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Analysis of cranial measures in the function of sex determination

Rifat Kesetovic[1], Vedo Tuco[1], Nevena Poljasevic[2]

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Abstract

Forensic anthropology was concerned with the problem of sex detrmination in different ways, including sex determination by measurements and morfology of skull. In this studyten separate measurements were measured: maximal cranial length, maximal cranial breadth, maximum cranial height, bizygomatic breadth, basion-prostion, nasion-prostion, basion-nasion, orbital width, orbital height and upper facial height. Sample consisted of 96 adult male and 28 adult female skulls. The logistic regression analysis showed that sex is significant predictor of all used variables. It would be highly desirable to measure on a large number of male and female skulls to provide formula for Bosnian population.

Key words: cranial measures, sex determination

Introduction

Although forensic Dna analysis is powerful tool for identification of skeletal remains, providing sex determination of victim also, traditional anthropological methods are still very important in this process, especially when it is not possible to isolate the genetic material from the bone for any reason. Forensic anthropology was concerned with the problem of sex detrmination in different ways, including sex determination by measurements and morfology of skull. In general, male bones are recognizable by their size and robustness, but in the case of robust series of female skulls could be classified as male. Discriminant function analysis should be used for skulls associated with the series for which the function can bind (Keen 1950). Kajanoja (1966) study 232 Finnish skull from Department of anatomy University of Helsinki. Most of skulls originated from autopsy room, less number from graves, and some of them are archeological excavation, known names, places and date of birth. Author has derived two function from 8 measures and correctly differentiated sex in 79,4% males and 79,1% females. Giles, Elliot (1963) made the formula on the basis of a study of 1022 specimens on american whites and blacks, which yielded results 82,9% correct for sex determination regardless of racial origin and this function correctly differentiated sex in 65% of Finnish series.

Material and methods

In this study 96 adult male and 28 adult female skulls are measured. Identification and sex determination of skulls was performed by dna analysis.

The following linear measures and diameters are measured (Martin and Saller 1957), (Rogers Spencer Lee, 1984).

Maximum cranial length: distance from*glabella*to*opisthocranion* (spreading caliper)

Maximum cranial breadth: maximum distance perpendicular to the median sagittal plan and above supramastoidal crests (spreading caliper)

Maximum cranialheight: distance from *basion* to *bregma* (spreading caliper)

Bizygomaticbreadth: *zygion-zygion*, greatest width between zygomatic arches (spreading caliper)

Basion-prostion diameter: distance from *basion* to *prostion* (spreading caliper)

Nasion-prostion diameter: distance from *nasion* to *prostion* (sliding caliper)

Basion- nasion height: distance from *basion* to *nasion* (spreading caliper)

Orbital width: distance from the *dacryon* to the middle of the external border of the orbit, the *ectoconchion.* (sliding caliper)

Orbital height: distance from the upper to the lower borders of the orbit in the middle of the orbit at right angles to the horizontal axis used in measuring the width. (sliding caliper)

Upper facial height: Distance from *nasion* to *upper alveolar point* (sliding caliper)

Results

Data analysis was performed by the method of parametric statistic. Measures of central tendency and dispersion measures have been calculated. From the central tendency measurements the arithmetic mean, median and modus was calculated, while the standard devation from dispersion measures, the minimum and maximum results. To determined significant gender differences in gender and applied variables, t-test was used for an independent sample of respondents. In order to verify the gender impact as a predictor of the criterion variables, a logistic regression analysis was performed. Research data is processed in the SPSS 20. for Windows statistical package.

Table 1 shows measures of central tendency and dispersion measures in male subjects. The arithmetic mean on the variable maximum cranial length is 176,69±7,24, median 179, mod 175 while the minimum and maximum results range from 160 to 200. The arithmetic mean on the variable maximum cranial breadth is 151,16±5,35, median 151,25, mod 150, while the minimum and maximum results range from 138,50 to168. The average cumulative height valueis 138,08, while the lowest height is 124 an highest 150. The mean value of the orbital width is 39,27±2,03, the height is 34,03±2,34, and the average value of upper facial height is 71,62±3,78.

Table 2 shows measures of central tendency and dispersion measures in female subjects. The arithmetic mean on the variable maximum cranial length is 170,77±7,16, median 173,50, mod 162 while the minimum and maximum results range from 155 to 180. The arithmetic mean on the variable maximum cranial breadth is 142,83±7,65, median 143, mod 145, while the minimum and maximum results range from 128 to166. The average cumulative height valueis 132,61, while the lowest height is 123 an highest 145. The mean value of the orbital width is 37,68±1,13, the height is 34,80±3,12, and the average value of upper facial height is 64,88±9,03.

Table 1. Measures of central tendency and dispersion measures in male subjects

Variable	AS	MED	MOD	SD	VAR	MIN	MAX
Maximum cranial length	179,69	179,00	175,00	7,24	52,37	160,00	200,00
Maximum cranial breadth	151,16	151,25	150,00	5,35	28,65	138,50	168,00
Maximum cranial height	138,02	138,25	135,00	5,33	28,45	124,00	150,00
Bizigomatic breadth	135,50	135,00	134,00	5,25	27,59	116,00	147,00
Basion prostion	94,75	94,50	91,00	5,82	33,84	83,60	118,00
Nasion prostion	67,16	66,50	65,00	5,40	29,11	58,50	93,10
Basion nasion	103,68	103,00	104,00	4,75	22,53	96,00	120,00
Orbital width	39,27	39,00	39,00	2,03	4,13	35,00	45,20
Orbital height	34,03	33,70	33,00	2,34	5,47	28,80	40,70
Upper facial height	71,62	71,70	71,60	3,78	14,32	63,40	81,40

Tabela 2. Measures of central tendency and dispersion measures in female subjects

Variable	AS	MED	MOD	SD	VAR	MIN	MAX
Maximum cranial length	170,77	173,50	162,00	7,16	51,22	155,00	180,00
Maximum cranial breadth	142,83	143,00	145,00	7,65	58,58	128,00	166,00
Maximum cranial height	132,61	130,75	126,00	6,38	40,71	123,00	145,00
Bizigomatic breadth	121,71	121,00	125,00	3,64	13,24	117,00	126,00
Basion prostion	-	-	-	-	-	-	-
Nasion prostion	-	-	-	-	-	-	-
Basion nasion	-	-	-	-	-	-	-
Orbital width	37,68	37,50	37,00	1,13	1,27	36,30	39,30
Orbital height	34,80	34,00	31,00	3,12	9,75	31,00	39,70
Upper facial height	64,88	62,20	62,00	9,03	81,47	55,70	90,70

Table 3. t-test results for an independent sample of respondents

Variable	Sex	AS	SD	t	p
Maximum cranial length	Male	179,69	7,24	5,41	**0,00**
	Female	170,77	7,16		
Maximum cranial breadth	Male	151,16	5,35	6,21	**0,00**
	Female	142,83	7,65		
Maximum cranial height	Male	138,02	5,33	4,13	**0,00**
	Female	132,61	6,38		
Bizygomatic breadth	Male	135,50	5,25	6,81	**0,00**
	Female	121,71	3,64		
Basionprostion	Male	94,75	5,82	-	-
	Female	.	.		
Nasionprostion	Male	67,16	5,40	-	-
	Female	.	.		
Basionnasion	Male	103,68	4,75	-	-
	Female	.	.		
Orbital width	Male	39,27	2,03	2,18	**0,03**
	Female	37,68	1,13		
Orbital height	Male	34,03	2,34	-0,92	0,36
	Female	34,80	3,12		
Orbital height	Male	71,62	3,78	3,71	**0,00**
	Female	64,88	9,03		

Table 3 shows t-test results for an independent sample of respondents. Based on the results of the research it can be concluded that at the level of statistical significance 0,01, subjects of male gender compared to female gender have a higher cranial length, breadth, height, bizygomatic breadth and upper facial height. Also, male sex respondents compared to female subjects at a statistical significance level of 0,05 have a greater orbital width.

In order to verify the influence of sex on observed variables the logistic regression analysis was applied. Since the aim of regression analysis is to predict predictor impacts on the criterion, in this research predictor or independent variable was sex, while criterion variable were maximum cranial length, breadth, height, bizygomatic breadth, orbital width, height and upper facial height.

Based on results of logistic regression analysis it can be concluded that sex is significant predictor of maximum cranial length, breadth, height, bizygomatic breadth, orbital width, height and upper facial height. The results of the coefficient determination showed that male respondents explain 18% of the maximum cranial length variance, 24% of cranial width, 12% of cranial height, 22% of bizygomatic breadth, 5% of orbital width and 31% of the upper facial height. Compared to the negative beta scores, the results can be interpreted in such a way that male sex subjects at the statistical significance level of 0,01 predict higher values on the applied anthropometric variables.

Discussion

Inadequate number of female skulls did not allow the use discriminant function analysis to provide sex differentiation formula. The logistic regression analysis showed that sex is significant predictor of all used variables. It is interesting that Gilles-Elliot formula provided correct sex differentiation in 86,5% male skulls from this study. Due to the damage of certain lendmarks the formula could not be applied to female skulls. It would be highly desirable to measure on a large number of male and female skulls to provide formula for Bosnian population.

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The relation between the subdimensions of alexithymia and gender in university students engaged ın sports

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Abstract

The main purpose of this study is to research the relationship between alexithymia in individuals engaged in spots and the variable of gender. 76 women (26.5%) and 211 men (73.5%), 287 students in total participated in this survey through filling in the Toronto Alexithymia Scale (TAS), which consisted of 20 questions with each having five likert-type answer options of 20 items. Internal consistency measurements have been conducted for the scale subdimensions and its totality, and these were compared with univariate and multivariate analysis of variance for each gender group. The scores of coefficient of internal consistence for the subdimensions and the totality, in which the scale have three subdimensions, are: "Difficulty Identifying Feelings" α=0.78, "Difficulty Describing Feelings" α=0.44, "Externally-Oriented Thinking" α=0.17, and for the totality of the scale it is α=0.69. There is a statistically significant difference between gender groups both with respect to subdimensions (Wilk's λ=0.95. $F_{3.283}$=4.503, $p<0.01$; η^2=0.046), and in terms of the general total point ($F_{1.285}$=5.659, $p<0.05$, η^2=0.019). While a difference between female and male students was not found in the subdimension of Difficulty Identifying Feelings, the point average of female students was higher than the other group in Difficulty Describing Feelings subdimension, and the point average of male students was higher in the Externally-Oriented Thinking subdimension. Male students had a higher point in general total point. Female students having a higher point in the subdimension of Difficulty Describing Feelings, and male students having a higher point in the subdimension of Externally-Oriented Thinking, show that they have higher characteristics of alexithymia. In the general total score, male students are seen to have higher characteristics of alexithymia than female students.

Keywords: Sports, Alexithymia, Gender

Introduction

The term alexithymia is used to define a group of symptoms that are related to emotional dysfunctions. The inability to describe feelings is the most striking characteristics of individuals with alexithymia (Sifneos, 1977).

The word alexithymia is derived from Greek and literally means "absence of words for emotions" (Dereboy 1990). Various studies were conducted on alexithymia and the focus has been on the personality traits rather than describing a clinical disorder. Socio-cultural factors have been highlighted as the roots of this personality trait as well (Sifneos, 1988).

Few studies explored the connection between alexithymia and sports. It has been reported that people with alexithymia personality trait become aware of their feelings more easily during high-risk events that involve feelings such as anxiety, and that their anxiety tends to decrease by engaging with high-risk activities. It has been observed that these people especially prefer high-risk areas or environments in order to achieve regulating their feelings (Woodman et al. 2008) (Allegra et al. 2007) (Lafollie and Scanff 2007).

Various studies report that athletes who have intensive trainings have explicit traits of alexithymia (Purper-Quakil et al. 2002). It is stated that women who engage in high-risk sports have more characteristics of alexithymia than women who engage in low-risk sports. It is emphasized that alexithymia is a significant motivation for these people to engage in risky sports (Cazenave 2007).

This study aims to examine the relationship between gender and alexithymia in university students who are doing sports.

Method

287 students engaged in university participated in this survey.

TAS is an effective psychometric assessment tool that was developed in order to diagnose alexithymia, consisting of twenty statements rated on a five point Likert scale (Bagby, 1994). In three subscales, it also assesses difficulties in identifying feelings and distinguishing bodily sensations from emotions (Difficulty Identifying Feelings), difficulty in expressing feelings (Difficulty Describing Feelings), and externally-oriented thinking (Externally-Oriented Thinking). The validity and reliability study of the Turkish form of this scale was conducted in 2001 (Sayar, 2001).

In this study, internal consistency measurements have been conducted for the scale subdimensions and its totality, and these were compared with univariate and multivariate analyses of variance for each gender group. Univariate and multivariate analyses of variance (MANOVA) were conducted in order to identify difference of subdimension and general total point according to genders.

Findings

76 female (26.5%) and 211 male (73.5%), 287 students in total participated in this study. First, the Cronbach Alpha coefficients of internal consistency were measured for the totality and subdimensions of TAS scale, for the whole scale of 20 statements the coefficient was established to be 0.69; 0.78 for the subdimension of Difficulty Identifying Feelings with 7 statements; 0.44 for the subdimension of Difficulty Describing Feelings; and 0.48 for subdimension of Externally-Oriented Thinking with 8 statements.

There are statistically significant differences between female and male students when the general total point average of TAS scale of participants were compared: $F_{1.285}$= 5.646; $p<0.05$; $\eta^2=0.019$. The general total point average of male students on TAS scale is statistically higher than the point average of female students. When we look at eta-squared, the role of gender is 0.019 in explaining the general total point of TAS scale.

Table 2 shows the total point average results of participants' TAS scale on the three subdimensions.

A statistically significant difference between the point averages of participants' TAS scale on three subdimensions based on gender was observed: Wilk's $\lambda = 0.95$ $F_{3.283}=4.503$; $p>0.01$; $\eta^2=0.046$. According to the results, while there is not a difference between female and male students in the subdimension of Difficulty in Identifying Feelings ($F_{1.283}=0.229$; $p>0.05$; $\eta^2=0.001$), the point average of male students in the subdimensions of Difficulty Describing Feelings ($F_{1.283}=3.767$; $p<0.05$; $\eta^2=0.013$) and Externally-Oriented Thinking ($F_{1.283}=11.618$; $p>0.001$; $\eta^2=0.039$) were statistically higher than point average of female students. When looking at eta-squared, the role of gender in explaining the total point of subdimension Difficulty Describing Feelings is 0.013, and the role of gender in explaining total point of the subdimension of Externally-Oriented Thinking is 0.039.

Discussion

This study examines the relationship between alexithymia and gender in university students engaged in sports.

Table 1. Provides the results of the general total point average of TAS scale according to the genders of the participants

Gender	TAS Point	Standard Deviation	N
Female	45.51	7.771	76
Male	48.19	8.659	211
Total	47.48	8.503	287

Sum of Squares	Degree of Freedom	Sum of Squares	F	p	Partial Eta-Squared (η^2)
Gender	1	401.659	5.646	.018	0.019

Table 2. Comparison of total points of TAS subdimension scale based on gender, using MANOVA analysis

TAS Subdimensions	Gender	Average	Standard Deviation	N
Difficulty Identifying Feelings	Female	14.00	4.648	76
	Male	14.32	5.159	211
	Total	14.24	5.023	287
Difficulty Describing Feelings	Female	11.57	3.193	76
	Male	12.36	3.035	211
	Total	12.15	3.093	287
Externally-Oriented Thinking	Female	19.95	3.261	76
	Male	21.51	3.476	211
	Total	21.09	3.483	287

Wilks' Lambda	F	Hypothesis Degree of Freedom	Error Degree of Freedom	P	Partial Eta-Squared (η^2)
.954	4.503[a]	3.000	283.000	.004	.046

TAS Subdimensions	Sum of Squares	Degree of Freedom	Sum of Squares	F	p	Partial Eta-Squared (η^2)
Difficulty Identifying Feelings	5.803	1	5.803	.229	,632	.001
Difficulty Describing Feelings	35,683	1	35,683	,053	,053	,013
Externally-Oriented Thinking	135.931	1	135.931	11.618	.000	.039

The presence of connection between gender and alexithymia is a controversial topic. There are as many studies which argue for the presence of a significant connection between gender and alexithymia as those that argue against (Kleiger JH and Jones NF. 1980; Krystal JH. et al. 1986, Wise et al., 1988; Parker et al. 1989; Joukamaa et al. 1996; Sakkinen et al. 2007; Moriguchi et al. 2007). Different parental attitudes towards male and female children can play a role on the gender differences in relation to alexithymia. Those studies that report observing alexithymia traits more in men (Feiguine 1988, Mattila et al. 2007, Parker et al. 1993; Salmine et al. 1999; Honkalampi et al. 2000; Kokkonen et al. 2001; Parker et al. 2003; Frans et al. 2007) highlight that male students have more alexithymia traits than female students in both subdimensions of Difficulty Describing Feelings and Externally-Oriented Thinking in terms of TAS general total point averages, as it was found in this study. Wester explained this in the study he conducted in 2002 as follows: One of the significant factors in having this situation is that male children experience difficulties in expressing their emotions verbally as a result of the impact of parental and social environment during their upbringing when compared to girls. Carpentar and Addis (2002) explain the differences between genders in relation to alexithymia with "complementary affect" and argue that this can be a result of socialization in the male gender roles. While emotional expressions are increasing in the girls during early puberty, boys have a limited emotional expression during the same period when compared to late puberty (Polce-Lynch et al. 1998). On the other hand, some studies argue that there is no difference between gender groups (Aslan and Alparslan 2001, Krystal et al. 1986, Ünal 2005).

In a study conducted by Zekioğlu et al. in 2014, even though the ratio of girls showing traits of alexithymia (11.1%) was slightly lower than those of boys (16.9), a statistical significance was not observed. When we look at the scale subdimensions in this study, a difference between female and male students was not observed in the subdimension of Difficulty Identifying Feelings, however the point average of male students were higher than the point averages of female students in the subdimensions of Difficulty Describing Feelings and Externally-Oriented Thinking. The studies conducted in 2007 by Sakkinen et al., and Moriguchi et al. found that women had higher point in Difficulty Identifying Feelings and men had higher point in Externally-Oriented Thinking, whereas no difference was found between their

points in Difficulty Describing Feelings. When analyzing the subdimensions of TAS scale, a difference between genders was not found in Difficulty Identifying Feelings, whereas male students were found to have higher point averages in the subdimensions of Difficulty Describing Feelings and Eternally-Oriented Thinking, in line with the result of this present study (Salminen et al. 1999; Franz et al. 2007). There are also other studies that found men to have a higher point in the subdimension of Externally-Oriented Thinking, but noted no difference between genders in other subdimensions (Brosig et al. 2004).

Contrary to these findings, there are also studies that report girls having a higher point in the subdimension of Difficulty Describing Feelings (Gunzelman et al. 2002).

The social and cultural surrounding is as effective as neurobiological factors in the etiopathogenesis of alexithymia. Many studies highlight that different cultural and social factors in the societies of the East and West play a role in the mental and psychological development of a person since childhood. Perspectives on genders in societies also impact the stages of individuals in these societies to comprehend, project and express their emotions. The outcome in this present study showing men to have higher scores in the subdimensions of Difficulty Describing Feelings and Externally-Oriented Thinking of alexithymia shows parallelism with the roles prescribed to men in our society. The social and cultural structure of the society one lives in plays a decisive role in evaluating the relation between alexithymia and genders.

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Long-term Postoperative Results of the Hautmann Ileal Orthotopic Neobladder Reconstruction After Radical Cystoprostatectomy of Bladder Cancer

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Abstract

Urinary bladder cancer is one of the most serious diseases of the urogenital system, and its treatment is dependent on the time of the diagnosis. pT1 and pT2 are the most suitable clinical and pathohistological stages for the successful surgical treatment of bladder cancer. Such cases are almost entirely treatable and result in the improvement of quality of life and longevity. For good outcomes, it is imperative that the disease be diagnosed as soon as possible, so that radical cystoprostatectomy and a orthotopicHautmann neobladder reconstructions could be performed.

An overall analysis of the cases was performed at the Urology Clinic of the University Clinical Center in Prishtina. All surgical cases of orthotopicHautmann neobladder reconstructions were collected in a nonrandomized fashion. Furthermore, complete review of long-term effects, the overall state of all the surgical cases, as well as the survival outcomes of this patient cohort, was performed.

The surgical treatment of bladder cancer patients with orthotopicHautmann neobladder reconstruction at the Urology Clinic of the University Clinical Center in Prishtina first begun in 1990. The first patient was A.K. born in 1926. Postoperatively, no surgical complications were noted, the patient lived in good health with a good quality of life. The patient expired in September of 2015 from old age. In the same year, 1990, another patient was treated with the same method, but unfortunately had expired within 24 hours of the surgery because of anesthesia complications. There was a 9-year hiatus because of the political situation of the '90s in Kosovo. The work resumed in 1999. 25 cases of radical cystoprostatectomy followed by orthotopicHautmann neobladder reconstructions were performed until 2005. The postoperative state of these patients was closely followed.

A complete analysis of the survival rates, especially of cases treated at stages pT1 and pT2, the successful post-op longevity, as well as the longevity of the most challenging and advanced cases treated with this method, are presented. Overall, patients were mostly continent, and urinated regularly and spontaneously.

Key words: orthotopicHautmann neobladder, cystoprostatectomy, urothelial

Introduction

Bladder cancer is a frequent urological disease with a difficult prognosis, with the ability to quickly advance. This disease is more prevalent in males than in females, at a 3:1 ratio. (1,2.) According to Jewwitt's data, the number of deaths resulting from the urinary bladder cancer is 3% of the overall cancers. The incidence in males is 6 to 40 cases in 100,000 people, whereas the incidence in females is 1 to 7 in 100,000. [2.] Unfortunately, the incidence of bladder cancer in Kosovo is unknown, because of lack of data and because there is still no national database of malignant diseases. But, based on the data available at the Urology Clinic of the University Clinical Center in Prishtina, it can be implied that the incidence of the urinary bladder cancer is rather high.

The prognosis and the successful outcome of bladder cancer depends on the time of discovery of the disease and its pathohistological stage. Therefore, the surgical prognosis, outcome, and longevity of patients undergoing the orthotopicHautmann neobladder reconstruction depends on the clinical pathology stage of the disease (4,5,6)

as well as the time when the patient is presented for surgical treatment. The most suitable stages for the surgery that results in favorable treatment outcomes are pT1 and pT2. Pathohistologically, 90% of the cases are classified as transitional cell carcinoma, (8.)5% are squamous cell carcinoma, and about 2% are adenocarcinoma.

Before proceeding with the surgical treatment, it is of utmost importance that the clinical stage according to the TNM convention be established.

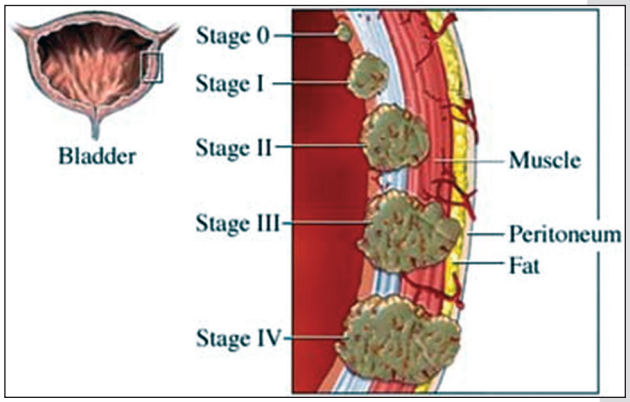

Figure 1. The TNM convention

The decision for the surgical treatment is taken after consulting the results of the preliminary TUR biopsy, and after identifying the stage of tumor differentiation (G1, G2, G3).

Purpose

The purpose of this work is to show the advantages of orthotopic Hautmann neobladder reconstruction and determine quality of life of patients with ilealorthotopic bladder, as well as their post-op longevity (3,7.)

Methods

To proceed with the Hautmann method, the scale of the invasion of bladder carcinoma is first determined. It is recommended that the cases with urothelial carcinoma be in the clinical stages T1-2, N0, M0, and also in pathological stages G1 and G2. The success of the ilealorthotopicbladder reconstruction is dependent on this. Moreover, patients should be between 50 and 70 years old, and in good health condition.

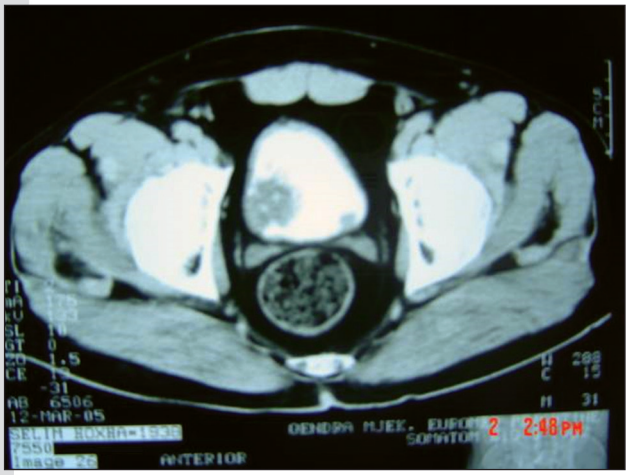

Figure 3. CT of the urinary bladder

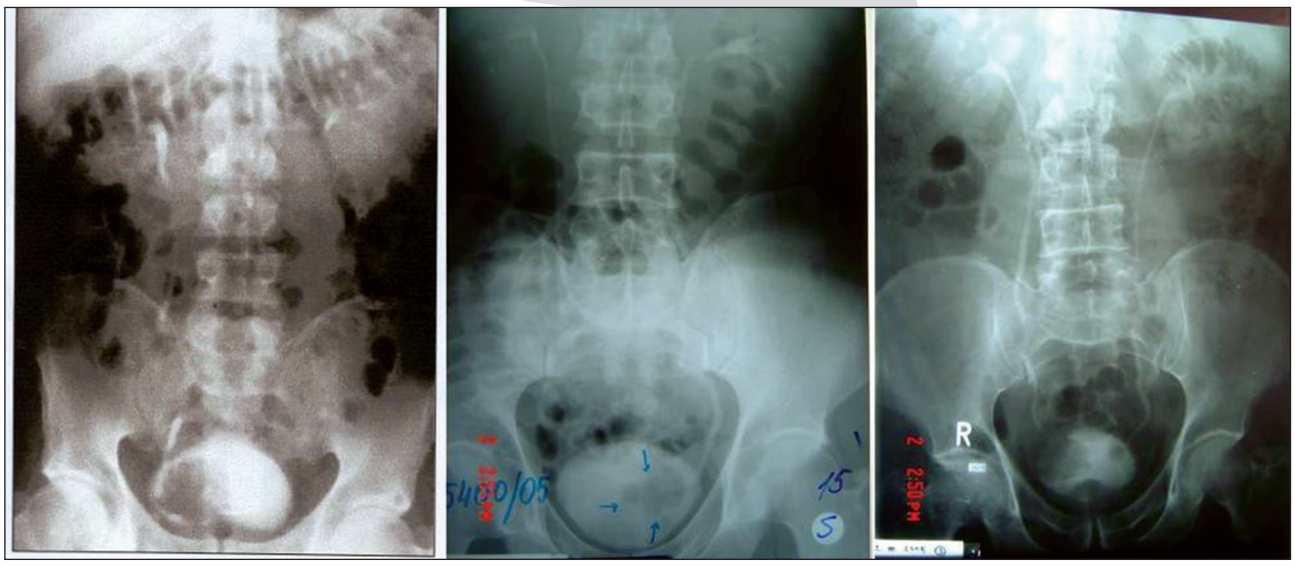

Figure 2. ntravenous Urography

Surgical Treatment

Fistly, the pelvic lymphadenectomy is performed. Then, radical cystoprostatectomy is performed, until the level of the outer sphincter, which has to be preserved with utmost care.

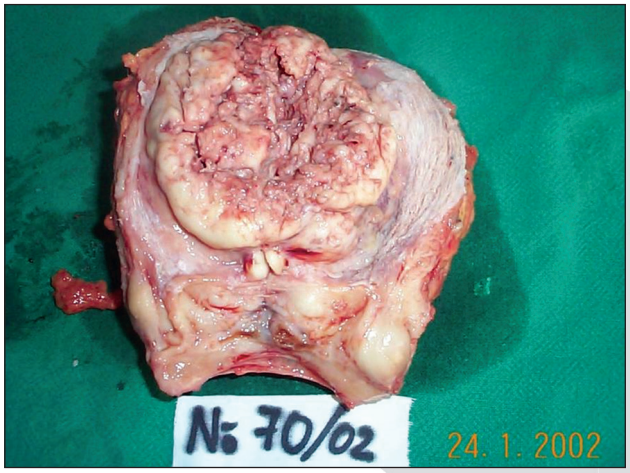

Figure 4. Cystoprostatectomy preparations/ samples

Then, ileal segment is resected in the length of 40-50 cm, with good vascularization, which is detubulated in order to form the ileal plate of the orthotopic bladder. Uretherocystoneostomy is performed on both sides, followed by the modeling of the ileal bladder. Finally, a 22 Chr tripling foley catheter is placed, and the urethroileal anastomosis is performed with sutures at 3, 6, 9, and 12 o'clock positions.

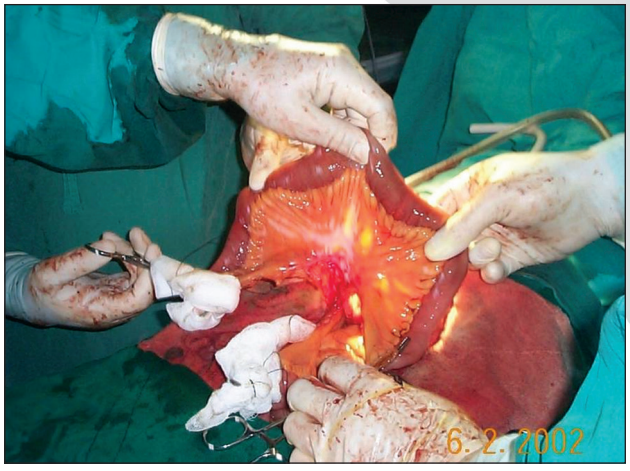

Figure 5. Ileal segment

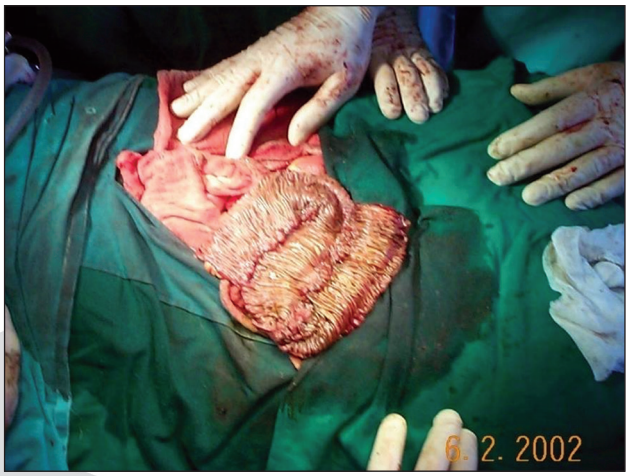

Figure 6. Ileal Plate

Results

25 cases of orthotopicHautmann neobladder reconstruction are presented. In 1990, 2 cases were performed. The first patient lived for 25 years after the operation. The second patient unfortunately expired because of anesthesia complications within the first 24 hours. No new cases were performed for the next 9 years after that, because of political situation during that time. The work resumed in July of 1999. 23 new cases of radical cystoprostatectomy with orthotopicHautmann neobladder reconstruction were performed until December 2005.

Table 1. Age Groups

Age groups	Cases	%
31-40	1	4%
41-50	3	12%
51-60	5	20%
61-70	12	48%
71-80	4	16%
Total	25 cases	100%

Table 2. Total Longevity

Longevity in Years	Patients	Percentage
0-1 years	5	20%
2-3 years	6	24%
3-5 years	5	20%
12-15 years	4	16%
25 years	1	4%
Post-op cases that failed to show for follow-up	4	16%

Table 3. Patients Who Are Still Alive

Patient initials	Date of Birth	Year of surgery	Survival Years
A.K.	1926	1990	25 years (expired in 2015)
M.U.	1926	2003	14 years (still living in 2017)
SH.N.	1941	2004	13 years (still living in 2017)
S.H.	1938	2005	12 years (still living in 2017)
Q.K.	1937	2005	12 years (still living in 2017)

In terms of postoperative longevity, according to Table 2, 5 patients (20%) have expired within one year of treatment; 6 patients (26%) survived after 2-3 years; 4 patients (16%) had a longevity between 12 to 15 years; as well as the first case (4%) operated in 1990, who had a longevity of 25 years, with a good quality of life, and without complications. Postoperatively, all of the patients were continent and with a wide urinary stream.

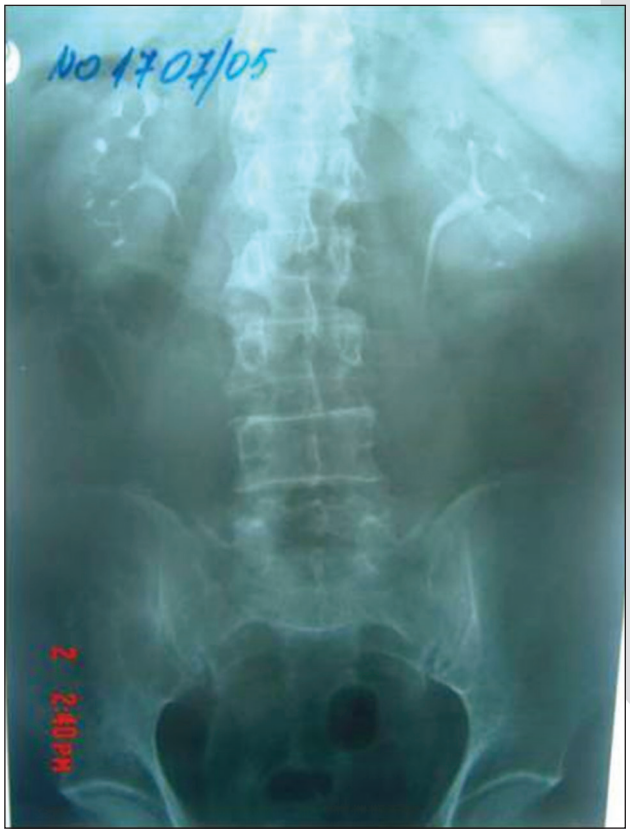

Figure 7. Post-operative Intravenous Urography

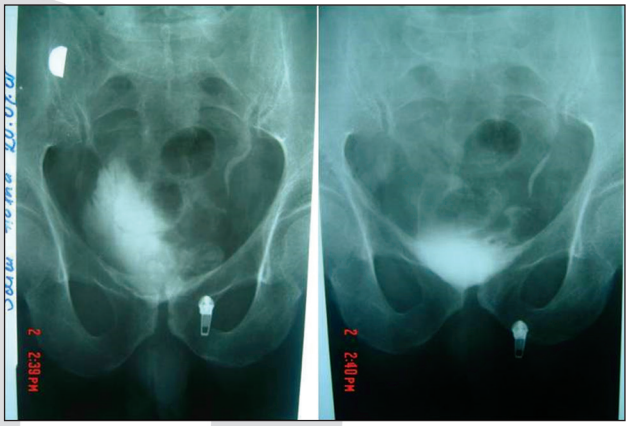

Figure 8. Cystography of the ileal bladder with intravenous urography

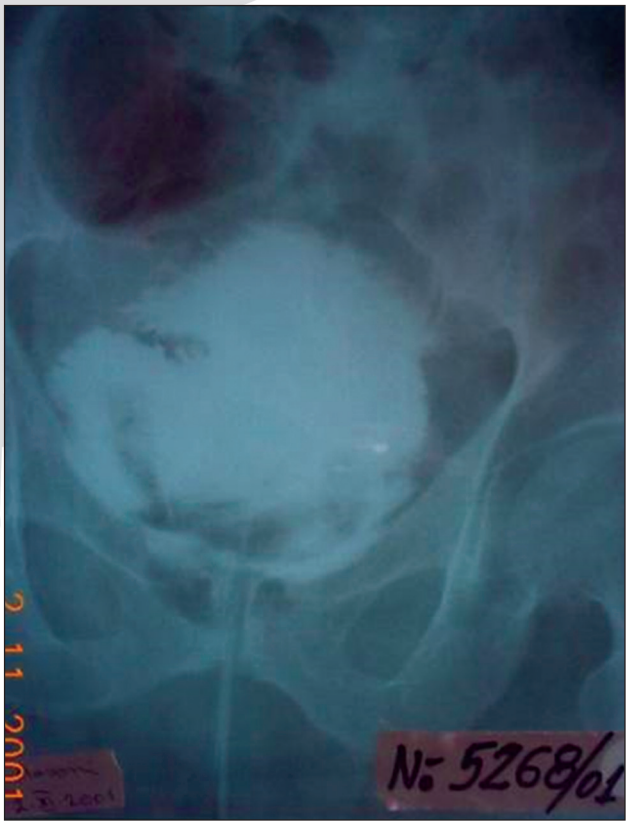

Figure 9. Retrograde urography of ileal bladder

Conclusion

In conclusion, orthotopic Hautmann neobladder reconstruction is the most advanced and practical method available in Kosovo. Furthermore, it is an acceptable method for patients. This type of surgery offers a more comfortable and happy life for the patients. The success and the longevity of the patients is dependent from the stage of the invasion of the urinary bladder carcinoma and the grading of the carcinoma of the urinary bladder. The most suitable stage for the surgical intervention is pT1 and pT2, which is observable in people who still live and in good health.

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Design and development of an herbal medicine based on *Actaea racemosa L.*, indicated for the relief of menopausal symptoms

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Abstract

The assays aimed to develop an herbal medicine from the dry extract, standardized in 23-epi-26-deoxyacetin, from the roots of the plant species *Actaea racemosa* L. (*Ranunculaceae*), popularly known as "black cohosh". The tablets were developed from the dry extract of *Actaea racemosa* L., and produced by direct compression. Subsequently, they were coated with the appropriate dispersion. Accelerated and long-term stability studies have been performed to define the period of use and validity. Finally, coated tablets, obtained from the dried extract of *Actaea racemosa* L., were standardized in 23-epi-26-deoxyacetin, and the analytical methodology was validated, in order to ensure its efficacy in relieving menopausal symptoms.

Keywords: *Ranunculaceae*. *Actaea racemosa* L. Black cohosh. Herbal medicine. Coated tablets.

Introduction

The plant species *Actaea racemosa* L. belongs to the family *Ranunculaceae*. This perennial herbaceous plant, popularly known as "black cohosh" or "St. Christopher's herb" grows naturally in North America, distributed from southern Canada to the State of Georgia (Compton et al., 1998).

According to the Brazilian Resolution of the Collegiate Board of Directors (RDC) nº 26 (Brazil, 2014a), "herbal medicines are those obtained with the exclusive use of active vegetal raw materials whose safety and efficacy are based on clinical evidences, which are characterized by the constancy of their quality ".

Thus, in Brazil, the dry extract, produced from the roots of the *Actaea racemosa* L. plant species, standardized in 23-epi-26-deoxyacetin, is classified as an herbal medicine, and indicated for the relief of menopausal symptoms, according to the "list of traditional phytotherapeutic products of simplified registration", published in Normative Instruction nº 02 (Brazil, 2014b).

Thus, the *Actaea racemosa* L. extract. is constantly investigated as a potential therapeutic agent because of its analgesic and anti-inflammatory activities, and favorable adverse effects profile compared to available synthetic alternatives such as non-steroidal anti-inflammatory drugs (Drewe et al., 2015, Maclennan et al., 2009).

The dried rhizomes of *Actaea racemosa* L. have been widely used as food supplement and herbal medicines for nearly five decades. Historically, Native American women ingested aqueous extract of *Actaea racemosa* L. to relieve pain during menstruation. In recent years, ethanolic and isopropanolic extracts of the plant species have been used to treat the general symptoms of menopause, including hot flashes, profuse sweating, irritability, and anxiety. In addition, their popularity has increased among women, since the use of plant species is an alternative to hormone replacement therapy, which has potential toxicity (Nadaoka et al., 2012).

Primary symptoms associated with climacteric include hot flashes, sweating, insomnia, nervousness and irritability, palpitations, changes in libido, pruritus and vaginal dryness, and increased bone remodeling (Crandall et al., 2011). These symptoms vary in frequency and severity and are

believed to be due to the physiological decrease of ovarian function (Hunter et al., 2012).

Climacteric symptoms, such as hot flashes and sweating, affect 24% to 93% of all women during the physiological transition from reproductive to post-reproductive life. For many years, estrogen-based hormone therapy was the main treatment for such symptoms, due to strong evidence that the therapy effectively reduces climacteric symptoms. Although effective, partial estrogenic compounds and hormone therapy are associated with a significant increase in breast cancer. Thus, the use of non-hormonal treatments is of great interest (Drewe et al., 2015, Maclennan et al., 2009).

Phytotherapy is considered a medicinal therapy of great potentiality, due to its significant growth in the world market (Yunes; Pedrosa; Cechinel Filho, 2001). It is estimated that over 50% of adult Americans use some type of herbal product (Radimer et al., 2004). Such use generated more than US$ 4.4 billion in sales only in the year 2005 (Blumenthal; Ferrier; Cavaliere, 2006).

In addition, advances in the scientific area have allowed the development of herbal-based products with proven safety and efficacy, as well as an increase in the population's search for less aggressive therapies for primary health care (Ribeiro; Leite; Dantas-Barros, 2005).

Given the importance of herbal medicines in the current world circumstance, the scientific study of plant species such as *Actaea racemosa* L. is considered of extreme relevance for the development of new therapeutic alternatives for the population (Lopes et al., 2016).

Materials and methods

Pharmacotechnical development

The tablet cores, developed from the dried extract, which was prepared from the roots of *Actaea racemosa* L. (*Ranunculaceae*), were produced by process of direct compression.

The dried extract of *Actaea racemosa* L. (*Ranunculaceae*), standardized in 23-epi-26-deoxyaceti 2,5% according to the United States Pharmacopoeia monograph (USA, 2014), as well as the pharmaceutical excipients were compressed in a single punch compressor, with a set of upper and lower punctures, and determined nominal compression force.

The design of experiment (DOE), based on the Design Expert® statistical program, was used to study the influence of composition and optimization of the formulation through experimental mixing design.

Physical-chemical tests, described in the Brazilian Pharmacopoeia 5th edition (Brazil, 2010), were applied to evaluate the tablet cores produced. For that, individual and medium weight, toughness, friability, and disintegration were determined.

Subsequently, the tablet cores were coated with the OPADRY® coating dispersion in Vector equipment, model LDCS-30, with 8 L drum, using a Schlick type pistol, 1.0 mm exit hole, with distance between the bed of cores and pistol equal to 8 cm for the aqueous coating, with four Fischer type blades and peristaltic pump. Additionally, the critical parameters of the coating process with the determined dispersion were evaluated, among them: energy consumption, coating uniformity, and yield (Alcorn *et al*., 1988; Smith; Macleod; Fell, 2003; HO *et al*., 2008).

Stability studies

Accelerated and long-term stability studies were designed according to the parameters defined in the table below to define the shelf-life and period of use in packaging and storage conditions specified for the herbal product developed from the dry extract, standardized in 23-epi-26-deoxyacetin 2,5% according to United States Pharmacopoeia monograph (USA, 2014), prepared from the roots of the plant species *Actaea racemosa* L. (*Ranunculaceae*), popularly known as "black cohosh."

Analytical validation

Sample preparation

The sample used for analytical validation, i.e., the 600 mg coated tablets developed, were ground into porcelain grains with a pistil until a homogeneous powder was formed.

Placebo preparation

For the validation analysis, a placebo was produced containing all the components used in the development of the formulation, except the dry extract of *Actaea racemosa* L. (*Ranunculaceae*).

Table 1. Stability study of the traditional herbal product

Storage condition	Packing	Temperature (accelerated)	Temperature (long-term)
15°C-30°C	Impermeable	40°C ± 2°C	30°C ± 2°C

**RH = relative humidity.*

Standard solution preparation

Exactly 5 mg of 23-epi-26-deoxyacetin was weighed, and quantitatively transferred to a 50 mL volumetric flask. The volume was quenched with methanol, and the volumetric flask was subjected to the ultrasonic bath for 10 minutes. A final concentration of 0.250 mg/mL was obtained.

Sample solution preparation

About 175.5 mg of the sample were weighed, and quantitatively transferred to a 50 mL volumetric flask. The volume was quenched with methanol, and the volumetric flask was subjected to the ultrasonic bath for 10 minutes to solubilize the sample completely. A final concentration of 0.250 mg/mL was obtained.

Placebo solution preparation

About 113 mg of the placebo were weighed, and transferred quantitatively to a 50 mL volumetric flask. The volume was quenched with methanol, and the volumetric flask was subjected to the ultrasonic bath for ten minutes in order to solubilize the placebo completely.

Specificity and selectivity

In order to evaluate the influence of excipients on the assay, the absorption spectra in the ultraviolet-visible region of the placebo solution, the standard solution and the sample solution were checked.

Linearity

In order to evaluate the linearity (L) of the method, a calibration curve was constructed at concentrations equivalent to 80%, 90%, 100%, 110%, and 120% of the reference standard concentration, prepared as specified previously. The final concentrations of 23-epi-26-deoxyacetin were 0.200 mg/mL, 0.225 mg/mL, 0.250 mg/mL, 0.275 mg/mL, 0.300 mg/mL, respectively. All solutions were prepared in triplicate.

Accuracy

The solutions corresponding to 80%, 100% and 120% of the reference solution concentration were evaluated for their concentration obtained, and the mean of the three concentrations was calculated.

$$A = \frac{C_o \text{ x } 100}{C_t} \quad \text{..... (1)}$$

Where:

- A refers to the accuracy;
- Co refers to the concentration obtained;
- Ct refers to the theoretical concentration.

Repeatability

In order to evaluate the repeatability of the method, the solutions corresponding to 80%, 100%, and 120% of the reference standard concentration of the 23-epi-26-deoxyacetin were evaluated for coefficient of variation (CV), Calculated from the following formula:

$$CV = \frac{SD \text{ x } 100}{Mean} \quad \text{..... (2)}$$

Where:

- ST refers to the standard deviation.

23-Epi-26-deoxyacetin content

Calculation of 23-epi-26-deoxyacetin content in the *Actaea racemosa* L. (*Ranunculaceae*) tablets was carried out during the study of stability in three different periods. The first assay was performed at the initial stage of the procedure, the second calculation was checked after 3 months of onset of stability, and finally the last assay was performed 6 months after tablet stability had begun. In order to verify the harpagoside content in the tablets of *Actaea racemosa* L. (*Ranunculaceae*). The following calculation was carried out:

$$[C]\text{obtained} = \frac{y-b}{a} \quad \text{..... (3)}$$

Where:

- [C] obtained refers to the concentration obtained by the calibration curve and the peak area of the chromatographic peak;
- y refers to the area of the chromatographic peak relative to the harpagoside;
- b refers to the linear coefficient of the curve;
- a refers to the angular coefficient of the curve.

Chromatographic conditions

- Column: C_{18} 250 x 4.6 mm x 5 µm;
- Temperature: 35ºC;
- Flow rate: 1.2 mL/min;
- Injection volume: 10 µL;
- Detection: ultraviolet at 280 nm;
- Mobile phase: H_2O:MeOH (50:50, v/v);
- Retention time in 13.0 ± 0.5 min.

Statistical analysis

The statistical analyses were established using analysis of variance (ANOVA) followed by the Tukey-Kramer multiple comparison tests (SOKAL; ROHLF, 2012). Results with $P < 0.05$ were considered to be significant. The data were expressed as mean (M) ± standard deviation (SD).

Results and discussion

The results were analyzed qualitatively and quantitatively. The internal and external validity of the experiments were observed, as well as the statistical methodology to be used in each test. In addition, the variables involved in these were adequately described, interpreted and discussed.

Pharmacotechnical development

The pharmacotechnical development of the tablet core was carried out from the preliminary study of the formulations and, later, from the statistical planning.

Study of the formulations

The development of a formulation from the standardized extract of the plant species *Actaea racemosa* L. (*Ranunculaceae*), popularly known as "black cohosh," which can be manufactured by direct compression is very convenient commercially.

For that, the main limitations are the low flow property, the low compression ability and the tendency for capping to be exhibited by the extract, whose therapeutic dose is high, which does not allow the addition of a large amount of excipient to correct these characteristics.

In view of such difficulties, a preliminary study was conducted to collect data, such as the size, thickness, and average weight of the tablets.

Several raw materials conventionally described in the literature were used to analyze the characteristics they would exhibit. Thus, it was verified the possibility of producing a 600 mg tablet by direct compression.

The development of the tablet cores from the extract of the plant species *Actaea racemosa* L. (*Ranunculaceae*), with a final weight of 400 mg, by direct compression was a great challenge.

For this, statistical techniques were used to obtain the desired formulations with the lowest number of experiments, based on preliminary study subsidies.

In order to develop formulations that met the pharmacopoeial specifications, and to study the influence of the composition on the physicochemical characteristics of the cores, the experimental design of the mixture was used through the statistical program Design Expert®.

For the experimental planning of mixing, the amount of the extract of the plant species *Actaea racemosa* L. (*Ranunculaceae*), was set at 140 mg. On the other hand, the total amount of excipients constituting the mixture amounted to 260 mg.

The maximum and minimum values of the variation were determined according to the normal amount of use of each excipient described in the literature. The Design Expert® program provided the formulation proposals, through the mixing technique, resulting in the formulation shown in the table 2.

Direct compression is a technique widely used in the production of tablets and its use has increased considerably (Nada, Graf, 1998; Eissens et al., 2002; Hauschild; Picker, 2004). The main advantages of this technique are related to: the reduction in the time of manufacture, increasing productivity; elimination of various processing steps, reducing the likelihood of cross-contamina-

tion; the reduction of energy consumption; and the reduction of the final cost of the product (Prista, Alves, Morgado, 1995).

Table 2. Formulation proposed for the tablet cores

Ingredient	Percentage	Quantity per dose
Actaea racemosa L.	35,00%	140,00 mg
Colloidal silicon dioxide	0,75%	3,00 mg
Croscarmellose sodium	2,00%	8,00 mg
Microcrystalline cellulose	46,25%	185,00 mg
Atomized lactose	15,00%	60,00 mg
Magnesium stearate	1,00%	4,00 mg

Direct compression also requires a smaller physical area and a reduced number of equipment, since it involves only three stages: the weighing of the powders that make up the formulation, the mixing of the powders, and the compression (Prista; Alves, Morgado, 1995).

In addition, the direct compression method is the one that best preserves the stability of the components of the formulation when compared to procedures that include granulation, since it does not use moisture (addition of binder solution) and heating (drying) during the production. Therefore, it is considered suitable for the processing of hygroscopic and thermolabile substances. Another advantage of direct compression is the optimization of tablet disintegration, where each drug particle is released from the tablet mass, and becomes available for dissolution (Shangraw, 1989).

The choice of the excipients or adjuvants for the composition of a formulation for direct compression deserves careful attention so that the physical stability of the resulting tablets is maintained. Diluents are inert and stable products, added to the formulation to give tablets of suitable weight in the case of active substances in small dosages. Lactose is an example of a soluble diluent and microcrystalline cellulose is an insoluble diluent (Prista; Alves, Morgado, 1995; Lachman; Lieberman; Daning, 2001).

As the excipients are only dry blended prior to compression, it is critical that the binder excipients have certain characteristics as good compaction, so that the tablets conform to the requirements of hardness and friability; smooth flow to meet content uniformity specifications; be inert so that there is no interaction with other substances; stable to meet the established shelf-life; and non-toxic to reconcile regulatory requirements (Eissens et al., 2002).

The determination of the hardness of a tablet evaluates its resistance to breakage. It is based on an indirect evaluation of the degree of consolidation of the tablets, that is, the formation of solid-solid bonds due to the reduction of the free surface energy of the solid particles (Lachman; Lieberman; Daning, 2001).

On the other hand, the determination of the friability of a tablet evaluates its rolling resistance. In addition, friability provides useful indications as to the resistance to frictional wear of the tablets in the packaging, transportation and other technological operations, as in the coating. In general, friability is an indicator of the compaction of the material, besides being a conditioning factor for the consumer's acceptance of the pharmaceutical form (Prista; Alves, Morgado, 1995).

Microcrystalline cellulose is presented as a white, odorless, tasteless, relatively free flowing powder practically free from inert and non-toxic inorganic and organic contaminants. It is insoluble in water, dilute acids and most organic solvents. It is practically insoluble in sodium hydroxide solutions (Merck Index, 2001).

Due to its characteristics of excellent compaction, good flowability and disintegration ability, microcrystalline cellulose is one of the most widely used excipients in tablet formulations by direct compression, and is easily obtained by several suppliers in several countries (Wu, Ho, Sheu, 2001).

Lactose is a disaccharide composed of one unit of galactose and one unit of glucose. It can be found in various solid forms, such as α-lactose monohydrate, anhydrous α-lactose, anhydrous β-lactose or atomized lactose, according to the manufacturing process (Busignies et al., 2004).

Atomized lactose is the oldest and most widely used diluent in direct compression. Atomized lactose presents good flow characteristics and is frequently used as a direct compression diluent associated with microcrystalline cellulose (Prista; Alves, Morgado, 1995).

Disintegrants, such as croscarmellose sodium, are added to the tablet formulation to provide breakdown or disintegration thereof when in the presence of water. The function of the disintegrant is to

neutralize the action of the diluent and the physical compressive forces required to form the tablet. They comprise a group of materials that, in contact with water, swell, hydrate, change in volume or position, or chemically react (Prista; Alves, Morgado, 1995; Lachman; Lieberman; Daning, 2001).

Lubricants, such as magnesium stearate, are added to the pharmaceutical formulations in order to reduce the friction of the powder mixture with the matrix walls and the puncture surfaces, allowing for easy ejection of the tablets (Prista; Alves, Morgado, 1995).

Slippers, such as colloidal silicon dioxide, are added to the pharmaceutical formulation to improve flow properties by reducing interparticular friction, facilitating the filling of the die of the compression machine. The effects produced by sliders depend on their physical and chemical nature, such as particle size and shape, moisture content and temperature (Prista; Alves, Morgado, 1995).

Determination of the mean weight

The mean weight of the cores, in milligrams (mg), was determined according to the results presented in the table 3.

Determination of thickness

The thickness of the cores, in millimeters (mm), was determined according to the results presented in the table 4.

Determination of friability

The friability (F) of the cores was determined according to the results presented below.

$$F = \frac{P_1 - P_2}{P_1} \quad \text{..... (4)}$$

Where:

- P1 refers to the mean weight of twenty tablets before the test;
- P1 refers to the mean weight of twenty tablets before the test;
- P2 refers to the mean weight of twenty tablets after the test.

Therefore, for P1 = 650.8 mg and P2 = 650.4 mg, the friability of the cores is equal to 0.06%. This value is in accordance with the specification of friability, which recommends that values below 1% are satisfactory (Brazil, 2010).

Coating of the tablet cores

The cores were coated with the OPADRY® coating dispersion, and critical process parameters were evaluated as shown in the table 5.

The coating gave protection to the dried extract obtained from the roots of the plant species *Actaea racemosa* L. (*Ranunculaceae*) against the destructive exposure of air, light and moisture and, also, masked the flavor thereof.

From the application of the dispersion of the OPADRY® coating, it was possible to obtain a modified, if any, gastro-resistant release profile, and additionally to provide aesthetic and differentiated qualities to the herbal product.

Stability study

The accelerated stability study plan was performed according to the results presented in the table 6.

The long-term stability study plan was performed according to the results presented in the table 7.

According to the "Guide to Stability Studies" (Brazil, 2005), "the stability of pharmaceuticals depends on environmental factors such as temper-

Table 3. Determination of the mean weight of the cores

1	2	3	4	5	6	7	8	9	10	Mean	SD**
398	401	400	399	402	400	402	401	399	400	1,32	0,33
403	401	400	400	399	402	398	400	401	401	1,43	0,36

***Standard deviation.*

Table 4. Determination of the thickness of the cores

1	2	3	4	5	6	7	8	9	10	Mean	SD
28	27	27	27	28	26	27	27	28	28	27,3	0,67
27	27	28	26	26	27	27	27	28	27	27,0	0,67

Table 5. Critical parameters of the coating process

Process time	Input temperature	Output temperature	Product temperature	Nebulization rate	Weight gain
0 min	65,3 ºC	46,3 ºC	45,0 ºC	-	0,00 %
5 min	65,2 ºC	45,5 ºC	43,6 ºC	4,6 g/min	0,46 %
10 min	65,0 ºC	45,2 ºC	42,8 ºC	4,4 g/min	0,90 %
15 min	65,4 ºC	45,6 ºC	43,2 ºC	4,2 g/min	1,72 %
20 min	65,7 ºC	46,2 ºC	44,0 ºC	4,0 g/min	2,14 %
25 min	63,2 ºC	45,6 ºC	43,8 ºC	4,4 g/min	2,86 %
30 min	64,3 ºC	45,8 ºC	43,9 ºC	4,0 g/min	3,56 %
40 min	63,0 ºC	45,4 ºC	43,5 ºC	4,1 g/min	4,38 %
50 min	62,6 ºC	45,0 ºC	43,0 ºC	4,2 g/min	5,42 %
60 min	62,3 ºC	45,3 ºC	43,2 ºC	4,3 g/min	6,92 %
70 min	63,2 ºC	45,6 ºC	43,5 ºC	4,6 g/min	8,00 %

Table 6. Accelerated stability study plan

Test	Specification	Initial	90 days	180 days
Aspect	Coated, circular and biconvex tablet	In accordance	In accordance	In accordance
Toughness	Informative	26,2 Kp	27,5 kP	26,4 k
Content	3,15 mg a 3,85 mg	3,62 mg	3,51 mg	3,48 mg
Bacteria	Max. 10.000 UFC/g	< 10.000 UFC/g	-	< 10.000 UFC/g
Yeasts	Max. 100 UFC/g	< 100 UFC/g	-	< 100 UFC/g
Salmonella sp.	Absent	Absent	-	Absent
S. aureus	Absent	Absent	-	Absent
E. coli	Absent	Absent	-	Absent

Table 7. Long-term stability study plan.

Test	Specification	Initial	3 months	6 months
Aspect	Coated, circular and biconvex tablet	In accordance	In accordance	In accordance
Toughness	Informative	26,2 kP	26,4 kP	26,9 kP
Content	3,15 mg a 3,85 mg	3,69 mg	3,57 mg	3,46 mg
Bacteria	Max. 10.000 UFC/g	< 10.000 UFC/g	-	< 10.000 UFC/g
Yeasts	Max. 100 UFC/g	< 100 UFC/g	-	< 100 UFC/g
Salmonella sp.	Absent	Absent	-	Absent
S. aureus	Absent	Absent	-	Absent
E. coli	Absent	Absent	-	Absent

ature, humidity and light, and others related to the product itself, such as the physical and chemical properties of substances Active and pharmaceutical excipients, pharmaceutical form and composition, manufacturing process, type and properties of the packaging materials ".

The shelf-life of a solid pharmaceutical product to be marketed in Brazil should be determined by the long-term stability study, according to the parameters defined in the table.

However, since the accelerated stability study (6 months) accompanied by preliminary results from the long-term study was successful; An interim period of validity of 24 months may be conferred on the product.

Analytical validation

The coated tablets, obtained from the dried extract of *Actaea racemosa* L. (*Ranunculaceae*), were standardized in 23-epi-26-deoxyacetin, according to Normative Instruction (IN) nº 02, of May 13th, 2014 (BRAZIL, 2014b), by high performance liquid chromatography (HPLC) with evaporative light scattering detector (ELSD) de-

tection, according to the United States Pharmacopoeia monograph (USA, 2014), and the analytical methodology was validated according to the criteria established in the "Guide for validation of analytical and bioanalytical methodologies" published in Resolution nº 899 (Brazil, 2003).

In this way, validation ensured that the method met the requirements of the analytical applications, thus ensuring the reliability of the results. In order to do so, it presented selectivity, linearity, interval, precision, accuracy and robustness, according to the "Guidance for registration of herbal medicines, and registration and notification of traditional herbal products", published in Normative Instruction nº 04, June 18th, 2014 (Brazil, 2014c).

Specificity and selectivity

Specificity and selectivity can be defined as the ability of the method to accurately measure a compound in the presence of other components, such as impurities or degradation compounds.

The method used to determine 23-epi-26-deoxyacetin content in *Actaea racemosa* L. (*Ranunculaceae*) tablets is specific and selective, since there was no influence of placebo, i.e., the excipients used in the preparation of the tablet, at the maximum absorption peak of 23-epi-26-deoxyacetin at 280 nm.

Linearity

Linearity may be defined as the ability of an analytical method to present a response directly proportional to the analyte concentration in the sample, within a specific range. In Table 8, it was inferred that the individual recovery varied between 98.9% and 102.0%, while mean recovery varied between 99.9% and 101.6%. These values are considered acceptable by Resolution nº 899 (Brazil, 2003).

In order to construct the calibration curve (Figure 1), the averages of the theoretical concentrations and the concentrations obtained were used, as shown in Table 9. The method is considered linear. A straight line with coefficient of determination (R^2) equal to 0.99857 was obtained, as observed in Figure 1.

Table 8. Evaluation of the linearity parameter

Samples	Theoretical concentration (mg/mL)	Concentration obtained (mg/mL)	Recovery (%)	Average recoveries (%)
80%	0,202	0,205	101,5	101,0
	0,199	0,198	99,5	
	0,196	0,200	102,0	
90%	0,222	0,225	101,3	100,4
	0,219	0,217	99,1	
	0,226	0,228	100,9	
100%	0,251	0,256	102,0	101,6
	0,254	0,258	101,6	
	0,246	0,249	101,2	
110%	0,277	0,274	98,9	99,9
	0,274	0,279	101,8	
	0,280	0,277	98,9	
120%	0,298	0,303	101,7	100,8
	0,294	0,293	99,7	
	0,292	0,295	101,0	

Table 9. Average of theoretical and obtained concentrations.

Samples	Mean of theoretical concentrations (mg/mL)	Mean of concentrations obtained (mg/mL)
80%	0,199	0,201
90%	0,222	0,223
100%	0,250	0,254
110%	0,277	0,277
120%	0,295	0,297

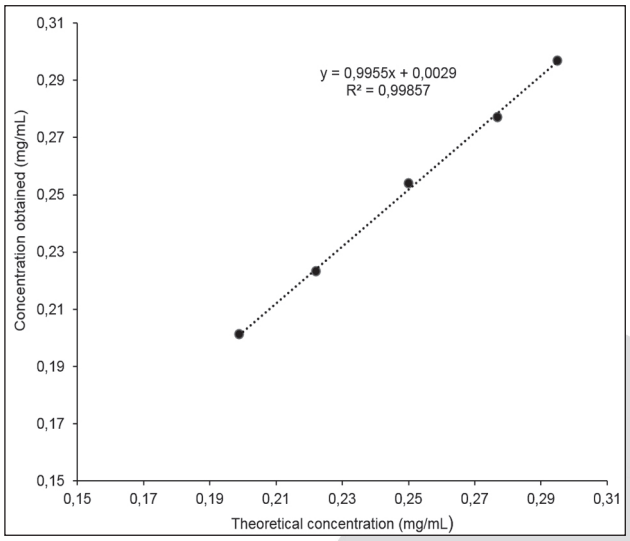

Figure 1. Calibration curve

Accuracy

Accuracy can be defined as the proximity of the results obtained by the method under study to the true value. The solutions corresponding to 80%, 100%, and 120% of the standard reference solution concentration were evaluated for the concentration obtained and theoretical as well as the average of the three concentrations.

From the results obtained in Table 10, it was verified that the variation of the individual recovery was of 99.5% to 102.0% and the mean of the recoveries was of 100.8% to 101.6%. These values are considered satisfactory, according to Resolution (RE) nº 899, of May 29th, 2003 (BRAZIL, 2003) and, therefore, prove the accuracy of the method under analysis.

Precision

Precision can be defined as the evaluation of the proximity of the results obtained in a series of measurements of a multiple sample of the same sample. The accuracy can be evaluated in three different modalities:

Repeatability: accordance between results within a short period of time with the same analyst and the same instrumentation.

Intermediate precision: agreement between results within the same laboratory, however, obtained on different days and with different analysts and equipment.

Reproducibility: agreement between the results obtained by different laboratories.

In the study in question, only the repeatability of the method was evaluated, in accordance with the requirements of Resolution (RE) No. 899, of May 29th, 2003 (BRAZIL, 2003).

The solutions corresponding to 80%, 100%, and 120% of the standard reference solution concentration were evaluated for the coefficient of variation. Observing Table 10, it was verified that the results found were 1.31%, 0.39%, and 1.01% respectively. Coefficients of variation below 5% are considered acceptable and prove the accuracy of the method under analysis.

Table 10. Evaluation of parameters accuracy and precision

Samples	Recovery	Average recoveries	CV
80%	101,5%	101,0%	1,31%
	99,5%		
	102,0%		
100%	102,0%	101,6%	0,39%
	101,6%		
	101,2%		
120%	101,7%	100,8%	1,01%
	99,7%		
	101,0%		

Conclusion

In the pharmacotechnical development of gastro-resistant coated tablets produced by direct compression from the standard extract of *Actaea racemosa* L. (*Ranunculaceae*). The presence of a glidant, such as the excipient colloidal silicon dioxide, was required to have sufficient flow to fill the matrix. Microcrystalline cellulose, in turn, constituted a suitable binder for this type of formulation, giving adequate compaction properties to the manufacturing process.

Experimental mixing planning was an extremely useful statistical tool in obtaining formulation of the tablets produced by direct compression from the standard extract of (*Ranunculaceae*). Through the use of this technique, it was possible to develop an optimized formulation, in which all physicochemical characteristics met the pharmacopoeial specifications.

The development of the supplements allowed to evaluate the influence of each excipient on the majority of the physical-chemical characteristics of

the formulations. In addition, the use of this technique allowed to reduce the number of tests and, consequently, to reduce the cost of the research. Finally, through the analytical validation, it was possible to verify that the analytical methodology used to determine the 23-epi-26-deoxyacetin content in the tablets is specific, selective, linear, accurate, and precise. Finally, through the assays performed and the process used, the results have presented a high performance tablet, with high content of the chemical marker and stability after the study, meeting the requirements for good manufacturing practice.

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Development of a patient education leaflet for asthma patients in Saudi Arabia: a systematic approach

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Abstract

Use of comprehensive educations tools could provide beneficial outcomes while delivering counseling to asthmatic patients. Providing a patient information leaflets on asthma may reinforce the pharmacist's counseling process and improve patient adherence to pharmacotherapy, lifestyle modifications and use of specialized aerosol devices that are crucial in asthma management. A review of existing literatures suggests patient information leaflets to be an important source of information to patients with chronic illnesses such as asthma. In general, the leaflets targeted at patients should be simple and easy to interpret. In this manuscript authors mentioned about the procedures followed in designing a patient information leaflet for asthma patients in Saudi Arabia. The main purpose for using an indigenously developed leaflet arises due to the need for self-management in asthma, importance of adherence to treatment, need for written information for patients, correct use of inhaler devices , self-monitoring using a peak flow mete, and to address psychological issues in asthma self-management. Authors reviewed various available guidelines for designing asthma leaflets followed the steps: *'identify the important areas for asthma, 'develop the booklet', 'review the booklet', and 'revise the booklet'*. The final version of the designed booklet had information on the disease, signs and symptoms, when to visit the hospital, asthma trigger factors, can asthma spread from one person to others, smoking and asthma, medicines to be avoided in asthma, evaluation of therapy response, common medicines used in asthma, use of meter dose inhalers and dry powder inhalers, spacers, nebulizers, and additional information on asthma and living with asthma.

Key words: Asthma, guidelines, patient information leaflets, Saudi Arabia

1. Background

As asthma is a chronic disease for which patients may need to take multiple medications, education is an important part of the management of asthmatic patients. Patients tend to forget the information provided during counseling, so comprehensive asthma education tools comprising pertinent information related to the disease, medications, lifestyle modifications, and prevention strategies would be beneficial for these patients. In this article, authors review the literature on usefulness of patient information leaflets in chronic disease conditions and provide an approach towards designing a leaflet for asthma patients in Saudi Arabia.

2. Competencies needed for counseling asthma patients

Several types and modes of providing patient education to asthmatic patients have been reported in the literature. These come in different formats, from simple PowerPoint slides to comprehensive videos and multimedia materials. The World Health Organization (WHO) has published guidelines for the preparation of educational tools for asthmatic patients, emphasizing the need for therapeutic patient education, which WHO describes as "education managed by health care providers trained in the education of patients, and designed to enable a patient (or a group of patients and families) to manage the treatment of their condition and prevent avoidable complications, while maintaining or improving quality of life" (World Health Organization, 1998). Its principal purpose is to produce a therapeutic effect additional to that of all other interventions (including pharmacological and physical therapy). Patient education in line with the WHO guidelines has brought about

a significant decrease in the number of hospital admissions of patients with bronchial asthma (WHO, 1998). The guidelines include the components shown in Table 1.

3. Patient educations tools for asthma patients

Achieving these competencies requires special education tools. In addition, the appropriate use of counseling aids also helps to reinforce the information provided by the pharmacist during counseling. Commonly used patient counseling aids used in the

Table 1. Competencies needed for asthma patients

Asthma patients should be able to
• select objectives for the management of their disease; • recognize their own symptoms; • treat an asthma attack with prescribed medicine(s); • take steps to prevent another attack;
Symptoms • recognize the symptoms of the onset of an attack; • implement their action plan accordingly; • contact immediately the treatment resource (ambulance, physician on duty) indicated by the symptoms;
Basic treatment • choose medicine according to its properties; • take anti-inflammatory medicine morning and evening, or as advised; • avoid interruption of anti-inflammatory treatment without medical advice;
Complementary • choose medicine according to its properties; • always carry anti-inflammatory medications; • use a bronchodilator at the first sign(s) of an attack;
Inhalation • shake spray before use and inhale deeply; • take one or more puffs into the mouth; • swallow gently and then breathe out;
Peak flow • use peak flow measure; • do a peak flow control mornings and evenings and when at risk; • rank peak flow values into one of the three categories: stable, unstable, attack;
Adaptation • adapt treatment (anti-inflammatory and bronchodilator) according to the values shown on peak flow control; • follow-up on the evolution of the attack every 2–3 hours according to the action plan; • take corticosteroids orally according to a specified peak flow value or if within the 'orange zone' of the action plan;
Precipitating factors • take action according to the environment (animals, dust, other allergens); • avoid 'at-risks' (food and additives, occupational agents, beta-blockers, aspirin, passive smoking); • adjust treatment immediately if an actual or possible precipitating factor occurs; • for preventive purposes, take an additional dose of a bronchodilator before beginning a physical activity (green zone); • take an additional dose of bronchodilator as soon as they remember;
To avoid relapse • recognize particular allergies and precipitating factors; • intensify peak flow control if destabilization is likely to occur; • always mention to the health care provider anything else that may affect the asthma; • continue normal social activities, exercise, and sports, if necessary by adjusting treatment.
Note. Taken and adapted from World Health Organization (1998).

counseling process include the following (International Pharmaceutical Federation, 2005).

3.1 Patient education slides

These can be shown during the counseling sessions. An example would be slides showing in a step-by-step manner how to use inhaled asthma medications.

3.2 Educational handouts

These include both hand-written and printed material provided to the patients during the counseling process.

3.3 Adherence aids

These include measuring aids, tablet cutters, and inhaler aids and would help in developing a plan to incorporate the medication regimen and monitoring into the daily routine of the patient.

3.4 Medication cards

These include lists of all the medications the patient is taking, which would help the patient to review his/her medications and to prevent drug-related problems such as under- or overdosing and interactions.

Table 2. Usefulness of leaflets as documented in published literature

Study design	Major findings	Comments	Reference
Compared and contrasted the views of pharmacists, GPs, and the general public on the value or otherwise of pharmacy-generated patient information leaflets.	All three groups understood the importance of leaflets and accepted that leaflets could improve patient adherence. Choice of a pharmacy by the public could be influenced by the option of having leaflets in the pharmacy.	General public willing to wait for a few additional minutes to receive patient information leaflets provided by the pharmacist.	Mottram and Reed (1997)
A standardized systematic rating of leaflets for hypertension in the UK to determine the quality of information (content, writing style, readability, and design of the leaflets) currently available to patients.	Adequate high-quality information was being provided via the leaflets, although a few of them were below standard.	Need for multiple leaflets available to patients to provide the opportunity to choose the better ones.	Fitzmaurice and Adams (2000)
Patients were surveyed at 32 community pharmacies in New York City metropolitan area to evaluate whether they read non-manufacturer-developed leaflets and to assess their opinions about the understandability and usefulness of these leaflets.	A good number of patients read the leaflets when they were prescribed new medications and also often for their prescribed medications. The majority of patients reported that the leaflets provided in the community pharmacies were useful and that they considered them important.	Pharmacists should encourage reading the leaflets and promote them as a useful resource.	Nathan Zerilli, Cicero, and Rosenberg (2007)
A descriptive study was undertaken to assess the quality (presentation, readability, and quality) of a range of 29 leaflets produced by the British Dental Association.	All leaflets scored quite well for readability. Areas of presentation that could be improved included font size, illustration use, and paper finish. Quality ratings were low. Most leaflets scored poorly in setting out clear aims in the opening paragraph, in identifying sources and dates of information provided, and other sources of advice and support available.	As well as readability, presentation of the information and quality must be taken into consideration.	Lewis and Newton (2006)

Descriptive study that used a sample of 24 leaflets designed by trained nurses in a large teaching hospital to examine the readability of nurse-designed written information leaflets using the Flesch Reading Ease score and the Frequency of Gobbledygook (FOG) and Simple measure of Gobbledygook (SMOG) readability formulae.	The evaluation showed that the leaflets produced had readability that was similar to that reported by other similar studies, and that there were problems in the readability of the leaflets.	The leaflets can be difficult for patients to understand and comprehend the available information.	Mumford (1997)
Evaluation of the information content and readability of 168 asthma leaflets available for patients in the UK from 49 practice settings. The contents of the information were compared with British Thoracic Society guidelines and the readability was evaluated using available standard formula.	20% of the leaflets possessed inaccurate and misleading statements about asthma and related areas, including unreasonable advice regarding the need to visit a doctor, exaggerating the role of cola drinks as an asthma trigger, incorrect information on the efficacy of desensitizing injections, wrong contact addresses and telephone numbers, and misinformation about obtaining a peak flow meter and not acknowledging the wide range of devices available.	Providing reliable information backed by scientific evidence is necessary.	Smith, Gooding, Brown, and Frew (1998)
A survey of 44 oncology healthcare professionals to identify important characteristics of effective print educational materials.	Appropriate reading level, clarity, and credibility of the information and whether the information is current/up A to A date and patient acceptance of material were rated as 'very important' aspects of print educational materials.	Format, design, and placement of materials for patient access need to be considered.	Frost, Thompson, and Thiemann. (1999)
Reviewed the literature on patients' need for appropriate information, with particular reference to head and neck cancer, based on searches of electronic databases.	Patient information leaflets are poorly written and are often difficult for cancer patients to interpret and understand.	Involvement of user population in the design and development of leaflets is necessary.	Semple and McGowan (2002)
An evaluation of the comprehensibility of various asthma education pamphlets available in Australia. The authors selected 50 leaflets on asthma from an asthma foundation, a teaching hospital, the pharmaceutical industry, the National Asthma Campaign, and from specialist books and journal articles.	A substantial number of leaflets were beyond the reading and comprehension abilities of the target population and patients faced difficulty in understanding the leaflets that were not user-friendly.	Readability and the comprehension abilities of the patients should be considered. Medical jargon must be avoided.	Sarma, Alpers, Prideaux, and Kroemer (1995)
Evaluation of the effectiveness of video and printed materials for promoting patient education in asthma among three groups of asthma patients in the United States. These groups received video-based, print-based, or no asthma education. The information provided was related to asthma symptoms and triggers.	Both groups that received intervention performed better that the control group. In relation to the use of metered-dose inhalers effectively, the video group performed better immediately following the intervention, which was better that the written information group. However, after a week, both the test groups performed similarly.	Video and printed information can be useful in asthma education.	Wilson et al. (2010)

3.5 Medicine-related pictograms

These could help communication with some populations, especially if there is a language barrier, limited literacy, or visual impairment. Table 2 presents a literature review regarding the usefulness of leaflets.

3.6 Usefulness of leaflets as documented in published literature

Various literatures on usefulness of leaflets were reviewed and the findings are tabulated in Table 2.

A closer view of these reports demonstrates that patient information leaflets are a very important source of information to patients with chronic illnesses. The range of information provided varied from information about the disease to lifestyle modifications and guidelines to improve adherence. However, it is evident that the information leaflets should present certain essential information and should be easy for the patients to understand. It is also evident that patients generally considered these leaflets as a primary source of information and were willing to read and follow the instructions if they were adequately prepared and contained essential information. There were also recommendations for involvement of the users in the design of the leaflets so as to enhance their utility.

As a chronic disease, asthma needs patient adherence with treatment and lifestyle modifications. The review of these studies provides clear evidence of the usefulness of patient information leaflets and other educational tools for asthma. There is also clear evidence of the need for written information for asthma patients. Thus, patient information leaflets have a significant role. However, the major concern regarding the use of leaflets is their general readability, simplicity, and user-friendliness. There was evidence that some leaflets contained misinformation and some may have had poor patient acceptability. Thus, improving these two aspects, content and user-friendliness, are the major challenges for patient information leaflets on asthma.

4. The purpose of the educational tool

Patient information leaflets are a commonly used educational tool to inform patients about their prescription medications. For asthmatic patients, they can be used for the following purposes:

4.1 Asthma self-management

Self-management is an important aspect of asthma management, with some guidelines recommending the need for self-management guidance for asthma patients. These guidelines stressed the importance of education and skills training, as well as for providing an action plan for unforeseen circumstances and for regular medication review (Global Initiative for Asthma, 2012; National Asthma Council Australia, 2014). It is recommended that all asthma patients should be encouraged to have a self-management plan. Parents should be involved in those for children.

As mentioned earlier, the main reason for recommending self-management protocols was to address problems related to the gradual deterioration of the asthmatic condition and sudden exacerbations of asthma, as well as for patients who showed inappropriate response to asthma. This had been shown to be beneficial and to add value to the treatment of asthma and for patients with poor adherence to their medications (Lahdensuo, 1999).

4.2 Adherence to treatment

Nonadherence to medications is a common problem in asthma, as in other chronic diseases. Adherence has been reported to be less than 50%. Various methods have been proposed to improve asthma patients' adherence, including patient education and the use of diaries (Kaiser, 2007). There are many reasons for unresolved issues of nonadherence, which may include the complexity of the treatment regimen, the routes of drug administration, patient beliefs about drug therapy, and other psychological factors (Cochrane, Horne, & Chanez, 1999).

4.3 Written information for patients

Patients with asthma often have difficulty in recalling the instructions provided by their physician and pharmacist, and so it is valuable to provide

written information to these patients. Authorities such as the National Institutes of Health (NIH) in the United States have indicated that written information should provide instructions and information on how to self-manage the asthma condition daily, including taking medications appropriately, identifying and avoiding exposure to allergens and irritants that can induce an asthma attack, recognizing and handling worsening asthma, and when, how, and whom to contact in an emergency (National Heart Lung and Blood Institute [NHLBI], 2007).

4.4 The correct use of inhaler devices

The correct use of inhaler devices is a real challenge in asthma management. (It has been well documented that even health providers often do not have adequate knowledge on how to use the inhaler devices appropriately. A study in Saudi Arabia demonstrated poor inhaler techniques by community pharmacists, who advised patients to use the inhaler by keeping their mouth open and puff, advice that was absolutely wrong (Abdulwahab, Al-Harbi, & Izham, 2012). In addition, none of the pharmacists advised patients about the important steps 'shake before use' and 'press on the top of the canister while breathing in,' which are the most important steps for ensuring drug deposition in the lungs to maximize therapeutic benefits. These findings further demonstrate the need for providing written information to asthma patients in Saudi Arabia.

4.5 Self-monitoring using a peak flow meter

Self-monitoring using a peak flow meter is a valuable method for patients, and it has been reported that patients with severe symptoms are known to benefit from this intervention (Grampian Asthma Study of Integrated Care [GRASSIC], 1994). This easy method of self-monitoring provides useful guidance to the patients on their disease progression and allows them to tailor their dosage regimen accordingly.

4.6 To address psychological issues in asthma self-management

Chronic diseases such as asthma have been recognized to have associated psychological factors. These can affect outcomes in asthma through their effects on treatment adherence, as well as the reporting of symptoms, faulty symptom attribution, adoption, or rejection of the sick role, and low self-esteem, which may lead to nonadherence (Van Lieshout & Macqueen, 2008). There have also been studies aimed at evaluating the efficacy of psychological therapies that could improve asthma control and QoL. One review (that considered 14 studies) assessed the effectiveness of psychological interventions for asthmatic patients and concluded that the data available were inadequate to confirm the evidence of usefulness of psychological interventions in asthma patients (Yorke, Fleming, & Shuldham, 2006).

5. Summary of available guidelines on the development of patient information leaflets

Several guidelines have been proposed to aid the preparation and development of patient information leaflets. These guidelines are presented in Tables 3, 5 and 6.

5.1 UK Medicines and Health products Regulatory Agency guidelines

Patient information leaflets have been a legal requirement in the UK since 1999 for all medicines. Table 3 summarizes the UK Medicines and Health products Regulatory Agency (MHRA) guidelines for producing a leaflet (MHRA, 2012).

Some of the key considerations for producing the leaflet are listed in Table 4.

5.2. UK National Health Service guidelines

Table 5 lists the questions the UK National Health Service (NHS) guidelines recommend should be addressed when designing a patient information leaflet (NHS, 2014).

5.3 Mater Misericordiae University Hospital (MMUH) elective surgery program

The MMUH in Dublin, Ireland, has produced guidelines on producing leaflets for patients (Table 6) (MMUH, 2014).

Table 3. MHRA guidelines on patient information leaflets

Identification of the medicine	The name, the active substance(s), the pharmaceutical form, and the strength of the product should be stated.
Therapeutic indications	The conditions for which the medicine is authorized must be listed. This section should include any benefit information considered appropriate.
Information necessary before taking a medication	Situations where the medicine should not be used, any precautions, warnings, interactions with other medicines or foods, information for special groups of patients (such as pregnant or nursing mothers), and any effects the medicine may have on the patient's ability to drive.
Dosage	How to take or use the medicine, including both the route and method of administration, how often it should be given, how long the course of treatment will last, what to do if a dose is missed and, if relevant, what to do in the event of an overdose and the risk of withdrawal effects.
Description of side effects	All the effects that may occur under normal use of the medicine and what action the patient should take if any of these occur. These should be listed by seriousness and then by frequency.
Additional information	This covers information on excipient details, a description of the product, registered pack sizes, storage conditions, name, and address of the market authorization holder and manufacturer.

Table 4. Key considerations when designing a patient information leaflet

Complex language and medical jargon cause difficulty in understanding for patients.
Translate all the information into lay language.
Make sure you use colloquial English (for the mock-ups of leaflets for the UK).
Use short sentences and/or bullet points.
Many of the phrases in the quality review documents template can be confusing, so consider more colloquial terms for the UK.
Do not use the system organ class arrangement for side effects, as patients are unable to follow this logic. Side effects should be grouped by seriousness to enable patients to understand when to take action and what that action should be.
Make sure risks are communicated clearly to patients. Guidance has already been published in Always Read the Leaflet and examples of best practice in this area are available. Explanations (including the frequency of the side effects) are known to be helpful to readers and can put the risk in context.

Table 5. NHS guidelines on patient information leaflets

Is there a need for the information?
Does the information leaflet already exist?
How can I make sure the information will be read or understood?
Are there any other tips I need to know?
Is there anything I should avoid?
How can I get my leaflet typed up?
Is there a Board policy on patient information leaflets?
How do I know my leaflet is any good?
Who needs to approve the content of my leaflet?
How can I find out more?

Table 6. MMUH elective surgery program guidelines

Aim for 1–3 pages.
Limit each paragraph to one idea.
Keep the amount of text to a minimum.
Use 'we' and 'you' in your writing as much as possible.
Use images and diagrams where possible to make the meaning clearer (but not to decorate the document).
Remember the document will be printed in black and white—keep this in mind when selecting images and use black font rather than color.
Use simple language.
Replace complicated words and phrases with everyday alternatives and avoid Latin or French words.
Do not use medical jargon.

These recommend sticking to what is meaningful and practical rather than trying to be comprehensive. The information leaflet should complement face-to-face discussions with the patient. These guidelines also recommend the use of simple terminology and suggest alternatives for complicated terms (Table 7).

Table 7. Examples of alternative terms to be used in patient information leaflets

Terms not to be used	Alternative terms to be used
Analgesic	Pain killer
Commence	Start, begin with
Hypertension	High blood pressure
Cannula	Bung/needle in arm for giving medication or fluids

6. Development process for the booklet

The process of developing an educational booklet about asthma comprised five steps (Table 8).

Table 8. Steps followed in designing of the leaflets

Step	Process
Step I	Identify the important areas for asthma education • Literature review • Standard guidelines
Step II	Develop the booklet • Select appropriate format and content
Step III	Review the booklet • By expert panel and potential users
Step IV	Revise the booklet
Step V	Final version of the booklet

6.1 Step I: Identifying the important areas for asthma education

The important areas to include in the booklet were identified from a review of the literature, as well as by referring to standard textbooks (Dipiro et al., 2011) and the asthma guidelines published by the British Thoracic Society Society (Healthcare Improvement Scotland [HIS], 2011). In addition, the general patient counseling guidelines of the American Society of Health-System Pharmacists (ASHP) (ASHP, 1997) helped form the basic framework of the booklet. The following were identified as important components to be included:

6.1.1 Information on the disease

This includes information related to the disease, such as a brief introduction to asthma, the common signs and symptoms, and the trigger factors, as well as reassuring the reader that asthma will not spread from one person to another.

6.1.2 Information on medications

This includes information on common asthma medications, medications that may induce and trigger asthmatic symptoms, and appropriate techniques to assess treatment responses. Also included is information related to the use of both MDIs and dry powder inhalers (DPIs), together with different type of spacers and nebulizers.

6.1.3 Information on lifestyle modifications

This specifically emphasizes the effects of smoking and related information on living with asthma.

6.2 Step 2: Development of the booklet

The booklet was developed from the guidelines mentioned in Step 1. The following points were considered during the preparation and design of the booklet:

6.2.1 Contents

The contents were the most important component of the booklet, and were chosen from the guidelines mentioned in Step 1.

6.2.2 Design

Great importance was given to the design of the booklet as the design and use of colors can directly influence the readability and user-friendliness for patients. The design features for the leaflet were chosen to make the information look attractive, simple, and easy-to-read. The purpose of the design was to invite the readers to delve into the content and to guide them through the material so that they could find information quickly.

6.2.3 Readability

Effort was taken to use simple words and to avoid complicated jargon. Easily understood words were used with the minimal use of medical terminology. Standard readability scales are often used to evaluate the readability of patient information leaflets; use of such a scale provides a rough estimate of the grade level of the written material in the leaflets.

6.2.4 Use of pictures

Pictures were used throughout the whole booklet, including for some core areas such as alerting the reader about cigarette smoking, the various types of inhalers, nebulizers, spacers, and triggering factors for asthma. The objective of these pictures was to enhance patient understanding and improve the recall of asthma-related information. Pictures generally help explain information and are especially helpful for people with low literacy. From a patient perspective, it is generally understood that pictures are usually easier to remember than text.

6.2.5 Font type and size

An appropriate, attractive font type and size was chosen depending upon the suitability.

6.2.6 Translation

The booklet was initially produced in the English language and subsequently translated into Arabic. Thus, there were two versions of the booklet.

6.3 Step 3: Review of the booklet

After the development of the booklet, panels of experts and asthma patients were involved to assess the face and content validity of the booklet.

6.3.1 Review by patients (face validation by potential users of the booklet)

The Arabic version of the booklet was shown to five asthma patients with appointments at the outpatient pharmacy. Their responses and feedbacks were recorded and taken into consideration for further improvement of the booklet. The feedback included the following:

1. The use of less information would make it easier for patients to understand.
2. Making the booklet more colorful would create interest for readers.

6.3.2 Review by experts (content validation)

The expert panel was chosen to include a mix of expertise, experience, and familiarity with the study setting. As the booklet to be validated was a pharmacy-based educational tool for asthma patients, four chest physicians were chosen along with a clinical pharmacy lecturer who was a registered pharmacist and also the main supervisor for the research. The feedback included the following:

1. Content of the information in the proposed leaflet.
2. The panelists noticed typographical errors in the booklet.
3. The devices used for asthma should be incorporated in the booklet.

6.4 Step 4: Revision of the booklet

All the responses and feedback gathered in Step 3 were considered during the revision of the booklet. The process continued until all the expert panelists reached a final agreement about the content of the booklet.

6.5 Step 5: Final version of the booklet

After the expert panels review of the initial draft of the booklet, their opinions, feedback and inputs were incorporated in the final draft of the booklet. The final contents of the booklet after incorporating the comments from the panels are listed in Table 9.

Table 9. Contents of the final version of the booklet

Contents	Comments
About the disease	Straightforward information about the sites affected by the disease such as the lungs and respiratory tract
Signs and symptoms	A description of common signs and symptoms of asthma
When to visit the hospital	Information on when the patient should consider visiting a hospital based on their signs and symptoms
Asthma trigger factors	Common trigger factors for asthma symptoms, with illustrations for a few of these
Spread from one person to others	Reassurance that asthma does not spread from one person to others through sharing clothes or shaking hands
Smoking and asthma	A warning that smoking worsens asthma symptoms and disease progression
Medicines to be avoided in asthma	Common medicines to be avoided in asthma such as NSAIDs
Evaluation of therapy response	Information on the peak flow meter and spirometry
Common medicines used in asthma	Information on various medicines used in asthma were mentioned
Use of MDIs	Steps to be followed while using MDIs
Use of DPIs	Steps to be followed while using DPIs
Spacers	Information on spacers, including their usage and administration procedures
Nebulizers	Information on the purpose and working of nebulizers
Additional information on asthma	Patients were advised to visit pharmacists for additional information on asthma
Living with asthma	A few tips on healthy living for asthma patients
Abbreviations:	NSAIDs: Nonsteroidal anti-inflammatory drugs MDIs: Metered-dose inhalers DPIs: Dry powder inhalers

7. Discussion and Conclusion

7.1 Discussion

As patients with chronic diseases need information beyond counseling, it is important to provide them with written information. Asthma requires specialized care by pharmacists that often goes beyond spoken communication.

It has been well recognized that patient information leaflets are of importance in asthma. In countries such as the UK, it is mandatory in law to provide information leaflets to asthma patients. Guidelines have been issued regarding the development of leaflets for patients. These clearly specify the contents and other factors to be followed when designing patient information leaflets such as simplicity, readability, and user-friendliness. In this study, all efforts were taken to follow these guidelines and to take a systematic approach in designing the asthma booklet. The content information was taken from standard sources, and the booklet was validated for face validity and content validity. Similar importance was given to other aspects such as readability and user-friendliness of the booklet.

7.2. Conclusion

With the expanding role of pharmacists in the healthcare system it is important for pharmacists to provide counseling to patients with asthma and other chronic diseases. Various guidelines are available for designing leaflets for asthma patients. A well-developed indigenous leaflet will certainly add value to patient counseling and hence worthwhile designing it.

7.3 Practice Implication

- The approach developed by researchers in this article could be taken as a model for designing patient information leaflets for asthma
- This approach could be also used for designing leaflets other chronic diseases.

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Abstract

In this paper the instructions for preparing camera ready paper for the Journal are given. The recommended, but not limited text processor is Microsoft Word. Insert an abstract of 50-100 words, giving a brief account of the most relevant aspects of the paper. It is recommended to use up to 5 key words.

Key words: Camera ready paper, Journal.

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Instructions for the authors

Times New Roman 12 points font should be used for normal text. Manuscript have to be prepared in a two column separated by 5 mm. The margins for A4 (210×297 mm2) paper are given in Table 1.

Table 1. Page layout description

Paper size	A4
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Regular paper may be divided in a number of sections. Section titles (including references and acknowledgement) should be typed using 12 pt fonts with **bold** option. For numbering use Times New Roman number. Sections can be split in subsection, which should be typed 12 pt *Italic* option. Figures should be one column wide. If it is impossible to place figure in one column, two column wide figures is allowed. Each figure must have a caption under the figure. Figures must be a resolution of 300 DPI, saved in TIFF format, width 10 cm min. For the figure captions 12 pt *Italic* font should be used. (1)

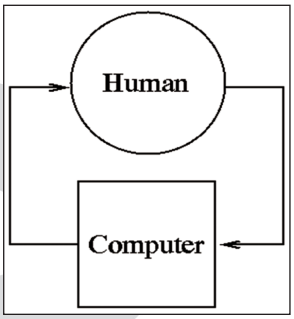

Figure 1. Text here

Conclusion

Be brief and give most important conclusion from your paper. Do not use equations and figures here.

Acknowledgements (If any)

These and the Reference headings are in bold but have no numbers.

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