes. The disintegration time of formulae F3, F4, F5, F8, F9, F10, F13 was less than 40 seconds. Formulae F3, F4, F5, F8, F9, F10 contained crospovidone as the main superdisintegrant, indicating that crospovidone had better and faster disintegration than croscarmellose, and that increasing the amount of crospovidone does not decrease disintegration time. Formulae F13 contained the highest amount of croscarmellose.

The dissolution profile of formulae F3, F4, F5, F10 showed that more that 98% of drug release in 2 minutes. This could be attributed to the fast disintegration of these formulae. Although F8 had good disintegration, it may be attributed to low force of compression empyloed because its hardness has low value which lead to lower disintegration time, the presence of calcium carbonate and the lower amount of crospovidone could explain the lower drug release than formula 10.

The aforementioned results revealed that formulae F4 was the best ketoprofen FDT.

References.

1. Yash Paul, Sarvan Tyagi and Bhupinder Singh, Formulation and Evaluation of Oral Dispersible Tablets of Zidovudine with different Superdisintegrants. International journal of current pharmaceutical review and research- volume 2, issue 2, May - July 2011.
2. Sehgal Prateek et al. (2012). Fast Dissolving Tablets: A New Venture in Drug Delivery. Am. J. PharmTech Res. ; 2(4)
3. Mahajan Anil Arun (2011). Formulation and evaluation of fast dissolving tablets of ketoprofen- Master dissertation. Rajiv Gandhi University of Health Sciences, Karnataka,

Bangalore.
4. Fu Y, Yang S, Jeong S.H., Kimura S, Park K. Orally fast disintegrating tablets: Development, technologies, taste-masking and clinical studies. Crit Rev Ther Drug Carrier Sys, 2004; 21:433-76.
5. Nayak AK, Manna K. Current developments in orally disintegrating tablet technology. Journal of Pharmaceutical Education and Research. 2011;2(1):21–34.
6. GOPAL.V et al. (2011). Formulation, design and evaluation of orally disintegrating tablets of loratadine using direct compression process. International Journal of Pharma and Bio Sciences -Vol 2, Issue 2: 389- 400.
7. Nikam et al. (2011). Mouth dissolving tablets: an overview. Pharmacologyonline 3: 562-58.
8. Tiwari et al. (2013), Formulation and Evaluation of Faast Dissolving Tablets, IJARPB: 3 (1), 60 – 69.
9. R. V. Keny, Chrisma Desouza, and C. F. Lourenco. (2010). Formulation and Evaluation of Rizatriptan Benzoate Mouth Disintegrating Tablets. Indian J Pharm Sci.; 72(1): 79–85
10. British Pharmacopoeia. (2013) .Volume I & II :Ketoprofen. Ph. Eur. monograph 0922.
11. Khan, J., Yuen, K.H., Bee Hong, N., Chitneni, M., Elhassan, G.O., Al-Dhali, S., & Kaleemullah, M. (2010). Preparation and In-vitro Evaluation of Different Controlled Release Polymeric Matrices Containing Ketoprofen. HealthMED, Vol. 4(2), 386-392.
12. USP. <616> Bulk density and tapped density. USP30 NF 25 (2007)
13. Hausner H. H(1967). Friction conditions in a mass of metal powder. Int. J. Powder Metall. ;3:7–13.
14. Carr R. L(1965). Evaluating flow properties of solids. Chem. Eng. ;72:69–72.
15. SIVAKRANTH. M et.al. (2011). formulation and evaluation of oral fast dissolving tablets of sildenafil citrate. International Journal of Pharmacy and Pharmaceutical Sciences. Vol 3, Suppl 2, 2011.
16. M.E. Aulton. Pharmaceutics, the science of dosage form design, second edition. Churchill Livingstone. (2002); p-114.
17. S. Basavaraj et.al. (2008). .; Development and Characterization Of Orodispersible Tablets of Famotidine Containing a Subliming Agent , Trop . J. Pharm. Res., 7(4):1185-1189.
18. AL- Buryhi,M,M; Doctor Thesis , Faculty Of Pharmacy , Cairo University , (2009).
19. Bolourtchian et.al. (2008). Formulation and Optimization of Captopril Sublingual Tablet Using D-Optimal Design , IJPR ; 7 (4) : 259- 267.
20. Singh, Jashanjit , Singh, and Rajmeet. (2009). Optimization and Formulation of Orodispersible Tablets of Meloxicam , Trop. J. Pharm. Res., 8(2):153-159.
21. M. Vikram et.al. (2009). Formulation, Characterization ,and Optimization Of Fast- Dissolve Tablets Containing Celecoxib Solid Dispersion ,Dissolution Technologies.
22. Bompilwar MS, Gawai NM and Biyani KR. (2013). Formulation and Evaluation of Orodispersible Tablet of Metformin HCl. International Journal of Research in Pharmaceutical and Biomedical Sciences. Vol. 4 (3) Jul– Sep 2013.
23. Sheetal Malke, Supriya Shidhaye, VJ Kadam. (2007). Formulation and evaluation of oxcarbazepine fast dissolve tablets. Indian journal of pharmaceutical sciences. Volume : 69, Issue : 2, Page : 211-214
24. Raymond C Rowe, Paul J Sheskey, Marian E Quinn. (2009). Handbook of Pharmaceutical Excipients. 6th edition. Pharmaceutical Press, UK. p-(206-208), 208-210, 581-585, 129-133, 404-407, 728-731, 424-428, 679-682, 48-50, 86-89, 185-18).
25. Juanita Tanuwijaya and Karsono, The Effects of Crospovidone and Croscarmellose Sodium as Superdisintegrants on the Characteristics of Piroxicam Nanoparticles ODT (Orally Disintegrating Tablet), IJPRIF, Vol.5, No.4, pp 1590-1597, Oct-Dec 2013.

Infrared Spectral Assignment:

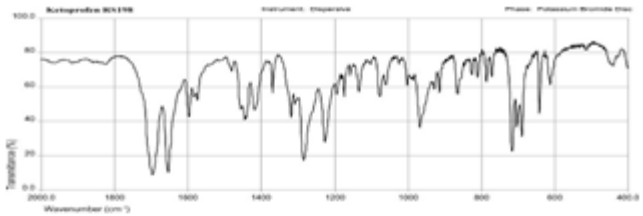


Figure (7.1): IR spectra of standard ketoprofen (from BP)

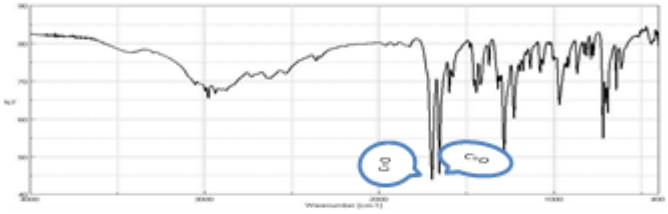


Figure (7.2): IR spectra of ketoprofen(sample 1)

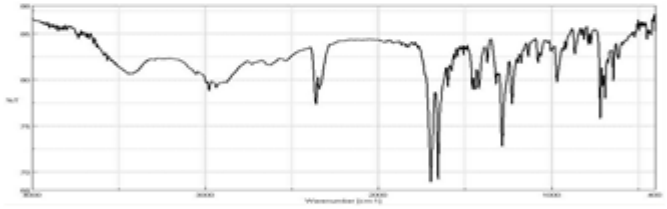


Figure (7.3): IR spectra of Croscarmellose with ketoprofen (sample 2

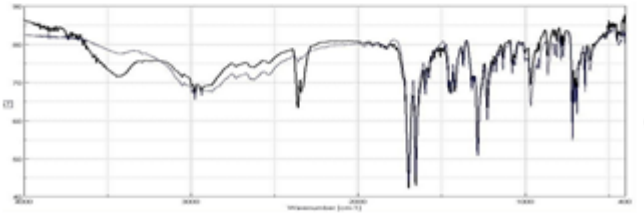


Figure (7.4): IR spectra of (sample 2) and ketoprofen (sample 1)

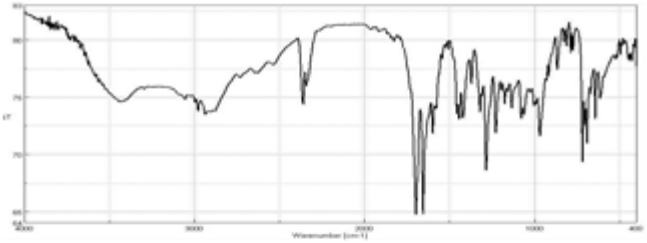


Figure (7.5): IR spectra of crospovidone with ketoprofen (sample 3)

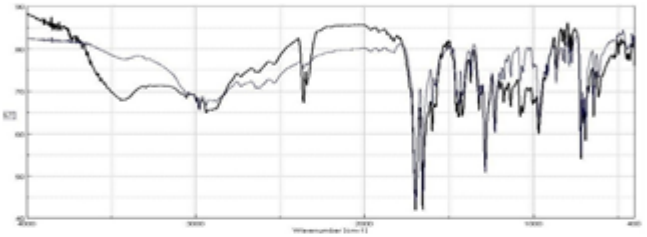


Figure (7.6): IR spectra of (sample 3) and ketoprofen (sample 1)

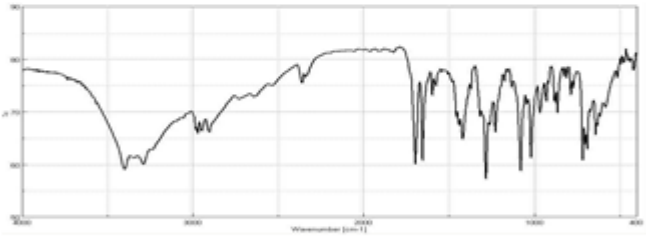


Figure (7.7): IR spectra of mannitol with ketoprofen (sample 4)

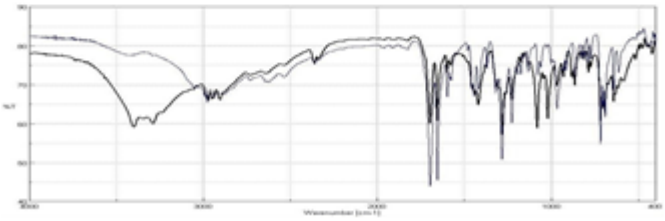


Figure (7.8): IR spectra of sample 4 and ketoprofen (sample 1)

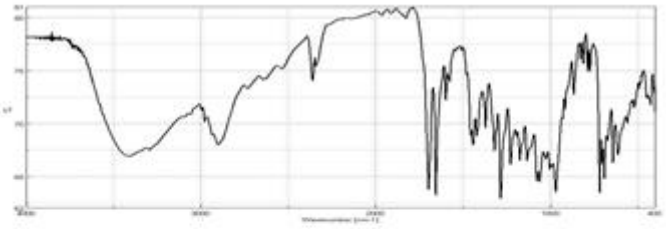


Figure (7.9): IR spectra of microcrystalline cellulose MCC with ketoprofen

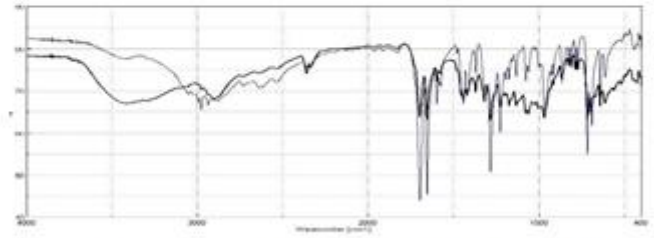


Figure (7..10): IR spectra of (sample 5) and ketoprofen (sample 1)

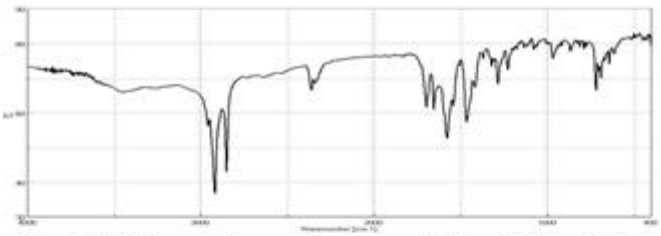


Figure (7.11): IR spectra of magnesium stearate with ketoprofen (sample 6)

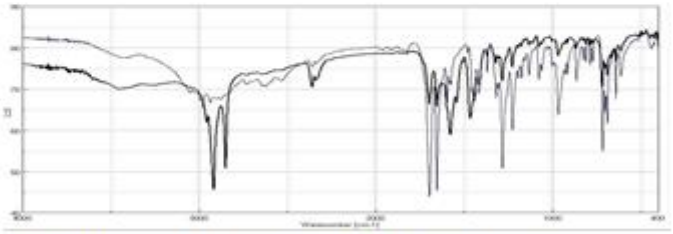


Figure (7.12): IR spectra of (sample 6) and ketoprofen (sample 1)

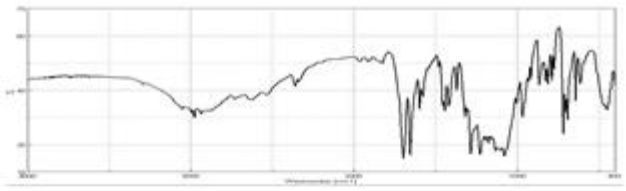


Figure (7.13): IR spectra of colloidal silicone dioxide with ketoprofen (sample7)

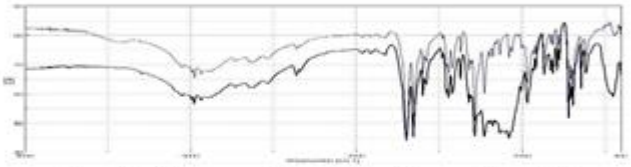


Figure (7.14): IR spectra of (sample 7) and ketoprofen(sample 1)

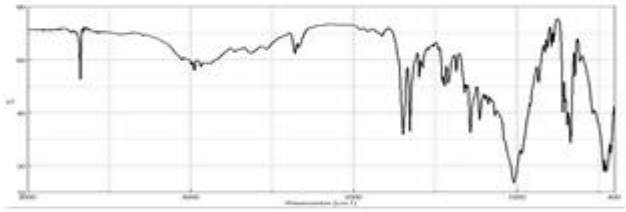


Figure (7.15): IR spectra of talc with ketoprofen (sample 8)

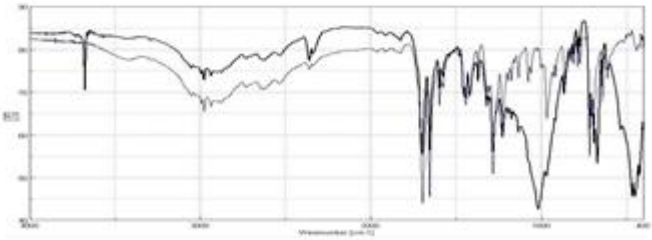


Figure (7.16): IR spectra of (sample 8) and ketoprofen (sample 1)

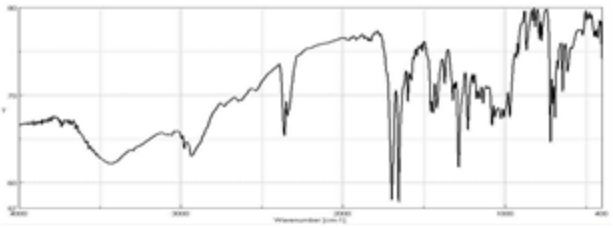


Figure (7.17): IR spectra of orange flavor with ketoprofen (sample 9)

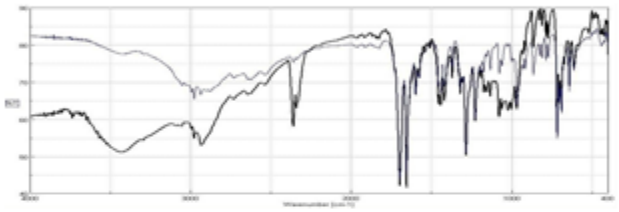


Figure (7.18): IR spectra of (sample 9) and ketoprofen (sample 1)

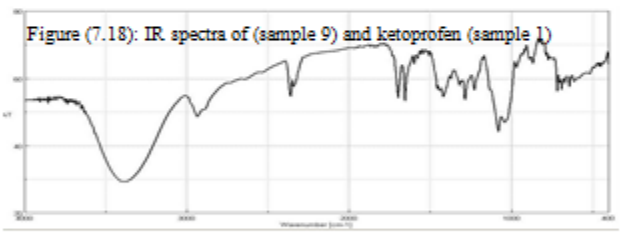


Figure (7.19): IR spectra of liquid sorbitol with ketoprofen (sample 10)

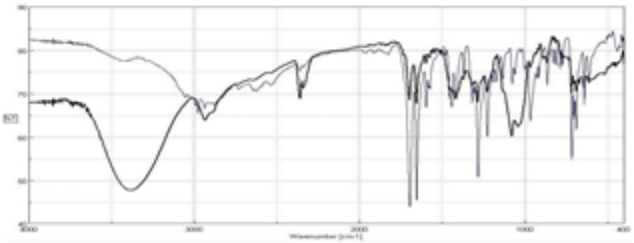


Figure (7.20): IR spectra of (sample 10) and ketoprofen (sample 1)

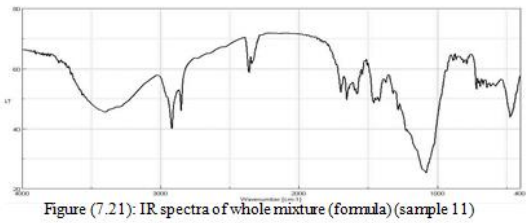


Figure (7.21): IR spectra of whole mixture (formula) (sample 11)

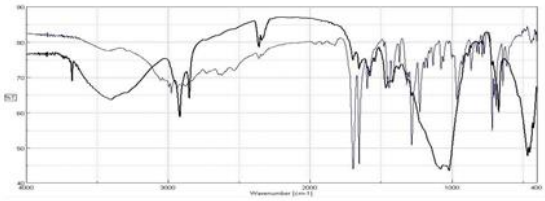


Figure (7.22): IR spectra of (sample 11) andketoprofen(sample 1)

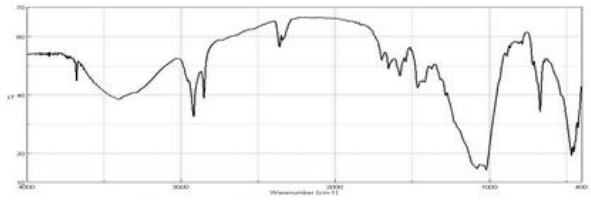


Figure (7.23): IR spectra of mixture without talc with ketoprofe (sample 12)

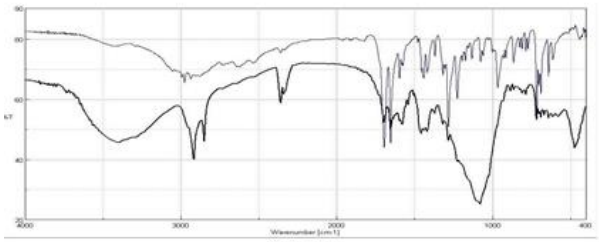


Figure (7.24): IR spectra of (sample 12) and ketoprofen (sample 1)