



## EVALUATION OF HERBAL MUCOADHESIVE GEL CONTAINING CORIANDRUM SATIVUM AND CURCUMIN AS A LOCAL DRUG DELIVERY AGENT - A NOVEL INVITRO STUDY

### Dental Science

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### ABSTRACT

Ayurveda is world's ancient system of medicine that evolved in India. A lot of herbal medicines are used for traditional healing. In comparison to synthetic medicines, they have low side effects, are effective and acceptable amongst patients. The current study evaluated the effects of combined herbal essential oil (Curcumin and Coriandrum sativum) in subjects with chronic periodontitis. Four bioadhesive polymers of mucoadhesive gels (curcumine 1g, coriandrum sativum 1g, carbopol 940, sodium carboxymethylcellulose) were prepared based on varying concentration of 0.5, 1 and 1.5 and labelled as formulations (F) - F1, F2 and F3. In this invitro study, their physicochemical tests, mucoadhesive strength, drug release and antibacterial activity against *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* were evaluated. Among the three gel formulations, F2 and F3 showed satisfactory mucoadhesion, homogeneity, viscosity, physical appearance, consistency and the formulations could flow easily through 21 G needle. However, F2 was better in terms of efficacy than F3 in terms of drug release. Based on in vitro release and mucoadhesion studies, F2 produced significant growth inhibition zones against *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*. It was concluded that F2 was best formulation for further clinical evaluation of the formulation.

### KEYWORDS

Herbal LDD, Coriandrum Sativum, Curmin, Periodontal Drug Delivery, Mucoadhesive Gel, Periodontitis

#### INTRODUCTION:

Periodontitis presents as a local destructive disease in periodontium and thus requires a much specific treatment. Clinical signs may vary from gingival bleeding, suppuration, tooth mobility, localized pain and periodontal pocket. The pocket is reservoir to many such pathogens (anaerobic and gram-negative bacterial species) and inflammatory cell concentrates. The major putative pathogens identified are *Porphyromonas gingivalis* (P.G.), a gram-negative anaerobic black-pigmented bacterium. These pathogens weaken the epithelial seal leading to deepening of pockets which is managed by plaque and calculus removal in scaling and root planning in which they dwell.<sup>1</sup> In cases where the pathogens find their deep niches in periodontal pocket, scaling and root planing procedures are ineffective. Therefore, an adjunctive use of antibiotics, usually in the form of a local delivery system is advisable.<sup>2</sup> Considering the side effects of antibiotics, these researchers have moved their interest towards herbal formulations.

Assyrian herbal dates back to 600 BC about use Turmeric as medicine which is native to India.<sup>3</sup> This plant (curcuma longa) which is a herbaceous perennial plant has been described in traditional Chinese and Indian medicine. The most active component of turmeric is curcumin, which makes up 2–5% of the spice. Curcumin (diferuloylmethane), the main yellow bioactive component of turmeric has been shown in the literature to have a wide spectrum of biological actions. These include its anti-inflammatory, antioxidant, anti-allergic, anticarcinogenic, antimutagenic, anticoagulant, antidiabetic, antibacterial, antifungal, antiprotozoal, antiviral, antifibrotic, anti-ulcer and many other.<sup>4-10</sup>

Native to Iran is widely cultivated *Coriandrum sativum* that belongs to Umbelliferae family. Linalool and tannin are the chemicals of biologic importance found in them.<sup>11-14</sup>

The current study aimed to evaluate formulations of Curcumin and fruit of *C. sativum* as a mucoadhesive gel suitable for subgingival delivery in subjects with chronic periodontitis.

#### MATERIALS AND METHODS:

Commercially available essential oils of *C. sativum* and curcumin were used for preparation of gel. Folin Ciocalteu reagent, sodium carbonate

anhydrous, carbopol 940, sodium CMC, HPMC K4M, polyethylene glycol 400 (PEG 400), methyl paraben, propyl paraben, and triethanolamine were obtained from Department of Pharmaceutics, Padmashree Vithalrao Vikhe Patil Foundation's college of Pharmacy, Ahmednagar.

Gelling agents like Carbopol 940 and sodium CMC polymers were used along with active ingredients like oils of Curcumin and *C. sativum*. Gel Formulation began with mixing of Methyl Paraben and propyl paraben in water at 80 degrees Celsius. The above two mentioned gelling agents were individually dissolved in water until a semisolid mass was obtained and then eventually to main mixture to form the gel base. The final gel was obtained by mixing PEG400.

**Table 1:** Composition of gel formulations with different polymers of Carbopol 940 and sodium CMC

Ingredients (g)	F1	F2	F3
Carbopol 940	1	1	0.5
Na-CMC	3	-	3
Curcumin	0.5	1	1.5
C. sativum extract	0.5	1	1.5
PEG 400	13	13	13
Methyl Paraben	0.18	0.18	0.18
Propyl Paraben	0.02	0.02	0.02
Triethanolamine	Qs.	-	-
Water Q.S. to	100	100	100

#### Evaluation of Gel Formulation:-

**Physical characteristics of the gel formulation** were evaluated by pressing some amount of gel between the thumb and the index finger. The consistency, clarity, color, odour, appearance and taste was assessed.<sup>15</sup>

**pH of Formulations** was measured using a electronic pH meter. 10 grams of the gel was added to water and then multiple pH values were determined. Average of the values was taken to obtain the pH of the gel.

**Centrifugal test** was done 48 hr after preparation. Formulations were

transferred into tubes and centrifuged at 2000 rpm for 60 min. Using a centrifugal device (Centrifuge 5430) stability of formulations were evaluated at the times of 5, 15, 30 and 60 min.<sup>16</sup>

**Drug content** was determined 60 h after preparation. One gram gel in 10 ml volumetric flask was dissolved in water up to 10 ml.<sup>17</sup> Total phenolic content was determined according to the Folin Ciocalteu method. 765 nm was measured absorbance value. Standard calibration curve of gallic acid was used for calculating polyphenols concentration.<sup>18</sup>

**In vitro mucoadhesive strength** was measurement by modified tensiometry method (Fisher's tensiometer). 0-100 dyne/cm was set to be the measurable surface tension on instrument. A thin mica disk was placed on the tensiometer ring. Sodium alginate of 1% (w/v) solution was placed into the 37°C water jacketed glass vial. Tensiometer was calibrated with standard weight and gel formulation of 200 mg from each group was placed on mica disk. This was now transferred where it was kept in contact with sodium alginate for 5 mins. The gel was detached, placed on blank and considered for test. After every six times of testing, the Palladium-Platinum ring was rinsed with methanol followed by acetone.<sup>19</sup>

**In vitro drug release study** was carried out by Franz diffusion cell through a cellulose acetate membrane. The cellulose acetate membrane received 0.5 gram of gel sample. With the help of 28 ml of purified water at 37 ± 1° dissolution medium was created. periodically at 0.5, 1, 2, 3, 4, 5 and 6 h, one ml sample from each group was taken. Then the samples were analysed for the drug content by using purified water as blank and concentrations of polyphenols were calculated from standard calibration curve of gallic acid.

$$C_n = C + \frac{C_{n-1} \cdot V}{V_t}$$

C<sub>n</sub> - actual concentration of drug released in sample n, C is the apparent concentration of drug released in sample n, C<sub>n-1</sub> is the actual concentration of drug released from sample before sample n, V is the sample volume, V<sub>t</sub> is the volume of receiver phase.<sup>16</sup>

**Determination of viscosity** (in cps) of the prepared gels was measured by a Brookfield DV viscometer at 100 rpm, using spindle number 7 at 25°C. Samples of the gels were to settle over 30 min at the room temperature, before the measurements were taken. The test was performed for three times on each formulation.<sup>20</sup>

**Syringeability** of gel formulations was evaluated through 21 G needle.<sup>21</sup>

**In vitro evaluation of antibacterial activity of gel-** Formulation against *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* using the disk diffusion method was prepared in lyophilized form from the Persian type culture collection of the Iranian research organization for science and technology. The lyophilized bacteria were resuscitated in the sterile conditions of the laboratory of both bacteria were cultured on supplemented brucella agar plates (prepared from the Iranian research organization for science and technology). Culture media were incubated for 72 h in anaerobic condition at 35°C in order to allow bacterial growth. After bacterial growth, a microbial suspension was prepared and transferred to the plates containing culture medium by sterile swab. Then, sterile paper discs with a diameter of 5 mm (Blank disc, Patan Teb, Iran) were smeared with gel formulation and were placed on the surface of the plates containing culture medium in equal distances. Then, the plates were incubated at 35°C for 72 h. After this period, the diameter of the zone of inhibition around the disc was measured in millimeters and the average of diameters noted. Test was conducted in triplicate. Sterile discs free of any material were used as negative control in culture medium. For positive control, tetracycline disc (30 µg/ml) was used.<sup>22-24</sup>

**RESULTS:**

The gel was examined for various parameters like physical property, homogeneity, pH, drug content, viscosity, syringeability, colour and odour. The results of which can be appreciated in table 1. All three formulations were tested, and the formulation 2 was found to be more stable and acceptable.

**Table 1: Gel Evaluation Parameters:-**

Parameters	F1 (0.5/0.5)	F2 (1/1)	F3 (1.5/1.5)
Physical Appearance	Good	Good	Fair
Homogeneity	Good	Good	Fair
Consistency	Very Good	Good	Poor
Centrifugal test	Good & Stable	Good & Stable	Unstable
pH	6.6	6.5	6.2
Drug (oil) content	1gm +/- 0.3	2gm +/- 0.3	3gm +/- 0.3
Mucoadhesive strength	12 +/- 0.5	13 +/- 0.5	15 +/- 0.5
Average Viscosity	7330	7820	8190
Syringeability	Good	Good	Good
Colour	Pale Yellow	Yellow	Yellowish Green
Odour	Pleasant	Pleasant	Pungent

The drug was tested for in vitro drug release in 6 hours interval. Total of three readings were noted. Formulation 2 and 3 gave satisfactory results. However, F2 was found to be most efficient as seen in table 2.

**Table 2: In vitro Drug Release Studies by Franz Diffusion Cell:- Drug release (in %) at 6 hours :-**

No.	F1	F2	F3
1	75.36	82.45	77.21
2	69.47	85.12	73.35
3	72.69	83.37	81.71

The antibacterial activity of F2 against *P.G.* and *A.A.* were evaluated by the disk diffusion method on supplemented brucella agar. The growth inhibition zones were measured. After 72 h of incubation, gel formulation F2 displayed observable zones of inhibition. The sterile filter disc as negative control produced no observable inhibitory effect for the bacteria. Table 3 shows inhibition zones diameter of F2 and tetracycline disc. The results showed that the mean of inhibition zone for gel formulation was satisfactory. For tetracycline disc as positive control, the mean of inhibition zone was 20mm.

**Table 3:- Inhibition zones diameter of gel formulations against P. gingivalis**

Bacterial species	(Mean ± SD)		
	F1	F2	F3
P.G.	15.21 ± 32	21.00 ± 31	17.27 ± 35
A.A.	17.19 ± 65	23.25 ± 54	19.22 ± 57

**DISCUSSION:**

Periodontitis is a chronic inflammatory disease caused by specific bacteria from the oral flora. The microbial flora induce an immune response within the connective tissue of the gingiva that result in prolonged release of inflammatory mediators that disrupt tissue homeostasis and lead to attachment loss. A gel with good mucoadhesive strength as an adjunct to scaling and root planing in periodontal pocket exhibits prolonged residence time, contact time and better clinical efficacy.<sup>19</sup>

The oils of Curcumin and fruits of *C. sativum*, according to the Folin-Ciocalteu method were found to contain 504.10 and 30.77 mg GAE/g of total phenolic content, respectively. Because consistency and physical appearance of F2 were good it was selected for doing other tests. Among all the test conducted, F2 showed better results.

The results of mucoadhesive strength measurement by modified tensiometer showed mucoadhesion of F2 was more than F1. Carbopols have high-molecular weight and swell in water up to 1000 times of the original volume, so make large adhesive surface with the mucin and give good mucoadhesiveness. Carbopols form secondary bioadhesion bonds with mucin, while other polymers form superficial bioadhesion. Carbopols are used in formulations as mucoadhesive polymers. The addition of mucoadhesive polymers in the formulation results in increase of the contact time with mucosa and prolongation of residence time. A significant characteristic of the oral gel is mucoadhesive strength for adhesion to the mucosa in the dental pocket. Good gel adhesion to the mucosal surface results in increase the contact time. The F2 formulation met all the criterias required for future clinical study of this formulation.

Curcumin enhances wound healing by causing an increase in fibronectin. It promotes migration of epithelial cells to wounded sites by promoting localization of TGF- $\beta$ 1 and thus, helping re-epithelization due to the diverse range of actions. Curcumin-treated sites showed faster resolution of inflammatory signs and greater reduction in probing depth than other treated sites. Curcumin enhances.<sup>25,26</sup>

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Silva F et al in their study concluded that the Gram-positive bacteria tested exhibited lower susceptibility than the Gram-negative bacteria to coriander oil. The flow cytometric assessment of some cellular functions demonstrated that the mode of action of coriander oil is similar in both Gram-positive and -negative bacteria.<sup>27</sup> the result achieved by Silva F is suggestive of antibacterial property of Coriander oil. However, only the formulation 2 showed good drug release and action against P. gingivalis.

Furthermore, the combination of two essential oils was tested in this invitro study. Literature describes various evidence based report on these two essential oils separately.<sup>25-27</sup> But, the comparatively individual effect and its efficacy in clinical environment could gain more sustainable reports. Furthermore, the flushing activity by crevicular fluid in the pocket could pose a difficulty in retaining the drug in the pocket for longer time. For all this evidence, further animal study or clinical study could be helpful for sustainable and clinical insights.

## CONCLUSION

Polyphenols can be used in periodontal pocket therapy due to antioxidant and antibacterial activity. It is concluded that F2 could be used as antiseptic in the treatment of periodontitis. F2 is now the subject of clinical investigation.

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