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Preparation of Ketamine Powder from Ketamine Hydrochloride and Study Their Physicochemical Properties

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Abstract The aim of the present study was extract pure ketamine powder from ketamine hydrochloride solution. Different concentrations of ketamine gel were prepared. Materials and methods: Ketamine powder was prepared from precipitation of ketamine hydrochloride solution and characterized by Infrared Spectroscopy (IR), Ultraviolet (UV), Micro elemental analysis (CHN) analysis, and measurement of melting point. Homogeneous gel from ketamine was prepared at (0.5, 1, 5, 10, and 15) % concentrations. The pH of the different concentrations of the ketamine gel also were measured. The results demonstrated that Ultraviolet (UV) spectra showed bands at 228, 268, 294 nm which confirm the groups in the ketamine structure. The CHN analysis showed that no difference between the theoretical calculated and practical percentage of the prepared ketamine powder. The pH ketamine gel measurement showed that there is no difference between pH in different concentration.

Keywords: *ketamine powder, ketamine gel, FTIR, UV, CHN*

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1. Introduction

Pain is one of the most common reasons for which people seek medical attention, thus, analgesics are the most commonly prescribed medication in clinical practice [1].

The analgesic drugs can be defined as a drug that relieves pain, [2]. There is a great interest to develop non-oral dosage forms of analgesic drug to minimize its gastric side effects and to provide relatively consistent drug levels at the application site for prolonged periods [3]. Among the latest innovations of the pharmaceutical industry is the technology of drug delivery that overcomes the disadvantages of oral administration, these effects including first-pass metabolism and adverse drug side effects [4].

An ultimate route of administration that by passing these events would offer the patient drug delivery through skin has been a promising concept for a long time because skin is easy to access, has a large surface area with fast exposure to circulating and lymphatic networks and the rout is noninvasive [5].

Ketamine, a phencyclidine (PCP) analog has been used for more than 30 years to produce "dissociative" anesthesia [6]. Ketamine can induce a state of sedation, immobility, relief from pain, and amnesia. It is abused for its ability to produce dissociative sensations and hallucinations [7].

Ketamine can be used in small doses as an analgesic, particularly for the treatment of pain associated with movement, neuropathic pain, and to relieve acute pain [8]. When used insmall doses, the psychotropic side effects, e.g. hallucinations [9].When used in sub-anesthetic doses, ketamine causes analgesia without loss of consciousness and can be used for the treatment of pain [10]. This type of analgesia is used for patients who are resistant or allergic to opioids [11]. The acute analgesic effect of ketamine in humans is closely associated with mental side effects, including various disturbances of sensory perception [12]. Ketamine may cause side effects, when given orally or intravenously [13]. The aims of present study to prepared new dosage form of ketamine with less side effects by:

-Extraction of ketamine powder from ketamine hydrochloride solution by precipitation, and examination of the purity and characterization of the ketamine powder by Infrared (IR), Ultraviolet (UV), Micro elemental analysis (CHN) and the measurement of melting point.

2. Materials And Methods

2.1. Preparation of Ketamine Powder from Ketamine Hydrochloride

Ten ml of (1M) sodium bicarbonate was slowly added to 100 ml of the aqueous ketamine hydrochloride solution 5% (HIKMA pharmaceuticals, Amman- Jordon) under continuous stirring until the pH of solution was close to pH 11, stirring was continued for one hour, and the ketamine was precipitated. The solution was eliminated by

filtration and washed several times with distilled water to removal the remaining of NaCl and then dried. The powder was studied by infrared and ultraviolet spectroscopy to characterized and confirm the structure of the product (Figure 1 and Figure 2).

Figure 1. preparation of ketaminepowder

Figure 2. showed the pure ketamine crystals from ketamine hydrochloride

2.2. Infrared Spectroscopy

Prepared ketamine was examined by using Bruker Tensor 27 IR spectrophotometer (Germany) in the region (400-4000 cm^{-1}) using KBr disc. This measurement was carried out in University of Mosul, College of Education, Iraq

2.3. Electronic Spectra Measurement

The measurement was carried out by using ethanol as a solvent with (1cm) diameter quartz cell by using Shimatsu-UV-Vis recording UV-160 spectrophotometer (Japan). This measurement was carried out in Mosul University, College of Science, and Department of Chemistry.

2.4. Micro Elemental Analysis (CHN)

The elemental analysis (CHN) was carried out in Mosul University, College of Science, Department of Chemistry, by using (Costech instruments elemental combustion system, Italy).

2.5. Melting Point Measurement

The measurement was carried out by using (Electro thermal melting point apparatus, England). This measurement was carried out in Mosul University, College of Dentistry, and Department of Basic Science. The measurement was carried out by putting the ketamine powder in the capillary tube and then put it in the apparatus.

2.6. Preparation of Ketamine Gel

Ketamine gel was prepared by mixing (0.5, 1, 5, 10, 15) gm. of ketamine powder in 100ml Vehical gel (Carboxy methyl cellulose and propylene glycol, Mediotic pharmaceuticals, Syria).)To give a final concentration of (0.5%, 1%, 5%, 10%, 15%) with continuous mixing using Vortex device to prepare a homogenous gel. Gels were kept in plastic containers and store at room temperature**.**

2.6.1. Determination of Gel pH

One gram of each of the gel formulations and the reference was accurately weighed and dispersed in 10 ml of purified water. The pH of the dispersion was measured with a pH meter (Eutech instrument, ecoscan, Singapore) [14].

2.7. Result

2.7.1. Measurement of Infrared and Ultraviolet Spectra

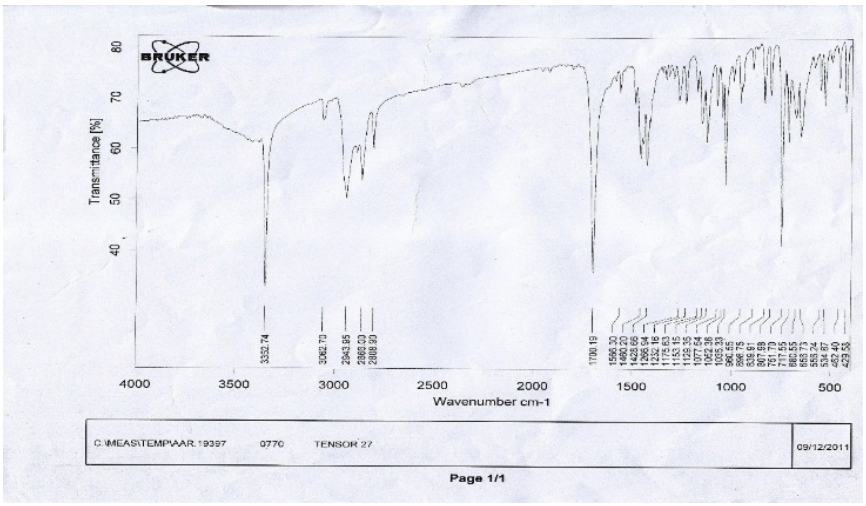

Figure 3. Pure ketamine extract measurement by FTIR (Infra-red) spectroscopy

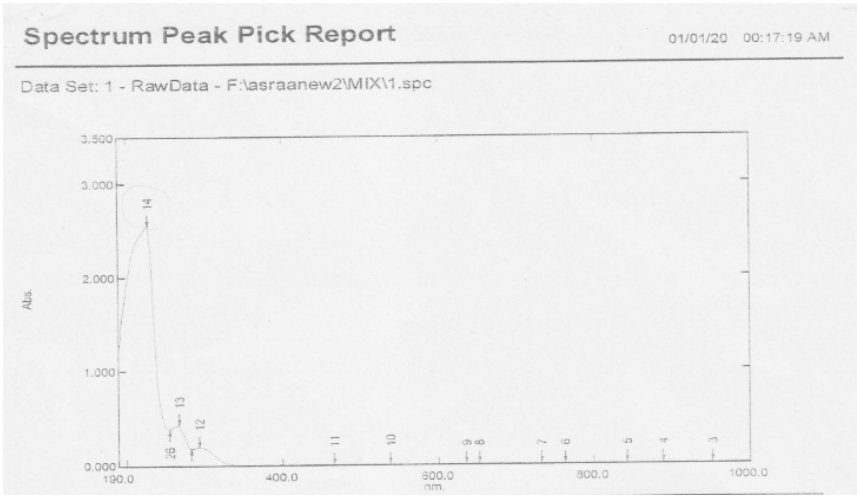

Figure 4. Pure ketamine extract measurement by UV (Ultra-Violet) Spectroscopy

In the present study, the spectrum of FTIR Figure 3 represents the vibration response of pure Ketamine when passed via an infrared beam. The spectrum showed band at 3352cm^{-1} which attributed to the N-H stretch from the amide group connected to the cyclohexanone. The spectrum also showed band at 3062 cm^{-1} which assign to C-H aromatic. The spectrum also showed band at 2866 cm^{-1} which assign to C-H stretch from an alkyl group. In this frequency, the alkyl group is generally a non-aromatic CH_3 or CH_2 stretch. The band at 1750 cm^{-1} due to R_2 – C=O stretch which appear very precise and typical stretch for cyclic ketones. In Ketamine, the carbonyl is connected to the cyclohexane ring. The band 1600 cm^{-1} assigned to C-N band (Generally expressed in C-NH2 and C-N=O compounds).The Figure 3 showed band at 1400-1500 cm^{-1} which attributed to C-H bend, this is another vibration mode of the CH_2 or CH_3 components of Ketamine. This is not the C-H bond from the aromatic carbons. The band at 1450cm^{-1} region due to C-C stretch. This carbon to carbon stretch is not for the aromatic species and hence characterizes the bonding involved in the morning and cyclohexane ring. Pure ketamine extract measurement by UV (Ultraviolet) spectroscopy (Figure 4). The structure showed bands at 228, 268, 294 nm these transitions were belong to the organic compound which contains double bond or hetero atom contains a pair of electrons conjugated with the double bond. These observations confirm the groups in the ketamine structure.

2.7.2. Micro Elemental Analysis (CHN)

Pure ketamine extract measurement by CHN analysis (Figure 5) and (Table 1) showed the calculated and found percentage of the prepared ketamine powder.

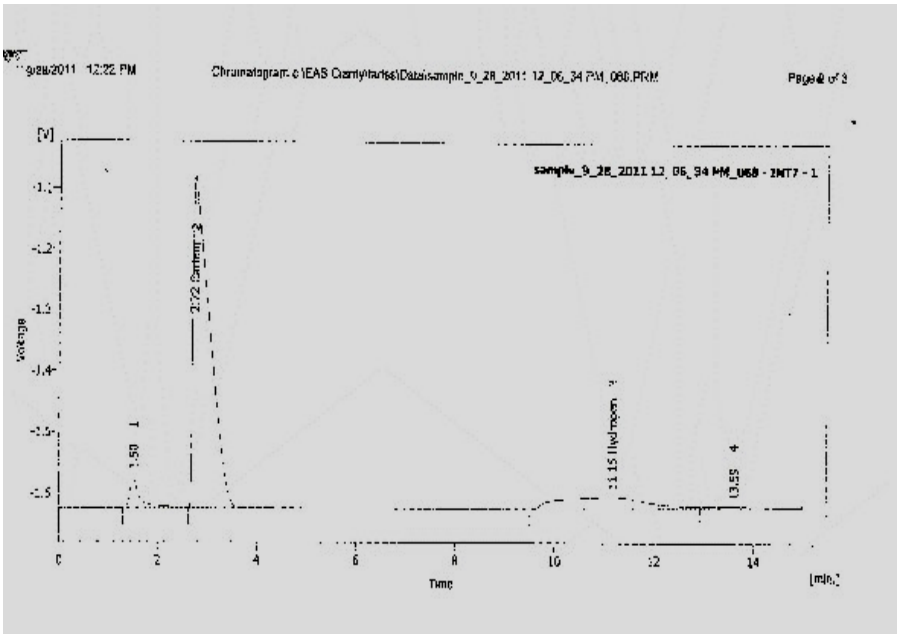

Figure 5. Pure ketamine extract measurement by CHN analyzer Costech instruments elemental combustion system

Table 1. calculated and found Percentage of the Prepared Ketamine

	Found	calculated
C%	65.4	64.52
H%	6.7	6.46

2.7.3. Measurement of Melting Point

Melting point of ketamine powdered is 92.5°C.

2.7.4. Determination of Gel pH

The pH ketamine gel showed the following results (Table 2).

Table 2. Measurement of pH in different concentration of ketamine gel

Concentration of the gel	pH
0%	7.23
0.5%	8.53
1%	8.58
5%	8.47
10%	8.44
15%	8.50

3. Discussion

Topical analgesics have many advantages over systemically administered analgesics, including the ability to provide effective analgesia with reduced systemic drug levels, a factor particularly beneficial to the elderly. An ideal formulation for topical application should exhibit easy of delivery, a good retention at the application site and a controlled release of the drug. The application of gel provides a long stay, adequate drug penetration, high efficiency and acceptability [15].

3.1. Physicochemical Measurements Analysis

The measurements of physical properties of ketamine (Infrared IR, Ultraviolet UV, CHN analysis) confirmed that a pure ketamine was obtained from ketamine hydrochloride.

3.1.1. Infrared (IR), Ultraviolet (UV) Spectroscopy

From the results of Infrared (IR) confirm that a pure ketamine was prepared. The structure was confirmed by measuring Ultraviolet UV spectra the results, showed bands at 228, 268, 294 nm which confirm the groups in the ketamine structure.

3.1.2. CHN Analysis

The data showed there are identical percentages returned to the suggested and prepared ketamine. These results indicated that pure ketamine was synthesized.

3.1.3. Melting Point

From the results of melting point for pure and synthesized ketamine there is identical degree in melting point. This indicated that a pure ketamine was prepared.

3.1.4. pH

The results of pH measurements showed that the increased of concentration of ketamine don't give any increased on the pH. This indicate that ketamine at maximum concentration have similar effect on pH. This mean the maximum concentration has low effect on the pH.

4. Conclusion

This study showed that can be extract pure ketamine powder from ketamine hydrochloride solution, and the extracted ketamine is pure according to IR, UV, CHN analysis and melting point measurments.

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