Preparation and Evaluation of Oral Disintegrating Tablets of Ketoprofen by Dirct Compression

Saddam J.Nasser [*,1],Laith H. Sameen[*] , Mowafaq M.Ghareeb[*]

*Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq

Abstract

Ketoprofen is a non-steroidal anti-inflammatory (NSAID) drug with analgesic, anti-inflammatory, and antipyretic effects. It is widely used in the treatment of inflammation and pain associated with rheumatic disorders such as rheumatoid arthritis, osteoarthritis, and in soft tissue injury. The purpose of this study was to prepare an oral disintegrating tablets of ketoprofen by simple method. The tablets were prepared by direct compression method and different ratios of various subliming agents or superdisintegrants were incorporated. Then these tablets were evaluated for hardness, friability, weight variation, water absorption ratio, disintegrating time and dissolution time. The results showed that Formula F11 batch had short disintegration time (18.0 sec) with good physical properties. This formula demonstrated a promised potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Key words: Rapid disintegrating tablets, Ketoprofen, Direct compression, Superdisintegrants.

تحضير وتقييم حبة الكتوبروفين سريعة التفكك بالفم بطريقة الكبس المباشر

صدام جمعة ناصر [*،1] وليث حمزة سمين *، موفق محمد غريب *

*فرع الصيدلانيات ، كليةالصيدلة ، جامعة بغداد، بغداد ، العراق

الخلاصة

دواء الكيتوبروفين هو مضاد التهابات غير ستيرويدي مع اثر مسكن وخافض للحرارة . انه شائع الاستعمال بعلاج الالتهابات والالام المصاحبة لامراض المفاصل كالرثوي والتهاب العظام وجروح الانسجة الرخوة . هدف الدراسة هو تحضير الكيتوبروفين على شكل حبوب سريعة التفتت بالفم بدون استعمال الماء بطريقة الكبس المباشر البسيطة وباستعمال عدة مواد وتراكيز مختلفة من المواد المتسامية ومسببات التفتت المتطورة. خضعت الحبوب المحضرة الى عدة اختبارات منها الصلابة والهشاشة واختلاف الوزن ونسبة امتصاص الماء ووقت التفتت والتحلل . أثبتت النتائج ان التركيبة (ف11) المتكونه من تركيز (w/w 10% crospovidone) وتركيز (Microcrystaline cellulose pH(102) 10% w/w) لها اقصر وقت تفتت (18.0)ثانية مع خواص فيزياوية جيدة . وهي تركيبة واعدة لزيادة الامتصاص وتحسن التوافر الحيوي وفعالية الدواء وتقبل المريض.

الكلمات المفتاحية :حبوب سريعة التفكك ، كيتوبروفين ، الكبس المباشر ، مواد سريعة التفكك .

Introduction

The conventional oral dosage forms (tablet and capsule) have wide acceptance up to 50-60 % of the total dosage forms [(1)]. Tablet is still most popular dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance [(1)]. Orally disintegrating tablets are also called as Orodispersible tablets (ODTs), quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rap melts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing [(2)].To overcome this problem, scientists have developed innovative drug delivery systems known as mouth dissolving tablets. Their characteristic advantages such as administration without water, anywhere, anytime which lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability and good stability made these tablets popular as a dosage form in the current market [(3,4)]. a non-steroidal anti-inflammatory (NSAID) has been indicated for various painful indications [(5)] and proved as effective as other NSAIDs with lower indications of gastro-intestinal adverse effects and thus, resulted in a greater compliance with treatment [(6)]. Ketoprofen is propionic acid derivative anti-rheumatic drug with well-known anti-inflammatory, antipyretic and analgesic properties to treat mild to moderate pain and dysmenorrhea the structure of Ketoprofen as shown in (fig.1) [(7, 8)].

[1] Corresponding author E- mail :Saddam- Jumaa @ yahoo.com

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Also it is an inhibitor of prostaglandin synthetase [9]. However, it is not freely soluble in water and causes systemic disturbances in gastrointestinal tract [10]. In the present study, an attempt has been made to develop mouth dissolving tablets of ketoprofen using different subliming agents on the disintegration of orodispersible tablets with good physical properties and acceptance.

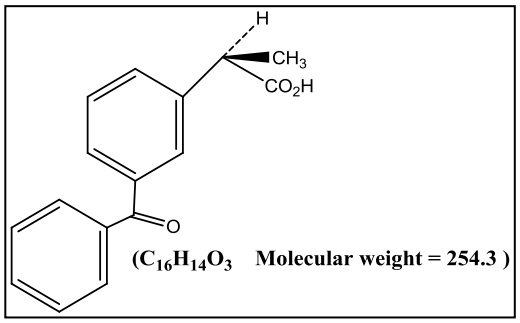

Figure 1: Ketoprofen chemical structure

Material and Methods

Materials

Ketoprofen powder, Crospovidone (CP), and Croscarmellose Sodium (CCS) were purchased from 3B pharmaceutical (Wuhan) international Co. Ltd, china. Microcrystalline Cellulose (Avicel PH 102)&(Avicel PH 101) were purchased from Hekma Drug Industry, Jordan. Magnesium stearate, Mannitol, Ammonium Bicarbonate were purchased from Riedel-De-Haen AG seelze, Germany. Camphor was purchased from Evans Medical Ltd, Liverpool, England. All other materials were of analytical grade.

Methods

Formulation of orodispersible tablets of ketoprofen

The orodispersible tablets of ketoprofen were prepared using the camphor and Ammonium bicarbonate as subliming agent, menthol and Crospovidone (CP), and Croscarmellose Sodium (CCS), and sodium starch glycolate (SSG) as superdisintegrant, microcrystalline cellulose (MCC) and mannitol as diluent, sodium saccharin as sweetening agent, and talc as flow promoter and magnesium stearate as lubricant, the composition of each batch is shown in Table 1. The ketoprofen (50mg) and excipients were passed through sieve (#80) to ensure the better mixing. The powder was compressed using Manesty, Type F_3 compression machine equipped with 8 mm round punch by direct compression technique. Sublimation was performed from tablets contain subliming agents at 60ºC. A minimum of 50 tablets was prepared for each batch.

Table 1: Composition of different batches of orodispersible tablets of ketoprofen

Material /mg	Formula No.											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
ketoprofen	50	50	50	50	50	50	50	50	50	50	50	50
Camphor	4.5 (2.5%) w/w											
Ammonium bicarbonate		4.5 (2.5%) w/w	9 (5%) w/w									
CCS				9 (5%) w/w	18 (10%) w/w	27 (15%) w/w						
SSG							9 (5%)	18 (10%) w/w	27 (15%) w/w			
CP										9 (5%) w/w	18 (10%) w/w	27 (15%) w/w
(MCC102)	18	18	18	18	18	18	18	18	18	18	18	18
Talc	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
Sodium saccharin	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
Mg stearate	1	1	1	1	1	1	1	1	1	1	1	1
Mannitol Q.S. to	180	180	180	180	180	180	180	180	180	180	180	180

Pre Compression Parameters

Angle of repose

Angle of repose was determined using funnel method [11]. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula;

$$\mathbf{Tan\ \theta = h/r}$$

Where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

Compressibility (Carr's) index

An accurate weight of formula granules was poured into a volumetric cylinder to occupy a volume (V_o) and then subjected to a standard tapping procedure onto a solid surface until a constant volume was achieved (V_f). The Carr's index was calculated using following equation [11].

$$\text{Compressibility Index} = 100 \times \frac{V_o - V_f}{V_o}$$

Evaluation of the prepared orodispersible ketoprofen tablets

Weight variation

Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±7.5%.

Uniformity of content

The content of the prepared ketoprofen orodispersible tablets was determined. Ten tablets were assayed individually. Each tablet was crushed individually and dissolved in 100ml of methanol .The filtrated solution was diluted appropriately and the drug content was measured spectrophotometrically at 260nm using (Carry UV- visible spectrophotometer) [11]. The requirement for this test is met if the amount of ingredient in each of the ten tablets lies within the range of (85-115) % of the drug present in each tablet.

Wetting time

A piece of tissue paper (12cm x10.75cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 10ml of buffer solution simulating saliva pH 6.8 and amaranth. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was recorded [12].

Hardness

The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading ± SD was recorded.

Friability

Twenty tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was calculated using following equation [13].

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

In vitro Disintegration Time

The disintegration time was defined as the time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measure in second using artificial saliva as disintegration medium. Six tablets were placed individually in each tube of disintegration test apparatus. The values reported are mean ± standard deviation [14, 15].

In - vitro drug dissolution test

Dissolution rate was studied by using USP XXIII Type-II dissolution apparatus employing a paddle stirrer at 50 rpm the two experiments were done for dissolution using two different dissolution media 900 ml of pH(6.8) phosphate buffer and 0.1 N HCl at 37±0.5ºC.One tablet was used in each test. A (5 ml) sample from dissolution medium was withdrawn at different time intervals (0, 1, 2, 4, 6, 8, 10, 15 and 20 min). The withdrawn sample was replaced by same amount of fresh dissolution medium to maintain sink conditions. The samples were filtered through 0.22 µm membrane filter and analyzed for drug content by measuring the absorbance at 260 nm using UV spectrophotometer [16].

Statistical analysis

The mean ± standard deviation of the experiments results were analyzed using one way analysis of variance (ANOVA).

Results and Discussion

Ketoprofen tablets were prepared by direct compression method. Twelve formulations were prepared with two different subliming agents or three different superdisinegrants. Each superdisinegrants was used in three different concentrations (5% (w/w), 10% (w/w) and 15% (w/w)). Table 2 shows the data obtained from the precompression evaluation of tablets. All batches of the tablets were evaluated for various pre and post compression parameters. precompression parameters like angle of repose, and compressibility index while post compression parameters such as hardness, friability, drug content, wetting time, water absorption ratio, and disintegration time were evaluated. Post compression parameters are reported in Table 3. All the above properties and value were near to boundary of standard limit except formula (F1) produced mechanically weak tablets with hardness and friability (2 kg/cm² and 1.21%) [13].All the tablets maintained hardness in the range 3.17–6.08 kg/cm^2. The loss in total weight of the tablets due to friability was in the range of 0.26-0.88%. The drug content in different formulation was highly uniform and in the range of 99.60-99.92%. [13].Wetting time is used as an indicator of the ease of tablet disintegration and found to be 8.9-41sec. Water absorption ratio ranged from 6.66-106.1. The result in vitro disintegration time indicated that formula (F1) has shortest disintegration time this decrease in the disintegration time may be attributed to the increasing porosity of the tablet so that the porous hydrophilic matrix will easily pick up the disintegration medium and thus facilitating the wicking action of the superdisintegrant and bringing about rapid tablet disintegration and shorter wetting time [17]. but unfortunately with unacceptable hardness (2 kg/cm^2) and in general formulas based on subliming agent produce longer disintegration time than formulas used superdisintegrant thus for formulas (F4-F12) the shortest disintegration time was 18.04 for formula F11 which contain 10% crospovidone as superdisintegrant .

An increasing in concentration of superdisintegrants over an optimum lead to increase in the disintegration time of orodispersible tablet. The reason behind this increase may be due to formulation of a viscous gel layer on the surface of tablet which prevents the further penetration of disintegration medium and hinder the disintegration [18]. This prevents the penetration of water to the core of the tablet. In contrast, CP has little tendency to form a gel [19].The formula (F11) contain 10% of CP resulted in an improvement of both disintegration time and wetting time due to the property of CP and a significant difference ($P<0.05$) in the DT value of tablets in presence of the CP, CCS and SSG superdisintegrants [20]. From this can concluded that the superdisintegrant efficiency is in following descending order; crospovidone > sodium starch glycolate > croscaramellose, and 10% is the optimum percent for good disintegration.The formula (F11) was selected as the best formula that subjected for dissolution studies in comparison to conventional (Toprec® tablet) formula as shown in figure (2) .The results of dissolution study indicated that the selected formula and the conventional one shows release 100, 32.8% respectively at 10 minutes.

Table 2.: Precompression parameters of ketoprofen orodispersible formulas

Formula Code	Carr's Index (%)	Angle of Repose(°)	Flow Characters
F1	10.00±0.50	28.75±0.39	Good
F2	30.29±0.41	29.41±1.55	Good
F3	30.83±0.76	29.41±1.55	Good
F4	31.71±0.62	29.87±0.76	Good
F5	29.83±0.28	31.60±1.27	Passable
F6	27.83±0.28	32.86±1.24	Passable
F7	33.20±0.14	30.73±1.51	Passable
F8	33.21±0.18	32.45±0.72	Passable
F9	33.61±0.34	29.42±0.76	Good
F10	35.70±0.81	32.00±1.92	Passable
F11	35.12±0.82	26.45±0.40	Good
F12	37.43±0.98	28.00±3.43	Good

Table 3.:Post compression parameters of prepared ketoprofen orodispersible tablets

Formula Code	Hardness (Kg/cm^2)	Friability (%)	Weight variation	Wetting Times (sec.)	Water Absorption Ratio (%)	In Vitro Disintegration Times (sec.)
F1	2.00 ± 0.10	1.21± 0.010	179 ± 1.14	12.25 ± 0.90	42.06 ± 27.86	14.51 ± 1.101
F2	4.00 ± 0.50	0.26± 0.008	179 ± 0.85	14.47 ± 2.54	42.88± 28.28	24.33 ± 1.506
F3	4.33 ± 0.76	0.61± 0.009	179 ± 1.14	41.00 ± 3.606	6.660 ± 3.360	51.50 ±1.761
F4	4.33 ± 0.58	0.88 ± 0.023	178 ± 1.48	21.90 ± 7.36	67.74 ± 11.87	23.95 ± 1.268
F5	3 .17 ± 0.29	0.78± 0.005	179 ± 0.94	21.01 ± 2.66	74.99 ± 0.638	34.09 ± 1.170
F6	3.33 ± 0.29	0.88± 0.013	179 ± 1.70	19.26 ± 1.58	98.68 ± 3.650	34.79 ± 0.944
F7	3.42 ± 0.38	0.84± 0.003	178 ± 1.41	21.00 ± 2.00	106.1 ± 0.630	25.06 ± 1.202
F8	3.50 ± 0.50	0.84± 0.003	178 ± 1.52	19.85 ± 2.55	104.9± 0.630	22.47 ± 3.224
F9	3.17 ± 0.29	0.85± 0.010	178 ± 1.41	22.00 ± 4.35	221.5 ± 8.146	29.17 ± 2.563
F10	6.08 ± 0.52	0.66± 0.010	178 ± 1.66	13.72 ± 2.29	92.55 ± 4.046	20.50 ± 0.548
F11	5.50 ± 0.50	0.75± 0.005	180 ± 1.79	8.950 ± 0.08	89.40 ± 1.189	18.04± 0.093
F12	5.17 ± 0.76	0.53± 0.028	179 ± 1.32	14.57 ± 2.34	98.48 ± 14.80	19.83 ± 3.267

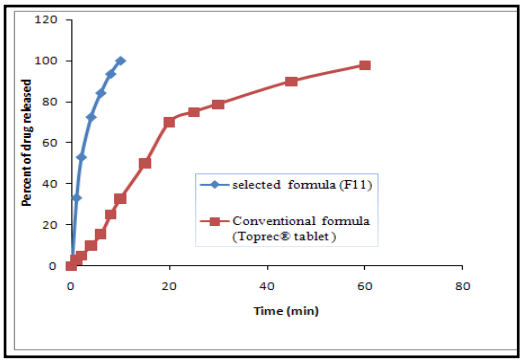

Figure 2: Dissolution profile of ketoprofen ODTs from selected formula (F11) and conventional formula in phosphate buffer,(pH=6.8)at 37°C ± 0.5°C and50 r.p.m.

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