Journal of Applied Pharmaceutical Science Vol. 8(07), pp 078-084, July, 2018
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2018.8713
ISSN 2231-3354

Screening of two glucocorticoids in non-prescription skin whitening creams purchased via internet in Iraq by HPLC method

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ARTICLE INFO

Article history:
Received on: 22/02/2018
Accepted on: 20/06/2018
Available online: 30/07/2018

Key words:
Betamethasone, Clobetasol, HPLC, validation, whitening cream.

ABSTRACT

Using illegal lightening creams or preparations were reported widely throughout the world. Therefore, the present study aimed to the simultaneous determination of clobetasol 17-propionate (CB) and betamethasone 17-valerate (BM) in skin whitening creams purchased via internet from Iraqi market. The liquid chromatography was performed with Zorbax Eclipse Plus C18 (150 × 3.0 mm ID, 5 µm), mobile phase acetonitrile (70): water (30), the flow rate of 1 ml/min and a UV detector at 240 nm. The method was validated in terms of linearity, selectivity, precision, accuracy, limit of detection and quantification and stability of working solutions. The analytical method proved to be linear in the range of 1-40 µg/ml for both CB and BM. The limits of detection and quantification for CB and BM were (0.024 µg/ml, 0.075 µg/ml) and (0.035 µg/ml, 0.107 µg/ml), respectively, which revealed the sensitivity of the method. The precision, accuracy and stability study of working solutions of the method were between 0.52 to 1.93%, 97.87 to 100.55% and 0.48 to 1.72%, respectively. The results revealed that all purchased samples from beauty/cosmetic shops contained different levels of CB and/or BM. Moreover, the mixed preparations which purchased from the pharmacies also contained either CB or BM. The present study offers simple and sensitive analytical method to be used in the quality control laboratories and forensic point of view to identify illegal or counterfeit medicinal products or cosmetic preparations. Moreover, a new and restrict regulations must be implemented to ban the use of topical corticosteroids without prescription.

INTRODUCTION

Now a day, the easy access to internet provides consumers with different health services and support. Hence, upsurge the sale of medicine via internet without face to face interaction with a healthcare professional. This could lead to insufficient information about the safety and appropriate use of medicine or even potential hazard from their use (Bessell *et al*., 2003; Fittler *et al*., 2013). The revolution of using the internet and especially the social media is great in Iraq since 2007. The social media access and more precisely Facebook is now easier because it is offered free of charge by mobile network operators (Al-Hammadany and Heshmati, 2011). This lead to the growth of illegal cosmetics market or what is called black market via the internet.

Using illegal lightening creams or preparations were reported widely throughout the world (Del Giudice and Yves, 2002; Ly *et al*., 2007; AlGhamdi, 2010). Moreover, many articles documented the abuse of whitening creams among African or Asian populations or even in western countries (Huang *et al*., 2004; Nnoruka and Okoye, 2006; Olumide *et al*., 2008; Gaudiano *et al*., 2010; Nam *et al*., 2011). A recent study in Korea found that many cosmetic preparations manufactured there have been suspected to contain corticosteroid medicine (Nam *et al*., 2011). Misuse of corticosteroids drugs resulting with topical side effect when used for more than 3 weeks like skin atopy, masking of infections, acne as well as adrenal suppression (Harris and Hunter, 1988; Solomon *et al*., 1996). The adverse effects of topical corticosteroids have become more prevalent due to the introduction of high potency topical corticosteroids. These adverse effects were documented in the literature (Lagos and Maibach, 1998; Keane *et al*., 2001; Del Giudice and Yves, 2002; Mahé *et al*., 2003; Dey, 2014).

The previous study in Iraq showed that the most used topical corticosteroids were clobetasol 17-propionate (CB) and betamethasone 17-valerate (BM) (Al Dhalimi and Al Jawahiry,

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2006). Due to their side effects, it is necessary to control their exposure to human by identifying or quantifying their levels in the advertised online skin lightening creams. Moreover, there was paucity in the literature regarding the abuse of corticosteroid drugs in whitening preparations purchase via internet in the Middle East region. Hence, the aim of this study was to develop simple and sensitive reverse-phase high-performance liquid chromatography analysis for simultaneous quantification of CB and BM in skin whitening creams purchased via internet from Iraqi market.

MATERIALS AND METHODS

Purchasing samples

Samples were purchased via the internet. The Google search was used with the keywords: mixed preparation, whitening cream, lightening cream and delivery to all areas of Baghdad city (the capital city of Iraq). Twenty-five beauty/cosmetic shops and pharmacies (15 and 10, respectively) were reached. The samples were purchased by local collaborators. The beauty shops vendors or the pharmacists were asked for the most effective preparation for whitening or lightening cream which suitable for all parts of the body (especially the face) to purchase. All beauty/cosmetic shops and 5 pharmacies offered mixed preparations while only 5 pharmacies offer already marketed preparations. The collaborators purchase 1 cream jar (50 gm) for the mixed preparations and the other marketed preparations (one purchase from each shop or pharmacy).

For method development, CB and BM creams were purchased from the local pharmacies because whitening preparations are most often creams. All purchased creams were coded as C1 to C3 and B1 to B2 for CB and BM, respectively. The most available pharmaceutical products in Iraqi pharmacies were: Dermoden® (The State Company for Drugs Industry and Medical Appliances (SDI), Samarra, Iraq, C1), Dermovate® (GSK, Glaxo Operation UK Limited, Barnard Castle, UK, C2), Dermotan® (Ibn Hayyan Pharmaceuticals, Homs-Syria, C3) creams for CB. While the purchased pharmaceutical products for BM were: Betnovate® (GSK, Glaxo Operation UK Limited, Barnard Castle, UK, B1), Betnosam® (The State Company for Drugs Industry and Medical Appliances (SDI), Samarra, Iraq B2) and Vasone® (Philadelphia Pharmaceuticals, Amman, Jordan).

Instrumentation and chromatographic conditions

The Chromatography was performed with a Shimadzu LC-20AD delivery pump (Shimadzu, Japan) equipped with UV/Vis detector (SPD-20A, Shimadzu, Japan), the SIL-20A HT prominence autosampler (Shimadzu, Japan), DGU20A3 prominence degasser (Shimadzu, Japan), fitted with 100 µL sample loop and the chromatointegrator (CBM-20A prominence communications bus model, Shimadzu, Japan). The chromatographic separation of the analytes was achieved at 40°C (CTO-10AS VP, Shimadzu column oven) using a Zorbax Eclipse Plus C18 (150 × 3.0 mm ID, 5 µm) (Agilent, USA). The mobile phase consisted of acetonitrile: water (70:30 v/v) was filtered through a 0.45 µm nylon membrane filter (Whatman, UK) under vacuum. The analysis was carried out at a flow rate of 1.0 ml/min. The detector wavelength was set at 240 nm. The injection volume was 20 µL. Acetonitrile and methanol were HPLC grade (J. T. Baker Analyzed, China). Clobetasol 17-propionate (purity >98.0%) and betamethasone 17-valerate (purity >97.0%) standards were obtained from TCI (Tokyo Chemical Industry Co. LTD, Toshima KITA-KU, Tokyo, Japan).

Standard solutions

Stock solutions of CB and BM were prepared by dissolving 100 mg of each in 50 ml of methanol in order to give the concentration of 2 mg/ml. The working standards for CB and BM (1 to 40 µg/ml) were freshly prepared from the standard stock solution by serial dilution with the mobile phase.

Sample solution preparation

Twenty ml methanol was added to accurately weighted 1 gm of the purchased creams then vortexed for 10 min and sonicated for 30 min until preparation dissolved. Thereafter, filter through 0.45 µm Minisart microfilter (Sartorius, Germany) and made up the volume to 100 ml with mobile phase.

Method validation

Linearity

To evaluate the linearity of the method, six calibration curves for CB and BM in the concentration range of 1 to 40 µg/ml were prepared. The calibration curves were plotted for a peak area of the analytes against the corresponding concentrations (µg/ml) which obtained by linear regression analysis. Twenty µL aliquots were injected (six times) and eluted with the mobile phase under the reported chromatographic conditions. A recommended accepted criterion was regression coefficient (R^2) is ≥0.999 (CDER, 1994).

Selectivity

Due to unknown ingredients in the purchased samples, a preliminary study was done as suggested before (Kazakevich and Lobrutto, 2007). Spiked and unspiked samples were prepared for pharmaceutical preparations of CB and BM to determine the desired chromatographic conditions and to understand the behavior of the impurities in the analyte samples. Samples (C1 to C3 and B1 to B3) were prepared as sample solution method preparation (mentioned before) with the addition of 10 µg/ml CB or BM (spiked samples) or without the addition of standard solutions (unspiked samples).

Precision

The intra-day and inter-day precision were evaluated by analyzing quality control samples at low, medium and high concentrations (1, 10 and 40 µg/ml) of CB and BM working standard solution. For the intra-day variation, sets of six replicates of quality control samples were analyzed on the same day and for the inter-day validation, six replicates of quality control samples were analyzed on three different days (Shaikh *et al*., 2008; Sahib, 2016). A recommended accepted criterion was %RSD < 2.0 (CDER, 1994).

Accuracy

A recovery study was carried out by standard additions method. All pharmaceutical preparations (C1 to C3 and B1 to B3)

were spiked with CB and BM in 80, 100, and 120% of the target test concentrations. Three replicate of each level was performed (Sahib, 2018). A recommended accepted criterion was %RSD < 2.0 (CDER, 1994).

Limits of detection and quantification

The sensitivity of the method was determined based on the standard deviation of the response and the slope as described before (ICH, 2005; Sahib *et al*., 2011). The limit of detection (LOD) and quantification (LOQ) were calculated according to the following equations:

$$LOD = 3.3\ \sigma/S; \qquad LOQ = 10\ \sigma/S,$$

where σ = the standard deviation of the response; S = the slope of the calibration curve.

Solution stability

Reference solutions were stored in the refrigerator for 14 days and re-analyzed in an injection sequence by employing freshly prepared standard solutions for a short-term stability. The above experiments were performed by using low, medium and high-quality control samples (Mohammadi *et al*., 2007; Sahib *et al*., 2010). A recommended accepted criterion was %RSD < 2.0 (CDER, 1994).

Method robustness

The robustness of the suggested method was assessed as a function of altering acetonitrile: water volume ratio and temperature; the changes were over a range of ±5% of the target experimental condition. The concentration of solution analyzed was 20 µg/ml (n = 6). A recommended accepted criterion was %RSD < 2.0 (CDER, 1994).

RESULTS AND DISCUSSION

Selectivity and system suitability

The study revealed that the column used in this study showed good selectivity. The column Zorbax Eclipse plus C18 was selected as especially suited for this study as it can achieve excellent peak shape with greater resolution and accuracy (Figure 1A). Regarding system suitability, 10 µg/ml of the mixture of CB and BM were injected five times. The results of system suitability were shown in Table 1. The mean resolution value between CB and BM peaks was 2.8 (%RSD: 0.01). All parameters were within acceptable values (CDER, 1994). Moreover, the results showed good peaks separation and resolution between CB and BM and the other excipients in their cream pharmaceutical formulations (Figure 1B and 1C). Moreover, no significant interfering peaks from the excipients were found at the specified retention time of the analysts in the purchased samples (Figure 1D). Hence, the developed analytical method was suitable and selective for CB and BM analysis in different formulations. Moreover, the method robustness results showed no marked changes in the chromatograms demonstrated with %RSD range from 0.05 to 1.88. The low values of the %RSD indicated the robustness of the suggested method.

Table 1: System suitability for simultaneous determination of Clobetasol 17- Propionate and Betamethasone 17-Valerate.

	Clobetasol 17- Propionate				Betamethasone 17-Valerate			
Injection	t_R	Area	N	Tailing factor	t_R	Area	N	Tailing factor
1	6.056	414345	9507	1.13	6.697	384484	10152	1.109
2	6.055	414144	9422	1.125	6.692	384155	9988	1.115
3	6.056	413985	9376	1.127	6.698	384100	9876	1.103
4	6.055	414104	9401	1.129	6.697	384330	10115	1.105
5	6.053	413860	9366	1.122	6.695	384560	10028	1.114
Mean	6.055	414087.6	9414.4	1.127	6.696	384325.8	10031.8	1.109
%RSD	0.020	0.044	0.597	0.285	0.036	0.052	1.087	0.479

t_R: retention time; N: theoretical plate number.

Linearity

The linear regression equation, correlation coefficient (R^2) and the limit of the detection and quantification in the analytical profile for CB and BM are listed in Table 2. The LOQ of this method allows the quantitation of both CB and BM even at ranges that are more typically addressed by the HPLC-Mass method.

Precision

Under the prescribed conditions, the precision is the closeness of agreement in the measurements of the same homogenous sample in different time intervals (ICH, 2005). The intra- and inter-day precisions (expressed as %RSD) were a ranged from 0.52 to 1.93. The %RSD of the peak area of six replicates was found to be within acceptable limits (Épshtein, 2004; Reolon *et al*., 2018). Table 3 shows the precision study results.

Table 2: Calibration curve results summary for Clobetasol 17-Propionate and Betamethasone 17-Valerate, n = 6.

Parameter	Clobetasol 17-Propionate	Betamethasone 17-Valerate
Concentration (µg/ml)	1, 5, 10, 20, 40	1, 5, 10, 20, 40
Regression equation	$y = 42013x - 6017.1$	$y = 36703x + 9988.2$
R^2	0.9999	0.9995
LOD (µg/ml)	0.024	0.035
LOQ (µg/ml)	0.075	0.107

R^2: correlation coefficient; LOD: limit of detection; LOQ: limit of quantification.

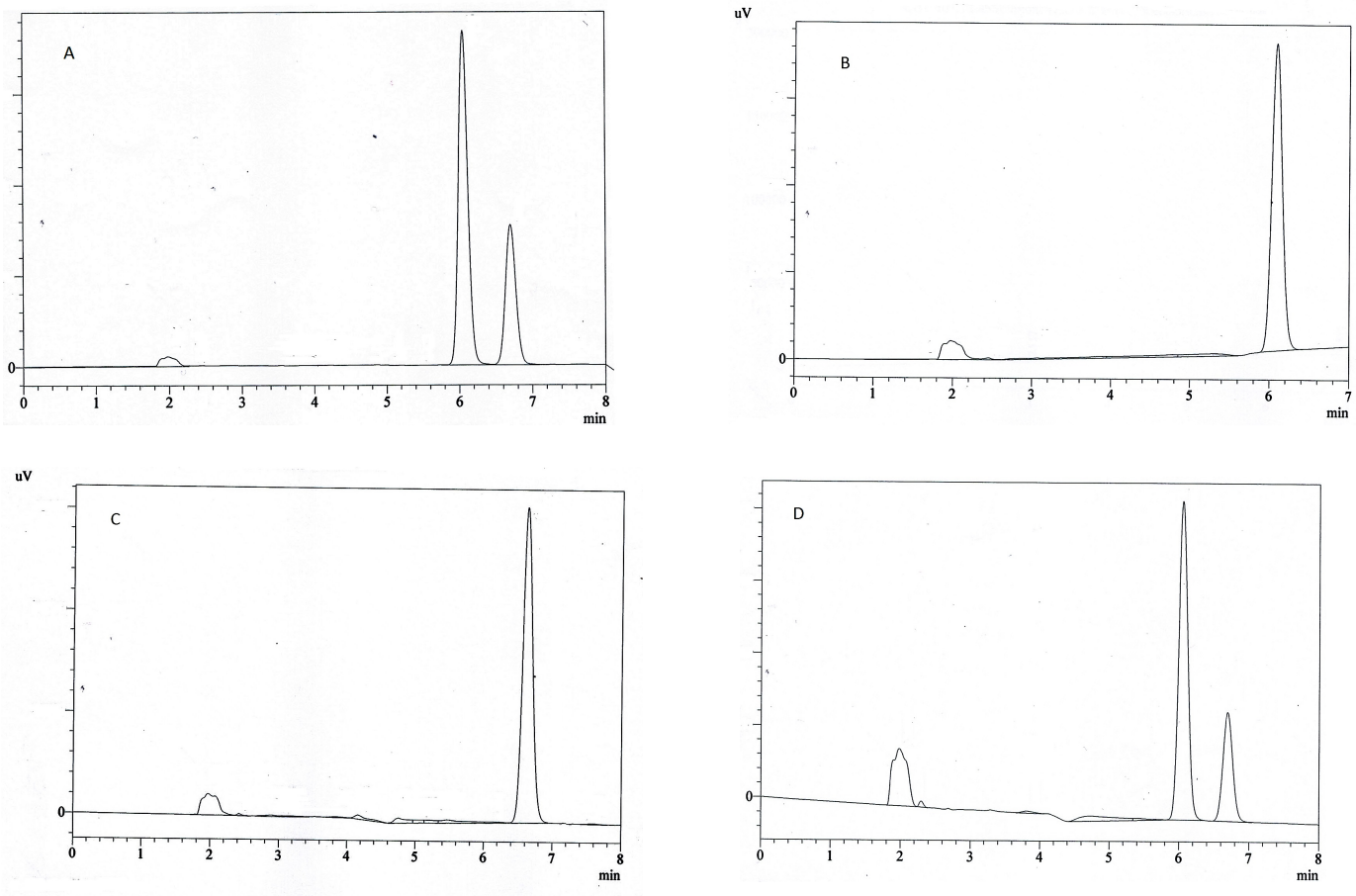

Fig. 1: Representative chromatogram of clobetasol 17-propionate (retention time 6.05 min) and Betamethasone 17-valerate (retention time 6.69 min, A); extracted Dermoden® (retention time 6.05 min, B); extracted Betnosam® (retention time 6.69 min, C); extracted sample number 7 (retention time 6.05 and 6.69 min, respectively, D).

Table 3: Intra-day and inter-day analysis and stability of the proposed analytical method of Clobetasol 17-Propionate and Betamethasone 17-Valerate.

Compounds	Theoretical concentration (µg/ml)	Concentration mean ± SD (%RSD)		Solution stability Concentration mean ± SD (%RSD)
		Intra-day*	Inter-day**	
Clobetasol 17-Propionate	1	0.997 ± 0.018 (1.80)	0.996 ± 0.019 (1.93)	1.00 ± 0.013 (1.38)
	10	9.988 ± 0.121 (1.22)	9.969 ± 0.156 (1.569)	9.933 ± 0.140 (1.41)
	40	39.996 ± 0.238 (0.59)	39.917 ± 0.273 (0.685)	39.903 ± 0.293 (0.73)
Betamethasone 17-Valerate	1	0.994 ± 0.017 (1.69)	0.999 ± 0.018 (1.88)	0.990 ± 0.015 (1.57)
	10	10.043 ± 0.131 (1.31)	9.907 ± 0.156 (1.57)	9.940 ± 0.171 (1.72)
	40	39.945 ± 0.296 (0.74)	39.925 ± 0.211 (0.52)	39.91 ± 0.914 (0.48)

*n = 6; **n = 18, six replicate in three different days.

Accuracy

The mean recovery percentages were a range between 97.87% and 100.55% (Table 4). In addition, the %RSD values were a range between 0.38% and 1.75%. The results revealed that the proposed method was within the acceptable limits and accurate with negligible systematic error (Sahib *et al*., 2011; Prabaningdyah *et al*., 2017).

Assay of the purchased whitening creams

The results of the present study showed that all purchased products from the beauty/cosmetic shops were contained different levels of CB and/or BM (Table 5). Moreover, the mixed preparations which purchased from the pharmacies also contain either CB or BM. Only 5 pharmacies offered commercially available products. Two of them contain corticosteroid drug (Mometasone Furoate 0.1%) and the other only contain bleaching/whitening agents.

This study showed that the use of topical corticosteroids is still uncontrolled in Iraqi community. The previous report from Iraq showed that 65.7% of the sample population were used topical corticosteroids for lightning effect (Al Dhalimi and Al Jawahiry, 2006). Other studies also showed a higher prevalence of using corticosteroids alone or in combinations with other whitening agents (Pitche *et al*., 1997; Wone *et al*., 2000; Adebajo, 2002; Nnoruka and Okoye, 2006; Saraswat *et al*., 2011). The Saudi Arabia study showed that 20.8% of the sample population was ready to use any whitening cream even the components were unknown if these cream give fast results (AlGhamdi, 2010). Other report showed that 25% of the sample population had used whitening products of unknown composition (Del Giudice and Yves, 2002). Moreover,

other researchers showed that the population had the awareness of the adverse effect of whitening cream but they did not have the knowledge of these products or how it was used (Dlova *et al*., 2014). Hence, using corticosteroids as a whitening agent is a global problem which needs to be addressed.

Table 4: Recovery study results of spiked and unspiked samples of Clobetasol 17-Propionate and Betamethasone 17-Valerate pharmaceutical creams.

Compound	Formula*	Concentration of the sample (mg/gm), Mean ± SD**	Spiked concentration (µg/ml)	Recovery (%) Mean ± SD (%RSD)
Clobetasol 17-Propionate	C1	0.493 ± 0.001	-	98.666 ± 1.320 (1.33)
	C1	0.887 ± 0.013	400	98.65 ± 1.554 (1.57)
	C1	0.986 ± 0.012	500	98.64 ± 1.202 (1.21)
	C1	1.090 ± 0.001	600	99.16 ± 0.876 (0.88)
	C2	0.491 ± 0.001	-	98.20 ± 1.070 (1.09)
	C2	0.885 ± 0.010	400	98.35 ± 1.194 (1.21)
	C2	0.978 ± 0.001	500	97.87 ± 0.729 (0.74)
	C2	1.090 ± 0.001	600	99.15 ± 0.888 (0.89)
	C3	0.492 ± 0.001	-	98.40 ± 0.650 (0.66)
	C3	0.881 ± 0.001	400	97.91 ± 1.043 (1.06)
	C3	0.983 ± 0.000	500	98.30 ± 0.495 (0.50)
	C3	1.091 ± 0.013	600	99.18 ± 1.233 (1.24)
Betamethasone 17-Valerate	B1	0.997 ± 0.001	-	99.71 ± 0.503 (0.50)
	B1	1.767 ± 0.025	800	98.21 ± 1.422 (1.44)
	B1	1.983 ± 0.023	1000	99.18 ± 1.172 (1.18)
	B1	2.164 ± 0.036	1200	98.39 ± 1.662 (1.68)
	B2	0.995 ± 0.001	-	99.56 ± 0.880 (0.88)
	B2	1.786 ± 0.031	800	99.27 ± 1.741 (1.75)
	B2	2.011 ± 0.016	1000	100.55 ± 0.828 (0.82)
	B2	2.181 ± 0.024	1200	99.16 ± 1.094 (1.10)
	B3	0.992 ± 0.004	-	99.253 ± 0.474 (0.47)
	B3	1.781 ± 0.028	800	98.96 ± 1.560 (1.57)
	B3	1.988 ± 0.020	1000	99.40 ± 1.028 (1.03)
	B3	2.172 ± 0.001	1200	98.75 ± 0.384 (0.38)

*C1 to C3 and B1 to B3 represent Clobetasol 17-Propionate and Betamethasone 17-Valerate in pharmaceutical creams; ** represent 3 replicates.

Table 5: Quantification of Clobetasol 17-Propionate and Betamethasone 17-Valerate in the purchased samples via the internet.

Sample*	Type of sample**	Amount detected (mg/g) cream	
		Clobetasol 17-Propionate	Betamethasone 17-Valerate
1	Mixed preparation	0.176	0.25
2	Mixed preparation	0.265	-
3	Mixed preparation	-	0.564
4	Mixed preparation	0.187	0.442
5	Mixed preparation	0.364	-
6	Mixed preparation	-	0.477
7	Mixed preparation	0.331	0.322
8	Mixed preparation	0.162	-
9	Mixed preparation	0.364	-
10	Mixed preparation	0.411	-
11	Mixed preparation	0.262	-
12	Mixed preparation	-	0.775
13	Mixed preparation	-	0.433
14	Mixed preparation	0.210	0.339
15	Mixed preparation	0.243	-
16	Mixed preparation	0.321	-
17	Mixed preparation	0.211	-
18	Mixed preparation	0.342	-
19	Mixed preparation	0.211	-
20	Mixed preparation	0.265	-
21	Melanot®	-	-
22	Philaquin Forte®	-	-
23	Eldoquin Forte®	-	-
24	Melacare®	-	-
25	Elocon®	-	-

*Samples 1 to 15 and samples 16 to 25 were purchased from Beauty/cosmetic shops and pharmacies, respectively. **Melanot® (Glycolic acid 10%, Arbutin 5%, Kojic acid 2%; Forte Pharma Laboratories, Monaco, France); Philaquin Forte® (Hydroquinone 4%, Philadelphia Pharmaceuticals, Amman, Jordan); Eldoquin Forte® (Hydroquinone 4%, ICN Pharmaceuticals Inc, California, USA); Melacare® (Hydroquinone 2%, Tretinoin 0.025%, Mometasone Furoate 0.1%, Ajanta Pharm Limited, Mumbai, India); Elocon® (Mometasone Furoate 0.1%, Universal Pharmaceutical Industry, Damascus, Syria).

Furthermore, the results revealed that using corticosteroids as whitening or depigmenting agent is still a common practice among Iraqi pharmacists. The result is consistent with the previous report in that the pharmacists responsible for the incorrect use or abuse of the medications (Al Dhalimi and Al Jawahiry, 2006). The present study showed another way to abuse medications by black market via the internet and, unfortunately, the pharmacists were involved in that. The present result was in agreement with another report. Al Dhalimi *et al*. showed that other persons beside the pharmacists were responsible for corticosteroids abuse like paramedical personnel (27%), self, friend or family member (20%), street vendor (20%), physician (11%) and dermatologist (4%) (Al Dhalimi and Al Jawahiry, 2006).

Therefore, the community based educational program is an urgent need to increase the knowledge and practice regarding the use of skin lightening agents. In addition, psychological aspects must be addressed or evaluated for this purpose because hyperpigmentation disorders have a great impact on the motivation of using lightening preparations, as well as, the quality of life (Ladizinski *et al*., 2011).

CONCLUSION

The present study offers simple and sensitive analytical method to be used in the quality control laboratories and forensic point of view to identify illegal or counterfeit medicinal products or cosmetic preparations. In addition, the simultaneous determination of CB and BM could potentially reduce the laboratory supply costs associated with a testing method for individual drugs. Moreover, a new and restrict regulations must be implemented to ban the use or purchase of topical corticosteroids without prescription.

CONFLICTS OF INTERESTS

The author has none to declare.

FUNDING SOURCES

The author has none to declare.

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How to cite this article:
Sahib MN. Screening of two glucocorticoids in non-prescription skin whitening creams purchased via internet in Iraq by HPLC method. J App Pharm Sci, 2018; 8(07): 078-084.