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TOPICAL GEL FORMULATION FOR DYSMENORRHEA: ADDRESSING PAIN WITHOUT HORMONAL SIDE EFFECT

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ABSTRACT

Menstrual cramps, referred to medically as dysmenorrhea, are a common gynecological issue that many women encounter during their reproductive years. However, myths and taboos have always surrounded it, restricting women's participation in certain social activities. This topic has been observed as a taboo for a long time in India. Many civilizations have taboos surrounding menstruation, which affect women's and girls' emotional health, attitude, lifestyle, and most importantly their health. Our society remains unaware of the scientific foundations behind certain traditions, including those related to menstruation, a regular cycle with concomitant limitations, has taken on more religious undertones. Although synthetic medications are available, like oral contraceptives and NSAIDs, most women avoid clearly due to side effects like irregular menstruation, hormone imbalances, and implications on a woman's ability to conceive after long-term use. Although there are a few more product which give us relief from pain like roll-on, Period patches have their benefits, but they also come with certain drawbacks. But topical formulation specially gel have less side effect. Menthol, eucalyptus, turmeric has significant anti-inflammatory and anti-dysmenorrheal properties. The pharmacological action and permeability rate are enhanced by the addition of excipients. The formulation quickly penetrates the stratum corneum. The formulation contains menthol,

which is beneficial in treating nausea, vomiting, and diarrhoea associated with dysmenorrhea because of its cooling and anti-spasmodic properties. Eucalyptus and turmeric has anti-inflammatory properties which help to decrease the inflammation by inhibiting the key cytokines and pro-inflammatory mediators. The gel proves to be significantly more effective than traditional NSAIDs, is simple to use, and will not disrupt the menstrual cycle.

KEYWORDS: Myth, Facts, Dysmenorrhea, NSAIDs, Menstrual cycle, Topical Gel.

1. INTRODUCTION

In the historical background of India, talking about the menstruation was considered taboo, even today people feel ashamed to talk about this openly.[1] It's a long-standing tradition in India to prohibit menstruation women from entering temple grounds and other places of worship.[2] Further in Hinduism daily chores were prohibited during menstruation. Before she can resume her daily activities and be with her family, she needs to be "purified. "Women are prohibited from entering the "puja room and kitchens.[3]"

In addition, it is thought that because menstruating women are unclean and unhygienic, the food they handle or prepare may become contaminated. In a 2011 study conducted by Kumar and Srivastava, the women who participated additional stated that while their period, their bodies released a particular ray or smell that ruined preserved food. Consequently, they were restricted from handling sour foods like pickles.[4]

Menstrual blood is thought to be harmful in Surinam, where a wicked individual could use black magic to harm a girl or woman who is going through her periods. Fascinatingly, these kinds of ideas are still followed throughout Asia, including India. But no rational or scientific explanation for this appears to exist.[5]

We are living in the 21st century but still some people hesitate to talk about it. In many pharmacies, sanitary napkins are given to customers in black polythene or wrapped in newspaper. In many regions of India, menstruating girls must also stick to severe eating habits, such as avoiding sour foods like pickles, tamarind, and curd.

The scientific basis for some of these customs—like the way menstruation, a regular cycle with accompanying restrictions, has taken on more religious overtones—is still unknown to our society.[6] Menstruation is the natural part of the reproductive cycle in which blood from

the uterus gets away through the vagina. It's a normal process that starts in girls between the ages of 11 and 14 and is a clear sign that puberty is about to start.[7]

Many women and girls experience discomfort and cramping in their abdomens during their menstrual cycle. "Dysmenorrhea" is the medical word for painful periods.[8] Dysmenorrhea can be classified into two main types:

1. **Primary dysmenorrhea**

- This is the more common form and occurs in the absence of any underlying pelvic pathology.
- It usually starts within a few years after a woman begins menstruating and tends to improve with age or after childbirth.
- The pain is caused by the excessive production of prostaglandins, which are hormone-like substances that cause the uterus to contract.
- Signs may consist of cramps in the lower abdomen, discomfort in the lower back, nausea, headaches, and occasionally diarrhoea.[9,10]

2. **Secondary dysmenorrhea**

- This type results from an underlying medical condition affecting the reproductive Organs.
- It typically begins later in life, frequently after the age of 25, and as time passes, the discomfort usually gets worse.
- Common causes include conditions such as endometriosis, fibroids, adenomyosis, pelvic inflammatory disease (PID), or the application of an intrauterine device (IUD).
- The discomfort might continue longer than the duration of menstruation and may be more severe than primary dysmenorrhea.[11,12]

2. CURRENT TREATMENT

Treatments for severe menstruation symptoms are typically helpful. You need to have a talk with your gynaecologist, if you get excruciatingly painful periods or if the discomfort seems to be growing worse over time. Endometriosis is one curable ailment that might occasionally be the cause of abdominal pain.[13]

Currently available therapies for dysmenorrhea, or period cramps, include

- **Over-the-counter pain relievers:** Ibuprofen and naproxen are two examples of non-steroidal anti-inflammatory medicines (NSAIDs), which are frequently used to treat pain and lower inflammation.
- **Hormonal birth control:** Menstrual cramps can be lessened by using hormonal contraceptives, such as the pill, patch, or IUD, which help control or stop periods.
- **Heat therapy:** Relaxing relief can be obtained by applying a hot water bottle or heating pad to the lower abdomen.
- **Lifestyle changes:** The severity of cramps can be lessened by regular exercise, a nutritious diet, and stress-reduction methods like yoga or meditation.
- **Supplements:** Certain individuals may find dietary supplements like omega-3 fatty acids, magnesium, or vitamin B1 to be beneficial.
- **Alternative therapies:** Herbal medicines, acupressure, and acupuncture may also beneficial to certain people.
- **Prescription drugs:** In extreme situations, physicians could recommend hormone therapies or more potent painkillers.[14]

Although there are synthetic medications like NSAIDs and oral contraceptives, most women avoid these because adverse effects include hormonal imbalances, effects on a woman's ability to conceive after long-term use, and irregular menstruation. Women would prefer suffer in pain than take these drugs.[15]

3. RELEVANCE OF TOPICAL GEL

Topical gels for menstrual cramps can relieve pain locally by administering analgesic or anti-inflammatory substances straight to the lower abdomen or other affected area. This targeted strategy may minimize discomfort without the systemic side effects of oral drugs. Because they reduce pain, ingredients like menthol and diclofenac are frequently utilized. They are also a practical choice for controlling menstruation pain due to their ease of use.[16]

4. MECHANISM OF MENSTRUAL CRAMPS

Menstrual cramps are caused due to the uterine muscles contracting which leads to shed the uterine lining during menstruation. The underlying mechanics involve several key physiological processes:

a) Prostaglandin production

Prostaglandins are hormone-like chemical compounds produced in the endometrium (uterine lining) and are the main cause of menstrual cramps. The contraction and relaxation of smooth muscle tissue are influenced by prostaglandins. Uterine contractions that are more painful are linked to higher prostaglandin levels.[17]

b) Uterine contractions

During menstruation, the uterus contracts to assist in the endometrium's release. Mild contractions are common, but severe contractions brought on by elevated prostaglandin levels can induce ischemia and which lowers blood supply to the uterus and increases to pain.[18]

c) Pain and ischemia

Excessive or frequent contractions of the uterine muscles might compress blood vessels, lowering blood supply to the uterine tissue. This causes ischemia, or a lack of oxygen in the muscle cells, which causes discomfort and cramping.[19]

d) Inflammatory response

In certain situations, prostaglandin release leads to inflammatory reaction that increases pain perception. The level of pain and duration of cramps may also be influenced by this inflammatory process.[20]

5. PATHOPHYSIOLOGY

Current research indicates that the pathogenesis of dysmenorrhea is caused by the increased secretion of prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2) in the uterus during endometrial shedding, even if the condition's pathophysiology is yet unknown. These prostaglandins lead to vasoconstriction and myometrial contractions, which cause uterine ischemia and the generation of anaerobic metabolites. As a result, pain fibres become hypersensitive, which eventually leads to pelvic pain.[21,22]

The cyclooxygenase (COX) pathway regulates the arachidonic acid cascade, which synthesized the prostaglandins. By use of the phospholipase A2 lysosomal enzyme, progesterone levels control the synthesis of arachidonic acid. The progesterone concentration increases during the peak of the luteal phase, the second phase of the menstrual cycle that comes after ovulation. If conception is ineffective, the corpus luteum degenerates and the blood's progesterone levels decrease. Menstrual bleeding, endometrial shedding, and

lysosomal enzymes' release, which results in the synthesis of arachidonic acid and prostaglandins.[23]

In the late luteal phase, endometrial prostaglandin levels are higher in women with regular menstrual cycles. However, a number of studies that used endometrial biopsies and menstrual fluids to evaluate prostaglandin concentrations in the luteal phase found that dysmenorrheic women have higher prostaglandin levels than eumenorrheic women.[24]

Higher levels of PGF2α and PGE2 in the endometrium are therefore directly linked to monthly cramps, pain intensity, and related symptoms.[25]

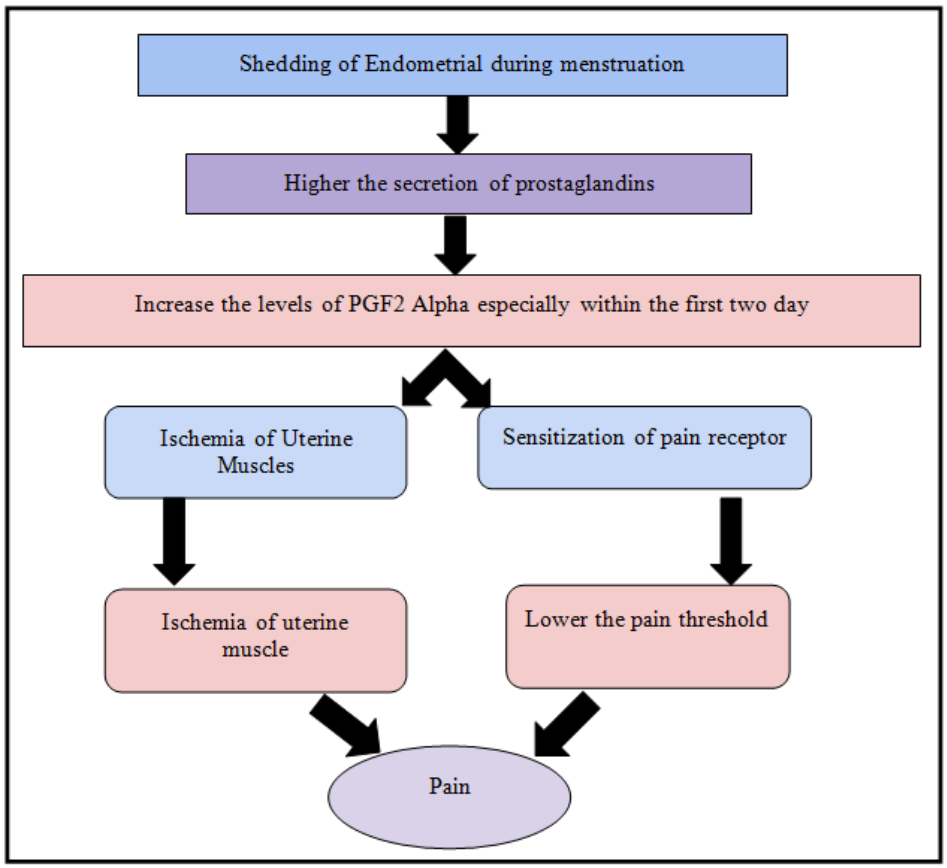

Fig. 1: Pathophysiology of Dysmenorrhea.

6. GEL

A semi-solid material with characteristics of both liquids and solids is called a gel. It consists of an interconnected network of molecules that form a flexible structure and frequently trap a lot of liquid. Because of this structure, gels have a distinct feel and maintain their shape. Gels are frequently utilized in many different fields, such as scientific research, food goods, cosmetics, and medicinal treatments.[26]

6.1. Ideal properties of Gel[27,28]

- The gel should be homogeneous and clear.
- The gel should be inert and safe in nature.
- The gel should be non-sticky.
- There should be no interactions between the gel and any other formulation ingredient.
- The gel should be stable in nature.
- It should not cause irritation, when applied to the skin or any other part of the body.
- The viscosity is should be optimum.
- It should have anti- microbial activity.

6.2. Advantages of Gel[29,30]

- Compared to other formulations, gels are quite easy to produce.
- Gel is a sophisticated, non-greasy composition.
- Gels exhibit outstanding adhesion to the application site.
- Gels are biocompatible and eco-friendly in nature.
- Gels have exceptional stress tolerance.

6.3. Disadvantages of Gel[31]

- Some drugs have a low skin permeability.
- Drugs are more difficult to absorb via the skin because of their greater particle size.
- Drugs that cause skin irritation or sensitization are inappropriate for this administration route.

6.4. Type of Gel Used for Menstrual Cramps

1. Ibuprofen Gel

Menstrual cramps and discomfort can be reduced by applying ibuprofen gel. It is a pain relief treatment that is applied directly to the lower abdomen. It functions by lowering inflammation and preventing the synthesis of prostaglandins, which cause pain. One well-liked and practical remedy for period cramps is ibuprofen gel.[32]

2. Topical NSAIDs

NSAIDs, are gels or creams that are administered directly to the skin to ease the discomfort and cramps due to menstruation. They function by lowering inflammation and preventing the synthesis of prostaglandins, which cause pain. For the treatment of menstrual cramps, topical NSAIDs are a well-liked and practical choice.[33]

3. Menthol Gel

Menthol gel serves as a viable substitute for prescription drugs. It provides a natural method for alleviating pain that can be used directly on the skin. It helps alleviate discomfort and menstrual cramps by cooling the surface and reducing inflammation.[34]

6.5. Mechanism of gel Formation

Gel are prepared by three type of cross linking:

1. **Chemical cross-linking:** Chemical cross-linking is also seen in polymers that are assembled from bound components. While cross-linking molecules are bringing the free group and the added chemical together, these polymers create an irreversible contact between them. In this type of reaction, gel formation is caused by an increase in viscosity upon reaching a specific concentration.[35]
2. **Physical cross-linking:** Hydrogen bonds can also be formed to address gel transitions through processes that involve changes in temperature, variations in concentration, and the dissolution of crystalline substances. There is evidence of physical cross-linking, For example, in dextran and cellulose gels.[36]
3. **Ionic cross-linking:** Gel is produced by applying a charge to the polymer or different particles (Solvent), which cause them to be drawn to one another. Ionic charges originate from molecular charges.[37,38]

6.6 Efficacy of Gel for Menstrual Cramps

The capacity of topical gels to deliver active components directly to the region of discomfort supports their effectiveness in reducing menstrual cramps. For example, topical NSAIDs function by lowering prostaglandin levels, which cause excruciating uterine contractions.[39]

For localized, temporary relief from menstrual cramps, gel-based medicines can be useful, particularly for mild to moderate pain.[40] Topical analgesic gels with lidocaine or menthol offer a cooling feeling that can divert attention from pain, while heat-activated gels simulate the pain relief of heating pads by providing warmth that relaxes muscles and increases blood flow.[41]

Herbal gels with essential oils like Eucalyptus, turmeric may also help, because of their anti-inflammatory and muscle-relaxing properties. Applying these gels directly provides quick absorption and targeted delivery of the active ingredients.[42]

It help to providing quick relief from cramps, bloating, and discomfort. As compared to oral medications, topical gels offer several advantages, including reduced systemic side effects, faster onset of action, and improved bioavailability. Additionally, gels can be applied directly to the lower abdomen, where the pain is most severe, increasing their effectiveness.[43]

However, while these gels can bring comfort, they generally only provide short-term relief and might not be effective for more intense pain or conditions like endometriosis.

6.7. Mechanism of Action of gel

Topical medications have the ability to act either locally or systemically. But first, the drug molecules need to stay in and pass through the skin's outermost layer.[44]

The drug is absorbed passively through diffusion across the skin's surface.[45,46] The drug may be absorbed through shunt pathways (distribution through sweat glands and hair follicles) or passively diffused directly through the epidermis (via transcellular or intercellular routes).[47]

Initially the transfollicular route may be used for drugs absorption. Transepidermal absorption may take the place of transfollicular absorption as the primary absorption channel once the medication has stabilized.[48]

The concentration gradient between the skin's surface and the body affects how well drugs are absorbed via the skin; a larger concentration gradient leads to a faster rate of absorption.[49] The rate of drug absorption can be maintained at a steady level as long as the concentration of the drug at the skin's surface is consistently and significantly more than what is present within the body.[50] Physiological factors, physicochemical properties of the drug, and gel qualities all affect how quickly the drug penetrates the epidermal barrier. The size of the application area, frequency, force, and skin characteristics are examples of physiological factors. The solubility, skin attraction, and metabolism of the drugs are examples of its physicochemical characteristics.[51]

Stability, thermodynamic activity, and occlusive qualities are some of the characteristics of gel. The drug may enter the dermal blood capillaries via penetrating deeper skin tissues. After that, it can move on to the circulation for a systemic impact.[52]

6.8. Method of Preparation of Gel[53,54]

Gels are prepared by mixing suitable thickening agent and aqueous vehicles. Drug is

dispersed in aqueous vehicle and thickening agent is added by triturating in a mortar. Trituration is carried out until a homogenous preparation is formed.

1. Fusion Method
2. Cold Method
3. Dispersion Method

1. Fusion Method

This technique use in variety of waxy substances as gelatin in non-polar media. When waxy components melted by fusion, the drug was added, and it was slowly agitated until a homogenous gel formed.

2. Cold Method

Water was put in a mixing container after being cooled to 4–10 °C. The gelling ingredient was added gradually and stirred until the solution was finished and the temperature lower than 100°C. The drug was introduced gradually while being gently mixed in solution form. Move the liquid to a container right away and let it warm up to room temperature until it turns into a clear gel.

3. Dispersion Method

The gelling component was mixed with water and stirred for 30 minutes at a speed of 1200 rpm until dissolved. A non-aqueous solvent containing a preservative was used to dissolve the drug. While stirring constantly, this solution was added to the gel above.

6.9. Formulation of Topical Gel[55,56,57]

I. Gelling Agent

Gelling agents assist in establishing the structure and consistency. These substances create a semi-solid framework that can retain water or other liquids, giving the gel its intended viscosity, texture, and stability.

E.g., Carbopol 940, 934, HPMC, CMC

II. Solvents or Vehicle

Purified water is frequently used as a solvent to improve the solubility of the therapeutic compound in the formulation. Moreover, it aids in the improved absorption of medication through the skin.

E.g., alcohol, glycerol, PG, PEG 400, etc.

III. Buffers

Aqueous and hydroalcoholic-based gels may use buffers to regulate the formulation's pH. Buffer salts become less soluble in hydroalcoholic-based vehicles.

E.g., Phosphate, citrate, etc.

IV. Preservatives

Certain preservatives interact with the hydrophilic polymers utilized in gel preparation, which reduces the amount of free (anti-microbial active) preservative present in the formulation. Therefore, it is essential to increase the initial concentration of these preservatives.

E.g., Parabens, phenol etc.

V. Antioxidants

To enhance the chemical stability of therapeutic compounds vulnerable to oxidative breakdown, these agents can be included in their formulation. The choice of gel formulation depends on the type of vehicle utilized. Typically, water-soluble antioxidants are employed since most gels are water-based.

E.g., Sodium metabisulphite, sodium formaldehyde sulfoxylate, etc.

6.10. Benefits Topical gel over other Route of Administration

Compared to alternative delivery methods, topical gels provide a number of benefits, especially when it comes to patient compliance and localized treatment. By applying these formulations directly to the afflicted location, systemic exposure and possible adverse effects are reduced. Gels' unique properties, such as their ease of application and ability to provide sustained drug release, make them a popular choice in many therapeutic fields.[58]

Localized Drug Delivery

- Topical gels deliver drug directly to the site of action and enhancing therapeutic efficacy.
- Topical gel reduces the risk of systemic side effects, as seen with oral route, which often lead to gastrointestinal complications.[59]

Enhanced Patient Compliance

- Because of their easy administration and non-greasy texture, gels are typically more user-friendly than other formulations like ointments or creams.
- It has ability to easily remove gels if adverse reactions occur, such as irritation, redness etc.[60]

Improved Drug Release Profiles

- By providing a controlled release of active ingredients, gels can extend the therapeutic effect and reduce the frequency of administration.
- Gels improve the stability and bioavailability of hydrophobic medications by facilitating their distribution.[61]

Conversely, while topical gels are advantageous for localized treatment, they may not be suitable for systemic conditions requiring broader drug distribution. In such cases, alternative routes like oral or intravenous administration might be more effective.

7. CHALLENGES AND LIMITATIONS VARIABILITY IN SKIN ABSORPTION

Variability in skin absorption presents significant challenges and limitations in accurately assessing dermal exposure to chemicals. Factors such as experimental design, anatomical site differences, and the physicochemical properties of substances contribute to this variability. Understanding these aspects is crucial for improving risk assessments and developing effective safety measures.

1. Experimental Design Variability

- Dermal absorption studies often yield inconsistent results due to variations in protocols and chemical formulations, as seen in studies of hexaconazole and diniconazole, where results differed significantly.
- The lack of standardized international guidelines leads to diverse experimental conditions, complicating data interpretation.[62]

2. Anatomical Site Differences

- Regional variations in percutaneous absorption indicate that absorption rates differ across body sites, with higher absorption observed in areas like the forehead and genital skin.
- This variability necessitates a more nuanced understanding of how different skin regions interact with chemicals.

3. Physicochemical Factors

- Factors such as dermal loading, irritative potential, and the vehicle used can significantly influence absorption rates. For instance, high dermal loading often results in lower relative absorption.
- The development of predictive models like DAME aims to address these complexities by

estimating absorption under various conditions.[63]

8. DISCUSSION

Menstrual cramp management with topical gels has become more popular as a handy and non-invasive pain reduction technique. Active compounds like menthol, camphor, diclofenac, or capsaicin are frequently found in these gels. These substances offer relief through a variety of processes, including heating, cooling, and anti-inflammatory actions. For example, diclofenac decreases inflammation and inhibits prostaglandin synthesis, addressing the underlying cause of cramping, while menthol and camphor stimulate nerve endings, producing a cooling or warming feeling that diverts attention from pain. Topical gels, as compared to oral treatments, provide localized pain relief with limited systemic absorption, lowering the possibility of adverse effects including gastrointestinal distress that are frequently linked to non-steroidal anti-inflammatory drugs (NSAIDs). They are suitable for convenient use since they work quickly and are easy to apply. Nonetheless, they might not offer enough relief for more intense cases of dysmenorrhea, since their effectiveness depends on consistent use.

9. CONCLUSION

When compared to other semisolid formulations such as creams, ointments, and pastes, gels are gaining popularity lately because of their controlled release and enhanced stability. The drug's bioavailability may be increased by the gel formulation's improved absorption properties. Patients may benefit from the gel formulation's therapeutic application if its stability properties are thoroughly examined over an extended length of time. The water-soluble polymer enables the formation of a gel that can be rinsed off, expanding its potential as a system for delivering topical medication. The primary advantage of delivering drugs topically, especially those with a short biological half-life and a narrow therapeutic window, is that it allows for high concentrations of medication to accumulate in the tissue and its vicinity, thereby enhancing the drug's effectiveness and directly targeting the area of concern. Topical gel acts as a secure and efficient solution for addressing skin problems, reducing inflammation, and alleviating pain.

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