

## Preparation of Ketamine Gel in Different Concentrations and Evaluation the Skin Irritating Test of this Gel in Rabbits

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### Abstract

**Aim:** The aim of the present study was to extract pure ketamine powder from ketamine hydrochloride solution.

**Materials and Methods:** Ketamine powder was prepared from precipitation of ketamine hydrochloride solution. 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.

**Results:** The pH ketamine gel measurement showed that there is no difference between pH in different concentration. The results showed that ketamine gel also is safe to be used topically and not irritant according to the skin irritation test, because the mean value of skin irritation index (SII) for erythema and edema was found to be zero after applied of ketamine gel in different concentrations.

**Conclusion:** From this study a ketamine gel can be prepared from ketamine powder and it is safe to be used topically and not irritant according to the skin irritation test.

**Keywords:** Ketamine Powder; Ketamine Gel; Skin Irritation Test

### Introduction

Ketamine, a phencyclidine (PCP) analog has been used for more than 30 years to produce “dissociative” anesthesia [1]. 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 [2]. Ketamine can be used in a small doses as an analgesic, particularly for the treatment of pain associated with movement, neuropathic pain, and to relieve acute pain [3]. When used in small doses, the psychotropic side effects, e.g. hallucinations [4]. Ketamine has been shown to be effective in treating depression in patients with bipolar disorder who have not responded to other anti-depressants [5]. It produces a rapid antidepressant effect, acting within two hours as opposed to the several weeks taken by typical antidepressants to work. Topical ketamine when administered to patients with chronic neuropathic pain is effective to reduce allodynia and hyperalgesia [6]. The aim of the present study is to prepare ketamine gel from ketamine powder and evaluate the pH of this gel and to examine the safety of this gel in rabbits by skin irritation test.

### Materials and Methods

**Preparation of Ketamine Gel:** Ketamine gel was prepared by mixing (0.5, 1, 5, 10, 15) gm. of ketamine powder [7] in 100 ml 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.

### 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) [8].

### Skin Irritation Test

This test was performed in accordance with Draize test [9,10]. A group of four male albino rabbits weighing approximately 1.5 - 2 kg used in the test. The ventral side of the animal was carefully shaved and seven circular area of 2 cm in diameter were drawn on the animals' abdomen. A proximately 0.5gm of the formulations (0, 0.5, 1, 5, 10, 15)% were placed on six of the circular area and a substance of known irritancy (histamine 10%) were injected 0.2 ml intradermally into the seventh circular area for purpose of calibration. The degree evaluation of edema and erythema were measured at (0, 1, 24, 48) hr according to score in table 1 and the skin irritation were evaluated from the following formula (Table 1) [11].

Erythema formation	Value	Oedema formation value	Value
No erythema	0	No edema	0
Very slight erythema (barely perceptible)	1	Very slight edema (barely perceptible)	1
Well-defined erythema	2	Slight edema (edges of area well defined)	2
Moderate to severe erythema	3	Moderate edema (raising approximately 1 mm)	3
Sever erythema (beet redness) to slight scar formation	4	Sever edema (raised more than 1mm and extending beyond the area of exposure)	4

**Table 1:** Skin irritation index (SII) = total mean \4.

### Statistical analysis

The data were expressed as mean  $\pm$  SD, difference between three experimental groups were statistically analyzed by one way analysis of variance (ANOVA) followed by the least significant difference test. The level of significance was at  $p \leq 0.05$  [12].

## Result

### Determination of Gel pH

The pH of the ketamine gel is showed in the table 2.

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

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

**Skin Irritation Test**

The mean value of skin irritation score observed after (0, 1, 24, 48) hr from application of ketamine gel (0.5,1,5,10,15)% and 10% histamine. The mean value of skin irritation index (SII) for erythema after histamine applied was found to be (0, 3/4, 3.5/4, 1/4) after (0, 1, 24, 48) hr respectively. The (SII) for edema was found it to be (0/4, 3.5/4, 0/4, 0/4) after (0, 1, 24, 48) hr after injection of histamine (Table 3) (Figure 1).

Rabbit no.	Erythema				Edema			
	0 hr	1 hr	24 hr	48 hr	0 hr	1 hr	24 hr	48 hr
1	0	2	4	1	0	3	0	0
2	0	3	4	1	0	3	0	0
3	0	3	3	1	0	4	0	0
4	0	4	3	1	0	4	0	0
Skin irritation index	0/4	3/4	3.5/4	1/4	0/4	3.5/4	0/4	0/4

**Table 3:** The mean value of (SII) for erythema and edema after histamine applied.



**Figure 1:** (SII) for erythema and edema after applying of histamine and different concentration of gel.

While, The mean value of skin irritation index (SII) for erythema and edema was found to be zero after applied of ketamine gel in different concentration (Table 4).

Rabbit no.	Erythema				Edema			
	0 hr	1 hr	24 hr	48 hr	0 hr	1 hr	24 hr	48 hr
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
Skin irritation index	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4

**Table 4:** The mean value of (SII) for erythema and edema after applied of ketamine gel in different concentration.

From these results of 2 days test, it was concluded that concentrations (0.5, 1, 5, 10, and 15)% were safe to be used as topical gel drug.

## Discussion

The results of pH measurements showed that the increased of concentration of ketamine did not effect on the alkaline pH. This indicates that ketamine at maximum concentration have similar effect on pH. This means the maximum concentration has a low effect on pH.

## Skin Irritation Test

Before the ketamine gel is considered for a human topical gel we confirm that a gel is not irritant and possess no harmful properties only a gel that appear to be non-irritating move into human topical gel to confirm their safety [13]. In the present study of the skin irritation test, it is confirmed that different concentrations of ketamine gel were safe to be used as topical gel drug compared with histamine applied on the rabbit skin. According to these results, we showed that mean value of skin irritation index (SII) for erythema and edema was found to be zero after application of ketamine gel in different concentrations while the mean value of skin irritation index (SII) for erythema after histamine applied was found to be (0, 3/4, 3.5/4, 1/4) after (0, 1, 24, 48) hr respectively. The (SII) for edema were found it to be (0/4, 3.5/4, 0/4, 0/4) after (0, 1,24, 48) hr after injection of histamine. This confirmed that the ketamine gel is not irritant, while the histamine is irritant.

Irritants are chemicals that cause skin damage and reversible. Clinical signs of irritation include the development of a rash, inflammation, swelling, scaling, and abnormal tissue growth in the affected area [14]. The results of this study agree with other studied that consider the gel is not irritant if it is not producing clinical sign of irritation [13]. Untreated skin areas serve as the control, a chemical (histamine and ketamine gel) is considered to be an irritant if it causes skin lesions, such as inflammation or other clinical signs, which heal partially or totally by the period of the time. Histamine which considered as irritant and its already shown to have adverse effects when applied it and the animals are observed for 24 hour for signs of erythema and edema in the skin test compared with ketamine gel [15].

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