The adjunctive use of locally delivered metformin as mucoadhesive slow releasing multiple layer film in the management of chronic periodontitis

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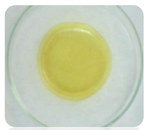
Introduction

Periodontitis is a group of chronic inflammatory conditions affecting the supportive structures of the teeth characterized by destruction of the periodontal ligament, resorption of the alveolar bone and the migration of the junctional epithelium along the tooth surface. The clinical signs of periodontitis include changes in the morphology of the affected gingival tissue, which causes the formation of a periodontal pocket .

Metformin (MF) is a drug that has been extensively used for the management of type 2 diabetes. Recently studies suggested that MF has an osteogenic effect. Local delivery of MF into the periodontal pocket was found to stimulate a significant increase in probing depth reduction, clinical attachment level gain, and improved intrabony defects depth reduction compared with placebo in adjunct to scaling and root planning.

Aim of Work

Development of a novel multilayered hydrogels film system , combining the mechanical properties of Carboxy methyl cellulose sodium (CMC Na) or sodium alginate (ALG Na) and enhanced mucoadhesive & controlled property of thiolated sodium alginate (TSA) to achieve a controlled release of metformin for local treatment of periodontal pockets.



Materials & Methods

Preparation of Films

Triple layer film was developed by double casting and compression methods. Either 6% Carboxy methyl cellulose sodium (CMC) or sodium alginate (ALG) was used as the inner drug (0.6%) loaded layer. Thiolated sodium alginate (TSA; 2 or 4%) constituted the outer drug free layers.

Characterization:

Films were characterized regarding drug content, water uptake (sponge method0 and *in vitro* drug release. Optimized formulation was assessed for in vitro mucoadhesion (displacement method) & morphologically by SEM, in addition to clinical assessment .

The study included two groups:

Treated group: included 10 interproximal sites that were treated by Scaling and root planning (SRP) and the application of metformin 1% film.

Control group: Included 10 interproximal sites that were treated only by SRP.

Results

The prepared patches were smooth in appearance, uniform in thickness & consistent in drug content The texture was hard enough, ensuring easy intra-pocket insertion.

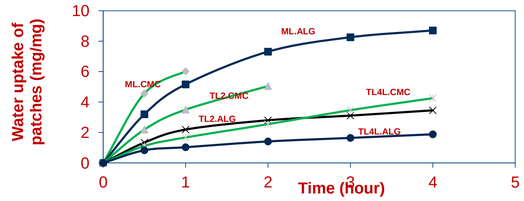
Physicochemical parameters of the formulated multilayered mucoadhesive films of Metformin hydrochloride

Formulation code	Thickness (µm ± SD)	Weight (mg± SD)	Drug content/ patch (mg ± SD)
ML. CMC	22.34±1.50	7.5±0.577	0.712±0.09
TL2. CMC	33.857±1.64	14.0±0.577	0.827±0.100
TL4. CMC	35.50±1.20	15.6±0.548	0.759± 0.09
ML. ALG	21.43±1.12	8.4±2.07	0.985±0.26
TL2. ALG	25.62±0.82	16.8±2.14	0.825±0.26
TL4. ALG	40.13±1.21	21.8±1.92	0.723±0.14

Results

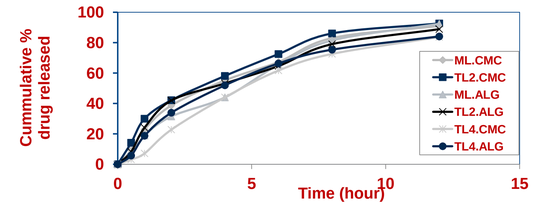
Water Uptake:

Triple layer films with 4% TSA exhibited lowest water uptake compared to fast erosion of monolayer films.

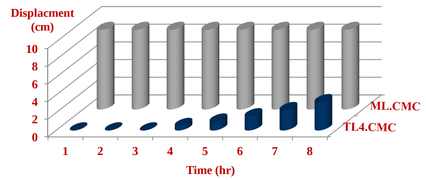


In Vitro Drug Release:

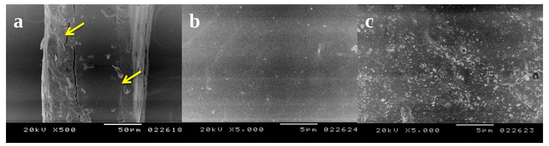
MF showed extended release from the films within 12 hours & more pronounced for TL4.CMC formula.



In Vitro Mucoadhesion: Enhanced mucoadhesive property was observed for CMC based film with TSA 4%



SEM photograph clearly show the fabrication of triple layer film in which a straight connective line between the layers is observed(a).



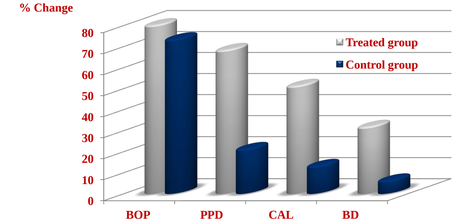
Surface structure of film presenting the drug free TSA layers was more or less smooth and compact with no apparent pores (b & c).

Results

Clinical Assessment:

The films showed marked muco-adhesive properties as soon as they were applied to the pockets. No discomfort , allergies or infection were noted during the follow- up period.

% change of all clinical parameters after 6 months post treatment compared to baseline values for the treated group were statistically significant compared to those of the control group.



Bleeding upon probing (BOP), Probing pocket depth (PPD), Clinical attachment level (CAL),, Bone depth (BD)

Conclusion

Mucoadhesive multiple layer films exhibited a good appearance and texture with homogeneous thickness and acceptable water uptake behavior making it suitable for intra-pocket application.

Clinical results suggested that local application of the mucoadhesive triple layer films based on CMC sodium loaded with metformin hydrochloride was able to manage moderate chronic periodontitis with good patient acceptance .

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