American Journal of Psychiatric Rehabilitation Expert Opinion Article

A comparative evaluation of the efficacy of herbal mucoadhesive patch with benzocaine mucoadhesive patch to relieve pain associated with placement of elastomeric separators.

Dr. Rahul Paul[1*], Dr. Deepti Yadav[2], Dr. Bhawani Singh Meena[3], Dr. Ish Kumar Sharma[4], Dr. Vandana Gulia[5], Dr. Prakher Saini[6].

[1*]Principal, Professor and Head of Department, Department of Orthodontics and Dentofacial Orthopaedics ,Inderprastha Dental College and Hospital, Ghaziabad, India.
[2]Professor, Department of Orthodontics and Dentofacial Orthopaedics ,Inderprastha Dental College and Hospital, Ghaziabad, India.
[3]Resident, Department of Orthodontics and Dentofacial Orthopaedics,Inderprastha Dental College and Hospital, Ghaziabad, India.
[4]Reader, Department of Orthodontics and Dentofacial Orthopaedics, Inderprastha Dental College and Hospital, Ghaziabad, India.
[5]Reader, Department of Orthodontics and Dentofacial Orthopaedics, Inderprastha Dental College and Hospital, Ghaziabad, India.
[6]Senior Lecturer, Department of Orthodontics and Dentofacial Orthopaedics, Inderprastha Dental College and Hospital, Ghaziabad, India.

***Corresponding Author**- Dr. Rahul Paul
*Principal, Professor and Head of Department, Department of Orthodontics and Dentofacial Orthopaedics ,Inderprastha Dental College and Hospital, Ghaziabad, India.

Abstract
Aims: The Purpose of this study was to evaluate the efficacy of benzocaine and herbal mucoadhesive patch in reducing pain caused by elastomeric separators.
Materials and methods: A sample size of 40 patients were selected for the study. Elastomeric separators were placed mesial and distal to first maxillary molars in both quadrants and the patches were placed buccal mucosa above the 1st maxillary molars. The medication patch and the placebo patch were distributed randomly among the two groups of 20 patients each. For both of their first maxillary molars, the patients were given Visual Analogue Scales (VAS). The Mann-Whitney U test and Krausal test analyses were done after data collection. The patient recorded readings every six hours beginning 30 minutes after the patch insertion. The mucoadhesive drug and placebo patch was replaced after 48 hours and every six hours, the reading was remarked, and the final marking was conducted at 72nd hour and mucoadhesive patch was replaced.
Results: There was statistically significant reduction in pain. when mucoadhesive drug patch was compared with the placebo patch. It was seen that benzocaine was most effective at 6th, 48th ,72nd hour, followed by quercetin patch which was effective at 6th, 48th ,72nd hour. When two drug patches were compared it was observed that benzocaine was significantly effective in relieving pain caused due to separators.
Conclusion: It can be concluded from the study that benzocaine and quercetin patches were effective in reducing pain caused by elastomeric separators as compared to the placebo patch. The use of benzocaine patches was most effective followed by a quercetin mucoadhesive patch.

INTRODUCTION:

Orthodontic discomfort is the most frequently reported detrimental effect of orthodontic force application and is a significant concern for patients, parents, and clinicians. Research has identified pain as a major factor discouraging individuals from seeking orthodontic treatment and a common reason for treatment discontinuation. Experience or fear of pain is the most important concern for patients and orthodontists, the worst aspect of treatment, and the main discouraging reason for opting for orthodontic care. Despite its clinical relevance, orthodontic pain remains underexplored, as evidenced by the relatively limited number of studies on this topic compared to other aspects of orthodontic research.[1] Over the past few decades, there has been a growing demand for enhancing both smile aesthetics and occlusal function. However, a significant number of patients, ranging from children to adults, continue to show concern about the pain and discomfort associated with orthodontic treatment. As a result, some patients may choose to refuse, postpone, or discontinue orthodontic treatment.[1,2] Orthodontic treatment typically begins with the placement of separators, which create space for orthodontic bands by exerting force to gradually wedge the teeth apart and loosen the tight interproximal contacts. The separation process generally takes between 2 to 7 days, depending on the type of separators used.[3,4]

Various types of separators have been employed in orthodontics, including brass wire, latex elastics, elastomerics, Kesling separators, Neet separators, and Maxian elastic separators, among others. Research indicates that in recent years, springs and elastomerics have been the most frequently utilized options.[5] The various types of separators differ in the level of discomfort they induce during the separation process.[6]

Due to the limited literature on the effectiveness of quercetin mucoadhesive patches and their relationship to pain management in orthodontic treatment, particularly during separator placement, this study was conducted to investigate the impact of quercetin on pain relief during elastomeric separator placement. In search of a more efficient patch of a mucoadhesive drug delivery system, this study evaluates the effect of quercetin drug by comparing it with a benzocaine patch. Ultimately, this research can improve patient acceptance and motivation towards orthodontic procedures due to better pain management.

AIM OF THE STUDY:

To evaluate and compare the effect on pain perception level following the placement of mucoadhesive buccal patch of benzocaine and quercetin drug.

MATERIALS AND METHOD:

40 patients were selected for the study based on inclusion and exclusion criteria who seek to the orthodontic treatment. The selected patients were informed about the study and its benefits and risks, and consent was obtained before the commencement of the study and placement of separators. Selected patients were introduced and instructions were given about the VAS method of pain assessment.

The selected 40 patients were randomly divided into 2 groups.

- **Group A:** Patients applied with Benzocaine Mucoadhesive patch. (n=20)
- **Group B:** Patients applied with Quercetin(herbal) Mucoadhesive patch. (n=20)

Where, n= number of samples in each group.

The study utilized a split-mouth design to eliminate potential biological variations. Elastomeric orthodontic separators were placed mesial and distal to first maxillary first molars in both quadrants, and the patches were placed on buccal mucosa above the 1st maxillary molars. The medication patch and the placebo patch were distributed randomly among the two groups of 20 patients each.

Group A, Patients applied a Benzocaine mucoadhesive patch (1X1 dimension) on the right side and a placebo patch on the left side to the buccal gingiva in the region of the first molar and second premolar

Group B, Patients applied a Quercetin (herbal) mucoadhesive patch (1x1) dimension on the right side and a placebo patch on the left side to the buccal gingiva in the region of the first molar and second premolar.

The patients were given Visual Analogue Scales (VAS) to record pain intensity. The mucoadhesive benzocaine, quercetin, and placebo patches were replaced at the 24th, 48th, and 72nd hours. The patients recorded their pain readings at the 6th, 12th, 18th, and 24th hours, followed by the 48th and 72nd hours.

The data for the present study was entered in Microsoft Excel 2010 and analysed using the SPSS statistical software 27.0 Version. The descriptive statistics included frequency and percentage. Kolmogorov-Smirnov Test was used to check the normality of the data. As the data did not follow the normal curve. Therefore, non-parametric tests were used for analysis. The results were analyzed in subgroups using the Mann-Whitney test used for intra group comparisons. For inter group comparisons, the Kruskal Wallis was employed. The level of significance for the present study was fixed at 5%

RESULTS:

The present study was performed to evaluate and compare the efficacy of mucoadhesive drug patches of benzocaine and quercetin (herbal) in relieving pain caused by elastomeric separators.

The study was initiated on forty patients who came to the Department of Orthodontics and Dentofacial Orthopaedics seeking orthodontic treatment. A split-mouth design was used in the study to rule out any biological variations. Elastomeric orthodontic separators were placed mesial and distal to first maxillary first molars in both quadrants, and the patches were placed on buccal mucosa above the 1st maxillary molars. The medication patch and the placebo patch were distributed randomly among the two groups of 20 patients each.

- Group A: Benzocaine Mucoadhesive Patches
- Group B: Quercetin Drug (Herbal) Mucoadhesive Patches

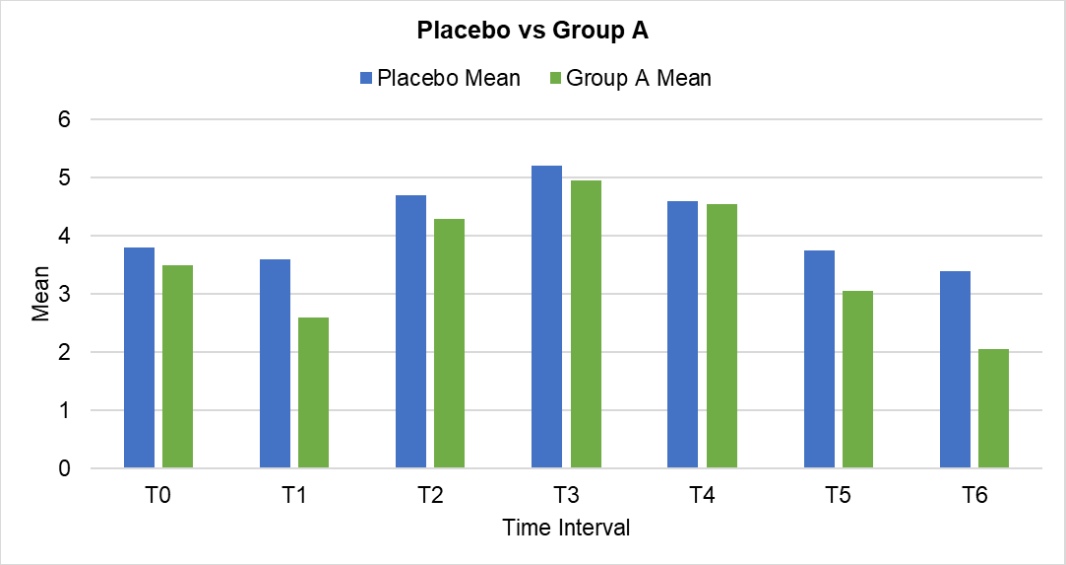
The patients were given Visual Analogue Scales (VAS) to record pain intensity. The mucoadhesive benzocaine, quercetin, and placebo patches were replaced at the 24th, 48th, and 72nd hours. The patients recorded their pain readings at the 6th, 12th, 18th, and 24th hours, followed by the 48th and 72nd hours.

Table 1 Shows the mean VAS scores for Group A, At T0 (Baseline), no significant difference (p=0.301) was seen between benzocaine and placebo patches, however VAS score was significantly lower as benzocaine side as compared to placebo at T1 (1.0±0.75) with p value = 0.017, at T5 (0.70±0.23) with p value = 0.024 and at T6 (1.35±0.14), p value = 0.001, but there was no significant difference observed at T2 (12th hour), T3 (18 hour) and T4 (24th hour).

Time Interval	Group A				Mean difference	p-value
	Benzocaine		Placebo			
	Mean	SD	Mean	SD		
T0	3.5	1.13	3.8	1.33	0.3±0.2	0.301
T1	2.6	0.75	3.6	1.5	1.0±0.75	**0.017***
T2	4.3	1.12	4.7	1.14	0.4±0.02	0.327
T3	4.95	0.99	5.2	0.76	0.25±0.23	0.429
T4	4.55	1.05	4.6	0.82	0.05±0.23	0.583
T5	3.05	0.88	3.75	1.11	0.70±0.23	**0.024***
T6	2.05	0.68	3.4	0.82	1.35±0.14	**0.001***

SD= Standard Deviation, p ≤ 0.05 = Significant, CI = 95 %

Table 1: Comparison of Pain Perception of Group A on Visual Analog Scale (VAS) At Different Intervals of Time



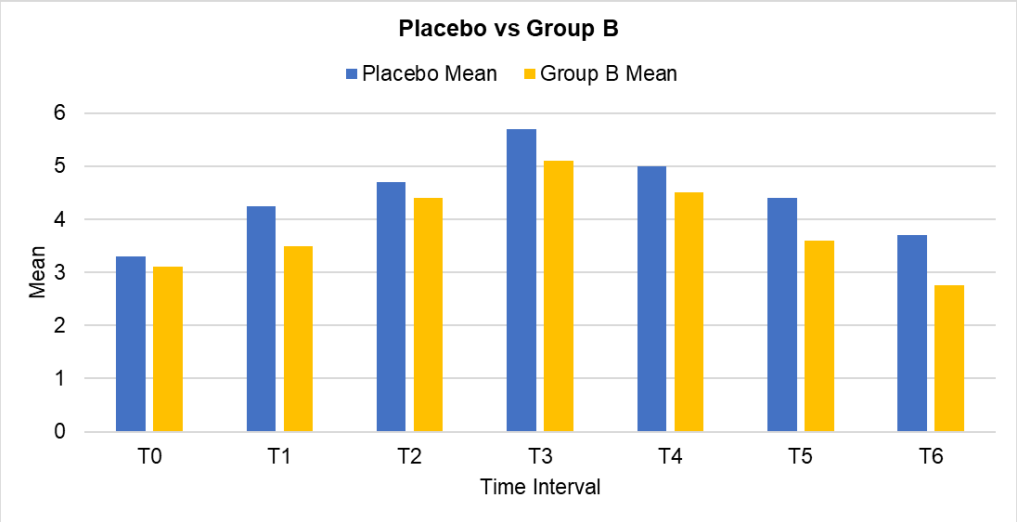
Graph 1: Comparison of Pain Perception of Group A Visual Analog Scale (VAS) At Different Intervals of Time

Table 2 Shows the mean VAS scores for Group B, At T0 (Baseline), no significant difference (p=0.301) was seen between quercetin and placebo patches, however pain VAS score was significantly lower in quercetin as compared to placebo at T1 (0.75±0.91) with p value = 0.049*, at T5 (0.8±0.06) with p value = 0.007* and at T6 (0.95±0.44), p value = 0.002* which was significantly different between both the subgroups, but there was no significant difference observed at T2 (12th hour), T3 (18 hour) and T4 (24th hour).

Time Interval	Group B				Mean difference	p-value
	Quercetin		Placebo			
	Mean	SD	Mean	SD		
T0	3.1	0.73	3.3	0.64	0.2±0.09	0.096
T1	3.5	1.35	4.25	0.44	0.75±0.91	**0.049***
T2	4.4	1.21	4.7	1.23	0.3±0.01	0.429
T3	5.1	0.85	5.7	0.65	0.6±0.19	0.052
T4	4.5	0.68	5	1.12	0.5±0.43	0.149
T5	3.6	0.75	4.4	0.82	0.8±0.06	**0.007***
T6	2.75	1.02	3.7	0.57	0.95±0.44	**0.002***

SD= Standard Deviation, p ≤ 0.05 = Significant, CI = 95 %

Table 2: Comparison of Pain Perception of Group B on Visual Analog Scale (VAS) At Different Intervals of Time



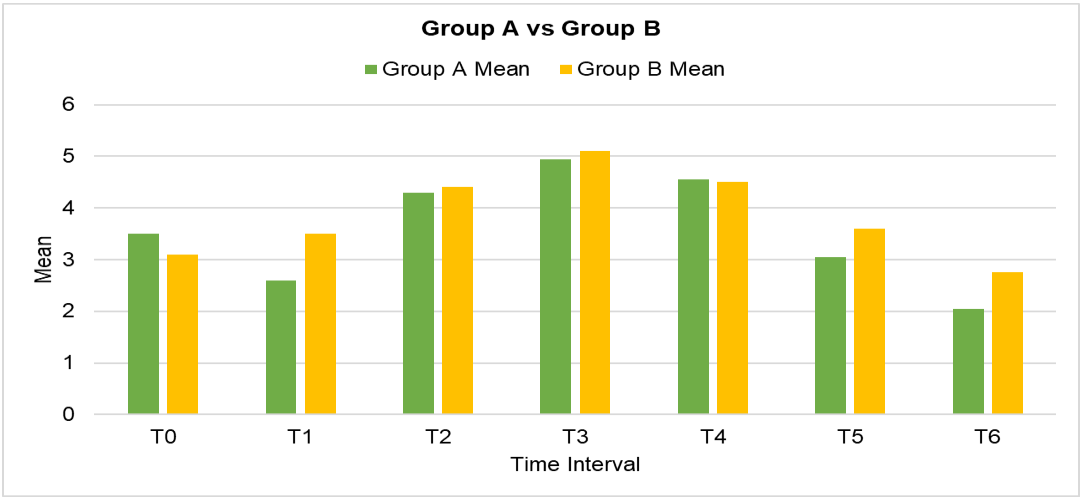
Graph 2: Comparison of Pain Perception of Group B On Visual Analog Scale (VAS) At Different Intervals Of Time

Table 3 Compares the mean VAS scores for Group A and Group B mucoadhesive patches, At T0 (Baseline), there was no significant difference between two groups (p=0.067). However, significant pain reduction was observed in Group A compared to Group B at T1 (6th hour), with a mean difference of 0.9±0.60 (p=0.029*); at T5 (48th hour), with a mean difference of 0.55±0.13 (p=0.043*); and at T6(72nd hour), with a mean difference of 0.7±0.34 (p=0.028*). No significant difference was observed between two groups at T2(12th hour), T3 (18th hour) and T4 (24th hours) (p>0.05).

Time Interval	Group A		Group B		Mean difference	p-value
	Mean	SD	Mean	SD		
T0	3.5	1.13	3.1	0.73	0.4±0.40	0.067
T1	2.6	0.75	3.5	1.35	0.9±0.60	**0.029***
T2	4.3	1.21	4.4	1.23	0.1±0.02	0.908
T3	4.95	0.99	5.1	0.85	0.15±0.14	0.627
T4	4.55	1.05	4.5	0.68	0.05±0.37	0.719
T5	3.05	0.88	3.6	0.75	0.55±0.13	**0.043***
T6	2.05	0.68	2.75	1.02	0.7±0.34	**0.028***

SD= Standard Deviation, p ≤ 0.05 = Significant, CI = 95 %

Table 3: Intergroup Comparison of The Efficacy of Group A Vs Group B



Graph 3: Intergroup Comparison of The Efficacy of Group A Vs Group B

DISCUSSION:

Dental care is frequently associated with pain. According to the clinical literature and some systematic research studies,[8,37,51,77] discomfort and pain are common during orthodontic treatment. The present study was conducted to evaluate patients' pain perception using Benzocaine and Quercetin mucoadhesive patches in response to elastomeric separators. For this purpose, 40 patients were included who decided to seek orthodontic treatment at the department of Orthodontics and Dentofacial Orthopaedics. Following the patient's consent, Elastomeric separators were used to create space for the bands. Then, a benzocaine and quercetin mucoadhesive patch was placed on right side quadrant and a placebo mucoadhesive patch on the left side quadrant above the buccal mucosa of the maxillary 1st molar respectively. The pain perception was recorded by the patient on the VAS chart 30 minutes after patch placement, every 6 hours for the next 24 hours, and then again at 48 and 72 hours.

On observation it was found that, pain aggravated on the first day and lasted until the fifth day after the separators placement. This observation coincides with a similar study done by Ngan et al,[83] which was also examined the pain in relation to separator placement and concluded that pain increased for over 24 hours and decreased within 7 days of separator insertion.

The results obtained in the current study indicated that a mucoadhesive patch of benzocaine and quercetin mucoadhesive patch showed a statistically significant reduction in the pain caused by elastomeric separators when compared with a placebo. The result of the present study aligns with studies conducted by Hersh EV et al,[37] Eslamian L et al,[51] John NE et al,[77] Paul R et al.[8] confirming the efficacy of benzocaine mucoadhesive patches in pain reduction when compared to placebo.

In the present study, Both the mucoadhesive patches were found to be effective in reducing pain at 6th hours,48th hours and 72nd hours in contrast to placebo mucoadhesive patches. Some studies gave a similar result Eslamian L et al,[60] in which 30 patients were studied and used a benzocaine and placebo patches at different time intervals to observed the pain intensity. At 2, 18, 24, 48, and 72 hours, there were considerable differences in pain perception between two groups. Pain perception did not differ between genders or jaws. Hersh et al. (2013),[49] found that benzocaine mucoadhesive patches containing 12 mg of benzocaine relieved the pain by 30 minutes and were significantly greater in the benzocaine group than in the placebo group (77% for Benzocaine and 47% for placebo). The significant result were 5.4 and 18.1 minutes for the benzocaine group, and 7.8 and 30.4 minutes for the placebo group. According to a study done by Pipalia et al. (2016),[61] patients who were administered a benzocaine mucoadhesive patch experienced a mean reduction in pain after 30 minutes, compared to those who received a placebo patch. The study noted that the patch dissolved within 30 minutes of application. The analgesic effect of benzocaine mucoadhesive patch was observable at 6th hours. These findings are in accordance with the results of the present study, which also demonstrated significant pain reduction at 6th hours following the application of benzocaine mucoadhesive patches.

Quercetin, a naturally occurring flavonoid with anti-inflammatory and analgesic properties, offers an alternative management option for pain reduction, Shemer A. et al. (2008),[19] Chaushu L. et al. (2015),[59] Jahromi B et al (2021),[84] Liu C et al. (2023),[85] conducted a similar study, which was also associated with pain. The results obtained indicated that a quercetin mucoadhesive patch showed a statistically significant reduction in the pain when compared with a placebo patch, recent studies indicate that quercetin may have a role in modulating pain through its antioxidant properties and ability to inhibit inflammatory pathways Liu C et al. (2023)[85]. Our findings demonstrated that quercetin patches also provided significant pain relief as measured by VAS scores, though the degree of relief was less pronounced than that of benzocaine.[2] quercetin mucoadhesive patch, the effect of the quercetin patch was significant at 6th hours,48th hours, and 72nd hours.

The pharmacological profile of quercetin suggests that its onset of action may not be as rapid as that of benzocaine, it may provide longer-lasting relief due to its anti-inflammatory effects[85]. The herbal nature of quercetin may appeal to patients look around for non-pharmacological pain management strategies, thus expanding their options during orthodontic treatment.

Comparative evaluation of the efficacy of these two mucoadhesive patches revealed distinct differences in pain management outcomes. Benzocaine demonstrated increased efficacy in immediate pain relief compared to quercetin. This result is supported by the work of Pahade et al. (2023),[86] who noted the significant advantages of topical anesthetics in acute pain management. However, the potential for quercetin as a complementary approach cannot be overlooked, particularly for patients who may prefer or require natural alternatives. Moreover, the choice of analgesic might also depend on patient-specific factors, including their pain tolerance, history of allergic reactions to components, and preferences for treatment types. Further research could explore the synergistic effects of combining both agents in a single patch or regimen to enhance overall efficacy Nobrega et al. (2023)[47].

In the present study, a benzocaine mucoadhesive patch was found to be effective in reducing pain compared to a quercetin patches , pain associated with the placement of orthodontic elastomeric separators.

CONCLUSION:

The following results can be drawn from the present study –

1. The benzocaine mucoadhesive patches were significantly more effective than the placebo in reducing pain caused by elastomeric separators.
2. The quercetin mucoadhesive patches were significantly more effective than the placebo in reducing pain caused by elastomeric separators.
3. When the two mucoadhesive patches were compared, it was found that benzocaine was most effective in reducing pain caused by elastomeric separators.

REFERENCES:

1. Tortamano A, Lenzi DC, Haddad ACSS, Bottino MC, Dominguez GC, Vigorito JW. Low-level laser therapy for pain caused by placement of the first orthodontic archwire: a randomized clinical trial. Am J Orthod Dentofac Orthop Off Publ Am Assoc Orthod Its Const Soc Am Board Orthod. 2009 Nov;136(5):662–7.
2. Nicotra C, Polizzi A, Zappalà G, Leonida A, Indelicato F, Caccianiga G. A Comparative Assessment of Pain Caused by the Placement of Banded Orthodontic Appliances with and without Low-Level Laser Therapy: A Randomized Controlled Prospective Study. Dent J. 2020 Mar 4;8(1):24.
3. Vallakati A, Jyothikiran H, Shanthraj R, Patel P. Orthodontic separators – a systemic review. J Orofac Health Sci. 2014 Jan;5(3):118.
4. Malagan MA, P P B, Muddaiah S, Reddy R, Shetty BK, Preetham J, et al. Comparison between efficacy of four different types of orthodontic separators. J Clin Diagn Res JCDR. 2014 Aug;8(8):41-44.
5. Eliades T, Brantley WA. Orthodontic applications of biomaterials: a clinical guide. Amsterdam: Elsevier; 2017.
2. Bondemark L, Fredriksson K, Ilros S. Separation effect and perception of pain and discomfort from two types of orthodontic separators. World J Orthod. 2004 Summer;5(2):172-6.
3. Hoffman WE. A study of four types of orthodontic separator. Am J Orthod. 1972 Jul;62(1):67–73.
4. Paul R, Yadav D, Gupta M, Gulia V, Babra S. A comparative evaluation of transdermal diclofenac patch with oral diclofenac sodium as an analgesic drug following periodontal flap surgery: A randomized controlled clinical study. Eur Chem Bull. 2024;12(special issue 4):5800–8.
5. Shenoy N, Shetty S, Ahmed J, Shenoy K A. The pain management in orthodontics. J Clin Diagn Res. 2013 Jun;7(6):1258-60.
6. Beck VJ, Farella M, Chandler NP, Kieser JA, Thomson WM. Factors associated with pain induced by orthodontic separators. J Oral Rehabil. 2014 Apr;41(4):282–8.
7. Simpson DM, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. Clin Ther. 2007 Apr;29(4):588-601.
8. Chandrashekar A, Annigeri RG, Thimmasetty J. Comparative evaluation of diclofenac and meloxicam as tablets and as transmucosal mucoadhesive patches in dental pain reduction. Int J Pharm Sci Res. 2020 May 1;11(5):2217-22.
9. Klimek L, Bergmann KC, Biedermann T, Bousquet J, Hellings P, Jung K, et al. Visual analogue scales (VAS): Measuring instruments for the documentation of symptoms and therapy monitoring in cases of allergic rhinitis in everyday health care: Position Paper of the German Society of Allergology (AeDA) and the German Society of Allergy and Clinical Immunology (DGAKI), ENT Section, in collaboration with the working group on Clinical Immunology, Allergology and Environmental Medicine of the German Society of Otorhinolaryngology, Head and Neck Surgery (DGHNOKHC). Allergo J Int. 2017 Jan 19;26(1):16.
10. Langley GB, Sheppeard H. The visual analogue scale: its use in pain measurement. Rheumatol Int. 1985;5(4):145-8.
11. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med. 1988 Nov;18(4):1007-19.
12. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med Off J Soc Acad Emerg Med. 2001 Dec;8(12):1153–7.
13. Keim RG. Managing orthodontic pain. J Clin Orthod. 2004 Dec;38(12):641-2.
14. Kubo K. Advancements in Pharmaceutical Chemistry: Innovations in Drug Discovery and Development. Res Rev J Pharm Anal. 2024 Sep 23;13(3):1–2.
15. Shemer A, Amichai B, Trau H, Nathansohn N, Mizrahi B, Domb AJ. Efficacy of a mucoadhesive patch compared with an oral solution for treatment of aphthous stomatitis. Drugs R D. 2008;9(1):29-35.
16. Shaikh R, Raj Singh TR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci. 2011 Jan;3(1):89-100.

17. Jacob S, Nair AB, Boddu SHS, Gorain B, Sreeharsha N, Shah J. An Updated Overview of the Emerging Role of Patch and Film-Based Buccal Delivery Systems. Pharmaceutics. 2021 Aug 5;13(8):1206.
18. Ezike TC, Okpala US, Onoja UL, Nwike CP, Ezeako EC, Okpara OJ, et al. Advances in drug delivery systems, challenges and future directions. Heliyon. 2023 Jun 24;9(6):e17488.
19. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery — A promising option for orally less efficient drugs. J Controlled Release. 2006 Aug 10;114(1):15–40.
20. Colley HE, Said Z, Santocildes-Romero ME, Baker SR, D'Apice K, Hansen J, et al. Pre-clinical evaluation of novel mucoadhesive bilayer patches for local delivery of clobetasol-17-propionate to the oral mucosa. Biomaterials. 2018 Sep 1;178:134–46.
21. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A clinical perspective on mucoadhesive buccal drug delivery systems. J Biomed Res. 2014 Mar;28(2):81–97.
22. Yang X, Wei X, Mu Y, Li Q, Liu J. A review of the mechanism of the central analgesic effect of lidocaine. Medicine (Baltimore). 2020 Apr 24;99(17):e19898.
23. Lee HS. Recent advances in topical anesthesia. J Dent Anesth Pain Med. 2016 Dec 31;16(4):237.
24. Maestrelli F, Capasso G, González-Rodríguez ML, Rabasco AM, Ghelardini C, Mura P. Effect of preparation technique on the properties and in vivo efficacy of benzocaine-loaded ethosomes. J Liposome Res. 2009;19(4):253-60.
25. Corega C, Vaida L, Festila DG, Rigoni G, Albanese M, D'Agostino A, et al. The benefits of Quercitin for dentistry and maxillofacial surgery: a systematic review. Minerva Stomatol. 2014 Jan;63(1-2):43-9.
26. Mirza MA, Mahmood S, Hilles AR, Ali A, Khan MZ, Zaidi SAA, et al. Quercetin as a Therapeutic Product: Evaluation of Its Pharmacological Action and Clinical Applications-A Review. Pharm Basel Switz. 2023 Nov 20;16(11):1631.
27. Jones M, Chan C. The pain and discomfort experienced during orthodontic treatment: a randomized controlled clinical trial of two initial aligning arch wires. Am J Orthod Dentofacial Orthop. 1992 Oct;102(4):373-81.
28. Primosch RE, Rolland-Asensi G. Comparison of topical EMLA 5% oral adhesive to benzocaine 20% on the pain experienced during palatal anesthetic infiltration in children. Pediatr Dent. 2001 Jan-Feb;23(1):11-4.
29. Kreider KA, Stratmann RG, Milano M, Agostini FG, Munsell M. Reducing children's injection pain: lidocaine patches versus topical benzocaine gel. Pediatr Dent. 2001 Jan-Feb;23(1):19-23.
30. Kluemper GT, Hiser DG, Rayens MK, Jay MJ. Efficacy of a wax containing benzocaine in the relief of oral mucosal pain caused by orthodontic appliances. Am J Orthod Dentofac Orthop Off Publ Am Assoc Orthod Its Const Soc Am Board Orthod. 2002 Oct;122(4):359–65.
31. Wu SJ, Julliard K. Children's preference of benzocaine gel versus the lidocaine patch. Pediatr Dent. 2003 Jul-Aug;25(4):401-5.
32. Nusstein JM, Beck M. Effectiveness of 20% benzocaine as a topical anesthetic for intraoral injections. Anesth Prog. 2003;50(4):159-63.
33. Hersh EV, DeRossi SS, Ciarrocca KN, Secreto SA, Ghassemi A. Efficacy and tolerability of an intraoral benzocaine patch in the relief of spontaneous toothache pain. J Clin Dent. 2003;14(1):1-6.
34. Hersh EV, Stoopler ET, Secreto SA, DeRossi SS. A study of benzocaine gel dosing for toothache. J Clin Dent. 2005;16(4):103-8.
35. Giannopoulou C, Dudic A, Kiliaridis S. Pain discomfort and crevicular fluid changes induced by orthodontic elastic separators in children. J Pain. 2006 May;7(5):367–76.
36. Al-Melh MA, Andersson L. Comparison of topical anesthetics (EMLA/Oraqix vs. benzocaine) on pain experienced during palatal needle injection. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 May;103(5):e16-20.
37. Nalbantgil D, Cakan DG, Oztoprak MO, Arun T. Perception of pain and discomfort during tooth separation. Aust Orthod J. 2009 Nov;25(2):110–5.
38. Patel RP, Patel G, Patel H, Baria A. Formulation and evaluation of transdermal patch of aceclofenac. Research Journal of Pharmaceutical Dosage Forms and Technology. 2009;1(2):108-15.
39. Bhaskar H, Kapoor P, Ragini. Comparison of transdermal diclofenac patch with oral diclofenac as an analgesic modality following multiple premolar extractions in orthodontic patients: A cross over efficacy trial. Contemp Clin Dent. 2010 Jul;1(3):158-63.
40. Habib, F., Shaltout, S., Azeem, M., Fetih, G., Safwat, M. Mucoadhesive buccal patches of lornoxicam: II– in-vivo evaluation and clinical efficacy. Bulletin of Pharmaceutical Sciences Assiut University, 2011; 34(1): 21-30.
41. Winning L, Polyzois I, Nylund K, Kelly A, Claffey N. A placebo-controlled trial to evaluate an anesthetic gel when probing in patients with advanced periodontitis. J Periodontol. 2012 Dec;83(12):1492-8.
42. Angelopoulou MV, Vlachou V, Halazonetis DJ. Pharmacological management of pain during orthodontic treatment: a meta-analysis. Orthod Craniofac Res. 2012 May;15(2):71-83.

43. Nóbrega C, da Silva EM, de Macedo CR. Low-level laser therapy for treatment of pain associated with orthodontic elastomeric separator placement: a placebo-controlled randomized double-blind clinical trial. Photomed Laser Surg. 2013 Jan;31(1):10-6.
44. Cavallari C, Fini A, Ospitali F. Mucoadhesive multiparticulate patch for the intrabuccal controlled delivery of lidocaine. Eur J Pharm Biopharm Off J Arbeitsgemeinschaft Pharm Verfahrenstechnik EV. 2013 Apr;83(3):405–14.
45. Hersh EV, Ciancio SG, Kuperstein AS, Stoopler ET, Moore PA, Boynes SG, et al. An evaluation of 10 percent and 20 percent benzocaine gels in patients with acute toothaches: efficacy, tolerability and compliance with label dose administration directions. J Am Dent Assoc 1939. 2013 May;144(5):517–26.
46. Sandhu SS, Sandhu J. A randomized clinical trial investigating pain associated with superelastic nickel–titanium and multistranded stainless steel archwires during the initial leveling and aligning phase of orthodontic treatment. J Orthod. 2013 Dec;40(4):276–85.
47. Eslamian L, Borzabadi-Farahani A, Edini HZ, Badiee MR, Lynch E, Mortazavi A. The analgesic effect of benzocaine mucoadhesive patches on orthodontic pain caused by elastomeric separators, a preliminary study. Acta Odontol Scand. 2013 Sep;71(5):1168–73.
48. Asiry MA, Albarakati SF, Al-Marwan MS, Al-Shammari RR. Perception of pain and discomfort from elastomeric separators in Saudi adolescents. Saudi Med J. 2014 May;35(5):504–7.
49. Sharma A, Suprabha BS, Shenoy R, Rao A. Efficacy of lignocaine in gel and spray form during buccal infiltration anesthesia in children: a randomized clinical trial. J Contemp Dent Pract. 2014 Nov 1;15(6):750–4.
50. Bhutkar KG. Formulation and evaluation of mucoadhesive herbal buccal patch of Psidium guava L. J Curr Pharma Res. 2014 Dec;5(1):1372-7.
51. Al-Samadani KH, Gazal G. Effectiveness of benzocaine in reducing deep cavity restoration and post-extraction stress in dental patients. Saudi Med J. 2015 Nov;36(11):1342–7.
52. Rajeswari SR, Gowda TM, Kumar TA, Thimmasetty J, Mehta DS. An appraisal of innovative meloxicam mucoadhesive films for periodontal postsurgical pain control: A double-blinded, randomized clinical trial of effectiveness. Contemp Clin Dent. 2015 Jul-Sep;6(3):299-304.
53. Lathwal G, Pandit IK, Gugnani N, Gupta M. Efficacy of Different Precooling Agents and Topical Anesthetics on the Pain Perception during Intraoral Injection: A Comparative Clinical Study. Int J Clin Pediatr Dent. 2015 May-Aug;8(2):119-22.
54. Annigeri RG, Jadhav M, Juturu T. Clinical evaluation of transmucosal mucoadhesive meloxicam patch in dental pain reduction: A preliminary study. Indian J Pain. 2015 May-Aug;29(2):82-85
55. Chaushu L, Weinreb M, Beitlitum I, Moses O, Nemcovsky CE. Evaluation of a topical herbal patch for soft tissue wound healing: an animal study. J Clin Periodontol. 2015;42(3):288–93.
56. Eslamian L, Borzabadi-Farahani A, Gholami H. The effect of benzocaine and ketoprofen gels on pain during fixed orthodontic appliance treatment: a randomised, double-blind, crossover trial. Aust Orthod J. 2016 May;32(1):64–72.
57. Pipalia PR, Annegeri RG, Juturu T, Mehta R. Control of odontogenic pain by diclofenac and meloxicam mucoadhesive patches: A randomized, double-blinded, placebo-controlled, preliminary study. J Indian Acad Oral Med Radiol. 2016 Sep;28(3):229.
58. Hashemi M, Ramezani V, Seyedabadi M, Ranjbar AM, Jafari H, Honarvar M, et al. Formulation and Optimization of Oral Mucoadhesive Patches of Myrtus Communis by Box Behnken Design. Adv Pharm Bull. 2017 Sep;7(3):441–50.
59. Eslamian L, Akbarian Rad N, Rahbani Nobar B, Mortazavi SA. Effect of a 5% naproxen patch on reducing pain caused by separators prior to fixed orthodontic treatment. J Dent Anesth Pain Med. 2018 Jun;18(3):151–9.
60. Clitherow KH, Murdoch C, Spain SG, Handler AM, Colley HE, Stie MB, et al. Mucoadhesive Electrospun Patch Delivery of Lidocaine to the Oral Mucosa and Investigation of Spatial Distribution in a Tissue Using MALDI-Mass Spectrometry Imaging. Mol Pharm. 2019 Sep 3;16(9):3948–56.
61. Diwan V, Srinivasa TS, Ramreddy KY, Agrawal V, Nagdeve S, Parvez H. A comparative evaluation of transdermal diclofenac patch with oral diclofenac sodium as an analgesic drug following periodontal flap surgery: A randomized controlled clinical study. Indian J Dent Res. 2019 Jan-Feb;30(1):57-60.
62. Kaur H, Bansal N, Abraham R. A randomized, single-blind, placebo-controlled trial to evaluate the effectiveness of verbal behavior modification and acetaminophen on orthodontic pain. Angle Orthod. 2019 Jul;89(4):617–23.
63. Al-Melh MA, Nada A, Badr H, Andersson L. Effect of an Anesthetic Chewing Gum on the Initial Pain or Discomfort from Orthodontic Elastomeric Separator Placement. J Contemp Dent Pract. 2019 Nov 1;20(11):1286–92.
64. Tripathi T, Singh N, Rai P, Khanna N. Separation and pain perception of Elastomeric, Kesling and Kansal separators. Dent Press J Orthod. 2019 Apr;24(2):42.

65. Escalona-Rayo CF, Serrano-Castañeda P, López-Cervantes M, et al. Optimization of unidirectional mucoadhesive buccal patches based on chitosan and Pluronic® F-127 for metoprolol controlled release: in vitro and ex vivo evaluations. J Pharm Innov. 2020 Dec;15:556–568.
66. Anantharaj A, Sabu JM, Ramakrishna S, Jagdeesh RB, Praveen P, Shankarappa PR. A comparative evaluation of pain perception following topical application of benzocaine gel, clove-papaya based anesthetic gel and precooling of the injection site before intraoral injections in children. J Indian Soc Pedod Prev Dent. 2020 Apr-Jun;38(2):184-189.
67. Almallah MME, Hajeer MY, Almahdi WH, Burhan AS, Latifeh Y, Madkhaneh SK. Assessment of a single versus double application of low-level laser therapy in pain reduction following orthodontic elastomeric separation: A randomized controlled trial. Dent Med Probl. 2020 Jan-Mar;57(1):45-52.
68. Arabi M, Mortazavi SA, Jafariazar Z, Farhadnejad H, Alipour Harisa G, Fatahi Y. Fabrication and In-vitro Evaluation of Buccal Mucoadhesive Tablet of Meloxicam. Iran J Pharm Res. 2020 Summer;19(3):63-76.
69. Ridwan RD, Yuliati Y, Sidarningsih S, Sholihah FM, Aljunaid M, Lashari DM. A study of the mucoadhesive patches loaded with mangosteen peel extract in periodontitis. J Taibah Univ Med Sci. 2021 Aug 7;16(6):864–9.
70. Havale R, Rao DG, S P S, M Tuppadmath K, Tharay N, Mathew I, et al. Comparative evaluation of pain perception following topical application of clove oil, betel leaf extract, lignocaine gel, and ice prior to intraoral injection in children aged 6-10 years: a randomized control study. J Dent Anesth Pain Med. 2021 Aug;21(4):329–36.
71. Soheilifar S, Zandian M, Fathi H, Soheilifar S, Farhadian M, Soheilifar S. Effect of menthol on pain perception after placing brass wire separators: A split-mouth randomized controlled trial. Clin Investig Orthod. 2022 Jul 3;81(3):153–60.
72. Molania T, Malekzadeh Shafaroudi A, Saeedi M, Moosazadeh M, Valipour F, Rostamkalaei SS, et al. Evaluation of cinnamaldehyde mucoadhesive patches on minor recurrent aphthous stomatitis: a randomized, double-blind, placebo-controlled clinical trial. BMC Oral Health. 2022 Jun 14;22(1):235.
73. John NE, Erakkodan R, Sreelakshmi N. Efficacy of benzocaine and lidocaine bioadhesive patches in various minor oral surgical procedures in children - An evaluative study. Indian J Dent Res. 2023 Apr-Jun;34(2):145-149.
74. Thejasri K, Singaraju GS, Marya A, Priyanka JSY, Shaik S, Mandava P. Separation effect, pain perception during functional activity and gingival inflammation of elastomeric and Kansal separators-a split mouth study. Clin Oral Investig. 2023 Oct;27(10):6015–26.
75. Attar ES, Chaudhari VH, Deokar CG, Dyawanapelly S, Devarajan PV. Nano Drug Delivery Strategies for an Oral Bioenhanced Quercetin Formulation. Eur J Drug Metab Pharmacokinet. 2023 Sep;48(5):495-514.
76. Petluru H, Nirmala S, Nuvvula S. A comparative evaluation of peppermint oil and lignocaine spray as topical anesthetic agents prior to local anesthesia in children: a randomized clinical trial. J Dent Anesth Pain Med. 2024 Apr;24(2):119–28.
77. Park K. Park's Textbook of Preventive and Social Medicine. 21st ed. Jabalpur: M/S Banarsidas Bhanot; 2018.
78. Liljequist D, Elfving B, Skavberg Roaldsen K. Intraclass correlation – A discussion and demonstration of basic features. PLoS ONE. 2019 Jul 22;14(7):e0219854.
79. Ngan P, Kess B, Wilson S. Perception of discomfort by patients undergoing orthodontic treatment. Am J Orthod Dentofac Orthop Off Publ Am Assoc Orthod Its Const Soc Am Board Orthod. 1989 Jul;96(1):47–53.
80. Jahromi B, Pirvulescu I, Candido KD, Knezevic NN. Herbal Medicine for Pain Management: Efficacy and Drug Interactions. Pharmaceutics. 2021 Feb 11;13(2):251.
81. Liu C, Liu DQ, Tian YK, Mei W, Tian XB, Xu AJ, Zhou YQ. The Emerging Role of Quercetin in the Treatment of Chronic Pain. Curr Neuropharmacol. 2022 Nov 15;20(12):2346-2353.
82. Pahade A, Bajaj P, Shirbhate U, John HA. Recent Modalities in Pain Control and Local Anesthesia in Dentistry: A Narrative Review. Cureus. 2023 Nov 7;15(11):e48428.