

A novel formulation for radiotherapy-induced oral mucositis: Triamcinolone acetonide mucoadhesive film

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Background: The main purpose of this study was to evaluate the effectiveness of triamcinolone acetonide (TA) mucoadhesive films versus placebo as a preventive and therapeutic intervention of oral mucositis (OM) induced by radiotherapy for head-and-neck cancer (HNC) patients. **Materials and Methods:** In this double-blind, randomized case-controlled clinical trial, 60 HNC patients were randomized to receive TA mucoadhesive films ($n = 30$) or placebo mucoadhesive films ($n = 30$) taken four times daily. Mucositis severity was assessed during the course of radiation therapy using the World Health Organization scales, and pain scores were assessed using visual analog scale. Repeated measures ANOVA was used for data analysis. **Results:** Mean \pm standard deviation age of the TA group was 58.53 ± 8.89 years and 60% were male, whereas in the placebo group, it was 56.46 ± 9.36 years and 56.7% were male ($P > 0.05$). The mean value of pain score was significantly reduced in the TA group (5.36 ± 1.29 vs. 2.20 ± 2.02) compared with the placebo group (5.34 ± 0.78 vs. 4.69 ± 0.77) during 4 weeks ($P < 0.001$); repeated measures ANOVA analysis showed that the mean value of grade mucositis was significantly reduced in the TA group (2.40 ± 0.49 vs. 0.96 ± 0.81) compared with the placebo group (2.36 ± 0.80 vs. 1.86 ± 0.93) during 4 weeks ($P < 0.001$). **Conclusion:** TA film could be considered as an effective approach for reducing the mucositis grading and pain score in the patients with OM.

Key words: Mucoadhesive film, oral mucositis, placebo, radiotherapy, triamcinolone acetonide

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INTRODUCTION

Today, both radiotherapy (RT) and chemotherapy are commonly used in the treatment of head-and-neck cancer (HNC) for nearly 80%–100% of the cases.^[1,2] These therapies not only have cytotoxic effects on tumor cells but also act on normal tissues with a high cell turnover. The oral mucosa represents a cellular compartment that possesses a high rate of cellular turnover. Disruption of the mucosal lining is associated with radiation therapy as a direct effect and as a secondary effect due to enhanced effects of physical, chemical, and microbial insults in the

mouth. Mucosal breakdown can become painful and may prevent the patients from eating, drinking, and speaking.

It is estimated that approximately 15% of patients treated with radical RT to the oral cavity and/or pharynx will require hospitalization for treatment-related complications. Ulcerative lesions of oral mucositis (OM) can cause significant pain, dysphasia, alteration in nutritional status, and increased risk for localized infections that could diffuse systemically while these complications can be distressing and be affecting negatively the patients' quality of life.^[3-11]

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The prevalence of this adverse effect depends on dosage, irradiated region, radiation protocol, and combination with RT.^[12,13] Other factors that may contribute to the severity of mucositis include continued smoking, the use of alcohol-based mouth rinses, and the presence of collagen vascular disease and HIV infection.^[14-18]

Until now, the treatment of OM has been challenged, and most of these studies show no consensus on the effective intervention for preventing or treating OM. Although nowadays a different type of triamcinolone acetonide (TA) is used for the treatment of OM, we are to present a kind of mucoadhesive films as a novel medication which can minimize the adverse effect of OM.

The main objective of this study was to evaluate the efficacy of TA mucoadhesive films in the treatment of mucositis and relief of pain associated with RT.

MATERIALS AND METHODS

Study design and intervention

The present study was a randomized, double-blind, case-control trial (NCT02075749) created to assess the safety and efficacy of TA mucoadhesive films in treating OM in HNC patients undergoing postoperative adjuvant or definitive RT. Considering type I error rate $\alpha = 0.05$ and statistical power $(1-\beta) = 80\%$ for detecting standardized effect size 0.8 according to the main outcome, the sample size was computed to be 26, and for compensatory possible retention, thirty patients in each group were recruited thus. Between June 2015 and February 2016, a total of sixty HNC patients in a university hospital were randomized to standard oral care plus TA (thirty patients) or placebo (thirty patients) taken four times daily (applied to the upper lip mucosal surface). We began the treatment when the mucositis with the World Health Organization (WHO) scales 2 and 3 was identified and continued for 4 weeks. The evaluation of safety and efficacy was diagnosed according to the adverse events, physical examination, laboratory determinations, vital signs, WHO scores, the ability to eat, body weight change, local control, and survival.

Eligibility criteria

The inclusion criteria were over 18 years of age, with documented histological diagnosis of HNC, and Grades 2 and 3 OM (as defined by the WHO scale). The severity of OM is commonly assessed by clinicians using the WHO oral toxicity scale, which is based on both objective and subjective criteria [Table 1],^[14] men and no pregnant women or women of childbearing age who were found not pregnant by pregnancy test or using medically prescribed contraceptives and an ability to remain in the study for its entire duration. The exclusion criteria were pregnant

Table 1: World Health Organization mucositis assessment scales

Grade 0	None
Grade 1	Soreness±erythema
Grade 2	Erythema, ulcers. Patient can swallow solid diet
Grade 3	Ulcers, extensive erythema. Patient cannot swallow solid diet
Grade 4	Mucositis to the extent that alimentation is not possible

women, concurrent RT, a history of heavy alcohol or drug abuse judged to be important by the investigator, concomitant therapy with an investigational drug, or cancer chemotherapeutics or immunosuppressive medications. Sensitivity or intolerance to the drug ingredients, lactose or similar formulations, inability to provide informed consent, actively bleeding gastric ulcer, severe esophageal reflux, major surgery, trauma or burns in the preceding 4 weeks, and clinically significant hepatic, neurologic, endocrine, or other systemic diseases that make implementation of the protocol or results difficult, were also defined as other exclusion criteria. Patients were also excluded if they had used investigational drug within 30 days before enrollment of this study. A medication compliance of <70% and visit compliance of <70% were also considered as dropout criteria.

The present study had two principal endpoints: first, the safety of the studied mucoadhesive films measured as the incidence of reported adverse events, abnormal physical and oral examination findings, laboratory determinations, and/or abnormal vital signs throughout the study, and second, the efficacy of TA measured as the incidence, severity, and duration of OM.^[13]

Treatment plan

RT was delivered in a two-dimensional cobalt-based technique. It was irradiated with 5600–6000 cGy in 28–30 fractions, daily 200 cGy per fraction. Informed consent was obtained from each participant who had the eligibility criteria, and they were randomized to one of the two groups after the occurrence of WHO Grades 2 and 3 mucositis, which were mostly observed at the 2nd week after the initiation of RT. The (HNC) RT normally did take 5–6 weeks, and the duration of the study (i.e., mucositis management with mucoadhesive films) was also about 4 weeks or until complete remission. As a result, RT and mucositis management were nearly completed simultaneously. One group received standard oral care plus TA applied four times daily (each film containing 0.5 mg TA); the other group received standard oral care plus placebo, composed of a formulation identical to that of the study product but containing no TA. The standard oral care included a frequent rinsing of the mouth with boiled water, regular toothbrushing and flossing habits, scaling, and plaque and

tartar removal during the course of RT. Patients or caregivers were instructed about using the study medications correctly. In addition, they were not allowed to use any form of analgesics or painkillers (e.g., paracetamol, lignocaine gel, nonsteroidal anti-inflammatory drug, or liquid morphine) before or during the study so as to prevent misinterpretation of visual analog scale (VAS) score assessed by investigators.

Following getting the patient's subjective assessment, two investigators carried out the clinical examination and independent rating of severity of mucositis independently, and the ascertainment of fulfillment of eligibility criteria, randomization to two groups including TA or placebo, was performed without further stratification and according to a randomization procedure by a third investigator who had no information about rating of severity preceding or current results of the treatment modalities within the present trial. To ensure advanced homogeneity of patient groups participating in the experimental and control groups and to exclude factors that could decrease the efficacy of the mucoadhesive application before the application of the drugs, a questionnaire form was used for each of the 60 patients, which included sociodemographic, individual, and illness-specific features. Treatment was stopped in case of complete response but continued for another period of 7 days in case of improvement without the complete resolution of symptoms and/or lesions. Treatment was discontinued in case of severe side effects or upon the patient's request.^[13]

Measurements (evaluation methods)

Researchers in this study collected data on the form including questions regarding gender, education level, presence of a systemic disease, cigarette use, nutrition, dentist visits prior to treatment, receipt of mouth care education, toothbrushing habits, presence of prosthesis, mouth dryness, loss of appetite, cancer stage, and length of disease. In addition, the WHO grade mucositis [Table 1] was used for the OM assessment of the patients. The patients were asked to place a mark corresponding to the degree of OM at the beginning of treatment (day = 1). By counting of used and unused films that were returned weekly, patients' compliance was assessed. Patients were evaluated weekly. Symptoms were assessed using VAS. Pain intensity was verified using a 10-cm (100-mm) VAS anchored by "no pain" at the one end and by "worst possible pain" at the opposite end. After instructing the patient with the goal of determining their pain score visually or numerically, the VAS was used to evaluate pain with the patient attributing a value that corresponded to the level of his or her pain. The threshold for efficient analgesia was defined as a 13-mm decline from the baseline VAS. In other words, at least a 13–30-mm decline on the scale was required to validate clinically significant pain relief. Symptoms evaluated by VAS were soreness/burning, pain on waking, pain with

drinking, pain with speaking, pain upon swallowing, dry mouth, burning with use of the study medications, and taste of the medication. Patients' use of caffeine-containing products, tobacco, and alcohol was noted.

Safety was assessed by physical examination, clinical laboratory testing of hematology (red blood cell count, indices, hemoglobin, hematocrit, white blood cell count, and differential and platelet count), biochemistry (blood urea nitrogen, creatinine, alkaline phosphates, serum glutamic oxaloacetic transaminase, lactate dehydrogenase, total protein, albumin, and electrolytes), urinalysis (pH, specific gravity, protein, glucose, ketones, and microscopic examination), and adverse experience evaluation.^[13]

Ethical consideration

Oral consent was obtained from the patients for their participation in the study before the questionnaire forms were administered. The patients were also informed of the study verbally. Participation was voluntary, and the patients could withdraw from the study at any time without giving a reason. Approval was obtained from the Ethics Committee of the Isfahan University of Medical Sciences.

Statistical analysis

Data were analyzed using the SPSS version 18.0 Statistical Package (SPSS Inc., Chicago, IL, USA). Quantitative and qualitative data were presented as mean \pm standard deviation (SD) and frequency (percentage). Normality of continuous data was evaluated using Kolmogorov–Smirnov test. Repeated measures ANOVA as a main statistical method was used for evaluating within- and between-group comparisons. Sphericity assumption was evaluated using Mauchly's test, and when it was violated, multivariate approach was adopted. Between-group comparisons were evaluated in each time point using independent samples *t*-test. Mann–Whitney U-test was used for comparing nonnormally distributed data between the groups. Qualitative data were compared between the groups using Chi-square test. Statistical significance level was set at $P < 0.05$.

RESULTS

Sixty patients were found to be eligible for this study. Mean \pm SD age of the TA group was 58.53 ± 8.89 years and 60% were male, whereas in the placebo group, it was 56.46 ± 9.36 years and 56.7% were male ($P > 0.05$). Distribution of sex, age, smoking, and status of denture of participants are shown in Table 2, which were not statistically significant difference between the two groups.

The repeated measures ANOVA showed that the mean value of pain scores among the two groups was statistically different ($P_{\text{Intervention}} < 0.05$). In addition, it showed that

significant decrease in both the groups was observed during the follow-up period ($P_{\text{Time}} < 0.05$), and we observed significant differences in terms of change over time between the two groups ($P_{\text{Time} \times \text{Intervention}} < 0.05$).

The comparison of mean pain score between the TA group and the placebo group in weeks 0, 1, and 2 showed no significant difference ($P > 0.05$), whereas the mean value of the pain score showed a significant difference between the groups in the 3rd and 4th weeks ($P < 0.05$), in which the mean of pain scores was significantly higher in the placebo group than the TA group [Table 3 and Figure 1].

Table 2: Baseline characteristics of the study participants

Variable	Control	Triamcinolone	P
Age	56.46±9.36	58.53±8.89	0.384*
Sex			
Male	17 (56.7)	18 (60)	0.793#
Female	13 (43.3)	12 (40)	
Smoking			
Yes	11 (36.7)	14 (46.7)	0.601#
Status of denture			
Yes	21 (70)	19 (63.3)	0.785#

Values are frequency (%) for categorical and mean±SD for quantitative variables. *Resulted from independent t-test; #Resulted from Chi-square test. SD=Standard deviation

Table 3: Comparison of the mean pain score in the study groups

	Control	Triamcinolone	P*
Pain score at week 0	5.34±0.78	5.36±1.29	0.935
Pain score at week 1	5.16±0.68	4.83±1.91	0.378
Pain score at week 2	4.96±0.67	4.56±1.67	0.428
Pain score at week 3	4.84±0.92	2.80±2.15	<0.001
Pain score at week 4	4.69±0.77	2.20±2.02	<0.001
P_{Time} #	0.016	<0.001	
$P_{\text{Intervention}}$ #	<0.001		
$P_{\text{Time} \times \text{Intervention}}$	<0.001		

Values are mean±SD. *Resulted from independent t-test; #Resulted from repeated measures ANOVA. SD=Standard deviation

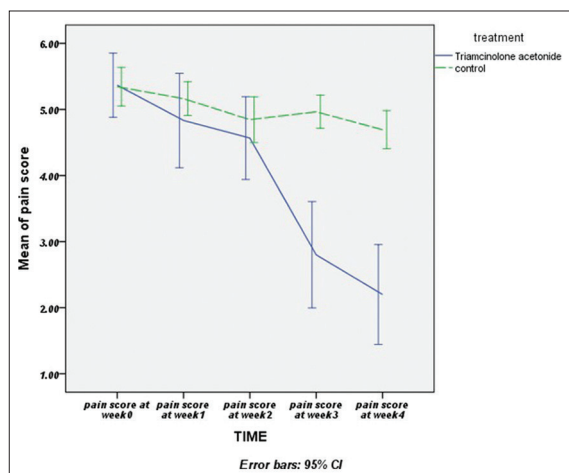


Figure 1: Mean pain score on the groups over study follow-up period

The mean value of grade mucositis between the TA group and the placebo group showed significant by repeated measures ANOVA ($P_{\text{Intervention}} < 0.05$). In addition, it showed that significant decrease in both the groups was observed during the follow-up period ($P_{\text{Time}} < 0.05$), and we observed significant differences in terms of change over time between the two groups ($P_{\text{Time} \times \text{Intervention}} < 0.05$).

The comparison of mean grade mucositis between the two groups in weeks 0, 1, and 2 showed no significant difference ($P > 0.05$), whereas the mean value of the grade mucositis showed a significant difference between the groups in the 3rd and 4th weeks ($P < 0.05$), in which the mean of grade mucositis was significantly higher in the placebo group than the TA group [Table 4 and Figure 2].

DISCUSSION

The management of OM remains a challenge and requires us to search for a standard care and to develop individualized care plans for improving patient outcomes. This is the first study to indicate an innovative formulation of TA as mucoadhesive film in reducing the grade mucositis and pain score associated with OM.

Kim *et al.* on an experimental animal study used triamcinolone acetonide (TAA)-loaded spray for the therapy of stomatitis. The spray formed a film containing TAA, Eudragit L, PEG 400, and ethanol at the drug dose of 1 mg with the excellent anti-inflammatory properties, similar to those of the commercial ointment. The results are congruent with our study.^[19]

The efficacy and safety of intralesional TA injection among ulcerative oral lichen planus (OLP) were assessed by Xia *et al.* The majority of their patients achieved lesion and pain resolution in ulcerative OLP. With regard to patients' satisfaction, this study is similar to ours.^[20]

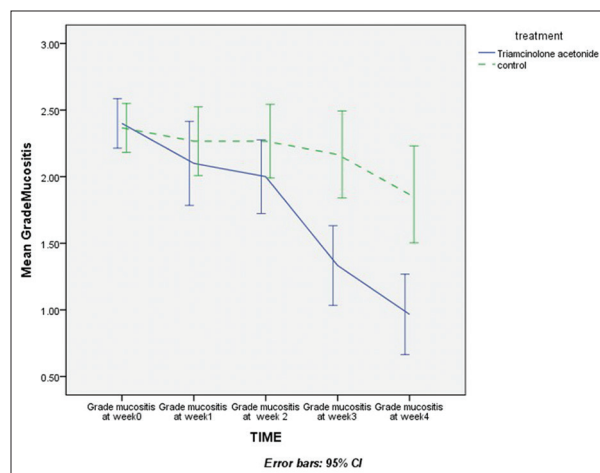


Figure 2: Mean grade mucositis on the groups over study follow-up period

Table 4: Comparison of the mean grade mucositis in the study groups

	Control	Triamcinolone	P*
Grade mucositis at week 0	2.36±0.80	2.40±0.49	0.848
Grade mucositis at week 1	2.23±0.81	2.10±0.84	0.537
Grade mucositis at week 2	2.20±0.76	2±0.74	0.307
Grade mucositis at week 3	1.96±0.92	1.33±0.80	0.006
Grade mucositis at week 4	1.86±0.93	0.96±0.81	<0.001
P _{Time} [#]	0.116	<0.001	
P _{Intervention} [#]	0.005		
P _{Time × intervention} [#]	<0.001		

Values are mean±SD. *Resulted from Mann-Whitney U-test; #Resulted from repeated measures ANOVA. SD=Standard deviation

In Iran, Abbasi *et al.* showed that TA oral paste (Adcortyl 0.1%) can decrease pain intensity, tingling, and size of recurrent aphthous stomatitis within 7 days.^[21]

Ungphaiboon *et al.* compared the therapeutic efficacy of TA mouthwash and commercially available TA paste for treatment of twenty patients with OLP after 1 month of administration. Response to treatment was assessed using VAS, the clinical score, and acceptance of patients. As a result, two formulations were developed applicable in improving the signs and symptoms of OLP; regarding the clinical response and patients' satisfaction, their results were consistent with our findings.^[22]

Based on the previous literature, it has been reported that the reduction of pain and oral inflammation is achieved using different types of oral medication containing gel, cream, paste, or adhesive forms. In the present study, we demonstrated a novel oral formulation as the mucoadhesive film with several advantages. These include by passing the hepatic first pass metabolism, improved drug bioavailability, and dose reduction which, consequently, will diminish side effects. . The possibility of covering taste for drugs with an unpleasant taste in mucoadhesive films by the use of taste masking strategy is a great advantage of this formulation that the patient can be satisfied with. Moreover, the prompt absorption, rapid onset of action, ease of transportation, beside convenient application and in one word, patient friendly nature of the drug are considered as the new formulation strengths.^[23,24]

Limitations

Like other researches in this field, this study had a major limitation.^[25] The study was conducted in a single university hospital with small sample size and specific patient population.

CONCLUSION

Overall, with respect to these properties, TA-mucoadhesive film can be proposed as an alternative therapy for

managing RT-induced mucositis. Although this treatment protocol has several advantages with approximately similar clinical outcome as to other preparations, we recommend an expanded multicentered study with different treatment protocols to be considered in designing of future researches.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Yen SH, Wang LW, Lin YH, Jen YM, Chung YL. Phenylbutyrate mouthwash mitigates oral mucositis during radiotherapy or chemoradiotherapy in patients with head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2012;82:1463-70.
- Barkokebas A, Silva IH, de Andrade SC, Carvalho AA, Gueiros LA, Paiva SM, *et al.* Impact of oral mucositis on oral-health-related quality of life of patients diagnosed with cancer. *J Oral Pathol Med* 2015;44:746-51.
- Anstay S. Communication. In: Penson J, Fisher R (eds). *Palliative Care for People with Cancer*. Arnold, London 1997. p. 168-246.
- Lionel D, Christophe L, Marc A, Jean-Luc C. Oral mucositis induced by anticancer treatments: physiopathology and treatments. *Ther Clin Risk Manag NotreDame* 2006;2:159-68.
- Avritscher E, Cooksley C, Elting L. Scope and epidemiology of cancer therapy-induced oral and gastrointestinal mucositis. *Semin Oncol Nurs Texas* 2004;20:3-10.
- Cheng K. Oral complications in patients with cancer. In: Kearney N, Richardson A (eds). *Nursing Patients with Cancer, Principles and Practice*. Elsevier, Edinburgh 2006. p. 575-600.
- Epstein JB, Wong FL. The efficacy of sucralfate suspension in the prevention of oral mucositis due to radiation therapy. *Int J Radiat Oncol Biol Phys* 1994;28:693-8.
- Clarke J, Edwards B, Srpek L, Regester G. Evaluation of bovine lactoferrin as a topical therapy for chemotherapy-induced mucositis in the golden Syrian hamster. *Oral Oncol* 1999;35:197-202.
- Clarkson JE, Worthington HV, Furness S, McCabe M, Khalid T, Meyer S, *et al.* Interventions for Treating Oral Mucositis for Patients with Cancer Receiving Treatment. *Cochrane Database Syst Rev* 2010;(8):CD001973.
- Cheng KK, Leung SF, Liang RH, Tai JW, Yeung RM, Thompson DR, *et al.* Severe oral mucositis associated with cancer therapy: Impact on oral functional status and quality of life. *Support Care Cancer* 2010;18:1477-85.
- Stone R, Flidner MC, Smiet AC. Management of oral mucositis in patients with cancer. *Eur J Oncol Nurs* 2005;9 Suppl 1:S24-32.
- Sahebjamee M, Mansourian A, Hajimirzamohammad M, Zadeh MT, Bekhradi R, Kazemian A, *et al.* Comparative efficacy of aloe vera and benzydamine mouthwashes on radiation-induced oral mucositis: A triple-blind, randomised, controlled clinical trial. *Oral Health Prev Dent* 2015;13:309-15.

13. Ghalayani P, Emami H, Pakravan F, Nasr Isfahani M. Comparison of triamcinolone acetonide mucoadhesive film with licorice mucoadhesive film on radiotherapy-induced oral mucositis: A randomized double-blinded clinical trial. *Asia Pac J Clin Oncol* 2017;13:e48-56.
14. Parulekar W, Mackenzie R, Bjarnason G, Jordan RC. Scoring oral mucositis. *Oral Oncol* 1998;34:63-71.
15. Rubenstein EB, Peterson DE, Schubert M, Keefe D, McGuire D, Epstein J, *et al.* Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer* 2004;100:2026-46.
16. Feller L, Essop R, Wood NH, Khammissa RA, Chikte UM, Meyerov R, *et al.* Chemotherapy- and radiotherapy-induced oral mucositis: Pathobiology, epidemiology and management. *SADJ* 2010;65:372-4.
17. Hejna M, Köstler WJ, Raderer M, Steger GG, Brodowicz T, Scheithauer W, *et al.* Decrease of duration and symptoms in chemotherapy-induced oral mucositis by topical GM-CSF: Results of a prospective randomised trial. *Eur J Cancer* 2001;37:1994-2002.
18. Goldberg SL, Chiang L, Selina N, Hamarman S. Patient perceptions about chemotherapy-induced oral mucositis: Implications for primary/secondary prophylaxis strategies. *Support Care Cancer* 2004;12:526-30.
19. Kim DW, Kim YI, Ud Din F, Cho KH, Kim JO, Choi HG, *et al.* Development of a novel triamcinolone acetonide-loaded spray solution for the treatment of stomatitis. *Pharmazie* 2014;69:512-7.
20. Xia J, Li C, Hong Y, Yang L, Huang Y, Cheng B, *et al.* Short-term clinical evaluation of intralesional triamcinolone acetonide injection for ulcerative oral lichen planus. *J Oral Pathol Med* 2006;35:327-31.
21. Abbasi F, Raoof M, Khatami R, Shadman N, Borjian-Borojeni F, Nazari F, *et al.* Effectiveness of amlexanox and adcortyl for the treatment of recurrent aphthous ulcers. *J Clin Exp Dent* 2016;8:e368-72.
22. Ungphaiboon S, Nittayananta W, Vuddhakul V, Maneenuan D, Kietthubthaw S, Wongpoowarak W, *et al.* Formulation and efficacy of triamcinolone acetonide mouthwash for treating oral lichen planus. *Am J Health Syst Pharm* 2005;62:485-91.
23. 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;9:29-35.
24. Silva BM, Borges AF, Silva C, Coelho JF, Simões S. Mucoadhesive oral films: The potential for unmet needs. *Int J Pharm* 2015;494:537-51.
25. Maree J, Combrink M, De Lange T, Toerien A, Bedeker M. Incidence, severity and management of cancer chemotherapy related oral mucositis in Eastern Cape and Western Cape. *Health SA Gesondheid, North America* 2012.