"Development and Evaluation of Curcumin-Piperine Mucoadhesive Gel for the Treatment of Oral Lichen Planus: A Novel Herbal Therapeutic Approach"

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Abstract:

Oral Lichen Planus (OLP) is a chronic condition that has mucocutaneous manifestations. The primary affliction concerns 0.5 to 2% of the population, with most patients being middle-aged women. The manifestations of this illness are lesions, pain, and burning sensations; this might have chances of malignant transformation in erosive and atrophic forms. This treatment is not very effective for corticosteroids, for which the use for a long period has many adverse effects like immune suppression, mucosal atrophy, and secondary candidiasis.

In the search for safer therapies, several natural compounds have been tested, one of which is curcumin derived from Curcuma longa. Curcumin has well-documented anti-inflammatory, antioxidant and anti-microbial, and anticancer properties, thus making it one of the possible candidates for the management of OLP. Nevertheless, poor solubility and rapid metabolism hinder its pharmacological effectiveness. Strategies to overcome these limitations include coadministration with piperine, nanoformulation, and mucoadhesive gels to improve absorption and bioavailability.

Key Words: Oral Lichen Planus (OLP), Curcumin, Mucoadhesive Gels, Bioavailability Enhancement, Nanoformulation of Curcumin, Alternative Treatment for OLP, Anti-inflammatory Therapy, Etiology and Pathogenesis.

I. Introduction:

The condition of OLP differentiates it from other diseases. Blisters may merge in clusters, thereby giving the interior surface of mouth an eroded appearance. A membrane of creamy white may develop on such patches, which is called pseudomembranous. In this case, the insides of the cheeks

appear to be reddish, as though the epithelium had been ripped off, while there is less special separation between skin cells as a result of this, being the white crowning of such layers. general human population. More intense in progression and more resistant to treatment than its skin-bound counterpart, the OLP, involves patients in their middle age, with more instances occurring in females than in males at a rough ratio of 2:1. OLP lesions range in severity from mild to severe, causing discomfort, pain, or a burning sensation. Occasionally, such lesions may harbor a risk of malignant transformation, exacerbating the relevance of proper management.

The manifestations mainly affect the buccal mucosa, tongue, gingiva, labial mucosa, and lower lip vermilion. Wickham striae and fine white lace-like lines constitute the quintessential clinical finding of OLP. Varieties of this abnormality include reticular, erosive, bullous, and atrophic; erosive and atrophic ones, on the contrary, have been associated with an increased risk of malignant transformation.

Corticosteroids have played a prominent role in the management of OLP, but prolonged application could have serious side effects, such as mucosal atrophy, altered taste sensation, and secondary candidiasis, which prompted the search for other treatments. Some of these are herbal or natural remedial procedures designed to maximize therapeutic gain and minimize adverse effects. Among these, curcumin from Curcuma longa is emerging, attributing distinct anti-inflammatory, antioxidant, antimicrobial, and anticancer properties. Other studies have attempted to manage a variety of oral diseases such as leukoplakia, oral submucous fibrosis, and occlusive mucosal lesions secondary to chemotherapy.

Notwithstanding the therapeutic promise, collation between curcumin and clinical use has been limited due to its solubility, poor bioavailability, and rapid metabolic alteration. Various formulation strategies have been adopted with the intent to combat these assorted challenges; they includes co-administration with piperine, incorporation into micelles; implementation into nano emulsions; use of nanoparticles; liposomes, and other advanced drug delivery systems. The combination of curcumin with piperine, the alkaloid from black pepper, shows encouraging promise for the increase of absorption and efficacy of curcumin.

Due to the limitations of conventional therapies, along with the promising pharmacological profile of curcumin, the study aims at formulating and evaluating a mucoadhesive gel of curcumin and piperine for the treatment of OLP. This herbal formulation is believed to increase bioavailability,

create prolonged adhesion to the mucosa, and serve as a safer alternative for long-term management of OLP.

This review highlights curcumin-based formulations as one of the potential candidates for OLP management, especially mucoadhesive gels. Clinically, curcumin has been proven to reduce lesion size, pain, and inflammation, thus serving as an attractive alternative or adjunct to the standard therapy. More studies and clinical experience will be required for optimizing formulation techniques and determining its long-term therapeutic benefits for curcumin in OLP.

Lichen planus is thought to result from an aberrant T-cell-mediated immune response in which basal epithelial cells are rendered 'foreign' because of alterations in the antigenicity of their cell surface. The reason for such immune-mediated basal cell injury is unknown. Likewise, it remains unclear whether lichen planus represents a single disease process or several closely related entities having similar clinical presentations. A recent immunologic comparison of two OLP variants implied that different immunopathogenic mechanisms might be involved.

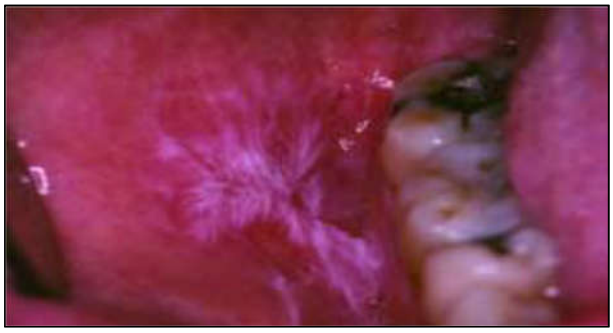


Figure 1 shows a cutaneous lichen planus on the wrist's flexor surface. Purple, polygonal, plaque-like lesions are the condition's initial manifestation.

1.1 Clinical Presentation

Lichen planus has a predilection for middle-aged adults, from 30-60 years of age, and occurs more often in women. It rarely occurs in children. Skin lesions that often affect the flexor aspects of the legs and arms, especially the wrists, can be described classically as purplish, polygonal, planar, pruritic papules and plaques. The nail beds may be involved, resulting in ridging and thinning and subungual hyperkeratosis. The head scalp when untreated can also attain scar formation and ultimately loss of hair.

These characteristic cutaneous lesions, found in 30% to 50% of patients with oral lesions, may help in diagnosing OLP.

There are many types of OLP documented, but the two principal forms are reticular and erosive OLP. It is not rare for the same patient to exhibit multiple forms of OLP at one time.

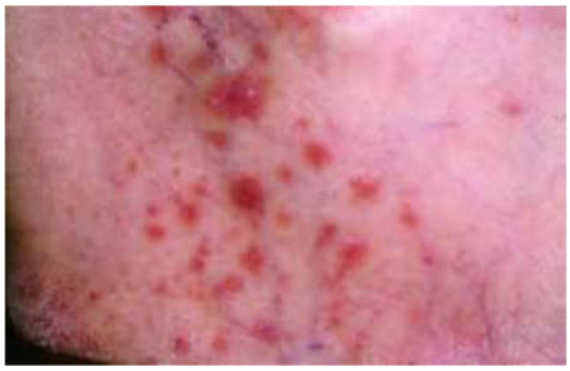


Figure 2: Buccal mucosal involvement in reticular oral lichen planus. There are several white keratotic lines that interlace.

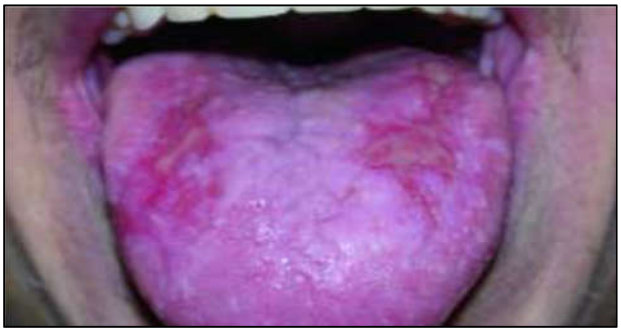


Figure 3: Erosive patches affecting the tongue's dorsum in a plaque-type form of reticular oral lichen planus.

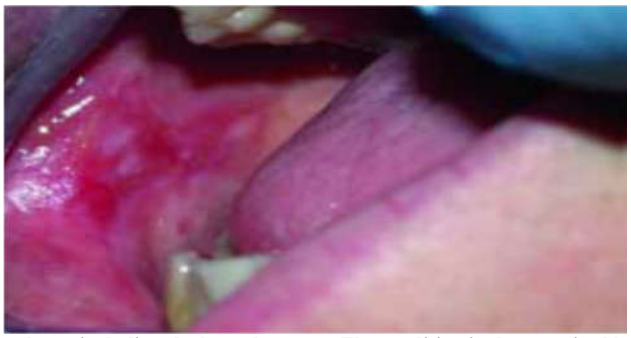


Figure 4: Erosive oral lichen planus including the buccal mucosa. The condition is characterized by erythematous patches and intermittent pseudomembranous areas.

1.2 Reticular OLP

The reticular form is the most common type of OLP. It presents as interlacing white keratotic lines (known as Wickham's striae) with an erythematous border. The striae are most often formed bilaterally on the buccal mucosa, mucobuccal fold, gingiva, and less often, tongue, palate, and lips.

A plaque-like form is a variant of reticular OLP, which clinically mimics leukoplakia but has a multifocal distribution. These plaque-like lesions can present anywhere from smooth and flat to irregular and elevated. This variant commonly occurs on the dorsum of the tongue and on the buccal mucosa. Typically, both reticular OLP and its plaque-like variant do not produce symptoms.

1.3 Erosive OLP

Erosive OLP is the second-most common form. It presents as a mixture of erythematous and ulcerated areas circumscribed with finely radiating keratotic striae. When erosive OLP involves the attached gingival tissue, the term used is desquamative gingivitis. The lesions of erosive OLP tend to migrate over time, and concurrently, the pattern is often said to be multifocal. Often the patients suffering from this OLP will report symptoms that range from episodic pain to severe discomfort that may hinder normal masticatory function.

The other two forms, atrophic and bullous, are regarded as erosive-type variants. Atrophic OLP looks like diffuse

erythematous patches framed by fine white striae, and very painful. In the bullous type, intraoral bullae on the buccal mucosa and the lateral borders of the tongue are being formed; these bullae rupture shortly after their appearance, leading to the classical form of erosive OLP.

II. Differential Diagnosis

The presence of characteristic cutaneous lesions will lend support to the diagnosis. In most cases, histopathological examination of lesional tissue is required to establish the diagnosis, except for the pathognomonic appearance of reticular OLP (bilateral white striae on the buccal mucosa). In fact, even classical cases can be considered for biopsy to determine baseline histopathological features.

The plaque form of reticular OLP may resemble oral leukoplakia. Other conditions that are included in the differential diagnosis of erosive OLP include squamous cell carcinoma, discoid lupus erythematosus, chronic candidiasis, benign mucous membrane pemphigoid, pemphigus vulgaris, chronic cheek chewing, lichenoid reaction to dental amalgam or drugs, graft versus host disease (GVHD), hypersensitivity mucositis, and erythema multiforme.

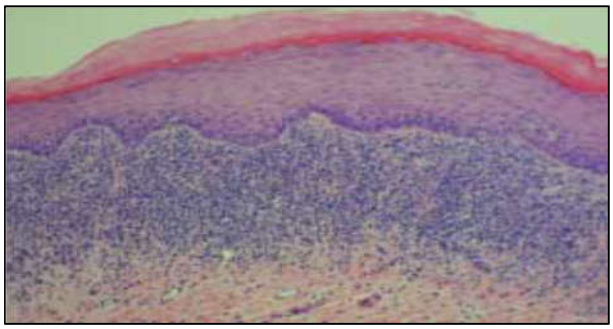


Figure 5: Histopathologic characteristics of oral lichen planus, such as hyperkeratinized epithelium and a dense, band-like lymphocytic infiltration at the interface between the epithelium and connective tissue as well as shorter rete pegs.

2.1 Biopsy Procedures

The definitive diagnosis of OLP rests with the histopathological examination of affected tissue. However, when it comes to biopsy of lesions, especially if the OLP is erosive, difficulties arise. To avoid removing the superficial epithelial layer from the underlying connective tissue, it is crucial to attempt to create an elliptical wedge of mucosa that extends beyond the afflicted area.

2.2 Histopathologic Features

A dense band-like lymphocytic infiltrate at the dermal-epithelial junction, focal areas of hyperkeratosis that clinically present as Wickham's striae, liquefactive necrosis of the basal cell layer with apoptotic keratinocytes, and intermittent zones of atrophic patchy epithelium where the rete pegs are shortened and pointed—known as sawtooth rete pegs—are all characteristic histopathologic features of OLP. The lower half of the surface epithelium frequently contains eosinophilic colloid bodies (Civatte bodies), which are indicative of degenerating keratinocytes. Despite its unique characteristics, PLP may share histologic characteristics with other lichenoid reactions to substances like medications and dental amalgam.

The concomitant situation is that the diagnosis of OLP may also become obscured by candidiasis, the latter itself obfuscating the interpretation of biopsy specimens showing ulceration. Findings of the biopsies in such situations may be interpreted as representing changes due to nonspecific chronic inflammatory processes.

In some instances, when the histopathologic findings are inconclusive, the oral pathologist referring the tissue will suggest that another biopsy be performed for better results through immunofluorescence. Immunofluorescent studies of OLP lesional tissues ordinarily reveal deposition of fibrinogen along the basement membrane zone. Chronic ulcerative stomatitis, which has only been recently described, has light microscope features similar to those of OLP but has a staining pattern unique to immunofluorescent tests. This condition is said to be less amenable to treatment with corticosteroids than OLP.

If biopsy findings do not correlate with the clinical impression or are in any way ambiguous, a second biopsy may be warranted, particularly in the situation of an isolated lesion on sites of higher risk for squamous cell carcinoma development, including the lateral or ventral surface of the tongue and the floor of the mouth.

2.3 Clinical Significance of OLP

OLP is a common mucosal disease afflicting the oral cavity. For this reason, dentists in clinical practice will frequently see patients with this condition.

At the same time, because patients with atrophic and erosive forms of OLP suffer a great deal of pain and are thus aware of available treatment, knowledge about treatment options is useful.

Since OLP has similarities with many other vesiculoulcerative conditions some having striking consequences, accurate diagnosis is necessary. For example, histology and clinical presentation may well overlap in OLP with GVHD-Graft versus Host Disease, a deadly complication of bone marrow transplantation with the potential for grafted marrow cells to attack the host. The extent of oral involvement would be a good predictor of the severity and prognosis of GVHD.

III. Role of Curcumin in OLP Treatment

Bioactivity of Curcumin: Anti-inflammatory, Antioxidant, and Antimicrobial Properties Curcumin, which is the primary chemical produced from the rhizomes of Curcuma longa, has been

proven to possess several pharmacological and antioxidant activities that include; anti-inflammatory, antibacterial and antioxidant.

It has been researched for its potential to influence many molecular signals that control inflammation and oxidative stress, which are important factors that are known to influence the development of OLP. This anti-inflammatory effect is through suppression on such cytokines like TNF-α, IL-1β, and IL-6 that play a role in the inflammation in OLP. It also decreases COX-2 (cyclooxygenase-2), the enzymes that synthesize inflammatory prostaglandins, interleukin 6 as well as nitric oxide synthase an enzyme that produces nitric oxide. Furthermore, owing to its antioxidant action, curcumin mitigates the generation of free radicals, thus reducing oxidative stress in oral tissues of the patients with periodontal diseases. In addition, it has antibacterial effect and this might help in preventing secondary infection in lesions of OLP .

3.1 Molecular Mechanisms of Curcumin in Reducing OLP Symptoms

There are two broad categories of molecular mechanisms in which curcumin has been considered to be effective in OLP, and those are based on the immunomodulatory effects of the drug. Curcumin suppresses the activity of NF-κBthus preventing over-activation of susceptible cytokines that induce inflammation. Furthermore, it controls mitogen activated protein kinases (MAPK) and JAK/STAT pathways that are involved in T cell activation and the inflammatory process of OLP . Due to its immunosuppressive effects, curcumin is likely to decrease the activation of CD8+ T-cells which exert cytotoxic actions toward basal epithelial cells of the oral mucosa. This action may help to reduce the characteristic painful ulcerations and lesions in OLP. Also, curcumin acting as anti-apoptotic, decrease in pro-apoptotic proteins and increases in anti-apoptotic proteins may flow assistance to tissue repair and regeneration.

3.2 Clinical Evidence Supporting Curcumin’s Efficacy

The use of curcumin in patients suffering from OLP has been demonstrated to be effective in a number of experimental studies as well as in different clinical trials. Another study by Dai et al. also concluded that curcumin gel application on the lesion resulted in the decrease in size of the lesions and pain intensity of the patient’s OLP . The study which Sookasem et al conducted in 2016 showed that curcumin did offer a better result in terms of symptoms and the level of improvement of the lesion size along with the comfort of the patients when taken at the same time with the standard antiasthmatic drugs . Moreover, a similar randomized controlled cross-sectional study by Bukhari et al (2018) also revealed that curcumin mouthwash may help in reducing the extent of burning sensation and discomforts among OLP patients thereby asserting this solution as safe and effective.

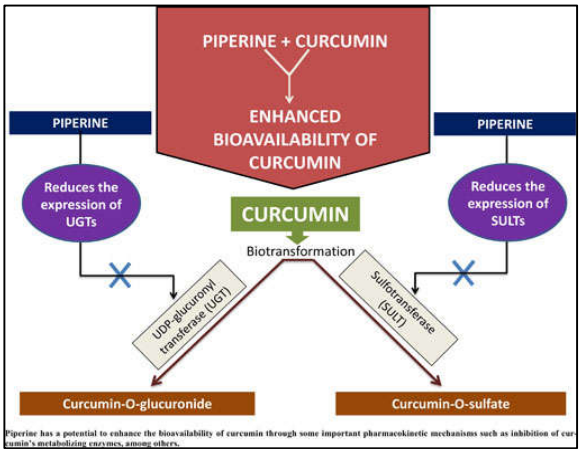
3.3 Challenges in Curcumin's Bioavailability and Absorption:

Nonetheless, curcumin has a wide pharmacological potential and possible therapeutic roles which is a problem of curcumin due to poor bioavailability and absorption. Curcumin which is the active sesquiterpene in turmeric gets absorbed through the GI tract, undergoes first pass liver metabolism and is mainly excreted through the urine which hinder its bio availability and tissue concentration . Different approaches have been tried to improve the bioavailability of curcumin for example the use of nano formulations, liposomal curcumin and curcumin together with Piperine that delays its metabolism thus improving its absorption . Some formulations include mucoadhesive gels and sublingual tablets in view of enhancing the local bioavailability of curcumin in the oral cavity. These formulations, means that curcumin remains at place of action for a longer period of time, making it more effective to treat OLP .

IV. Role of Piperine in Enhancing Curcumin's Efficacy

4.1 Pharmacokinetic Properties of Piperine

From black pepper, there is an alkaline known as piperine that has been found to improve the absorptivity and other properties of physiologically active substances for instance curcumin. This is because piperine also suppresses the enzymes found in the liver known to contribute to curcumin metabolism including cytochrome P450. This inhibits the metabolism of curcumin by the liver and hence, increases the level of curcumin in the blood stream and extends its therapeutic value. Furthermore, piperine prevents the first-pass degradation of curcumin by contributing to the efficient movement through the intestinal wall to the bloodstream . An overview on absorption and distribution of piperine reveals that this compound is well absorbed and the maximum plasma concentration is reported within 1-2 hour after oral administration. After its absorption, piperine has relatively long half-life and, therefore, is able to serve its function for a considerable amount of time (P4). This can be combined well with curcumin that has very poor bioavailability and short half-life otherwise.



Figure; 6 [Piperine in Enhancing Curcumin's Efficacy]

4.2 Synergistic Effects of Curcumin and Piperine

Actually, the mixture of curcumin and piperine due to the ability of piperine to increase solubility, bioavailability and therapeutic concentration of curcumin is called synergistic. It has also been demonstrated that the addition of piperine has the positive effect on the bioavailability of curcumin that can reach 2000%. This is because piperine help in preventing the rapid metabolism of curcumin or increase its bioavailability to support the bodies' utilization.

Curcumin and piperine activity together become combined to enhance the anti-inflammatory, anti-oxidative, and anti-cancer potential of curcumin. All these compounds help in regulating cytokines, immune response, and oxidative stress which plays an essential role in diseases such as OLP because inflammation and immune dysfunction are primary factors to the disease.

V. Mucoadhesive Gel Formulation of Curcumin-Piperine.

Materials for use:

Active Ingredients:

i Curcumin (extract from Curcuma longa)- 1-2%
ii Piperine (extract from Piper nigrum)- 0.5%
iii Chitosan (Mucoadhesive polymer)- 2%

Gelling Agents:

i Carbopol 934- 1%
ii HPMC K100M- 2%
iii Permeation Enhancer:
iv β-cyclodextrin- 0.5%
v Bioavailability Enhancer:
vi Phosphatidylcholine (Liposomal carrier)-1%

pH Adjuster:

Triethanolamine - qs
i Solvent System distillate-water: qs 100%
ii Ethanol (5%)- to solubilize.

Preservatives:

i Methylparaben-0.05%,
ii Propylparaben-0.01%.

Methodology for Formulation

1. Preparation of Curcumin-Piperine Complex:

Curcumin and piperine, in a 1:1 molar ratio, are co-processed with β-cyclodextrin via a solvent evaporation method.

The mixture is dissolved in ethanol and maintained at 50°C until a clear solution forms.

The solvent recycling is performed under reduced pressure to give a solid complex that helps in improving curcumin solubility.

2. Preparation of Mucoadhesive Gel Base:

Carbopol 934 is dispersed in distilled water and allowed to swell overnight.

HPMC K100M is separately dissolved in water and mixed with chitosan solution prepared in 1% acetic acid.

Both dispersions are combined under continuous stirring at 500 rpm to make them homogeneous.

3. Addition of Liposomal Carrier for Enhanced Bioavailability:

Dissolve phosphatidylcholine in ethanol and sonicate to prepare liposomes.

Add the curcumin-piperine complex into the liposomal dispersion and mix gently.

4. Final Gel Formation- The liposomal drug complex is added slowly into the gel base while stirring.

Adjust the pH to 6.5-7.0 using triethanolamine.

The preservatives methylparaben and propylparaben are added.

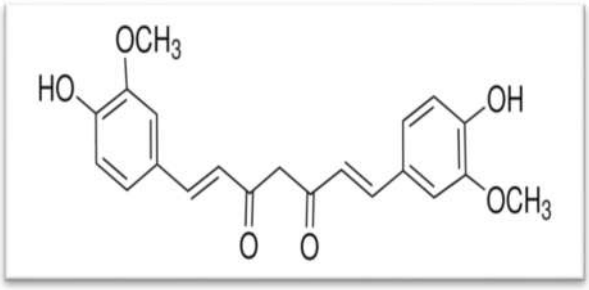


Figure 7: Curcuma longa

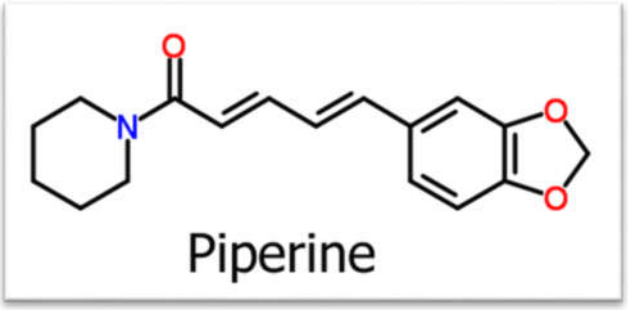


Figure 8: Piperine

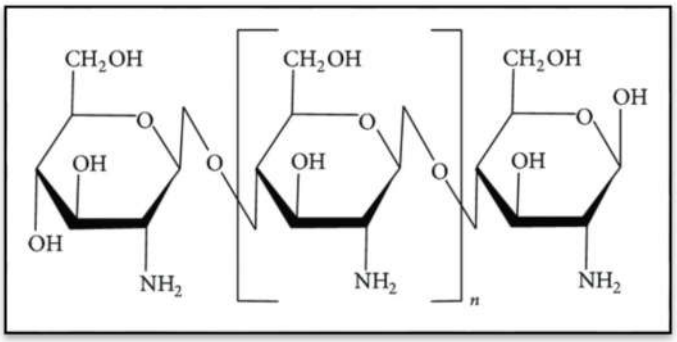


Figure9: [Chitosone]

Evaluation Parameters for Mucoadhesive Gel

Parameter	Methodology
Appearance & Texture	Visual inspection, tactile feel
pH Measurement	Digital pH meter
Viscosity	Brookfield viscometer
Spreadability	Parallel plate method
Mucoadhesive Strength	Modified tensile strength test using porcine buccal mucosa
In-vitro Drug Release	Franz diffusion cell using simulated saliva (pH 6.8)
Ex-vivo Permeation Study	Porcine buccal mucosa with HPLC detection
Stability Study	ICH guidelines (40°C ± 2°C, 75% RH) for 3 months

Table:1 Evaluation parameters

Novelty of this formulation

- Curcumin-Piperine-β-Cyclodextrin Complex: Solubility and permeation improvement.
- Improved bioavailability and retention in oral mucosa - Liposomal Delivery System.
- Combination of Chitosan and Carbopol: Ample mucoadhesion for prolonged drug release.
- Bioadhesive Gel Matrix: Longer retention, thus therapeutic enhancement in OLP.

Conclusion

Oral Lichen Planus (OLP) is still a notoriously difficult condition to manage because it is said to be chronic, painful, and with a risk of malignant transformation in erosive forms. Conventional forms of therapy such as corticosteroids can be effective but have side effects when used for an extended length of time; hence, development of alternative herbal formulations starts gaining ground, finding curcumin as an attractive candidate because of its potent anti-inflammatory,

antioxidant, and antimicrobial activities. Owing to its insolubility and poor bioavailability, the clinical usefulness of even curcumin gets hindered.

This review provides an insight into utilizing a curcumin-piperine mucoadhesive gel formulation as a new technique for improved therapeutics of OLP. Piperine can greatly increase curcumin's bioavailability by inhibiting its metabolism, while mucoadhesive gels enhance the contact time between the local drug and the oral mucosa so that drug retention can be prolonged. This will give a synergistic therapeutic approach through curcumin and piperine along with state-of-the-art formulation strategies such as liposomal carriers and cyclodextrin complexation to overcome pharmacological and delivery aspects.

Thus, curcumin-piperine mucoadhesive gel is a promising herbal approach with scope for better symptom control and patient compliance in the treatment of OLP. More clinical trials should confirm its long-term safety and efficacy.

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