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# Formulation and evaluation of honey loaded povidone iodine gel for topical application

**[1] Jamal Mohamed A*, [1] Perinbam K , [1] Vahitha V, [2] Devanesan S and [3] Janaki Raman KKK.**

[1] PG and Research Department of Plant Biology and Biotechnology, Government Arts College for Men (Autonomous), Nandanam, Chennai, Tamil Nadu, India.

[2] College of Sciences, King Saud University, Saudi Arabia.

[3] Senior Research Scientist, Product Development and Research (Formulation) Department, Sun Pharmaceutical Industries Limited-Gurgaon, India.

* **Corresponding Author:** E-Mail**:** jamalmohamed786@yahoo.com

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**ABSTRACT**

Wound care management and its therapeutic obstacles represent an economically challenging important burden on global healthcare. Wound healing is a dynamic and complex process, which transforms devitalized and missing cellular structures and tissue layers. Povidone Iodine is a commonly acceptable antiseptic, due to their broad-spectrum antimicrobial activity against bacteria. The in-vitro and in-vivo studies report showed the higher concentration of Povidone Iodine is toxic to fibroblast. To overcome these difficulties, we propose using honey with Povidone Iodine to improve the therapeutic efficacy. The Povidone iodine 5.00 % with honey 3.00 % gel was prepared using polyethylene glycol grades. The formulations physical stability was optimized on the basics of acceptable gel characterization parameters. Among the four formulations, HPG-03 showed an acceptable appearance, pH, spread ability, consistency, and drug content; there is no proof of a separation phase and ease of removal.

**Keywords:** Wound Healing, Honey, Povidone Iodine, Gel, Spreadability, Extrudability.

## 1. INTRODUCTION

Wound care management and its therapeutic obstacles represents an economically challenging important burden on global healthcare.[1] It has been estimated that a chronic wounds carriers a cost of nearly USD 25 billion per year in United states of America, with the number of patients affected growing yearly from 6.5 million.[2] The wound care market is expected to reach USD 22.01 billion by 2022 from USD 18.35 billion in 2017, at a CAGR of 3.7%.[3] From 2001 to 2003 in India, An Indian community-based epidemiological study of wounds reported, the prevalence of chronic wounds was 4.48 per 1000 populations.[4] Wound healing is a dynamic and complex process, which transforms devitalized and missing cellular structures and tissue layers.[5] The wound healing process can be characterized by three overlapping but distinct cellular phases: the initial phase of hemostasis and inflammation, followed by the phase of re-epithelialization and granulation tissue formation, new tissue formation, and final phase is tissue remodeling. [6, 7] Healing wounds are regulated by a variety of cytokines and growth factors, acting as an important intermediary for differentiation, proliferation, and preservation of important cells in the repair process through different mechanisms.[8] Decisions on the choice of wound treatment include two basic considerations: (i) The safety of the treatment; and (ii) The effectiveness of the treatment. The safety of wound care can be determined by whether treatment delays the progression of the wound during the healing stages (Infections, reproduction/cell re-implantation, and reconstruction). [9] The acute wounds can be treated successfully within an anticipated time frame with no patient or environmental factors delaying healing.[10] Nevertheless, chronic wounds may require some years to heal and some remain unhealed for decades. During this period, patients can experience severe pain, significant emotional and physical distress, reduced movement and social loneliness [11, 12] antiseptics, as an alternative for topical wound management, tend to be microbicidal and have a broader spectrum of

antimicrobial activity than antibiotics. In general antiseptics have antibacterial and delaying actions and are generally safe when applied to intact skin. [13] To date, many antiseptics have been effectively used for the treatment of acute and chronic wounds includes, Cadexomer iodine, [15] Chlorhexidine gluconate, [13, 16] Hydrogen peroxide, [17] N-halamines, [13, 18] Povidone-iodine, [9,13,19-21] Quaternary ammonium salt, [13, 19, 22] Silver, and Zinc oxide. [13, 23, 24,] Among these, Povidone iodine has acted as one of the most popular antiseptic for wound healing applications, which was considered as a most important antiseptic, referring to therapeutic management and health care, because it is less toxic, economists in the commercial field, easy obtainable and controllable in loading iodine, long-term stability and durability under harsh condition, etc.. [13]

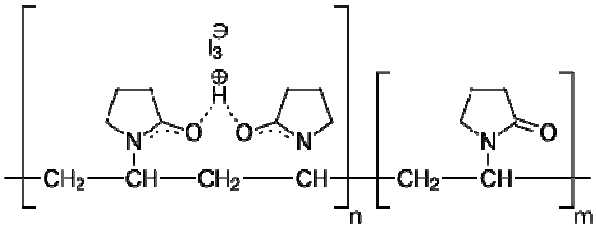

**Figure 1: Structure of Povidone Iodine**

In 1811, the natural element of iodine was first discovered by French pharmacist Dijon Bernard courtist and that bactericidal efficacy was first described by davaine in 1980. Later, the H.A. Shelanski and M.V. Shelanski discovered the stable chemical complex of Povidone iodine in 1955 at the Industrial Toxicology Laboratories in Philadelphia.[20] Povidone iodine is a commonly acceptable antiseptic, due to their unique features, such as broad-spectrum antimicrobial activity against bacteria, molds and certain viruses, high bactericidal efficiency, nonirritation and persistence. [13] The in-vitro and in-vivo studies report showed the higher concentration of Povidone iodine (10 %) is toxic to fibroblast. When the dose is reduced from 10.00 % to 5.00 %, also reduced efficacy and healing effect delayed. [25] To overcome these difficulties, we propose using honey with Povidone iodine 5.00 % to improve the therapeutic efficacy and stability by topical drug delivery.

In this study, we aimed to develop the Povidone Iodine Gel using honey for topical applications. In general gels are becoming more popular due to ease of application and better percutaneous absorption, than other semisolid preparations. Gels can resist the physiological stress caused by skin flexion, blinking and mucociliary movement, adopting the shape of applied area and control the drug release.

## 2. MATERIALS AND METHODS

### 2.1. Materials

Povidone Iodine was kindly gifted from, Drakt Pharmaceuticals, Vadodara, India. Honey was purchased from local Agriculturalists, India. Polyethylene glycol 400 and Polyethylene glycol 4000 were purchased from SD Fine Chem Ltd, Mumbai, India. All other chemicals and reagents used were of analytical grade. The double distilled water was filtered through a 0.45 µm membrane (cellulose acetate) before use.

### 2.2. Methods

#### 2.2.1. Preparation of Povidone Iodine Gel formulations

The Povidone Iodine 5.00 % gel was formulated by a conventional technique and the compositions of the gel percentage (% w/w) with their codes is listed in **Table 1**. The gel phase consisted of polyethylene glycol 400 and polyethylene glycol was 4000 heated up to 72°C ± 1°C, cooled the content under continuous stirring at 1500 rpm until to form gel. Povidone Iodine was dissolved in polyethylene glycol 400, then add into the gel phase under continuous stirring condition. Add honey slowly into the mixture under stirring condition. Finally, the speed of the stirrer was decreased to 800 rpm until the gel was cooled to room temperature.

**Table – 1:- Formulae of Honey loaded Povidone Iodine Gel**

| Ingredients (% Used) | Formulations | | | |
|---|---|---|---|---|
| | PSG-01 | PSG-02 | PSG-03 | PSG-04 |
| Povidone Iodine | 5.00 | 5.00 | 5.00 | 5.00 |
| Honey | 3.00 | 3.00 | 3.00 | 3.00 |
| Polyethylene Glycol-400 | 72.00 | 74.00 | 77.00 | 80.00 |
| Polyethylene Glycol-4000 | 20.00 | 18.00 | 15.00 | 12.00 |
| Total | 100.00 | 100.00 | 100.00 | 100.00 |

*Physical examination*

The prepared Povidone Iodine Gel formulations organoleptic and physical appearance were examined by visual inspection under a good light, viewed against a black and white background.[26, 27]

*pH determination*

The pH was determined, 3.00 g each formulation were dispersed in 30.00 ml of purified water then measured by using a pH meter (pH meMettler-Toledo GmbH, Switzerland). The measurements of pH of each formulation were replicated three times.[26, 28]

*Viscosity*

The prepared Povidone iodine Gel formulation viscosity was measured by using Brookfield Rotational Digital Viscometer DV II, model LVDV-E (in cPs). 500 g of prepared gel sample was taken in the griffin standard beaker and the T-bar spindle (S-96) was at 10 rpm, the temperature was maintained as 25±1 °C.[26]

*Spreadability*

Two sets of glass slides with standard dimension were taken. Place the Povidone Iodine gel on the one slide. The other side was placed on the top of gel, so that the gel was placed between the two slides in an area of 7.5 cm along the slide. The 100 g of weight is placed on the upper slide so that the gel is pressed between the two slices uniformly to form a thin layer. The weight was removed and the excess of gel was removed from joining the slides. The two slides are mounted on the stand without discomfort and in such a way that only the top slide slip freely by the associated weight strength. The weight of 20 grams was carefully tied to the top slide it was noted that the time taken by the top slides to travel 7.5 cm and separated from the lower slide under the influence of weight. The experiment was repeated three times and the average time taken for calculations.[29, 30]

Spreadability was calculated by using the following formula;

$S = mX\ 1/t$

Where,

S - Spreadability,

m - Weight tied to the upper slide (20 g),

l - Length of the glass (7.5 cm),

t - Time taken in seconds.

*Extrudability*

In this test, a closed collapsible aluminum tube containing about 20 g of Povidone Iodine gel was pressed firmly at the crimped end and a clamp was applied to prevent any rollback. The cap was removed and the gel was extruded until the pressure was dissipated.[29]

*Centrifugation tests*

The prepared Povidone Iodine gel formulations were performed centrifuge test at 3750rpm for 5 hrs. Accurately weighed 15g samples were placed in centrifuge tubes and examined the gel physical stability.

*Drug content*

Assay of available Iodine: The content of Povidone iodine in the prepared formulations, standard and sample were analyzed using the official USP method.

The sodium thiosulfate was prepared 0.02 N VS by dissolving 3.16 g of sodium thiosulfate in 1000 ml of distilled water. PVP-I concentrations were determined using the titration method described in the USP as follows: Transfer the accurately weighed amount of gel equivalent to 50 milligrams of iodine to a 100 ml glass cup, add the water to make a total volume of at least 30 ml, and stir until the complete dissolution of the formulations. Immediately titrate with 0.32 N sodium thiosulfate VS, and determine the endpoint visually by using the starch solution as an indicator. Perform a blank determination, and make any required correction. Each ml of 0.02 N sodium thiosulfate is equivalent to 2.538 mg of available iodine. The color of the solution at the end point is that of the blank solution. The sodium thiosulfate solution used in both methods was equal, suggesting that both methods were interchangeable.[31, 32]

## 3. RESULTS AND DISCUSSION

Povidone iodine has acted as one of the most popular antiseptic for wound healing applications, which was considered as a most important antiseptic, referring to therapeutic management and health care. Even though, the higher concentration of Povidone iodine (10.00 % w/w) in-vitro and in-vivo studies report shows, the Povidone iodine (10.00 % w/w) is toxic to fibroblast. To overcome this problem, the concentration of Povidone Iodine was reduced and the therapeutic activity was increased, by the addition of honey. Honey is a nutritious thick carbohydrate-rich syrup, which was successfully used since ancient eras in traditional medicine. Today, honey is widely used due to its evidenced broad therapeutic uses. It is a well-known antiseptic, anti-parasitic and pain-reliever. Honey contains an enzyme called glucose oxidase, which breaks down glucose sugars and generates hydrogen peroxide. This hydrogen peroxide acts

**Table – 2: Characterizations of Honey loaded Povidone Iodine Gel**

| Formulations | Parameters # | | | | | | |
|---|---|---|---|---|---|---|---|
| | Appearance | pH | Viscosity cPs | Spreadability gm cm/sec | Extrudability | Centrifuge | Drug Content % w/w |
| HPG-01 | Brown homogenous viscous gel | 4.51 | 19,042.04 | 36.12 | ++ | No phase separation/ liquefaction | 99.16 |
| HPG-02 | | 4.79 | 27,384.15 | 34.46 | ++ | | 102.45 |
| HPG-03 | | 5.12 | 31,560.05 | 33.80 | +++ | | 100.09 |
| HPG-04 | | 6.40 | 34,601.84 | 29.91 | +++ | | 102.17 |

# (n = 3, ±SD); +++ Excellent; ++ Good;

hydrogen peroxide. This hydrogen peroxide acts as an antiseptic for wounds.

The findings revealed that the freshly prepared Povidone iodine loaded formulation were shown brown color homogenous viscous gel with a weak iodine flavor. Slight changes in color were observed in the Gel formulation HPG-04. Monitoring the pH value is crucial for determining the emulsion stability. In fact, pH changes indicate the occurrence of chemical reactions that can give an idea on the quality of the final product. The pH of human skin normally ranges from 4.5 to 6.0. The developed formulations pH range was 5.2 to 6.1, which is close to neutral pH, non greasy and easily removable after the application. The centrifuge test may accelerate the phase separation/liquefaction of gel stability, prediction of gel shelf life based on this method. The test results shown, there is no phase separation/liquefaction in the prepared Povidone Iodine Gel. The rheology behavior and thixotropic properties can serve as important indicators for evaluation of physical properties and the structural stability of the gel formulation. The prepared Povidone Iodine gel formulation viscosity results range 26000 to 38000. The formulated gel Spreadability and Extrudability was shown in the **Table - 2**. The viscosity of gel is often reported to play a vital role in its flow properties. The formulation viscosity affects the release of the drug from the gel. If the gel consists of more viscosity the drug release from the formulation is reduced. If the same gel possesses less viscosity the drug diffuses immediately into the diffusion medium. Hence, for the gel formulation optimum viscosity is necessary to get the maximum drug release. The prepared Povidone iodine gel formulation viscosity was found in the range 19,042.04 to 34,601.84 cPs. Higher viscosity was achieved by the addition of the high concentration of polyethylene glycol-4000. The centrifuge study results shown there was no formulation was settled down in that centrifuge tube, it indicates the prepared formulations were physically stable. The drug content of was performed to estimate the amount of the Povidone iodine present in the gel formulations and the values were depicted in **Table-II**. The drug content of the prepared formulation results was within the acceptable limits.

## 4. CONCLUSION

In the current work, the traditional honey was loaded successfully in Povidone iodine gel by conventional method. The honey was loaded successfully in Povidone iodine gel formulation were evaluated for physical examination, pH, viscosity, centrifugation test, spreadability, extrudability and drug content. The formulations were incorporated in polyethylene glycol base. A direct relationship was noted between spreadability and extrudability. The higher concentration of polyethylene glycol 4000 had higher viscosity values. Our study indicated that the formulation HPG-03 was more stable as compare with other formulations. This formulation was not greasy and easily removable after application.

***Conflict of interest statement:***

We declare that we have no conflict of interest.

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