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Comparing the Physicochemical and Pharmaceutical Properties of Brand-Name and Generic Ketoprofen Gel Products

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Abstract

Summary: Topical gel formulations are of increasing interest in the pharmaceutical industry, they are typically transparent or translucent, water-based semisolids with good spreading properties and pleasing aesthetic characteristics. Thus, the physicochemical characteristics of preparations may vary in spite of the fact that they contain the same ingredients or additives. This study examined differences in brand-name and generic versions of ketoprofen gels.

Material and Methods: Four types of commercial ketoprofen gels (Ket1 – Ket4) were used, and different physcichemical properties and chemical qualitative and quantitative assay of each preparation was determined using the brand product (ket1) as a reference.

Results: Comparison of the pH, refractive indices, spreadability, and homogeneity of the four different preparations revealed that Ket1, Ket2, and Ket3 are very similar to the brand product (Ket4). The four products showed similar ketoprofen contents and were within the pharmacopoeial limit using UV-visible spectrophotometry (92.5-107.5%). The absorption spectra of the four ketoprofen products were achieved and indicate the presence of the active ingredients without any interaction with the other pharmaceutical additives.

Conclusion: The drug content of all gel formulations was found to be within the limit of the British pharmacopeia. The generic products (ket2-ket4) meet various patient needs when compared with a brand-name product.

Keywords: Ketoprofen; Gels; Absorption; FTIR

Abbreviations: UPLC: Ultra Performance Liquid Chromatography; HPLC: High-Performance Liquid Chromatography; GC: Gas Chromatography; WHO: World Health Organization; NSAID: Non-Steroidal Anti-Inflammatory Drugs.

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Introduction

Ketoprofen belongs to propionic acid class of non-steroidal anti-inflammatory drugs (NSAID) with analgesic and antipyretic effects. It works by nonselective reversible inhibition of both cyclooxygenase-1 and -2 (COX-1 and COX-2) enzymes, which play *vital role in* the inflammation cascade (responsible for prostaglandin production) [1,2]. Additionally, it decreases the formation of thromboxane A2 synthesis, by thromboxane synthase, thus inhibiting platelet aggregation [3,4]. Ketoprofen is widely used in acute and chronic inflammatory diseases, especially in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and abdominal cramps associated with menstruation [5]. It is currently available in many dosage forms, and recently an increased attention is given for topical gel formulations as they allows for a higher local concentration of the drug at the site of initiation of the pain and decrease or remove systemic adverse effects [6,7].

The quality of drugs has always been an apprehension of the WHO (World Health Organization). It is essential for drugs to guarantee the required standards of safety, quality, and effectiveness; otherwise health service is evidently affected [8,9]. Pharmaceutical companies must guarantee that their marketed products have sufficient efficacy and safety for populations everywhere in the world. Consequently, the validation of professional analytical methods utilized in the quality control of marketed drugs in Libya is of major importance. The stability of ketoprofen gel could be established through evaluation of its physicochemical properties, and measurement of qualitative, and quantitative chemical content while the product protected from light and moisture. The physicochemical evaluation includes visual inspection of colour, clarity, homogeneity, in addition to measurement of pH, viscosity, and spreadability. There are numerous published studies describing the development of analytical methods (qualitative and quantitative) for analysis of ketoprofen in different dosage forms [10-12]. This includes ultra-performance liquid chromatography (UPLC), high-performance liquid chromatography (HPLC), gas chromatography (GC) and Gas Chromatography-Mass Spectrometry [13-15]. However, the majority of the current methods use vastly potential toxic solvents for the operators and the environment. In the current study, we aimed to evaluate the different generic ketoprofen gels products in term of physical and chemical stability and compare them with brand-name product as reference. In addition, we implant the use of infrared spectrophotometry technique as it permits a qualitative study of ketoprofen without using organic solvents. The infrared spectrophotometry technique does not require any extraction step of the sample and therefore can also be used for substances with solubility problems. Hence this technique constitutes a versatile and environmentally friendly analytical method. In addition, these vibrational spectroscopic techniques are widely documented providing suitable analytical results for authentication of pharmaceutical products [16-18].

Materials and methods

Equipment: For spectrophotometric analysis, a spectrophotometer FTIR Shimadzu (Kyoto, Japan), IR Prestige-21 model, was used. This equipment was connected to a computer to exploit the "IR Solution" software for analysis of the spectra. The construction of calibration curves was achieved using Microsoft Excel (2018). Additional equipment used was Specord 200 UV Visible Spectrophotometer model 202 (Analytic Jena AG, Germany) and pH meter model pH 50+ (XS Instruments, Italy).

Physical evaluation of gels

The four products of the ketoprofen gel formulations were inspected visually for their color, clarity, homogeneity, pH and refractive index. All gels were tested again for color, clarity and homogeneity by visual inspection after the gels have been set in the container. They were also tested for the presence of any aggregates or air bubbles. The pH values of 1% aqueous solutions of each gel were measured by a pH meter. The pH of gels was checked to avoid the risk of irritation upon application to the skin the acceptable pH was determined around 5.5 [19,20]. Refractive index measurements were carried out at room temperature (25- 27°C) using a refractometer DR6000 (A. Krüss Optronic, Germany). The refractive index of liquid is determined by using the effect of total reflection. Ketoprofen gel was placed between two prisms made of highly refracting glass with refractive index N. The light passes through the illumination prism and hits the interface with the specimen under different angles. A small quantity of sample was placed on the measuring prism, covered, and its RI value measured. Water, as a reference had a value of 1.332. The gel (20 g samples) was placed on the refractometer prism and the refractive index was measured [21,22].

Spreadability

The therapeutic efficacy of a formulation also depends on its spreading value. Spreadability is employed to express the extent of area to which the gel readily spreads on application to the skin or affected part. Spreadability was determined by a wooden block and glass slide apparatus.

Weights about 20 g were added to the pan and the time were noted for the upper slides (movable) to separate completely from the fixed slides. Spreadability was then calculated by using the formula: S = M x L / T, where, S = Spreadability; M = Weight tide to upper slide; L =Length of glass slide; T = Time taken to separate the slide completely from each other. A shorter interval indicates better spreadability [23,24].

Chemicals and reagents

All chemical solvents and materials were of highest purity and utilized with no further purification were from Aytas company (Turkey), Carlo Erba (Italy) and Sigma-Aldrich chemical company (UK). Standard -Ketoprofen was purchased from Ketoprofen (Jordan) and was dissolved in 96% ethanol to the required drug concentrations.

Qualitative analysis

For experiments a FTIR Shimadzu spectrophotometer was used, sample weight of 500 mg ketoprofen gels containing 12.5 mg of ketoprofen were solubilized in 10 ml of 96% ethanol. The spectral region for qualitative analysis was from 2200 to 800 cm^{-1}. The background of 96% ethanol was subtracted from all spectra. Transmittance spectra were obtained with the aid of "IR Solution" software (Shimadzu, Kyoto, Japan). Spectra were measured at a resolution of 8 cm^{-1} and 40 scans were used for each spectrum to achieve a suitable signal-to-noise *ratio* and were performed in triplicate. In order to identify the ketoprofen in the presence of different excipients, a reference ketoprofen spectrum was created. Triplicate spectra of the reference samples (ketoprofen and excipients) were recorded. There was no detectable difference in absorbance bands and peak data between individual replicates of the same material. Reproducible spectral data based on both absorbance bands and peak intensities were achieved after method optimization. Finally, a comparison of the spectra obtained from the four ketoprofen products with standard ketoprofen (Hikma Pharmaceuticals, Jordan) spectra was performed to verify the similarity.

Quantitative analysis

The four ketoprofen products were tested for uniformity of the drug content. Quantitative assays were performed using a Specord 200 UV Visible Spectrophotometer. An UV spectroscopic scanning run (230-360 nm) was carried out with reference solution to select the best UV-visible wavelength (λ_{max}) for detection of ketoprofen in 95% methanol solution [25,26]. Analyses were carried out using 95% methanol as blank. Linearity was confirmed by linear regression of least squares and statistical analysis by ANOVA. Six series of standard solutions of ketoprofen (1, 5, 10, 15, 20, 25 and 30 µg ml^{-1}) were prepared by the dilution of the stock standard solution in 95% methanol. Absorbances were measured in triplicate at 258 nm. The concentrations were determined by the necessary dilutions to the wavelength of maximum absorption of ketoprofen (λ= 258 nm; ε =20433 l mol^{-1} cm^{-1}) using methanol as solvent during the dilution process.

Selectivity

Selectivity was analyzed in order to verify the ability of the method to quantify ketoprofen in the presence of the adjuvants present in the gel. The utilized method has been formerly described for qualitative analysis [27].

Results and Discussion

All Ketoprofen gel formulations physical parameters are given in table 1, the tested products contain ingredients other than Ketoprofen (Table 2) that are essential for their manufacture, stability and function. Gel formulation usually includes a gelling agent such as carbomers, hydroxyethyl cellulose or, hydroxypropyl cellulose which are widely used. Because the tested formulations contain different excipients the gel can be transparent, translucent, or opaque.

Evaluation of physicochemical properties of ketoprofen gel formulations

Ketoprofen gels (Ket1-Ket4) were evaluated for clarity, colour, pH, spreadability, and homogeneity, and all products showed acceptable properties (pH, spreadability, homogeneity) as shown in table 1. The pH values of all formulations ranged from 5.64 to 5.75, and as the adult skin has a pH of ~5.5, consequently the tested formulations are considered acceptable to avoid the risk of irritation upon application to the skin. It is evident from Table 1 that all the systems are within the required physiologic pH range accepted for dermal preparations (5.0–7.5 pH units, BP 2013). Based on spreadability values which shown in Table 1, and as shorter interval indicates better spreadability, all tested formulations under study are accepted according to literature spreadability parameters [23,24]. The refractive index measurements for all tested gel products were in the range expected for transparent isotropic systems [28].

Formulations	Clarity	Color	Homogeneity	pH	Spreadability (g.cm/s)	Refractive Index
Ket1	+++	colorless	Good	5.64±0.12	5.7 ± 0.2	1.3622
Ket2	++++	colorless	Good	5.73±0.21	6.1 ± 0.1	1.3678
Ket3	++	colorless	Good	5.75±0.11	5.9 ± 0.1	1.3674
Ket4	++	colorless	Good	5.75±0.13	6.2 ± 0.1	1.3670

Table 1: Physical evaluation of ketoprofen gels of four different products (Mean±SD, n=3).
Ket1= Fastum 2.5% gel, Minapharma, Egypt; Ket2= Axen 2.5% gel ,Opalia, Tunisia; Ket3= Flexen 2.5% gel , Lifepharma, Italy; Ket4= Lachifen 2.5% gel , Lachipharma, Italy.

Additives	Ket1	Ket2	Ket3	Ket4
Ethanol	√	√	√	√
Carbomer 940	√	-	-	√
Carbopol 980	-	√	-	-
Carboxypolymethylene	-	-	√	-
Neroli essence	√	-	-	-
Diethanolamine	-	√	√	√
Lavender essence	√	-	-	-
Glycerol	-	√	√	√
Trolamine	√	-	-	-
Methyl parahydroxybenzoate	-	√	√	-
Propyl parahydroxybenzoate	-	√	√	-
Purified water	√	√	√	√

Table 2: Additives (1-7) used in ketoprofen gel formulations for the four different products. All the formulations contain 2.5 % ketoprofen.

Qualitative analysis

Infrared spectrophotometry is based on the fact that chemical bonds of the molecules have natural vibrational frequencies. Each organic molecule only absorbs selected frequencies of radiation in the infrared region, which are equivalent to its natural vibrational frequencies, this absorption increase the amplitude of vibrational motion of the chemical bonds. Thus, the frequency of vibration may be associated with a particular type of the band. The region of the infrared spectrum from 1500 to 400 cm^{-1} is called the fingerprint region, this region is notable for large number of infrared bands that are found there. This region is often the most complex and confusing region to interpret and is usually the last section of a spectrum to be interpreted, however, the utility of the fingerprint region in this part of the current study is essential in identifying of Ketoprofen in the presence of other additives to the tested formulations. The four products spectra were recorded and compared with the reference spectra and the peaks of the fingerprint region matched indicating the presence of the Ketoprofen. Figure 1 shows absorption spectra of the Ket1, Ket2, Ket3 and Ket4 samples, and the spectral range of 2200 to 800 cm^{-1} chosen for qualitative analysis. Many different vibrations for Ketoprofen bonds, including C-O and C-C single bond stretches, C-H bending vibrations, and some bands due to benzene rings are found in fingerprint region. Comparison of Ket1, ket2, ket3 and ket4 in figure 1 showed little difference in absorbance over the ranges 1800 cm^{-1} to 825 cm^{-1}. This characteristic peak approach was compared with the mixture analysis application in the FTIR software. This software application matches spectra by automatically combining the reference and tested sample spectra. The matches indicate similarities reaching up to 99.8% and generally, a match at 90% or greater is a confirmation [29]. The most noticeable change in figure 1 is the reduction of the absorbance of some bands for Ket3 between 1800 and 825 cm^{-1} which could be related to the excipients.

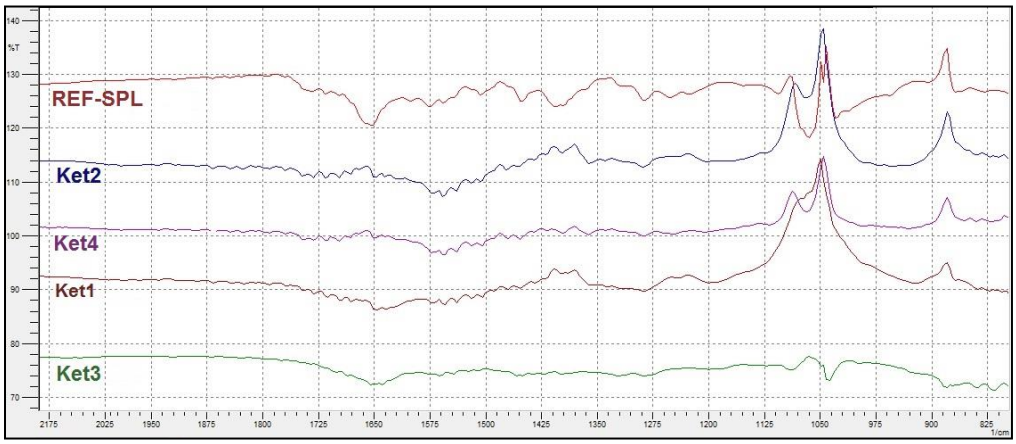

Figure 1: Absorption spectra in the mid-infrared region of the ketoprofen gels. Spectral range was chosen for qualitative analysis from 2200 to 800 cm^{-1}.

Aside from comparing the whole spectra, individual characteristic peaks were used to indicate the presence of a specified ketoprofen in more complex gel samples containing several excipients. For the reference ketoprofen sample, the characteristic stretching peaks of the carboxylic and ketonic carbonyl groups are at 1654.92 and 1651.07 cm^{-1} respectively, while the hydroxyl group appear as broad band at 2735.06 – 3203.03 cm^{-1}. The assignment of obtained frequencies of the four tested samples (Table 3) is in total agreement with the characteristic transmission bands of reference ketoprofen sample [30,31]. This proves that no chemical interaction occurs between the ketoprofen and the additives used in each formulation, and such conclusion was reported.

Formulations	IR peaks cm^{-1}		% Drug content
	C=O	OH (carboxylic)	
Ketoprofen (Reference)	- 1651.07 - 1654.92	2735.06 – 3203.03	
Ket1	- 1645.64 - 1649.21	2977.36 – 3218.73	100±1.12
Ket2	- 1645.62 - 1651.07	2946.38 – 3205.69	100±1.32
Ket3	- 1649.49 - 1653.07	2982.42 – 3218.13	100±1.11
Ket4	- 1647.21 - 1651.07	2993.52 – 3201.83	100±1.22

Table 3: Qualitative (IR peaks) and quantitative (drug content) of ketoprofen in tested gel formulation.

Quantitative analysis

Quantitative ketoprofen assay for uniformity of the drug content in all tested formulation were performed according to official method using British pharmacopeia 2015 [32]. And the achieved data were listed in Table 3. A linear relationship was found between the absorbance at 256 nm and the concentration of ketoprofen in the range of 0.50 to 18.0 µg ml^{-1}. The correlation coefficient was 0.9998 indicating good linearity ($r > 0.999$). The representative linear equation was $y = 0.0390x + 0.0019$, calculated by the least square method. The limit of quantification (LOQ) was found as 1.25 µg ml^{-1}. The limit of detection (LOD) was 0.50 µg ml^{-1}. Although the calculated LOQ was 1.25 µg ml^{-1} it was possible to include the concentration of 0.75 µg ml^{-1} in the analytical curve, which showed relative standard deviation below 1.40%. All tested products were within the pharmacopeial limit and found to contain ketoprofen not less than 92.5 % and not more than 107.5 % of the stated amount of ketoprofen, $C_{16}H_{14}O_3$. The observed peaks in the UV absorbance spectrum of methanol solution are assigned

to the corresponding functional groups with reference to the standard values of ketoprofen. The maximum absorption is at 258 nm is a characteristic peak assigned to C=0 and an aromatic ring [33,34]. The drug content of all gel formulations was found to be within the limit of the British pharmacopeia (92.5-107.5%) [35].

Conclusion

In the present study, four ketoprofen gel formulations were characterized for different parameters to assist their use suitability based on their post marketing study. The visual inspection, color, pH, spreadability, and homogeneity, prove that all ketoprofen gel samples have acceptable physical properties. The fourier transform infrared spectrophotometry and the UV-visible spectrophotometry have fulfilled all requirements to identify and quantify ketoprofen gels. Moreover, FTIR spectra proved that no possible interactions between ketoprofen and excipients in the tested products. The achieved data from all experiment showed that the generic products (ket2-ket4) are very close in their pharmaceutical properties when compared with a brand-name product (ket1) suggesting that they meet various patient needs.

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