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ORIGINAL ARTICLE

Formulation and evaluation of diclofenac potassium fast-disintegrating tablets and their clinical application in migraine patients

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Abstract

The aim of this study was to prepare fast-disintegrating tablets (FDTs) of diclofenac potassium with sufficient integrity as well as a pleasant taste, using two different fillers and binders: Tablettose 70® and Di-Pac®. Tablets were made with direct compression method. Tablet properties such as porosity, hardness, and disintegration time were determined. Diclofenac potassium determinations were carried out using a validated spectrophotometric method for the analysis of drug. Furthermore, in vivo experiments were carried out to compare the analgesic effect and the time to relieve migraine headache between the commercial tablets and FDTs of diclofenac potassium against placebo. Results showed that FDTs of diclofenac potassium with durable structure and desirable taste can be prepared using both fillers and binders but tablets prepared with Di-Pac had a better taste so the tablet formulation containing Di-Pac was chosen for in vivo experiments. Placebo controlled in vivo trial demonstrated that 50 mg diclofenac potassium, administered as a single dose of FDTs or commercial tablets, was effective in relieving the pain and both of them were superior to placebo.

Key words: Di-Pac®, diclofenac potassium, fast-disintegrating tablets, migraine, Tablettose 70®

Introduction

Recent advances in novel drug-delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for the administration. Difficulty in swallowing (i.e., dysphagia) is experienced by patients such as pediatric, geriatric, bedridden, disabled, mentally ill, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of noncompliance and ineffective therapy[1]. To improve the quality of life and treatment compliance, great efforts have been made to develop fast-disintegrating tablets (FDTs) in the oral cavity, using jelly, water-absorbing, and swelling-gelated materials or water-soluble polymers[2].

The FDTs in the oral cavity are of very practical use because they can be swallowed with a small amount of water or saliva. When such tablets are placed in the oral cavity, saliva quickly penetrates into the pores to cause rapid tablet disintegration.

FDTs have several characteristics to distinguish them from the more traditional dosage forms. Taste masking is of critical importance in the formulation of an acceptable FDT. Traditional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Current methods of taste masking in FDTs include sweeteners and flavors[3,4].

The major advantage of the FDT formulation is that it combines the advantages of both the liquid and conventional tablet formulations, whereas also offering advantages over both traditional dosage forms. It provides the convenience of a tablet formulation while also allowing the ease of swallowing provided by a liquid formulation.

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FDTs allow the luxury of much more accurate dosing than the primary alternative, oral liquids[3].

A major claim of some FDTs is increased bioavailability compared to traditional tablets. Because of dispersion in saliva while still in the oral cavity, there can be pre-gastric absorption from some formulations in those cases where the drug dissolves quickly[5]. Buccal, pharyngeal, and gastric regions are all areas of absorption of the many formulations[6]. However, other formulations show nearly identical plasma-concentration profiles[7]. Any pre-gastric absorption avoids first-pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism. However, if the amount of swallowed drug varies, there is the potential for inconsistent bioavailability. Although the claimed increase in bioavailability is disputable, it is clear that the major advantage of the formulation is conveniet[3].

FDTs have been produced by various methods such as

1. drying after filling the pockets of the press-through pack with dispersed solution of the drug;
2. drying after low-pressure compression of humid powder granules containing the drug[8];
3. compression of dry powder granules containing the drug and shaping by direct compression after mixing excipients and the drug[2,9].

The tablets manufactured by any of the above-mentioned methods are usually composed of the drug and saccharides, which disintegrate in a small amount of water or saliva in the oral cavity within about 30 seconds. Direct compression is the most convenient method because no special manufacturing facilities or granulation process is required[2].

Diclofenac is a potent NSAID that has been in clinical use for many years, particularly for the treatment of inflammatory degenerative and rheumatic diseases and soft-tissue rheumatism. It is also effective in treating non-rheumatic painful and inflammatory conditions such as posttraumatic and postoperative pain[10] and migraine[11].

Diclofenac is available in both sodium and potassium salts. The potassium salt of diclofenac has a higher solubility in water than the sodium salt and is more rapidly absorbed. Therefore, diclofenac potassium preparations are indicated for the management of acute and chronic pain and are especially well suited for treating conditions for which a fast onset of action is important, such as migraine[12].

In the present study, a patient-friendly new formulation is developed as a FDT containing diclofenac potassium. Two issues were considered in the development of diclofenac potassium FDTs. The first issue is to manage a well and fast onset of analgesic effect which is very important in migraine. The second issue is to develop a tablet formulation that is easy for the patient to use with a pleasant taste.

In our study, diclofenac potassium FDT formulation containing 50 mg of diclofenac potassium has been developed and its analgesic effect and time to onset of action is evaluated and compared in treating the pain and of migraine against placebo and the diclofenac potassium tablets that are available in the drug market. The measurements used were consistent with other migraine trials, and with the guidelines of the International Headache Society Committee for the conduct of clinical trials in migraine and with current European guidelines for clinical studies in migraine[13].

Materials

Diclofenac potassium was chosen as an active ingredient and was kindly gifted by Novartis, Turkey. Lactose (Tablettose 70, Meggle, Germany), sucrose (Di-Pac, Domino, USA), directly compressible (DC) mannitol (Roquette, France), cross-linked sodium carboxymethylcellulose (Ac-di-sol, Asahi Kasei, Japan), magnesium stearate (Turkey) were used. All other reagents were of analytical grade.

Methods

Analytical method of validation for diclofenac potassium

In this study, a spectrophotometric method reported for the determination of diclofenac potassium in pharmaceutical formulations[14] was modified and validated for the analysis of diclofenac potassium in dissolution medium and water. Because of the matrix and analyst change, determination method was partially validated in terms of selectivity, linearity, stability, accuracy, precision, repeatability, and reproducibilty[15].

A stock solution of diclofenac potassium (1000 μg/mL) was prepared in distilled water. Working standard solutions were diluted from the stock solution ranging from 10 to 60 μg/mL. Spectrophotometric determinations were performed by an Agilent 8453 combined with DAD UV–Vis spectrophotometer at 276 nm using 1 cm quartz cells.

Physical properties of excipients

Particle density of each tablet component was measured with a helium pycnometer (Quantachrome Corporation, Ultrapycnometer 1000). Data are listed in Table 1.

Table 1. True density results of tablet formulation components.

Formulation component	True density results (g/cc)
Mannitol	1.728
Ac-di-sol	1.802
Mg stearate	1.197
Tablettose 70	1.502
Di-Pac	1.504
Diclofenac K	1.658

Preparation of tablets

We formulated diclofenac potassium with Tablettose 70® Lactose Fast-Flo/Di-Pac® 97% sucrose and 3% dextrin, DC mannitol, Ac-di-sol, and magnesium stearate.

Mannitol was used as one of the basic excipients because it has a sweet taste and leaves a cooling sensation in the mouth. Tablettose 70® was used as a filler and binder. Also, Di-Pac®, was used as a second filler and binder for another example of directly compressible excipient, which consists of 97% sucrose and 3% dextrin and its sweet taste makes it suitable for most directly compressible chewable tablets and lozenges. Ac-di-sol and magnesium stearate were used as disintegrant and lubricant.

FDTs were prepared according to the following procedure. First, DC mannitol, Tablettose 70® (or Di-Pac) and Ac-di-sol were mixed using a cubic mixer (Erweka AR 400) for 15 minutes. Subsequently, diclofenac potassium was added to this powder mixture and then, magnesium stearate was mixed for 5 minutes. To prepare 500 mg of FDTs, the above-mentioned mixtures of each type of binder and other excipients were compressed with a 12 mm flat-faced punch at 30 rpm compression speed using a single-punch tablet machine with a 20 kN/cm^2 compression pressure (Korsch).

Evaluation of tablets

Measurement of tablet hardness

This test was applied with a tablet hardness tester (Monsanto, tablet hardness tester) on 10 tablets for each formulation[15].

Measurement of tablet porosity

Tablet porosity ε was calculated as follows[8,16];

$$\varepsilon = 1 - \frac{m}{\rho_t V} \quad (1)$$

where ρ_t is the true density, and m and V are the weight and volume of the tablet, respectively.

Measurement of friability

Ten tablets were weighed and put into the friabilitor (Roche Friabilitor). Tablets were rotated at 25 rpm, then the friability percentage was calculated[17].

Measurement of wetting time and water absorption

A piece of paper tissue (10.75 × 12 mm) folded twice was placed in a culture dish (d = 6.5 cm) containing 6 mL of water. A tablet was put on the paper, and the time for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined according to the following equation[8]:

$$R = \frac{100(W_a - W_b)}{W_b}, \quad (2)$$

where W_a and W_b are the weight after and before water absorption, respectively.

Measurement of disintegration time

The disintegration test was performed according to the USP 24 paddle method (Aymes, D96D) at a rotation speed of 100 rpm. Distilled water (900 mL) was maintained at 37°C and stirred with a paddle at 100 rpm and was used as the disintegration fluid. Disintegration time was determined at the point at which the tablet disintegrated completely[18].

Disintegration in the oral cavity

Determination of the disintegration time in the mouth were carried out according to the method of Kimura et al.[19] and Ishikawa et al.[20]. Six healthy volunteers, from whom informed consent was obtained, randomly took one prepared tablet and the time required for complete disintegration of the tablet without bitting was recorded. Immediately, after the in vivo disintegration test, volunteers rinsed their mouths without ingesting the disintegrated materials[19,20].

Determination of drug amount

At the first step, 10 diclofenac potassium tablets (containing 50 mg diclofenac potassium) were weighed and finely powdered in a mortar (İldam Kimya, Turkey). The average weight of a tablet was calculated. A sufficient quantity equivalent to the average weight of a tablet content was accurately weighed from the tablet powder and water was added to dissolve the active material and made up to the volume of 100 mL in a volumetric flask (İldam Kimya). It was sonicated for 10 minutes and was filtered. Then 1 mL of this solution was taken and put into another volumetric flask. Then it was completed to 25 mL with distilled water and in this solution absorbance value at 276 nm was determined using UV–Vis spectrophotometrically, and with the aid of the calibration equation drug amount in the sample was calculated[17].

Clinical application

The current trial, conducted as part of a clinical development study for diclofenac potassium FDTs, evaluated the efficacy and time to onset of action and comparison of diclofenac potassium FDTs with the conventional diclofenac potassium tablets and placebo in treating the pain and associated clinical signs of migraine. The measurements used were consistent with other migraine trials, and with the guidelines of the International Headache Society Committee for the conduct of clinical trials in migraine and with current European guidelines for clinical studies in migraine[12].

The study was performed after the preparation of FDTs and the application of quality control tests on these tablets. After the evaluation of quality control test results, the best FDT formulation was chosen for the clinical trial.

Patients and methods

This was a double-blind, randomized, cross-over trial comparing 50 mg diclofenac potassium FDTs, 50 mg diclofenac potassium conventional tablets, and placebo in patients with migraine. The protocol was consistent with the declaration of Helsinki and was approved by both the local and general ethics committees. All human subjects signed an informed consent explaining the requirements and risks associated with the study. The primary objective was to determine whether a single dose of diclofenac potassium FDT was superior to placebo and non-inferior to diclofenac potassium conventional tablets in treating the pain in migraine headache. Secondary objective was to evaluate the time to onset of analgesic effect of diclofenac potassium FDTs in comparison of diclofenac conventional tablets and placebo.

Male or female patients, 18–50 years, suffering from migraine with or without aura, but without interval headaches between migraine attacks, were eligible. Patients had to have a disease duration of at least 1 year. Females who were pregnant, lactating, or considered at risk of pregnancy were not eligible.

Each patient was informed about the nature and aim of the study, and written informed consent was obtained. Patients were excluded if they suffered from other types of migraine such as menstrual migraine, had received lithium, digoxine, methotraxate, cyclosporin, phenobarbital, or any other long-acting analgesic formulations during the study. Patients with a known hypersensitivity to NSAIDs, acetylsalicylic acid, or other drugs with prostaglandin-synthetase inhibiting activity, with severe cardiac, liver or acute renal insufficiency, active peptic ulcer disease, or a history of significant gastrointestinal disease were excluded.

Study procedures

Eligible patients were randomized and received study medication to treat three separate migraine attacks at home. For each attack study, medication was self-administered by the patient as soon as they were certain they were experiencing symptoms of a migraine attack. A patient diary was used to record efficacy parameters over a 6 hours period. Patients had to return the study clinic at least every 4 weeks for continued review and for a final study visit after three migraine attacks had been treated. At each visit, completed patient diaries were collected. Maximum study duration for each patient was planned for 3 months.

Patients received three sets of study tablets, designated as A, B, and C where; one of them was commercial diclofenac potassium tablets, the other one was diclofenac potassium FDTs, and the last one was placebo FDTs. Commercial diclofenac potassium tablets were bought from the market and packed like the FDTs are packed. This preparation step was only known by the pharmacist and clinicians and patients did not know which kind of diclofenac potassium tablet was applied. Tablets were taken in a predefined treatment sequence. Clinician requested the patient to take the tablet and before swallowing, to keep the tablet in the oral cavity about a minute and then with a very small amount of water to swallow the residues of the tablet.

Headache intensity was recorded before taking the tablet (baseline, time = 0) and at 1, 2, 3, 4, 5, and 6 hours post dose on a verbal scale assessed as '*none*' (0), '*mild*' (1), '*moderate*' (2), or '*severe*' (3), and pain relief was rated on a five-point scale '*no relief*' (0), '*a little*' (1), '*some*' (2), '*a lot*' (3), and '*complete relief*' (4)[21].

Results and discussion

Analytical validation

Absorbance values of diclofenac potassium working standards prepared in distilled water, pH 7.2 phosphate buffer and pH 1.2 HCl at the concentrations of 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, and 90 μg/mL was measured at 276 nm. Under acidic conditions (pH = 1.2), diclofenac potassium was precipitated[14]. For this reason, a calibration curve could not be plotted in acidic medium. Calibration curves in water and pH 7.2 phosphate buffer were constructed by plotting absorbance values versus diclofenac potassium concentrations. Regression analysis indicated linear relationships between absorbance and concentrations and there was not any significant difference observed in two different media. Therefore, water was chosen in the rest of study. The calibration curve was linear in the range of 10–60 μg/mL with a regression equation of $y = 0.0567x + 0.0561$ ($R^2 = 0.9991$).

Accuracy, repeatability, and reproducibility results of the analytical validation method are given in Tables 2 and 3.

Table 2. Accuracy and repeatability results of the spectrophotometric method for diclofenac potassium determination.

Added (μg/mL)	10	30	60
Mean of found (μg/mL)	9.96	30.11	59.97
SD of found	0.06	0.26	0.32
RSD of found (%)	0.62	0.85	0.54
Recovery (%)	99.65	100.36	99.94

SD, standard deviation; RSD, relative standard deviation.

Table 3. Reproducibility of spectrophotometric method for diclofenac potassium determination.

	Results of 1. operator	Results of 2. operator
Mean	30.32	30.27
SD	0.24	0.26
RSD (%)	0.79	0.86

SD, standard deviation; RSD, relative standard deviation.

Evaluation of tablets

Effect of Tablettose® and Di-Pac® on physical properties of tablets

Tablettose 70® is made up almost entirely of aggregated crystals of α-lactose monohydrate; it contains no amorphous lactose. It is a white or almost white, odorless, free-flowing powder. It is freely but slowly soluble in water, practically insoluble in alcohol.

Tablettose is resistant to attrition under conditions of low shear blending in a plenatary mixer. The binding properties of Tablettose are better than α-lactose monohydrate but not as good as those of spray-dried lactose or anhydrous β-lactose. On the other hand, when the compactibility of Tablettose compared with α-lactose monohydrate must be attributed to the granular texture, Tablettose enhances the fragmentation potential more than α-lactose monohydrate[22,23].

Di-Pac is a directly compressible, co-crystallized sugar. It is a free-flowing, agglomerated product consisting of hundreds of small sucrose crystals glued together by the highly modified dextrin. At high-moisture level, Di-Pac begins to cake and loose its fluidity. Tablets containing a high proportion of Di-Pac tend to harden after compression at higher relative humidity. Its sweet taste makes it suitable for most directly compressible chewable tablets and lozenges. Because of high solubility of Di-Pac, the tablets do not disintegrate but dissolve during disintegration and dissolution[22].

David and Augsberger investigated the effect of time of compression and the presence of a lubricant on the tablet strength of various materials including Di-Pac. It was concluded that particle fracture played a dominant role during compaction of Di-Pac or lactose than during compaction of microcrystalline cellulose or compressible starch[24,25].

Rizzuto et al.[26] demonstrated that co-crystallized sucrose and dextrin deformed readily by plastic fracture to provide much harder compacts than those obtained from sucrose crystals alone. Rizzuto et al.[26] also informed that placebo Di-Pac tablets pick up less than 0.1% moisture during storage for 30 days at 25°C/75%. Di-Pac has few incompatibilities but it is incompatible with primary and many secondary amines.

Tablet compositions are given in Table 4 and physical properties of resultant tablets prepared with Tablettose 70® and Di-Pac are shown in Table 5.

Table 4. Formulation of tablets.

Formula	Formulation A	Formulation B
Diclofenac K (mg)	50	50
Tablettose 70 (mg)	340	—
Di-Pac (mg)	—	340
Mannitol (mg)	100	100
Ac-di-sol (mg)	5	5
Magnesium stearate (mg)	5	5
	Total weight: 500 mg	Total weight: 500 mg

Table 5. Physical properties of diclofenac potassium FDT.

Parameter ($n = 6$) (mean ± SD)	Formulation A	Formulation B
Weight (mg)	500.00 ±0.01	500.00 ± 0.01
Diameter (cm)	1.19 ± 0.01	1.20 ± 0.01
Thickness (cm)	0.40 ± 0.00	0.41 ± 0.00
Hardness (kg)	4.0 ± 0.12	4.5 ± 0.10
Wetting time (seconds)	45.00 ± 0.02	56.00 ± 0.05
Water absorption ratio (%)	21.204 ± 0.11	36.23 ± 0.09
Disintegration time (seconds)	40.07 ± 0.65	44.13 ± 1.23
Oral disintegration time (seconds)	34.00 ± 0.16	36.00 ± 0.24
Friability ($n = 3$)	0.54 ± 0.11	0.59 ± 0.05
Drug content (mg) ($n = 3$)	98.97 ± 0.76	99.42 ± 1.13
Porosity (%)	16.23 ± 043	16.78 ± 0.72

Tablets which were compressed with a single-punch tablet machine and had a friability which was in the range of 0.54–0.59% (Table 5) was below 1% indicating a sufficient mechanical integrity. Hardness value was determined in the range of 4.0–4.5 kg (Table 5).

The water penetration rate into the powder bed is proportional to the pore radius and is affected by factors such as the hydrophilicity of powders and liquid viscosity[16] and it is closely related to the inner structure of the tablets. The delayed wetting of Ac-di-sol is made by a cross-linking (esterification) reaction of sodium carboxymethylcellulose. This cross-linking greatly reduced the water solubility of sodium carboxymethylcellulose while permitting the material to swell and absorb many times its weight the water without loosing individual fiber integrity[16,27]. When Ac-di-sol is added to tablet formulations, its absorption of water might cause an increase in viscosity of the liquid within the tablet, and further water penetration would be delayed. As water absorption is an important step in the disintegration process, disintegration of the tablets showed the same tendency as wetting time[16,22]. Disintegration time is of much importance in the formulation of FDTs, it was tried to keep the disintegration time less than a minute. The in vitro disintegration time was found in the range of 40–44 seconds.

After the preparation and evaluation of FDTs with the help of in vitro quality control tests FDTs prepared with Di-Pac was chosen for clinical trials especially for their better sweety taste because both FDT formulations met the design specification of FDTs.

Effect of mannitol on physical properties of tablets

To produce FDTs with commonly used methods and equipments, the raw materials used should have a quick disintegration rate in the mouth and a high compressibility to yield an adequate hardness when compressed.

Various saccharides, which are generally used as formulation additives, were examined as the raw material for FDTs by Mizumoto. The results showed that mannitol, lactose, and glucose had quick disintegration time, but low hardness. On the other hand, maltose and multitol exhibited high hardness, but a significantly slow

disintegration time. Mannitol's low-compressibility characteristic is improved by using granulated maltose binder. With the help of this combination, it is reported that a hardness of 5.9 kp and a disintegration time about 20 seconds is maintained[28].

Ishikawa[20] reported that to obtain an adequate and shorter disintegration time (within 15 seconds), the hardness of tablets should be maintained at 3–5 kg. Therefore, in the present study, the hardness of the tablets which can be obtained with mannitol without any saccharide combination is chosen. Disintegration time increased with increasing hardness.

The true density (also called true particle density) of a particulate solid or powder, is the density of the particles excluding open and closed pores that make up the powder, in contrast to the bulk density, which measures the average density of a large volume of the powder in a specific medium (usually air)[29,30].

True densities of the commercial direct compression agents and diclofenac potassium used in the study are given in Table 1, the true density results ranges between 1.197 and 1.802 g/cc.

When tablet porosity is high, water can be absorbed easily, and destruction of tablets is not very difficult. Disintegration is hardly affected by tablet formulation. However, when tablet porosity is not extremely high, disintegration will be influenced by the properties of the excipients used[16,22].

Although porosities of formulations (Table 5) are not very high, as both formulations contained water-soluble filler and binders, so tablets met the disintegration time specifications of FDTs.

Clinical results

Study population

A total of 15 patients were randomized to treatment. All the patients received three sets of study tablets, designated as A, B, and C where one of them was conventional diclofenac potassium tablets, the other one was diclofenac potassium FDTs, and the last one was placebo FDTs. For each attack, patients are told to take the study medication starting with A and continuing with B and C for consequent attacks as soon as they were certain they were experiencing symptoms of a migraine attack.

Table 6. Demographic characteristics of treated patients.

	*
Demographic data	
Number of patients	15
Mean age in years (SD)	54 ± 1.14
Mean weight in kg (SD)	71 ± 3.26
Baseline pain intensity (%)	
Mild	33.4
Moderate	59.1
Severe	7.5
Complete relief at 2 hours (%)	
Diclofenac potassium conventional tablets	91
Diclofenac potassium FDTs	95
Placebo	7.9

*All three tablets (diclofenac potassium conventional tablets, diclofenac potassium FDTs, and placebo tablets) were applied to all treated patients. Among 15 patients, 10 of them were women.

The baseline characteristics among the treatment group were generally similar with respect to sex, age, and baseline pain intensity (Table 6).

Efficacy results

The pain relief profiles of the treatment group over the 6 hours post-dose assessment period are shown in Figure 1. The treatment group provided significantly superior pain relief with both diclofenac potassium tablets versus placebo starting at the range of 30 minutes to 1 hour post dosing ($P \leq 0.05$) and at all later time points ($P < 0.01$). The level of analgesia increased rapidly in the first hour after dosing with diclofenac potassium FDTs so that a mean level of = 3 '*a lot of relief*' was approached

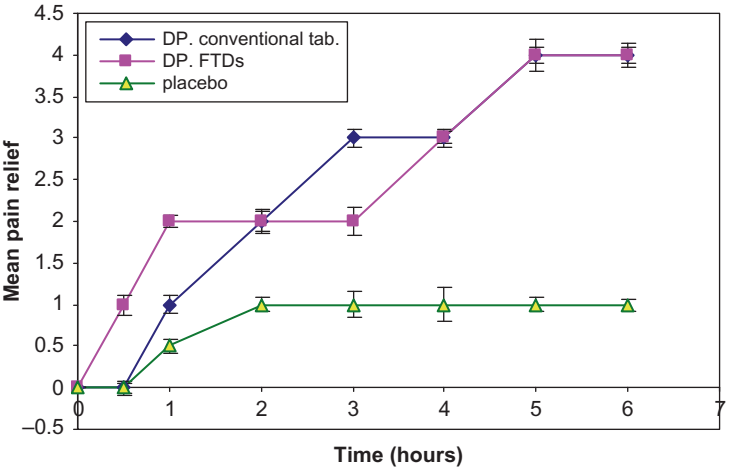

Figure 1. Mean profile of pain relief by treatment group. Relief scale: 0 = no relief, 1 = a little, 2 = some, 3 = a lot, 4 = complete relief.

at 1 hour and exceeded shortly thereafter. At later time points, the mean level of relief with diclofenac potassium conventional tablets was slightly greater than diclofenac potassium FDTs but the differences did not achieve statistical significance.

Both diclofenac potassium tablets were superior to placebo ($P < 0.01$). Almost more than 90% of patients had achieved pain relief with both diclofenac potassium tablets over the full 6 hours, compared to placebo (Figure 2).

Pain intensity

The profile of pain intensity differences of patients in the treatment group over the 6 hours post-dose assessment period is illustrated in Figure 3. Both diclofenac potassium tablets provided significantly superior pain intensity decrease versus placebo at all time points from 1 hour post dosing and onwards ($P < 0.01$). Mean baseline level of pain intensity across the treatment group was in the range of 2.01–2.39 (2 = moderate) on the four-point pain intensity. With diclofenac potassium FDTs starting at 30 minutes and with diclofenac potassium conventional tablets starting at 1 hour post dosing, levels of pain decreased rapidly in the treatment group and the average decrease reached a full point between the first and second hour. Mean pain intensity continued to decrease over the entire 6 hours assessment period. Both tablets were significantly superior to placebo ($P < 0.01$).

Complete relief of headache at 2 hours post dose

Almost 95% of subjects had obtained complete relief from headache within 2 hours of dosing with both of the diclofenac potassium tablets, compared to about 7.9% in the placebo group (Table 6). Both diclofenac potassium tablets were superior to placebo ($P < 0.01$).

Expanding the definition of success a 'complete relief' was obtained with both diclofenac potassium tablets within 2 hours, and they did not differ significantly among each other.

Conclusion

In the present study, a patient-friendly new formulation has been developed as a FDT containing diclofenac

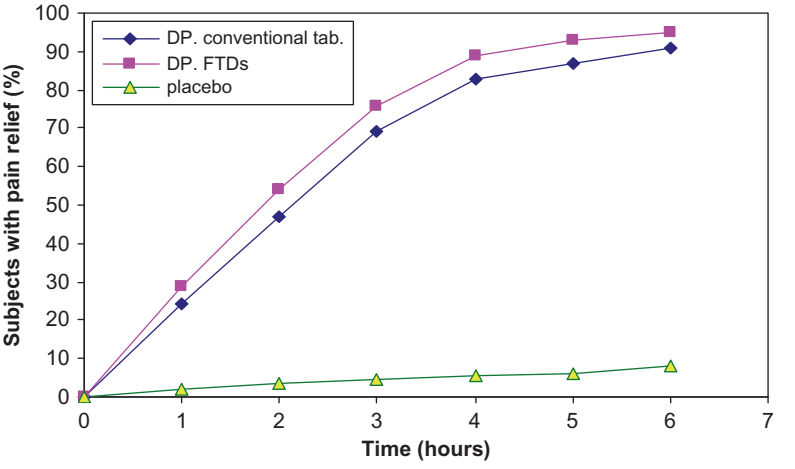

Figure 2. Percent of subjects rating the pain relief.

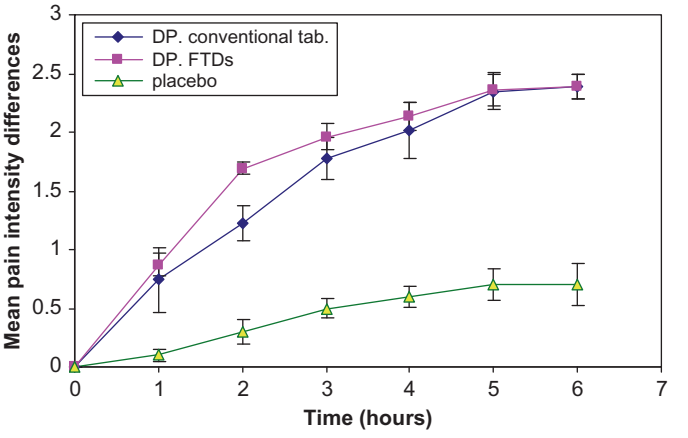

Figure 3. Mean profile of pain intensity differences by treatment group. Pain intensity scale: 0 = no pain, 1 = mild, 2 = moderate, and 3 = severe pain.

potassium that is easy for the patient to use with a pleasant taste. This new formulation prepared by direct compression having good mechanical properties may improve patient compliance with treatment, may be of particular benefit to patients who have difficulty in swallowing and elderly patients.

Placebo controlled in vivo trial has demonstrated that 50 mg diclofenac potassium, administered as a single dose of FDTs or commercial tablets, is effective in relieving the pain and both of them are superior to placebo.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Mishra DN, Bindal M, Singh SK, Kumar SGV. (2006). Spray dried excipient base: A novel technique for the formulation of orally disintegrating tablets. Chem Pharm Bull, 54(1):99–102.
2. Shu T, Suzuki H, Hironaka K, Ito K. (2002). Studies of rapidly disintegrating tablets in the oral cavity using co-ground mixtures of mannitol with crospovidone. Chem Pharm Bull, 50(2):193–8.
3. Bogner RH, Wilkosz MF. Fast dissolving tablets. http://www.uspharmacist.com [accessed May 20, 2010].
4. Bolhuis GK, Rexwinkel EG, Zuurman K. (2009). Polyols as fillers-binders for disintegrating tablets prepared by direct compaction. Drug Dev Ind Pharm, 35(6):671–7.
5. Chang RK, Guo X, Couch RA. (2000). Fast dissolving tablets. Pharm.Technol, 6:52–8.
6. Seager H. (1998). Drug-delivery products and the Zydis fast-dissolving dosage form. J Pharm Pharmacol, 50:375–82.
7. Habib W, Khankari RK, Hontz J. (2000) Fast dissolve drug delivery systems. Crit Rev Ther Drug Carrier Sys, 17:61–72.
8. Jacob S, Shirwaikar A, Nair A. (2009). Preparation and evaluation of fast-disintegrating effervescent tablets of glibenclamide. Drug Dev Ind Pharm, 35(3):321–8.
9. Sunada H, Bi Y. (2002). Preparation, evaluation and optimization of rapidly disintegrating tablets. Powder Technol, 122:188–98.
10. Chang DJ, Desjardins PJ, Chen E, Polis AB, McAvoy M, Mockoviak SH, et al. (2002). Comparison of the analgesic efficacy of rofecoxib and enteric-coated diclofenac sodium in the treatment of postoperative dental pain: A randomized, placebo-controlled clinical trial. Clin Ther 24(4):490–503.
11. McNeely W, Goa KL. (1999). Diclofenac-potassium in migraine: A review. Drugs, 57(6):991–1003.
12. Diener HC, Montagna GG, Lyczak P, Schumann G, Zöller B, Mulder LJMM, et al. (2005). Efficacy and tolerability of diclofenac potassium sachets in migraine: a randomized, double-blind, cross-over study in comparison with diclofenac potassium tablets and placebo. Cephalalgia, 26:537–47.
13. Silberstein SD, Freitag FG. (2003). Preventive treatment of migraine. Neurology 60(7)Suppl.2:38–44.
14. Bucci R, Magrì AD, Magrì AL. (1998). Determination of diclofenac salts in pharmaceutical formulations. Fresenius J Anal Chem, 362:577–82.
15. ICH Guideline (1996). Validation of analytical procedures: Text and methodology Q2 (R1).
16. Bi YX, Sunada Y, Yonezawa Y, Danjo K. (1999). Evaluation of rapidly disintegrating tablets prepared by a direct compression method. Drug Dev Ind Pharm, 25(5):571–81.
17. Comoglu T, Gönül N. (2005). Quality control studies on conventional carbamazepine tablets that are available in Turkish drug market. Turk J Med Sci, 35:217–21.
18. Klancke J. (2003). Dissolution testing of orally disintegrating tablets. *Dissolution Technologies*, May: 6–8.
19. Kimura S, Imai T, Ueno M, Otagiri M. (1992). Pharmaceutical evaluation of ibuprofen fast absorbed syrup containing low-molecular weight gelatin. J Pharm Sci, 81:141–4.
20. Ishikawa T, Mukai B, Shiraishi S, Utoguchi N, Fujii M, Matsumoto M, et al. (2001). Preparation of rapidly disintegrating tablet using new types of microcrystalline cellulose (PH-M series) and low substituted-hydroxypropylcellulose or spherical sugar granules by direct compression method. Chem Pharm Bull, 49(2):134–9.
21. Kubitzek F, Ziegler G, Gold MS, Liu JMH, Ionescu E. (2003). Low-dose diclofenac potassium in the treatment of episodic tension-type headache. Eur J Pain, 7:155–62.
22. Bolhius GK, Chowhan ZT. (1996). Materials for direct compression. In: Alderborn G, Nystrom C, eds. Pharmaceutical powder compaction technology. New York: Marcel Dekker Inc., 476–80.
23. Ilic I, Kasa JP, Dreu R, Hodi-Pintye K, Srcic S. (2009). The compressibility and compactibility of different types of lactose. Drug Dev Ind Pharm, 35(10):1271–80.
24. David ST, Augsberger LL. (1977). Plastic flow during compression of directly compressible fillers and its effect on tablet strength. J Pharm Sci 66:155.
25. Gohel MC, Jogani PD. (2005). A review of co-processed directly compressible excipients. J Pharm Pharmaceut Sci, 8(1):76–93, www.cspscanada.org [accessed May 20, 2010].
26. Rizzuto AB, Chen AC, Veign MF. (1984). Effect of moisture content on compression properties of two dextrose-based directly compressible diluents. Pharm Tech 8(9):32.
27. Shangraw R, Mitrejev A, Shah M. (1980). A new era of tablet disintegrants. Pharm Tech 4:49–57.
28. Mizumoto T, Yoshinori M, Yamamoto T, Yonemochi E, Terada K. (2005). Formulation design of a novel fast-disintegrating tablet. Int J Pharm 306: 83–90.
29. Webb PA. Volume and density determinations for particle technologists. *Micromeritics Instrument Corp*. 2001: p. 4. www.particletesting.com/docs/density_determinations.pdf [accessed May 20, 2010].
30. en.wiktionary.org/wiki/true_density [accessed May 20, 2010].