The controlled release profile of risedronate emulgel to inhibit relapse movement in orthodontic treatment

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ABSTRACT

Introduction: Relapse is one of the undesirable effects of orthodontic treatment. Prevention of relapse has been carried out with the use of retainer devices. Several studies also have been carried out to prevent relapse with pharmacological agents such as bisphosphonates. One of the strongest bisphosphonates is risedronate. Systemic use of bisphosphonates can cause bisphosphonate-related necrosis of the jaw (BRONJ). Systemic effects can be minimised by topical preparations locally, where the virgin coconut oil (VCO) emulgel is one of the topical preparations which controls the release of drugs. This study aims to analyse the release profile of risedronate emulgel as a material to inhibit relapse movement. **Methods:** This research was conducted in an experimental laboratory. Group 1 was emulgel without bisphosphonate risedronate with virgin coconut oil (VCO), Group 2 was VCO emulgel with bisphosphonates risedronate, and Group 3 was a pure bisphosphonate risedronate solution. Each group weighing 100 mg was placed in 10 ml PBS, and the release test was conducted with UV/VIS Spectrophotometer wavelength λ 262 nm at intervals of 1, 2, 4, 8, 24, 48, and 96 hours with three replications at each group. **Results:** Grup 2 yielded a controlled drug release of risedronate until 96 hours, while a pure solution of risedronate resulted in an uncontrolled drug release of risedronate, which was released entirely in 4 hours. **Conclusion:** Risedronate emulgel with VCO had a controlled drug release compared to pure bisphosphonate solution to potentially be applied topically to inhibit relapse movement.

Keywords: relapse; emulgel; bisphosphonate risedronate; controlled release

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INTRODUCTION

Malocclusion is a deviation of dental occlusion from normal conditions and is the third-highest oral health problem.[1] Malocclusion can be corrected with orthodontic treatment[2], which aims to move teeth and affect orthopedically and the surrounding tissue.[3] However, orthodontic treatment has an undesirable effect, the relapse occurrence, which is the teeth state back to their

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original position before orthodontic treatment.[4,5] Relapse occurs due to osteoclast resorption and osteoblast formation around the alveolar bone.[6] Relapse can be prevented by orthodontic retention, which is the final stage of orthodontic treatment to maintain the teeth' position after orthodontic treatment using retainers.[7] Nevertheless, relapse incidence is still relatively high due to patient non-compliance in using retainers and several other factors that can cause relapses, so various studies have been developed to prevent relapse by using pharmacological therapy.

A study using pharmacological agents to prevent relapse by Zhao et al.[8] regarding local injection of osteoprotegerin (OPG) and succeeded in preventing relapse in rat teeth. Research by Esfahani et al.[9] utilised local simvastatin injection to reduce tooth root resorption associated with orthodontic treatment. Igarashi et al.[10] used a local injection of risedronate bisphosphonate to reduce tooth root resorption, and Kim et al.[11] employed systemic injection of pamidronate bisphosphonate to prevent tooth relapse. Bisphosphonates are drugs used to treat bone and calcium metabolism disorders.[12] This drug can prevent relapse by inhibiting osteoclast activity by giving the effect of osteoclast apoptosis. There are two types of bisphosphonates, non-nitrogen bisphosphonate (BP) and nitrogen bisphosphonate (N-BP).[13] N-BP is more effective in inhibiting bone resorption than BP[14], where one of the strongest examples of N-BP is risedronate.[15]

Bisphosphonates can cause side effects, which is known as bisphosphonate-related osteonecrosis of the jaw (BRONJ).[16] BRONJ is a necrotic bone condition in the oral cavity due to exposure to bisphosphonates that does not heal for eight weeks.[17] It is due to the duration, dosage, and route of administration of bisphosphonates intravenously and orally[16], which cause a systemic effect.[18]

Systemic effects can be avoided by topical preparations with local effects that maximise the drug in the target area.[19,20] Utari et al.[21] used hydrogel risedronate topical preparation to prevent relapse in guinea pigs; however, its application was still tricky to insert into the gingival groove. Besides, Parlina et al.[22] utilised zoledronate bisphosphonate emulgel topical preparation to increase osteoclast cell apoptosis.[22]

Emulgel is an emulsion that can be in oil-in-water or water-in-oil type, gelled and mixed with a gelling agent.[23] Emulgel preparations have several advantages, including a hydrophobic drug and good loading capacity, enabling production, low production costs, and controlled drug release.[24]

Making emulgel in this current study was conducted using virgin coconut oil (VCO). VCO contains a rich source of medium-chain fatty acids, especially lauric acid which has antiviral, antibacterial, anticaries, antiplaque, and antiprotozoal components. Another characteristic of VCO also has a smooth surface due to the fat content, which can be used to increase penetration.[19]

Emulgel has a mucoadhesive drug delivery system, which is a drug delivery system that interacts with the mucus layer on the surface of the mucosal epithelium and mucin molecules by forming intensive contact between the drug and the target area, thereby extending the residence time of drug preparations in the target area of application.[22,25] The mucoadhesive drug delivery system has a controlled drug release pattern.[25] Controlled drug release is the controlled release of drugs for less drug administration, more optimal drug use, and increasing patient compliance to drug use.[26] It is necessary to know the release profile when making a new preparation.[27]

The previous research on drug release profile has been conducted by Saito & Tabata using UV/VIS Spectrophotometer.[28] UV/VIS Spectrophotometer has the advantage of being accessible, specific, and low cost.[29] The bisphosphonate risedronate, which is the strongest N-BP, can prevent movement of relapse and should be prepared in the form of an emulgel with many advantages. However, previous studies using risedronate to inhibit tooth movement still use the injection method, which can have a systemic effect. Changing to an emulgel preparation is expected to avoid the side effects caused; therefore, this study aims to describe the release profile of risedronate emulgel as a material to inhibit relapse movement.

METHODS

Experimental laboratory research was conducted at the Laboratory of Pharmaceutical Technology and Laboratory of Molecular Medicine and

Therapy of the Faculty of Medicine and Health Sciences, Muhammadiyah University of Yogyakarta. The study used triplicate for three treatment groups. Treatment Group 1 was emulgel without bisphosphonate risedronate with virgin coconut oil (VCO), treatment Group 2 was emulgel bisphosphonate risedronate with VCO, and treatment Group 3 was a pure solution of bisphosphonate risedronate.

Risedronate bisphosphonate emulgel with VCO was processed by mixing 2 grams of carboxymethylcellulose (CMC), 5 grams of VCO, 2.05 grams of Tween 80, 1 gram of Span 80, 0.44 grams of sodium benzoate, and 0.009 grams of butylated hydroxytoluene (BHT), utilising Ultra Turrax homogenizer scale 2. Afterwards, 0.16 grams of risedronate in 1 ml of NaCl was added to the emulgel and mixed until homogeneous, using Ultra Turrax scale 2. The 100 mg emulgel produced was put into an ointment pot, where every 100 mg contained 0.16 mg of risedronate. Next, a pure bisphosphonate risedronate solution was prepared by mixing 0.16 grams of risedronate into 100 ml of phosphate buffer saline (PBS) on a hotplate stirrer at 37^{0}C for 20 minutes. Every 100 ml of solution contained 0.16 mg of risedronate.

The drug release test was performed with each group weighing 100 mg included in 10 ml PBS and incubated at 37°C. The supernatant was taken, and the PBS was replaced with a new one after 1, 2, 4, 8, 24, 48, and 96 hours. The absorbance value was measured using a UV/VIS Spectrophotometer at a wavelength of λ262 nm. The release percentage was calculated by dividing the total absorbance value by the absorbance value at X hour, and the result was converted to the percentage form.

The degradation test was performed with an emulgel sample without risedronate bisphosphonate with 100 mg VCO included in 10 ml PBS and incubated at 37°C. The supernatant was taken, and the PBS was replaced with a new one after 1, 2, 4, 8, 24, 48, and 96 hours. After 96 hours, the PBS solution was replaced with 1 N HCl, then incubated again for 48 hours until the sample was used. The absorbance value was measured and calculated with a similar method applied to the drug release test.

The data obtained were analysed with the Shapiro-Wilk test. The Group 1 test results showed that the data were normally distributed; therefore, the advance test was conducted using the one-way ANOVA test. Meanwhile, the test results for Group 2 and Group 3 revealed not normally distributed data; therefore, the proper test performed was the Kruskal-Wallis test.

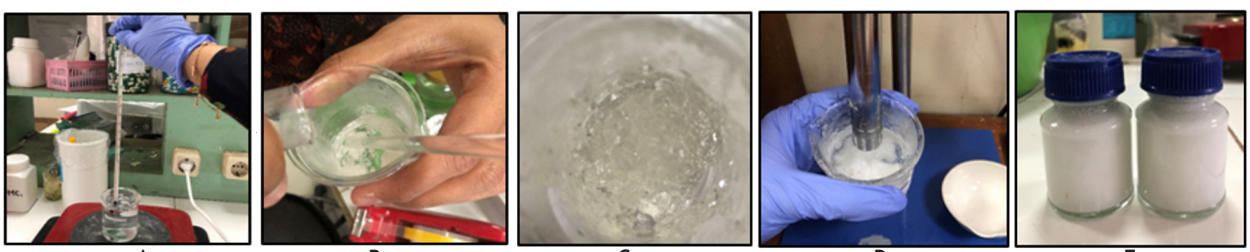

Figure 1. Emulgel process

A. Heat the aquadest over the electric stove; B. Add aquadest to Na-CMC; C. Na-CMC is allowed to expand 24 hours to make CMC; D. The ingredients are stirred with Ultra Turrax Scale 2; E. Emulgel in a Glass Pot Container store at 18°C.

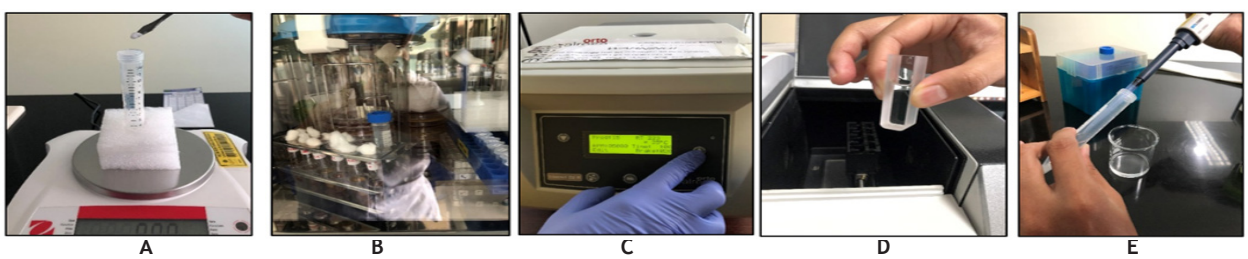

Figure 2. Test release

A. Add emulgel 100 mg into the Conicale tube; B. Risedronate bisphosphonate emulgel as a sample with VCO, incubated at 37°C; C. Centrifuge the sample at 5000 rpm for 15 minutes, then take 2.5 ml of sample and put it into cuvette; D. Insert the cuvette into the spectrophotometer UV/VIS cuvette holder; E. Replace the PBS solution and change with a new one.

RESULTS

Table 1. Absorbance value means of treatment groups at the wavelength of λ262 nm

Hours	Group 1 (VCO emulgel without risedronate bisphosphonate)	Group 2 (risedronate bisphosphonate emulgel with VCO)	Group 3 (pure risedronate bisphosphonate solution)
1	0.1519	0.2323	0.1539
2	0.0680	0.1313	0.0252
4	0.0392	0.0925	0.0072
8	0.0328	0.0813	0
24	0.0607	0.1447	0
48	0.0632	0.1432	0
96	0.1339	0.1771	0
HCl	0.0306	-	-
Total	**0.5804**	**1.0025**	**0.1863**

Table 1 presents the absorbance value of treatment groups: Group 1 (VCO emulgel without risedronate bisphosphonate); Group 2 (risedronate bisphosphonate emulgel with VCO); Group 3 (pure risedronate bisphosphonate solution); at the wavelength of 262 nm. Groups 2 and 3 revealed the highest absorbance values in the first hour. In Group 2, the absorbance value increased with release duration after the first hour. However, in Group 3, the absorbance value after the first hour decreased and showed no absorbance value after four hours.

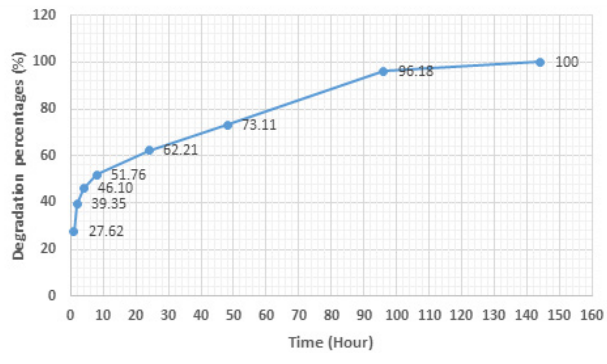

Figure 3. The degradation profile of Group 1

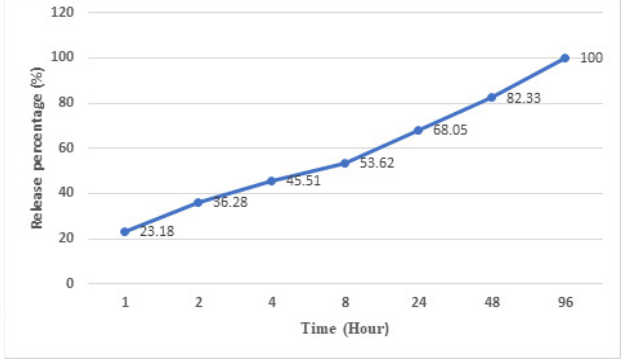

Figure 4. The release profile of Group 2

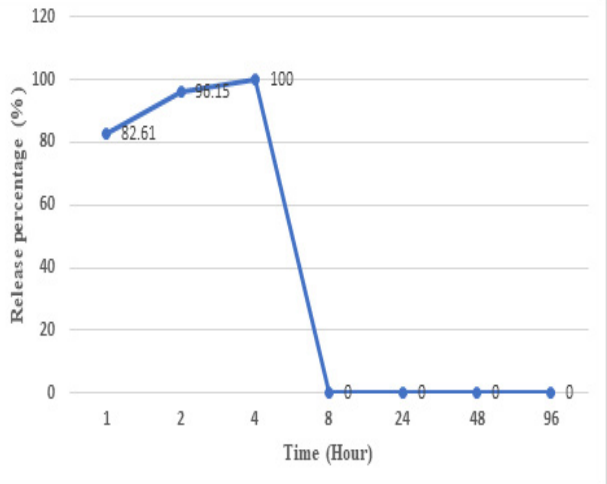

Figure 5. The release profile of Group 3

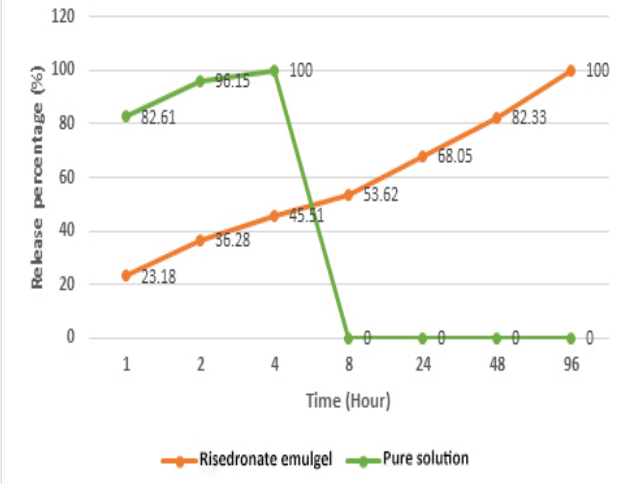

Figure 6. Comparison of release profiles of Group 2 and 3

Figure 3 presents the degradation profile of Group 1 (VCO emulgel without risedronate bisphosphonate), which showed significant degradation each hour. Within four hours, almost 50% of the emulgel was degraded, while at the same time, 45.51% of the risedronate was released in Group 2 (risedronate bisphosphonate emulgel with VCO) (Figure 4). The release profile of Group 3 (pure risedronate biphosphonate solution) was presented full release (100%) at four hours (Figure 5).

Figure 6 exhibits the comparison of release profiles for Group 2 and Group 3. Group 2 underwent a controlled release until 96 hours, while Group 3 showed uncontrolled release because it was entirely released after four hours.

Table 2. Normality test results of Group 1 (VCO emulgel without risedronate bisphosphonate)

		Kolmogorov-Smirnov (a)			Shapiro-Wilk		
	Time (hour)	Statistic	df	Sig	Statistic	df	Sig
Absorbance	1	0.355	3	0.0	0.819	3	0.161
	2	0.192	3	0.0	0.997	3	0.896
	4	0.191	3	0.0	0.997	3	0.900
	8	0.221	3	0.0	0.986	3	0.772
	24	0.265	3	0.0	0.953	3	0.583
	48	0.277	3	0.0	0.941	3	0.533
	96	0.343	3	0.0	0.843	3	0.222

(a) Lilliefors Significance Correction

Table 3. One-way ANOVA test results of Group 1 (VCO emulgel without risedronate bisphosphonate)

Absorbance	Sum of square	df	Mean square	F	Sig
Between groups	0.038	6	0.006	52.152	0.000
Within groups	0.002	14	0.000		
Total	**0.040**	**20**			

The statistical results for Group 1 are presented in Tables 2 and 3, which revealed that the normality test results had a significance value of $p \geq 0.05$, which suggested normally distributed data. The one-way ANOVA test results revealed a significance value of $p \leq 0.05$. The p-value$\leq$0.05 indicated a significant difference between the hour groups.

Table 4. Normality test results of Group 2 (risedronate bisphosphonate emulgel with VCO)

		Kolmogorov-Smirnov (a)			Shapiro-Wilk		
	Time (hour)	Statistic	df	Sig	Statistic	df	Sig
Absorbance	1	0.248	3	0.0	0.968	3	0.659
	2	0.201	3	0.0	0.995	3	0.859
	4	0.381	3	0.0	0.760	3	0.022
	8	0.315	3	0.0	0.891	3	0.358
	24	0.227	3	0.0	0.983	3	0.748
	48	0.214	3	0.0	0.989	3	0.802
	96	0.302	3	0.0	0.910	3	0.417

(a) Lilliefors Significance Correction

Table 5. Kruskal-Wallis test results of Group 2 (risedronate bisphosphonate emulgel with VCO)

Statistical tests (a, b)	
	Absorbance
Chi-square	17.825
df	6
Asymp. Sig.	0.007

The statistical results of Group 2, which are presented in Tables 4 and 5, showed the normality test results that the samples at hours 1, 2, 8, 24, 48, and 96 yielded a significance value of $p \geq 0.05$, where the distribution of sample data at that hour was normal. Meanwhile, at the 4th hour, it had a significance value of $p \leq 0.05$, indicating

that the sample data distribution at that hour was abnormal. The Kruskal Wallis statistical test results disclosed a significance value of 0.007 ($p \leq 0.05$). The sig p-value$\leq$0.05 signified a significant difference between the hour groups. Significant differences indicated differences in the amount of risedronate regardless of time.

The statistical results of Group 3 indicated that the normality test results of the sample at the 1st and 4th hours had a significance value of $p \geq 0.05$, where the distribution of sample data at that hour was normal. Meanwhile, at the 2nd hour, it had a significance value of $p \leq 0.05$, meaning that the sample data distribution at that hour was abnormal. Samples at the 8th, 24th, 48th, and 96th hours could not be assessed because the numbers were constant. The Kruskal-Wallis statistical test results exposed a significance value of 0.003 ($p \leq 0.05$). The sig p-value$\leq$0.05 suggested a significant difference between the hour groups. Significant differences signified differences in the amount of risedronate regardless of time. All of these results can be seen in Tables 6 and 7.

DISCUSSION

Group 1 experienced degradation with a significant difference in each time group results based on the present study results. Within 4 hours, as much as 47.13% emulgel could degrade, and as much as 100% emulgel could degrade within 96 hours. Parlina et al.[22] used a zoledronate emulgel with VCO to increase osteoclast apoptosis, where the emulgel used in the study was VCO and CMC. In this study, risedronate was used because risedronate is the strongest nitrogen bisphosphonate. The manufacture of emulgel in this study was carried out with the same process but using VCO with a different brand; however, the contents were the same. VCO was employed as the oil phase because of its advantages, namely containing polyphenols and α-tocopherols, which can reduce cholesterol, have antioxidant effects, and as a penetration enhancer.[19] Besides, CMC is a water-soluble fiber at room temperature used as a mucoadhesive polymer to adhere to the oral mucosa and as a thickening agent.[22,30]

The interaction between drug and polymer will result in controlled drug release.[31] Polymers in controlled drug release are utilized to increase drug stability and aid in drug release.[26] Moreover, CMC is a polymer with a hydrophilic matrix system.[32] The hydrophilic matrix system drug release occurs when the polymer swells in contact with the aqueous medium and forms a gel layer. In addition, CMC is known to have an erosive drug release mechanism.[33] Erosion of the drug release mechanism occurs when the polymer matrix dissolves, and then drug molecules are released.[32] Thus, CMC and VCO are used in making emulgel because of their advantages as polymers and penetration enhancers.

Group 2, compared to Group 3, experienced controlled release until 96 hours. Then, group 2 experienced burst release at 1 and 2 hours, and then the absorbance value decreased, followed by an increase in the absorbance value of risedronate, which was directly proportional to the length of release time. Therefore, it aligns with Berdey & Voyt[34] that emulgel is a biphasic semisolid preparation. Biphasic preparations will produce burst release, a condition in which the drug is released outside of the preparation particle; then, after being released, the drug on the inside of the particles will slowly release.[35] Shelke & Kulkarni[36] revealed that releasing the nifedipine emulgel resulted in an initial burst release, then released slowly after 2 hours. In Group 3, it can be seen that the absorbance value from 1 hour to 96 hours decreased and was released entirely in the fourth hour. Thus, it could be concluded that Group 3 did not experience controlled release.

The study results of Group 2 are consistent with Shelke & Sharma[37], who stated that the doxycycline hyclate and eugenol emulgel produced controlled release, whereas the doxycycline hyclate and eugenol emulgel released as much as 68-77% within 48 hours. A similar study was conducted by Wakhet et al.[38], which showed that hydrogel, emulgel, and bigel controlled release of the drug metronidazole, and there was no significant difference between the three dosages forms.

The research results of Group 3 are consistent with Altaani et al.[39], who compared injection release of teriparatide with teriparatide nanoemulsion. The injection release of teriparatide resulted in a rapid release, whereas the teriparatide nanoemulsion release caused a controlled release.[39] Similar research was

carried out by Fazil et al.[40], who demonstrated that a pure solution of risedronate resulted in a rapid, unsustainable release at the desired time compared to polymeric nanoparticles (NPs) of risedronate sodium, which caused controlled release.

Controlled release of drugs is one of the characteristics of drug preparations with a mucoadhesive delivery system. A mucoadhesive drug delivery system is a drug delivery system that interacts with the mucus layer on the mucosal epithelium and mucin molecules' surface and will prolong the residence time of drug preparations in the target area of application. This system works by establishing intensive contact between the drug preparation and the surface of the target area, thereby increasing the drug's therapeutic performance.[25] One topical preparation has a mucoadhesive drug delivery system, namely emulgel.[22]

Emulgel emits either oil-in-water or water-in-oil type, gelled and mixed with a gelling agent.[23] This preparation consists of two components, namely emulsion and gel.[41] An emulsion is a mixture of two or more immiscible liquids using an emulsifier to stabilize the dispersed phase.[42] Meanwhile, a gel is a semisolid system consisting of large and small molecules in a dilute liquid and then thickened using a gelling agent.[43] Emulgel is an example of a topical drug delivery preparation.[44]

Topical drug delivery is known to be a local drug application in the target area so that systemic effects can be avoided.[45] The advantages of topical drug delivery are that it avoids the first-pass metabolism, is easy to apply, avoids the risks and inconveniences of intravenous therapy and variations in adsorption effects, such as the presence of enzymes and pH changes, can absorb drugs in the target area, avoid gastrointestinal incompatibility, improve patient compliance, and can be used as self-medication.[41]

Risedronate is a white crystalline powder with a molecular weight of 283,112 g/mol, which is soluble in water and is absorbed in a wavelength of λ 262 nm UV Spectrophotometer.[29] Parlina et al [22], used zoledronate emulgel topical application to increase osteoclast cell apoptosis. Zoledronate and risedronate are the same types of drugs, and they are both N-BP13.

The same type of drug is included as a pharmaceutical equivalent. A pharmaceutical equivalent is a formulation containing the same type of drug, salt or ester of a therapeutic compound, dosage form, and route.[46] Besides, bisphosphonates are drugs used to treat bone diseases and disorders of calcium metabolism.[12] Bisphosphonates work by binding to hydroxyapatite at the hydroxyapatite binding site, commonly found in bone remodelling areas. When bisphosphonates enter the body, these drugs leave blood circulation and deposit on the bone surface, especially in osteoclast activity areas. After that, bisphosphonates will enter the osteoclasts and inhibit osteoclast activity by giving a toxic effect so that it ends with osteoclast apoptosis.[13] Bisphosphonates can cause BRONJ, a bone necrosis condition that does not heal in the oral cavity for eight weeks. It can be due to the duration, dose, and route of intravenous and oral administration of bisphosphonates, which have a systemic effect.[17]

Inhibition of bone resorption is known to prevent relapse.[47] Relapse is a condition in which the tooth returns to its pre-orthodontic position.[5] Orthodontic treatment affects orthopaedics and the surrounding tissue and aims to move the teeth[3]. Orthodontic treatment should be performed on malocclusion teeth.[48] because malocclusion is a relatively large deviation of normal occlusion and can cause dissatisfaction in function and aesthetics.[49]

CONCLUSIONS

Risedronate emulgel with VCO had a controlled drug release compared to pure bisphosphonate solution to potentially be applied topically to inhibit relapse movement. However, further research is needed regarding its stability and penetration tests on mucous membranes.

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