

FABRICATION, EVALUATION AND PRELIMINARY CLINICAL STUDY OF BI-LAYER OROBUCCAL DEVICES CONTAINING KETOROLAC TROMETHAMINE AND CHLORHEXIDINE HCL FOR TREATMENT OF ORAL INFLAMMATION

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ABSTRACT

Objective: Formulation and Evaluation of Ketorolac Tromethamine and Chlorhexidine hydrochloride Oro buccal Devices and preliminary clinical study of selected ketorolac tromethamine and chlorhexidine hydrochloride orobuccal devices.

Methods: Ketorolac tromethamine [KT] is a well known non-steroidal anti-inflammatory drug with potent analgesic activity. Chlorhexidine hydrochloride [Chx.HCl] is an antiseptic drug effective against a wide variety of gram-negative and gram-positive organisms, facultative anaerobes, aerobes, and yeast. A dosage form containing both of the two aforementioned drugs was a good choice for oral inflammation treatment. New mucoadhesive orobuccal devices containing both of the previous drugs in the form of bi-layer devices for treatment of oral inflammation were developed. Seven bi-layer mucoadhesive devices were prepared by sticking KT and Chx.HCL films to each other. Drug/ drug interactions were investigated using Fourier transform infrared spectroscopy [FTIR], and Spectrophotometric analysis of Chx.HCl and KT by overlying. Derivative Spectroscopy for simultaneous determination of Chx.HCl and KT in distilled water was performed [calibration Curve Construction for Chx.HCl in distilled water by first derivative spectroscopy, and a recovery Study of Chx.HCl and KT mixture using distilled water as a solvent were done]. The prepared bi-layer devices were evaluated for their drug content, film thickness, film folding endurance, in vitro disintegration time, in vivo disintegration time, in-vitro drug release, and microbiological activity of the prepared devices. Bi-layer orobuccal devices containing both Chx.HCl and KT were designed and prepared to produce an intraoral controlled delivery. Each layer was loaded with 3.3mg/cm² of KT and the other layer was loaded with 0.66 mg/cm² of Chx.HCl. These devices when applied to the oral mucosa produced mucoadhesion and were supposed to release rapidly high Chx.HCl followed by KT. Five devices namely M1, M2, M3, M4, and M7 were subjected to evaluate their effectiveness on periodontal pockets by using the Plaque Index [PI], Bleeding on Probing [BOP], Pocket Probing Depths [PPD], and Probing Attachment Levels [PAL]. Moreover, M1 and M3 were subjected to evaluate their effect on relieving pain of aphthous ulcers.

Results: All selected formulae achieved a good sound in treatment of periodontal pocket in terms of their selected clinical parameters. M1 and M3 showed very good satisfaction in terms of pain relief and taste for all examined patients with no complaint of irritation. **Conclusion:** devices which contained both of KT and Chx.HCl are a promising medicine in treatment periodontal pocket and aphthous ulcers.

Keywords: Ketorolac, Chlorhexidine hydrochloride, orobuccal bi-layer devices, formulation, evaluation, mucoadhesion, oral inflammation, periodontal pockets, aphthous ulcers

INTRODUCTION

Periodontal disease is a general term encompassing several pathological conditions such as chronic periodontitis, aggressive periodontitis, systemic disease-associated periodontitis, and necrotizing periodontitis [1]. The clinical signs of periodontitis include changes in the morphology of gingival tissue such as oedema, redness, reduction in consistence, and bleeding upon probing as well as loss of attachment and periodontal pocket formation. Periodontal pocket provides an ideal environment for the growth and proliferation of anaerobic pathogenic bacteria [2]. Elevated levels of PG are detected in the crevicular fluid of periodontitis patients, a finding that has been associated with increased severity of the disease. Additionally, administration of non-steroidal anti-inflammatory drugs [NSAIDs], which inhibit PGGH synthetase [cyclooxygenase], has proven beneficial in treating periodontitis patients [3]. However, the side effects resulting from NSAIDs pose a serious burden to their routine use, particularly in patients with pre-existing gastro duodenal hemorrhagic episodes or renal function damage[4]. Currently the treatment of periodontal disease, aimed at arresting the progression of the destructive process and preventing recurrence after treatment, is mainly through the mechanical cleaning of the tooth surface to remove bacterial plaque and calculus. However, as specific bacteria are thought to play a major role in the disease process [5], antimicrobial agents have also been used as adjuncts to mechanical treatment, particularly in treating early-onset and refractory cases [6]. The potential side-effects in administering systemic antibiotics and the

inability of antiseptic mouthwash to penetrate the periodontal pocket have fuelled interest in the sustained delivery of therapeutic agents within the periodontal pocket, thus ensuring a high effective concentration of antimicrobial agent at the site of infection. To our knowledge, there is no drug in the market as an orobuccal formulation consisting of combined therapy agents [7]. Therefore, the present study was planned to develop and evaluate an orobuccal bilayer formulation containing KT and Chx.HCl. The promising formulae were used in preclinical study to treat periodontal pocket and aphthous ulcer.

MATERIALS AND METHODS

Materials

Ketorolac Tromethamine [Hetero Drugs Limited, Erragadda, Hyderabad - AP. India], Chlorhexidine hydrochloride [Arab Drug Company for pharmaceuticals, Cairo, Egypt]. Ethyl cellulose [EC], [BDH Chemicals Ltd., Poole, England], Methanol [S D Fine-Chem limited, Mumbai, India], Carbopol 934 [CP] [B.F., Goodrich Chemical Company, Ohio, USA], Methylcellulose, [MC], [Dow Chemical Company, Midland Michgam-USA]. Hydroxypropyl methylcellulose [HPMC E15], [Colorcon Limited, Kent, England], Methylene chloride, [pure analytical grades], Triethanolamine, [E. Merk, Germany], Sodium Carboxymethylcellulose [SCMC] [C.B.H. Lab Chemicals, Nottingham, U.K.], Eudragit RL-100 [Central Drug House, Mumbai, India], Propylene glycol [E. Merck Ltd, Mumbai, India], Lutrol F 127 [Sigma-Aldrich], Potassium sulfate, [VEB Laborchemie, Apolda, West Germany].

Methods

Compatibility study for Chlorhexidine HCl and Ketorolac Tromethamine Mixture

a] Equal amounts of both drugs were mixed and then FTIR was performed.

b] Spectrophotometric Analysis of Chx.HCl and KT mixture. Overlaying for both of KT and Chx.HCl scanning was done by using the data stored in a computer for the two drugs.

Derivative Spectroscopy for simultaneous determination of Chx.HCl and KT in distilled water, calibration curve construction for Chx.HCl

in distilled water by first derivative spectroscopy, and recovery study of Chx.HCl and KT mixture using distilled water as a solvent, were done.

Preparation of bi-layer devices containing Chlorhexidine HCl and Ketorolac Tromethamine

Seven devices [M1-M7] were prepared, each device is composed of two layers, and each film layer contains either KT or Chx.HCl. The composition of KT films as well as Chx.HCl films are shown in table [1].

Table 1: it shows Composition of the prepared bi-layer devices

Bi-layer device [KT film + Chx.HCl film] [M]	[F] KT film [composition, ratio]	[C] Chx.HCl film [composition, ratio]
M1	F1 [HPMC: NaCMC, 9:1]	C1 [HPMC:MC 7:3]
M2	F2 [HPMC:Lutrol 5:5]	C2 [HPMC:Lutrol 8:2]
M3	F3 [HPMC:Ed 9:1]	C3 [HPMC:Ed. 9:1]
M4	F4 [HPMC:NaCMC 6:4]	C4 [HPMC:MC 6:4]
M5	F5 [HPMC:CP 9:1]	C5 [HPMC:MC 8:2]
M6	F6 [HPMC:EC 8:2]	C6 [HPMC:Ed 7:3]
M7	F7 [HPMC:Ed 8:2]	C7 [HPMC:EC 8:2]

Evaluation of the prepared bi-layer devices

The parameters of evaluation are shown in table [2]

a] Determination of drug content in bi-layer device

One square centimeter [1cm²] sample was dissolved in distilled water and the solution was filtered using 0.45µm membrane filter and KT was assayed by UV spectrophotometry at λ_{max} 323 nm against a blank of distilled water and Chx.HCl was assayed using first derivative spectroscopy at λ_{max} 271 nm against a blank of distilled water.

b] Determination of device thickness

The thickness of the prepared devices was determined by means of micrometer [Mitutoyo corporation, model PK-1012E, Japan] at three different places and the mean value was calculated.

c] Device folding endurance

Three devices of each formulation of size [1×2 cm] were cut by using sharp blade. Folding endurance of the buccal film devices were determined by repeatedly folding one device at the same place till it was broken or folded up to 200 times at the same place without breaking [8].

d] In vitro Disintegration Time of bi-layer devices

The test was performed using the method mentioned by Rawas-Qalaji et al [9] with slight modification. The device size required for dose delivery [2x2 cm] was placed on a watch glass containing 3mL of distilled water. The time required for the film device [n=3] to break was noted as in vitro disintegration time.

e] In vivo Disintegration Time of bi-layer devices

The selected orobuccal devices were tested in three healthy volunteers aged from 32 to 45 years. After wiping off excessive saliva, each bi-layer film was applied to either the tongue or buccal

mucus membrane by pressing for 30 s onto mucosa. The volunteers were asked to record the following [10]:

- The adhesion time and time of detachment of device.
- The strength of adhesion [very adhesive, adhesive, slightly adhesive, unadhesive or slippery].
- Any local signs of irritation [severe, moderate, slight or non irritant].
- Bitterness due to swallowing [very, moderate, slight or none].

The disintegration of the orobuccal film in the buccal cavity [high, moderate, slight, or none].

f] In-vitro drug release studies from devices

The in-vitro release test was performed using USP XXX dissolution apparatus [Dr. Schleuniger Pharmatron AG Dissolution Tester DIS6000, Switzerland]. The release studies were carried out at 37 ± 0.5 oC with stirring speed of 50 rpm. The bi-layer film size required for dose delivery [2x2 cm] was attached to glass plates [5x4.5cm] using cyanoacrylate adhesive.

The edges of the film were covered with cyanoacrylate adhesive to avoid direct drug release from edges. The glass plate assembly was immersed in 300 ml of freshly distilled water [11, 12]. Aliquots of 3ml of release media were collected at predetermined time intervals of 5, 10, 15, 20, 30, 45, and 60 min and replaced with equal volumes of distilled water.

The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved drug was determined spectrophotometrically at λ_{max} 323 and 271 nm for KT and Chx.HCl, respectively. The results were the average of three determinations.

Table 2: It shows the evaluation of bi-layer devices

Device	Drug content [mg %]		Film thickness [mm]	In-vitro Disintegration time [sec]	In-vivo Disintegration time [sec]
	KT film	Chx.HCl film			
M1	120±3.70	114±3.52	0.28±0.01	149±1.71#	79.00±1.61
M2	111±3.35	101±3.05	0.33±0.01	134±1.51#	60.00±1.53
M3	100±3.01	100±3.01	0.36±0.01	242±3.79	114.00±3.75
M4	117±3.53	99±2.99	0.27±0.01	153±2.40	73.00±1.52
M5	102±3.92	103±3.96	0.33±0.01	158±2.30	101.00±1.16
M6	115±3.51	98±2.99	0.35±0.01	253±2.93	142.00±1.59#
M7	95±2.93	114±3.52	0.35±0.02	250±2.81	134.00±2.10

g) Microbiological activity of the prepared devices

I- Determination of Minimum Inhibitory Concentration [MIC] of Chx. HCl

Representative microorganisms were used in this study. These include *Candida albicans* ATCC [fungi], and *Staphylococcus aureus*. Minimum inhibitory concentration technique was done by agar dilution according to the National Committee for Clinical Laboratory Standards [13]. Media used: Sabouraud-dextrose broth [oxoid] and Muller-Hinton broth or agar [oxoid] for growing of *Candida albicans* ATCC [fungi], and *Staphylococcus aureus*, respectively.

II- In-vitro susceptibility test for the selected devices

A fresh culture of the tested strain of the above-mentioned microorganisms was sub cultured in Sabouraud-dextrose broth for *Candida albicans* and in Muller-Hinton broth for *Staphylococcus aureus* and incubated at 30°C for 24 hours. Plates of the respective agar medium were then surface inoculated with the fresh culture of the tested strain [106CFU/ml]. After agar solidification, cups [9 mm diameter] were made aseptically in the agar and filled aseptically with 8 mm diameter cut circle films. Also 33mg of Corsodyl gel [standard] [equivalent to the dose of the prepared films] was subjected to the same procedures. Plates were incubated at 30°C for 24 hours. The diameter of zone of inhibition was recorded after 24 hours. Each assay was done in triplicate at least [14].

The percentage antimicrobial activity was calculated according to the following equation:

$$\% \text{ antimicrobial activity} = \frac{\text{inhibition zone in mm [test]}}{\text{inhibition zone in mm [standard]}} \times 100$$

h) Preliminary Clinical Study of Selected Ketorolac Tromethamine and Chlorhexidine hydrochloride Orobuccal Devices

I- Effect of bi-layer devices on periodontal pockets

Ethical approval for the clinical part of the study was obtained from the Research Ethical Committee, Faculty of Pharmacy, Cairo University.

Ten out patients attending The Clinic of Oral Medicine, Periodontology and Oral Diagnosis Department, Faculty of Dentistry, Misr university for science and technology [MUST], were chosen. They were four females and six males ranging from 29-45 years [mean 37] undergoing a periodontal examination at baseline [week 0] and after 2 weeks. All patients [15] showed at least 2 teeth with periodontal pockets of 5-8mm in depth without involving the apex of the tooth.

Each patient was supplied with a new toothbrush and they were asked to clean their mouth and teeth with a tooth paste and brush. Then the dentist cleaned each pocket by scaling to remove tartar and bacteria from tooth surface and beneath gum.

Scaling was followed by root planning to smoothen the root surfaces discouraging further build up of tartar [16]. One bi-layer device was applied at the base of the periodontal pocket and each pocket was inserted

Treated sites were evaluated during two weeks. Clinical periodontal parameters were recorded, namely, the Plaque Index [PI], Bleeding on Probing [BOP], Pocket Probing Depths [PPD] and Probing Attachment Levels [PAL] at pocket site of tooth as shown in table [3].

Criteria of volunteers

Inclusion Criteria

- Signed informed consent form
- Good general health
- Male or female subjects aged >25 years old
- Minimum of 8 natural teeth
- Availability for the 25 weeks duration of the study
- Periodontal disease on a natural teeth characterized by the presence of at least 2 teeth with periodontal pockets of 6-9 mm in depth [target teeth] in order to reach baseline [day 1] with periodontal pockets of 5-8 mm in depth, without involving the apex of the tooth.
- Females of childbearing potential must be non pregnant at entry and agree to use an adequate method of birth control during the study.
- Demonstrate bleeding on probing at the base of the pocket [the pockets selected at the time of screening.]

Exclusion Criteria

- Presence of oral local mechanical factors that could [in the opinion of the investigator] influences the outcome of the study.
- Presence of orthodontic appliances or any removable appliance that impinges on the tissues being assessed.
- Presence of soft or hard tissue tumours of the oral cavity.
- Presence of dental implant adjacent to target tooth.
- Presence of periodontal pockets of more than 9 mm in depth.
- General systemic antibiotics therapy or periodontal/mechanical/local delivery therapy within 6 weeks prior to study entry and throughout the study duration.
- Presence of history of allergy to chlorhexidine, ketorolac or to other non-steroidal anti-inflammatory drugs [NSAIDs].
- Subjects taking diphenylhydantoin, nifedepine and/or cyclosporine, which might influence the pattern of tissue response.
- Subjects treated with non-steroidal anti-inflammatory drugs [NSAIDs] within 14 days prior to entry into the study and throughout the study duration.
- Pregnant women or those planning to become pregnant or lactating women.
- Presence of the following conditions: Type 1 diabetes, major recurrent apthae, stomatitis and related oral pathologies.
- The presence of any medical or psychiatric condition or any other condition that in the opinion of the investigator could affect the successful participation of the subject in the study.
- Subjects participating in any other clinical study 30 days prior to the start of the study and throughout the study duration.
- Subjects using chlorhexidine oral rinses or mouthwashes on a regular basis.

Table 3: it shows cumulative clinical data of different devices

	M1	M2	M3	M4	M7
Plaque Index [PI]	-0.3	-0.3	-0.3	-0.2	-0.2
Bleeding on Probing [BOP]	-0.5	-0.6	-0.5	-0.8	-0.7
Pocket Probing Depths [PPD]	-3	-2	-3	-3	-2
Probing Attachment Levels [PAL]	-3	-2	-3	-3	-2

II- Effect of bi-layer devices on the pain sensation of Aphthous Ulcers

Six patients ranging in age from 14 to 63 years [mean 38.5 years] were selected from out-patient Clinic of Oral Medicine, Periodontology and Oral Diagnosis Department, Faculty of Dentistry, Misr university for science and technology [MUST].

Patients were suffering from minor to moderate aphthous ulcers with severe pain sensation; they have no specific pathology of the oral mucosa other than minor aphthous ulcers. Exclusion Criteria were the same as under periodontal pockets section previously mentioned.

Contributing patients were informed of the nature and objectives of the study and willingness to apply topical treatment. Each patient applied a bi-layer device of either M1 or M3 on the ulcer. The pain sensation was recorded as scores for each patient as shown in tables [4, 5].

The Scoring System [17]

In case of aphthous ulcer, a scoring system was used to evaluate the progress of cases. The system included several questions and patients should answer on a scale from zero to four as the following:

Rate your current pain at rest.

[zero = no pain; four = worst pain you can imagine]

Grade any distress and bother from the film taste.

[zero = not at all; four = very much]

Grade any distress and bother from mucus irritation after film application.

[zero = not at all; four = very much]

How satisfied are you with your pain treatment.

[zero = not at all; four = very much]

Table 4: it shows the effect of bi-layer device [M1] on patients of aphthous ulcer

The object of scoring	Scoring Patient I	Scoring Patient II	Scoring Patient III
Rate your current pain at rest on a scale from zero to four	Four	Four	Three
Grade any distress and bother from the film taste	One [Bitter but bearable]	Zero	Zero
Grade any distress and bother from mucus irritation after film application	Zero	Zero	Zero
How satisfied are you with your pain treatment	Four	Four	Four

Table 5: it shows the effect of bi-layer device [M4] on patients of aphthous ulcer

The object of scoring	Scoring Patient I	Scoring Patient II	Scoring Patient III
Rate your current pain at rest on a scale from zero to four	Four	Four	Four
Grade any distress and bother from the film taste	One	Zero	Zero
Grade any distress and bother from mucus irritation after film application	Zero	Zero	Zero
How satisfied are you with your pain treatment	Three	Four	Three

RESULTS AND DISCUSSION

Figure [1] showed FTIR spectra of each of KT, Chx.HCl, and a physical mixture for both. Comparing the major peaks of single drugs with those in mixture revealed the presence of interaction between KT and Chx.HCl. These results illustrated that each drug of the combination should be put in a separated matrix film layer to prevent their interaction. Figure [2] shows that at λ_{max} 323 nm of KT, there was no reading for Chlorhexidine HCl giving zero absorption, so there was no interference for measurement of KT in presence of Chx.HCl. On the other hand, at λ_{max} of Chlorhexidine HCl there was a reading for Ketorolac which means there was overlapping between the investigated drugs, so first derivative spectroscopy was adopted to measure Chlorhexidine HCl in presence of Ketorolac.

The absorbance and first derivative Spectra for both Chx.HCl and KT solution in distilled water are shown in figure [3]. The Zero Crossing Method, revealed that the zero crossing of KT was at λ 271 nm so this could be suitable for measurement of Chx.HCl with no interference from KT. The degree of interference was calculated from the recovery percent of the mixtures. No significant interference was detected in different mixtures. The drug content for accepted formulae ranged from 95 to 120% for KT film and ranged from 98 to 114% for Chx.HCl film.

The thickness of bi-layer devices ranged from 0.27 to 0.35 mm which varied according to the type of co-polymers that were used and their ratio. All devices showed no breaking or appearing of fissures during the folding process. In vitro disintegration time varied from 134 to 253 sec. This variation might be related to the ratio of hydrophobic or hydrophilic co-polymers in each formula composition as shown in table [2]. In vivo disintegration time

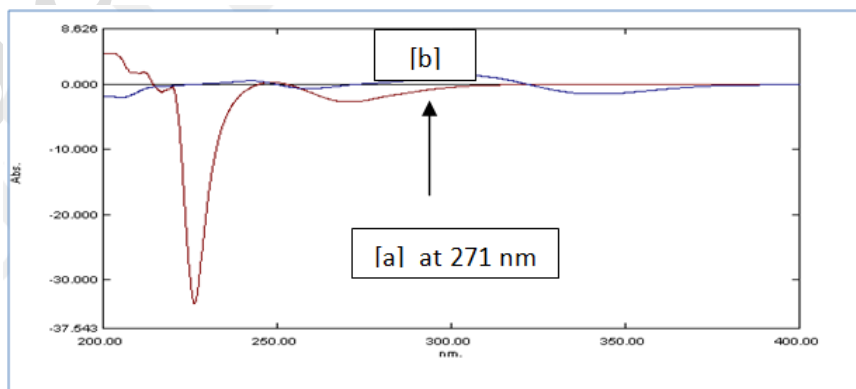
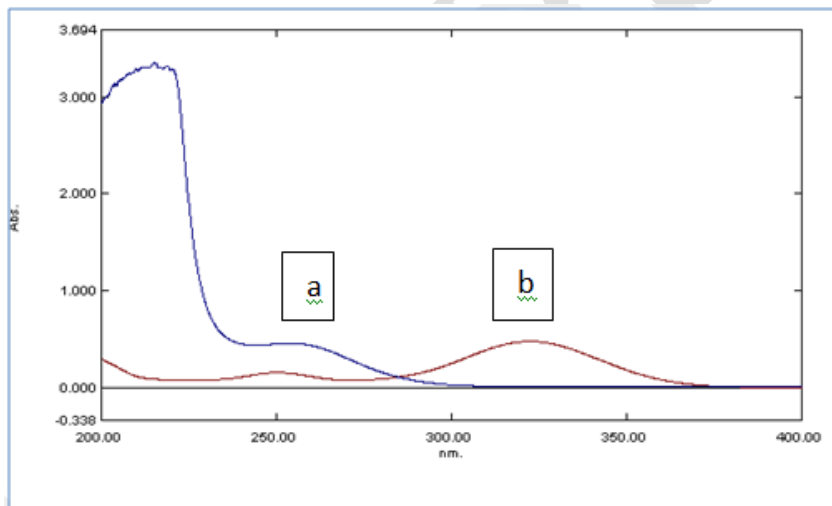
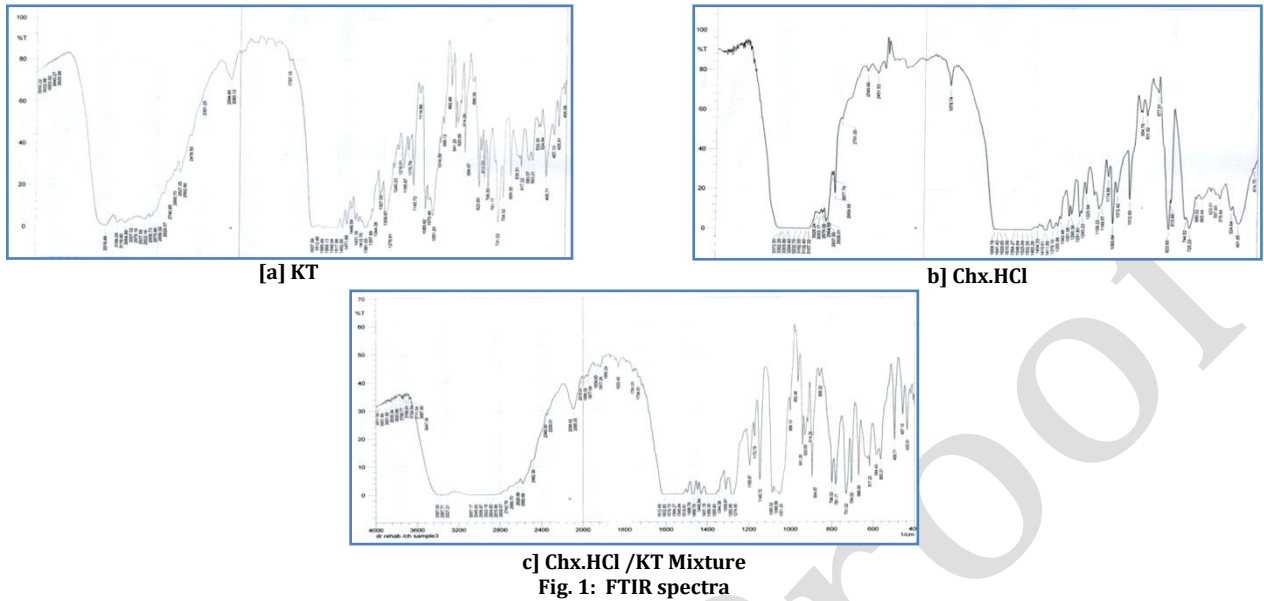
reflected the results of in vitro disintegration time test in term of the effect of the nature of co-polymers used [hydrophobic or hydrophilic]. Rapid disintegration time in films containing hydrophilic copolymer was attributed to the penetration of water into the hydrophilic matrix by means of capillary action of the pores and subsequent disruption of the hydrogen bonds [18]. Figure [4] showed the release profiles of the orobuccal bi-layer prepared devices. All devices showed a higher drug release percent for Chx.HCl than KT for a certain time. This release pattern was in contrary to the release of drugs from single film layer since the percent release of KT was higher than Chx.HCl [19].

This release pattern might be related to the arrangement of the two layers where the upper layer containing Chx.HCl was facing directly the dissolution media. All devices showed about 100% KT release during 90min. All devices gave more than 90% of Chx.HCl after 90 min except M5 [66% after 90 min and CP as a co-polymer] and M6 [86.5% after 90 min and Eudragit as a co-polymer]. This might be due to the effect of increasing the viscosity in case of Carboxypol and due to increasing the hydrophobicity in case of Eudragit. Figure [5] showed the microbiological effect of the bi-layer devices. In case of Staphylococcus aureus, the antimicrobial activity could be arranged in descending order as follow M5, M6 > M3 > M1 > M2, M4 > M7 = Corsodyl gel. In case of Candida albicans, the antimicrobial activity could be arranged in descending order as follow M3 > M2 > M4 > M1 > M5 = M6 = M7 = Corsodyl gel.

The selected formulae M1, M2, M3, M4, and M7 were subjected to test their effect on treatment of periodontal pocket and their effect on pain relief on different cases. M1 and M3 devices achieved a good sound in treatment of periodontal pocket in terms of their selected clinical parameters: the Plaque Index [PI], Bleeding on Probing [BOP], Pocket Probing Depths [PPD] and Probing Attachment Levels

[PAL]. All tested formulae reduced all the previous parameters with significant values compared with their controls as shown in table [3]. Special scoring system was used for testing the analgesic and the therapeutic effect for the prepared devices in some of periodontal

inflammation. It was noticed that all formulae showed very good satisfaction for all examined patients with no complaint of irritation. All formulae showed no bad taste except for M4 device where patients



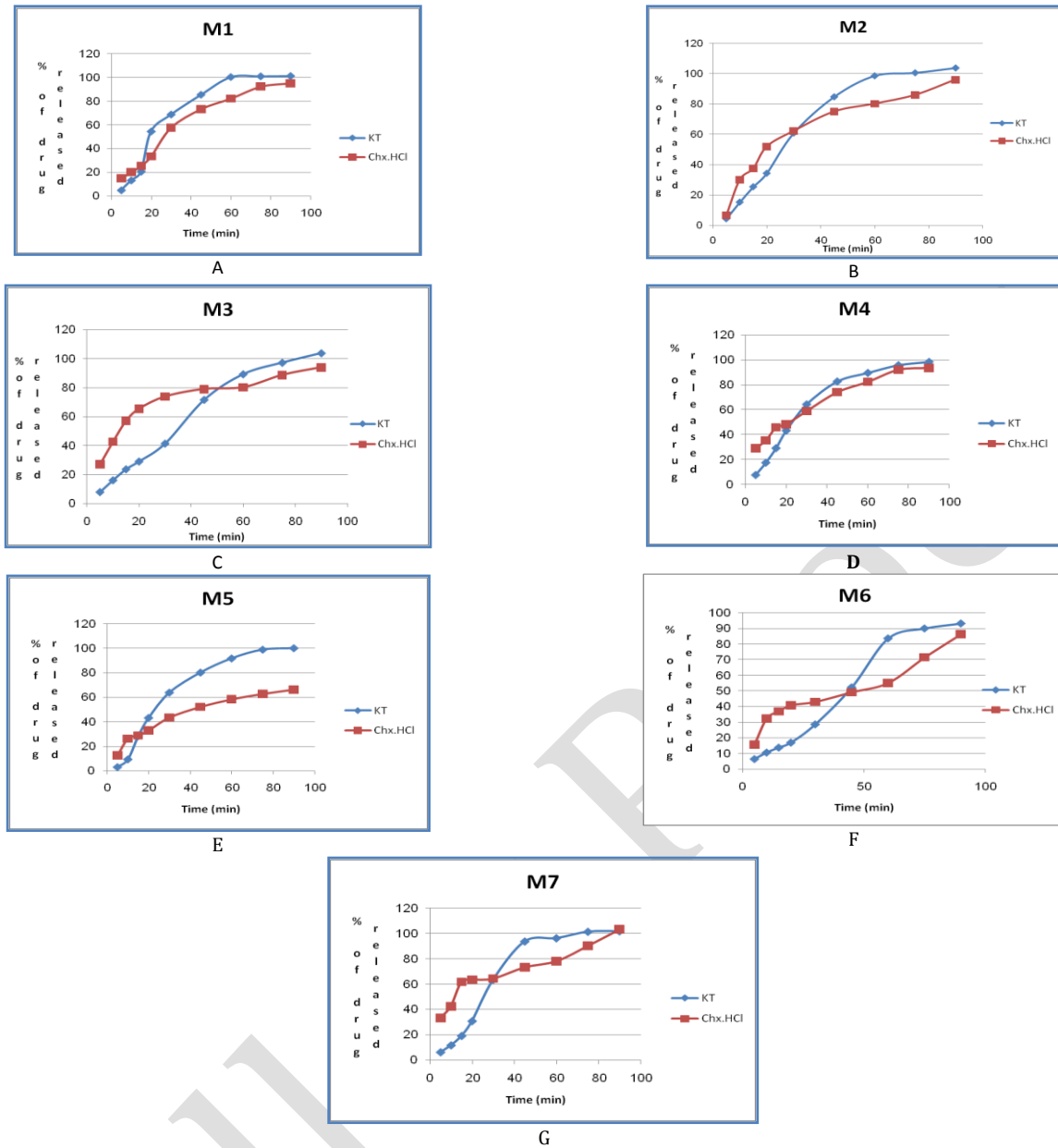


Fig. 4: Percent of Ketorolac and Chlorhexidine HCl release from different devices M1[a], M2[b], M3[c], M4[d], M5[e], M6[f], M7[g]

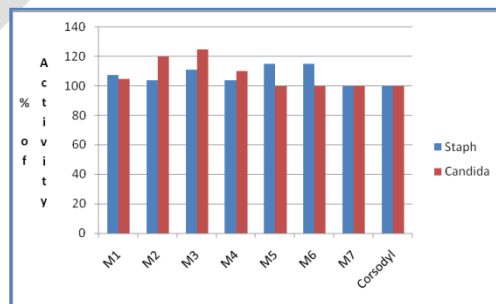


Fig. 5: Histogram of the percent anti- microbiological activity of the prepared devices on Staphylococcus aureus and Candida albicans

It was of interest to note that the levels of Chx.HCl in excess of MIC continued for days due to presence of Eudragit polymer. Chx.HCl is known to adsorb to the root surface through a process of demineralization/chelation and may also be absorbed into the adjacent gingival connective tissues.

The clinical reductions in bleeding on probing, reductions in probing depth and gains in attachment level were substantial and consistent with a reduction of inflammation pain in the adjacent gingival tissues and a healing at the base of the pocket. The reduction in inflammation and presence of healing in the connective tissue

subadjacent to the junctional epithelium has been shown to be the primary reason for reducing the depth of periodontal probe penetration after standard treatment.

Evaluation the possible positive effect of the prepared bi-layer devices achieved by study cases of patients suffering from pain sensation due to aphthous ulcers.

KT promotes action through decreasing the inflammatory challenge and hence accelerates healing of ulcer and consequently relief pain. However, the underlying cause of tissue irritation that is related to denture construction should be controlled in order to achieve permanent pain relief [20]. M1 device showed flash relief of ulcer pain than M3 device. This can be attributed to its high mucoadhesion force. M1 device is more effective for aphthous ulcer than M3 device due to the presence of NaCMC which showed a higher mucoadhesion to mucous tissue than M3. M1 and M3 showed good satisfaction for all examined patients with no complaint of irritation.

CONCLUSION

M1 and M3 devices achieved a good sound in treatment of periodontal pocket than other devices in terms of their selected clinical parameters: the Plaque Index [PI], Bleeding on Probing [BOP], Pocket Probing Depths [PPD] and Probing Attachment Levels [PAL] compared with their controls. M1 device showed flash relief of ulcer pain than M3 device. This can be attributed to its high mucoadhesion force. M1 and M3 showed good satisfaction for all examined patients with no complaint of irritation. All devices showed no bad taste and patient compliance. A device which contains both drugs [KT and Chx.HCl] is a safe, well tolerated, and highly effective promising new adjunctive treatment for healing common aphthous ulcers. No systematic side effects associated with the device medication were noted. In view of the relative in effectiveness of systemic analgesics and topical anesthetics for these conditions. KT and Chx.HCl promise to be a useful addition to the therapeutic activity.

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