



Post Marketing Surveillance on Propranolol and Atenolol Tablets Manufactured in Iran

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Abstract

Propranolol, a prototypical β -adrenergic receptor antagonist and atenolol, a cardio-selective β -antagonist are widely used in therapeutic regimens for treatment of hypertensive patients. In Iran, several pharmaceutical manufacturers formulate these two β -blockers. As the formulation of a dosage form is essential for the patient's safety and drug efficacy, in this study we aimed to evaluate the quality of the tablets which are formulated by the above manufacturers. Atenolol (100 mg) tablet manufactured by APOTEX in Canada also was evaluated. The commercially available preparations of the following dosage forms were studied: propranolol (10 mg, 40 mg) manufactured by TOLID DARU and ROSE DARU (*a, b, c, d*), atenolol (50 mg) manufactured by DARUPAKHSH (*e*), atenolol (100 mg) manufactured by DARUPAKHSH, TOLID DARU, SOBHAN, LORESTAN and APOTEX (*f, g, h, i, j*). The quality and safety of the dosage forms of these drugs were evaluated by PMS studies. For this purpose, the weight variation, hardness, thickness, content assay, content uniformity, disintegration time and dissolution rate of the dosage forms were compared to British Pharmacopeia (BP) and United States Pharmacopeia (USP) standards. The results verify that all dosage forms show evidence of the USP and BP quality assessment.

Keywords: Propranolol, Atenolol, PMS, Tablet.

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1. Introduction

Post-marketing surveillance (PMS) or monitoring involves all activities undertaken to obtain more data and information about a product after it has been granted marketing authorization and made available for public use

[1]. Physicians and patients expect that when medications are prescribed correctly for labeled indications and are used as directed, these medications generally will have beneficial effects and will not cause significant harm. This confidence in pharmaceutical products reflects trust in the effectiveness and integrity of the drug approval and monitoring process [2].

Interest in PMS of new drugs has been

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Table 1. Samples of propranolol and atenolol tablets.

Code	Dosage, Medicine	Manufacture	Batch Number
<i>a</i>	10 mg, propranolol	TOLID DARU	529
<i>b</i>	10 mg, propranolol	ROSE DARU	PR 1-3-1
<i>c</i>	40 mg, propranolol	TOLID DARU	221
<i>d</i>	40 mg, propranolol	ROSE DARU	PR 4
<i>e</i>	50 mg, atenolol	D ARUPAKHSH	51
<i>f</i>	100 mg, atenolol	DARUPAKHSH	666
<i>g</i>	100 mg, atenolol	TOLID DARU	765
<i>h</i>	100 mg, atenolol	SOBHAN	2911123
<i>i</i>	100 mg, atenolol	LORESTAN	8008069
<i>j</i>	100 mg, atenolol	APOTEX	00773697

growing steadily for the past few years and has attracted the attention of Governments, Pharmaceutical Industries and the professionals [3]. Various kinds of PMS have been proposed over the past decade to monitor and aid in modifying the use of drugs. The principle focus of PMS proposals has been on the safe use of prescription drugs, even though the range of issues has encompassed both efficacy and safety considerations, e.g., concern over refinements in use as well as better definition of drug risks [4].

Solid dosage forms for oral administration are widely prescribed in clinical practice because they are practical, stable, economical, and usually safe. On the other hand, they pose bioavailability problems related to the absorption process. Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or

solubilization of the drug under physiological conditions and the permeability across the gastrointestinal tract. This highlights the importance of dissolution tests and dissolution profile for the establishment of pharmaceutical equivalence as well as the importance in further bioequivalence studies. These tests are also essential to evaluate batch-to-batch quality, guide the development of new dosage forms and to guarantee quality and performance after any change in the dosage form, production process or the scale of the manufacturing process. In addition, dissolution is a requirement for regulatory approval for product marketing [5].

As tablets of propranolol and atenolol have been extensively and successfully used in the treatment of a range of cardiovascular disorders [6], this study was undertaken to justify the generic substitution of propranolol and atenolol brands in the Iranian market.

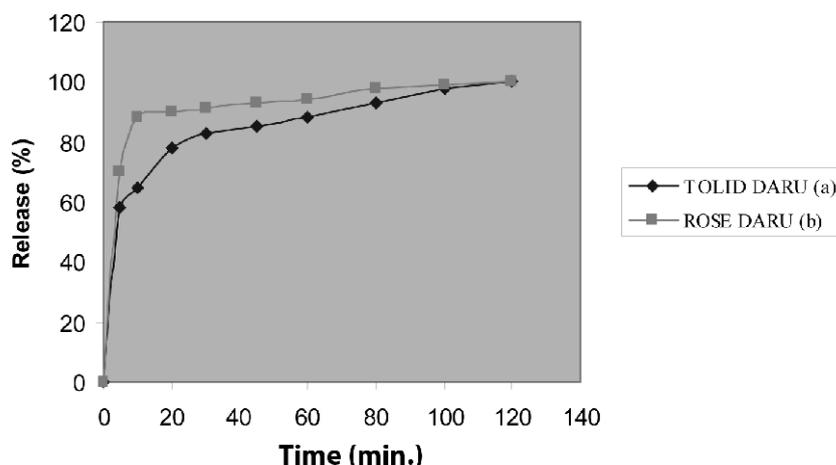
**Figure 1.** Dissolution rate for 10 mg propranolol tablets.

Table 2. A summary of the quality control test undertaken on the propranolol and atenolol tablets.

Code	Average weight (g)	% Deviation from average weight	Average hardness (kg/cm ²)	% Deviation from average hardness
<i>a</i>	78.2	2.56	3.5	11.4
<i>b</i>	91.1	4.39	5.25	17.3
<i>c</i>	150.4	0.7	4	8
<i>d</i>	153.5	3.9	5.5	13.6
<i>e</i>	149.1	2.2	3.25	11.4
<i>f</i>	349.4	0.9	5.75	13.9
<i>g</i>	354.8	1.1	5.25	12.8
<i>h</i>	297.0	1.0	4.75	14.3
<i>i</i>	359.7	1.7	5	16.4
<i>j</i>	338.7	1.5	5	11.6

The current investigation was conducted through a multi-centric PMS study using quality control tests of uniformity of weight, hardness, thickness, assay, content uniformity, disintegration and dissolution times.

2. Experimental

2.1. Instruments and materials

The instruments used comprised of: TEC Scale, Heater stirrer, hardness tester (Erweka TB-24, Germany), disintegration apparatus (Erweka ZT-34, Germany), dissolution apparatus (Erweka DT-70, Germany), Double beam UV Spectrophotometer (Cecil 9000, UK), Micrometer (7058925-193-111, Japan). Ten different brands of propranolol and atenolol tablets as shown in Table 1 were tested. Pure propranolol HCl and atenolol powder was supplied by DARUPAKHSH.

2.2. Determination of uniformity of weight

Weight uniformity test was undertaken

using BP pharmacopea method [7]. Twenty tablets from each brand were weighed individually with an analytical weighing balance. The average weights for each brand as well as the percentage deviation from the mean value were obtained.

2.3. Hardness test

Ten tablets were randomly selected from each brand and the crushing strength was determined with a tablet hardness tester. The pressure at which each tablet was crushed was recorded.

2.4. Determination of thickness

The thicknesses of 10 tablets from each brand were determined individually with a micrometer. The average thicknesses for each brand as well as the percentage deviation from the mean value were obtained.

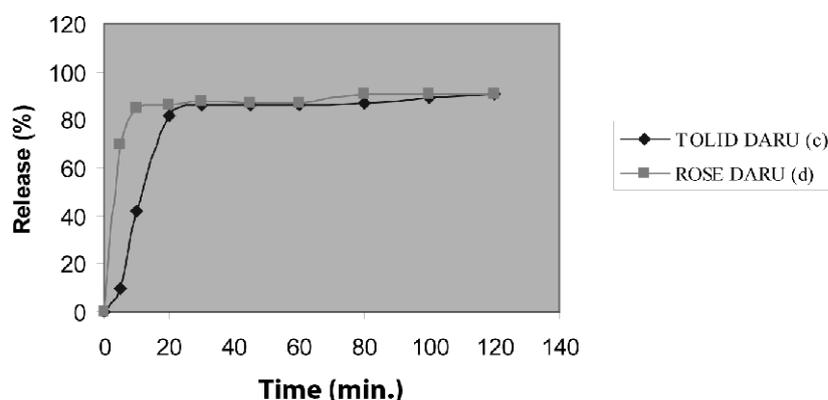


Figure 2. Dissolution rate for 40 mg propranolol tablets.

Table 2. Continued.

Code	Average thickness (mm)	% Deviation from average thickness	Average assay (%)	% Deviation from average assay
<i>a</i>	2.58	2.2	9.8	2
<i>b</i>	3.10	3.6	9.9	4
<i>c</i>	3.73	0.1	39.8	1.5
<i>d</i>	3.29	0.9	39.4	0.5
<i>e</i>	3.45	1.2	50	1
<i>f</i>	4.46	1.6	100.9	1.5
<i>g</i>	4.87	0.4	102.9	0.5
<i>h</i>	4.34	1	99.1	0.2
<i>i</i>	5.08	0.6	96	0.3
<i>j</i>	4.64	0.9	106	2.5

2.5. Assay

Assay test was undertaken using BP pharmacopea method by ultraviolet spectrophotometer.

2.5.1. Propranolol tablets

Twenty tablets from each brand were weighed together and crushed. Twenty mg of the powdered samples were weighed, 20 ml water was added, shaken well and made up to 100 ml with methanol while shaking. The solution was filtered and 10 ml of filtrate was diluted with methanol to 50 ml. The absorbance of the final solution was read at 290 nm. The percentage content was calculated for each brand on the basis of absorbance of 206 for a 1% propranolol solution.

2.5.2. Atenolol tablets

Twenty tablets from each brand were weighed together and crushed. 300 ml methanol was added to the powdered samples and stirred at 60 °C for 15 min. The solution was diluted with methanol to 500 ml after cooling and filtered. A 0.01% concentration (w/w, 100 mg/ml) was prepared. The absorbance of the final solution was read at 275 nm. The percentage content was calculated for each brand on the basis of absorbance of 53.7 for a 1% atenolol solution.

2.6. Content uniformity

The content of 10 tablets from each brand was extracted individually. The concentration of each sample was determined from a calibration curve obtained from pure samples of propranolol and atenolol. The average content, percentage of coefficient variation as

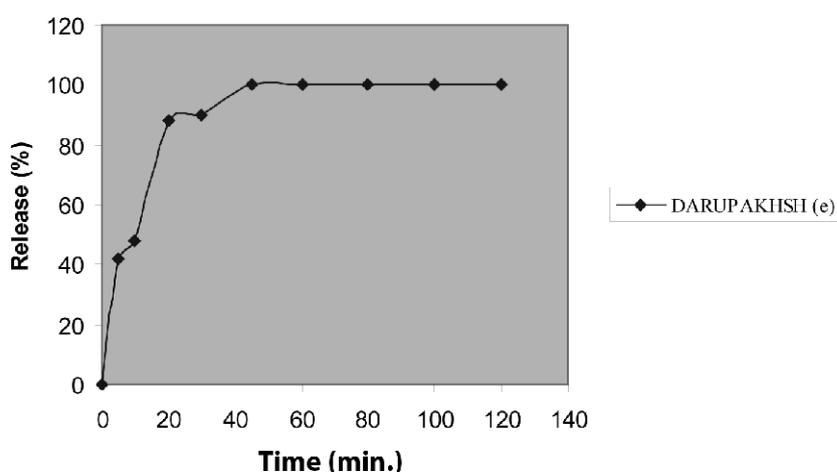


Figure 3. Dissolution rate for 50 mg atenolol tablets.

Table 2. Continued.

Code	Content uniformity (mg)	% Deviation from content uniformity	Average disintegration time (min)	% Deviation from average disintegration time
<i>a</i>	9.9	4	3.7	22.2
<i>b</i>	9.4	4.3	3.3	15.8
<i>c</i>	37.6	3.2	4.5	12.2
<i>d</i>	39.1	4.6	4.2	17.9
<i>e</i>	52.8	4	8	11.1
<i>f</i>	102.2	6.3	11.5	7.3
<i>g</i>	102.1	5.6	5.7	21.2
<i>h</i>	99.9	4.2	6	21
<i>i</i>	91.6	7.9	12.7	23.1
<i>j</i>	101.4	2.7	11	8.1

well as percentage deviation from the mean value for each brand were obtained.

2.7. Disintegration test

Disintegration test was undertaken using BP method. Six tablets from each brand were employed in 1000 ml distilled water, using erweka disintegration apparatus at 28-32 rpm/min for 30 min. at 37 °C. The average disintegration time for each brand were obtained.

2.8. Dissolution test

The dissolution test was undertaken using USP method [8]. The dissolution medium for propranolol was 1000 ml diluted HCl (1/100) using erweka dissolution apparatus (I) at 100 rpm. The medium for atenolol was 900 ml distilled water using erweka dissolution

apparatus (II) at 50 rpm.

Six tablets from each brand were employed. In all the experiments, 4 ml of dissolution sample was withdrawn at 0, 5, 10, 20, 30, 45, 60, 80, 100 and 120 min. and replaced with equal volume to maintain sink condition. Samples were filtered and assayed with ultraviolet spectrophotometer at 290 nm for propranolol and 275 nm for atenolol. The concentration of each sample was determined from a calibration curve obtained from pure samples of propranolol and atenolol.

3. Results and discussion

3.1. Uniformity of weight

The weight variation test is a satisfactory method of determining the drug content uniformity of tablets [9]. All propranolol and atenolol tablets in different brands had

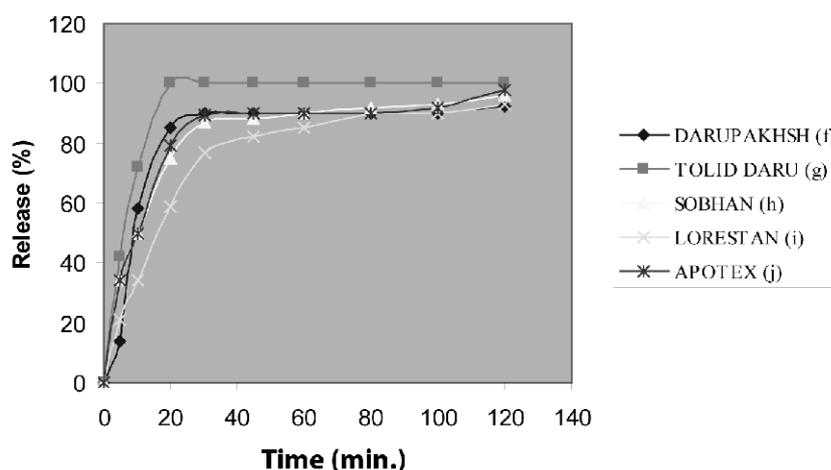


Figure 4. Dissolution rate for 100 mg atenolol tablets.

acceptable uniformity of weight except 1 tablet in category **b** and 1 tablet in category **d**. Brands **b** and **d** showed more variation in the uniformity of weight than **a** and **c**. Uniformity of weight for atenolol tablets showed higher variation in category **i** and less variation in category **f**.

3.2. Hardness

Tablet hardness is an important quality control parameter that is usually measured during bulk tablet manufacturing. The role of hardness in disintegration and dissolution is well documented [10]. Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance [9]. Propranolol tablets in brands **b** and **d** were harder and also more variable than propranolol tablets in brands **a** and **c**. The order of hardness of the atenolol tablets were $f > g > i > j > h > e$. Atenolol tablets in category **i** are more and in category **e** are less variable.

3.3. Thickness

All propranolol and atenolol tablets in different brands had acceptable thickness. Brands **b** and **d** showed more variation than **a** and **c**. The order of thickness of the atenolol tablets were $i > g > j > f > h$. Atenolol tablets in category **f** are more and in category **g** are less variable.

3.4. Assay

According to BP all propranolol and atenolol tablets in different brands had acceptable effective substance. The percent of deviation from the label on the dosage forms in brand **a** was more than **b** and in brand **d** was more than **c**. The order of percent of deviation from the label on the dosage forms for atenolol tablets were $j > i > g > h > f > e$.

3.5. Content uniformity

Three factors can directly contribute to content uniformity problems: 1) no uniform distribution of drug substances throughout

the powder mixture or granulation, 2) segregation of the powder mixture or granulation during the various manufacturing processes and 3) tablet weight variation [9]. According to BP all propranolol and atenolol tablets in different brands had acceptable content uniformity. Brands **b** and **d** showed more variation than **a** and **c**. The order of variation for atenolol tablets were $i > f > g > h > e > j$.

3.6. Disintegration

Disintegration of compressed tablets is an important quality parameter and it is strongly influenced by the properties of the excipients, such as particle size distributions and the compression force. It is well established that the compression force is essential for the tablet manufacturing process since an increase in the compression force causes a reduction of tablet porosity and, as a consequence, a linear increase of the disintegration time [11].

All propranolol and atenolol tablets in different brands were disintegrated in less than 5 minutes in according to BP and USP. Disintegration times in brands **b** and **d** were less than **a** and **c**.

3.7. Dissolution

Commonly used diluents and disintegrants, such as various grades of lactose and starch, in the preparation of tablets and capsules have been shown to influence the dissolution rate of a drug. In determining the dissolution rate of drugs from solid dosage forms under standardized conditions, one has to consider several physiochemical processes in addition to the processes involved in the dissolution of pure chemical substances. The physical characteristics of the dosage form, the wettability of the dosage unit, the penetration ability of the dissolution medium, the swelling process, the disintegration and deaggregation of the dosage form are few of the factors that influence the dissolution characteristics of a drug [12]. In this study all propranolol and

atenolol tablets in different brands had dissolution profile according to USP Pharmacopea. Propranolol tablets released 100% of their effective ingredient in dosage forms **a** and **b** (Figure 1) and 90.7% in dosage forms **c** and **d** (Figure 2) after 2 h. Atenolol tablets released 100%, 100%, 92.3%, 97.6%, 96%, 93.3% of their effective ingredient in dosage forms **e** (Figure 3), **g,f,j,h** and **i** (Figure 4) after 2 h, respectively. A summary of the results are shown in Table 2.

4. Conclusion

Tablet dosage form is mainly composed of the drug and excipients such as a diluent, a binder, a lubricant, a disintegrant, and a glidant. Lubricant is an important excipient to improve the quality and manufacturing efficiency of tableting process. Lubricant also has profound influence on disintegration time, hardness and drug dissolution. Therefore, it is important to optimize concentration of lubricant in the formulation [13]. The results of assay and content uniformity tests serve as a pointer to good manufacturing practices as well as active pharmaceutical ingredient when compared with BP standards. Average weight, hardness, thickness and disintegration time for all propranolol and atenolol tablets complied with USP and BP standards.

According to USP Pharmacopea releasing of 75% of the active content after 30 min. is desirable. Dissolution rate for all propranolol and atenolol tablets complied with USP standards. Atenolol tablets in brand **g** released 100% of its pharmaceutical ingredients after 20 minutes but the other brands (100 mg) didn't released 100% of its pharmaceutical ingredients even after 2 h.

Acknowledgments

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