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IN VITRO COMPARATIVE EVALUATION AND STABILITY STUDIES OF DIFFERENT BRANDS OF PREGABALIN (75 MG) CAPSULES MARKETED IN KARACHI, PAKISTAN: A CASE STUDY

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ABSTRACT:: *Pregabalin is a drug of choice for the treatment of epilepsy. Several brands are available in the market which makes it difficult to select the safe, effective and economic one. Therefore, the current study was designed to evaluate and compare the quality and physicochemical characteristics of six different pharmaceutical brands of Pregabalin (75 mg) capsules available in the pharmacies of Karachi, Pakistan. The comparison was based on different parameters such as, price, uniformity of dosage unit, disintegration time, dissolution assessment, chemical assay and stability of Pregabalin using standard methods. The result showed that almost all brands of Pregabalin are within the limits of manufacturers claim and meet USP/BP specifications. However, statistical calculations and similarity factor (f_2) studies also revealed that all brands are pharmaceutically equivalent in their quality aspects. On the basis of achieved results, it was concluded that the cost-effective brands of Pregabalin should be utilized for the treatment of epilepsy*.

Keywords: *Pregabalin; comparative study; quality parameters; HPLC, Pakistan*

INTRODUCTION:

Pregabalin is a drug of choice in epilepsy and also use as an analgesic. United States and European Union was recently approved it for adjunctive therapy in partial seizures. It is structurally and pharmacological activity simulated with Gabapentin [1-3]. Pregabalin produces effects by specific binding with alpha 2-delta (α2δ) subunits of calcium regulated channels [4]. It also suppress neuronal responses of muscles by reducing calcium influx in brain synapses [5, 6]. Pregabalin consider as a useful medicine in inflammation, gastrointestinal disorders, insomnia, alcoholism and different psychiatric problems like mania and bipolar disorders [7].

Drug regulatory authority of Pakistan has granted marketing authorization of different medicines for public use on the behalf of limited clinical trials and literature review information [8]. Difference therapeutic responses have been observed in marketed products while each contained same active pharmaceutical ingredients [9]. Furthermore, variation in price of different brands of same generic drugs results in significant variation in quality of products [10]. Moreover, Pakistan also include among those countries which are listed for the largest importer of counterfeit drugs [11]. Due to these facts, uses of substandard and counterfeit medicines result in increasing cases of morbidity, mortality and patient's un-compliance has been observed [12]. Therefore, it is necessary to access the quality of different brands by conducting post-marketing surveillance in Pakistan. A number of research articles were reported that physicochemical evaluation of different quality parameters are needed to know the pharmaceutical equivalence of drugs [13-17].

Different researchers have reported the comparison of quality control parameters in different brands of medicines [18-21]. However, no study is available on the comparison of Pregabalin capsules marketed in Karachi. Different brands of Pregabalin (75 mg) capsules of both local and multinational pharmaceuticals are available in different pharmacies at Karachi. Therefore, the current study was carried out to evaluate and compare the quality control parameters of Pregabalin (75 mg) capsules and their stability studies available in pharmacies of different Government hospital of Karachi. The samples were collected from different pharmacies of government hospitals because there was a chance of counterfeit and placebo drugs to be found. The quality was assessed in terms of uniformity of dosage units, disintegration, dissolution, assay of Pregabalin content and stability study. Furthermore, the achieved parameters were compared with United State and British Pharmacopeias specifications. This study will be useful in cost effective therapy of epilepsy by selecting low cost brand having same quality standards.

MATERIAL AND METHODS:

Chemicals and reagents

Acetonitrile, methanol and hydrochloric acid analytical grade were purchased from Merck (Darmstadt Germany). Di-Potassium hydrogen orthophosphate was procured from Sigma-Aldrich (St. Louis, MO, USA). Highly purified water (18 MΩ•cm) was prepared by processing de-ionized (DI) water (H2O) through a Pure Lab Ultra system (ELGA, UK). Reference standard of Pregabalin was received as a gift from Ali Gohar Private Limited, Karachi, Pakistan.

Instrumentation

The HPLC system was consisted of a pump (Model # L-2130; VWR-Hitachi, Darmstadt, Germany), an auto-sampler (Model # L-2200; Merck-Hitachi, Tokyo, Japan), a column (C18, 5 µm, 250×4.6mm; µBondapack®, Hiber), a UV

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detector (Model # 2420; VWR-Hitachi, Darmstadt, Germany). Disintegration test apparatus (Model # TD-20S, Agilent California, US) and dissolution test apparatus USP apparatus II (Model # 708-D, Agilent California, US).

Sample Collection

Six brands of different manufacturer of Pregabalin capsules (75 mg) were collected from various pharmacies of different government hospitals in Karachi-Pakistan. The collected samples were coded as P-1, P-2, P-3, P-4, P-5 and P-6. The details of each brand are summarized in **Table 1**.

Table 1: Labeling information of six brands of Pregabalin (75 mg) capsules.

Brand code	Batch number	Manufacturing date	Expiry date	Retail price/10 units[a]
P-1	151867	August-2015	August-2017	150.00
P-2	l33602	April-2015	March-2018	714.28
P-3	157C25	July-2015	July-2017	195.00
P-4	5515	October-2015	October-2017	185.71
P-5	5E310	May-2015	April-2017	169.28
P-6	BN115524	May-2015	May-2017	185.71

Assessment of quality control parameters

Six brands of Pregabalin (75 mg) capsules were selected for the comparative study of different quality control parameters such as uniformity of dosage units, disintegration, dissolution, assay of Pregabalin content and stability studies.

Uniformity of dosage unit (BY WEIGHT VARIAION)

The uniformity of weight is the evaluation parameter which assures the uniformity of dosage units during filling. Twenty capsules of each brand were selected randomly and weighed individually using analytical weighting balance. The percentage weight variation was calculated using the following formula:

$$\%\ \boldsymbol{Weight\ variation} = \frac{\%\ \boldsymbol{Assay} \times \boldsymbol{Wt.of individual\ capsule}}{\boldsymbol{Avg.filled\ wt.of\ capsules}}$$

However, upper and lower control limits of weight variation were using the following formulas:

$$\boldsymbol{Upper\ control\ limit} = \boldsymbol{Mean} + (\mathbf{3} \times \boldsymbol{standard\ deviation}) \quad \textbf{Eq. 2}$$

$$\boldsymbol{Lower\ control\ limit} = \boldsymbol{Mean} - (\mathbf{3} \times \boldsymbol{standard\ deviation}) \quad \textbf{Eq. 3}$$

Disintegration time

The disintegration test is performed to evaluate whether tablets or capsules are disintegrate within the acceptable time when placed in a respective fluid medium. Six capsules of each brand were selected randomly to evaluate the disintegration time using disintegration apparatus. The samples were placed in basket rack assembly of the disintegration apparatus. The DI water was used as a medium and maintained at 37±2 ^{o}C. The time was recorded at which the capsules were completely disintegrated. The disintegration time for each brand was compared with the maximum acceptable limit of Pharmacopeia regulated by USP [22].

Dissolution assessment

The dissolution test is performed to determine the amount of active part released from oral solid dosage form of tablet or capsules in the known volume of medium. The dissolution test was performed using dissolution USP type II apparatus. One capsules of each brand was placed in the bowl of dissolution apparatus. The bowl was filled with the 450 ml of 0.1 N HCl solution, agitated with constant speed at 100 rpm and maintained at 37±0.5 ^{o}C. The samples were collected from each bowl at different time interval 10, 20 and 30 minutes from surface, medium and bottom of bowl using syringe and filtered using Whatman filter paper having 0.45 micron pores size. The dissolve amount of Pregabalin was quantified using HPLC system consisted with UV detector. The mobile phase composition and HPLC operating conditions are mentioned below. The concentration of Pregabalin was assessed in comparison with the reference working standard solution having a concentration of 5.0 µg/ml. However, the percentage of dissolution of Pregabalin in each capsule was calculated using the following formula:

$$\boldsymbol{\%\ Pregabalin\ dissolved} = \frac{\boldsymbol{Au}}{\boldsymbol{As}} \times \frac{\boldsymbol{Ws}}{\mathbf{100}} \times \frac{\boldsymbol{Ps}}{\mathbf{100}} \times \frac{\boldsymbol{Ps}}{\mathbf{1}(\boldsymbol{Capsule})} \times \frac{\mathbf{100}}{\boldsymbol{Lc}} \quad \textbf{Eq. 4}$$

Where,

Au = Peak area of sample solution of each caps

As = Peak area of standard solution

Ps = Potency of standard

Ws = weigh of standard in mg

LC = Label claim of Pregabalin

Chemical Assay

The assay content of Pregabalin was carried out according to the method described by the Gujral et al [23]. Briefly, ten capsules of each brand were randomly selected and the average content weight of capsules was calculated. An amount of 75 mg of homogenized powder of Pregabalin was accurately weighed and transferred into 50 ml volumetric flask. An aliquot of 20 ml mobile phase was added and sonicated it for 10 min. The volume was made up to mark with the mobile phase, mixed, and filtered through Whatman filter paper having 0.45 micron pores size. The clear solution was injected on to the HPLC system. The mobile phase composition was H_2O:ACN:MeOH (80/5/15, v/v/v) containing 2.2 g of di-potassium hydrogen orthophosphate. An aliquot of 20 µl was injected to HPLC system through an auto-sampler. Separation was performed in isocratic mode with a flow rate of 1 ml/min. Detection of Pregabalin was carried out at 210 nm wavelengths. The total run time was about 5 min. The assay content of Pregabalin was assessed in comparison with the reference working standard solution having a concentration 5.0 µg/ml. The content weight of Pregabalin per capsules was calculated as mentioned below formula:

$$Weight\ of\ content\left(\frac{mg}{capsule}\right) = \frac{Au}{As} \times \frac{Ws}{50} \times \frac{Ps}{100} \times \frac{50}{Wu} \times Wa \quad \text{Eq. 5}$$

Where,
Au = Mean peak area of sample
As = Mean peak area of standard
Wu = Weight of sample taken in mg
Ws = Weight of standard in mg
Wa = Average filled weight of content in capsules
Ps = Potency of standard.
Furthermore, percentage of assay calculated using the following formula:

$$\%\ Assay = \frac{Content\ wt.of\ each\ capsules\ (mg)}{Label\ claim\ (mg)} \times 100 \quad \text{Eq. 6}$$

Stability studies

After initial testing all collected brands were subjected to the stability testing conditions recommended by the International Conference on Harmonization (ICH) guidelines [24]. Samples of Pregabalin (75 mg) capsules in their original packages were stored in stability chamber at temperature of 30 ± 2 °C and relative humidity (RH) of 65 ± 5%. The capsules was monitored over the period of 3 months for changes in their appearance, drug content and drug release using the official USP release test.

Release profile comparison

The similarity factor (f_2) provides simple interpretation of data to compare release profile of different Pregabalin brands. According to the FDA guidelines if the values of f_2 are within range of 50-100% indicates equivalence and if f_1 values are less than 50% ensure that there is no similarity between two dissolution profiles. The brand P-2 (multinational) is used as a standard to assess the similarity of different brands in their dissolution pattern.

Statistical analysis

The all experiments were performed in triplicates. The achieved data were analyzed using SPSS and statistical data analysis was carried out using the Student's t-test with $p < 0.05$ as the minimal level of significance unless indicated otherwise. All experimental data were reported as the means ± standard deviation (SD). Furthermore, One-way Analysis of Variance (ANOVA) was utilized to evaluate the differences between the different brands of Pregabalin.

RESULTS AND DISCUSSION:

The current study was designed to compare the quality of different brands of Pregabalin (75 mg) capsule and their stability after three months. The quality was determined in terms of price variation, weight variation, disintegration time, dissolution and chemical assay. At the time of current study, all the collected samples were within shelf life and registered with the Drugs Regulatory Authority of Pakistan (DRAP).

Price variation

The prices variation of different brands is presented in **Table 1**. The results indicate that there is no significant variation in the price of five brands of Pregabalin (Rs. 150-195). However, one brand (P-2) has higher price in comparison with other brands (Rs. 714).

Uniformity of dosage unit

The minor variation in capsules weight content is given an indication of good manufacturing practices (GMP). The weight variation in Pregabalin capsules is showed in **Table 2.** The results showed that average weight of Pregabalin brands was within range of 90−260 mg. According to USP specifications for capsules that not more than 2 capsules are deviate ±10% from the average weight of 20 capsules [25]. Present study revealed that all brands of Pregabalin are within limits of USP/B.P specs. However, the variation in the weight indicates that different manufacturers used different types of excipients in formulation.

Table 2: Statistical weight variation in Pregabalin (75 mg) capsules. Triplicate analyses were made for all measurements.

Brand code	Batch number	Average weight[a] (mg ± SD[b])	UCL[c] (Mean + 3SD)	LCL[d] (Mean - 3SD)	B.P/USP Limits	Results
P-1	151867	100 ± 1.6	105	95	±10%	Complies
P-2	l33602	196 ± 7.2	217	174	±10%	Complies
P-3	157C25	98 ± 0.9	101	95	±10%	Complies
P-4	5515	227 ± 17.0	278	175	±10%	Complies
P-5	5E310	238 ± 13.0	277	198	±10%	Complies
P-6	BN115524	177 ± 8.1	201	152	±10%	Complies

[a]Average weight of 20 capsules
[b]Standard deviation
[c]Upper control limit
[d]Lower control limit

Disintegration test

A disintegration test is a very helpful parameter for assessing the overall quality of the product. It is directly correlates with release and absorption of drug inside the body. Six brands of Pregabalin (75 mg) capsules were subjected for disintegration test. The achieved results are presented in **Table 3**. The results found within the range of 7 to 13 minutes. The overall results showed that brand P-2 takes more time about 12 min to disintegrate completely while brand P-1 are best in among them which taken a minimum disintegration time about 7.5 min. This may occur due to variation in the excipients types and quantities added in the formulation. According to USP guideline, hard gelatin capsules should be disintegrating within 15 min [22]. The results of disintegration test showed that all brands complies USP limits.

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Table 3: Disintegration assessment of different commercial brands of Pregabalin (75 mg) capsules. Disintegration analyses done in triplets.

Brand Code	Disintegration Time (Mean ± S.D)	Compendia Limits (USP)	D.T Compliance
P-1	7.5 ± 0.12	15 minutes	Complied
P-2	12.4 ± 0.19	15 minutes	Complied
P-3	9.3 ± 0.15	15 minutes	Complied
P-4	10.3 ± 0.06	15 minutes	Complied
P-5	9.0 ± 0.41	15 minutes	Complied
P-6	8.3 ± 0.21	15 minutes	Complied

Dissolution assessment

Drug content should dissolve not less than 80% of their label claim in their respective dissolution medium according to USP guidelines [26]. The present studies showed that all six Pregabalin brands dissolved their content within the range of 81.74 to 100.75% as show in **Table 4**. The results showed that all brands complied the USP and B.P criteria. Statistical analysis of data (ANOVA) and results of similarity factor (f_2) also indicates that there is no significant difference was found in between and within the different brands of Pregabalin capsules as shown in **Table 4, 5**.

Table 4: Dissolution profile at different time interval of different brands of Pregabalin (75 mg) capsules.

Brand code	Dissolution rate at different time interval (Mean ±S.D)			Compendia Limits (USP) At 30 min	Dissolution Compliance	F_2 values (%)
	10 mins	20 mins	30 mins			
P-1	53.2 ± 0.12	71.1 ± 0.11	89.4 ± 0.34	Not less than 80%	Complied	85.17
P-2	51.1 ± 0.34	81.2 ± 0.42	88.6 ± 0.51	Not less than 80%	Complied	—*
P-3	60.5 ± 0.18	78.0 ± 0.23	95.2 ± 0.45	Not less than 80%	Complied	52.43
P-4	56.0 ± 0.05	82.6 ± 0.41	100.7 ± 0.11	Not less than 80%	Complied	53.02
P-5	59.2 ± 0.32	81.4 ± 0.32	95.0 ± 0.23	Not less than 80%	Complied	53.62
P-6	58.1 ± 0.19	77.1 ± 0.49	83.5 ± 0.12	Not less than 80%	Complied	54.34

*Brand P-2 is used as a reference standard for similarity calculation

Table 5: One-way ANOVA for the dissolution profile of different brands of Pregabalin (75 mg) capsules.

Variation Source	SS	Df	MS	P-value	F
Between Groups	29.767	1	29.767	0.8043	0.5867
Within Groups	507.382	10	50.738		
Total	537.149	11			

Chemical Assay

The chemical assay is given to assure that each unit of capsules contain equivalent amount of drug with respect to its label claim. The chemical assay results are illustrated in **Table 6**. The results showed that the chemical assays of different Pregabalin brands were found in the range of 95.62 to 102.68%. The results were found within the manufacturer label claim (75 mg). The results also indicated that all Pregabalin brands are having same physicochemical characteristics and qualities. Furthermore, this investigation indicates that all Pregabalin brands complied USP specification for assay. Moreover, statistical analysis of data (ANOVA) also indicates that there is no significant difference in the content of assay in different Pregabalin brands **Table 7.**

Table 6: Assay results of different brands of Pregabalin (75 mg) capsules. Triplicate analyses were made for all measurements.

Brand code	Amount of drug (mg)	Label claim (mg)	Assay (%)	U.S.P limits	Assay compliance
P-1	72.4	75	96.5	L.C[a] ± 5%	Complied
P-2	74.7	75	99.6	L.C ± 5%	Complied
P-3	71.7	75	95.6	L.C ± 5%	Complied
P-4	73.4	75	97.9	L.C ± 5%	Complied
P-5	77.0	75	102.6	L.C ± 5%	Complied
P-6	74.3	75	99.0	L.C ± 5%	Complied

[a]Amount of drug on label claim

Table 7: One-way ANOVA for the assay content of different brands of Pregabalin (75 mg) capsules.

Variation Source	SS	Df	MS	P-value	F
Between Groups	3.575	1	3.575	0.7496	0.7895
Within Groups	45.285	10	4.529		
Total	48.86	11			

Stability studies

After three months retained in stability chamber at defined conditions, each brand were evaluated its quality parameters. The results showed that all brands were unchanged physically and complied its disintegration and assay content tests as shown in **Table 8.** The stability studies also showed that all six Pregabalin brands dissolved their content within the compendia limits

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Table 8: Quality assessment studies of different brands of Pregabalin (75 mg) capsules after three months.

Brand code	Physical Appearance	Disintegration Time	Dissolution rate at different time interval (Mean ±S.D)			Assay (%)	F_2 values (%)
			10 mins	20 mins	30 mins		
P-1	Unchanged	9.1 ± 0.18	42.3 ± 0.21	67.3 ± 0.21	85.2 ± 0.12	95.6	88.31
P-2	Unchanged	11.6 ± 0.25	45.2 ± 0.23	76.5 ± 0.34	83.6 ± 0.31	97.0	—*
P-3	Unchanged	13.4 ± 0.10	53.2 ± 0.17	73.3 ± 0.21	89.0 ± 0.2	95.1	63.12
P-4	Unchanged	10.7 ± 0.16	43.5 ± 0.35	77.2 ± 0.31	95.3 ± 0.16	96.1	55.44
P-5	Unchanged	12.8 ± 0.27	46.6 ± 0.09	75.4 ± 0.12	87.33 ± 0.31	98.33	78.71
P-6	Unchanged	6.3 ± 0.33	50.4 ± 0.1	81.3 ± 0.39	80.1 ± 0.23	96.41	67.51

*Brand P-2 is used as a reference standard for similarity calculation

Release profile comparison

The released pattern of different brands was compared by using DD solver. The values of f_2 indicate that all brands shown similarity with each other in their releasing pattern while Brand P-2 was taken as reference standard as shown in **Table 4, 8.**

CONCLUSION:

It was observed that a major variation in price within the same generic brands of Pregabalin from 150 to 714.28 Pak rupees/10 units. However, according to the results of a current study reflect that there was no considerable difference in the quality of testing Pregabalin brands. The quality in terms of weight, disintegration, dissolution and chemical assay were assessed and found comparable to each other. Also stability studies also indicate each brand is equivalence to each other. Hence, it is proving that low cost drugs also provide good pharmaceutical outcomes. Therefore, it was concluded that the cost effective drug should be utilized and can be prescribe other brand in place of that un-available brand.

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